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ACTA REUMATOLÓGICA PORTUGUESA

Vol 36 • Nº1 Janeiro/Março 2011

SUMÁRIO / CONTENTS

EDITORIAIS / EDITORIALS

ARTIGOS ORIGINAIS / ORIGINAL PAPERS

PRÁTICA CLÍNICA / CLINICAL PRACTICE

CASOS CLÍNICOS / CLINICAL CASES

Sociedade Portuguesa de Reumatologia

ACTA REUMATOLÓGICA PORTUGUESA

Vol 36 • Nº1 Janeiro/Março 2011

SUMÁRIO / CONTENTS

ARE WE READY TO CHANGE THE PACE OF ARTHRITIS TREATMENT? TREATING PRE-ARTHRITIS AND VERY EARLY ARTHRITIS

Paul P. Tak*

Rheumatoid arthritis (RA) is a prototype immune-mediated inflammatory disease, characterized by a symmetric polyarthritis usually involving the small joints of the hands and feet. Autoantibody positive RA is associated with more aggressive articular disease, higher frequency of extra-articular manifestations, and increased mortality. It has been estimated that 55–70% of RA patients have progressive disease resulting in joint destruction with as a consequence disability, loss of quality of life, reduced ability to work and increased health care utilization. RA is still associated with long-term morbidity and early mortality despite major developments in antirheumatic therapy. Among the connective tissue diseases RA is the commonest and the most important in socio-economic terms.

The past few years, research in the field of RA has focused on the earliest stages of disease, leading to the discovery that circulating auto-antibodies, increased acute phase reactants and asymptomatic synovitis[1,2] precede the clinical onset of the disease. Before the onset of any signs of arthritis, elevated levels of auto-antibodies like IgM-rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can be found in blood samples. These auto-antibodies may be present at a median of 5 years before clinical symptoms appear. Subjects with these auto-antibodies and arthralgia have a chance of 40-70% of developing RA within 5 years[3].

Moreover, histological studies have shown all features of chronic synovial inflammation to be present in the earliest stages of the disease[4,5]. Consistent with the notion that early arthritis represents chronic synovitis, a notable percentage of RA patients have signs of joint destruction at the time of initial diagnosis[6]. Taken together, these data form strong evidence that clinical signs and symptoms may be preceded by a pre-clinical phase for several years and that early RA (as defined at present clinically) in fact represents chronic synovitis, although the duration of that presymtomatic synovitis has been unclear.

To determine whether the synovium is already affected during the earliest phases preceding clinical signs and symptoms of RA, we performed MRI and synovial biopsy in IgM-RF- and/or ACPA-positive individuals without a history of arthritis who were prospectively followed up[7]. The results show that the synovium is not abnormal during this stage, even in those who develop arthritis during follow-up. The presence of subclinical synovitis may probably last several weeks rather than months. Thus, systemic autoimmunity precedes the development of synovitis, suggesting that a 'second hit' is involved (Figure 1)[7]. This strengthens the rationale for exploring preventive strategies aimed at interfering with the humoral immune response before synovial inflammation develops. The individual and socioeconomic burden of this disease would support the development of preventive strategies. The outline of such a study aimed at in-

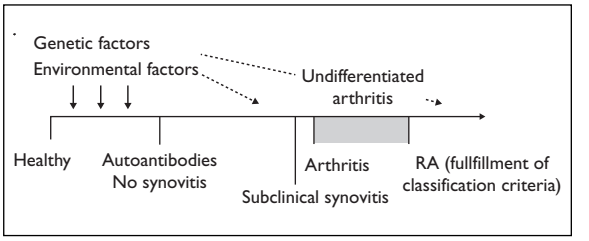

Figure 1. Timeline of autoantibody-positive rheumatoid arthritis (RA): the different stages of disease. Autoantibody formation may precede the development of clinical signs and symptoms of RA by several years. The presence of subclinical synovitis may probably last several weeks rather than months.

van de Sande M G H et al. Ann Rheum Dis doi:10.1136/ard.2010.139527

*Div. Clinical Immunology & Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, the Netherlands

terfering with the humoral response during the preclinical stage of RA will be discussed during this presentation at the Arthritis and Bone Symposium.

Correspondence to
Paul P. Tak, MD, PhD
Div. Clinical Immunology & Rheumatology,
Academic Medical Center/University of Amsterdam,
Amsterdam, the Netherlands
E-mail: p.p.tak@amc.uva.il

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ASIA OR SHOENFELD'S SYNDROME: HIGHLIGHTING DIFFERENT PERSPECTIVES FOR DIFFUSE CHRONIC PAIN

Jozélio Freire Carvalho*, Solange Murta Barros**, Jaime C. Branco***, João Eurico Fonseca****

Is the Gulf War Syndrome (GWS) and the silicone related scleroderma –like syndrome spectres of the same disease? What do they have in common with a rare aluminium induced myopathic syndrome described for the first time in France in 1998? The logic answer was suggested by an elegant integration of the existing evidence into the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) proposed recently by Shoenfeld in a paper published in *Journal of Autoimmunity*[1]. A mosaic of environmental factors can be classified as adjuvants. In fact, we know for decades a variety of compounds that are able to induce autoimmunity in animal models and used in clinical practice to increase the immunogenicity of vaccines, but also known to be able, in genetic susceptible individuals, to induce autoimmune diseases[2,3]. In this vast group of substances bacterial antigens, hormones, aluminium, silicone and several other molecules have been included[4].

The GWS was described in veterans that were suffering from atypical rheumatic symptoms, such as arthralgia, myalgia, lymphadenopaty, chronic fatigue syndrome, malar rash and autoimmune thyroiditis[5].

A cohort study performed 10 years ago compared the titter of anti squalene antibodies of 144 Golf War immunized veterans or medical employees, 48 blood donors, 40 systemic lupus erythematosus patients, 34 silicone breast implant recipients and 30 chronic fatigue syndrome patients. The majority (95%) of overtly ill deployed GWS patients had antibodies to squalene. All (100%) GWS patients immunized for service in Desert Shield/ /Desert Storm who were not in the fighting front had antibodies to squalen. In contrast, none (0%) of the veterans that were in the fighting zone and were not showing signs and symptoms of GWS have antibodies to squalen. Neither patients with idiopathic autoimmune disease nor healthy controls had detectable serum antibodies to squalene. The majority of symptomatic GWS patients had serum antibodies to squalene[6]. The authors proposed that GWS was not a result of the exposition to weapons but rather induced by the intense vaccination program that they were submitted to. It is ironic that more solders were ill due to an oil adjuvant injected in their organisms than fighting against the hostile environment and the armed enemies.

Silicon was considered an inert material and thus unable to induce immune reactions. Recent metanalysis have supported this view, as the risk of silicon exposed individuals for developing a diffuse connective tissue disease is only 0.8%, not significantly higher than the risk of the general population. However, that is not the case for more unspecific symptoms such as arthralgia and myalgia and even some diffuse neurologic manifestations that appear to be more common in individuals exposed to silicon implants[7]. The possible association between chronic fatigue syndrome, fibromyalgia, and previous silicone mammoplasty was proposed almost two decades ago[8].

The post vaccination muscle disease described by Gehardi *et al.* in 1987 is of particular interest as it is based in well defined histologic features[9]. It is a miofasceitis that has the presence of macrophages with aluminum inclusions, which occurs associated with vaccination. Clinically the disease is expressed by systemic symptoms such as fatigue, myalgia, arthalgia, fever and, in some cases, by a demyelinating condition similar to Guillain-Barré, with electromyographic changes. Elevated acute

*Serviço de Reumatologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
**Serviço de Reumatologia do Hospital Naval Marcílio Dias, Rio de Janeiro, RJ, Brazil.
***CEDOC – Faculdade Ciências Médicas, Universidade Nova de Lisboa, and Serviço de Reumatologia, CHLO, EPE-Hospital Egas Moniz, Lisboa, Portugal.
****Unidade de Investigação em Reumatologia, Faculdade de Medicina da Universidade de Lisboa and Serviço de Reumatologia do Hospital de Santa Maria, Lisboa, Portugal.

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Table I. Criteria suggested by Shoenfeld for ASIA diagnosis

Major Criteria

- Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
- The appearance of 'typical' clinical manifestations:
  - Myalgia, myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syndrome)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease

For ASIA's diagnosis: at least 2 major criteria or 2 minor and 1 major.

phase proteins and creatine quinase also occur. The same group determined that the disease occurs only in HLA DRB1*01 positive individuals[9]. On top of that, it was shown that aluminum can persist in the local of injection, up to 10 years after vaccine administration, which can explain the persistence of this condition in some individuals[10].

These conditions and other observations, regarding for instance de H1N1 vaccination, have motivated the definition of the ASIA syndrome, with the criteria proposed by Shoenfeld listed in Table I[1]. These criteria, if properly validated, are of great clinical relevance, as they raise a major clinical doubt on the classification of some patients with chronic pain syndromes, as chronic fatigue syndrome, or even fibromyalgia. In fact, if we compare the cardinal symptoms of the Shoenfeld's ASIA syndrome with the typical clinical manifestations of patients with diffuse chronic pain we came quickly to the conclusion that reviewing the recent exposition to adjuvants and other potential exogenous stimulus seems to be a wise attitude. This is also in line with the characteristic symptoms of fibromyalgia and chronic fatigue syndrome that frequently occur in patients with well-defined Lyme disease, even after adequate treatment. Lyme disease is caused by an infection due to *Borrelia burgdorferi* spirochete and most of the clinical symptoms are in fact a consequence of an immune response to this infectious agent. Although a biological relationship between Lyme disease and diffuse pain syndromes has not been established, in fact this can be encompassed by the ASIA syndrome[11]. In addition, recent studies have detected the presence of retroviral sequences like xenotropic murine leukemia virus-related virus (XMRV) and polytropic murine leukemia virus related--virus (PMLV) in chronic fatigue syndrome patients, expanding, in fact, the need for thinking on alternative diagnosis in patients classified into these conditions[12]. Consequently, countries such as Australia, Canada, New Zealand and the UK elaborated restrictive guidelines for "blood donors with a history of current diagnosis of CFS". If upcoming research will confirm these observations and validate the ASIA/Shoenfeld criteria, a major paradigm shift will have to occur in the way rheumatologists perceive some cases of diffuse chronic pain. Interestingly, in this issue of Acta Reumatologica Portuguesa 2 case reports related to the ASIA/Shoenfeld are reported[13,14].

Correspondence to
Jozélio Freire de Carvalho MD, PhD
Faculdade de Medicina da Universidade de São Paulo,
Disciplina de Reumatologia
Av. Dr. Arnaldo 455, 3º andar
Sala 3105, São Paulo – SP
01246-903, Brazil
FAX: 55-1130617490
E-mail: jotafc@gmail.com

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ASSOCIATION OF SEROTONIN TRANSPORTER GENE POLYMORPHISM 5HTTVNTR WITH OSTEOPOROSIS

Joana T. Ferreira[*], Pilar Q. Levy[*], Claudia R. Marinho[*], Manuel P. Bicho[*,****], Mário Rui G. Mascarenhas[*,**,***]

Abstract

Aim: To study the association of serotonin transporter gene polymorphisms and osteoporosis.
Material and Methods: Blood samples were collected from 186 individuals with normal bone mineral density and 89 with osteoporosis. Serotonin transporter gene polymorphisms 5HTTVNTR and 5HTTLPR were studied by PCR and statistical analyses used to test the association between groups.
Results: The frequency of 12/10 and 12/12 genotypes of 5HTTVNTR was significantly higher among the osteoporotic patients (OR=2,620 CI 95% [1,112--6,172], P=0,037). For 5HTTLPR we did not find significant differences between the two studied groups.
Conclusions: As far as we know, this is one of the few studies that report an association between 5HTTVNTR and osteoporosis opening the hypothesis that the determination of this specific serotonin transporter gene polymorphism may contribute to the identification of individuals at high risk for the development of osteoporosis.

Keywords: Osteoporosis; Bone Remodeling; Serotonin Transporter Polymorphisms.

Introduction

Osteoporosis is a severe metabolic bone disease characterized by microarchitectural deterioration and a decrease in bone strength leading to an increased risk of fractures. It occurs as a consequence of poor bone mass acquisition during growth or more frequently as a consequence of bone loss due to increased bone resorption. In post-menopausal osteoporosis there is an imbalance between osteoblastic and osteoclastic activity favoring bone resorption[1] mainly due to variations in hormonal factors with an impact in bone, with a especially relevant role for estrogens. Many other factors intervene in the regulation of bone metabolism, including the components of neuronal system like leptin, neuropeptide Y receptors and neurotransmitters and its transporters like glutamate and glutamate/aspartate transporter[2-4].

Serotonin (5HT) is a neurotransmitter with relevant functions in the central nervous and cardiovascular systems (CNS; CVS) and in the gastrointestinal tract (GIT)[1,5,6]. It was postulated that the serotoninergic neurotransmitter system may have, somehow, a role in bone metabolism[7-9] and more recently a relationship with leptin was also highlighted[10].

Although some studies support the hypothesis that 5HT is also produced by bone cells, this is still unclear[1].

5HT synaptic and extracellular concentrations are strictly regulated by a specific serotonin transporter (5HTT, SLC6A4) responsible for its reuptake after release[11].

5HTT gene is located in 17p11.2 region and is organized in 14 exons spanning 31Kb[12]. Two polymorphic regions have been reported in this gene. One located in the promoter (5HTTLPR) is an insertion/ /deletion polymorphism of 44 bp leading to long (L) and short (S) alleles which differ in their transcriptional activity (allele L has the highest)[13] . The other polymorphism sited in the intron 2 (5HTTVNTR) consists of a variable number of tandem repeats (VNTR) containing 9, 10 or 12 copies of a 17 bp element. This gives rise to 3 different alleles (9, 10 and 12) and 6 different genotypes (12/12, 12/10, 12/9, 10/10, 10/9, 9/9). Allele 9 is the less common and may not even appear in some populations. Although located in an intronic region, recent studies have shown that VNTR operates as an enhancer of gene transcription leading to quantitative and qualitative differences in transcriptional rate. Allele 12 is re-

*Genetics Laboratory, Centre of Metabolism and Endocrinology, Lisbon Medical School, University of Lisbon, Lisbon, Portugal
**Clinic of Endocrinology, Diabetes and Metabolism of Lisbon (CEDML, Lda), Portugal
***Endocrinology Department, CHLN, Lisbon, Portugal
****Instituto Bento da Rocha Cabral, Lisbon, Portugal

portedly associated with higher gene transcription[14]. Regarding the organization of the human 5HTT gene, the role of VNTR in the regulation of 5HTT expression is probably related to the fact that this polymorphism is followed by an activating protein (AP-1) motif, a putative binding site for a transcription factor comprising the heterodimer c-fos / c-jun, which may play a role in the regulation of 5-HTT expression. Alternatively, a small number of VNTR repeats may influence the stability of messenger RNA transcription[12].

Studies on the role of 5HT in the regulation of bone metabolism have been advanced by the identification of functional 5HT receptors in osteoblasts, osteocytes and in a population containing osteoblast precursor cells. Serotonin transporter (5HTT) was described in osteoblasts, osteoclasts and osteocytes[7,8]. 5HTT is responsible for 5HT uptake in osteoblasts and osteocytes. In osteoclasts, it seems to regulate cell differentiation but not its activation[7, 8].

Recent studies demonstrated a direct relation between selective 5HT reuptake inhibitors (SSRIs) and a decrease in bone mass[15]. On the other hand, other studies revealed that a 5HTT blockade reduces osteoclast differentiation but not activation[7]. Both studies support the hypothesis that 5HT has a relevant role in the regulation of bone metabolism. The 5HT transporter seems to play a role, but the exact biological mechanisms involved remain unclear.

The aim of this study was to evaluate the association of 5HTT gene polymorphisms 5HTTVNTR and 5HTTLPR with osteoporosis.

Materials and Methods

Subjects

Blood samples were obtained from 275 Caucasian individuals, 218 Females and 57 Males (Clínica de Endocrinologia, Diabetes e Metabolismo de Lisboa) after they were assessed for bone mineral density (g/cm^2) by dual X-ray absorptiometry (DXA) at the lumbar spine (L1-L4), proximal femur and distal forearm, using the QDR Discovery W densitometer (Hologic Inc.). T-scores at lumbar spine, femoral neck and total hip were used to classify the bone mineral density, according to the World Health Organization operational definition of osteoporosis. Patients having at least one T Score ≤ -2,5 at one or more measurement sites were classified as osteoporotic (regardless whether they had primary or secondary osteoporosis). Those with a T-Score ≥ -1 were included in the normal bone mass group. Osteopenic individuals were excluded. All of them signed an informed consent. Some clinical characteristics of controls (normal bone mass) and patients (osteoporotic) are summarized in Table I.

DNA Extraction

Peripheral Blood was collected into 5 ml tubes containing EDTA and stored at –20 ºC until analysis. DNA was isolated from leukocytes by an adapted non-enzymatic DNA extraction procedure[16].

Genetic polymorphisms identification. 5HTT 2nd intron VNTR and 5HTT promoter variant analysis

Genomic DNA was amplified by polymerase chain reaction (PCR) to identify two different polymorphisms in 5HTT gene, one located within intron 2 (5HTTVNTR) and the other in the promoter (5HTTLPR). Primers used as well as PCR conditions were designed by the authors. For 5HTTVNTR we used the primers 5'GTCAGTATCACAGGCTGCGAG3' and 5'TGTTCCTAGTCTTACGCCAGTG3' and the amplification reaction was made in a final volume of 50 µl containing 200 ng DNA, 10 pmol of each primer, 0.2 mM dNTPs, 1.5 mM MgCl2 and 2U Taq Polymerase. The amplification program comprised an hot start of 94ºC/2 min, 35 cycles of denaturation 94ºC/30s, annealing 57ºC/30s and extension 72ºC/30s and a final extension of 72ºC/5min. For 5HTTLPR we used the primers 5'GGCGTTGCCGCTCTGAATGC3' and 5'GGGACTGAGCTGGACAACCAC3' and the amplification reaction followed the protocol above using 1U Taq Polymerase and an annealing temperature of 61ºC.

Both polymorphisms resulted in different amplicons as determined by 4 or 3% agarose gel (Figure 1).

Statistical analysis

Statistical analysis was performed with the program SPSS 16.0. Continuous variables showed a normal distribution (One-Sample Kolmogorov-Smirnov Test) and so we used T-test and ANOVA to compare controls and patients. To compare allele and genotype frequencies we used Chi-square test and Odds Ratio.

For 5HTTVNTR, as alleles 10 and 9 are the ones associated with a decrease in gene transcriptional rate when we compared allele frequencies between groups we did it in two different ways. We started by analyzing the three alleles separately and then we assessed combined allele 9 and 10 in just one

Table I. Characterization of normal bone mass and osteoporosis groups

	Normal bone mass			Osteoporosis			P (χ^2 test[a] and ANOVA)
	Female (F)	**Male (M)**	**F+M**	**Female (F)**	**Male (M)**	**F+M**	
N	**150 (80,6%)**	**36 (19,4%)**	**186**	**68 (76,4%)**	**21 (23,6%)**	**89**	**0,540[a]**
Age (years)	47,01±12,40	54,40±12,67	**48,44±12,79**	64,59±10,34	61,45±7,11	**63,85±9,73**	<0.001
Body Mass Index (BMI) (kg/m^2)	29,99±5,61	30,96±4,12	**30,18±5,38**	26,66±4,63	27,62±4,07	**26,89±4,50**	<0.001
BMD Lumbar spine (L1-L4) (g/cm^2)	1,07±0,10	1,19±0,14	**1,10±0,12**	0,74±0,11	0,84±0,15	**0,76±0,13**	<0.001
BMD Trochanter (g/cm^2)	0,77±0,09	0,90±0,12	**0,79±0,11**	0,58±0,08	0,67±0,14	**0,60±0,10**	<0.001
BMD Neck of the femur (g/cm^2)	0,90±0,11	1,00±0,14	**0,92±0,12**	0,67±0,10	0,77±0,14	**0,70±0,12**	<0.001
BMD Total Femur (g/cm^2)	1,01±0,11	1,16±1,13	**1,04±0,13**	0,77±0,09	0,92±0,15	**0,81±0,12**	<0.001
BMD Distal forearm (g/cm^2)	0,70±0,05	0,80±0,08	**0,71±0,07**	0,57±0,08	0,67±0,06	**0,59±0,09**	<0.001

group. In respect to genotype frequencies we studied the 4 genotypes separately and then we did different genotype combinations.

Differences between groups were considered significant for *P*-values < 0.05.

Results

Table I shows the characterization of the two studied groups in terms of age, Body Mass Index (BMI) and Body Mineral Density (BMD) in different parts of the skeleton. It shows that the two studied groups (osteoporosis and normal bone mass) have a similar gender distribution and that they differ significantly in terms of age and BMI.

To account for this differences, we compare age and BMI of each 5HTTVNTR genotype (12/9, 10/10, 12/10, 12/12) in each studied population separately (OST and NBM) and in all individuals (OST + NBM). We did not find association between age or BMI and 5HTTVNTR (Tables II and III).

Table IV shows allele and genotype frequencies for the intronic polymorphism (5HTTVNTR) in patients and controls. These two groups were in Hardy-Weinberg equilibrium for genotype distribution (data not shown).

Regarding allele frequencies, although we did not find significant differences, we could be able to observe higher frequency of allele 12 among osteoporotic patients.

In genotype frequencies, as we expected by knowing how this polymorphism affects gene transcription, we just found significant differences when we included individuals 10/10 and 12/9 (homozygotes for one of the shorter alleles, allele 10 and carriers of allele 9) in one group and individuals 12/10 and 12/12 (homozygotes for the long allele and heterozygotes) in another group. Significant higher frequencies of 12/10 and 12/12 genotypes were detected in the osteoporosis group (92.1% vs 81.7%). They show a risk factor of 2,620

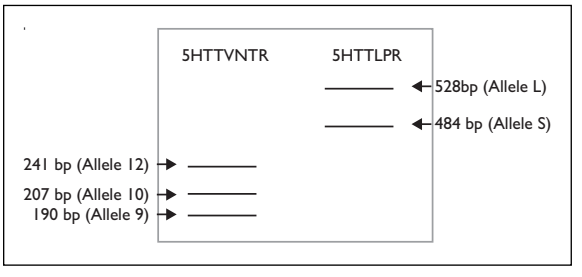

Figure 1. Diagram representing an agarose gel showing the number of base pairs of each allele for the two studied polymorphisms

Table II. 5HTTVNTR genotype frequencies according to age

	12/9	10/10	12/10	12/12	P (ANOVA)
OST	–	57,80±15,94 (n=7)	66,10±8,57 (n=42)	62,54±9,14 (n=40)	0,057
NBM	45,08±8,21 (n=4)	50,79±15,40 (n=30)	48,37±11,90 (n=82)	47,71±12,89 (n=70)	0,680
OST+NBM	45,08±8,21 (n=4)	52,12±15,53 (n=37)	54,37±513,74 (n=124)	53,10±13,66 (n=110)	0,494

OST– Osteoporosis group; NBM– Normal Bone Mass group

Table III. 5HTTVNTR genotype frequencies according to Body Mass Index (BMI)

	12/9	10/10	12/10	12/12	P (ANOVA)
OST	–	28,84±6,84 (n=7)	26,82±3,65 (n=42)	26,62±4,86	0,484 (n=40)
NBM	30,95±4,09 (n=4)	30,91±5,83 (n=30)	29,75±5,42 (n=82)	30,32±5,24 (n=70)	0,754
OST+NBM	30,95±4,09 (n=4)	30,52±5,99 (n=37)	28,76±5,08 (n=124)	28,98±5,39 (n=110)	0,300

OST – Osteoporosis group; NBM – Normal Bone Mass group

(OR=2,620 CI 95% [1,112-6,172], P=0,037) for the development of this pathology comparing with individuals with genotypes 10/10 and 12/9.

No association was observed in the osteoporosis group for the polymorphism in the promoter – 5HTTLPR (Table V).

Discussion

As Serotonin has been implicated in the control of eating behavior and body weight[17], changes in its metabolism, for example, as a result of 5HTTVNTR, may induce differences in BMI. In spite of this, in our study, this variable doesn't seem to be manipulated by 5HTTVNTR.

Previous studies from our research group pointed to a deregulation of 5HT metabolism in osteoporosis as we demonstrated that intraplatelet 5HT is increased in osteoporotic patients (data not published).

We hypothesize that individuals carrying genotypes 12/12 or 12/10 of 5HTTVNTR have higher amounts of 5HTT. If we consider what is known about the role of this transporter in osteoblasts, we may assume that the reuptake process by this cells should be activated leading to an increase in bone mass as reported by other authors[15]. On the other hand, if we regarded the role of 5HTT in both formation and differentiation of osteoclasts we may assume that in these individuals these processes are activated leading to a deregulation of bone homeostasis through an increase of osteoclastic function.

Although our results are in accordance with some data already published[7], they are contradictory with other studies, especially those regarding the role of SSRIs in bone mass[16]. In that way, our study may be assumed as a support for the improvement of studies regarding the role of SSRIs in the regulation of bone mass and as a contribution for the knowledge about the role of 5HT metabolism in bone remodeling process.

Osteoporotic patients, as we expected, are older than the ones with normal bone mass. This may represent an important limitation to the study and compromise our conclusion. We can not predict whether individuals with NBM will still in the same group if they were older or if they will have osteoporosis or not. It would be interesting if we could

Table IV. Allele and genotype 5HTTVNTR frequencies

	Allele 12	Allele 10	Allele 9	P (χ^2 test)	Allele 12	Allele 9+10	P (χ^2 test)
OST (n= 89)	122 (68,5%)	56 (31,5%)	0	0,102	122 (68,5%)	56 (31,5%)	0,093
NBM (n= 186)	226 (61,4%)	142 (38,6%)	4 (1,1%)		226 (60,7%)	146 (39,3%)	

	12/9	10/10	12/10	12/12	P (χ^2 test)
OST (n= 89)	0	7 (7,9%)	42 (47,2%)	40 (44,9%)	0,308
NBM (n= 186)	4 (2,2%)	30 (16,1%)	82 (44,1%)	70 (37,6%)	

	12/9+10/10	12/10	12/12	P (χ^2 test)
OST (n= 89)	7 (7,9%)	42 (47,2%)	40 (44,9%)	0,070
NBM (n= 186)	34 (18,3%)	82 (44,1%)	70 (37,6%)	

	12/9+10/10	12/10+12/12	P (χ^2 test)/Odds Ratio
OST (n= 89)	7 (7,9%)	82 (92,1%)	**0,037**
NBM (n= 186)	34 (18,3%)	152 (81,7%)	**OR=2,620 CI 95% [1,112-6,172]**

	12/9+12/10+12/12	10/10	P (χ^2 test)
OST (n= 89)	82 (92,1%)	7 (7,9%)	0,091
NBM (n= 186)	156 (83,9%)	30 (16,1%)	

	12/9+10/10+12/10	12/12	P (χ^2 test)
OST (n= 89)	49 (55,1%)	40 (44,9%)	0,305
NBM (n= 186)	116 (62,4%)	70 (37,6%)	

OST – Osteoporosis group; NBM – Normal Bone Mass group
Note: Numbers above the percentages represent the number of individuals within the group

Table IV. Allele and genotype 5HTTLPR frequencies

	L/L	L/S	S/S	P (χ^2 test)	Allele L	Allele S	P (χ^2 test)
OST (n= 73)	25 (34,2%)	37 (50,7%)	11 (15,1%)	0.883	87 (59,6%)	59 (40,4%)	0.704
NBM (n= 179)	56 (31,3%)	93 (52,0%)	30 (16,7%)		205 (57,3%)	153 (42,7%)	

OST – Osteoporosis group; NBM – Normal Bone Mass group
Note: Numbers above the percentages represent the number of individuals within the group

perform a prospective study of these individuals or if we could pare the ages of the two studied groups (OST and NBM).

In spite of this limitation, as far as we know, this is one of the few studies that report a possible association between 5HTTVNTR and osteoporosis opening the hypothesis that the determination of this specific polymorphism of serotonin transporter gene may contribute to the identification of individuals at high risk for the development of osteoporosis.

Correspondence to
Joana T. Ferreira
Genetics Laboratory, Centre of Metabolism and Endocrinology, Lisbon Medical School, University of Lisbon, Lisbon, Portugal
Avenida Prof. Egas Moniz
Faculdade de Medicina de Lisboa
Edíficio Egas Moniz, Piso 1C
1649-028 Lisboa, Portugal
Fax: +351217999451
E-mail: jogtff@iol.pt

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ANTI-SACCHAROMYCES CEREVISIAE (ASCA) AND ANTI-NEUTROPHIL CYTOPLASMIC (ANCA) ANTIBODIES ARE NOT INCREASED IN TAKAYASU ARTERITIS

Fatma Ozbakir*, Serdal Ugurlu**, Aykut F. Celik***, Emire Seyahi**

Abstract

Objectives: Takayasu arteritis (TA) may be associated with inflammatory bowel disease (IBD). As there is such an overlap and since both diseases show granulomatous histopathological lesions we reasoned similar biological pathways might be implicated in both conditions. Therefore, we investigated the prevalence of anti-*Saccharomyces cerevisiae* (ASCA) and anti-neutrophil cytoplasmic (ANCA) antibodies - serological markers for IBD--among patients with TA.

Methods: Thirty-two patients with TA, 21 with Crohn's disease (CD), 17 with ulcerative colitis (UC) and 34 healthy controls were studied. Among 32 patients with TA, 2 had CD and one had UC concomitantly. ASCA Ig A and Ig G antibodies were analyzed using a commercial ELISA kit. Immune fluorescence analysis (IFA) was used to assess the presence of ANCA antibodies.

