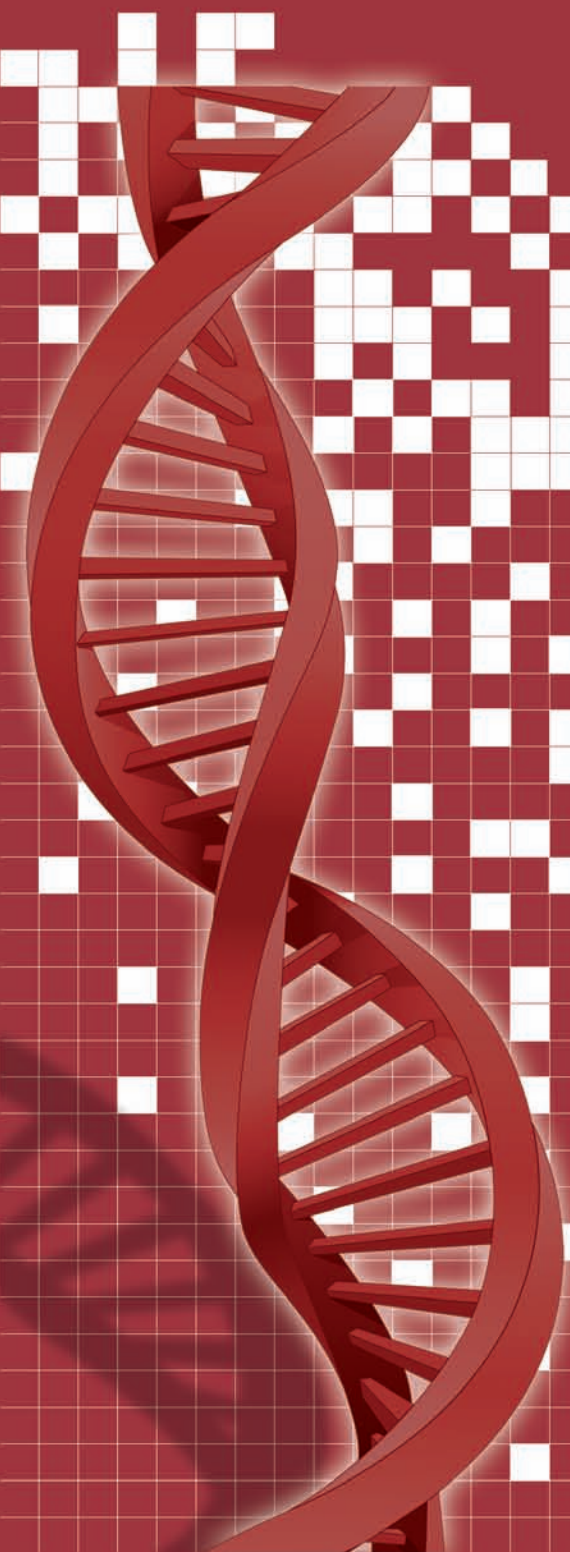
Systemic Autoimmune Diseases Cases Report Book II

Carlos Dias



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Preface

Preface

Dear colleagues,

During the accomplishment of the tenth International Medinterna Meeting on Systemic Autoimmune Diseases we are publishing the second case reports book on autoimmune diseases to offer all the attendants of the meeting and also in the International Autoimmunity Congress in Granada, Spain.

This is a project of EASI Portugal (European Autoimmunity Standardization Initiative) and we think that these editions are very important to create discussion and motivate the study of autoimmune-mediated diseases, specially for internal medicine or rheumatology residents.

In this edition we publish 11 case reports from several portuguese hospitals, presented by internal medicine and rheumatology. This way of presentation is very important to discuss the special aspects of each disease, like systemic sclerosis, Sjogren syndrome, sarcoidosis, vasculitis, Behçet´s disease and antiphospholipid syndrome.

We thank Thermo Fisher Scientific company to support the edition of this case reports book.

We hope this book may be useful to all the clinicians interested in these diseases and we promise to continue, probably in two years, this project.

