ARTHRITIS AND X-LINKED AGAMMAGLOBULINEMIA

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Abstract

Primary immunodeficiencies are defined as genetically determined functional and/or quantitative abnormalities in one or more of the components of the immune system. Immunodeficiency and arthritis can be related, although the mechanisms are not always clear. Different causes for immunodeficiency can secondarily be found in patients with arthritis; on the other hand, arthritis can be a manifestation of primary immunodeficiency. Arthritis occurs chiefly in humoral primary immunodeficiencies, namely in X-linked agammaglobulinemia and common variable immunodeficiency, and may be one of the warning signs for primary immunodeficiency. We report a case of arthritis as the presenting feature of X-linked agammaglobulinemia. In X-linked agammaglobulinemia, arthritis may be a consequence of infection, most notably by *Mycoplasma,* or of immune dysfunction itself. In children, and occasionally in young adults, a combination of arthritis and hypogammaglobulinemia should suggest primary immunodeficiency, although other causes of hypogammaglobulinemia must be excluded. Physicians evaluating patients with arthritis should be aware of this fact so that an early diagnosis can be pursued as it is of extreme importance in the optimal management and prognosis of these patients.

Keywords: Arthritis; X-linked Agammaglobulinemia; Hypogammaglobulinemia; Primary Immunodeficiency; Immunoglobulin

Resumo

As imunodeficiências primárias definem-se como defeitos quantitativos e/ou funcionais geneticamente determinados, em um ou mais componentes do sistema imunitário. Imunodeficiência e artrite podem estar relacionadas, mas os mecanismos que as relacionam nem sempre são claros. Diferentes causas de imunodeficiência podem surgir secundariamente em doentes com artrite; por outro lado, a artrite pode ser uma manifestação de imunodeficiência primária. A artrite ocorre predominantemente em doentes com imunodeficiências humorais, nomeadamente na agamaglobulinémia ligada ao X e na imunodeficiência comum variável, e pode ser um dos sinais de alarme para imunodeficiência primária. Os autores apresentam um caso em que a artrite fez parte do quadro de apresentação da agamaglobulinémia ligada ao X. Nesta imunodeficiência, a artrite pode ser consequência de infecção, particularmente por *Mycoplasma*, ou da própria disfunção imunitária. Em crianças e ocasionalmente em adultos jovens, a conjugação de artrite com hipogamaglobulinémia deve sugerir imunodeficiência primária, sem descurar a exclusão de outras causas de hipogamaglobulinémia. Os médicos envolvidos na avaliação de doentes com artrite devem estar cientes desta possibilidade, de modo a assegurarem um diagnóstico precoce, um objectivo primordial para a optimização terapêutica e prognóstico destes doentes.

Palavras-chave: Artrite; Agamaglobulinémia Ligada ao X; Hipogamaglobulinémia; Imunodeficiência primária; Imunoglobulina

Introduction

Primary immunodeficiencies (PIDs) are defined as genetically determined functional and/or quantitative abnormalities in one or more of the immune system components. Immunodeficiency and arthritis can be related, although the mechanisms are not always clear. Different causes for immunodeficiency can secondarily be found in patients

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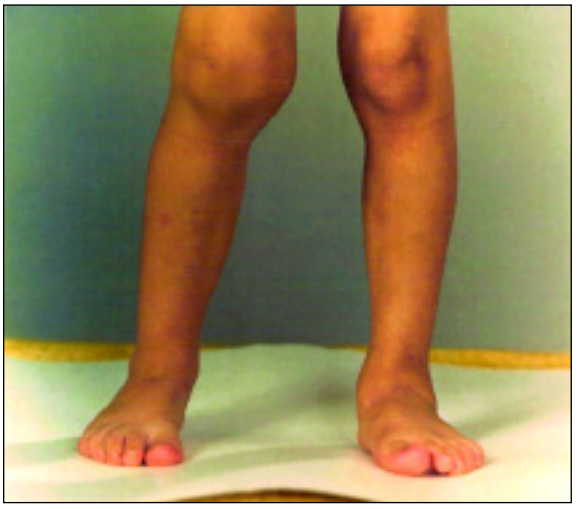