Results: Only patients with CD had significantly higher levels of both ASCA Ig A and Ig G, compared to patients with TA and healthy controls. Similarly, the frequency of ASCA positive patients was higher only among patients with CD. ASCA Ig A and Ig G antibodies were found in 16 % (5/32) of patients with TA. Among 3 patients, in whom TA and IBD co-existed, only one (one with CD) had positive ASCA Ig G and A antibodies. The p-ANCA antibodies were present among patients with UC (35 %) and CD (10 %).

Conclusion: ASCA positivity in TA was similar to that found in UC and healthy controls.

No ANCA antibodies were detected among patients with TA.

*Central Research Laboratory, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey
**Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey
***Division of Gastroenterology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

Keywords: Takayasu Arteritis; Anti-*Saccharomyces Cerevisiae* Antibodies; Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Anti-neutrophil Cytoplasmic Antibodies.

Introdution

Takayasu's arteritis (TA) is a chronic inflammatory disease of large arteries[1]. It involves primarily the aorta and its major branches, causing thickening of the vessel wall and narrowing or occlusion in the lumen. The disease is seen mostly in females and seems to be more prevalent in Asia, compared to other parts of the world.

The association of TA with inflammatory bowel diseases (IBD), although rare, is well known based on several case reports[2-9]. Both TA and IBD have unknown etiology and are reported to share similar chronic granulomatous histopathology[10-11].

The anti-*Saccharomyces cerevisiae* (ASCA) and anti-neutrophil cytoplasmic (ANCA) antibodies are used as serological markers for IBD. While ASCA is reported in 50 to 80% of patients with CD and 2-14% of patients with UC, ANCA (especially p-ANCA) is found in 40-80 % of patients with UC and 5-25 % of patients with CD[12-15].

As TA and IBD may coexist and have a common histopathology, we thought that these diseases may have common pathogenesis. In this study, we investigated the frequency of ASCA and ANCA antibodies in TA patients comparing with patients with CD and UC and healthy controls.

Patients and methods

We studied 32 (all female) consecutive patients with TA, diagnosed according to the criteria defined by the ACR 1990 and seen in the rheumatology out-

patient clinic of Cerrahpasa Medical Faculty in Istanbul[16]. We also studied 17 patients with UC and 21 patients with CD, who were followed by the gastroenterology outpatient clinic of the same hospital, as diseased control groups. Patients with UC and CD were all females. Thirty four (7 M/ 27 F) apparently healthy individuals, chosen among the hospital staff, constituted our healthy controls. All participants gave informed consent and the local ethic committee of Cerrahpasa Medical School approved the study.

Sera were collected by centrifugation of venous blood samples and stored at -20°C, until being analyzed. Serum levels of ASCA IgG and IgA were determined using a commercial Enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun-Germany) and that of Anti-MPO and Anti-PR3 were determined by using a commercial ELISA kit (Trinity--USA). Immune fluorescence analysis (IFA) was used to assess the presence of ANCA antibodies. Cut-off values accepted according to the manufacturer's instructions were ≥ 20 U/ml for ASCA and ≥ 0.91 EU /ml for anti-MPO and anti-PR3, respectively.

Statistical analysis

Comparisons of continuous variables between groups were made by one-way analysis of variance using the Bonferroni correction. The categorical variables were compared by the chi-square test or the Fisher exact test. All tests were performed using SPSS for Windows, version 13.0, software (SPSS Inc, Chicago, IL).

Results

The mean age was similar between the study groups (TA: 40 ±12 years; CD: 39±11 years; UC: 38 ± 11 years) and healthy controls (38±9 years), (P= 0.890). The mean disease duration of TA patients (9 ± 5 years) was significantly longer than that of patients with CD (4 ± 5 years) and UC (6 ± 5 years), (P < 0.001).

Arterial involvement sites were subclavian artery (25/32; 78 %), common carotid artery (18/ 32; 56 %), abdominal aorta (12/ 32; 38 %), thoracic aorta (6/32; 19 %) and renal artery (4/ 32; 13 %). At the time of the study 15 (47 %) of the patients with TA had active disease, according to the criteria defined by Kerr et al[1] and 84 % (27/ 32) were under treatment with immunosuppressives (corticosteroids: 23, azathioprine: 14 and methothrexate: 11).

Two patients had concomitant CD, while one had UC. In all 3, the diagnosis of IBD preceded the diagnosis of TA (1, 3 and 5 years ago). All 3 were in remission for both diseases at the time of the study.

As shown in Table I and Figure 1, serum levels of ASCA (Ig G and Ig A) and the frequency of ASCA positivity (Ig G and Ig A) were almost twice increased among patients with TA, compared to that found among healthy controls, however, the difference was not statistically significant. ASCA Ig G and Ig A antibodies were present in 5 patients with TA (15.6 %), whereas, they were only present in 3 (8.8 %) healthy controls (P = 0.397). Of the 5 patients with TA, who had positive ASCA Ig G and A antibodies, 2 (40 %) were active in terms of TA. Among 3 patients, in whom TA and IBD co-existed,

Table I. The mean serum levels and positivity rates of ASCA and ANCA antibodies among patients and controls

	Takayasu arteritis (n=32)	Crohn's disease (n=21)	Ulcerative Colitis (n=17)	Healthy controls (n= 34)	P
ASCA Ig G, U/ml	17.85±43.10	46.81±48.12	14.74±26.41	8.73±6.9	0.001*†‡
ASCA Ig A, U/ml	12.82±32	31.81±45.42	23.55±40.38	6.91±14.73	0.033‡
ASCA Ig G+, n (%)	4 (12.5%)	9 (42.9%)	2 (11.8%)	2 (5.9%)	0.003*†‡
ASCA Ig A+, n (%)	2 (6.3%)	6 (28.6%)	4 (23.5%)	1 (2.9%)	0.013‡
ASCA Ig G and A+, n (%)	5 (15.6%)	10 (47.6%)	6 (35.3%)	3 (8.8%)	0.004‡
p-ANCA +, n (%)	0	2 (10)	6 (35)	0	<0.001
c-ANCA +, n (%)	0	1	0	0	–
Anti-MPO, EU/ml	0.63±0.24	0.67±0.11	0.70±0.11	0.61±0.17	0.286
Anti-PR3, EU/ml	0.35±0.11	0.35±0.07	0.75±0.95	0.39±0.16	0.005§¶**

*: CD vs TA; †: CD vs UC; ‡: CD vs Healthy controls; §: UC vs TA; ¶: UC vs CD; **: UC vs Healthy controls

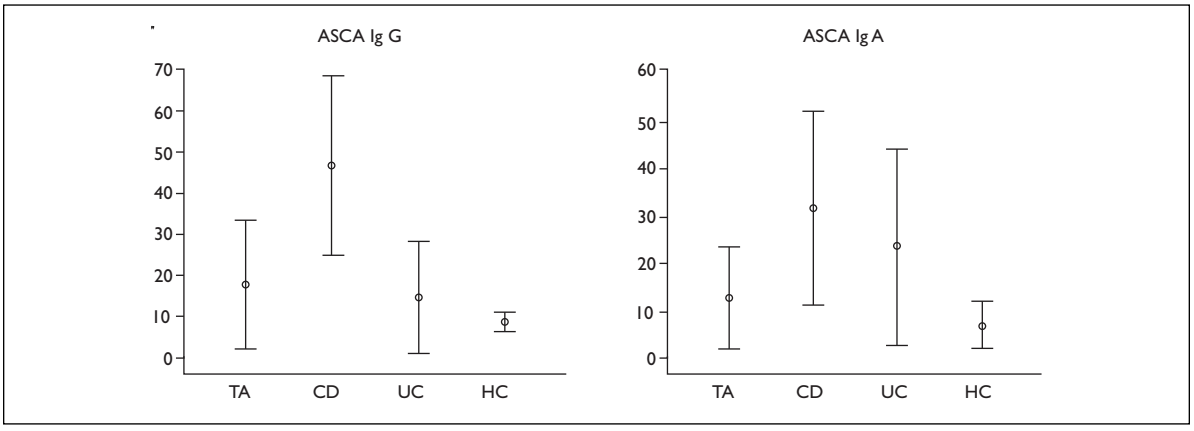

Figure 1. ASCA Ig G and A antibody levels within 95 % confidence intervals

TA: Takayasu arteritis (n =32), CD: Crohn's disease (n =21), UC: Ulcerative colitis (n = 17), Healthy controls (n = 34). Vertical bars represent means and 95% confidence intervals.

only one (one with CD) had positive ASCA Ig G and Ig A antibodies. Therefore, results remained the same, even after exclusion of patients, in whom TA and IBD co-existed. Serum levels of ASCA Ig G and A were increased only among patients with CD. ASCA Ig G antibodies were increased only among patients with CD, while ASCA Ig A antibodies were increased among both patients with CD and UC. Positivity for any ASCA (Ig G and Ig A) was increased significantly only among patients with CD.

P-ANCA antibodies were present only among patients with UC (35 %) and CD (10 %). Similarly, only patients with UC had significantly higher levels of anti-PR3. Mean anti-MPO levels did not differ between the study groups. C-ANCA antibodies were positive only in one patient with CD.

Discussion

In this controlled study, we showed that the frequency of ASCA positivity in TA was similar to that found in UC and healthy controls. ANCA antibodies were not found in patients with TA. As expected, patients with CD had significantly higher levels of ASCA, while patients with UC had significantly increased frequency for p-ANCA positivity.

We are not aware of any published data with regard to ASCA prevalence in TA. The lack of reliable serologic markers in TA often causes difficulties in assessment of disease activity. Few of them are consistently elevated in TA. Anti-endothelial cell antibodies, IL-6, IL- 18 and serum amyloid A may be listed as such examples[17-21]. On the other hand, ANCA, ANA, anti-DNA, and anti-Ro antibodies were often reported to be negative among patients with TA[21]. Similarly, surrogate markers of disease activity; such as soluble vascular adhesion molecules, von Willebrand factor antigen, factor VII, thrombomodulin, and angiotensin converting enzyme were either not increased or were not helpful in monitoring disease activity[22-23].

The percentage of ASCA positivity among our patients with CD and UC was in the previously reported range[12-15]. ASCA seems to be helpful in detecting patients with CD; nevertheless, its specificity for CD is low, since other diseases - such as intestinal Behçet's syndrome, autoimmune hepatitis and ankylosing spondylitis – also show moderately high ASCA positivity[24-27].

There were 3 patients with IBD (9 %) in our TA group. A French study reported also a frequency of 9 % (4/ 44) for TA-CD co-existence[2]. Similar granulomatous histopathology and inflammatory pathways may suggest common ethiopathogenesis[2,10-11]. More studies are needed to clarify this interesting association.

In conclusion, TA and IBD may co-exist. ASCA and ANCA antibodies do not seem to be useful in the diagnosis of patients with TA.

Correspondence to
Emire Seyahi,
Halaskargazi Cad. No: 209-211, Huzur Ap. D: 2,
Sisli, Istanbul, Turkey, 34360
Telephone: + 90-533-8184234 / Fax: +90-212-5890808
E-mail: eseyahi@yahoo.com

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CORTICAL STRUT ALLOGRAFTING IN RECONSTRUCTIVE ORTHOPAEDIC SURGERY

Fernando Judas*, Maria João Saavedra**, Alexandrina Ferreira Mendes***, Rui Dias****

Abstract

Many approaches are used in the repair of skeletal defects in reconstructive orthopaedic surgery, and bone grafting is involved in virtually every procedure. Autografting remains the gold standard for replacing bone loss. However, the limited amount of bone that can be harvested and the morbidity associated with that procedure are major constraints to the clinical use of autografts. In contrast, bone allografts can be used in any kind of surgery, whether involving minor defects or major bone loss. Cortical strut allografts unite to host bone through callus formation, restoring bone stock and can be used as an onlay biological plate. These struts can be made from hemicylinders of tibia being fixed to host bone by circumferential metallic cables or by screws.

The purpose of this study was to analyze the radiographic outcomes of twelve cryopreserved cortical onlay strut allografts, used in a group of nine patients, for revision hip arthroplasty of the femoral side, to stabilize femoral periprosthetic fractures, to reinforce poor cortical bone and to treat one atrophic femoral nonunion. The average follow-up period was 4.3 years (range, 1.6 to 9 years).

No fractures, nonunions or progressive resorption of the bone allografts were observed. All struts were incorporated to the native femur with minimal resorption, within the first year after surgery. There was no failure of any of the allograft reconstructions.

The results obtained show that cortical onlay strut allografts, either alone or in conjunction with metallic plate or cancellous bone allografts, are a valuable adjunct for reconstructive surgery of the hip and to treat atrophic femoral nonunion.

Keywords: Cortical Strut Allografts; Reconstructive Surgery of the Hip; Radiographic Results.

Introduction

The orthopaedic surgeon can avail himself of a wide spectrum of surgical techniques for the treatment of musculoskeletal diseases. These techniques involve, among others, the use of bone allografts and synthetic bone substitutes. Bone allografts have long been used as a natural substitute to repair skeletal defects. They offer an attractive alternative to bone autograft because their supply is unlimited, they allow structural restoration of the skeleton, and their surfaces support bone formation. Approximately 1 million musculoskeletal allografts were distributed for use in the United States in 2004[1-3].

Different kinds of bone allograft are available to the surgeon, and the clinical applications for each type are dictated by the structure and biochemical properties of the allograft. Cancellous bone allograft and demineralized bone matrix (DBM) are used to fill cavitary defects, facilitate spinal arthrodesis, and repair nonunions. They can also be used as a cancellous autograft extender in these situations. Cortical bone allografts are used for bridging structural defects in long bones, spinal arthrodesis, buttress or strut grafts in limb salvage procedures, revision arthroplasty, and periprosthetic fractures. Advantages include vast supply and selection of bones to fit a specific need, and matching to better serve a given function[2,4,5].

The major concern regarding the use of allograft materials is the possibility of viral disease transmission, including hepatitis C and HIV. However, the risk of disease transmission will be remote if the

*Orthopaedic Surgeon, Chief of Service, Professor of the Faculty of Medicine, University of Coimbra, Department of Orthopaedics, Hospitais da Universidade de Coimbra
**Specialist of Rheumatology, Department of Rheumatology and Bone Metabolic Diseases, Hospital de Santa Maria, Lisbon
***Professor of the Faculty of Pharmacy, University of Coimbra
****Orthopaedic Surgeon/ Graduated Assistant, Department of Orthopaedics, Hospitais da Universidade de Coimbra

protocols of the quality assurance are followed and the quarantine period is respected[6]. On the other hand, host response to bone allografts is still poorly understood. Experimental works have shown reduced immunogenicity when grafts were deep frozen and a marked decrease when freeze-dried. Clearly, the immune system plays an important role in bone graft incorporation, but the exact nature of this relationship is unknown[7].

Synthetic or engineered bone graft substitutes present the opportunity to provide materials that enhance bone regeneration without concerns of disease transmission or availability. However, these biomaterials are not appropriate for structural reconstruction because they are weak in terms of mechanical resistance. Synthetic graft substitutes consist of an osteoconductive matrix to which osteoinductive proteins and/or osteoprogenitor cells may be added[8].

Cortical strut allografts are diaphyseal segments of bone allograft. They are made from hemicylinders of tibia, femur or humerus or full circumferential segments of fibula[9,10]. In our institution, tibial struts are mainly used for revision arthroplasty of the hip on the femoral side, with the following indications: to restore bone stock for noncircumferential loss of cortical bone, to reinforce the repair of cortical windows, to bypass stress risers, and as a biological plate to stabilize periprosthetic fractures.

The clinical success of bone transplantation depends on many factors, some related to the host and others to the allograft and/or the donor, namely the site of transplantation, the quality of the bone bed from witch most of the revascularization arises, the host bed preparation, the preservation techniques used to store the allograft bone, systemic and local diseases, and mechanical stability of the host-graft interface. These factors are largely reliant on the surgeon and emphasize the importance of the surgical technique. The host bed must be prepared to leave bleeding bone. For optimal incorporation of the allograft, the host bed should either already contain enough pre-osteogenic or osteogenic cells, or must be enriched with a source of these cells, such as autograft or autogenous bone marrow[11,12].

A radiographic study was performed on twelve cryopreserved cortical strut allografts, which were used in reconstructive surgery of the hip and in proximal femoral fractures, with an average follow-up period of 4.3 years.

Materials and Methods

Nine patients were treated with cortical strut allografts: one man and eight women with an average age of sixty-one years at the time of surgery (range 38 to 74 years old). The etiology of the preoperative condition was as follows: periprosthetic proximal femoral fracture (n=4); aseptic loosening of total hip prosthesis – femoral component – (n=3); primary total hip prosthesis in congenital hip dislocation in adult (n=1) and atrophic nonunion of the femur (n=1).

Twelve cortical strut allografts were used to restore femoral bone stock, reinforce the repair of cortical windows, bypass stress risers, and as a biological plate to stabilize bone fractures and femoral osteotomy. X rays were taken at 6 weeks and 3, 6, and 12 months after surgery and yearly thereafter.

Cortical strut allografts of the tibia were processed (debridement, cleaning and treatment in 70% ethanol and 30% hydrogen peroxide solutions), aseptically preserved in liquid nitrogen, and further prepared according to the HUC Tissue Banking protocol (Figure 1) which is in agreement with internationally accepted standards[13,14].

The struts were fashioned to fit the femur. Excessive debridement of soft tissue was avoided to preserve the periosteal circulation, and care was taken to ensure adequate surface area between the graft and the cortical layer of the femur without interposition of soft tissue. The endosteal surface of the allograft strut is contoured to match the outer diameter of the host femur, and the interfaces are augmented with allograft cancellous bone graft. To apply the strut allografts, the vastus lateralis was dissected of the linea aspera of the femur and stripped it from the femur and retracted it anteriorly.

The struts were fixed by metallic cables or by the screws of the metallic plates, and most of them were placed laterally to restore noncircumferential bone loss (Figure 2). The average length of the struts was 125 mm (range, 90 to 180 mm). In five cases metallic plates were used in conjunction with one or two cortical struts. Four patients were treated with cortical onlay strut allografts alone. In the case of the atrophic nonunion, a metallic plate in conjunction with cortical strut and cancellous bone allograft were used. The cortical allograft was fixed to the host femur with the screws of the metallic plate.

Study of serial postoperative radiographs pro-

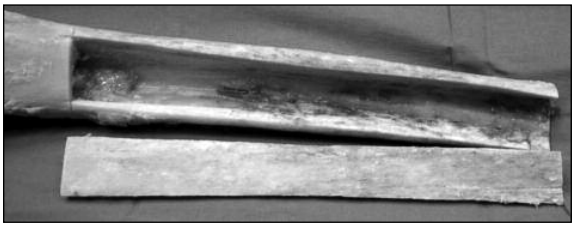

Figure 1. Preparation of a tibial cortical strut allografting.

duced a cortical strut categorization as follow: (1) round off, (2) scalloping; (3) partial bridging, (4) complete bridging, (5) cancellization, and (6) resorption. A strut could have none, one, or any number of these conditions. This information was analyzed to determine the average time to union, the percentage of struts that had united, and the allograft resorption. Each strut was treated individually, despite some patients having more than one strut. The radiographic criterion of union of strut graft to host bone was defined as trabecular bridging between any part of the graft and the host femur[9,15].

Results

The mean duration of follow-up was 4.3 years (range, 1.6 to 9 years). Union was achieved along the entire length of the cortical struts. All bone allografts were incorporated as demonstrated by radiography. A layer of new appositional bone was observed in the interface graft-host bone, in an average postoperative follow-up period of 8 months (range, 6 to 12 months). No cases of nonunion were noted. A consistent callus formation was observed at 8 months of the postoperative period in the clinical situation of nonunion of the femur. There was no failure of any of the allograft reconstructions.

Progressive resorption of the allografts was not observed. The minor localized resorption was usually seen at the sites of cables but no other resorption could be measured. There was a slight loss of length of strut grafts by the remodeling process at the ends of the allograft. No cases of strut fractures were noted.

In the case of the congenital hip dislocation, a dislocation of the total hip prosthesis and a superficial infection (cellulite) were noted and successfully treated with antibiotics without significant repercussion on the clinical and radiographic results.

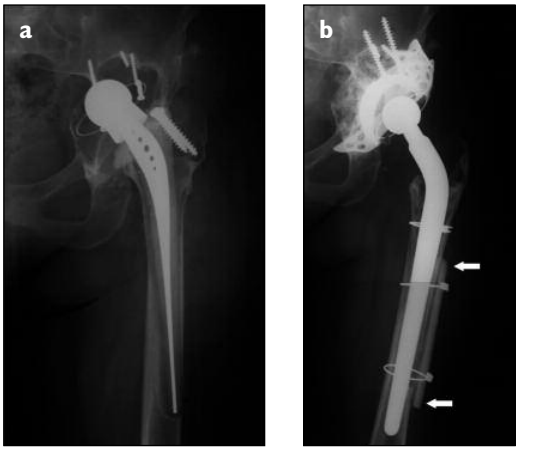

Figure 2 a) and b). Surgical treatment of an aseptic loosening of a total prosthesis using a cementless femoral stem revision and a cortical onlay strut allografting (arrows), with 5 years of follow-up. Reconstruction of the acetabulum with a metallic cage and particulate cancellous bone allograft.

Discussion

The treatment of periprosthetic femoral fractures, aseptic loosening of total hip prostheses, congenital hip dislocation in adults and nonunion of the femur remains challenging. These clinical situations can be effectively treated with metallic implants in conjunction with some forms of bone grafting. Segmental loss of cortical bone from the proximal femur is common in revision surgery. Bone allografting is becoming a common procedure in the orthopaedic operating room. Cortical onlay strut allografts are used as biological bone plate, with or without a metallic plate fixation, and they are an extremely versatile resource for the reconstructive surgery of osteoarticular prostheses replacement and also in orthopaedic trauma surgery. Appropriate placement of the graft is critical[8,16-19].

In our study twelve cryopreserved cortical onlay strut allografts were radiographically analyzed, demonstrating satisfactory mechanical results. In fact, evidence of strut-to-host bridging was seen in all of the patients, and no cases of progressive graft resorption or graft fracture were noted (Figure 3). There was no failure of any of the allograft reconstructions. They were consistently united to bone and restored bone stock. These grafts performed

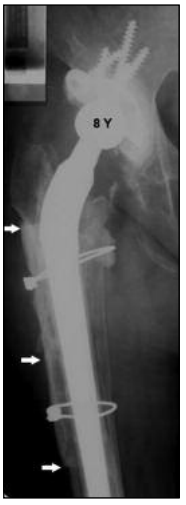

Figure 3. Incorporation of a cortical onlay strut allografting (arrows), with 8 years of follow-up, used to bridging a femoral structural defect in a revision hip arthroplasty.

better when stabilized with metallic cables in close proximity to vascularized host bone.

Cancellous bone allografts were placed between the ends of the struts and the host bone, because they promote the bone healing process and enhance strut-to-host bone union[17,20,21]. Strut union was seen within the first year after surgery. Studies of retrieved specimens have shown a close correlation between radiographic evidence of union and histologic observations[22]. Gradual callus formation occurs at the junction site, extending from the periosteal surface of the native bone to the outer surface of the cortical bone allograft. There is some degree of creeping substitution at the allograft host junction, but the bulk of the cortical strut remains dead but structurally intact. On the external surface of the allograft, mesenchymal proliferation from the adjacent host cells leads to a thin layer of bone formation that becomes incorporated into the allograft cortex. In fact, the initial host response to the allograft bone strut is rapid mobilization of mesenchymal tissue, initiating intense osteogenesis. The healing process of cortical allograft to host bone is prolonged, following the steps of hematoma formation, inflammatory process, resorption of graft bone and revascularization, and finally replacement of graft with new host bone. Nevertheless, the graft is never entirely replaced with new host bone[4,5].

Processed and preserved bone allografts are favoured in clinical practice. Processing involves the removal of antigenic cells and proteins; preservation techniques include deep-freezing or freeze-drying. Deep frozen cortical struts retain their mechanical properties and may be implanted after thawing, however, freeze-dried cortical struts are vulnerable in torsion and bending, because freeze-drying may alter the mechanical properties of the bone[23-25]. We therefore used struts stored in liquid nitrogen (cryopreserved) in order to achieve immediate structural support.

In the case of treatment of the atrophic nonunion two very important requisites for successful bone formation were achieved: vascularity and mechanical stability. These factors are largely surgeon-dependent and emphasise the importance of the surgical approach and the preparation of the site to be grafted.

Conclusion

Cryopreserved cortical onlay strut allografts act as biological bone plates, serving both a mechanical and a biological function. The results obtained in the present study show that the use of cortical struts, either alone or in conjunction with a metallic plate or with cancellous bone allografts, is a useful adjunct for revision hip arthroplasty of the femoral side, stabilization of femoral periprosthetic fractures, reinforcement of poor cortical bone and for the treatment of femoral nonunion.

Correspondence to
Fernando Judas
Orthopedics Department of Coimbra University Hospitals (HUC)
Praceta Prof. Mota Pinto, Bloco de Celas
3000 Coimbra, Portugal.
E-mail: fernandojudas@gmail.com

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ANTI-β_2-GLYCOPROTEIN I ANTIBODIES ARE HIGHLY PREVALENT IN A LARGE NUMBER OF BRAZILIAN LEPROSY PATIENTS

Sandra L. E. Ribeiro[*,**], Helena L.A. Pereira[*,**], Neusa P. Silva[**], Alexandre W.S. Souza[**], Emilia I. Sato[**]

Abstract

Objectives: To determine the prevalence of anticardiolipin (aCL) and anti-β_2-glycoprotein I (anti-β_2GPI) antibodies in leprosy patients, during and after specific multidrug therapy (MDT), and to evaluate a possible association between these antibodies and some clinical characteristics of leprosy, including clinical forms, reactional episodes and treatment.

Methods: The study included 158 leprosy patients, 129 gender-and-age matched healthy individuals, and 38 women with primary antiphospholipid syndrome (APS). Clinical and demographic characteristic of leprosy patients were collected, and serum samples, obtained from all participants, were kept frozen at - 20°C. Antibodies were measured either by an in house-developed ELISA (aCL) or by a commercial ELISA (anti-β_2GPI**).**

Results and Conclusions: Increased levels of aCL and anti-β_2GPI antibodies were found in leprosy patients and in the APS group, however, in contrast to APS, the predominant isotype in leprosy was IgM. The frequency of aCL and anti-β_2GPI antibodies was significantly higher in leprosy patients than in healthy individuals (15.8% vs. 3.1%; p<0.01; 46.2% vs. 9.4%, p<0.01**),** respectively. The lepromatous form predominated among aCL positive leprosy patients (p<0.01). There was no difference in aCL and anti-β_2GPI positivity between leprosy patients taking MDT and those completed MDT as cured. Furthermore the duration of discharged period (period between discharge from MDT and the realization of the study) had no effect on anti-β_2GPI positivity, and a slight increase in aCL positivity was observed in patients with longer follow up periods (p=0.04), suggesting that the presence of antiphospholipid antibodies (aPL) was not a transient phenomenon. Although aPL in leprosy were frequent and β_2GPI-dependent as those found in APS, IgM was the predominant isotype, and there was no association with thrombosis or other APS manifestations.

Keywords: Leprosy; Anti-β_2-glycoprotein I antibodies; Antiphospholipid antibodies; Anticardiolipin antibodies; Antiphospholipid syndrome.

Introduction

Antiphospholipid antibodies (aPL) are a heterogeneous group of autoantibodies, which have been reported in many autoimmune diseases, mainly in systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome (APS), in association with vascular thrombosis, pregnancy morbidity, and a number of other less commonly found manifestations[1]. aPL have also been reported in the context of several infections such as leprosy, tuberculosis, malaria, syphilis, hepatitis C virus (HCV), human immunodeficiency virus (HIV), leptospirosis, and B19 parvovirus infections[2-5]. Interestingly, the presence of aPL in infectious diseases is not usually associated with the clinical complications attributed to APS[6], and they are often transient and may disappear after treatment[7].

Anticardiolipin (aCL) antibodies constitute the main group of aPL studied in primary and secondary APS and other autoimmune and infectious diseases. In the last two decades, several studies have indicated that β_2-glycoprotein I, a phospholipid binding protein, besides its role as cofactor for aCL antibodies detection[8-10], may be itself an antigen, eliciting pathogenic anti-β_2-glycoprotein I antibodies in APS[11].

Although the aCL antibodies detected in infectious disorders were initially reported to be main-

*Rheumatology Division of Universidade Federal do Amazonas, Brazil
**Rheumatology Division of Universidade Federal de São Paulo, Brazil

ly β_2GPI-independent, β_2GPI-dependent aCL, and antibodies against the proteins β_2GPI and prothrombin have also been reported in some infections[12,13].

Leprosy is an infectious disease caused by *Mycobacterium leprae* affecting primarily the peripheral nervous system, and secondarily involving skin and other tissues. The clinical spectrum is characterized by two stable poles forms of disease. At one pole, tuberculoid leprosy, the host is able to keep the disease under control due to an efficient T-cell--mediated immune response; while at opposite pole, lepromatous leprosy, cell-mediated immunity is inefficient leading to excessive bacillary multiplication and dissemination. Between the two stable poles are unstable forms of leprosy, named borderline that may combine characteristics of the polar forms. A broad spectrum of clinical lesions and a high frequency of autoantibodies, especially aCL antibodies are seen in leprosy[14-16]. Despite the disease chronicity and the aCL persistence[16], aPL-related thromboembolic complications have rarely been reported in leprosy[17,18].

Although aCL have been reported in 20-98% of leprosy patients with different clinical forms, it seems to be more prevalent in the lepromatous form[3,4,15,16,19-24]. The prevalence of anti-β2-glycoprotein I antibodies (anti-β2GPI) is highly variable, ranging from 2.9 to 89%[3,16,21,23,24].

The objectives of this study were to determine the prevalence of aCL and anti-β_2GPI antibodies in a large number of Amazon leprosy patients taking multidrug therapy (MDT) and in completed MDT as cured, and to evaluate a possible association between these antibodies and clinical forms of disease, and reactional episodes.