Carlos Dias

Contents

Case Report 1

The Lord of the Rings - A Peculiar Presentation of Microscopic Polyangiitis

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Introduction

Microscopic Polyangiitis (MPA) is an anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. It's characterized by small vessel necrotizing inflammation, with few or no immune deposits affecting the blood vessels, including arterioles, capillaries and venules. ANCA positivity is the hallmark of MPA. It can affect several organ systems, leading to a variety of clinical manifestations, including renal, skin, respiratory and neurological symptoms.

Case report

We present the case of a 60 year old caucasian male, retired (former truck driver), presenting in the Emergency Department (ER) with 4 to 5 months' complaints of predominantly late afternoon relapsing fever (maximum temperatures of 38ºC), with chills. He also complained of asthenia, anorexia and a six kilogram weight loss.

A week prior to admission in the ER, the patient noticed three erythematous skin lesions: one on the left inner thigh and the other two in both gluteal areas, all three painless and non-pruriginous. He also complained of lower limbs myalgia and dry cough, both with a four week evolution. He remembered a similar episode one year before, self-limited, with transient skin lesions.

Due to his longstanding clinical picture, basic ambulatory diagnostic

workup by his GP revealed inflammatory anemia (hemoglobin 11 g/dL, normocytic, normochromic; diminished blood iron and transferrin saturation, raised ferritin) and a C-reactive protein (CRP) of 18 mg/dL, erythrocyte sedimentation rate (ESR) of 18 mm in the first hour; a normal renal function was documented a few months prior to presentation. No relevant personal or familial history was detected.

In the ER he was noted to have muco-cutaneous pallor, hyperpyrexia (39ºC) and a slight uremic breath. No lymph nodes were noted on examination; normal heart and pulmonary auscultation, and abdomen without enlarged organs. He had a 5 to 6 cm wide ringform or target-like skin lesion on the left inner thigh (Fig.1), with erythematous border and scaly center, and two other similar though smaller lesions in the gluteal areas, bilaterally (Fig.2).

Fig. 1 - **Left inner thigh erythema annular centrifugum lesion.**

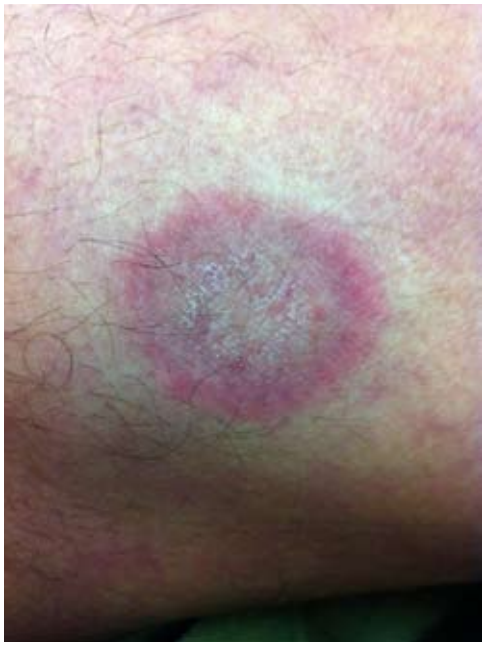
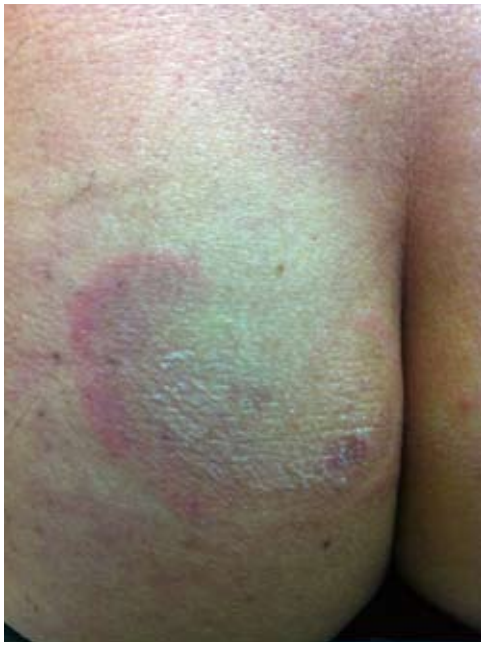


Fig. 2 - **Left gluteal erythema annular centrifugum lesion.**



Initial lab workup at the ER showed normocytic normochromic anemia (Hemoglobin 11,8 g/dL), increased CRP(17,9 mg/dL), acute kidney

failure – urea (185 mg/dL) and creatinin (9,1 mg/dL). Arterial blood gas revealed "compensated" metabolic acidosis (pH 7,35, HCO3- 18,1 mmol/L, pCO2 29 mmHg and base deficit -8,5 mmol/L). He was started on urgent hemodyalisis.