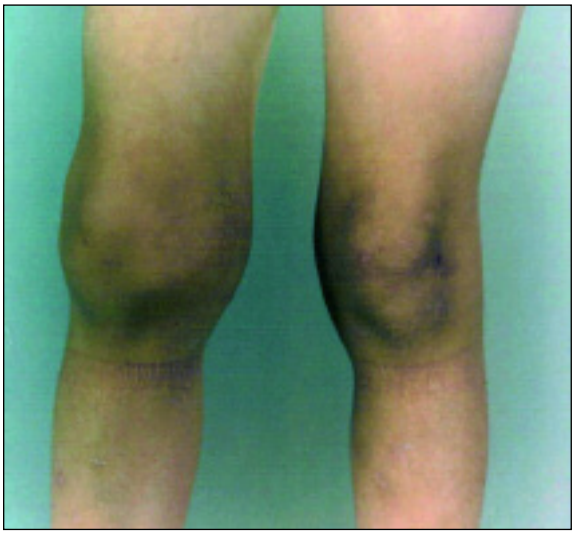

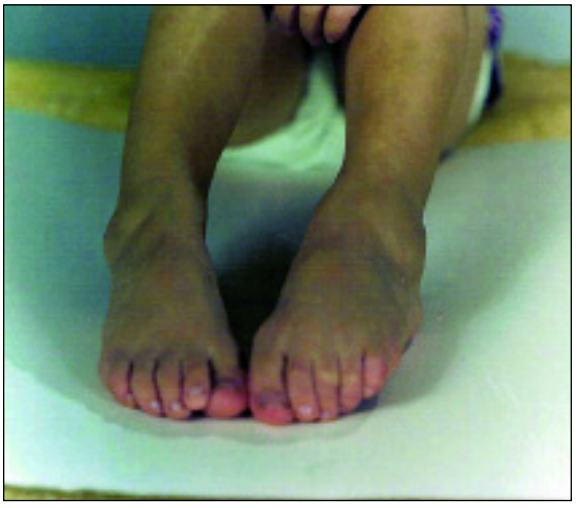

Figure 1, 2 and 3. Arthritis of the right knee and left ankle at the age of 3. Right tight and leg wasting are also visible.

with arthritis; on the other hand, arthritis can be a manifestation of PID.

Arthritis occurs chiefly in humoral PID, namely in X-linked agammaglobulinemia (XLA) and common variable immunodeficiency, and may be one of the warning signs for primary immunodeficiency. Indeed, Bruton[1] first described XLA in a patient with arthritis. In this paper, we report a case of arthritis in a patient with XLA, and discuss it regarding the literature about the relationship between arthritis and PIDs.

Case Report

A white male, currently 30 years old, presented at the age of 3 years with arthritis of the right knee and left ankle (Figures 1, 2 and 3). Right thigh and leg wasting were already evident when the child was observed, 11 months after the first episode of arthritis. He had a history of recurrent upper respiratory tract infections, conjunctivitis and gastroenteritis (including *Giardia lamblia* and *Salmonella*), and bronchopneumonia requiring hospital admission at the age of 4 months. He had been repeatedly given antibiotics, often during long periods of time.

The child's growth and psychomotor development were normal. His non-consanguineous parents and paternal half-brother were healthy. A maternal uncle had died of pneumonia at the age of 9.

Initial investigations at the age of 3 years revealed normal blood cell count (including total lymphocyte count), normal urinalysis and erythrocyte sedimentation rate, increased C-reactive protein and severe hypogammaglobulinemia with low levels of all immunoglobulin isotypes (IgG 0.5 g/L, IgM 0.4 g/L, IgA<0.07 g/L and IgE<18 UI/mL). Rheumatoid factor was absent.

A humoral primary immunodeficiency was the probable diagnosis and treatment was initiated at the age of 4 years with weekly intramuscular (IM) immunoglobulin (later fortnightly), acetylsalicylic acid (later naproxen) and physiotherapy. At that time (about 30 years ago) IM immunoglobulin was the only one available, intravenous (IV) immunoglobulin only becoming available about 10 years later.