Patients and Methods

The study group included 158 leprosy patients (113 males and 45 females, mean age of 39.9±15.2 years) followed up at the Tropical Dermatology and Venereal Clinic of Alfredo da Matta Foundation (Manaus, Amazon, Brazil) from July 2004 to October 2006. Leprosy diagnosis was established according to Ridley and Jopling classification criteria[25]. To determine the presence of antiphospholipid antibodies, 20 mL of peripheral venous blood were collected from all participants. The leprosy patients present with the following clinical and therapeutic characteristics: Fifty-six cases had lepromatous, 35 borderline lepromatous, 25 borderline, 32 tuberculoid borderline, 6 tuberculoid, and 4 indeterminate form. Reactional episodes as erythema nodosum lepromatosum (ENL), reversal reaction (RR) and neuritis were present in 58/158 (36.7%) of the patients, during the study. The criterion for a diagnosis of ENL was the presence of tender skin nodules. This could be accompanied by fever and other systemic symptoms such as joint pain, bone tenderness, neuritis, edema, malaise, anorexia, and/or lymphadenopathy; for the reversal reaction, acute inflammation, as pain, erithema, infiltration and edema of pre existing lesions sometimes accompanied of new lesions and neuritis. Sixty four patients were taking MDT and 94 had already completed MDT. In those patients who completed MDT(period cured), the period between discharge and the realization of the study ranged from 1 to 115 months (median of 31 months). All were submitted to complete physical exam and a questionnaire and none of them had any event suggestive of APS (vascular thrombosis, pregnancy morbidity or thrombocytopenia) or any concomitant rheumatic disease.

The control group was composed by 129 healthy individuals, gender-and-age matched to the leprosy group (mean age of 40.9±14.1 years), living in the same geographic region. The APS group was constituted by 38 women with primary APS (mean age of 40.2±13.8 years)[26] , who were recruited from a outpatient clinic of rheumatology, Universidade Federal de São Paulo (UNIFESP), Brazil, meeting the Sapporo criteria[27]. The most frequent manifestations of these patients were pregnancy morbidity (44.7%), lower limb venous thrombosis (39.4%) and stroke (28.9%). Many of them had more than one manifestation. The age distribution of the APS group did not differ from the leprosy and control groups (p=0.649).

Blood samples were collected from all participants and kept at -20°C, until analyzed at the Rheumatology Division of Universidade Federal de São Paulo. The study was approved by both Institutional Review Boards, and all participants signed the informed consent form.

Anticardiolipin antibodies (aCL)

IgG and IgM aCL antibodies were tested in all serum samples with an in house-developed ELISA. Normal ranges for aCL antibodies in Brazilian po-

pulation were previously determined in a sample of 200 healthy blood donors and the 95th percentile cutoff points, established with the use of international APL calibrators (LAP-GM-200 calibrators, Louisvulle APL Diagnostics, Inc, GA, USA) were 20 GPL and 10 MPL, respectively. One GPL or MPL unit is defined as the cardiolipin binding activity of 1 g/mL of an affinity purified IgG or IgM aCL preparation from a standard serum.

Anti-β_2-glycoprotein I antibodies

Serum IgG and IgM anti-β_2GPI antibodies were tested by a commercial ELISA (The Binding Site, Birmingham, UK) according to the manufacturer's instructions. The cutoff values according to the kit were 10 U/mL for IgM and 20 U/mL for IgG. Due to our limitations, only 106 control sera were included in this test.

Statistical analysis

Statistical analysis was performed with the SPSS 15.0.1 software (Chicago, USA). Kruskal-Wallis test was used for age distribution comparison between groups. Chi-square test was used to compare gender distribution, and aCL and anti-β_2GPI antibody frequencies between groups. Binomial test was used to compare the proportion of clinical forms among aCL and anti-β_2GPI antibodies positive leprosy patients. Student's t-test was used to compare duration of completed MDT (cured period) and aPL positivity between groups. P values < 0.05 were considered statistically significant.

Results

In the APS group aCL antibodies were positive in 34/38 (89.5%) patients, and GPL or MPL titers >40 U/mL were found in 26/34 (76.5%) of the positive sera. In the leprosy group, aCL antibodies were positive in 25/158 (15.8%) patients, and GPL or MPL titers >40 U/mL were found in 20/25 (80%) of the positive sera. There was no difference in aCL positivity between leprosy patients in completed MDT and those taking MDT (p=0.41). In the control group, aCL antibodies were found in only 4/129 (3.1%) individuals, none of them with GPL or MPL titers higher than 40 U/mL. Anticardiolipin antibodies were more frequent in leprosy patients than in healthy controls (p <0.01), but less frequent than in APS (p <0.01). Mean aCL titers in leprosy were 57 GPL U/mL and 56 MPL U/mL.

Among the 25 aCL positive leprosy sera, IgM isotype was more frequent than IgG (88% vs 16%; p<0.01). In contrast, in the APS group, IgG isotype was more frequent than IgM (91.2% vs 44.1%, respectively; p<0.01). All the four positive healthy controls had IgM aCL antibodies (Table I).

The clinical forms of disease were not equally distributed between aCL positive and negative leprosy patients (p<0.01,) as shown on Table 2. Among the aCL positive leprosy patients, the lepromatous form was found in a higher percentage (72%) than the other forms (p<0.01), while among aCL negative patients there was no predominant form. There was no association between the presence of reactional episodes and aCL antibodies (p=0.41). However, among the 58 leprosy patients with reactional episodes, the distribution of reaction type was different between aCL positive and negative patients (p=0.03). ENL was the most prevalent reaction type in both aCL positive and aCL negative patients with reactional episodes, however, all the aCL positive patients presented ENL type (100%) while in aCL negative, ENL was found in only 57.4% (p=0.02).

Anti-β_2GPI antibodies were found in 9/38 (23.7%) patients of the APS group, and titers >40

Table I. Frequency of aCL and anti-β2GPI antibodies according to isotype distribution in leprosy patients, healthy controls, and APS group

	Leprosy patients (n=158)		Healthy controls (n=129)	(n=106)	Primary APS patients (n=38)	
Isotype	**aCL**	**anti-β2GPI**	**aCL**	**anti-β2GPI**	**aCL**	**anti-β2GPI**
IgG alone	3	1	0	1	18	3
IgM alone	21	64	4	9	3	2
IgG + IgM	1	8	0	0	13	4
Total	25 (15.8%)	73 (46.2%)	4 (3.1%)	10 (9.4%)	34 (89.5%)	9 (23.6%)

Table II. Distribution of anticardiolipin antibody in leprosy patients accordingly to Ridley & Jopling classification

	Classification													
	I		TT		BT		BB		BL		LL		TOTAL	
aCL	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Negative	4	3,0	6	4,5	31	23,3	22	16,5	32	24,1	38	28,6	133	100
Positive	0	0	0	0	1	4	3	12	3	12	18	72	25	100
TOTAL	4	2,5	6	3,8	32	20,3	25	15,8	35	22,2	56	35,4	158	100

aCL=anticardiolipin antibodies; BB=borderline; BV=borderline lepromatous; BT=borderline tubercuoid; I=indeterminated; TT=tuberculoid; VV= lepromatous

U/mL were found in 66.7% of them. In the leprosy group, anti-β_2-GP1 antibodies were found in 73/158 (46.2%) patients, and titers >40 U/mL were found in 26 (35.6%) of them. There was no difference in anti-β_2GPI positivity between leprosy patients who completed MDT and those taking MDT (p=0.07). In the control group, anti-β_2-GPI antibodies were found in only 10/106 (9.4%) individuals, and none of them had titers >40 U/mL. Anti-β_2-GPI antibodies were more frequent in leprosy patients than in healthy controls (p<0.01) or APS (p=0.01). The mean titers of anti-β_2-GPI in leprosy patients were 112 U/mL for IgG and 94 U/mL for IgM antibodies.

Among the 73 anti-β_2GPI positive leprosy sera, IgM isotype was more frequent than IgG (97.3% vs. 12.3%, p<0.01). In the APS group, both isotypes were equally frequent. Among the anti-β_2GPI positive healthy controls, IgM isotype was also more frequent than IgG (90% vs. 10%, respectively; p <0.01) (Table I).

The distribution of the clinical forms of disease according the Ridley Jopling classification was similar in anti-β_2GPI positive and negative leprosy patients (p=0.09), Table III. Anti-β_2GPI positivity was also similar in patients with and without reactional episodes (51.7% vs. 43%, respectively, p=0.29), There was no difference in the proportions of the reaction types between anti-β_2GPI positive and negative patients (p=0.18).

Among the 158 leprosy patients, 77 (48.7%) were positive for at least one aPL antibody (Figure 1).

Interestingly, as depicted in Table II, among the

Table III. Distribution of anti-β_2GPI in leprosy patients accordingly to Ridley & Jopling classification

	Classification													
anti-	I		TT		BT		BB		BL		LL		TOTAL	
β_2GPI	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Negative	3	3,5	5	5,9	21	24,7	14	16,5	20	23,5	22	25,9	85	100
Positive	1	1,4	1	1,4	11	15,1	11	15,1	15	20,5	34	46,6	73	100
TOTAL	4	2,5	6	3,8	32	20,3	25	15,8	35	22,2	56	34,4	158	100

BB=borderline; BL=borderline lepromatous; BT=borderline tubercuoóid; I=indeterminated; TT=tuberculoid

Table IV. Prevalence of aCL and anti-ß2GPI antibodies among leprosy patients

		aCL		
		Positive	Negative	TOTAL
anti-β_2GPI	Positive	21	52	73
	Negative	4	81	85
TOTAL		25	133	158

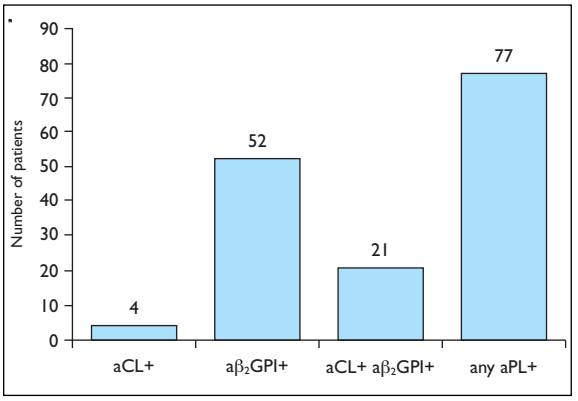

Figure 1. Frequency of the diverse aPL antibodies in leprosy patients

25 aCL positive leprosy patients, 21 (95%) were also positive for anti-β_2GP1 antibodies ($p<0.01$).

Among the leprosy population under study, 94 patients had completed MDT in the period of sera collection to test the antibodies aFL. This period ranged from 1 to 115 months (median 31.3 months) and had no influence in anti-β_2GPI positivity ($p=0.20$). A slight increase in aCL positivity was observed in patients with longer time completed MDT ($p=0.04$).

Discussion

Antiphospholipid antibodies have been widely studied in autoimmune diseases, and their association with thrombotic events as well as pregnancy morbidity is well known. However, aPL related to some viral or bacterial infections are not usually associated with the clinical manifestations attributed to APS. This lack of pathogenicity was first attributed to β_2GPI independency, either as a cofactor or as an autoantigen[7-10].

Nevertheless, the distinction between autoimmune (APS associated), and infectious (β_2GPI independent) aPL has been recently challenged, with some studies reporting the occurrence of antibodies to β_2GPI in patients with viral or bacterial infections[3,23,28].

In infectious diseases, aPL could be induced by disturbances of cellular and humoral immune regulation, during the immune response. Alternatively, this induction could be attributed to the exposure of phospholipid antigens by tissue damage in the course of infection. One current hypothesis is that infections may be a «trigger» for the generation of pathogenic aPL in genetically predisposed individuals[4,29,30]. In this case, bacterial or viral peptides with homology to the β_2GPI molecule would be presented to T lymphocytes, which will stimulate B lymphocytes to produce antibodies against the cross-reacting heterologous sequence[30].

Anticardiolipin and anti-β_2GPI antibodies have been reported in leprosy patients, mainly in association with lepromatous leprosy, and usually without APS-related clinical manifestations[3,4,15,16,19-24].

In our study, the positivity of cofactor-dependent aCL antibodies was lower than that reported in other studies, although there is a large variability in the literature[3,4,16,20-24]. This variability could be attributed to methodological differences including the cutoff value established for different populations, variation in the reagents used in home-based assays, calibration aspects, and other factors[31].

Our study selected a large cohort of leprosy patients representing the spectrum and clinical features of the disease. The frequency of aCL antibodies in our leprosy patients was higher in the lepromatous form, in agreement with several authors[3,15,16,20,22,23], and the presence of aCL antibodies, even in high titers, was not associated with reactional episodes. However, we observed that all patients with a reactional episode who were positive for aCL presented erythema nodosum leprosy. Several studies addressed the isotype prevalence of aPL in the sera from leprosy patients with varied results. We observed a predominance of the IgM isotype in aCL antibodies, corroborating the data of some authors[3], however, other studies found a higher prevalence of the IgG isotype[15,16,20], and one study, in black South African patients, found a higher prevalence of the IgA isotype[4].

Antibodies with specificity towards β_2GPI have been suggested to be a better marker of APS than aCL alone [32,34] and in 3-10% of APS patients, anti-β_2GPI antibodies may be the only positive test[35-37]. According to these evidences, recently, the presence of anti-β_2GPI antibodies regardless of isotype was included as part of the modified Sapporo classification criteria for APS[27].

According to the literature, anti-β_2GPI antibodies are less frequently found in infectious diseases than in APS[12,13,32,34]. Furthermore, most APS studies have shown a relationship between IgG isotype anti-β_2GPI antibodies and venous thrombosis and

lack of association with the IgM isotype[12,32,34,38,39]. However, associations between IgM anti-β_2GPI antibodies and arterial thrombosis, fetal loss and thrombocytopenia have also been reported in APS[39-43].

In the literature, the prevalence of anti-β_2GPI antibodies in leprosy ranges from 2.9% up to 89%[4,21]. We found anti-β_2GPI antibodies in 46.2% of leprosy patients, some of which displaying high titers. In our leprosy population, IgM was the most frequent isotype of anti-β_2GPI antibodies, in agreement with other studies[3,4]. However, another study, including 177 leprosy patients, showed no favorite isotype[23].

In our study, 20.5% of the anti-β_2GPI positive leprosy patients had antibody titers higher than 100 U/mL. According to the literature, high titers of anti-β_2GPI antibodies are associated with risk of thrombosis, but the definition of the boundaries for medium and high titers is a difficult task[27].

We found a higher prevalence of anti-β_2GPI (46.2%) than aCL (15.8%) antibodies in leprosy, corroborating the results of Loizou et al (2003)[4]. However, there are other studies reporting a higher prevalence of aCL than of anti-β_2GPI antibodies in leprosy[16,21].

Anticardiolipin and anti-β_2GPI antibodies were simultaneously found in 13.3% of our leprosy patients, and in 70% of those, antibody titers for both specificities were higher than 40 U/mL. However, in agreement with the literature, we found no association between the presence of aCL and/or anti-β_2GPI antibodies and thrombotic events[3,4,23,24].

In APS, thrombotic events are usually associated with the IgG isotype of aCL and anti-β_2GPI antibodies. In our study, IgM was the most prevalent isotype in leprosy whereas IgG was more frequent in primary APS. It has been suggested that IgG isotype may be an important factor in determining clinical complications of aCL.[44] There is also an interesting paper suggesting that IgG anti-β_2GPI antibodies specifically directed against a positively charged epitope on the first domain of β_2GPI correlate with thrombosis[45].

In addition, it has been reported that aPL cause endothelial cell activation and blood coagulation by binding to β_2GPI on the surface of endothelial cells[46,47]. Martinuzzo et al, demonstrated that sera from leprosy patients APL positive showed platelet and endothelial cell activation to the same extend that patients with APS, however they not show a procoagulant state as demonstred by normal levels of markers of blood coagulation[48].

We did not find association between treatment and positivity for aCL or anti-β_2GPI antibodies, and the increase in those who completed MDT as cured was not associated with a decrease in aPL positivity, suggesting that aPL may not be as transient as in other infections. Arvieux et al, 2002 also reported persistence of anti-β_2GPI antibodies in six leprosy patients followed for over two years.

There are a few case reports referring aPL and thrombotic phenomenon in patients with leprosy[17,18,49]. However, this may be just a coincidence since the pathological significance of these antibodies in leprosy is not very clear.

In conclusion, aCL and β_2GPI-dependent in leprosy are as frequent as those found in APS patients, however leprosy patients do not present clinical manifestations of APS. In leprosy-related aPL, IgM was the prevalent isotype whereas in APS, IgG was the main isotype. It is possible that the presence of aPL in leprosy may be simply another marker of autoimmunity. In contrast to previous suggestions, we found no evidence to support the presence of aPL as a transient phenomenon. It would be interesting to perform a longitudinal follow-up to evaluate the persistence of these antibodies, and to compare the fine specificity of APS and leprosy-associated anti-β_2GPI antibodies.

Correspondence to
Sandra Lúcia Euzébio Ribeiro
Avenida Apurinã 04, Bairro Praça 14,
Manaus – Amazonas State,
BRAZIL 69020-170
Tel: (0XX92) 3633-4977,
E-mail: sandraeuzebio@vivax.com.br

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2º Simpósio SPR – Artrite e Osso

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EFEITOS IMEDIATOS SOBRE A ESTATURA DA TRACÇÃO MECÂNICA LOMBAR COM DIFERENTES INTENSIDADES

Sofia Santos*, Fernando Ribeiro*,**

Resumo

Objectivos: comparar a eficácia da tracção vertebral mecânica da região lombar realizada com baixa (10% do peso corporal) e elevada (50% do peso corporal) força de tracção na separação dos corpos vertebrais *in vivo* usando variações na estatura como critério. Adicionalmente, pretendeu-se determinar o espaço temporal após o qual o efeito da tracção na estatura é revertido.
Material e Métodos: Trinta indivíduos aparentemente saudáveis (idade: 20,9 ± 1,7 anos), 14 do sexo masculino e 16 do sexo feminino, foram submetidos a dois protocolos de 15 minutos de tracção contínua (com intensidade de 10% e 50% do peso corporal), em sessões distintas com uma semana de intervalo, sendo a ordem de aplicação determinada aleatoriamente. A avaliação da estatura foi efectuada antes e imediatamente após os protocolos e a cada cinco minutos após a sua aplicação até perfazer 30 minutos.
Resultados: Imediatamente após a aplicação da tracção, ambos os protocolos promoveram um aumento significativo da estatura, contudo a magnitude desse aumento foi significativamente superior no protocolo de 50% do peso corporal (0,567 ± 0,049 vs. 0,298 ± 0,041 cm, p<0,001). No protocolo com força de tracção de 50% do peso corporal o aumento da estatura foi mantido até dez minutos após o término da tracção, enquanto que no protocolo com 10% do peso corporal o efeito da tracção na estatura desapareceu após cinco minutos.
Conclusões: A tracção vertebral mecânica da região lombar executada com uma força de 50% do peso corporal durante 15 minutos de forma contínua induz um aumento na estatura significativamente superior e mais duradouro no tempo do que o aumento promovido por uma força de 10% do peso corporal.

Palavras-chave: Tracção vertebral Mecânica; Estatura; Intensidade; Peso Corporal; Separação Vertebral.

Abstract

Purposes: to compare the efficacy of mechanical lumbar traction with low (10% of body weight) and high traction force (50% of body weight) on the separation of the vertebrae *in vivo* using stature variations as criterion. Additionally, we aimed to determine the time that the effects of traction last.
Material and Methods: Thirty apparently healthy subjects (age: 20.9 ± 1.7 years old), 14 male and 16 female, were submitted to two protocols of 15 minutes of continuous traction (with intensity of 10% and 50% of body weight), in two sessions one week apart. The protocol order was determined randomly. Stature was assessed before and immediately after the traction and every five minutes for 30 minutes after traction ceased.
Results: Immediately after the traction both protocols induced a significant increase in stature, however the magnitude of the increase was significantly superior in the traction with 50% of body weight (0.567 ± 0.049 vs. 0.298 ± 0.041 cm, p<0.001). After the traction with 50% of body weight the increase in the stature was maintained until ten minutes after the end of the traction, while after the traction with 10% of body weight the effects on stature disappeared after five minutes.
Conclusions: The mechanical vertebral traction of the lumbar region performed continuously with 50% of body weight during 15 minutes induced an increase in stature superior and longer in time than that observed with a traction force of 10% of body weight.

*Instituto Politécnico de Saúde do Norte, Departamento de Fisioterapia
**Universidade do Porto, Faculdade de Desporto, Centro de Investigação em Actividade Física, Saúde e Lazer

Keywords: Mechanical Vertebral Traction; Stature; Intensity; Body Weight; Vertebrae Separation.

Introdução

A tracção vertebral refere-se ao uso de qualquer método de separação das vértebras usando uma força aplicada directamente ao longo do eixo cefalo-caudado da coluna vertebral[1]. É um procedimento terapêutico usado para aumentar o espaço intervertebral ou para reduzir a protusão discal[2], com o intuito de promover a normalização de défices neurológicos, o alívio da dor e de melhorar a mobilidade articular[3]. Vários mecanismos de acção têm sido propostos para explicar os benefícios clínicos da tracção vertebral, nomeadamente na dor lombar crónica, sendo que presentemente se aceita que os efeitos da tracção surgem como uma combinação de efeitos biomecânicos e neurofisiológicos[1,3,4]. É sugerido que o alongamento da coluna vertebral promovido pela tracção, ao diminuir a lordose lombar e ao aumentar o espaço intervertebral, inibe os impulsos nociceptivos, melhora a mobilidade, diminui o *stress* mecânico e a pressão intradiscal, reduz a protusão discal, o espasmo muscular e/ou a compressão da raiz nervosa, e liberta possíveis aderências nas articulações zigoapofisárias e anel fibroso[2-4].

As formas mais comuns de aplicação de tracção são a tracção mecânica ou motorizada, tracção manual e auto-tracção. A tracção manual, aplicada pelo Fisioterapeuta usando o peso do seu corpo, e a auto-tracção, aplicada pelo paciente, são difíceis de manter durante um período específico de tempo devido à fadiga ou à intolerância à força ou posição e não permitem um controlo rigoroso da intensidade da força de tracção que é aplicada[2,5]. De facto, apenas a tracção mecânica permite estandardizar a força de tracção[4]. Este aspecto é de extrema importância uma vez que a intensidade da força é um parâmetro fundamental para a eficácia da tracção; adicionalmente, o seu valor deve ter em conta as resistências que podem levar à dispersão da força de tracção, tais como a tensão dos músculos lombares, o estiramento da pele, a pressão abdominal, e a fricção sobre a marquesa de tracção[4].

Apesar de ser um parâmetro crucial da tracção vertebral, não existe consenso na literatura relativamente à intensidade da força a aplicar. Na literatura são apresentadas duas formas de aplicação de tracção quanto à intensidade da força: doses baixas (<20% do peso corporal) e doses elevadas (geralmente entre 30-50% do peso corporal)[1]. Contudo, alguns autores[2,6,7] defendem que forças inferiores a 20% do peso corporal constituem-se como placebo, enquanto que outros[3,5] indicam que com forças com essa intensidade se consegue afastamento dos corpos vertebrais promovendo assim efeitos positivos.

A compreensão da intensidade da força necessária para promover o afastamento dos corpos vertebrais com consequente aumento do espaço intervertebral é fundamental para melhorar os protocolos de tratamento em pacientes com dor lombar crónica. Desta forma, o objectivo do presente estudo foi comparar a eficácia da tracção vertebral mecânica lombar realizada com baixa (10% do peso corporal) e elevada (50% do peso corporal) força de tracção na separação dos corpos vertebrais *in vivo* usando variações na estatura como critério. Adicionalmente, pretendeu-se determinar o espaço temporal após o qual o efeito da tracção na estatura é revertido.

Metodologia

Amostra

A amostra foi constituída por 30 estudantes do ensino superior, 14 do sexo masculino e 16 do sexo feminino, seleccionados por conveniência. Para ser incluído no estudo os indivíduos deveriam ter idade igual ou superior a 18 anos e não ter nenhum dos seguintes critérios de exclusão: dor nos movimentos activos da coluna lombar, osteoporose, história de fractura ou cirurgia à coluna vertebral, alterações morfológicas da coluna lombar, gravidez, doença sistémica com afecção do sistema músculo-esquelético, obesidade mórbida, neoplasia abdominal ou pélvica e aneurisma da aorta. Todos os participantes no estudo deram o seu consentimento informado e todos os procedimentos foram efectuados de acordo com a declaração de Helsínquia.

Procedimentos

Todos os indivíduos foram submetidos a dois protocolos de tracção vertebral mecânica de intensidade diferente (10% e 50% do peso corporal), em sessões distintas com uma semana de intervalo, sendo a ordem de aplicação determinada aleatoriamente. Antes da aplicação dos protocolos de

tracção foram esclarecidas todas as dúvidas dos participantes sobre os procedimentos inerentes ao estudo. Todos os procedimentos foram conduzidos pelo mesmo examinador. A variável dependente do presente estudo, a estatura dos indivíduos, foi avaliada antes, imediatamente após e a cada cinco minutos durante os 30 minutos seguintes à aplicação dos protocolos de tracção.

AVALIAÇÃO DA ESTATURA

A avaliação da estatura foi efectuada através de um estadiómetro (SECA, Birmingham, UK), imediatamente antes e imediatamente após a tracção, e a cada cinco minutos até perfazer 30 minutos após a tracção. Nos 30 minutos subjacentes à aplicação da tracção vertebral os indivíduos permaneceram sentados de forma a estandardizar a postura assumida por todos os participantes no estudo.

Para avaliar a estatura os indivíduos permaneceram na base do estadiómetro com os joelhos em extensão, o peso distribuído por ambas os membros inferiores e com os braços ao longo do corpo. Os indivíduos mantiveram a cabeça alinhada com o resto do corpo, e tiveram de evitar qualquer movimento durante a medição. Para garantir a estandardização do processo de avaliação da estatura foi utilizado um pequeno nível colocado no braço do estadiómetro para garantir que este se encontrava sempre na mesma posição. Adicionalmente, foi colocado um colar cervical nos indivíduos para limitar o movimento da coluna cervical (Figura 1).

Esta metodologia de avaliação foi alvo de estudo da fiabilidade Teste-Reteste. Desta forma, utilizando um grupo de dez indivíduos obedecendo aos critérios de inclusão/exclusão previamente definidos avaliou-se a estatura em dois momentos com uma semana de intervalo para determinar o coeficiente de correlação intraclasse (ICC). Os resultados demonstraram uma fiabilidade Teste-Reteste excelente com ICC=0.999, com intervalo de confiança entre 0.998 e 1.00.

PROTOCOLOS DE TRACÇÃO VERTEBRAL MECÂNICA DA COLUNA LOMBAR

Após a avaliação inicial da estatura procedeu-se à aplicação da tracção vertebral. A posição assumida durante a tracção foi a posição de decúbito dorsal, com a cabeça em posição neutra, com a pélvis em retroversão, a articulação coxo-femoral a 90º de flexão e as pernas suportadas num plano elevado. Foi colocado um cinto a estabilizar o tórax e outro na pélvis para efectuar a tracção (Figura 2). Esta posição permite manter a coxo-femoral num ângulo de 90º de flexão durante a tracção o que produz uma rectificação da coluna lombar facilitando desta forma a separação vertebral[8,9]. O ângulo da articulação coxo-femoral foi confirmado usando um goniómetro universal.

A duração da aplicação da tracção foi de 15 minutos. Os indivíduos poderiam interromper a tracção se assim o desejassem, tendo para isso um comando ao seu alcance.

Esta metodologia de aplicação de tracção vertebral foi alvo de estudo da fiabilidade Teste-Reteste. Desta forma, utilizando um grupo de cinco indivíduos obedecendo aos critérios de inclusão/exclusão previamente definidos avaliou-se o efeito da tracção vertebral mecânica com 10% do peso corporal na estatura em dois momentos com

Figura 1. Posição estandardizada de avaliação da estatura

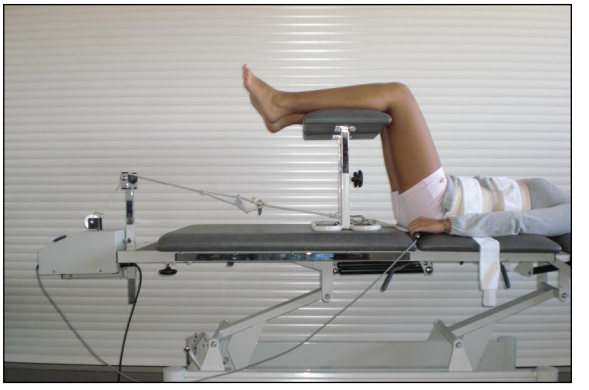

Figura 2 Posição de execução da tracção vertebral

Tabela I. Efeito dos protocolos de tracção vertebral mecânica na estatura

	Protocolo 50% do peso corporal		Protocolo 10% do peso corporal	
Momento de Avaliação	**Estatura (cm)**	**Valor de prova (diferença para antes)**	**Estatura (cm)**	**Valor de prova (diferença para antes)**
Antes	166,25 ± 7,22	____	166,29 ± 7,18	____
Após	166,81 ± 7,14	0,000	166,58 ± 7,18	0,000
5 min	166,55 ± 7,14	0,000	166,46 ± 7,21	0,000
10 min	166,42 ± 7,20	0,035	166,33 ± 7,20	1,000
15 min	166,24 ± 7,26	1,000	166,30 ± 7,19	1,000
20 min	166,25 ± 7,23	1,000	166,28 ± 7,19	1,000
25 min	166,30 ± 7,24	1,000	166,25 ± 7,20	1,000
30 min	166,24 ± 7,23	1,000	166,27 ± 7,18	1,000

uma semana de intervalo para determinar o coeficiente de correlação intraclasse (ICC). Os resultados demonstraram uma fiabilidade Teste-Reteste excelente com ICC=0.963, com intervalo de confiança entre 0.643 e 0.996.