He was then admitted to the Internal Medicine ward, to proceed with the diagnostic assessment. Three major groups of entities were pursued in the diagnostic evaluation: infectious, systemic/inflammatory, oncological diseases. Amongst the inflammatory group, the prime suspects were systemic lupus erythematosus and ANCA associated small vessel vasculitis, namely Wegener's granulomatosis and MPA. Lyme disease was also one of our first hypothesis because the skin lesions fulfilled criteria for epidemiologic definition of case (migratory erythema at least 5 cm wide); also, rickettsial infections were on our mind, since the patient lived in a rural area were such infections are frequent. Cancer in the elderly, with systemic symptoms had to be excluded, both solid and hematological malignancies. Also, HIV infection can have a similar form of presentation.

Further studies revealed a raised ESR of 104 mm in the first hour, a 24 hour proteinuria quantified as 835,66 mg. Bacterial and viral serologies were negative for acute infection, including serology for HIV infection, syphilis, Borrelia burgdorferi, Rickettsia conorii (the Mediterranean rickettsial), Coxiella burnetti, Leptospira species, Huddleson test. The head, thorax, abdomen and pelvis CT showed no suspect lesions or masses. A kidney biopsy detected a pauci-immune necrotizing crescentic glomerulonephritis (Fig. 3 to 5).

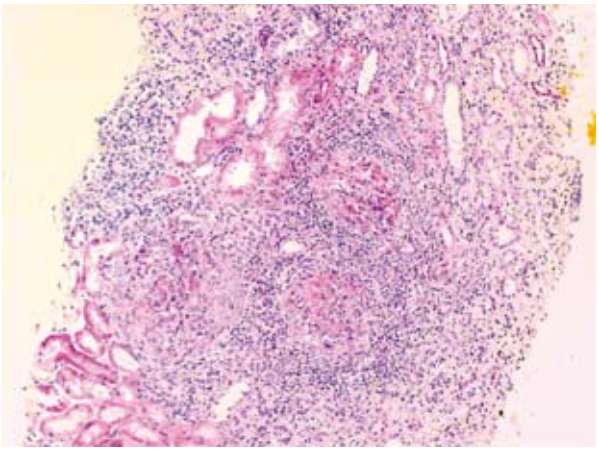


Fig.3
Renal biopsy. Hematoxylin and eosin: crescentic glomerular destruction; lymphocytic infiltrate; magnification 100x.

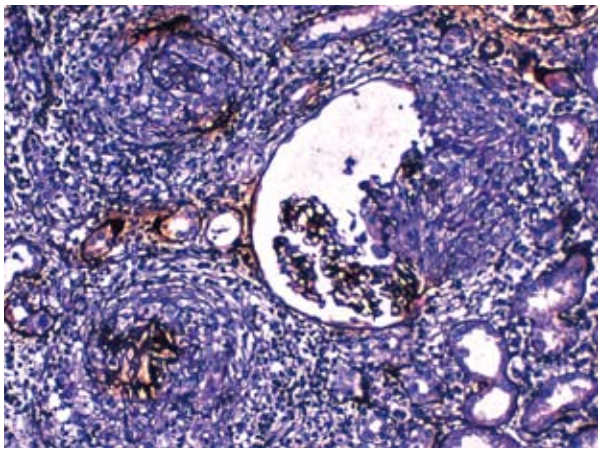


Fig.4
Renal biopsy. Silver stain: capillary tuft destructed by crescents; crescent contacting the interstitium (right glomerulus); magnification 200x.