Additional evaluation later performed revealed 1% of CD19+ cells, normal complement levels and negative assays for nuclear autoantibodies. More recently, molecular analysis confirmed the diagno-

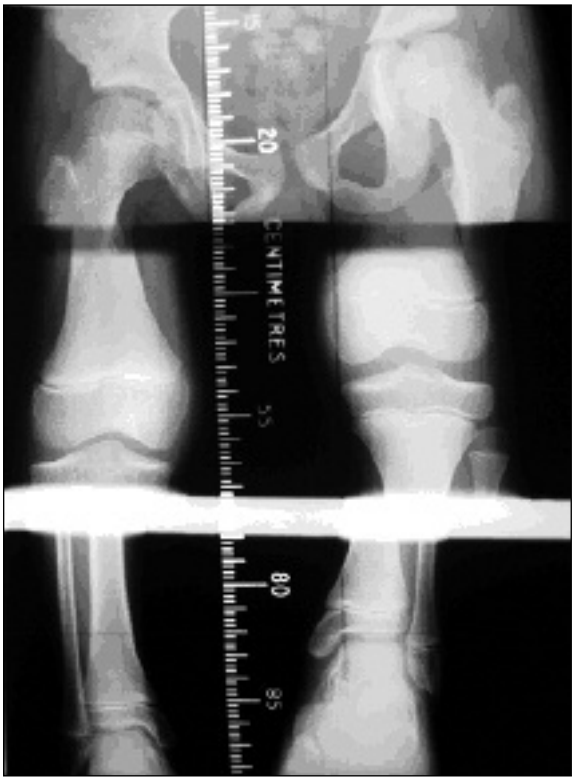

Figure 4. Inferior limb dysmetry (4 cm) on metric radiography at the age of 10

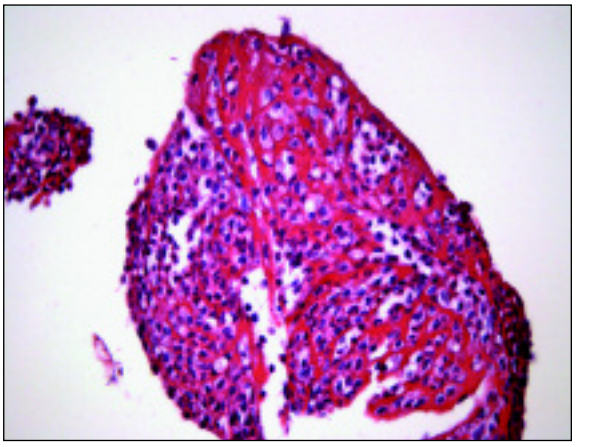

Figure 5. Left knee synovial biopsy at the age of 23, showing hyperplasia and capillary proliferation predominantly with neutrophilic infiltrate (stain, hematoxylin and eosin; original magnification, x400).

sis of XLA, showing a nonsense BTK mutation (R255X).

Several complications were observed during childhood: gastroenteritis, conjunctivitis, adenoiditis, pharingitis, sinusitis, bronquitis and suppurated otitis media with perforation (without hearing loss). Multiple antibiotics were given. An improvement in the frequency and severity of the infectious episodes was noticed with immunoglobulin replacement.

Left ankle arthritis resolved after initiating immunoglobulin therapy, but right knee arthritis became relapsing until the age of 8, responding to higher doses of IM immunoglobulin given during arthritis flares. Left knee arthritis was observed at the age of 10 and 15, again responding to higher doses of IM immunoglobulin. The boy also developed a 4 cm inferior limb dysmetry (Figure 4) compensated with heal on left shoe.

Since the age of 16, he has been given IV immunoglobulin (Octagam®, 400-600 mg/Kg, every three to four weeks, aiming at serum IgG levels above 6g/L), with significant improvement of the serum immunoglobulin levels. Infections became less frequent and severe, and antibiotics-free periods became longer after starting IV immunoglobulin. Higher doses have been given at the age of 23, when he had a prolonged episode of arthritis (see below). He has recently initiated subcutaneous immunoglobulin (Gammanorm®, 100 mg/Kg, weekly), with a positive impact on his quality of life and more stable serum IgG levels. Chronic sinusitis, chronic mastoiditis and bilateral bronchiectasis (cylindrical and sacular, predominantly in the lower lobes and on the right) have been observed as additional complications of the disease.

