AMYLOIDOSIS SECONDARY TO RHEUMATIC DISEASES – 16 CASES

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Abstract

Introduction: Secondary amyloidosis (SA) results of tissue deposition of an acute phase reactant protein produced by chronic inflammation. Its incidence appears to be declining, following the improvement of medical care to primary diseases. Our aim is to assess a group of Portuguese patients with amyloidosis secondary to inflammatory rheumatic diseases, and their evolution over the past 10 years.
Methods: The study comprised 16 patients with SA confirmed by tissue biopsy, hospitalized in the Rheumatology Department of Hospital São João in Oporto in the last 10 years. We made a protocol on epidemiological, clinical and analytical data focusing the rheumatic disease and SA, and possible elements of connection between them.
Results: Of the 16 patients, mainly women (81,2%), with mean age at entry of 56 years, 68,8% had rheumatoid arthritis. Amyloidosis was diagnosed in average at 13,5 years of primary rheumatic disease, and its main manifestation was kidney involvement, which together with infection and orthopaedic surgery or its complications, were the leading causes of hospitalization. In this time interval, 6 patients died. They were older, with longer duration and lower rate of treatment of the primary rheumatic disease, and had SA diagnosed 1,5 years before death (different of the 5 years of those that still alive). They had higher rate of gastrointestinal, neurological and serious kidney involvement, and hospitalizations.
Conclusions: Improving medical care in rheumatic inflammatory diseases has reduced the incidence of SA. Also, biotherapy appears to be achieving positive results in established amyloidosis, whatever the mechanisms involved. Our data, on Portuguese patients, seems to follow this trend.

Keywords: Secondary amyloidosis; Amyloid A; Rheumatic diseases.

Introduction

Secondary amyloidosis (SA) is a disorder resulting from the extracellular tissue deposition of protein fragments of serum amyloid A, an acute phase reactant, produced by ongoing or recurring inflammation[1-3]. The overall incidence in autopsies in western countries is estimated at 0,5 to 0,86%, where the most frequent underlying diseases are rheumatoid arthritis (RA) (23-51%), juvenile idiopathic arthritis (JIA) (7-48%), and ankylosing spondylitis (ASp) (0-12%). However, in other areas, autoinflammatory and chronic infectious disorders are more frequently associated[4-7]. The reason why other rheumatic diseases like systemic lupus erythematosus (SLE) have lower incidence of SA is unknown, but it may be related to activation of different proteolytic pathways[7,8]. In living patients with RA, the incidence of AA found in biopsies ranges 7-29%, and 2-11% of RA patients have symptomatic disease[7,9-12]. It predominantly affects seropositive, long-standing (mean duration of RA at SA diagnosis of 15,4 years), poorly controlled, severe and extrarticular disease[4,7,10,13].

Renal involvement, manifesting in 59% of RA patients, is the most characteristic initial presentation, with proteinuria in 70% of cases, and contributes to

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39% of deaths. In JIA and ASp patients with SA, kidney involvement occurs in almost all, and contributes to 43% and 6% of deaths, respectively[6,7,14]. Other less frequent manifestations concern the gastrointestinal (24-58%), cardiac (9-40%), (peripheral and central) nervous, hematologic and pulmonary systems[3,7,15,16]. Musculoskeletal and skin manifestations of SA are rare. Clinical presentation is often difficult to differentiate from the primary rheumatic disease itself. Also its multiple possible mechanisms of pathogenesis and co-morbidities, like drug induced, immune-complex and cardiovascular disease, make this task nearly impossible. Therefore, diagnosis is suggested by the clinical manifestations, but established only by tissue biopsy[3,7].

SA is generally associated to a poor prognosis, with a 4-year survival rate of 58% from the time of diagnosis, being considered responsible for shortening of lifespan of RA patients by 7,7 years. Treatment is directed to the underlying inflammatory disorder, and better control of the primary rheumatic disease seems to be reducing the incidence of SA[4,17]. Also recent studies suggest a specific role of anti-cytokine therapies, interfering in the hepatic amyloid precursor synthesis induced by interleukins 1, 6 and tumour necrosis factor[16,18-21]. The levels of some proinflammatory cytokines correlate with synovitis, and have also been demonstrated to correlate with levels of serum AA and disease course in patients with established SA[22]. In addition, new approaches specifically aimed at established amyloidosis are under investigation[16,23-25].