Análise estatística

A análise estatística foi realizada com recurso ao programa informático *Statistical Package for Social Sciences* versão 17.0 (Chicago, Illinois, USA). Para verificar a normalidade da distribuição dos dados foi usado o teste Shapiro-Wilk e a análise de histogramas. Utilizou-se a ANOVA de medidas repetidas para detectar diferenças na estatura após a aplicação da tracção. Posteriormente, utilizou-se a Teste de *Bonferroni* para localizar essas diferenças entre os momentos de avaliação. Recorreu-se ao teste *T-Student* emparelhado para comparar as diferenças obtidas na estatura entre os dois protocolos em estudo. O nível de significância para a rejeição da hipótese nula estabelecido foi de 0.05, com um intervalo de confiança de 95%.

Resultados

Neste estudo participaram 30 indivíduos, dos quais 16 do sexo feminino (46,7%) e 14 do sexo masculino (53,3%), com idades compreendidas entre os 18 e 24 anos (média: 20,9 ± 1,7 anos de idade), com 166,2 ± 7,2 cm de altura e 64,7 ± 9,5 kg de peso.

Imediatamente após a aplicação da tracção, ambos os protocolos (Protocolo 50%: $F_{7.203}$ = 22.466, p<0.001; Protocolo 10%: $F_{7.203}$ = 31.351, p<0,001) promoveram um aumento significativo da estatura (Tabela I). Aumento esse que se manteve em ambos os protocolos até 5 minutos após o término da tracção. Apenas a tracção com 50% do peso corporal permite manter o aumento da estatura até 10 minutos após o término da tracção (Tabela I).

Apesar de ambos os protocolos terem induzido aumento significativo da estatura, a magnitude desse aumento foi significativamente superior no protocolo de 50% comparativamente ao protocolo de 10% (Figura 3). De facto, imediatamente após a aplicação da tracção, o protocolo de 50% do peso corporal promoveu aproximadamente o dobro do aumento induzido pelo protocolo de 10% do peso corporal (0,57 ± 0,05 vs 0,30 ± 0,04 cm, p<0,001).

Discussão

O principal resultado do presente estudo indica que a tracção vertebral mecânica lombar com magnitude elevada (50% do peso corporal) induz aumento da estatura de maior magnitude e duração do que tracção com doses baixas (10% do peso corporal).

Importa discutir algumas questões metodológicas. Primeiro, o instrumento utilizado para determinar a eficácia da tracção vertebral não é específico para a região lombar, não permitindo detectar variações segmentares da coluna vertebral. É possível que os outros segmentos da coluna vertebral que não foram sujeitos ao protocolo de tracção possam ter sofrido algum grau de variação de comprimento devido à posição de decúbito dorsal. Apesar de ter sido utilizado em estudos anteriores[10-12], este instrumento permite apenas uma avaliação global da coluna vertebral, e uma vez que a tracção foi aplicada apenas na região lombar as alterações globais na estatura devem ser interpretadas cuidadosamente. Segundo, de referir que a opção de manter os indivíduos sentados nos 30 minutos subsequentes à aplicação da tracção teve como objec-

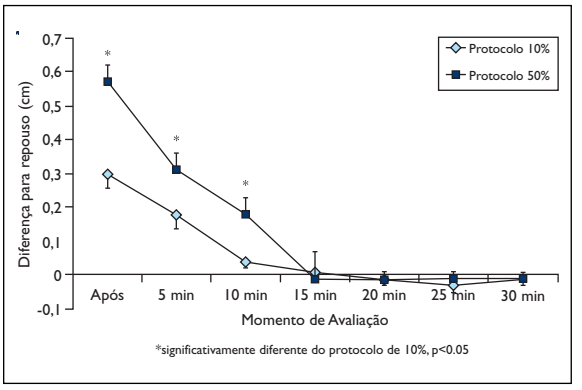

Figura 3. Diferenças na estatura induzidas pela tracção lombar com 10% e 50% do peso corporal

tivo estandardizar a posição durante esse período. A posição preferencial seria a posição bípede, no entanto esta não é uma posição confortável para permanecer imóvel durante 30 minutos, sendo também difícil controlar a adopção de posturas viciosas. A posição de sentado também impõe carga à coluna lombar, é facilmente controlável, podendo-se reproduzir a mesma posição para todos os indivíduos usando-se para isso a mesma cadeira e pedindo para permanecerem bem encostados e apoiados.

No presente estudo o aumento observado na estatura com o protocolo de 50% do peso corporal é similar ao reportado por Rodacki *et al.*[10] usando força de tracção de 60% do peso corporal (7,01 mm), contudo inferior ao descrito por Bridger *et al.*[13] usando um protocolo de apenas 33% do peso corporal (8,94 mm). As diferenças para os nossos resultados podem ser explicadas pelo tempo de aplicação da tracção. De facto, no estudo de Bridger *et al.*[13] apesar da força de tracção ser inferior, a sua duração foi (25 minutos) muito superior aos 15 usados no nosso estudo.

O protocolo com 10% do peso corporal também promoveu aumento na estatura. Contudo, convém realçar que em menor magnitude e com efeito menos duradouro do que na tracção com 50% do peso corporal. A questão que se coloca é se o aumento da estatura obtido com esta força de tracção é suficiente para produzir um aumento significativo no espaço intervertebral em indivíduos com patologia, de forma a reduzir a sintomatologia. A literatura parece indicar que não, uma vez que um estudo em sujeitos com dor lombar e sintomatologia indicativa de compressão radicular, reportou que apenas a tracção lombar com forças de 30 e 60% do peso corporal, em contraste com tracção com 10%, melhorou a sintomatologia[14]. Adicionalmente, estudos avaliando o feito crónico da tracção vertebral em indivíduos com patologia da coluna lombar indicaram que forças de tracção de baixa intensidade (até 20% do peso corporal) devem ser consideradas como *placebo*[15,16].

Os ganhos significativamente superiores observados na estatura com a força de 50% parecem indicar que a magnitude da força de tracção tem um efeito importante na estatura. De facto, forças de maior intensidade apresentam maior capacidade para ultrapassar a resistência muscular (reflexa e voluntária) e ligamentar, a fricção sobre a marquesa, e para deformar os elementos elásticos do disco intervertebral, resultando, desta forma, em maior alteração da estatura[3]. Por oposição, forças de tracção de baixa intensidade parecem ser insuficientes para causar separação vertebral significativa, uma vez que são dissipadas pelos tecidos moles que envolvem a coluna vertebral[3].

A perda progressiva dos efeitos da tracção na estatura observada no presente estudo vai de encontro ao descrito na literatura, a qual tem reportado que o efeito da tracção na estatura é revertido 10 a 30 minutos após a sua aplicação[8,10,17].

A principal limitação do presente estudo advém do uso do estadiómetro para determinar a eficácia da tracção vertebral mecânica, uma vez que este, tal como referido anteriormente, apenas permite efectuar uma avaliação global da coluna vertebral. Seria de todo preferível a utilização de um método imagiológico, o que permitiria uma avaliação segmentar da coluna vertebral.

Os resultados deste estudo realizado em indivíduos saudáveis não podem ser transferidos para populações com patologia lombar uma vez que o alongamento dos tecidos moles parece ser superior em indivíduos saudáveis comparativamente a indivíduos com patologias degenerativas[8], assim são necessários futuros estudos em populações com patologia lombar para verificar se os resultados dos protocolos em estudo seguem o mesmo padrão.

Conclusão

Este estudo indica que a tracção vertebral mecânica da região lombar executada com uma força de 50% do peso corporal durante 15 minutos de for-

ma contínua provoca um aumento na estatura superior, e mais duradouro no tempo, do que o aumento promovido por uma força de 10% do peso corporal. Adicionalmente, verifica-se que dez minutos após o término da tracção o seu efeito na estatura é perdido.

Correspondência para
Fernando Ribeiro
Faculdade de Desporto da Universidade do Porto
Centro de Investigação em Actividade Física, Saúde e Lazer
Rua Dr. Plácido Costa, 91
4200-450 Porto, Portugal
E-mail: fernando.silva.ribeiro@gmail.com

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REUMA.PT – THE RHEUMATIC DISEASES PORTUGUESE REGISTER

Helena Canhão*, Augusto Faustino**, Fernando Martins***, João Eurico Fonseca****
on behalf of the Rheumatic Diseases Portuguese Register Board Coordination,
Portuguese Society of Rheumatology:
Elsa Vieira-Sousa, JA Pereira Silva, Maria José Santos, J Canas Silva, JA Melo Gomes, Cátia Duarte, José António Silva, Luís Cunha-Miranda, Ana Teixeira, Walter Castelão, Jaime Branco, José António Costa, Domingos Araujo, Teresa Nóvoa, Guilherme Figueiredo, Herberto Jesus, Alberto Quintal, Ana Rita Cravo, Graça Sequeira, Patrícia Pinto, Rui André, Miguel Bernardes, Francisco Ventura, Inês Cunha, Anabela Barcelos, Patrícia Nero, Margarida Cruz

Abstract

Introduction: Since June 2008, Portuguese rheumatologists have been collecting on a routine basis, data into the nationwide Reuma.pt, the Rheumatic Diseases Portuguese Register from the Portuguese Society of Rheumatology (SPR), which includes rheumatic patients (rheumatoid arthritis – RA, ankylosing spondylitis – AS, psoriatic arthritis – PsA and juvenile idiopathic arthritis – JIA) receiving biological therapies or patients receiving synthetic disease modifying anti-rheumatic drugs (DMARDs).

The aim of this publication is to describe the structure of Reuma.pt and the population registered since June 2008.

Methods: Demographic and anthropometric data, life style habits, work status, co-morbidities, disease activity and functional assessment scores, previous and current therapies, adverse events codified by the Medical Dictionary for Regulatory Activities (MedDRA), reasons for discontinuation and laboratory measurements are registered at each visit. The platform is based on a structured electronic medical record linked to a SQL Server database. All Rheumatology Departments assigned to the Portuguese National Health Service (n=21), 2 Military Hospitals (Lisboa and Porto), 1 public-private Institution and 6 private centers adhered to the Register. Until now, 18 centers have entered data into Reuma.pt.

Results: By January 2011, 3438 patients and 16130 visits had been registered. 2162 (63%) were RA patients, 700 of them treated with biological agents and 1462 with synthetic DMARDs. From the 515 (15%) AS patients, 297 were medicated with biological and 218 with non-biological therapies. 293 (8%) were PsA patients, 151 treated with biological drugs and 142 with other treatment strategies. 368 (11%) had the diagnosis of JIA, 68 were under biological treatment and 300 were managed with other treatment options. The register also includes 100 (3%) patients with other rheumatic diseases, submitted to treatments that required hospital day care infusions including 18 exposed to biological therapies.

Conclusions: Registers are crucial to ensure correct clinical use, adequate assessment of post-marketing biological therapies' efficacy and safety, thus contributing for a better cost-benefit ratio. Reuma.pt, is a powerful and accurate tool to answer to these unmet needs. It presents a national coverage of the rheumatology centers and constitutes an invaluable resource for scientific research and to improve rheumatic patients care.

Keywords: Register; Biological therapies; Reuma.pt; Rheumatic diseases; Portuguese Society of Rheumatology

*Scientific coordinator Reuma.pt. Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular. Faculdade de Medicina de Lisboa, Lisboa e Serviço de Reumatologia e Doenças Ósseas Metabólicas do CHLN - Hospital de Santa Maria. Lisboa.
**National coordinator Reuma.pt. Instituto Português de Reumatologia e Clínica de Reumatologia de Lisboa.
***Sociedade Portuguesa de Reumatologia
****Executive coordinator Reuma.pt. Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular. Faculdade de Medicina de Lisboa, Lisboa e Serviço de Reumatologia e Doenças Ósseas Metabólicas do CHLN - Hospital de Santa Maria. Lisboa.

Introduction

The Rheumatic Diseases Portuguese Register (RNDR), Reuma.pt, developed by the Portuguese Society of Rheumatology (SPR), became active in June 2008 and includes patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA). The ultimate goal is to register all patients in Portugal (Mainland, Madeira and Azores Islands) with rheumatic diseases, treated with biological treatments and to follow them up to determine treatment efficacy, safety and long-term co-morbidities. The Register is also recruiting comparison cohorts of patients with RA, AS, PsA and JIA treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) and other treatment strategies (such as non-steroidal anti-inflammatory drugs in AS). This will enable to weigh the relative contribution of disease factors and standard treatments, whenever biological treatment effects (beneficial and hazardous) are being evaluated. Reuma.pt also includes BioGeral, a register for additional rheumatic diseases treated at rheumatology day care units, such as systemic lupus erythematosus, systemic sclerosis, vasculitis, Behçet's disease, myositis, idiopathic, uveitis and osteoporosis.

During the last decade, many rheumatology national societies and rheumatology organizations have developed large registries (BSRBR[1], DANBIO[2], RABBIT[3], BIOBADASER[4], CORRONA database[5], ARTIS[6]). In spite of differences regarding informatics platforms, designs, data collection, national coverage and inclusion criteria, they all have a common mission of collecting data and increasing knowledge fostering the improvement of medical care of rheumatic patients. Moreover commonly used cores of validated measures such as ACR response components, RA disease activity score (DAS28), health assessment questionnaire (HAQ), Bath ankylosing spondylitis disease activity index (BASDAI) and adverse events are being registered.

Reuma.pt was designed based on previously published standard observational protocols, which were in use for local printed registries[7-9] and on national recommendations for the use of biological agents[10-13]. Reuma.pt displays a user friendly clinical chart scenario and has been subdivided for the medical users in several slightly different disease specific applications: BioRePortAR (the database for RA patients treated with biological therapies), BioRePortEA (for AS), BioRePortAP (for PsA) and BioRePortAIJ (for JIA). RegistAR is similar to BioRePortAR and was designed to collect information from RA patients who are not treated with biological therapy. RegistEA, RegistAP and RegistAIJ are the correspondent databases to the other diseases. BioGeral is the registry used for rheumatic patients not included on the previous interfaces. All databases share the same platform and are linked upon the global register, Reuma.pt.

The aim of this publication is to describe the structure of Reuma.pt and the population registered since June 2008.

Methods

Technical specifications

Reuma.pt is accessed through an electronic medical record (EMR) application developed using Visual Studio, an integrated development environment (IDE) from Microsoft. It was written in *VB.NET* for the *.NET Framework*. The *.NET Framework* provides generic functionalities for Windows applications. It includes a large set of software components, and it supports several programming languages that allow language interoperability (each language can use code written in other languages). Programs written for the *.NET Framework* execute in virtual machine, known as the Common Language Runtime (CLR). The CLR provides several important services such as security, memory management, and exception handling.

Data are collected in a standardized format, through almost a hundred classification lists, that include drugs, pathologies, etc. All dates and numeric fields are also validated. The only fields that can be freely typed, are the fields specifically assigned for notes.

All entered data is stored in a SQL Server database, a relational model database management system produced by Microsoft. The application communicates with an instance of SQL Server by sending Transact-SQL statements to the server. SQL Server ensures that any change to the data is compliant with a set of properties (atomicity, consistency, isolation, durability), which guarantees that the database will always revert to a known consistent state on failure.

Besides pre-formatted reports, Reuma.pt allows each center to export raw data to common data analysis packages, such as SAS, Stata, R and SPSS.

All entered data can be selected for exportation accordingly to each analysis needs. A model of data exportation can also be selected. This can be done by choosing a longitudinal model (one row per visit) and/or the data grid model (lists as the ones seen on most common application screens).

Nowadays, each center (hospital or medical office) has its own local installation of Reuma.pt. There is also a central server that stores data from all centers. However, this requires a regular data transfer from each center to the central server. Later this year, a Reuma.pt web version will be launched. This new version is a rich internet application (RIA) built on Microsoft Silverlight. Silverlight is a platform that enables to develop Web-based applications with a modern and efficient user interface, and also secure user interactions with desktop files, devices, data and applications such as Microsoft Office. This will leverage Reuma.pt to higher levels of accessibility. Additionally, all entered data will be stored in a single web server, suppressing data transfers from local installations to a central server. All databases are linked, i.e. if a patient is already registered in RegistAR and starts a biological agent, once that information is inserted in the database, the patient is automatically switched to BioRePortAR environment.

Reuma.pt description and contents

Reuma.pt access is protected by username and password, which are unique to each rheumatologist. New users can be authorized by current users. In the first menu the physician can create a new patient or a new visit, or edit previous visits. On the left hand side, Reuma.pt screen displays a tree format table of contents (Figure 1A). Some screens are the same across all databases: identification data, demographic data, work status, life styles, body mass index, previous medical history, joint surgeries, co-morbidities, SF-36 questionnaire, laboratorial results form, past and current therapies, adverse events, tuberculosis screening, observations/notes and charts while others are disease-specific. For RA, disease activity assessments include 3 visual analogue scales (VAS) (patient and physician disease activity and patient reported pain), 3 homunculus (tender joints, swollen joints and non evaluable joints), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). When data needed for DAS28 (DAS 28 with 3 and 4 variables, and with ESR or CRP) is inserted the score is automatically computed (Figure 1B). ACR responses between 2 requested time points are also automatically displayed (Figure 1C). Other screens include health assessment questionnaire, hand and feet X-rays Sharp/van der Heijde score and RA features like extra-articular manifestations, rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Screens are user friendly and give assisted support to fill in the boxes (scroll options, clever writing, pre-written tables, classification systems, MedDRA), but without neglecting detailed data collection. For instance «therapy fields» include start and end dates, frequency, dose, route of administration, reasons for discontinuation and a link to the «adverse events window». «Adverse events» capture thorough information according to regulatory authorities demand (Figure 1D), including type, severity, causality, actions taken and evolution. Registers dedicated to ankylosing spondylitis include BASDAI, BASFI, BASMI, ASDAS, ASAS response, Stoke ankylosing spondylitis spine score, HLA B27 antigen and extra-articular manifestations. Psoriatic arthritis registers allow the patient disease classification in «AS-like» (axial disease) and/or «RA-like» (peripheral disease) and the choice of the best evaluation measures for a specific patient. In addition, PASI is also collected. JIA patients have also specific questionnaires like the child health assessment questionnaire (CHAQ) and validated assessments (active joints, joints with decreased mobility and ACR30 responses). In BioGeral instruments for SLE evaluation were included: SLE disease activity index (SLEDAI) and SLICC damage index.

All screens are printable (before and/or after filled). After data collection, Reuma.pt can generate a pre-formatted report, integrating all information.

Reuma.pt Management

Reuma.pt was approved by National Data Protection Board and by the local Ethics Committees. Patients sign an informed consent for data research use and applications.

SPR owns the Register and controls data access, data analysis and its release. The Reuma.pt Coordination Board (CC RNDR) consisting of a Steering Committee with an Executive Coordinator from SPR Board (JEF), a National Coordinator (AF) responsible for Centers liaison, a Scientific Coordinator (HC) and a representative from each participating center, all appointed for a 2 years period

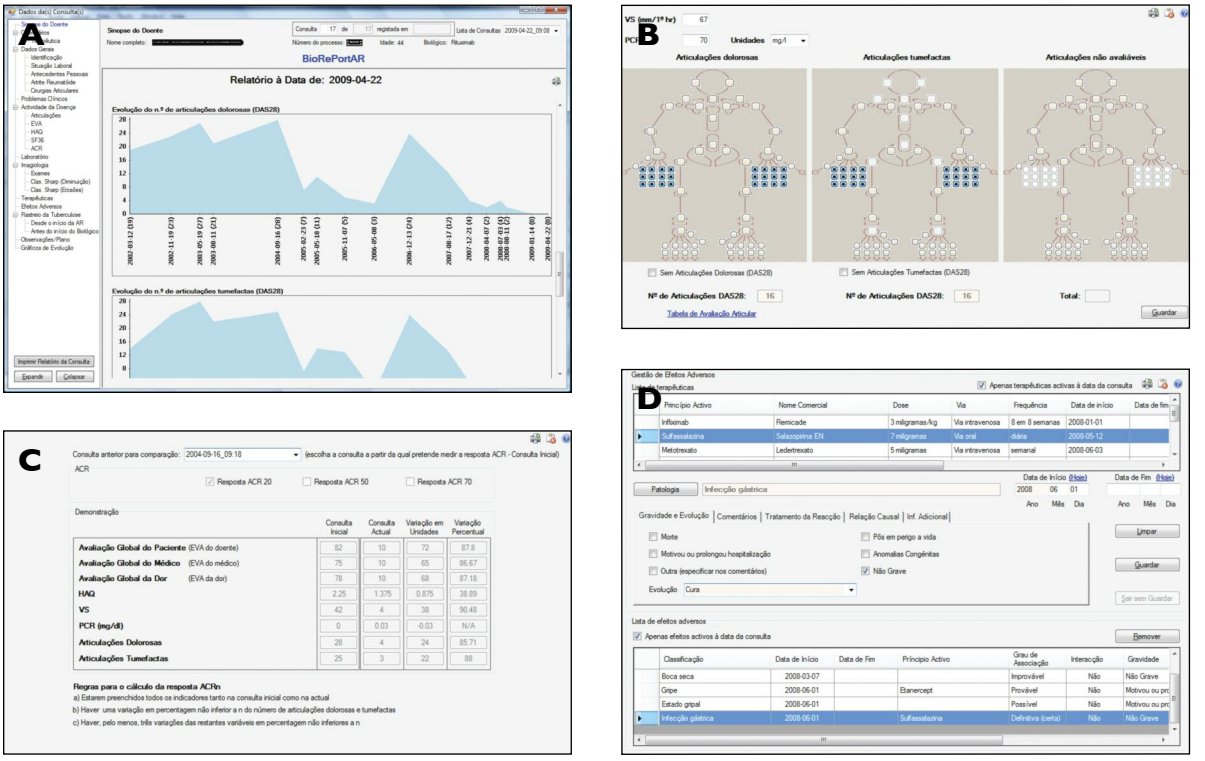

Figure 1. Reuma.pt screens for patient synopsis (**A**), joint involvement (**B**), automatically display of ACR responses (**C**) and adverse events (**D**)

(the duration of a SPR electoral mandate). CC RNDR ordinary meetings are held every 6 months but extraordinary meetings can be scheduled whenever considered necessary. Regulations for data access, rules governing pharmaceuticals relationship, project application forms, data agreement utilization and regulations for payment for data insertion were approved by CC RNDR and are publicly available at www.spreumatologia.pt. Individual research projects addressing specific questions can be submitted to CC RNDR by SPR members.

Reuma.pt Implementation

Reuma.pt's very early development was undertaken by SPR in a collaborative work with Instituto de Medicina Preventiva, Faculdade de Medicina de Lisboa.

Currently, Reuma.pt is widely established, encompassing all Portuguese rheumatology centers. Identifying the contributing factors for this generalized adherence could be of importance for countries trying to establish new registers. From the beginning, we have involved representatives from all centers who had an important role in the design of the interface and in the selection of the variables included in Reuma.pt. During the development, these representatives performed tests in their own centers and proposed changes. The database development process has taken those suggestions into consideration and has been shaped fitting general agreement. Moreover, advertisements and practical training sessions were done during the major SPR meetings. The steering committee has been periodically promoting local sessions with rheumatologists, informatics and hospital management staff, in order to facilitate Reuma.pt local implementation. For eligible cases a fee has been paid for data insertion. Reuma.pt applications allowed the link with the electronic system from the hospital, namely the electronic medical record, avoiding double-typing and record duplications. Some tools like the automated calculation of DAS and HAQ, patients' disease activity profile graphically displayed, easy search of therapies and co-morbidities history, adverse event report based on the same classification system used by regulatory authorities and analysis of data for each center have been other important facilitating factors for the success

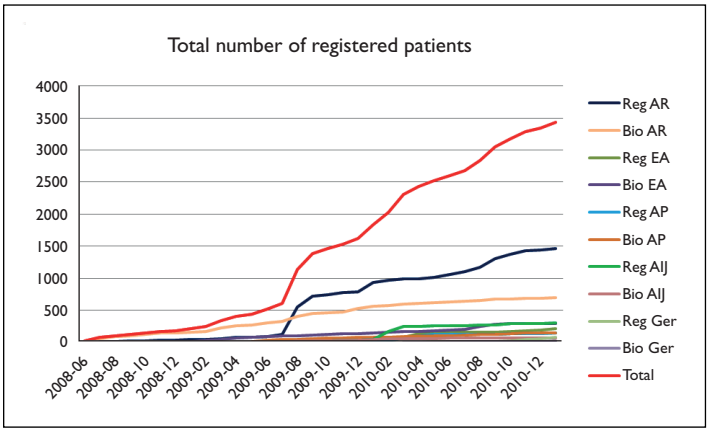

Figure 2. Total number of patients registered in Reuma.pt

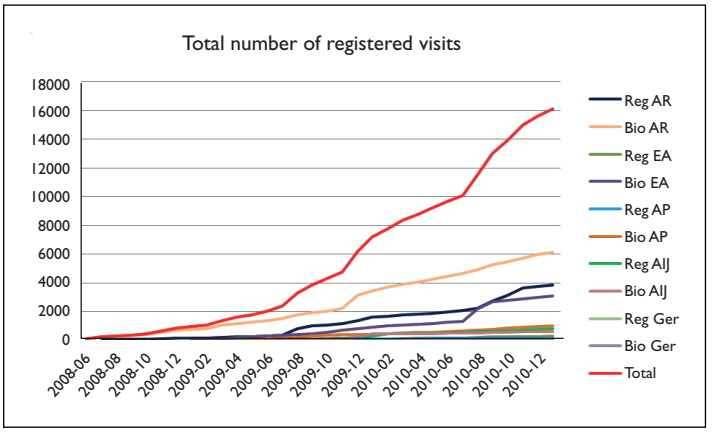

Figure 3. Total number of visits registered in Reuma.pt

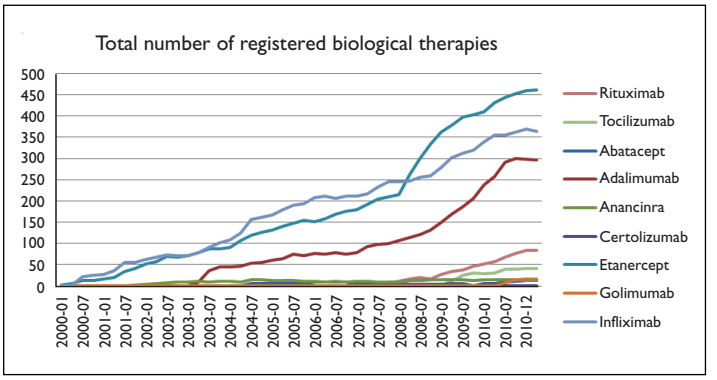

Figure 4. Total number of biological therapies registered in Reuma.pt

of Reuma.pt.

The collaborative work with Direcção Geral de Saúde (Portuguese Health Directorate) and also with international registers (such as the METEOR) has also been a priority. Reuma.pt has been funded by unrestricted grants from pharmaceutical companies (Abbott, Bristol Myers Squibb, Merck Sharp and Dohme, Pfizer, Roche and UCB Pharma), which have not direct data access neither influence the research projects or data analysis. CC RNDR releases semiannual reports with detailed description of the data inserted. Every 2 months, a Newsletter including a FAQ section and news is sent for all SPR members and is posted on SPR website.

Results

First BioRePortAR patients were registered in June 2008 and progressively centers have begun inserting patients and visits, with a steep increment since September 2009 (Figures 2 and 3). Data is prospectively inserted at each visit, but at the same time, rheumatologists have been inserting information recorded in paper forms before 2008, as part of the local printed registries that had been previously settled. Thus, Reuma.pt contains information on biological therapies since year 2000 (Figure 4).

On January 2011, 3438 patients and 16130 visits were registered. From this global number, 2162 (63%) were RA patients, 700 treated with biological agents and 1462 exposed to synthetic DMARDs. From the 515 (15%) AS patients, 297 were medicated with biological and 218 with non-biological therapies. 293 (8%) were PsA patients, 151 treated with biological drugs and 142 with standard non-biological therapy. Of the 368 (11%) patients with the diagnosis of JIA, 68 were under biological treatment and 300 were managed with other strategies. The register also includes 100 (3%) patients with other diagnosis, submitted to treatments that required hospital day care infusions, including 18 exposed to biological therapies. This register's environment includes diagnosis such as systemic lupus erythematosus, systemic sclerosis, myositis, idiopathic uveitis, vasculitis, Behçet's disease and osteoporosis. All Rheumatology De-

Table I. Demographic features of patients registered in Reuma.pt, according to rheumatic disease.

	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Juvenile idiopathic arthritis
Number of patients (total)	2162	515	293	368
with biological	700	297	151	68
non-biological	1462	218	142	300
Current age	59.7 ± 13.8	44.3 ± 12.7	53.3 ± 13	19.3 ± 11.1
Age at diagnosis	46.9 ± 14.4	31.9 ± 12.2	40.6 ± 12,9	6.6 ± 4.6
Age at biological onset	53.2 ± 12.6	40.6 ± 11.9	47.3 ± 11.1	20.6 ± 10.1
Mean disease duration at last observation	13.6 ± 9.9	17.7 ± 10.6	15.9 ± 9.5	13.3 ± 10.5
Mean disease duration at biological onset	10.6 ± 9.1	13.4 ± 10	12.5 ± 9.5	11.4 ± 9.6
Female	83.6%	38.2%	47.4%	68.2%
Biological	88.4%	35%	49%	73.5%

Biological – biological therapy group; Non-biological – Non-biological therapy group.

partments assigned to the Portuguese National Health Service (n=21), 2 Military Hospitals (Lisboa and Porto), 1 public-private Institution and 6 private centers adhered to the Register. Until now, 18 centers have entered data into Reuma.pt.