At the age of 23, he had the last episode of arthritis, with the left knee being affected. Initially, it did not resolve with an increase in IV immunoglobulin dose (800mg/Kg every three to four weeks) and further investigation was undertaken. Synovial fluid analysis revealed an aseptic inflammatory fluid without crystals: the fluid was yellow and translucent with a white blood cell count of 41400/mm3 and 88% polymorphonuclear leukocytes; gram stain and cultures (including *Mycobacterium*) were negative and crystals were absent. Magnetic resonance imaging showed a minor subcondral sclerosis of the lateral tibial plate and marginal osteophytosis of tibial spines; there was a large intra-articular effusion and extended synovitis; the nodular and polilobulated hypointense appearance of the synovial raised the hypothesis of pigmented villonodular synovitis. Biopsy was performed (Figure 5) revealing synovial hyperplasia and capillary

Table I. Diagnostic criteria of X-linked agammaglobulinemia

Definitive:

– Male patient with less than 2% CD19+ B cells and at least one of the following:
  1) Mutation in Btk, 2) Absent Btk mRNA on northern blot analysis of neutrophils or monocytes, 3) Absent Btk protein in monocytes or platelets, 4) Maternal cousins, uncles or nephews with less than 2% CD19+ B cells

Probable:

– Male patient with less than 2% CD19+ B cells in whom all of the following are positive:
  1) Onset of recurrent bacterial infections in the first 5 years of life, 2) Serum IgG, IgM and IgA more than 2SD below normal for age, 3) Absent isohemagglutinins and /or poor response to vaccines, 4) Other causes of hypogammaglobulinemia have been excluded (see Table II)

Possible:

– Male patient with less than 2% CD19+ B cells in whom other causes of hypogammaglobulinemia have been excluded (see Table II) and at least one of the following is positive:
  1) Onset of recurrent bacterial infections in the first 5 years of life, 2) Serum IgG, IgM and IgA more than 2 SD below normal for age, 3) Absent isohemagglutinins

Source: European Society for Immunodeficiencies. http://www.esid.org/workingparty.php?party=3&sub=2&id=73. Acceded 24 April 2008.

proliferation predominantly with neutrophilic infiltrate. Arthritis progressively resolved over a six-month period of high doses of IV immunoglobulin (800mg/Kg every three to four weeks), aiming at serum immunoglobulin levels above 8g/L. No further episodes of arthritis have occurred so far.

Discussion

XLA is a PID caused by mutations in the Bruton tyrosine kinase (BTK) gene, which is essential for B-cell development and proliferation.[2] Affected individuals have hypogammaglobulinemia, markedly reduced levels of serum antibodies and markedly reduced levels of B cells.

Clinical symptoms usually start after the age of 6 months, once maternal antibodies disappear from the infant's blood stream, and mainly consist of recurrent respiratory and gastrointestinal infections. The microorganisms most commonly implicated[3] are encapsulated bacteria (e.g. *Streptococcus, Haemophilus influenza, Staphylococcus aureus* and *Pseudomonas*) affecting the respiratory tract, skin, bone, joints and central nervous system. The anti-viral immunity is generally preserved, except for Enterovirus (*Poliovirus, Echovirus* and *Coxsackievirus*) which may cause central nervous system infection. In the gastrointestinal tract, apart from gastroenteritis (*Giardia, Campylobacter* and *Salmonella* are common bacterial agents and Rotavirus and Enterovirus are common viral agents), inflammatory bowel disease mimicking Chron's disease may occur. Other manifestations can be arthritis, osteomyelitis, sepsis, and more rare disorders such as hepatitis, vaccine-related polio, wild polio, hand-foot-and-mouth disease and neutropenia.[3] The criteria for the diagnosis of XLA were established by the European Society for Primary Immunodeficiencies and are listed in Table I. Differential diagnosis of hypogammaglobulinemia are presented in Table II.