We intend to make the characterization of a Portuguese population of patients with amyloidosis secondary to inflammatory rheumatic diseases, and their evolution in the last 10 years.

Methods

This study included 16 adult patients with a rheumatic disease and SA confirmed by positive Congored staining in tissue biopsy (in abdominal fat pad, kidney or rectal mucosa), hospitalized in the Rheumatology Department of Hospital São João in Oporto, in the last 10 years (2000-2009). We excluded patients with primary and dialysis-related amyloidosis, and also a patient with SLE and organ-specific (tongue) amyloidosis. Their clinical histories were reviewed, collecting epidemiological, clinical and analytical data focusing on the primary disease features possibly related to SA, as described in the literature, and its manifestations and outcome. We registered the primary rheumatic disease, its duration, treatment with corticosteroid, disease modifying antirheumatic drugs (DMARD) and biologic drugs (anti-tumor necrosis factor α), seropositivity for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), and their titre, in relation with levels of sedimentation rate and C-reactive protein, in the computerized records of serial analysis over the years of follow-up on an outpatient basis, history of (non-traumatic) orthopaedic surgery, sex, age (at the 1st hospitalization, and at the time of the study or at time of death), number of hospitalizations in the Rheumatology department and other services, their mean duration and main causes, and death. Focusing amyloidosis, we recorded the date of diagnosis, the technique of biopsy that confirmed it, the initial manifestations (that involved renal, cardiac, gastrointestinal and neurologic systems), and the evolution, namely the analytical parameters since the beginning of biotherapy, and the need for dialysis.

Results

The population's main features evaluated in this study are summarized in Table I. Of the 16 patients included, mainly women (81,2%), 6 with a mean age at entry of 64 years, died. Of these, all women, 4 had the diagnosis of RA, one JIA and the other one, SLE. Their primary rheumatic disease had an average of 23 years duration, 21,5 years of disease when diagnosed SA. They died, on average, 1,5 years after this diagnosis. They had an average of 5 hospitalizations (1 in the Rheumatology department), with a duration of 16,8 days each (median), mainly due to infectious complications, and less frequently for orthopaedic surgery. Only 16,7% underwent surgery for prosthetic joint placement or correction of deformities secondary to the underlying disease (Figures 1, 2). 5 patients have records of having been discharged from hospital after an episode of sepsis (3 with starting point in infected bedsores, one with respiratory infection, and another with appendicitis and abscess). One of these died for sepsis in a subsequent hospitalization.

The remaining 10 patients, alive, had mean age at entry of 47 years. 70% are women, and 70% have RA. The other primary rheumatic diseases are 2 cases of ASp (both male), and one of JIA (RF positive). Comparing with the 6 patients deceased, these