Rheumatoid arthritis (BioRePortAR and RegistAR)

As previously referred 2162 RA patients (700 were treated with biological agents and 1462 with synthetic DMARDs), with a currently mean age of 59.7 ± 13.8 years old, are registered in Reuma.pt. RA patients treated with synthetic DMARDs had a mean age of 61.5 ± 14.2 years-old and those treated with biological agents were 56.1 ± 12.2 years old. Mean age at time of diagnosis was 46.9 ± 14.4 years old and at the beginning of biological treatment was of 53.2 ± 12.6 years old. Mean disease duration at last observation was of 13.6 ± 9.9 years and at the starting of the biological was of 10.6 ± 9.1 years. Females represent 83.6% of patients, 81.3% in the group treated with synthetic DMARDs and 88.4% in the group treated with biological therapies (Table I). Rheumatoid factor was found in 73.6% and anti-CCP in 70.9% of the cases. The disease was erosive in 72% of the patients. 35.7% of the patients treated with DMARDs and 35.6% treated with a biological agent presented extra-articular manifestations.

Forty five point five percent were exposed to at least one administration of etanercept, 35.3% to infliximab, 31.1% to adalimumab, 11.2% to rituximab, 6.3% to tocilizumab, 2.2% to abatacept, 2.1% to anakinra and 1.4% to golimumab. The total biological treatment's exposure was of 2869.4 years (Table II).

In the group of patients treated with synthetic DMARDs, current mean DAS28 (DAS 4 variables, with ESR) is 3.4 ± 1.5. 35.7% of patients with more than 6 months of follow-up were in remission defined by a DAS28 lower than 2.6 and 14.6% had a high disease activity (DAS28 above 5.1).

At the beginning of biological therapy, patients exhibited a mean DAS28 of 5.6 ± 1.7. Currently mean DAS28 is 3.6 ± 1.5 for patients under active treatment with a biological drug for more than 6 months and of 3.5 ± 1.4 for the group actively treated for at least 1 year. The proportion of patients with a DAS28 below 2.6 is inferior in the biological treated group: 26.4% of the patients treated for at least 6 months and 26.9% for those with more than 1 year of treatment.

Current mean HAQ is 1.07 ± 0.75 for patients on synthetic DMARDs. Baseline mean HAQ was of 1.47 ± 0.63 for patients starting biological agents, 1.13 ± 0.69 when patients were treated for more than 6 months and 1.1 ± 0.69 in patients who had been treated with biological therapies for at least 1 year.

From the 804 RA patients who did at least one administration of a biological drug, 495 (61.5%) remain on the first biological treatment registered into BioRePortAR, 108 (13.4%) definitely withdrew

Table II. Proportion of patients exposed to at least one drug's administration and total amount of biological treatment's exposure in years

Proportion of patient's exposed to at least one administration of	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Juvenile Idiopathic arthritis
Abatacept	2.2%	–	–	8.1%
Adalimumab	31.1%	31.7%	36.3%	21.6%
Anakinra	2.1%	–	–	10.8%
Etanercept	45.5%	35.9%	50%	68.9%
Golimumab	1.4%	0.6%	2.5%	-
Infliximab	35.3%	53.8%	36.9%	9.5%
Rituximab	11.2%	–	–	1.3%
Tocilizumab	6.3%	–	–	2.7%
Total of biological	2869.4	987.6	512.3	275.3

from the biological therapy and 201 (25 %) have been switched to other biological agent. From the group of 201 patients who switched therapies, 138 (68.7%) of them have switched once, 43 (21.4%) twice and 20 (9.9%) patients switched three or more times (Table III).

Considering 1096 biological therapies prescribed in BioRePortAR, drug was discontinued in 398 cases (36.35%). As we saw before, in 108 (27.1%) patients the drug was not resumed, and it was replaced by another biological agent in 290 (72.9%) of the cases. The main reason for discontinuation was inefficacy (52.8%) and in a lesser degree, adverse events (21.1%) or other causes (22.7%) (Table IV).

Ankylosing spondylitis (BioRePortEA and RegistEA)

From the 515 (15% of the registered patients) AS patients, 297 were medicated with biological and 218 with non-biological therapies. The mean age at diagnosis was 31.9 ± 12.2 years old. Current mean age is 44.3 ± 12.7 years old. Mean age at biological treatment onset was of 40.6 ± 11.9 years old. Mean disease duration at last observation was of 17.7 ± 10.6 years and at the starting of the biological was of 13.4 ± 10 years. Males were 61.8%, 57.3% in the group without biological therapy and 65% in the group exposed to biological therapy (Table I). In this AS sample 82.3% were HLAB27 positive and 44% had extra-articular manifestations.

Considering all AS patients exposed to biologi-

Table III. Proportion of patients remaining on the first biological drug, withdrew biological therapy and switched between biological agents

Patients	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Juvenile idiopathic arthritis
Remaining in the first biological therapy	495 61.5%	235 75.3%	118 73.7%	55 74.3%
Withdrew from biological	108 13.4%	15 4.8%	9 5.6%	6 8.1%
Switched	201 25%	62 19.9%	33 20.6%	13 17.6%
Once	68.7%	83.9%	72.7%	53.8%
Twice	21.4%	16.1%	27.3%	30.8%

Table IV. Reasons for biological therapy discontinuation

Therapies	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Juvenile idiopathic arthritis
Drug discontinuation	398	89	51	29
(number and %)	36.3%	23.2%	25.2%	30.8%
Adverse event	21.1%	38.2%	39.2%	10.3%
Inefficacy	52.8%	51.7%	43.1%	44.8%
Lost for follow-up	0.55%	1.1%	–	3.5%
No indication	1.25%	–	2%	–
Remission	0.25%	–	–	–
Patient's refusal	1%	2.2%	–	3.5%
Death	0.25%	–	–	–

Table V. Proportion of juvenile idiopathic arthritis (JIA) subtypes in patients treated with synthetic and biological therapies

JIA subtypes	Synthetic DMARDs	Biological Therapies
Persistent oligoarthritis	42.6%	12.3%
Extended oligoarthritis	11.8%	12.3%
Poliarthritis with rheumatoid factor positive	8.8%	26.3%
Poliarthritis with rheumatoid factor negative	13.2%	19.3%
Systemic	10.3%	21.1%
Arthritis related with entesitis	11.8%	7%

DMARDs – disease modifying anti-rheumatic drugs

cals, 53.8% of the patients received at least one administration of infliximab, 35.9% of etanercept, 31.7% of adalimumab and 0.64% of golimumab. The total amount of biological treatment's exposure was of 987.6 years (Table II).

The mean BASDAI was reduced from 6 ± 2 at biological therapy onset to 2.7 ± 2.2 in the group of patients treated for at least 6 months and 2.5 ± 2.1 for those treated for at least 1 year.

The mean ASDAS improved from 3.8 ± 1 at baseline visit to 1.8 ± 1.1 in patients treated for 6 months or longer and to 1.7 ± 1 for patients under at least 1 year of biological therapy.

The mean BASFI was of 5.5 ± 2.4 at start and it is now of 2.9 ± 2.5 and 2.8 ± 2.4 for patients treated at least 6 months and 1 year with biological therapies, respectively.

At 6 months, the ASAS20 response was achieved by ~95% patients treated with biological therapies. Forty five per cent of AS patients treated with a biological agent for at least 6 months presented a BASDAI lesser than 2, and if the treatment was maintained for a minimum of 1 year this proportion was of 47.2%.

From the 312 AS patients who did at least one administration of a biological drug, 235 (75.3%) remain on the first biological treatment registered into BioRePortEA, 15 (4.8%) definitely withdrew from the biological therapy and 62 (19.9 %) have been switched to other biological therapies. From the group of 62 patients who switched therapies, 52 (83.9%) of them have switched once and 10 (16.1%) twice (Table III).

Considering the 384 biological therapies prescribed in BioRePortEA, the biological agent was discontinued in 89 cases (23.2%). As we have seen before, in 15 (16.8%) patients the drug was not resumed, and it was replaced by another biological agent in 74 (83.2%) of the cases. The reasons for discontinuation were inefficacy (51.7%) in most cases and in a lesser degree, adverse events (38.2%) (Table IV).

Psoriatic arthritis (BioRePortAP and RegistAP)

Two hundred and ninety three patients had PsA and they accounted for 8% of the patients registered in Reuma.pt; 151 were treated with biological drugs and 142 with non-biological therapies. The total biological treatment's exposure was of 512.3 years.

Current mean age was of 53.3 ± 13 years old, 56.2 ± 14.7 years old for patients without biological therapies and 50.6 ± 10.5 years old for patients treated with biological agents. The mean age of disease onset was of 37.4 ± 13.6 years old, the diagnosis was made, on average, at 40.6 ± 12.9 years old and the biological therapy initiated at a mean age of 47.3 ± 11.1 years old. Mean disease duration at last observation was of 15.9 ± 9.5 years and at the starting of the biological was of 12.5 ± 9.5 years. Considering all PsA patients, 52.6% of the patients were males; 54.3% were medicated with conventional therapies and 51% with biological drugs (Table I).

From the group of patients treated with biological therapies 74.3% were classified as having «RA-like» psoriatic arthritis and 25.7% had an «AS--like» disease. 30.6% of PsA patients were HLAB27 positive. 50% of the patients were exposed to at least one administration of etanercept, 36.9% to infliximab, 36.3% to adalimumab and 2.5% to golimumab (Table II).

The number of tender joints was of 13.1 ± 11.2 in the beginning of biological therapy and was 3.4 ± 6.1 and 3 ± 5.7 after 6 months and 1 year under therapy, respectively. The correspondent figures for swollen joints were 6 ± 7.6, 0.9 ± 2.5 and 0.8 ± 2.3.

«RA-like» PsA group presented an initial mean DAS28 of 5.1 ± 1.6 and after at least 6 months and 1 year of biological therapy it was of 2.7± 1.4 and 2.6 ± 1,3, respectively. Currently, 49.1% of the patients treated at least for 6 months and 51.1% in the group treated at least for 1 year present a DAS28 below 2.6. Mean DAS28 is currently of 4 ± 1.6 in patients treated with synthetic DMARDs.

For the «AS-like» group, mean BASDAI was of 6.5 ± 1.8 at the beginning of biological therapy, it was 3.6 ± 2.4 after a minimum of 6 months of treatment and 3.4 ± 2.4 after 1 year.

Functional assessment in the «RA-like» group revealed a mean HAQ of 1.3 ± 0.7 when patients started biological therapy. It decreased to 0.85 ± 0.7 in patients treated for 6 months and to 0.82 ± 0.71 for treatments over 1 year. Current HAQ in the group of patients treated with standard treatments was of 0.81 ± 0.65.

In spondylitis PsA patients, mean BASFI was of 5.7 ± 2.1 at baseline, and is currently of 3.5 ± 2.4 in patients treated for more than 6 months and of 3.4 ± 2.4 in those treated for more than 1 year.

From the 160 PsA patients who did at least one administration of a biological drug, 118 (73.7%) remain on the first biological treatment registered into BioRePortAP, 9 (5.6%) definitely withdrew from the biological therapy regimen and 33 (20.6 %) have been switched to other biological therapy. From the group of 33 patients who switched therapies, 24 (72.7%) of them have switched once and 9 (27.3%) twice (Table III).

Considering 202 biological therapies prescribed in BioRePortAP, drug was discontinued in 51 cases (25.2%). As we saw before, in 9 (17.6%) times the drug was not resumed, and it was replaced by another biological agent in 42 (82.4%) of the cases. The main reasons for discontinuation were inefficacy in 43.1% and adverse events in 39.2% of cases (Table IV).

Juvenile idiopathic arthritis (BioRePortAIJ and RegistAIJ)

Three hundred sixty eight (11%) Reuma.pt patients had the diagnosis of JIA. 68 were currently medicated with biological agents while 300 were being managed with non-biological treatments. Mean age at disease onset was 6.6 ± 4.6 years old. Mean age at beginning of biological therapy was of 20.6 ± 10.1 years old. We clearly noticed two groups of JIA patients medicated with biological drugs. A group of JIA patients (n=32) who started biological therapies during childhood and whose mean age was of 12.8 ± 4.1 years old, and a group of JIA patients (n=38) who started biological therapies already as young adults with a mean age of 27.2 ± 8.9 years old at the beginning of biological treatment. The 300 JIA patients treated with synthetic DMARDs presented a mean age of 18.3 ± 11.1 years old. Mean disease duration at last observation was of 13.3 ± 10.5 years and at the starting of the biological treatment was of 11.4 ± 9.6 years. Females account for 68.2% of patients; they were 67% in the synthetic treated group and represented 73.5% in the biological treated group (Table I).

The proportion of patients assigned to JIA subtypes differed in patients treated with non biological or biological therapies (Table V).

Antinuclear antibodies were positive in 35% of patients and 21.4% were HLAB27 positive.

Rheumatoid factor was found in 22.1% and anti--CCP in 31.2% of the patients. Extra-articular manifestations were reported in 35.2% of patients from the conventional DMARDs group and 55.4% in the biological treated group.

The total amount of biological treatment's exposure was of 275.3 years. Taking into account all JIA patients treated with biologics, 68.9% were exposed to at least one administration of etanercept, 21.6% to adalimumab, 10.8% to anakinra, 9.5% to infliximab, 8.1% to abatacept, 2.7% to tocilizumab and to 1.3% rituximab (Table II).

The mean active joint count reported at beginning of biological therapies was 8.5 ± 8.4 and decreased to 1.3 ± 2.2 and 1.4 ± 2.3 after 6 months and one year of therapy, respectively. Limitation of passive motion (LOM) was observed at baseline in 4.7 ± 5 joints and after 6 months and 1 year in, respectively, 3.9 ± 8.8 and 4.2 ± 9.3 joints. Mean ESR was of 31.5 ± 21.4 mm/1st hour at biological treatment onset and of 16.6 ± 15.5 and 17.3 ± 15.7 after, respectively, 6 months and 1 year of treatment. Mean Child health assessment questionnaire (CHAQ) and for adult patients HAQ scores showed 0.99 ± 0.7 at baseline, 0.42 ± 0.53 after 6 months and 0.45 ± 0.55 after at least 1 year of treatment.

From the 74 JIA patients who did at least one administration of a biological drug, 55 (74.3%) remain on the first biological treatment registered into BioRePortAIJ, 6 (8.1%) definitely withdrew from the biological therapy and 13 (17.6%) have been switched to other biological therapy. From the group of 13 patients who switched therapies, 7 (53.8%) of them have switched once, 4 (30.8%) twice and 2 (15.4%) patients switched three or more times (Table III).

Considering 94 biological therapies prescribed in BioRePortAIJ, the drug was discontinued in 29 cases (30.8%). As we have seen before, in 6 (20.7%) of the times, the drug was not resumed, and it was replaced by another biological agent in 23 (79.3%) cases. The reasons for discontinuation were inefficacy in 44.8% of the cases and other reasons in 37.9%. Interestingly adverse events only accounted for 10.3% of the reasons reported for discontinuing therapy in JIA patients (Table IV).

Discussion

The aim of this work was to present the structure, organization, management and first available data from Reuma.pt, the Rheumatic Diseases Portuguese Register from SPR, after 2.5 years of its launch.

In 2005, SPR published two nationwide analyses of 376 rheumatoid arthritis[14] and 113 ankylosing spondylitis[15] patients treated with biological therapies. Also, single center's analyses were performed[16-17]. At that time, observations were periodically registered using paper forms with a common core of measures. With Reuma.pt development and implementation a huge step has been made towards a more efficient and accurate data collection, storage and analysis.

In this work we have presented data that supports the important role performed by registers in the evaluation of rheumatic patients treated with conventional or biological therapies. Treatment's long term efficacy, drug's survival time and analysis of switches between biologics are accurately evaluated by our and other registers.

Short and long term safety of biological agents in clinical practice pose additional challenges to registers. Similarly with the regulatory health authority INFARMED, we have adopted MedDRA as our classification system for adverse events. However in clinical daily practice, reporting all adverse events is a difficult task for the overwhelmed physician and currently there are discrepancies between centers in the criteria for registering adverse events in Reuma.pt. The CC RNSR is developing recommendations for adverse events collection, prioritizing adverse events by clinical relevance and/or severity in order to guarantee an adequate and reliable reporting from all centers.

Safety data analyses from Reuma.pt have been previously presented, based on a single center data. In an evaluation in 136 RA patients registered in BioRePortAR[18], with a mean follow-up of 3.7± 2.8 years and an exposure to biological therapies of 510 patient-years, the authors have reported 311 adverse events, 242 of them classified by the rheumatologist as being related with the biological therapy. Twenty four (7.7%) were classified as serious adverse events which corresponded to an incidence rate of 5.8 serious adverse events/100 patients-year (2.2 infections /100 pt-years and 1.5 hypersensitivity reactions/ 100 pt-years).

Other analysis[19] of 42 BioRePortAP patients reported 56 adverse events. Only one has been assigned as a serious adverse event (incidence rate of 1.3 serious adverse events/100 patients year) and it was classified as unlikely related to anti-TNF

therapy. The remaining adverse events were not severe and 67% of them were due to infections.

Also, in a group of 24 BioRePortAIJ patients[20], 3 serious adverse events (1 forearm fasciitis necrosans, 1 orchiepididymitis and 1 allergic reaction) were reported, none of them resulted in patient's death. There were no reports of opportunistic infections.

Latent tuberculosis infection (LTBI) is still a problem in Portugal. Due to that, SPR issued recommendations[21] for LTBI screening in patients starting biological therapies. In a previous nationwide study[22], based on the paper registry forms prior to Reuma.pt launch, we have reported 13 cases of tuberculosis between 1999 and 2005 in patients treated with biological therapies. Nine patients had RA (in 639 RA exposed patients, 1.4%), 3 AS (in 200 AS exposed patients, 1.5%) and 1 had PsA (in 101 PsA exposed patients, 1%). Tuberculin skin test (TST) was performed in 9 out of the 13 patients. In 3 cases, the TST response was 0 mm. Also in 3 cases, the TST response was superior to 10 mm, and all of them were treated with isoniazid treatment 300 mg/d during 9 months. The time between first symptoms and TB diagnosis was 2.6 +/ /-2.9 months. One death was reported; all of the other cases had a good outcome after anti-TB treatment. Four cases have occurred before the widespread screening established for all patients in 2003. The 2006 and 2008 update[21] of the recommendations for tuberculosis screening and LTBI treatment were more stringent, with the decrease of TST positivity threshold to 5mm and the introduction of a TST retest 2 weeks apart. Reuma.pt comprehends specific questions to address the issue of tuberculosis and a report will be prepared specifically on this issue.

In conclusion, patient registries are an important source for longitudinal observational studies in rheumatic diseases, which in turn are an essential complement to data obtained from randomized clinical trials. In fact, registers are crucial to ensure correct clinical use, adequate assessment of post-marketing biological therapies' efficacy and safety, therefore contributing for a rational cost--benefit ratio. Several registers across Europe and North America have demonstrated to be excellent tools for monitoring quality of care and for conducting scientific research that deals with important daily clinical problems. Reuma.pt, the national register from SPR, is also a powerful and accurate tool that will be able to contribute to some of the unmet needs in the field of clinical rheumatology. In the near future, we are planning to develop synergies with international registers and to present Reuma.pt data in major scientific meetings and major international peer-review journals.

Correspondence to
Helena Canhão
Unidade de Investigação em Reumatologia
Instituto de Medicina Molecular
Faculdade de Medicina de Lisboa
Edifício Egas Moniz
Av Egas Moniz
1649-028 Lisboa
E-mail: helenacanhao@netcabo.pt

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ESPONDILODISCITE TUBERCULOSA LOMBAR: ABORDAGEM CIRÚRGICA MINIMAMENTE INVASIVA

Bruno Carvalho, Paulo Pereira, Pedro Santos Silva, Joana Silva, Madalena Pinto, Rui Vaz*

Resumo

Introdução: A espondilodiscite tuberculosa é a manifestação mais comum e grave da tuberculose extra-pulmonar, representando cerca de 40 a 50% dos casos em que ocorre atingimento osteo-articular. Apesar do tratamento de base permanecer a quimioterapia antibacilar, o tratamento cirúrgico revela-se importante em algumas situações. As abordagens convencionais de desbridamento radical têm vindo a dar lugar a técnicas cirúrgicas minimamente invasivas.
Caso Clínico: Os autores descrevem o caso clínico de um homem de 86 anos, a quem foi diagnosticada espondilodiscite tuberculosa em L2-L3 complicada por abcesso epidural anterior, abcessos dos músculos psoas bilaterais e meningoencefalite. O doente foi abordado com acessos posteriores paramedianos minimamente invasivos com retractores tubulares e submetido a discectomia L2-L3, drenagem dos abcessos referidos e fixação transpedicular percutânea L2-L3. O procedimento decorreu sem complicações e a evolução pós-operatória foi favorável.
Discussão: A abordagem posterior minimamente invasiva permite um acesso adequado ao canal vertebral para descompressão nervosa em situações de infecção vertebral. Combinada com fixação interna percutânea previne a perda do alinhamento vertebral a longo prazo e facilita a mobilização precoce.

Palavras-chave: Tuberculose Vertebral; Abcesso Epidural; Espondilodiscite; Procedimentos Cirúrgicos Minimamente Invasivos.

Abstract

Introduction: Tuberculous spondylodiscitis is the most frequent and severe manifestation of extrapulmonary tuberculosis, accounting for 40 to 50 percent of the cases with osteoarticular involvement. Although antituberculous drugs remain the cornerstone of therapy, surgical treatment still has an important role in the management of some situations. Classical approaches of radical debridement have been gradually replaced by minimally invasive surgical procedures.
Case Report: The authors describe a case of an 86-year-old male, diagnosed with a L2-L3 tuberculous spondylodiscitis complicated by an anterior epidural abscess, bilateral psoas muscle abscesses and meningoencephalitis. The patient underwent surgery by minimally invasive posterior paramedian approaches with tubular retractors. A L2-L3 discectomy, drainage of the abscesses and L2-L3 percutaneous transpedicular fixation were performed. The procedure and postoperative period were uneventful and the patient had a favourable outcome.
Discussion: A minimally invasive posterior approach allows adequate access to the spinal canal for neural decompression in cases of spinal infection. Combined with percutaneous internal fixation the procedure prevents the loss of vertebral alignment and facilitates an early mobilization of the patient.

Keywords: Spinal Tuberculosis; Epidural Abscess; Spondylodiscitis; Minimally Invasive Surgical Procedures.

Introdução

A espondilodiscite tuberculosa é a forma mais grave e comum de tuberculose extra-pulmonar, representando cerca de 40 a 50% dos casos em que ocorre atingimento osteo-articular. A sua incidência

*Serviço de Neurocirurgia e Serviço de Neurologia do Hospital de São João, Porto, Portugal

global tem vindo a aumentar devido a fenómenos de migração, malnutrição, sobrepovoamento e ao incremento da taxa de infecção por HIV[1].

Apesar do tratamento de base permanecer a quimioterapia antibacilar, o tratamento cirúrgico assume um papel importante em algumas situações, nomeadamente na presença de défice neurológico, instabilidade e deformidade vertebral significativa, sépsis grave, abcessos paravertebrais e epidurais, na necessidade de biopsia diagnóstica e no caso de falência do tratamento médico[2].

Vários procedimentos cirúrgicos de desbridamento, fusão e instrumentação têm sido descritos para a tuberculose da coluna lombar, sendo a abordagem mais convencional o desbridamento radical anterior, fusão com enxerto e reconstrução vertebral que, apesar da agressividade, possibilita bons resultados neurológicos e uma reduzida taxa de recorrência da infecção. As técnicas posteriores apresentam resultados superiores na correcção da deformidade angular e na estabilização vertebral permitindo, em alguns casos, o desbridamento adequado[2]. A escolha da via de abordagem cirúrgica é controversa e depende, sobretudo, da extensão de destruição vertebral, do local de compressão dural e da condição médica do doente[3].

Nas últimas décadas, o desenvolvimento das técnicas de diagnóstico e imagem, de esquemas antibacilares mais eficazes e de técnicas de instrumentação posterior para a estabilização da coluna, levou a um paradigma mais conservador no tratamento da tuberculose vertebral, tendo as técnicas menos invasivas assumido um lugar de destaque[2, 4].

Os autores descrevem o caso clínico de um doente com espondilodiscite tuberculosa L2-L3 complicada por abcesso epidural, abcessos dos psoas bilaterais e meningoencefalite, submetido a técnica cirúrgica posterior minimamente invasiva com drenagem das colecções supuradas e estabilização com fixação interna percutânea.

Caso Clínico

Doente do sexo masculino, de 86 anos, com antecedentes de tuberculose pleural (há cerca de 30 anos) e doença pulmonar obstrutiva crónica, admitido por lombalgia com 3 semanas de evolução associada a febre, perda de mobilidade, períodos de sonolência e desorientação espácio-temporal, discurso inadequado, alucinações visuais, incontinência urinária e fecal e deterioração progressiva do estado de consciência.

Ao exame neurológico: estado estuporoso, pares cranianos sem alterações, mobilização dos quatro membros sem lateralização/assimetrias, reflexos osteo-tendinosos vivos e simétricos.

Da investigação realizada destaca-se: TC cerebral sem alterações relevantes, hemoglobina de 11,5 g/dL, sem leucocitose, com hipoproteinemia e hipoalbuminemia, GGT – 58 U/L, ADA – 38 UI/L, proteína C reactiva (PCR) – 111,9 mg/L, função tiroideia normal, serologia de sífilis, doença de Lyme e reacção de Wright negativas. Punção lombar com 32 células (93 % mononucleares), proteínas 1,69 g/L, glicose 0,4 mmol/L, serologia *Borrelia* e *Aspergillus* negativas, FTA/ABS e VDRL negativos, antigénio *Criptococcus* negativo, *Polymerase Chain Reaction* de DNA HSV1, HSV2 e *Mycobacterium tuberculosis* (MT) negativos, exame directo e cultural de MT negativo. Prova tuberculínica (0,0002 mg/mL – 2U) positiva com 25 mm. Exame directo e cultural das secreções brônquicas negativos, uroculturas e hemoculturas negativas. Broncofibroscopia sem citologia maligna no escovado brônquico, pesquisa de DNA de MT, exame directo e culturas negativos.

A ressonância magnética (RM) lombar (Figura 1) evidenciou espondilodiscite em L2-L3 com envolvimento dos corpos vertebrais e tecidos paravertebrais, abcessos bilaterais dos músculos psoas e extensão intracanalar, com abcesso epidural anterior comprimindo e desviando posteriormente o saco tecal e invasão dos buracos de conjugação bilateralmente em L2-L3 e L3-L4.

O doente foi submetido a cirurgia, com acessos posteriores paramedianos minimamente invasivos com retractores tubulares expansíveis METRx X-Tubes™ (Medtronic, Inc.), desbridamento do espaço discal L2-L3, drenagem de abcessos epidural anterior e dos psoas bilateralmente e fixação transpedicular percutânea L2-L3 com sistemas MAST Legacy™ e Sextant II (Medtronic Inc.). O procedimento durou 3 horas e decorreu sem complicações, sem necessidade de transfusão de sangue intra ou pós-operatório. O estudo microbiológico do pús do abcesso epidural anterior permitiu o isolamento de DNA do MT por biologia molecular confirmando o diagnóstico etiológico.

No pós-operatório constatou-se evolução analítica favorável com diminuição progressiva da PCR. Iniciou terapêutica antibacilar (isoniazida 300 mg id, rifampicina 600 mg id, pirazinamida 1500 mg id

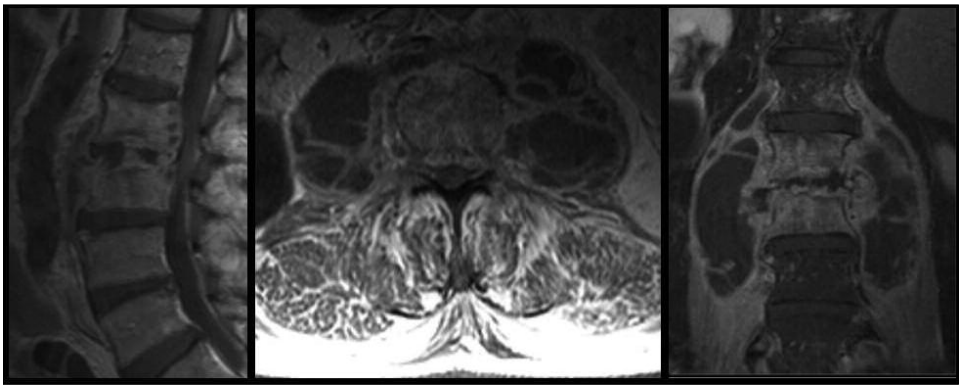

Figura 1. RM lombar T1 sagital e coronal com contraste pré-operatório: Espondilodiscite L2-L3 com abcessos dos psoas bilaterais e abcesso epidural anterior.

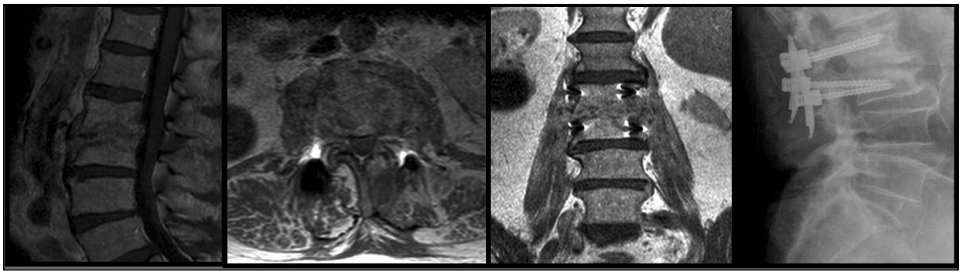

Figura 2. RM e radiografia lombar aos 6 meses de pós-operatório.

e etambutol mg 1200 id). O doente apresentou melhoria progressiva do estado de consciência, com alívio significativo da dor e início progressivo de marcha com ortótese lombar e apoio.