In the case we describe, the child's growth and psychomotor development were normal. Although infections were frequent, they were considered to be mild to moderate in severity, except for one episode of infection in which hospitalization was required. These two factors probably contributed to a delay in diagnosis and emphasise the need of a high index of suspicion for the disease. In a cohort of 201 patients from the United States of America,[3] only about half of the patients were diagnosed with agammaglobulinemia/hypogammaglobulinemia by 2 years of age, and about 20% were still undiagnosed by school age. A few patients were not diagnosed until adolescence or adulthood, some in spite of a positive family history at the time of their birth. Other authors have reported families in which affected individuals have not been diagnosed with an immunodeficiency until adulthood, some of whom had relatively mild symptoms and/or late onset of symptoms,[4-6] highlighting the need for a high index of suspicion and that although gene defects are known, there are no ge-

Table II. Differential diagnosis of hypogammaglobulinemia

Drug Induced:
Antimalarial agents, Captopril, Carbamazepine, Glucocorticoids, Fenclofenac, Gold salts, Penicillamine, Phenytoin, Sulfasalazine
Genetic Disorders:
Ataxia Telangiectasia, Autosomal forms of SCID, Hyper IgM Immunodeficiency, Transcobalamin II deficiency and hypogammaglobulinemia, X-linked agammaglobulinemia, X-linked lymphoproliferative disorder (EBV associated), X-linked SCID, Some metabolic disorders, Chromosomal Anomalies, Chromosome 18q- Syndrome, Monosomy 22, Trisomy 8, Trisomy 21
Infectious Diseases:
HIV, Congenital Rubella, Congenital infection with CMV, Congenital infection with Toxoplasma gondii, Epstein-Barr Virus
Malignancy:
Chronic Lymphocytic Leukemia, Immunodeficiency with Thymoma, Non Hodgkin's lymphoma, B cell malignancy
Systemic Disorders:
Immunodeficiency caused by hypercatabolism of immunoglobulin, Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, severe diarrhea)

Source: European Society for Immunodeficiencies. http://www.esid.org/workingparty.php?party=3&sub=2&id=73. Acceded 24 April 2008.

notype-phenotype associations.

Janeway[7] back in 1956 found an increased incidence of arthritis, with negative joint fluid cultures, in children with XLA. Later, it was found that some of these patients may have arthritis due to *Mycoplasma* infections, although in many cases no pathogen could be identified in the joint fluid.[8]

Patients with humoral PIDs are more prone to arthritis, most notably XLA, common variable immunodeficiency[9] (CVID), hyper-IgM syndromes,[10] and IgA deficiency.[11] A few cases of arthritis have been reported in patients with chronic granulomatous disease,[12] Wiskott-Aldrich syndrome,[13] interleukin-1 receptor-associated kinase-4 deficiency[14,15] (a more recently described immunodeficiency affecting the toll-like receptor pathways) and cellular or combined immunodeficiency syndromes.[11] In patients with humoral PID, the prevalence of joint manifestations before treatment has ranged from 5% to 40% in different studies.[11]

Hansel *et al*[16] identified seven cases of monoarthritis and one case of oligoarthritis among 69 patients with agammaglobulinemia, as well as one case of monoarthritis and seven cases of oligoarthritis among 161 patients with CVID. Importantly, arthritis can reveal PID in children and is occasionally the presenting symptom of CVID in adults. Incontrovertible evidence of infection is found in some cases, whereas in others an immune dysregulation-related synovial disorder seems to be involved.

Our patient presented at the age of 3 with chronic asymmetric oligoarthritis and a history of relapsing episodes of arthritis until the age of 23, when he developed a persistent episode of monoarthritis.

About 10–30% of arthritis cases in patients with humoral PIDs seem aseptic.[17] Similarly to our patient, it has been reported that aseptic arthritis may be more common among children and males, most notably those with agammaglobulinemia or profound hypogammaglobulinemia.[17] Contrary to our patient, polyarthritis has been described by some as the most common pattern in aseptic arthritis. Studies of affected families found no increase in the rate of joint manifestations among immunocompetent first-degree relatives, a finding that suggests the direct link between apparently aseptic arthritis and decreased immunoglobulin levels.[18] Therefore, the history of chronic asymmetric oligoarthritis in a young child with hypogammaglobulinemia seems more likely related to an immune dysregulation-related synovial disorder, as does the history of relapsing episodes of arthritis until the age of 23. This is further supported by the good response to increasing doses of immunoglobulin.[19]