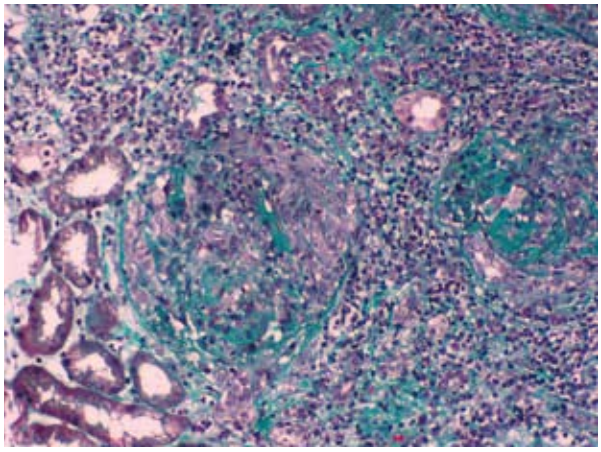


Fig.5
Renal biopsy. Trichrome stain: cellular crescent (right glomerulus); magnification 200x.

A Dermatology consultation identified the lesions as erythema annulare centrifugum and a skin biopsy of the thigh lesion was also performed, but showed only superficial perivascular dermatitis. Anti-MPO ANCA positivity was found (165,47 U/mL); the rest of the immunological profile was unremarkable.

The association of skin lesions, rapidly progressive renal failure, systemic features, along with necrotizing crescentic glomerulonephritis and MPO-ANCA positivity led to a diagnosis of microscopic polyangiitis (MPA).

He was started on methylprednisolone pulses (three daily pulses of 1 g, followed by prednisolone 1 mg/kg/day), plasmapheresis and

cyclophosphamide.

He currently presents a 3,7 mg/dL plasma creatinin (non-oliguric renal failure) and is dyalisis-free. Regression of constitutional symptoms and cutaneous lesions was achieved. He still presents a slight inflammatory anemia.

Despite current therapy, two months after the diagnosis of MPA, he was noted to have a steppage gait. On examination, he had a right foot drop. Neurophysiologic studies showed a demyelinating peroneal mononeuropathy. Corticosteroid therapy was being tapered, but it was stepped up and intense physical therapy was started. Currently, he's on monthly iv cyclophosphamide therapy and daily prednisolone (0,5 mg/kg/day).

Discussion

ANCA-associated vasculitis (AAV) are a group of diseases that affect small vessels' walls. This group includes Wegener's Granulomatosis, Churg--Strauss Syndrome and Microscopic Polyangiitis.

Vasculitis must be considered in patients with multisystemic involvement after firm exclusion of infectious and neoplasic etiologies, especially in patients presenting with recent onset renal failure, skin lesions, neuropathy, and constitutional symptoms, such as the presented case.

As a small vessel vasculitis, MPA was recognized as a separate entity from polyarteritis nodosa since 1994 Chappel Hill's Conference. Histologically, MPA has a few distinguishing features: small vessel involvement, including arterioles, capillaries and venules, necrotizing lesions and few or no immune deposits on immunofluorescence (pauci-immune). The absence of granuloma formation helps to distinguish it from Wegener's granulomatosis. [1, 2]

MPA shows a slight preference for males. The approximate age of onset is 50-60 years old. [4]

Clinically, MPA can present with a wide range of manifestations. The most frequently reported manifestation is rapidly progressive glomerulonephritis, seconded by pulmonary hemoptysis. However, general symptoms, like fever, fatigue, myalgias, arthralgias and other general symptoms are also quite frequent. Other organ systems frequently affected are the peripheral and central nervous system, gastrointestinal system, skin.

Depending on the department reporting the case series, the frequency of several clinical manifestations is variable. Obviously, nephrology series report a high prevalence of glomerulonephritis, pneumology series report alveolar hemorrhage more often and neurologist find multiplex mononeuropathy to be more frequent than internal medicine series. [1]

Renal involvement is by far the most frequent type of organ involvement, with a reported prevalence of 75 to 90% [2, 3]. The renal involvement is usually in the form of necrotizing pauci-immune crescentic glomerulopnephritis. Signs of kidney affection are raised plasma creatinin, elevated proteinuria and hematuria.