A reavaliação imagiológica por RM e radiografia dinâmica da coluna lombar mostrou evolução favorável do processo infeccioso com resolução das colecções supuradas e fusão intersomática vertebral (Figura 2). Aos 2 meses após a cirurgia o doente encontrava-se consciente, colaborante e orientado, com lombalgia residual mínima e deambulando sem ajuda.

Discussão

Com a apresentação deste caso clínico os autores pretendem realçar a possibilidade da utilização de técnicas minimamente invasivas no tratamento cirúrgico da espondilodiscite tuberculosa. Embora a base do tratamento seja a quimioterapia antibacilar, esta por si só não é suficiente para tratar a destruição óssea e articular e evitar a deformidade cifótica e instabilidade, tornando-se a cirurgia necessária em doentes nos quais estes processos sejam significativos[5].

Os objectivos da intervenção neurocirúrgica na espondilodiscite tuberculosa são: o isolamento do microorganismo responsável, a drenagem e desbridamento do foco infeccioso e assegurar a estabilidade neurológica e mecânica[6]. Os procedimentos de drenagem e fixação podem ser realizados de forma simultânea ou sequencial, pelo que as técnicas existentes são múltiplas.

A abordagem clássica de desbridamento radical e fusão anterior com enxerto («Hong Kong operation»), descrita por Ito em 1934 e Hodgson em 1960, surgiu numa era de diagnóstico tardio com défices neurológicos graves e destruição óssea avançada[7-8]. Na presença de instabilidade vertebral esta técnica é geralmente complementada por fixação por via posterior[9].

Com a evolução das técnicas laboratoriais e imagiológicas e um diagnóstico mais precoce, têm sido possíveis opções cirúrgicas mais conservadoras do que a abordagem radical anterior, realçando-se a importância da adequação do procedimento cirúrgico às necessidades individuais do doente[4]. Nussbaum *et al*[10] propõem um tratamento cirúrgico ajustado ao grau de destruição óssea,

em que o desbridamento agressivo e a fusão são reservados para doentes com envolvimento extenso do corpo vertebral resultando em cifose. Rezai *et al*[11] defendem a abordagem cirúrgica radical quando a destruição do corpo vertebral excede os 50 %. Neste contexto, foram desenvolvidas técnicas de abordagem posterior isoladas com descompressão e fixação para os casos de tuberculose vertebral menos avançada. Segundo Güven *et al*[12] e *Lee et al*[13], a instrumentação posterior com sistemas de fixação rígidos com parafusos transpediculares possibilita boa estabilização, prevenção da cifose e deformidade angular e alívio da dor.

Realça-se a segurança da colocação do material de instrumentação em áreas com infecção bacilar. Vários estudos demonstraram que o MT tem menor capacidade para formar biofilmes e aderências aos implantes (sobretudo ligas de titânio), quando comparado com infecções estafilocócicas, o que confere segurança adicional ao procedimento de fixação[14-15].

Com este caso clínico os autores confirmam que a abordagem posterior minimamente invasiva permite um acesso adequado ao canal vertebral para descompressão nervosa em situações de infecção vertebral com componente epidural anterior. A idade, o estado clínico do doente e as co-morbilidades existentes reforçaram a indicação para o uso de uma técnica cirúrgica menos agressiva. A descompressão nervosa e o desbridamento cirúrgico por técnica minimamente invasiva combinada com fixação interna percutânea contribuíram para a melhoria do estado neurológico e para a mobilização precoce do doente e preveniram a perda do alinhamento vertebral.

Correspondência para
Bruno Carvalho
Serviço de Neurocirurgia do Hospital de São João,
Porto, Portugal
E-mail: bmfcarvalho@gmail.com

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HANSEN´S DISEASE MIMICKING A SYSTEMIC VASCULITIS

Luzia Sampaio*, Lígia Silva*, Georgina Terroso*, Sofia Pimenta*, Filipe Brandão*, José Pinto*, António Prisca**, José Brito*, Francisco Ventura*

Abstract

Hansen's disease, caused by *Mycobacterium leprae*, classically presents with cutaneous and neurological manifestations. Rheumatologic manifestations present in 1 to 5% of the patients, and include arthritis, arthralgias, Charcot arthropathy, erythema nodosum and vasculitis. We report a case of a 86 year old woman with polyarthritis, subcutaneous nodules and leg ulcers whose differential diagnosis included primary vasculitis and diffuse connective tissue diseases and ended to be leprosy in a non endemic country.

Keywords: Hansen Disease; Leprosy; Vasculitis; Arthritis

Introduction

Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae*, with predominant involvement of skin and nerves[1]. It is an endemic disease that presents as a spectrum of clinical manifestations depending on the immune response of the host: lepromatous, tuberculoid, borderline lepromatous, borderline tuberculoid and mid borderline[1,2]. Lepra reactions are acute inflammatory states that commonly precede diagnosis or occur after the initiation of appropriate chemotherapy.

The classical presentation of leprosy is in the form of macules or papulo nodular lesions and paresthesias or sensori-motor mononeuropathy, mononeuritis multiplex or polyneuropathy[1,2].

Musculoskeletal manifestations range from 1 to 5% for patients with leprosy but may increase to 50 to 70% during reactional states[3]. They include arthritis, arthralgias, Charcot arthropathy, erythema nodosum and vasculitis[4].

We present a clinical case with polyarthritis, subcutaneous nodules and leg ulcers that simulated a rheumatic disease.

Case Report

A 86 years old, caucasian female, presented with a five years history of symmetric polyarthritis of metacarpophalangeal, proximal interphalangeal, wrists and elbows, treated with predisolone 5mg id and naproxen 500mg bid. In 2003 she reports painless subcutaneous nodules in the legs, and one year ago the spread of this nodules, to the upper and inferior extremities, ulcerative lesions in the legs and distal paresthesias of both upper and inferior extremities. She denied infectious diseases or journeys to endemic countries for leprosy.

She was admitted to our hospital, presenting painful nodular lesions on the extremities (Figure 1), some of them ulcerated, leg ulcers (Figure 2), symmetric polyarthritis of proximal interphalangeal and metacarpophalangeal, ulnar deviation of fingers, and distal and symmetric hypoesthesia of the upper and lower limbs. She was apyretic, with palpable and symmetric peripheral arterial pulses, and normal cardiovascular, respiratory and abdominal examination.

Laboratory blood tests revealed anaemia (Hgb 10,6 g/dL), elevated erytrhrocyte sedimentation rate (62 mm) and C-reactive protein (7,6 mg/L), with normal renal and liver function, urianalysis and immunoglobulins. Rheumatoid factor, antinuclear antibody, and anti-neutrophil cytoplasmic antibodies were negative.

Microbiology examination of leg ulcer isolated a *Staphylococcus aureus* sensitive to ciprofloxacin

*Serviços de Reumatologia do Hospital de São João e da Faculdade de Medicina do Porto
**Serviços de Doenças Infecciosas do Hospital de São João e da Faculdade de Medicina do Porto

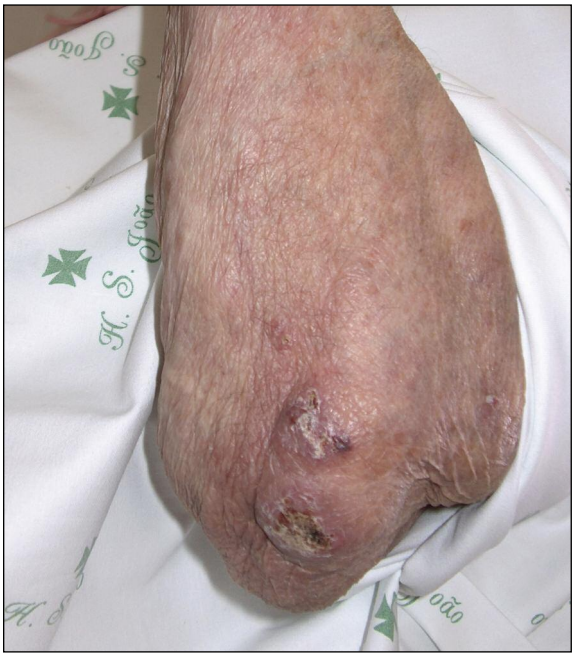

Figure 1. Nodular lesions in the arm

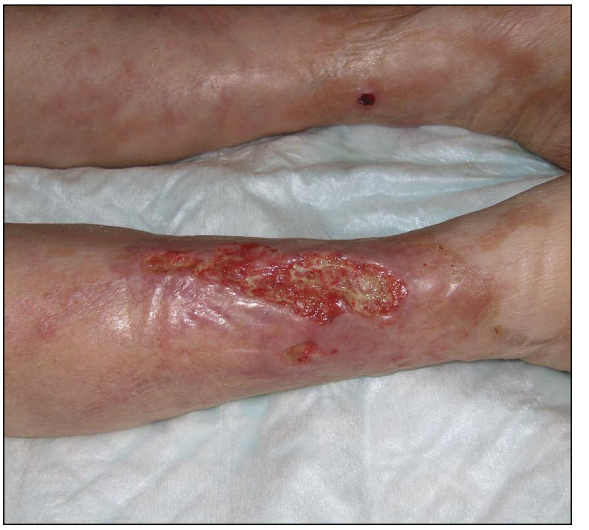

Figure 2. Leg ulcer with 12x2cm

which was instituted for 15 days.

Chest x-ray was normal.

Hands and feet radiographs revealed bone erosions in the first interphalangeal of the left hand (Figure 3).

The electromyography revealed mononeuritis multiplex.

Biopsy of a forearm nodule revealed a dermal lymphohistiocytic and plasma cell nodular infiltrate. Histochemistry staining (PAS, Grocott, Fite-Faracco) showed macrophages containing abundant Mycobacterium leprae (Figure 4).

The diagnosis of reactional lepromatous leprosy with skin lesions compatible with Lucio's phenomenon was made, and started rifampin 600 mg id, dapsone 100mg id and clofazimine 50mg id. This treatment continued for thirty days, with progressive amelioration of skin lesions, leg ulcers and arthritis. Rifampin was reduced to 600 mg per month, with dapsone 100mg id, clofomazine 50mg id and prednisolone 5mg id, maintaining a good response after six months of follow up.

Discussion

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The route of transmission remains uncertain and may be multiple: nasal droplet infection, contact with infected soil, and even insect vectors have been considered the prime candidates. In endemic countries 50% of leprosy patients have a history of intimate contact with an infected person, while for unknown reasons leprosy patients in nonendemic locales can identify such contact only 10% of the time.

The husband of this patient lived in Africa forty years ago during 5 years, and had leprosy in that

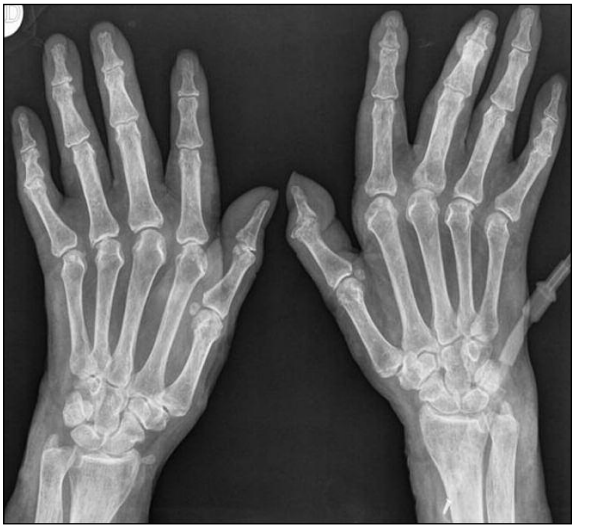

Figure 3. Hand x-ray. Periarticular osteoporosis in the metacarpophalangeal, joint space narrowing, geodes on the first and second metacarpo, and erosions in the first interphalangeal of the left hand.

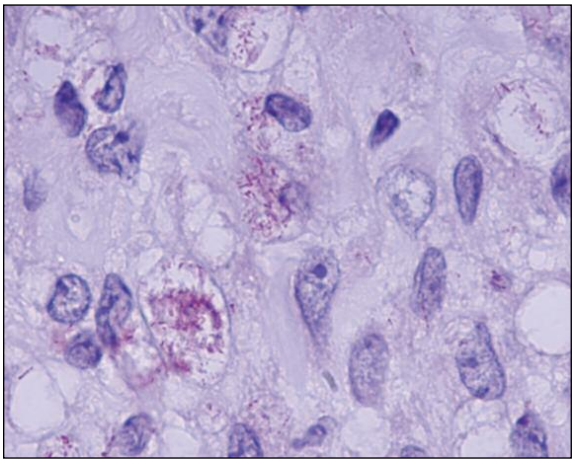

Figure 4. Subcutaneous nodule biopsy (Fite-Faracco staining): macrophages with abundant Mycobacterium leprae

period. He was treated and considered cured.

Lepromatous leprosy is characterized by a reduced immune response with a predominance of T CD8 cells and a large number of bacilli in the tissues. This form of leprosy has some clinical and serologic similarities with rheumatic diseases, such as erythematosous macules, subcutaneous nodules, arthralgias, polyarthritis and sometimes rheumatoid factor, antinuclear antibody or anti-neutrophil cytoplasmic antibodies[4,5].

Lucio's phenomenon is an unusual reaction that occurs in untreated lepromatous leprosy, characterized by recurrent crops of large ulcerative lesions, particularly on the lower extremities, without significant general symptoms. These lesions are histologically characterized by ischemic necrosis of the epidermis and superficial dermis, and heavy parasitism of cells with acid-fast bacilli[5].

Arthritis in leprosy can be acute or chronic. Acute arthritis is associated with reactional states and is characterized by a symmetric polyarthritis involving the knees, ankles, wrists, elbows, proximal interphalangeal, metacarpophalangeal and metatarsophalangeal, without radiographic abnormalities. The synovial fluid is inflammatory and sterile, and synovial biopsy can show lymphoplasmocytic infiltrate with bacilli. Chronic arthritis is the commonest form, and is characterized by an insidious symmetric polyarthritis involving the wrist, small joints of the hands and feet, and knees. Radiographs can rarely show bony erosions[6]. In most cases polyarthritis manifests concomitant to the skin lesions, although in some cases it can precedes the cutaneous manifestations, as in this clinical case, and have a slow progression[7].

Vasculitis can be seen in Lucio s phenomenon and is characterized by endothelial proliferation, ischemic necrosis, mononuclear infiltrate and bacilli in small vessel walls[4,5].

In this case, the patient had chronic polyarthritis, with few bone erosions, without RF and subsequently developed painful subcutaneous nodules, ulcerative lesions in both legs and mononeuritis multiplex, in a non endemic country, mimicking rheumatic diseases.

We suspected of primary vasculitis, like polyarteritis nodosa, or vasculitis secondary to connective tissue disorders like rheumatoid arthritis. The biopsy was the main exam that allowed the correct diagnosis and treatment of leprosy, avoiding the institution of immunosuppressive drugs that would have led to high morbidity[8].

The therapeutic regime instituted was based on the World Health Organization recommendations for the chemotherapy of leprosy. It classifies patients as multibacillary if they have six or more skin lesions, and as paucibacillary if they have fewer. The WHO recommends that paucibacillary adults should be treated with dapsone 100mg id and rifampin 600mg monthly for 6 months, and multibacillary adults be treated with dapsone 100mg and clofazimine 50mg daily unsupervised, and rifampin 600mg and clofazimine 300mg monthly supervised, for 1 to 2 years[9].

In this case as the clinical presentation was a severe form of multibacillary, it was decided to start with rifampin 600mg daily during one month, since it is the only bactericidal drug, and maintain clofazimine 50mg/d during all the treatment, with gradual improvement.

Correspondence to
Luzia Sampaio
Hospital São João,
Serviço de Reumatologia,
Alameda Professor Hernani Monteiro,
4200-319 Porto
Telefone: 225 512 100
E-mail: luziasampaio@hotmail.com

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28th Annual General Meeting of the British Society for Rheumatology

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Taipei, Tailândia
15 a 17 Abril 2011

SHOENFELD´S SYNDROME AFTER PANDEMIC INFLUENZA A/H1N1 VACCINATION

Solange Murta Barros*, Jozélio Freire de Carvalho**

Abstract

Recently, reports have suggested grouping different autoimmune conditions that are triggered by external stimuli as a single syndrome called autoimmune/inflammatory syndrome induced by adjuvants (ASIA). This syndrome is characterized by the appearance of myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, and the possible emergence of a demyelinating autoimmune disease caused by systemic exposure after vaccines and adjuvants. In the current study, the authors reported the first Brazilian case of a woman who developed ASIA, which was characterized by arthralgia, changes in inflammatory markers, and chronic fatigue, after the pandemic anti-influenza A/H1N1 vaccine without causing any other rheumatic disease, and it had a positive outcome.

Keywords: Pandemic H1N1 Influenza; Vaccination.

Introduction

A new influenza pandemic originated in North America during June of 2009, quickly spread throughout the world and resulted in a high mortality in young adults, especially in pregnant women and patients with chronic diseases[1]. It was nicknamed «Swine flu» and was soon identified as an epidemic of the influenza A/H1N1 virus without any regard to the cross-transmission by other animals. Laboratories quickly produced specific vaccines, and after preliminary studies on its immunogenicity and safety, the vaccines were released for mass immunization. The World Health Organization (WHO), which was already on high alert and modeling their control strategy on the H5N1 bird flu, called for the vaccination of the population, primarily the vaccination of professionals, those suffering from chronic diseases, pregnant women and other groups at risk, to contain the pandemic[1,2]. Currently, vaccination appears to be an efficient tool for controlling pandemic influenza A/H1N1, which still presents cases in India and Oceania[3]. WHO and its Global Advisory Committee on Vaccine Safety contend that monovalent anti-influenza vaccines, for influenza A/H1N1, produced from adjuvant or non- adjuvant viral fragments, are as safe and effective as the use of seasonal influenza polyvalent vaccines in the general population. Furthermore, its side effects are primarily local, minor and of short duration, such as pain at the injection site, a low-grade fever, coryza and myalgia and, very rarely, an allergic phenomena, such as urticaria, edema or bronchospasm. They also argued that adverse effects are less common than with other live virus vaccines. The adjuvants that are added by some manufacturers to reduce the amount of antigens used to stimulate and increase the immune response have been proven safe for use in immunization programs associated with other pathologies[4-6]. However, these same references warn that preclinical and clinical studies would not be able to identify all of the rare events that could occur during the application in a mass population, and they recommended a comprehensive surveillance system to collect information regarding the most serious post-vaccination effects, which in Brazil is coordinated by the National Agency of Sanitary Surveillance Agency (ANVISA)[7,8].

Recently, Shoenfeld suggested grouping different autoimmune conditions that are triggered by external stimuli as a single syndrome called autoimmune/inflammatory syndrome induced by adjuvants (ASIA). This syndrome is characterized by clinical manifestations, such as myalgia, myositis, muscle weakness, arthralgia or arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, as well as pos-

*Rheumatology Division, Hospital Naval Marcílio Dias, Rio de Janeiro – RJ, Brazil
**Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo-SP, Brazil

sible emergence of either a demyelinating or systemic autoimmune disease after exposure to vaccines and adjuvants (Table I)[9,10].

In this article, the authors describe the case of a woman who developed an atypical presentation of ASIA with arthralgia, changes in inflammatory markers, and chronic fatigue after administration of the pandemic anti-influenza A/H1N1 vaccine. The vaccine did not cause any other currently known rheumatic disease. This clinical case helps to establish the diagnosis of an auto-inflammatory syndrome induced by adjuvants, according to Shoenfeld's criteria[9].

Case report

We describe a case of a 44-year-old female patient, with a history of allergic rhinitis, hyperprolactinemia and systemic arterial hypertension, treated with 25-mg/day of atenolol for seven years, and history of a single episode of idiopathic uveitis on her left eye and treated without sequelae more than fifteen years ago. Two years before this, she had a history of trivalent seasonal influenza vaccinations without any reports of adverse reactions. Her mother has rheumatoid arthritis. The patient had been immunized with a single 3.75 µg dose intramuscularly with the monovalent vaccine strain, H1N1/California/7/2009 virus, which was propagated in eggs containing the AS03 squalene as an adjuvant, two weeks prior to the development of acute symptoms and the rapid progression of the complains. The patient presented with chronic fatigue not relieved after rest, myalgia, muscle weakness, diffuse arthralgia in her hands, wrists, ankles and feet, with inflammatory characteristics and neck pain. Upon examination, the pain was expressed in all proximal interphalangeal, second, and third metacarpophalangeal joints symmetrically. The patient also had painful palpation of the metatarsal and calcaneal region, without pain with ankle mobilization. We also found tender points located at the upper edge of the trapezoid, all bilaterally and on the epicondyle side. C-reactive protein (CRP) levels increased early, followed by a significant increase in the erythrocyte sedimentation rate (ESR). On the 21st, 30th, 60th, and 90th days after immunization the CRP levels were 1.03 mg/L, 2.36 mg/L (maximum), 1.66 mg/L and 0.15 mg/L (normal value <0.5 mg/L); and, moreover, the ESR of 25 mm/1st hour, 37 mm/1st hour, 41 mm/1st hour (maximum), and 9 mm/1st hour rates, respectively (Figure 1). The patient had a negative rheumatoid factor and negative anti-CCP antibodies with the absence of hypergammaglobulinemia, antinuclear antibodies, and anti-Ro/SS-A antibodies. Serologies for toxoplasmosis, Epstein-Barr virus, cytomegalovirus, parvovirus B19, HIV, and Hepa-

Table I. Criteria suggested by Shoenfeld for ASIA diagnosis

Major criteria:

- Exposure to an external stimuli (infection, vaccine, silicone, or adjuvant) prior to clinical manifestations
- Appearance of one of the clinical manifestations listed below:
  - Myalgia, myositis, or muscular weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, non-restful sleep, or sleep disturbances
  - Neurological manifestations (especially those associated with demyelization)
  - Cognitive alterations and loss of memory
  - Fever and dry mouth
- Removal of the initiating agent induces improvement
- Typical biopsy of the involved organs

Minor criteria:

- Appearance of autoantibodies directed against the suspected adjuvant
- Other clinical manifestations (e.g., irritable bowel syndrome)
- Specific HLA (e.g., HLA DRB1, HLA DQB1)
- Initiation of an autoimmune illness (e.g., multiple sclerosis or systemic sclerosis)

For the diagnosis of ASIA, the presence of at least 2 major or 1 major and 2 minor criteria must be apparent. This is a reproduction obtained with the author's permission.

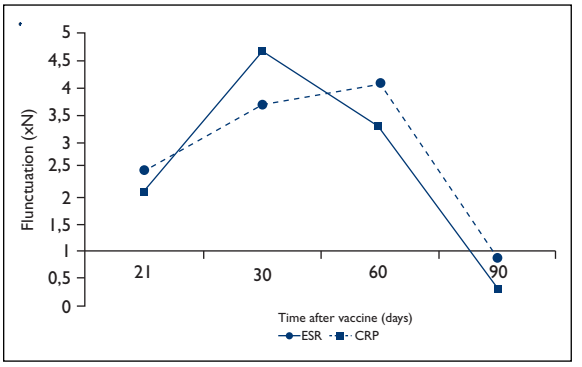

Figure 1. The evolution of inflammatory biomarkers after vaccination

N: reference value adjusted for 1 unit; xN: times the normal upper limit value; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

titis B and C were also negative. Normal thyroid hormones and a slight increase of prolactin (29.47 ng/mL compared to a normal value of <20 ng/mL) were observed. The initial radiological evaluation of the hands, wrists, ankles, and feet showed no abnormalities. The diagnosis of Shoenfeld's syndrome or an autoimmune/inflammatory syndrome induced by adjuvants was performed based on Shoenfeld's proposed criteria[9] (Table I). The patient was treated with 1 g paracetamol three times daily, 400 mg ibuprofen four times daily for the first few months, and 400 mg hydroxychloroquine daily, and a gradual improvement of pain was observed after four weeks of anti-malarial drug administration. Chloroquine was used trying to block the autoimmune mechanisms and seemed to be successful. No significant new complaints appeared during the two months after starting the treatment. The evolution of the pathology had a significant impact on the daily functional and work activities of the patient. Currently, the patient was able to complete her important daily activities with no need to control the pain and did not present any new symptoms.

Discussion

The authors describe the first case of post-vaccination ASIA in Brazil for prophylaxis pandemic influenza A/H1N1 recommended for application in mass population situation officially declared pandemic.

This patient developed symptoms abruptly (fourteen days after vaccination of the monovalent adjuvanted anti-influenza A/H1N1 by compound squalene). These symptoms were chronic fatigue syndrome with arthralgia, myalgia, chronic fatigue no relieved after rest and difficulty maintaining their usual activities. The patient had never presented similar symptoms, had no standardized number of tender points that were sufficient for a diagnosis of fibromyalgia, and had no important local reaction and high inflammatory activity at the vaccination site. In addition, the patient had no criteria suggesting a manifestation of early rheumatoid arthritis, scleroderma, polymyositis, systemic lupus erythematosus or any other systemic collagen-specific pathology. These findings led the authors to consider ASIA[9] (Table I).

A clear temporal relationship herein observed exists between the immunogenic vaccine and the degree of the functional impairment and it was seen two weeks after vaccination. The association between the vaccination and the onset of autoimmune manifestations have been described in the literature like the reaction to the vaccination against seasonal influenza and cases of Guillain-Barre[10], inflammatory myopathy triggered by the adjuvant aluminum in vaccines administered in France[11], and compulsory immunization in polyform sent to military operations in the Persian Gulf[12], namely the vaccination against anthrax. Specific antibodies against major adjuvants have been isolated from healthy vaccine recipients, and extensive discussion has been conducted on the meaning of these clinical findings[12,13]. However, these occurrences are more frequent when associated with rare genetic preconditions in the general population, which was observed with myositis in the macrophage caused by aluminum[11].

The relationship between infections with viral agents that serve as a trigger for self-harm responses and the subsequent development of autoimmune changes can be caused either directly by infection with an impairment of lymphocyte function or cytolysis with intracellular exposure. For several other mechanisms to stimulate the aberrant production of autoantibodies and chemotropic, a phenomenon must occur that is independent of viral replication and, therefore, may occur after exposure of the fractions found in inactivated viral vaccines[14]. The increase in the immune response is the purpose of the use of adjuvants. Although they are considered safe for use on a large scale, they are not absolutely free of side ef-

fects[13,15,16]. The assessment of the safety of the influenza vaccine and adjuvants were not exhaustive due to the fast response, production, and marketing that was required by the pandemic[2]. Furthermore, their use was excluded from trials of individuals with a history of atopy or prior immunodeficiency (congenital or acquired) or patients that were receiving immunosuppressive therapy or steroids prior to vaccination[17].

Although does not exist clear evidence that the vaccination against influenza A/H1N1 could trigger the onset or aggravate the course of an autoimmune disorder in recipients receiving the vaccine, fear remains that preventive viral immunization is the biological stimulus that is sufficient to trigger an atypical autoimmune reaction with a disproportionate risk/benefit ratio for the target.

To our knowledge, after the pan-immunization campaign against the recent influenza H1N1 virus in this country, no published cases of a similar reaction have been reported. The diagnosis applied to this case is recognized as the first Shoenfeld's syndrome case reported in Brazil.

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Correspondence to
Jozélio Freire de Carvalho
Disciplina de Reumatologia da Faculdade de Medicina da Universidade de São Paulo
Av. Dr. Arnaldo, 455, 3 andar, sala 3190, Cerqueira César, São Paulo-SP, Brasil CEP 01246-903
E-mail: jotafc@gmail.com

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PROTRACTED FEBRILE MYALGIA SYNDROME COM PÚRPURA DE HENOCH-SCHÖNLEIN: FORMA ATÍPICA DE APRESENTAÇÃO DE FEBRE MEDITERRÂNICA FAMILIAR

Marta Cabral*, Marta Conde**, Maria João Brito***, Helena Almeida****, José António Melo Gomes*****

Resumo

A Febre Mediterrânica Familiar (FMF) é uma doença hereditária autossómica recessiva caracterizada por episódios de febre recorrente, artrite e poliserosite – peritonite, pleurite e/ou pericardite. A sua principal complicação é a amiloidose AA sistémica.

Menina de 8 anos, origem africana, com febre recorrente desde os 5 anos e três internamentos com febre, dor abdominal e elevação dos reagentes de fase aguda. No primeiro episódio foi sujeita a apendicectomia e no terceiro o quadro clínico acompanhou-se de mialgias, púrpura e proteinúria não nefrótica. A biopsia renal foi compatível com nefrite de Henoch-Schönlein. Durante os episódios de febre e dor abdominal registou-se um nível sérico de amilóide A - 92 mg/L (VR < 6.8) que levantou a suspeita de FMF. Posteriormente o diagnóstico foi confirmado por estudo genético (homozigotia para M694V no gene *MEFV*). Iniciou colchicina e actualmente encontra-se em remissão completa.

A FMF deve ser considerada no diagnóstico diferencial de febre e dor abdominal recorrente na criança, mesmo quando a forma de apresentação é atípica (p.e. *Protracted Febrile Myalgia Syndrome)*. O estudo genético permite confirmar o diagnóstico e tem valor em termos de prognóstico.

*Interna do Internato Complementar de Pediatria, Departamento de Pediatria do Hospital Prof. Doutor Fernando Fonseca E.P.E., Amadora

**Assistente Hospitalar de Pediatria, Consulta de Reumatologia Pediátrica, Departamento de Pediatria do Hospital Prof. Doutor Fernando Fonseca E.P.E., Amadora

***Assistente Graduada de Pediatria, Consulta de Infecciologia Pediátrica, Departamento de Pediatria do Hospital Prof. Doutor Fernando Fonseca E.P.E., Amadora

****Chefe de Serviço de Pediatria de Cuidados Intensivos de Pediatria, Departamento de Pediatria do Hospital Prof. Doutor Fernando Fonseca E.P.E., Amadora

*****Assistente Graduado de Reumatologia, Unidade de Reumatologia Infantil, do Adolescente e do Adulto Jovem, Instituto Português de Reumatologia, Lisboa

Palavras-chave: Febre Mediterrânica Familiar; *MEFV*; Púrpura de Henoch-Schönlein; Mialgia.