Table I. Main features of the population

	Global population (n=16)	Alive patients (n=10)	Deceased patients (n=6)	P value
Female (%)	81,2	70	100	0,25
Age (years), median (P25-P75):				
at 1st hospitalization	56 (42,5-65,5)	47 (35-60)	64 (56-71)	0,03
at the time of the study/at time of death	NA	57 (44-64)	66,5 (64-71)	0,06
Primary rheumatic disease:				
duration (years), median (P_{25}-P_{75})	19 (13-26,5)	18 (14-22)	23 (11-31)	0,59
rheumatoid arthritis (%)	68,8	70	66,7	>0,99
RF and/or ACPA positive (%)	68,8	80	50	0,29
orthopaedic surgery (%)	50	70	16,7	0,12
Treatment with:				
corticosteroids (%)	100	100	100	>0,99
DMARDs (%)	62,5	80	33,3	0,12
biotherapy (%)	37,5	60	0	0,03
Amyloidosis				
Duration (years), median (P_{25}-P_{75})	4 (2-5,5)	5 (3-6)	1,5 (1-2)	0,03
Time since onset of primary rheumatic disease and diagnosis of amyloidosis (years, median)	13,5 (10-23)	11 (10-16)	21,5 (9,9-24)	0,30
Confirming biopsy:				
abdominal subcutaneous fat (%)	43,8	50	33,3	
kidney (%)	50	50	50	0,63
rectal mucosa (%)	6,2	0	16,7	
Renal involvement (%)	93,3	90	100	>0,99
Initial presentation:				
proteinuria (%)	68,8	60	83,3	0,59
renal insufficiency (%)	68,8	70	66,7	>0,99
Evolution:				
progressive deterioration - dialysis (%)	37,5	30	50	0,61
improve after start biotherapy (%)	13,3	40	NA	NA
Cardiac involvement (%)	37,5	40	33,3	>0,99
Gastrointestinal involvement (%)	37,5	10	83,3	0,01
Neurological involvement (%)	25	10	50	0,12
Hospitalizations:				
Number per patient, median (P_{25}-P_{75}):				
total	4,5 (3-7)	3,5 (3-7)	5 (4-7)	0,62
Rheumatology department	1,5 (1-4)	2,5 (1-4)	1 (1-4)	0,68
Duration of each (days), median (P_{25}-P_{75})	12,1 (8-21,5)	11 (6,8-15)	16,8 (12-30,3)	0,16

Notes: a) NA: not applicable. b) Differences between proportions were tested using Fisher's exact test, and differences in distributions of continuous variables were compared with the Wilcoxon test. c) P25-P75: 25th-75th percentiles of each distribution (limits of the interquartile range).

younger patients were sooner and more often treated with DMARD (80% versus 33,3%) and biotherapies (60% versus 0%), and 70% (versus 16,7%) underwent orthopaedic surgery (for non-traumatic reasons). Their primary rheumatic disease was diagnosed in average 18 years before, 11 years at the time of amyloidosis diagnosis. They have this diagnosis, in average, for 5 years. Their hospitalizations were most frequently due to orthopaedic surgery or its complications (like placement or revision of prosthetic joint), but also for other various reasons, like suspected septic arthritis, iatrogenic cytope-

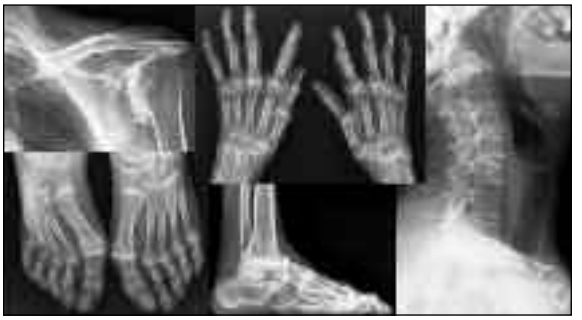

Figure 1. 37-year-old female with Juvenile Idiopathic Arthritis, polyarticular, rheumatoid factor and anti-citrullinated protein antibodies positive, with 31 years of evolution

nia, respiratory or urinary infections with worsening of primary disease or renal function.

Focusing amyloidosis, the study of subcutaneous abdominal fat confirmed the diagnosis in 43,8% of cases. In the remaining cases, either because it was negative (but persisted a strong clinical suspicion) or to exclude other pathogenic mechanisms, patients underwent kidney biopsy (Figures 3, 4), and in one case, biopsy of rectal mucosa.

The initial presentation of kidney involvement, present in 15 patients, was proteinuria and renal insufficiency in 68,8% of cases, each. Of the 6 patients treated with biologic drugs, now for an average of 4,8 years, all of them still alive, and 4 improved their analytical parameters of sedimentation rate, C-reactive protein, titres of RF and ACPA, and 2 (in 5 with renal involvement) improved their renal function (proteinuria and creatinine clearance). The one patient without renal involvement is treated with anti-TNFα for 6 years.