Skin lesions are also frequent in MPA, with reported prevalences ranging from 20 to 70%. Cutaneous disease can be in the form of palpable purpura, oral ulcers, splinter hemorrhages, facial edema, livedo. Palpable purpura is the most frequently reported [3,4]. Histology of skin lesions usually shows leukocytoclastic vasculitis with neutrophilic infiltration of small-vessels of the superficial dermis. However, it can also show a nonspecific perivascular lymphocytic infiltration, as was the case of our patient [4]. Anually recurring forms of erythema annulare have been reported, with a matching histology (perivascular lymphocytic infiltration of the dermis), always without causal agent identification [6]. Erythema annular centrifugum has been described in association with Sjögren Syndrome, systemic lupus erythematosus and subacute cutaneous lupus erythematosus, infectious diseases such as dermatophytosis, M. contagiosum infection, M. tuberculosis infection, as a paraneoplastic syndrome in myeloma, leukemia and Hodgkin's disease, and many other conditions (Table 1).

Table 1 - Erythema Annular Centrifugum differential diagnosis.

Etiology	Disease
Infectious	*Molluscum contagiosum*, Epstein Barr virus, ascariasis, yersiniosis, Streptococcal infections, *M. tuberculosis*, dermatophytoses, *C. albicans*.
Collagen Diseases	SLE, Sjogren syndrome, CREST syndrome.
Malignancies	Hodgkin's disease, leukemia, myeloma
Granulomatous Diseases	Sarcoidosis
Skin Diseases	Bullous pemphigoid, lineal IgA disease, pemphigus, psoriasis
Endocrine Diseases	Hashimoto's thyroiditis, Graves disease
Miscellaneous Diseases	Hypereosinophilic syndrome, idiopathic, familial

To the best of our knowledge, erythema annulare centrifugum has not been reported so far as a cutaneous manifestation of MPA. [3, 4, 6]

Pulmonary disease is also frequent. Hemoptysis may be the presenting complaint in a significant proportion of patients, but it may also be asymptomatic. Usually, lung involvement takes form as alveolar cappilaritis, with consequent hemorrhage. Radiologically, patients with lung disease present diffuse alveolar infiltrates. [1, 3, 4]

Peripheral nervous system involvement as multiplex mononeuropathy has been reported in about 14 to 36% of MPA patients. Central nervous system manifestations reported are usually cerebral thrombosis and hemorrhage. [5]

MPA is associated with antineutrophil cytoplasmic antibodies (ANCA). The prevalence of anti-proteinase 3 (PR3; cytoplasmic staining pattern – c-ANCA) and anti-myeloperoxidase (MPO; perinuclear staining pattern – p-ANCA) antibodies depends on the series. Most of the studies published show a stronger correlation with MPO-ANCA. However, PR3-ANCA can be the ANCA involved in up to 50% of MPA cases [2]. Therefore, the ANCA pattern alone is insufficient to distinguish among MPA, Wegener's granulomatosis, idiopathic necrotizing glomerulonephritis, Churg-Strauss Syndrome. Also, p-ANCA can be found in several other diseases, like inflammatory bowel disease, primary sclerosing cholangitis, infection, auto-immune liver disease and several other conditions. [2]

Some authors suggest that MPO-ANCA disease is associated with a more indolent disease course, namely a slower decline in renal function. [2]

Conclusion

This case has a few characteristics noteworthy: first, like most MPA, it presents with general symptoms; second, erythema annular, one of the main presenting features in this patient, is quite unusual as a skin manifestation of MPA; third, glomerulonephritis with rapidly progressive renal failure is also present, like in most cases of MPA; fourth, the ANCA activity is anti-MPO; fifth, a demyelinating mononeuropathy developed shortly after the initial presentation; there's no lung involvement.

The rapid recognition of this disease is crucial for starting prompt therapy.

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Case Report 2

Neurosarcoidosis

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Introduction

Sarcoidosis is a multisystemic inflammatory disorder of unknown cause [1] that affects individuals worlwide[2] and pathologically is characterized by the presence of epithelioid noncaseating granulomas in affected organs. Various infectious, organic and anorganic agents are considered to cause a granulomatous reaction in susceptible hosts. Some genetic factors alter expression of the disease [3].