Abstract

Familial Mediterranean Fever (FMF) is an hereditary autosomal recessive disease characterized by recurrent attacks of fever, arthritis and serositis: peritonitis, pleurisy and/or pericarditis. Its main complication is systemic AA amyloidosis.

The authors present a case of a 8-years-old female child with african ancestry, who was admitted three times since 5 years-old with abdominal pain, fever and high acute phase reactants. At the first admission appendectomy was made and at the third hospital admission the clinical picture was accompanied by myalgia, purpuric lesions and non nephrotic proteinuria. A renal biopsy was performed and was compatible with Henoch-Schönlein nephritis. Serum Amyloid A protein had high levels - 92 mg/L (< 6.8) and a diagnosis of Familial Mediterranean Fever was confirmed by genetic test (homozygote for M694V in *MEFV* gene). She started colchicine and is doing well, without any further complaints.

FMF must be considered in the differential diagnosis of recurrent attacks of fever and abdominal pain in children, even with an atypical presentation (p.e. *Protracted Febrile Myalgia Syndrome*). Genetic study allows the confirmation of the diagnosis and has prognostic implications.

Keywords: Familial Mediterranean Fever; *MEFV*; Henoch-Schönlein Purpura; Myalgia.

Introdução

Os síndromes febris periódicos hereditários constituem um grupo de doenças caracterizadas por

febre recorrente e inflamação sistémica, sem uma causa infecciosa ou autoimune, e que remitem espontaneamente[1,2]. Destes, a Febre Mediterrânica Familiar (FMF) é o mais prevalente[1,3].

Actualmente, com a possibilidade da identificação de mutações do gene *MEFV*, localizadas no braço curto do cromossoma humano 16p, a FMF é reconhecida em todo o mundo[4-6].

A FMF caracteriza-se por episódios recorrentes de febre e inflamação sistémica com serosite, com 1 a 4 dias de duração e intervalos irregulares (semanas a anos), com grande variabilidade individual. Os episódios são autolimitados, remitem espontaneamente e, no intervalo dos mesmos, os doentes permanecem assintomáticos. Raramente pode apresentar-se com febre prolongada (semanas de duração) e mialgias – «*Protracted Myalgia Syndrome*», o que pode levantar dificuldades diagnósticas[7-9]. Durante os episódios agudos os parâmetros laboratoriais de inflamação elevam-se de forma significativa, normalizando ou permanecendo ligeiramente aumentados no intervalo dos episódios, à excepção da proteína amilóide A sérica (AAS), que pode persistir elevada indefinidamente[1]. A principal complicação é a amiloidose AA, com depósitos generalizados de amilóide nos tecidos, particularmente no rim, podendo cursar com consequente insuficiência renal crónica e óbito[10].

O diagnóstico de FMF depende do reconhecimento das manifestações clínicas características, sendo actualmente possível a sua confirmação por estudo genético. A proteína codificada pelo *MEFV*, a pirina, é expressa predominantemente nos neutrófilos e monócitos, tendo um papel regulador na activação do factor nuclear B (NF-κB), produção de IL-1β e apoptose. Uma mutação na proteína pirina desregula a intensidade da resposta inflamatória, conduzindo à produção excessiva de citocinas pró-inflamatórias, como a IL-1b, que desencadeiam as crises inflamatórias e a apoptose celular[11].

O prognóstico da FMF depende da prevenção do desenvolvimento de amiloidose sistémica, sobretudo renal. O tratamento diário com colchicina previne a recorrência das «crises», diminuindo a sua frequência, intensidade e duração, e limita simultaneamente a progressão da amiloidose sistémica[5,3]. A mutação M694V tem sido associada a maior risco de amiloidose e, portanto, a pior prognóstico[12].

O caso descrito é uma apresentação atípica de Febre Mediterrânica Familiar – *Protracted Myalgia Syndrome* – associado a Púrpura de Henoch-Schönlein, cuja incidência está aumentada nos doentes com FMF[13].

Caso clínico

Criança de 8 anos, sexo feminino, origem africana (Cabo Verde), pais não consanguíneos e sem história familiar de doenças inflamatórias crónicas. Sem antecedentes pessoais relevantes até aos 5 anos, quando foi internada por febre (máx. 39,5ºC) persistente, dor abdominal intensa e elevação dos parâmetros laboratoriais de inflamação (leucocitose com neutrofilia e proteína C-reactiva (PCR) 23,4 mg/dL). Por suspeita de abdómen agudo foi apendicectomizada mas o exame histológico do fragmento apendicular foi normal. Teve alta após três dias sendo reinternada cinco dias depois por recorrência da febre e dor abdominal.

Realizou colonoscopia com biopsia que não revelou alterações e em dois dias houve remissão dos sintomas apenas com tratamento sintomático (analgésicos).

Aos 8 anos é reinternada por febre (máx. 40ºC), anorexia, astenia, emagrecimento, dor abdominal difusa intensa e mialgias dos membros inferiores com incapacidade para a marcha, com duas semanas de evolução. Apresentava prostração, palidez da pele e mucosas e taquicárdia (frequência cardíaca: 120-150 bpm); abdómen muito doloroso na região periumbilical, com defesa e sinais de irritação peritoneal. Analiticamente apresentava hemoglobina (Hb) 10,1 g/dL, VGM 73,9 fL, leucócitos 18.000/ L (75,4% de neutrófilos), plaquetas 576.000/ L, PCR 33,1 mg/dL, velocidade de sedimentação (VS) 102 mm/1ªh, fibrinogénio 823mg/dL, D-Dímeros 1.100 g/mL, lactato desidrogenase (LDH) 880 U/L, creatina quinase (CK) 143 U/L. Função renal e aminotransferases hepáticas, amilasémia e análise sumária de urina eram normais. A radiografia do abdómen simples em pé evidenciou distensão gasosa do cólon descendente, com níveis hidroaéreos e espessamento da parede intestinal nesse segmento. A ecografia abdominal revelou múltiplas adenopatias mesentéricas e periaórticas e espessamento parietal da metade esquerda do cólon transverso e segmento superior do cólon descendente, sem colecções líquidas intra-abdominais. Iniciou ampicilina, gentamicina e metronidazol e analgesia.

Apesar da terapêutica manteve febre, anorexia,

dor abdominal e mialgias intensas dos membros inferiores, a que se associaram, ao 16º dia de internamento, lesões cutâneas purpúricas palpáveis e simétricas nos membros inferiores, artrite da tibio-társica direita e joelhos, hipertensão arterial, microhematúria e proteinúria não nefrótica, com função renal normal. A endoscopia digestiva alta revelou «mucosa gástrica com lesões vasculíticas eritematosas»; a TC tóraco-abdominal evidenciou fina lâmina de derrame pleural bilateral, espessamento parietal da metade esquerda do cólon e rins com múltiplos defeitos de captação do contraste. A cintigrafia renal com DMSA mostrou rins assimétricos, com contornos irregulares e lesões recentes compatíveis com cicatriz *versus* vasculite; função renal relativamente conservada. O *doppler* dos vasos renais e mesentéricos, angio-TC abdominal e cintigrafia abdominal com eritrócitos marcados não revelaram alterações. A avaliação por oftalmologia e cardiologia excluiu inflamação ocular e/ou cardiopatia estrutural ou derrame pericárdico respectivamente.

Excluiu-se processo tromboembólico e etiologia infecciosa (Tabela I). Do estudo imunológico salienta-se: aumento de IgA, anticorpo antinuclear (ANA) (máx.1/320), padrão fino granular, e Anticoagulante lúpico (55.9 segundos (< 38) positivos (Tabela I), que posteriormente negativaram.

Realizou biopsia renal e o exame histológico com imunofluorescência indirecta revelou glomerulonefrite com depósito mesangial de IgA e C3, sem crescentes, compatível com nefrite de Púrpura de Henoch-Schönlein. Iniciou prednisolona oral 2mg/kg/dia e terapêutica antihipertensora (nifedipina, propanolol e enalapril), com posterior remissão completa da artrite e lesões cutâneas.

Manteve febre intermitente, com intervalos de 3 a 7 dias entre os episódios de duração variável, dor abdominal, mialgias e elevação dos parâmetros laboratoriais de inflamação (leucócitos 23.000/ L com neutrofilia, plaquetas 1305.000/ L e PCR- 32mg/dL) (Figura 1) até ao 41º dia de internamento. Desde então, assistiu-se à remissão dos sintomas, com melhoria gradual do estado geral e normalização das alterações analíticas, incluindo resolução completa da proteinúria (Tabela II). Teve alta ao 45º dia de internamento, com o diagnóstico de Púrpura de Henoch-Schönlein com nefrite. Na Consulta de Reumatologia Pediátrica, por suspeita de FMF, foi doseada AAS (92 mg/L (< 6,8)) e realizado estudo genético para FMF, que identificou homozigotia para M694V no gene *MEFV* (cromossoma 16p13). Iniciou colchicina 1 mg/dia oral, e em 4 anos de seguimento e manutenção terapêutica permanece assintomática, normotensa e com avaliação laboratorial dentro da normalidade, incluindo níveis de AAS normais.

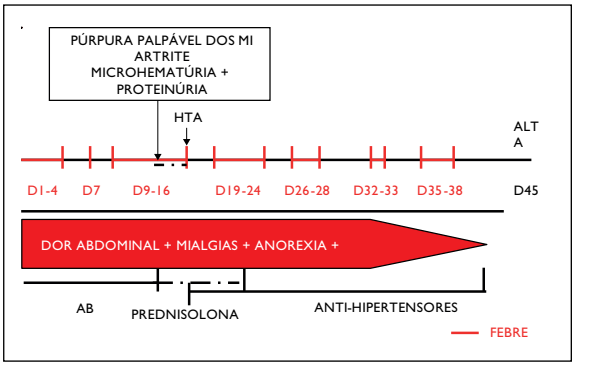

Figura 1. Evolução clínica ao longo do terceiro internamento

Discussão

A FMF é uma doença rara, autoinflamatória, com início mais frequente na infância tal como verificado no presente caso clínico[1]. 90% dos doentes experiencia o primeiro episódio febril antes dos 20 anos e aproximadamente 60% antes dos 10 anos de idade tornando-a uma patologia com incidência predominantemente pediátrica[1].

Afecta ambos os sexos embora alguns estudos tenham reportado um predomínio no sexo masculino[14]. Apresenta uma incidência aumentada em determinados grupos étnicos mediterrânicos como árabes (norte de África), turcos, descendentes armenianos e judeus sefarditas, italianos, gregos e libaneses, não existindo descrições da sua incidência na raça negra, especificamente de origem africana[15].

O diagnóstico baseia-se em critérios clínicos, exclusão de outros síndromes febris periódicos hereditários, história familiar, estudo genético e resposta terapêutica à colchicina.

Vários estudos sugerem um estímulo inflamatório no desencadeamento da doença e dos episódios febris, como imunizações, frio, infecções virais ou distúrbios emocionais, resultando numa resposta inflamatória exagerada[10], mas nesta doente não encontrámos qualquer pródromo precedendo os episódios febris.

Tabela I. Exames complementares de diagnóstico realizados no decurso da investigação etiológica

Etiologia trombo-embólica		
Proteína S	90%	(22-62)
Proteína C	79,8%	(45-93)
Factor V Leiden	3.8	(>2.5)
Antitrombina III	91,7%	(90-131)
Homocisteína	8,56 µmol/L	(5-12)
Anticoagulante lúpico	55.9 segundos	(< 38)
Anticorpo anti-cardiolipina IgM / IgG	2,9 / 5,2 U/mL	(<10)
Anticorpo anti- β2glicoproteina I IgM / IgG	0,9 / 3,6 U/mL	(<7)
Etiologia infecciosa		
TASO	194 U/mL	(<200)
Anti-DNase B	<200	(<200)
Rosa Bengala	Negativo	
Serologias		
Vírus da imunodeficiência humana (VIH) 1 e 2, vírus Epstein-Barr, citomegalovirus, Bartonella sp, Yersínia sp	Negativas	
Intradermo-reacção de Mantoux	Anérgica	
Pesquisa de Mycobacterium tuberculosis no suco gástrico (3x)	Negativa	
Hemoculturas (2), hemocultura para Brucella sp, urinoculturas (2), coproculturas (3)	Negativas	
Etiologia imunológica/autoimunidade		
IgG	2.230 mg/dl	(589-1717)
IgD	29 mg/dl	(<100)
IgA	377 mg/dl	(41-218)
IgM	213 mg/dl	(62-270)
Anticorpo antinuclear (ANA) (3 determinações)	Positivo (1/80–1/160–1/320) padrão fino granular	
Factor reumatóide, reacção waller rose, anticorpos anti-DNA dupla hélice, anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-centrómero, cANCA, pANCA e ASCA	Negativos	
Teste de Coombs directo	Negativo	
C3, C4, CH50	Normais	
Outros		
Proteínas totais	7,1 mg/dl	(6-8)
Albumina	2,9 mg/dl	(3,8-5,6)
Electroforese das proteinas	α1, α2, β1 e β2 globulinas elevadas	
Ferritina	665 ng/ml	(12-60)
Electroforese das hemoglobinas	Normal	
Esfregaço de sangue periférico	Anisopoiquilocitose, com alguns esquizocitos	

A clínica caracteriza-se por febre recorrente e poliserosite – peritonite, pleurite e/ou pericardite, sendo as manifestações acompanhantes mais frequentes a dor abdominal (95%) e artrite (40--75%)[3,15,16]. A peritonite simula frequentemente um quadro de abdómen agudo, justificando as laparotomias múltiplas, apendicectomias e avaliações psiquiátricas prévias ao diagnóstico de FMF, como aconteceu nesta doente[15,16].

Nesta doente o diagnóstico foi tardio. O facto de

Tabela II. Evolução das alterações laboratoriais ao longo do terceiro internamento: persistência da anemia, leucocitose, trombocitose e elevação dos reagentes de fase aguda

Dia de internamento	D1	D2	D3	D4	D7	D10	D15	D20	D26	D30	D38	Unidades
Hemoglobina	10,1	9,7	9,2	8,5	7,9	8,7	8,5	8,5	7,4	8,3	8,3	g/dL
Leucócitos	18	18,4	22,9	19,7	18,3	34,1	21,2	29,2	26,6	14,6	7,6	X10³/µl
Plaquetas	576	578	596	614	729	1249	1008	1305	736	629	589	X10³/µl
PCR	33,1	32,3	32,9	38,8	22,4	29,5	25,4	32,7	23,3	13,1	4,4	mg/dL
VS	102	–	–	80	–	99	>120	–	107	115	107	mm/1ªh

a FMF ser uma entidade rara ou subdiagnosticada em Portugal e a apresentação clínica ter sido atípica - *"Protracted febrile myalgia"* com vasculite, podem justificar esse atraso.

A mialgia febril prolongada *("Protracted febrile myalgia syndrome")* é uma entidade rara associada à FMF, que cursa com dor muscular intensa e incapacitante, preferencialmente bilateral, dos membros inferiores e/ou superiores, lesões purpúricas transitórias e persistência da febre (4 a 6 semanas), ao contrário da remissão espontânea e completa num curto espaço de tempo (1 a 4 dias) que caracteriza a crise habitual da FMF e que é de importância diagnóstica[7-9]. São necessárias doses elevadas de prednisolona para melhorar a sintomatologia, que se pode prolongar por mais de 6 semanas sem tratamento[3,8]. A apresentação clínica e evolução desta doente são sobreponíveis às descritas na literatura. Curiosamente e tal como aconteceu também neste caso, os doentes com FMF que cursa com artrite apresentam uma idade de início da doença precoce, maior incidência de mialgia e vasculite[3].

A glomerulonefrite por si só é uma manifestação rara na FMF, tornando-se suspeita pela detecção ocasional de hematúria e proteinúria não nefrótica[3]. Mas nos doentes com FMF algumas vasculites são mais frequentes que na restante população, nomeadamente a púrpura de Henoch-Schönlein (PHS)[1,3]. O diagnóstico de PHS deve ser considerado nos doentes com FMF que desenvolvem púrpura de distribuição típica simétrica nos membros inferiores e região glútea, associada a artrite, vasculite gastrointestinal e/ou glomerulonefrite, tal como aconteceu no presente caso clínico[3].

O aumento dos parâmetros inflamatórios nesta doente, habitualmente não presente na PHS, contribuiu para levantar a suspeita de FMF, que classicamente cursa com elevação marcada dos reagentes de fase aguda – PCR, VS, leucocitose, neutrofilia e trombocitose, nos episódios febris, que normalizam ou se mantêm ligeiramente elevados nos intervalos dos mesmos[1].

O diagnóstico de poliartrite nodosa (PAN) ou poliangiite microscópica (PAM), que podem também surgir associadas à FMF, seriam de considerar na presença de uma criança com alteração do estado geral, emagrecimento, febre persistente, artrite, mialgias, HTA e elevação dos reagentes de fase aguda. No entanto, os anticorpos anti-citoplasma dos neutrófilos (ANCAs) negativos, os exames de imagem e histológicos permitiram excluir estas entidades. Apesar de a doente reunir 4 possíveis critérios para o diagnóstico de Lúpus eritematoso sistémico juvenil (ANA e anticoagulante lúpico positivos, artrite e compromisso renal), esse diagnóstico não foi assumido pelo quadro de proteinúria transitória associada temporalmente a púrpura palpável dos membros inferiores e biopsia renal compatível com nefropatia com depósito mesangial de IgA, corroborando o diagnóstico de PHS e excluindo nefrite lúpica.

O diagnóstico diferencial inclui diversas patologias considerando que febre e dor abdominal são uma situação frequente em pediatria, no entanto, FMF deve ser sempre suspeitada na criança que apresenta um quadro recorrente, mesmo quando a forma de apresentação é atípica (*Protracted Febrile Myalgia Syndrome),* como neste caso.

Os diferentes fenótipos tornam a FMF uma doença heterogénea e não se correlacionam directamente com as diferentes mutações, o que sugere a possibilidade de outros factores genéticos influenciarem a expressão da doença[16,17].

O estudo genético, através da detecção de mutações no gene *MEFV*, é importante para estabelecer o diagnóstico definitivo de FMF.[1] No entanto, é importante ter em consideração que em 10 a 20%

dos doentes nenhuma mutação é detectada[10,17]. Mais de 100 mutações no gene *MEFV* foram identificadas, sendo a M694V umas das mais frequentes[17,18]. De acordo com a literatura, a homozigotia para a mutação, que foi identificada nesta doente, parece associar-se ao início precoce da doença, envolvimento articular[1] e maior gravidade clínica: intensidade e duração das crises e desenvolvimento de complicações, entre as quais, amiloidose AA sistémica[1,15-17]. No presente caso, a biopsia renal não revelou alterações histológicas sugestivas de amiloidose renal.

A terapêutica de primeira linha na FMF é a colchicina oral diária, que tem demonstrado eficácia na indução da remissão completa da doença (67%) ou marcada redução na frequência, duração e intensidade dos episódios febris (25%), assim como na redução dos níveis de AAS, como se verificou nesta doente. É igualmente eficaz na prevenção da amiloidose AA e subsequente comprometimento renal[1,3,16,19]. A resistência à colchicina é rara (5--10%)[20]. Nestes casos, outras terapêuticas têm-se demonstrado promissoras no controlo da doença e prevenção da amiloidose sistémica, como os agentes biológicos anti-IL-1 (anakinra)[21], anti--TNFα (etanercept)[21] e talidomida[21], mas estudos randomizados e controlados serão necessários para confirmar a sua eficácia e segurança.

Correspondência para
Marta Cabral
Hospital Prof. Doutor Fernando Fonseca E.P.E.
Estrada da Venteira, IC19, 2720-276 Amadora
E-mail: mssr.cabral@gmail.com

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MACROPHAGIC MYOFASCIITIS: A CASE REPORT OF AUTOIMMUNE/INFLAMMATORY SYNDROME INDUCED BY ADJUVANTS [ASIA]

Joaquim Polido Pereira[*,**], Cândida Barroso[***], Teresinha Evangelista[***], João Eurico Fonseca[*,**], José Alberto Pereira da Silva[**]

Introduction

Macrophagic myofasciitis is an immune mediated disease known at least since 1993[1,2]. This disease has unclear etiology, although it is often related with aluminium hydroxide adjuvant used in vaccines, as depicted in an electron microscopy study[3]. It manifests with myalgia, arthralgia, marked asthenia, muscle weakness, chronic fatigue, and low grade fever. Some authors postulate that this disease might be a feature of a common syndrome: ASIA – autoimmune/inflammatory syndrome induced by adjuvants. It is estimated that 30 % of the patients have elevations of creatinine kinase (CK) and less than 30 % have a myopathic electromyogram[1,4].

Case Report

This case report refers to a 47 years-old female, observed due to diffuse mechanical arthralgia, low back pain, asthenia and fatigue that lasted for more than 4 years. The observation was normal, except for the presence of two Heberden nodes, and 12 fibromyalgia tender points, fulfilling the classical ACR diagnostic criteria for this disease. The laboratory evaluation showed slightly increased (399 U/L; N 33-211 U/L) creatinine kinase and ESR (41 mm/1st hour), she was HLA-B27 positive and anti-nuclear antibodies (including anti-Jo-1) were negative. The radiographs were compatible with osteoarthritis affecting the cervical and dorsal spine, as well as the hips, shoulders and hands. Sacroiliac joints were normal. Treatment with glucosamine sulphate, paracetamol, NSAIDs and cyclobenzaprine was ineffective. Due to slight diminished proximal strength a muscle biopsy was performed and showed features compatible with macrophagic myofasciitis. As shown in Figure 1, there is a centripetal infiltration of the endomysium by sheets of large cells of the monocyte/macrophage lineage, absence of necrosis, of both epithelioid and giant cells, and of mitotic figures. These features might also be found in the inflammatory myopathy with abundant macrophages (IMAN), usually associated with dermatomyositis features that were absent in this patient[5]. No vaccine correlation could be established, although there was a Tetanus-pertussis vaccination three years before. The electromyography was normal. Prednisolone 0,5 mg/ /kg/day was started with slight improvement.

Conclusion

Macrophagic myofasciitis is a rare entity within the context of inflammatory myopathies and fascii-

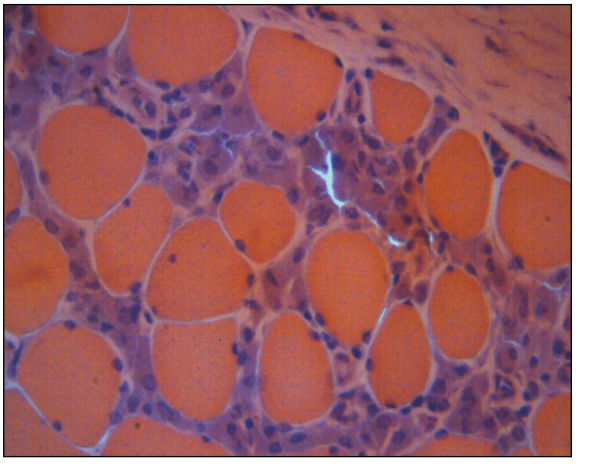

Figure 1. Muscle biopsy, 400x, Hematoxilin & Eosin, macrophagic perifascicular infiltrate

*Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa
**Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal
***Neurology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal

tides. It does not correspond to any of the previously described histiocytoses or any known macrophage-overload disease. The clinical manifestations are unspecific and the diagnosis can only be established on a muscular biopsy with fascia. In this particular case, the abundant macrophagic infiltrate of the endomysium might also suggest IMAN, although the absence of dermatomyositis features is against this hypothesis[5]. No precise treatment recommendations have been established, but the disease tends to respond to steroids and immunossupressants, although antibiotics have also been used[2,6,7].

Correspondence to
Joaquim Polido Pereira
Rheumatology Research Unit,
Instituto de Medicina Molecular
Faculdade de Medicina da Universidade de Lisboa
Av. Professor Egas Moniz
1649-028, Lisbon, Portugal
E-mail: polidopereira@gmail.com

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IV Jornadas dos Serviços de Reumatologia do Hospital de São João e da Faculdade de Medicina do Porto

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PANICULITE LÚPICA E LÚPUS ERITEMATOSO SISTÊMICO

Sâmia Araújo de Sousa Studart*, Kirla Wagner Poti Gomes**, Francisco Vileimar Andrade de Azevedo*, André Xenofonte Cartaxo Sampaio**, Dalgimar Beserra de Menezes***, Walber Pinto Vieira****

Paniculite lúpica (PL) representa uma alteração cutânea rara, primeiramente descrita por Kaposi em 1883 e posteriormente nomeada por Irgang em 1940[1,2]. Caracteriza-se pelo surgimento de nódulos ou placas eritematosas na derme profunda e no tecido gorduroso subcutâneo com evolução para áreas de lipoatrofia[3,4].

Manifesta-se clinicamente na forma isolada ou associada ao lúpus eritematoso sistêmico (LES) ou discóide (LED)[5]. Atinge preferencialmente as mulheres, sendo a face e os membros superiores os locais mais acometidos[6]. É considerada um marcador de evolução mais branda no LES[7].

Caso clínico

Doente, 18 anos de idade, sexo feminino, admitida por quadro de lesões cutâneas profundas e extensas atingindo a face, braços e coxas, de caráter progressivo, com cerca de quatro meses de evolução. Relatava que as manifestações acima foram precedidas por máculas e placas eritematosas indolores. Diagnóstico de LES há cinco anos quando apresentou um quadro de alopécia, rash malar, trombocitopenia, lesões discóides e anticorpos antinucleares (ANA) positivos. Encontrava-se sob terapêutica com hidroxicloroquina 400mg/d e prednisona 20mg/d utilizados irregularmente. Ao exame físico apresentava *rash* malar e áreas de atrofia cutânea extensas, hipercrômicas, não descamativas, aderentes aos planos profundos na região anterior e posterior das coxas, face e membro superior direito (Figuras 1 e 2).

Os exames laboratoriais revelaram: hemoglobina 11,8 g/dL, linfócitos 2.350/mm³, plaquetas 55.900/mm³, C3 85,4 mg/dL (VR: 90-180mg/dL), C4 12,3 mg/dL (VR: 10-40mg/dL), velocidade de hemossedimentação 73 mm; ANA pontilhado grosso 1/10000 e anti-Sm positivo.

O exame histopatológico das lesões evidenciou um infiltrado linfohistiocitário ao redor dos capilares e tecido adiposo associado a áreas de necrose hialina compatível com paniculite lúpica (Figura 3).

Associou-se metotrexato na dose de 15 mg/semana, tendo a doente recebido alta hospitalar para acompanhamento em regime de ambulatório.

Discussão

Uma apresentação clínica incomum do lúpus é a PL. Manifesta-se como lesão isolada ou, com maior freqüência, associada ao lúpus discóide e sistêmico, estando o primeiro presente em até 70% dos casos[8,9]. Acomete 2% a 5% dos doentes com LES,

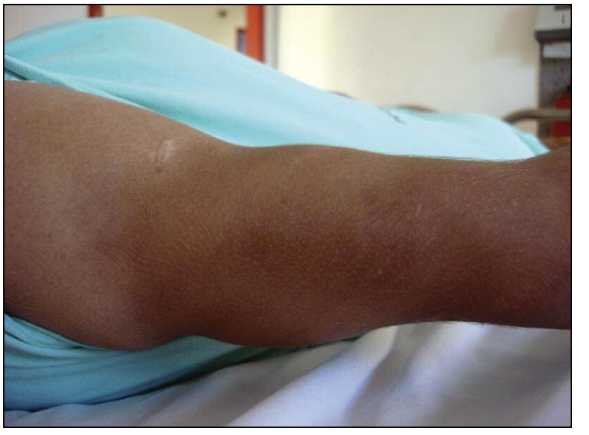

Figura 1. Lesões atróficas no braço direito.

* Médico Residente do Serviço de Reumatologia do Hospital Geral de Fortaleza (HGF).
** Reumatologista e Preceptor da Residência de Reumatologia do HGF
*** Chefe do Serviço de Patologia do HGF e Livre Docente em Anatomia Patológica pela Universidade Estadual do Ceará (UECE).
**** Chefe do Serviço de Reumatologia do HGF e Professor Colaborador da Faculdade de Medicina da UECE.

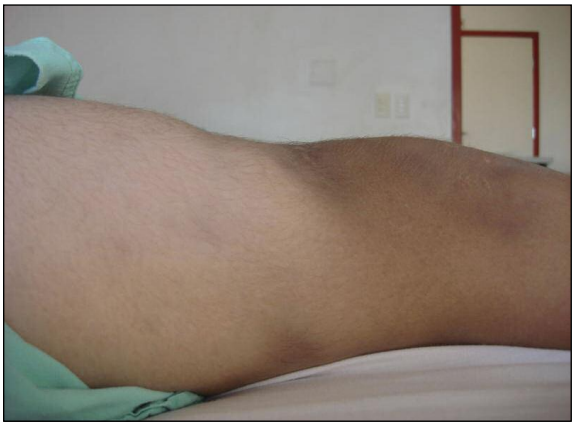

Figura 2. Lesões atróficas na coxa direita

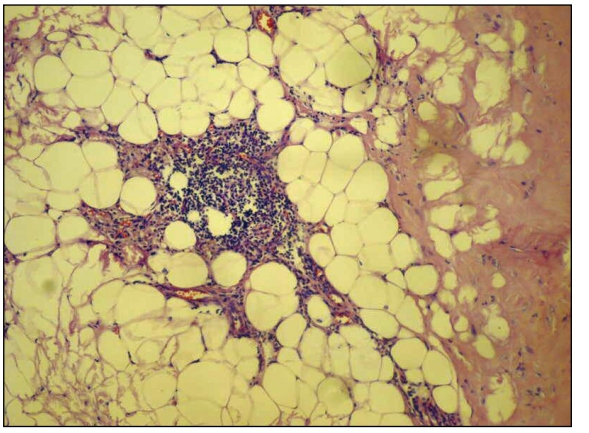

Figura 3. Corte histológico de biópsia cutânea. Agregado linfóide parasseptal e lobular. À direita: esclerose hialina estendendo-se ao lóbulo. Achados compatíveis com paniculite lúpica. (H&E). Aumento de 400x.

principalmente mulheres[10]. Os principais locais de lesão são a face, couro cabeludo, região proximal dos membros superiores e tronco[1,2].