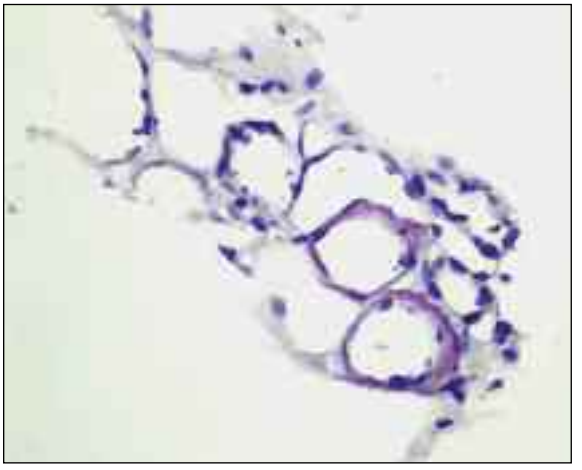

Figure 3. Kidney biopsy – Congo red staining

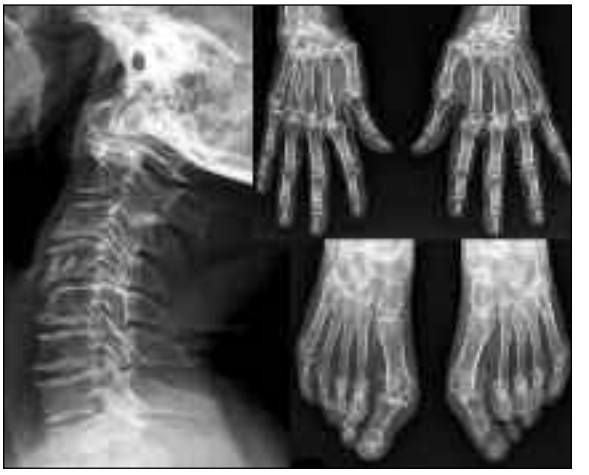

Figure 2. 64-year-old patient, seropositive Rheumatoid Arthritis with 15 years of evolution

The other main manifestations of amyloidosis were cardiac (mainly dilated cardiomyopathy and conduction disorders), gastrointestinal (changes in bowel habits and hepatomegaly), and neurological (2 cases of stroke, 1 case of autonomic and another with peripheral neuropathy).

Discussion

It is difficult to document the course of SA, since its nonspecific and slowly progressive manifestations and findings in diagnostic procedures, rarely allow to determine when this complication began. This

Figure 4. Kidney biopsy- Congo red staining shows characteristic apple-green birefringence under polarized light, positive for amyloid

is especially true when it comes to rheumatic diseases, with symptoms frequently overlapping[3,7,10]. As in previous studies, we also felt these limitations, reflected in the small number of patients included. Here too, nephropathy (renal insufficiency), cardiomyopathy (cardiac insufficiency), gastrointestinal symptoms and infections were the main causes of morbidity (and hospital admissions)[3,7,15,16]. We were unable to determine the direct cause of death in most cases, because only one patient died during hospitalization. However, records of last admissions suggest that their overall clinical condition was too fragile (3 of them bedridden, with ulcers, and one with terminal nephropathy in dialysis).

The older age at 1st hospitalization, higher mean number of admissions, and longer duration and lower rate of treatment of the primary rheumatic disease, can point to a weaker medical monitoring of the 6 patients who later died, and explain a delay in diagnosis of amyloidosis, in average 1,5 years before death. This probably also explains their higher rate of gastrointestinal, neurological and serious kidney involvement (50% of patients required dialysis). These patients were older, which is consistent with data showing that improving medical care in rheumatic inflammatory diseases has reduced the incidence and morbidity of SA[4,17]. The use of biotherapies seems to have obtained good results in established amyloidosis, regardless of what has been the mechanism involved[16,18-22,25].

This assessment, which addressed Portuguese patients not previously evaluated, approaches to data published in other populations, but much remains to be done.

Conclusions

Improved treatment protocols on rheumatic diseases appear to be decisive in reducing the incidence of SA. Some biotherapies directed to the primary rheumatic disease, are surprising for their positive effects on established SA, which may be related to common pathogenic pathways. Moreover, efforts are being developed to diagnose and treat SA earlier and in a targeted way.

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