Frequently presents with bilateral hilar lymphadenopathy and pulmonary infiltration [3], but there can be eye, skin, joint, liver, spleen, heart and nervous system abnormalities.[1,3,4] Clinical neurological involvement occur in about 5%-15% of patients with sarcoidosis and any part of the central or peripheral nervous system can be affected by sarcoidosis [2].

Spontaneous recovery may occur, but the disease can also become chronic and progressive, estimated in up to 25% of the cases. Overall, mortality from sarcoidosis is 1-5% [4].

Case report

The authors report a case of a 45-years-old caucasian male, referred to our Autoimmune Diseases outpatient clinic where he first came in November 2009. Six years before he had developed fatigue, dyspnoea and syncope, being the investigation started at another hospital. In the chest radiography performed by that time there was a large mediastinum and the computed tomography scan of the chest revealed mediastinal lymphadenopathy. A lymph node biopsy showed confluent epithelioid noncaseating granulomas,

being negative for acid-fast bacteria and malignant cells. Serum ACE was elevated and Gallium-67 scintigraphy showed uptake in the rigt superior mediastinum. The diagnostic of a stage I thoracic sarcoidosis was made and the patient started on corticosteroids (deflazacort - maximum dosage 30mg id).

In his first visit to our outpatient clinic he complained about exertion dyspnea, orthopnea, severe daytime sleepiness, morning headache and snoring. He had a 36Kg weight gain (from 75 to 111Kg) in the last 5 years and had been diagnosed hypercholesterolemia, hypertriglyceridemia, hepatic steatosis (liver biopsy in 2007) with persistent elevated serum liver enzymes, type 2 diabetes mellitus and depression. Polyuria and polydipsia were also present. Physical examination revealed central obesity, with a BMI of 42kg/m^2, conjunctive injection, heart and breath sounds diminished of intensity and lower extremities oedema. The examination was otherwise normal. The investigation and follow-up started at this point in our outpatient clinic intended to evaluate the extent and severity of organ involvement and are described next.

Fig. 1 – **Chest radiography: Stage II Sarcoidosis**

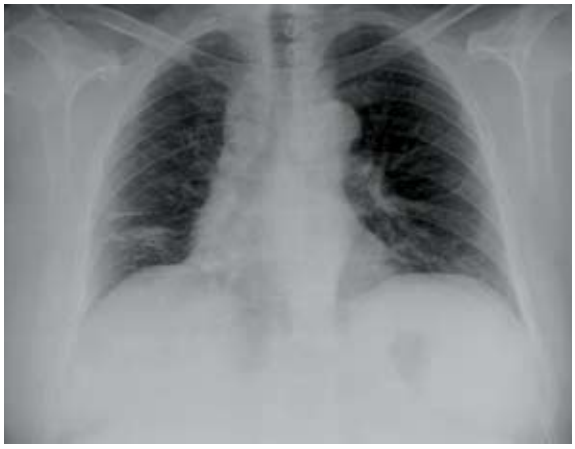
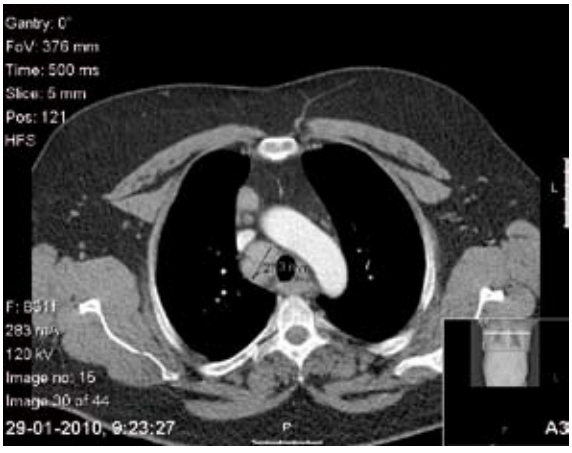


Fig. 2 – **Thoracic CT scan: multiple hilar lymphadenopathy, the larger paratracheal.**