The absence of rheumatoid factor and anti-nuclear autoantibodies is typical of patients with humoral PID because of decreased immunoglobulin synthesis. Noticeable, classical rheumatoid arthritis may occur in hypogammaglobulinemia, but is uncommon and rheumatoid factor is absent. In an

analysis of 248 patients with CVID, five patients had concurrent rheumatoid arthritis and four had polyarticular juvenile idiopathic arthritis.[9,20] Classical RA is even more uncommon in XLA,[21,22] a situation that has attracted attention as B-cell depletion by rituximab leads to improvement in RA in immunocompetent individuals.[23]

Persistent monoarthritis at the age of 23 not responding to high doses of immunoglobulin was particularly worrisome. Infection or a coexisting local or systemic disease had to be thoroughly investigated. Joint infection has always to be beard in mind in a patient with humoral PID and arthritis. The likelihood of septic arthritis is greatest in patients with monoarthritis, as was the case of our patient at the age of 23, with only one affected joint. Pyogenic bacteria account for most cases (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*). The profound IgG deficiency found in many patients with PID results in considerable vulnerability to encapsulated organisms. Viral arthritis is uncommon, the main causes being adenovirus type I and echovirus 11.[24-27] *Mycoplasma* is a major cause of arthritis in patients with humoral PID and *Ureaplasma urealyticum* has been the most commonly recovered mycoplasmal agent, although *M. pneumoniae*, *M. hominis*, and *M. salivarium* have also been incriminated.[11,28,29] In a study of patients with hypogammaglobulinemia, Furr *et al*[29] found a 38% rate of *Mycoplasma*-positive cultures from joints with arthritis.

The mechanisms underlying the link between humoral PID and mycoplasmal arthritis are unclear. Increased susceptibility to mucosal colonization with mycoplasmas in patients with hypogammaglobulinemia has been demonstrated[29] and might be explained by the lack of protective antibodies at mucosal surfaces. The possibility of higher mucosal colonization in patients lacking sufficient antibodies may also account for the increased risk of dissemination from the respiratory and urogenital tracts to the joints and other distant sites in these patients. It is not fully understood why *Mycoplasma* species have a tendency to infect the joints of these patients. *In vitro* work has suggested that minor trauma common to large joints attracts neutrophils and neutrophils have been shown to take up mycoplasmas into phagocytic vacuoles in the absence of specific antibodies where they remain viable and are subsequently released into joint spaces.[30] Additionally, synovial fluid is presumed to be a favourable environment in which mycoplasmas can grow.

In the case we report, at the age of 23, no microorganisms were identified in synovial fluid, when analysis was performed for persistent monoarthritis. By definition, in immune dysregulation-related arthritis, the synovial specimens are negative for infectious agents, including *Mycoplasma*. However, as previously highlighted, this does not rule out low-level intrasynovial infection. The degree of cellular infiltration in our patient's synovial tissue was higher than usually found in patients with aseptic arthritis and PID, where the most common pattern of histological abnormalities is synovial hyperplasia and capillary proliferation with no major lymphocytic or neutrophilic infiltrate, little or no plasma cells and B cells, most of the T cells being CD8+ cells for which neither the inducing mechanism nor the target is known.[31,32] This pattern contrasts with the one of rheumatoid arthritis, where the synovial infiltrate contains large numbers of CD4+ T cells and of B cells.[33] Thus, histological examination of the synovial membrane may be a useful diagnostic tool in patients with synovitis and hypogammaglobulinemia. In the case we present it also allowed us to rule out the hypothesis of pigmented villonodular synovitis.

IV immunoglobulin replacement therapy has been described as being promptly effective in many cases of immune dysregulation-related arthritis[17,19,32] but has not been consistently effective for the prevention and treatment of mycoplasmal arthritis.[34] An anti-inflammatory effect of the immunoglobulin may be responsible for the rapid resolution in some cases of immune dysregulation-related arthritis (although IV immunoglobulin is not usually given at immunomodulatory doses). Reports of low efficacy of IV immunoglobulin in the treatment and prevention of both immune dysregulation-related arthritis and mycoplasmal arthritis may be ascribable to inadequate doses of IV immunoglobulin[34] and in the case of mycoplasmal arthritis, also hypothetically related to low contents of anti-*Mycoplasma* antibodies and IgA in the infusion, but little is known about humoral immune responses to *Mycoplasma* infections.