Os achados clínicos clássicos são placas ou nódulos eritematosos, restritos à derme profunda e ao tecido adiposo subcutâneo, com posterior evolução para áreas de atrofia[9]. Apresentações menos freqüentes são a linear, anular e morféia-like[3,11].

Na biópsia evidencia-se um infiltrado inflamatório ao redor dos vasos sanguíneos e lóbulos do tecido adiposo subcutâneo composto principalmente por linfócitos T helper e citotóxicos α/β associados a linfócitos B, ambos detectados através da análise imunohistoquímica. Alterações histopatológicas compatíveis com LED são observadas em 50% a 75% dos casos[2].

Os antimaláricos são os fármacos de primeira linha. Os corticóides sistêmicos são reservados para as lesões difusas e refratárias. Apesar da eficácia, o uso da talidomida é limitado pelos seus efeitos colaterais graves. Bons resultados são descritos com a dapsona, azatioprina, micofenolato mofetil, ciclofosfamida e metotrexato[2,9].

Em síntese, a paniculite lúpica é uma manifestação rara do lúpus, podendo inclusive antecedê-lo. No presente caso, o diagnóstico prévio do LES auxiliou a suspeita e investigação clínica desta patologia.

Correspondência para
Sâmia Araújo de Sousa Studart
Rua Thomaz Pompeu, 570, Apartamento 902,
Meireles, Fortaleza-CE-Brasil, CEP 60160-080.
E-mail: samiasousa@yahoo.com.br

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GOTA TOFÁCEA INTRAÓSSEA – A REALIDADE OCULTA...

Dulcídia Sá*, Anabela Barcelos**

A Gota (também denominada artrite úrica ou artrite gotosa) consiste na inflamação articular ou periarticular desencadeada por cristais de monourato de sódio. Os depósitos destes cristais podem ocorrer em qualquer local, desde a sinovial, o osso subcondral ao tecido subcutâneo. Originam erosões ósseas grosseiras marginais nas epifíses ósseas formando conglomerados que podem bloquear mecanicamente o movimento articular. Alguns destes depósitos tornam-se palpáveis – tofos – localizando-se preferencialmente sobre as articulações da mão, superfície de extensão dos cotovelos, nas bolsas serosas olecraneana e pré-patelar e pavilhões auriculares.

Os tofos gotosos são uma das causas bem conhecidas de nefropatia úrica, de destruição articular e sobreinfectam com facilidade quando ulceram.

A deposição intraóssea de cristais de monourato de sódio – tofos gotosos intraósseos - é rara e são escassas as descrições na literatura. Ocorrem mais frequentemente em doentes com doença de longa evolução e doença renal severa. Os locais mais frequentes são os punhos, mãos e pés, embora possa ocorrer em qualquer localização.

Na maioria do casos, a radiologia convencional não evidencia alterações sendo a TAC e a RMN os exames de escolha para o diagnóstico. O diagnóstico diferencial com entidades como a Artrite Reumatóide, sinovite vilonodular pigmentada, artrite infecciosa e amiloidose deve ser considerado, uma vez que as imagens radiológicas não são específicas e podem ser comuns a várias entidades.

Os autores apresentam o caso clínico de um doente do sexo masculino, de 44 anos de idade, com diagnóstico de artrite gotosa tofácea cuja queixa principal era gonalgia direita de ritmo mecânico com incapacidade para a marcha com alguns meses de evolução. Objectivamente, o joelho direito não apresentava tofos subcutâneos visíveis nem derrame articular, apresentando movimentos de flexão e extensão entre os 0 e os 110º. A radiografia dos joelhos evidenciou alterações degenerativas. Por persistência das queixas do doente, apesar da medicação instituída, associado à limitação funcional que apresentava interferindo no desempenho da actividade profissional (cantoneiro) foi solicitada RMN do joelho direito. Esta evidenciou a existência de «...lesão osteolítica ao longo do côndilo externo do fémur, na zona de inserção do liga-

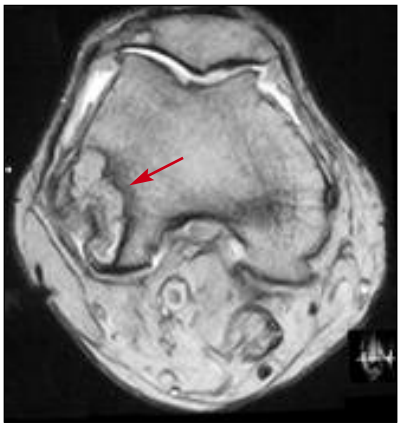

Figura 1. Tofo gotoso intra-ósseo no côndilo femural externo, junto à zona de inserção do ligamento lateral.

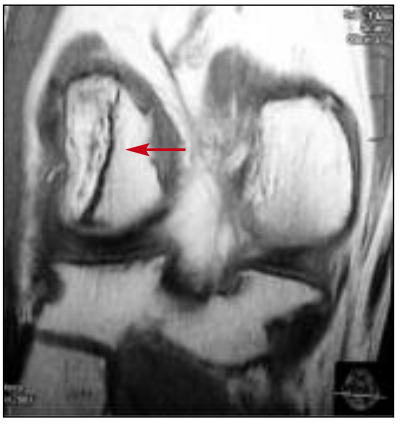

Figura 2. Tofo gotoso intra-ósseo no côndilo femural externo.

*Interna do Internato Complementar de Medicina Interna do Hospital Infante D. Pedro, Aveiro.
**Directora do Serviço de Reumatologia do Hospital Infante D. Pedro, Aveiro.

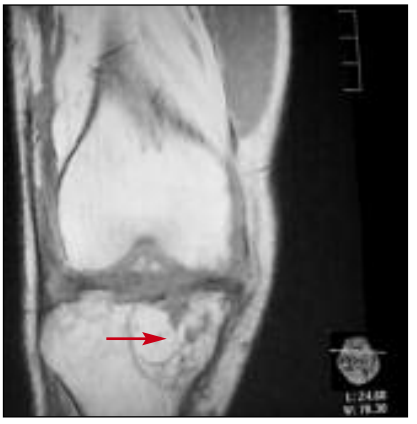

Figura 3. Tofo gotoso intra-ósseo nos pratos tibiais.

mento lateral, com textura heterogénea. Idênticas alterações também visíveis na epífise da tíbia, junto da inserção do ligamento cruzado anterior e nos ângulos articulares dos pratos tibiais - imagens sugestivas de tofos intraósseos» (Figuras 1 a 3).

O doente foi enviado à consulta de Ortopedia onde foi submetido a cirurgia para remoção da lesão supracitada cuja análise anátomo-patológica revelou tratar-se de um tofo gotoso. Mais tarde, o doente realizou ainda fisioterapia com melhoria franca da amplitude de movimentos regressando à actividade profissional.

Perante um doente com artrite gotosa tofácea que apresenta limitação da amplitude de movimentos dos joelhos, mesmo na ausência de tofos subcutâneos visíveis à observação clínica e ausência de alterações radiográficas, a existência de tofos intraósseos deve ser considerada.

Correspondência para
Dulcídia Sá
Serviço de Medicina II
Hospital Infante D. Pedro, E.P.E.
3810-014 Aveiro
E-mail: dulcidia.1978@gmail.com

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WEGENER'S GRANULOMATOSIS: SKIN DEEP

Inês Pires Silva*, Carla Noronha**, António Panarra***, Nuno Riso****, Manuel Vaz Riscado****

Wegener s Granulomatosis (WG) is an ANCA-associated vasculitis whose clinical triad involves the upper respiratory airway, lungs and kidneys[1]. Skin involvement has been observed in 14-47% of patients, either during or at onset of the disease and may develop on unusual sites such as trunk, neck and face[2].

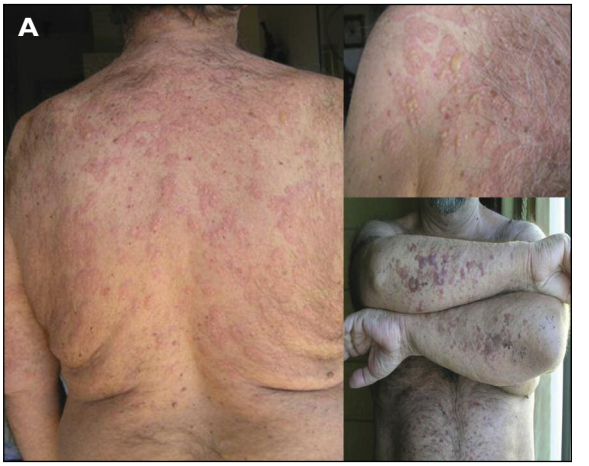
Necrosis, granulomatous inflammation and vasculitis are histological hallmarks.

Case-report: 60 year-old, diabetic, caucasian male complaining of an eight months' evolution sero-hematic rhinorrhea, nasal obstruction and crusting and a diffuse purplish vesicular rash (Figures 1A, 1B), compatible with leucocytoclastic vasculitis; prednisolone 30 mg/day was then prescribed. A paranasal polipoid mass was excised via rhinoscopy (Figure 2), compatible with a chronic inflammatory process, fibrosis and media thickening of small arteries.

Microhematuria (though normal renal biopsy), polyarthralgia and bilateral recurrent episcleritis were also noted.

Chest X-ray, routine lab and immunological workup (including ANCA) were normal. A small-vessel vasculitis was diagnosed, probably WG. Due to an exuberant skin involvement and refractoriety to corticosteroids, clinical remission was achieved with a 6 months' regimen pulsed cyclophosphamide (1g/m^2/month) plus prednisolone (1 mg/kg/ /day). He relapsed under AZA maintenance therapy (250 mg/day), leading to the use of Mycophenolate Mofetil (MMF- 3g/day), with sustained clinical improvement (Figure 3).

This clinical case is particular in four keypoints: *an exuberant cutaneous involvement*, resembling pyoderma gangrenosum, a rare manifestation of WG; the uncommon *absence of pulmonary or renal involvement* (20% of cases)[1]; *a negative c-ANCA*, possible in limited or inactive GW (65-70%), which, adding to predominant skin and nasal affection,



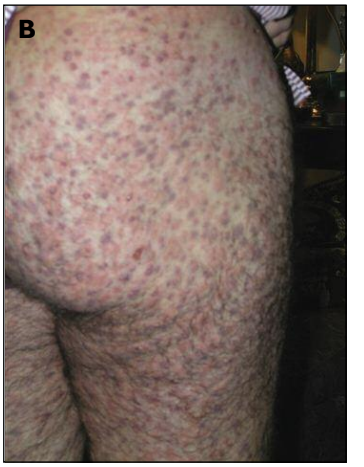


Figure 1A and 1B. Exuberant cutaneous involvement characterized by lesions in several stages-diffuse purplish papules, pustules, vesicles, nodules, coalescent and sometimes necrotic (Pyoderma Gangrenosum-like)

*Oncology Resident, Oncology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal; Programme for Advanced Medical Education
**Attending Physician in Internal Medicine, Autoimmune Diseases' Unit, Medical Department 2, Curry Cabral Hospital, Lisbon, Portugal
***Consultant Physician in Internal Medicine, Autoimmune Diseases' Unit, Medical Department 2, Curry Cabral Hospital, Lisbon, Portugal
****Chief of Department in Internal Medicine, Autoimmune Diseases' Unit, Medical Department 2, Curry Cabral Hospital, Lisbon, Portugal

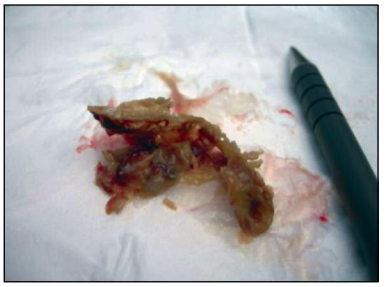


Figure 2. Polipoid mass in the paranasal sinuses (macroscopic aspect)

favors a limited WG diagnosis in our case; and a *sustained clinical remission under maintenance with MMF, without toxicity.*

A high rate of disease relapse (20-45%) after cyclophosphamide's induction therapy prompts the need for additional options[10]. Our choice was dictated by MMF safety profile, case series reports[3-7] and satisfactory experience in lupus and small-vessel vasculitis. Nowack[9] established MMF as well tolerable and effective for maintenance therapy in 9 patients with WG and 2 patients with microscopic polyangiitis, proving to be a promising, but still poorly studied drug in vasculitis.

Correspondence to
Dr. Inês Pires da Silva
Rua Manuel Marques, nr. 10, 9ºB;
1750-171 Lisboa, Portugal
E-mail: inespiresilva@gmail.com

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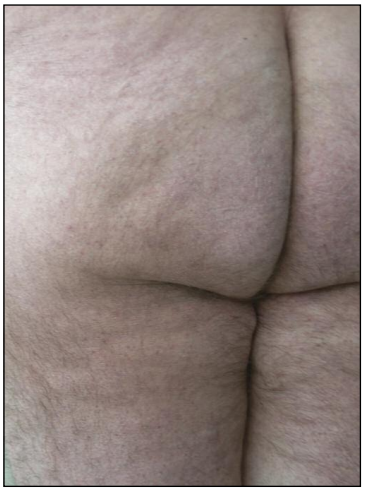

Figure 3. Clinical improvement regarding cutaneous involvement

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NODULOSE ACELERADA NA ARTRITE IDIOPÁTICA JUVENIL EM DOENTE MEDICADA COM METOTREXATO

A. Paúl*, P. Estanqueiro**, M. Salgado***

Ao Exmo. Editor

Os nódulos reumatóides (NR) afectam 20% a 25% dos doentes com artrite reumatóide (AR)[1,2]. A sua prevalência nas artrites idiopáticas juvenis (AIJs) é de 5% a 10%, maioritariamente no subtipo AIJ poliarticular factor reumatóide (FR) positivo[1-4]. O metotrexato (MTX) é o fármaco de primeira linha exercendo, para além da actividade anti-folato, acção anti-inflamatória, com libertação de adenosina (potente mediador anti-inflamatório endógeno). Desconhecem-se os mecanismos que levam a uma variabilidade inter-pessoal na sua eficácia e toxicidade, embora haja evidência de que factores genéticos possam exercer influência. Uma das possíveis complicações é a nodulose acelerada (NA) – progressão rápida de nódulos pré-existentes ou que surgem «de novo», em doentes com conectivite. Surge mais frequentemente na AR (8% a 11%)[2,5], sendo menos comum em crianças[6]. Estes nódulos podem ser únicos ou múltiplos e localizam-se preferencialmente junto às proeminências ósseas nas faces de extensão dos membros, em regiões de maior pressão mecânica[1,4]. Podem surgir em orgãos internos[1,7]. Acredita-se que esta complicação seja consequente a uma estimulação inadequada dos receptores macrofágicos de adenosina tipo A1 (efeitos pró-inflamatórios), em detrimento dos receptores tipo A2 (efeitos anti-inflamatórios)[5-8]. A biópsia é útil para o diagnóstico definitivo de NR, embora possa ser dispensada nos quadros típicos[1,9].

Descreve-se o caso clínico de uma adolescente de 17 anos seguida na Consulta de Reumatologia do Hospital Pediátrico por AIJ FR positivo, sob tratamento com MTX oral, numa dose constante de 12 mg/m²/semana, desde o início do quadro. Aos 10 meses de tratamento, após um período de estabilização da doença, verificou-se reagravamento da poliartrite e foram constatados 5 nódulos subcutâneos, móveis, não dolorosos, de consistência duro-elástica, com 1 cm a 2,5 cm de diâmetro, compatíveis com NA. Localizavam-se junto a proeminências ósseas no cotovelo (Figura 1) e punho direitos e nos tarsos direito e esquerdo. Aos 13 meses de tratamento com MTX foi associada hidroxicloroquina (HCQ), 5 mg/kg/dia, por progressão da nodulose (máximo - 8 nódulos), contrastando com a melhoria gradual da poliartrite. Nos meses seguintes constatou-se regressão progressiva do número e tamanho dos nódulos e actualmente, com 29 meses de tratamento com MTX e 16 meses de HCQ, apresenta apenas 2 nódulos subcutâneos, o maior com 0,8 cm, no cotovelo direito.

A nodulose reumatóide e a NA pelo MTX podem ser difíceis de se diferenciar, tanto clínica como histológicamente. É ainda controverso se a presença destes nódulos fazem parte da evolução natural da doença ou se podem ser causados pelo uso de determinados fármacos, como o MTX. No sentido de esclarecer esta dúvida, foram feitos estudos, onde se verificou que a nodulose regredia ou desaparecia com a suspensão deste fármaco ou com a di-

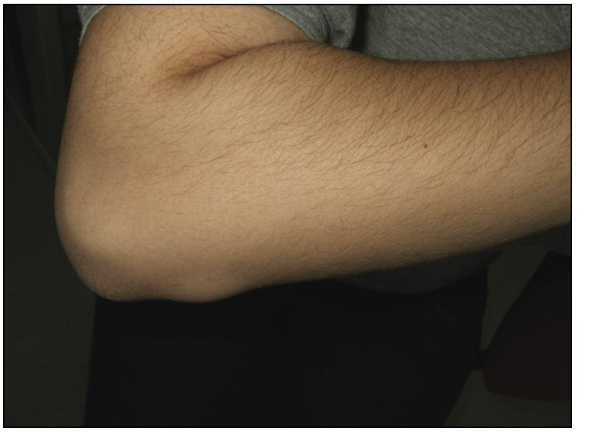

Figura 1. Nódulo junto ao cotovelo direito.

*Interna Complementar de Pediatria do Hospital Pediátrico de Coimbra, Centro Hospitalar de Coimbra
**Assistente Hospitalar de Pediatria, Consulta de Reumatologia Pediátrica, Hospital Pediátrico de Coimbra, Centro Hospitalar de Coimbra
***Assistente Hospitalar Graduado de Pediatria, Consulta de Reumatologia Pediátrica, Hospital Pediátrico de Coimbra, Centro Hospitalar de Coimbra

minuição da sua dose, bem como reaparecia com a sua reintrodução[2-4]. No caso descrito, o aparecimento destes nódulos ocorreu de forma rápida, «de novo» e no período de tempo documentado para o aparecimento de NA por MTX[5,7] havendo, no entanto, reagravamento concomitante da poliartrite. Seguidamente, assistiu-se à melhoria gradual do quadro inflamatório poliarticular, contrastando com o agravamento dos NR, tal como descrito em alguns casos de NA por MTX[4,5]. De salientar que, alguns meses após a associação da HCQ ao MTX, constatou-se regressão gradual da nodulose.

Há evidências de que a HCQ possa ajudar na estabilização ou regressão da NA, embora o mecanismo de acção não seja conhecido[2,4,6,7,10]. Não há grande consenso relativamente às diversas opções terapêuticas nestes casos. A substituição do MTX, a sua associação com outros fármacos (nomeadamente a HCQ), ou a continuação do tratamento exclusivo com este fármaco, são opções terapêuticas válidas. É sugerida a sua continuação, particularmente em casos de artrite activa, a menos que os nódulos sejam dolorosos ou causem algum tipo de desconforto[4].

Correspondência para
Alexandra Paúl
Rua Lourenço Almeida Azevedo nº19, 3º andar
3000-250 Coimbra
E-mail: xana.paul@gmail.com

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Todos os manuscritos que não estejam em conformidade com as instruções que se seguem podem ser enviados para modificações antes de serem revistos pelos consultores.

Todos os trabalhos devem ser enviados por e-mail para: **edtecnicarp@gmail.com.**

Os manuscritos devem ser acompanhados de declaração de originalidade e de cedência dos direitos de propriedade do artigo, assinada por todos os autores, conforme minuta publicada em anexo.

O texto deve ser enviado em formato digital (e-mail), a dois espaços, com letra tamanho12 e com margens não inferiores a 2,5 cm, em Word para Windows. Todas as páginas devem ser numeradas.

As imagens devem ser fornecidas independentemente do texto em formato JPEG ou TIFF.

Os textos devem ser organizados da seguinte forma:

Página 1

a) Título em português e inglês

b) Nome dos autores e respectiva afiliação

c) Serviço(s) ou organismo(s) onde o trabalho foi executado

d) Subsídio(s) ou bolsa(s) que contribuíram para a realização do trabalho

e) Morada e e-mail do autor responsável pela correspondência relativa ao manuscrito

f) Título breve para rodapé

Página 2

a) Título (sem autores)

b) Resumo em português e inglês, que para os artigos originais deve ser estruturado da seguinte forma: Objectivos, Material e Métodos, Resultados, Conclusões. O resumo dos artigos originais não deve exceder as 350 palavras e o dos casos clínicos as 180 palavras.

c) Palavras-chave em português e em inglês (Keywords)

Um máximo de 5 palavras-chave, utilizando a terminologia que consta na lista do Index Medicus: «Medical Subject Headings» (MeSH), deve seguir-se ao resumo.

Página 3 e seguintes

Artigos originais: O texto deve ser apresentado com os seguintes subtítulos: Introdução (incluindo Objectivos), Material e Métodos, Resultados, Discussão, Conclusões, Agradecimentos (se aplicável), Referências.

Os artigos originais não deverão exceder as 4.000 palavras, com um total de 6 figuras/tabelas e 60 referências.

Caso clínico: os subtítulos serão, Introdução, Caso clínico, Discussão, Referências.

O caso clínico não deve exceder as 2.000 palavras e 25 referências. Deve ser acompanhado de figuras ilustrativas. O número de tabelas/figuras não deve ser superior a 6.

A partir da segunda página, inclusive, todas as páginas devem ter em rodapé o título breve indicado na página 1.

Referências: As referências bibliográficas devem ser classificadas e numeradas por ordem de entrada no texto, em *superscript* e não entre parêntesis. As abreviaturas usadas na nomeação das revistas devem ser as utilizadas pelo *Index Medicus*.

Nas referências com 6 ou menos autores todos devem ser nomeados. Nas referências com 7 ou mais autores devem ser nomeados os 3 primeiros seguidos de et al.

Notas: Os números da página inicial e final devem ser totalmente apresentados (565-569 e não 565-9)

Não indicar o número da revista nem o mês da publicação.

Seguem-se alguns exemplos de como devem constar os vários tipos de referências:

– Revista

Apelido e iniciais do(s) autor(es). Título do artigo. Nome da revista Ano; Volume: Páginas.

Ex.: Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic. Ann Rheum Dis 1992; 51:195-197.

– Artigo publicado online (inserir DOI)

Ex.: Peter A Merkel, David Curthbertson, Bernhard Hellmich et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008. 097758

– Capítulo de livro

Nome(s) e iniciais do(s) autor(es) do capítulo. Título do capítulo. In: Nome(s) e iniciais do(s) editor(es) médico(s). Título do livro. Cidade: Nome da casa editora, ano de publicação: primeira a última página do capítulo.

Ex.: Stewart AF. Hypercalcemia resulting from medications. In: Favus MJ, ed. Primer on the Metabolic Bone Diseases and Disorder of Mineral Metabolism. New York: Raven Press, 1993: 177-178.

– Livro

Nome(s) e iniciais do(s) autor(es). Título do livro. Cidade: Nome da casa editora, ano de publicação: página(s).

Ex.: Lorig K. Patient Education. A practical approach. St. Louis: Mosby-Year Book;1992: 51.

– Documento electrónico

Ex: Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde - Divisão de Doenças Transmissíveis, Março de 2005 http://www.dgsaude.pt/upload/membro.id/ ficheiros/ i006875.pdf. Acedido em 25 Janeiro de 2008

As referências a trabalhos ainda não publicados, comunicações em reuniões, não publicadas em livros de resumos, ou comunicações pessoais devem ser citadas no texto e não como referências formais.

A exactidão e o rigor das referências são da responsabilidade do autor.

Tabelas: As tabelas a inserir devem ser assinaladas no texto em numeração romana e cumprir o limite descrito acima. Cada tabela deverá ser apresentada em folha separada, dactilografada a 2 espaços. Na parte superior devem apresentar um título sucinto mas informativo, de modo a poder ser compreendido sem recurso ao texto. Na parte inferior da tabela deve constar a explicação das abreviaturas utilizadas. Nas tabelas devem ser evitados os traços verticais e os traços horizontais, estes devem servir apenas como separadores de títulos e subtítulos.

Figuras: As figuras a inserir devem ser assinaladas no texto em numeração árabe e cumprir o limite definido acima. As legendas das figuras devem ser dactilografadas a dois espaços numa folha separada, depois da bibliografia. As figuras devem ser enviadas em suporte informático com ficheiros separados para cada figura, em formato JPEG ou TIFF.

Editoriais: Os editoriais serão solicitados por convite do Editor. Os editoriais serão comentários sobre tópicos actuais ou sobre artigos publicados na revista. O texto dos editoriais não deve exceder as 1.200 palavras, um máximo de 15 referências e não deve conter quadros ou figuras.

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O artigo de revisão não deve exceder as 4.000 palavras, 6 tabelas/figuras e 100 referências.

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Imagens em reumatologia: Podem ser submetidas imagens de particular interesse. As figuras, no máximo de 4, devem ser enviadas em formato JPEG ou TIFF de boa resolução. O texto acompanhante não deve ultrapassar as 500 palavras.

Modificações e revisões: No caso da aceitação do artigo ser condicionada a modificações, estas deverão ser feitas pelos autores no prazo de 1 mês.

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As provas tipográficas serão, sempre que possível, enviadas aos autores contendo a indicação do prazo para revisão consoante as necessidades editoriais da revista.

Minuta da carta de submissão a enviar ao Editor, digitalizada, por e-mail:

Enviar este documento com o manuscrito para:
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All the comments made by the reviewers will be sent to the author.

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Text should be sent in digital support by e-mail, typed double-spaced, type 12, with 1-inch margins, in Word for Windows. All pages must be sequentially numbered.

Images should be sent independently from the text in JPEG or TIFF file.

Manuscripts should be organized as explained below:

Page 1

a) Title in Portuguese and in English;

b) Authors' names and affiliations;

c) Institution(s) to which the work should be attributed;

d) Source(s) of grants support;

e) Name, address and e-mail of the corresponding author

f) Short running title.

Page 2

a) Title (without authors)

b) Abstract

Abstract in English structured as follows for the original articles: Objectives; Patients and Methods; Results; Conclusions. The abstract should not exceed 350 words for original articles and 180 words for case reports.

c) Keywords

A maximum of 5 keywords – must be MeSH terms – should be presented after the abstract.

Page 3 and following pages

Original papers: The text of original papers should be presented with the following subtitles: Introduction, Objectives, Patients and Methods, Results, Discussion, Conclusions, Acknowledgements, References.

Original papers should not exceed 4,000 words, 6 Tables/Figures and 60 references.

Case report: Subtitles for case reports should be: Introduction, Case report, Discussion, References.

A case report should not exceed 2,000 words and 25 references. It should present illustrative figures. The number of Tables/Figures should not exceed 6.

From the second page on, all pages should have a short title on footnote.

References: References should be cited by the numerical system, superscript and listed, in the order cited in the text. Journal titles are abbreviated in accordance with the style of Index Medicus.

List all authors when 6 or less; when 7 or more list only first 3 and add "et al".

Do not abbreviate the page number (i.e. correct: 565--569 and not: 565-9).

The Journal number and the month of publication should not be presented.

References of unpublished work, presentations or personal observations should be inserted in the text (in parenthesis) and not as a "classical" or true reference.

Authors are responsible for the accuracy of the references.

Examples:

– Journal article

Name(s) and initials of author(s). Article title. Journal name Year; Volume or number: Page(s).

Ex: Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic: Ann Rheum Dis 1992; 51: 195-197.

– Article published Online (insert DOI)

Ex.: Peter A Merkel, David Curthbertson, Bernhard Hellmich et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008.097758

– Chapter in Book

Name(s) and initials of author(s) of chapter. Chapter title. In: Name(s) and initials of editor(s). Book title. City: Name of publisher, year of publication: pages.

Ex: Stewart AF. Hypercalcemia resulting from medications. In: Favus MD, ed Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. New York: Raven Press, 1991: 177-178.

– Book

Name(s) and initials of author(s). Book title. City: Name of publisher, year of publication: page(s).

Ex: Lorig K. Patient Education. A practical approach. St Louis: Mosby-Year Book, 1992: 51.

– Online document

Ex:Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde - Divisão de Doenças Transmissíveis, Março de 2005 http://www.dgsaude.pt/upload/membro.id/ ficheiros/i006875.pdf. Accessed em 25 Janeiro de 2008

Tables: Tables should be cited in the text with Roman numerals. Each table should be double typed on a separate sheet, have a title and contain no vertical rulers. Horizontal lines should be used only as separators between titles and subtitles. Explain all abbreviations at the bottom.

The number of tables should be limited as described above.

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Review articles: Review articles will be commissioned by the editor. However, authors interested in presenting a review article are welcomed to contact the editor.

Review articles should not exceed 4000 words, 6 tables/figures and 100 references.

Letters: Letters to the editor must be a comment on a journal article or a short clinical study or case report. They cannot exceed 600 words, a maximum of 10 references and one table or one figure.

Images in Rheumatology: Images of particularly interest can be submitted. They should contain a maximum of 4 figures, in JPEG or TIFF format. The accompanying text must have a maximum of 500 words.

Modifications and proofreading: Articles accepted subject to modifications, will be sent to the authors that will have 1 month to modify them according to suggestions. A letter should be written for each reviewer and the changes should be highlighted in the main manuscript with a different font color. Contributors will receive page proofs of the accepted papers for approval.

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