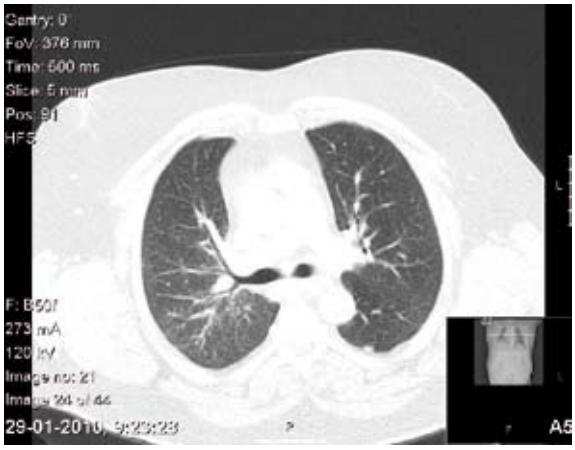


The chest radiography showed a large mediastinum and a bilateral diffuse reticular infiltrate, allowing classification as Stage II Sarcoidosis (Fig.1). The CT scan of the chest and abdomen evidenced multiple hilar and mediastinal lymphadenopathy (larger

paratracheal with 27mm – Fig. 2), micronodules along bronchovascular bundles mainly in the upper right lobe (Fig. 3), multiple retroperitoneum lymphadenopathy (the larger with 24mm) and homogeneous hepato-splenomegaly.

A whole-body Gallium-67 scanning was performed, showing only mediastinal lymphadenopathy without systemic involvement.

Fig. 3 – **Thoracic CT scan: pulmonary micronodules along bronchovascular bundles.**



Ventilatory function tests revealed a restrictive pattern and arterial blood gas showed mild hypoxia (PO2 65mmHg) without hypercapnia. Incremental aerobic exercise tests were uncertain, as 6-minute walk test was normal and cycle ergometer test revealed chronotropic incompetence. In order to make this clear the patient went on ECG, 24-hr Holter monitoring and echocardiography that were normal.

The polysomnographic examination evidenced a severe obstructive sleep apnea and the patient started on bilevel continuous positive airway pressure therapy during sleep.

An endocrine study was performed in order to evaluate hypophysis function and hypothalamic involvement. The routine laboratory tests revealed hypopituitarism (table 1): hypothyroidism, hypogonadotropic hypogonadism and adrenal insufficiency. The thyroid gland ultrasonography was normal. The 24-hr urine collected had a volume of 5700ml and an osmolarity of 257mOsm/Kg, so a fluid depravation test was performed. As this test did not result in urine concentration, desmopressin was administered with an increase of urine osmolarity around 50% 2-hr later (119 to 235mOsm/Kg) suggesting a pituitary diabetes insipidus. In face of these results the patient started on levothyroxin 0.25 ug po id, testosterone 250mg IM each month and nasal desmopressin 5ug bid.

Table I - Endocrine study

Variable	Reference Range	On April 2010
Prolactin (ng/ml)	4.0 – 15.2	17.9
TSH (uUI/ml)	0.35 494	2.05
$T4_{free}$ (rg/dl)	0.70 - 1.48	0.66
$T3_{free}$ (pg/ml)	1.71 – 3.71	1.44
FSH (mUI/ml)	1.5 – 12.4	0.70
LH (mUI/ml)	1.7 – 8.6	<0.10
Testosterone (rg/ml)	2.8 – 8.0	<0.03
Estradiol (pg/ml)	7.6 – 42.6	11.3
SHBG (nmol/L)	14.5 – 48.5	30.9
ACTH (pg/ml)	< 63.3	<0.1
DHEA-S (ug/dl)	44.3 – 331	<0.1
Androstenodione (ng/ml)	0.60 – 2.63	<0.3
Cortisol (morning/evening ug/dl)	6.2 – 19.4 / 23 – 11.9	1.0/09.5
Urinary free cortisol (ug/d)	36 – 137	4.4

Completing this evaluation with a brain MRI it showed hypothalamic, pituitary gland and fourth ventricle thickening, optic chiasma, left optic tract and sublenticular region involvement. (Figure 4 to 7). These lesions were enhanced by contrast suggesting granulomatous meningitis in the setting of sarcoidosis. Take notice that the ophthalmologic evaluation was normal and the serum ACE was elevated (77 for a normal value below 52U/L).