In the treatment of *Mycoplasma* arthritis, macrolides, quinolones and, above all, tetracyclines can be effective,[35-37] perhaps not only via their known anti-*Mycoplasma* activity, but also via immunomodulating effects;[38] however, the potential benefit of this immunomodulating effect in mycoplasmal arthritis in patients with PID has not been

evaluated to date; if necessary, antibiotic treatment can be continued for a prolonged period of 2-6 months in these patients.[19,27,39]

Infectious arthritis usually occurs only in patients with profound hypogammaglobulinemia. In practice, keeping the serum immunoglobulin level above 8 g/L is usually highly effective in preventing *Mycoplasma* infections[34,40] and in the report by Franz *et al*[34] this level is advised as the minimum IgG trough level. Because of the difficulty in ruling out low-level intrasynovial infection, concomitant oral or intravenous administration of antibiotics effective against *Mycoplasma* has been recommended, even in patients with negative results from cultures and *Polimerase Chain Reaction* assays of synovial specimens.[19] Because mycoplasmas are the most common cause of arthritis in patients with humoral PID, it has been recommended that antibiotic treatment should not be delayed while waiting for results of cultures.[34] These strategies remain controversial.

An additional issue is that the diagnosis of *Mycoplasma/Ureaplasma* infection may be missed because appropriate culture media or special techniques are not used. This may have happened in our patient. We believe that synovial fluid from affected joints in patients with PID should be promptly aspirated and cultured and that early suspicion of a mycoplasmal infection is crucial to ensure that appropriate culture media for mycoplasmas and ureaplasmas are used, bearing in mind that certain individual species need special culture conditions. In fact, some mycoplasmal species may require additional nonculture methods such as a polymerase chain reaction assay,[41] 16S rRNA sequence analysis,[39] or DNA hybridization[42] to identify the particular organism. Cultures may need to be incubated for a minimum of 6 weeks.

Our patient's treatment plan aimed at the maintenance of high levels of serum immunoglobulin (above 8g/L) during the arthritis flare. This approach was based on the reported efficacy of IV immunoglobulin in many cases of immune dysregulation-related arthritis.[17,19,32] Although no evidence of *Mycoplasma/ Ureaplasma* infection was found, this approach was also based on published studies[42,43] suggesting that, while mycoplasmal arthritis can develop on inadequately dosed IV immunoglobulin therapy, it can also be seen in patients on standard IV immunoglobulin.[34,39,40,44,45] Higher immunoglobulin levels could presumably improve immune regulation and also improve the immune means of clearing occult synovial infection. Aiming at levels of serum immunoglobulin above 8g/L as a general measure/approach in XLA patients is further supported by retrospective analyses of agammaglobulinemic children revealing that the number and severity of infectious complications is inversely correlated with the dose of IGIV administered.[46,47] In particular, when IgG trough levels were maintained at greater than 8 g/L, serious bacterial illness and enteroviral meningoencephalitis were prevented.[46] Further studies are needed to clarify the cost-effectiveness of such strategy.

Arthritis at the age of 23 eventually resolved over a few months and although it was not done we believe that a concomitant trial of tetracyclines would have also been a well supported strategy at that time. Such decision could be justified by the current evidence for *Mycoplasma/Ureaplasma* as the main cause of arthritis in patients with XLA and CVID and by the difficulty in ruling out low-level intrasynovial infection and culturing these organisms, which hamper the diagnosis of such infection.

In conclusion, we wish to highlight that among immunodeficiencies, arthritis occurs chiefly in humoral PID, namely XLA or CVID, and may be one of the warning signs for PID. It may be related to infection, most notably by *Mycoplasma,* or immune dysfunction. In children and occasionally in young adults, a combination of arthritis and hypogammaglobulinemia should suggest PID, although other causes of hypogammaglobulinemia must be excluded. Physicians evaluating patients with arthritis should be aware of that fact so that an early diagnosis can be pursued, as it is of extreme importance in the optimal management and prognosis of patients with PID. Immunoglobulin replacement therapy should be promptly started irrespective of the clinical phenotype, as soon as the diagnosis is established.

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We dedicate this article to the memory of Dr. Nicolau da Fonseca.

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