Fig. 4 – **Brain MRI: axial flair.**

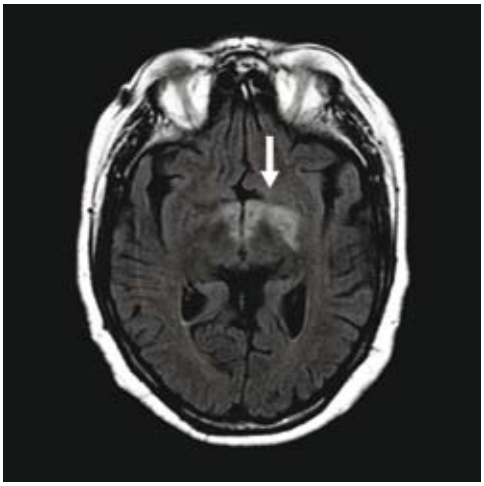


Fig. 5 – **Brain MRI: axial flair.**

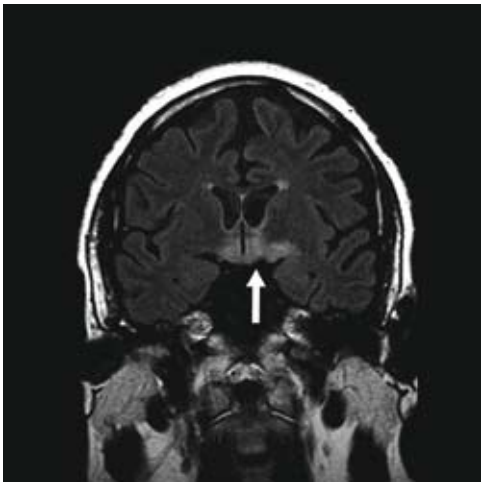


Fig. 6 – **Brain MRI: sagital flair.**

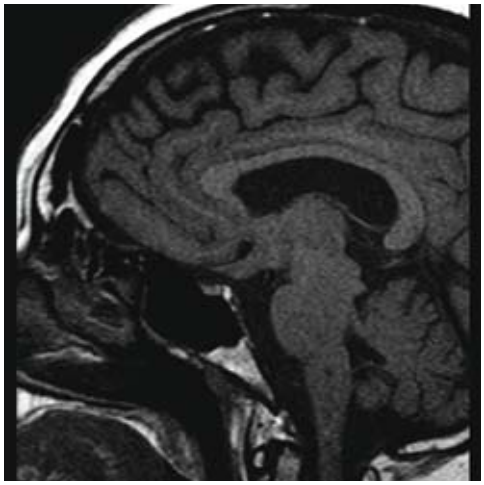
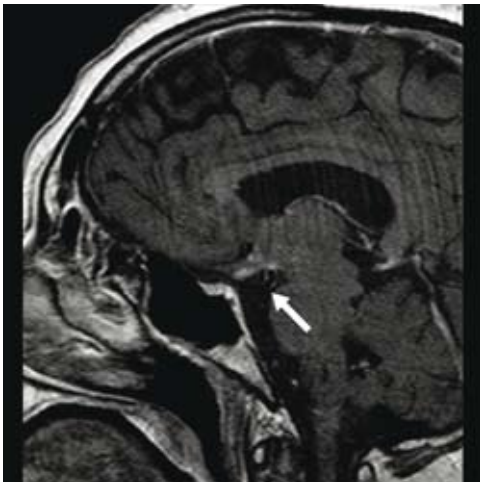


Fig. 7 – **Brain MRI: sagital flair gadolinium-enhanced.**



At this point, in June 2010 the patient started on Azathioprine 50mg per day reaching the dosage of 150mg per day five months later.

With direct treatment the symptoms reported at the first consult in our outpatient clinic improved and the brain MRI performed in February 2011 showed no lesions.

Discussion

Central nervous system involvement can be a severe and potentially life-threatening manifestation of sarcoidosis. The most common manifestation of neurosarcoidosis is facial nerve palsy [1]. However any part of the nervous system can be attacked by sarcoidosis, being hypothalamus and pituitary gland commonly involved [2, 3].

Neuroimaging studies are the most sensitive diagnostic tools in detecting and localising neurological lesions [2]. Gadolinium-enhanced MRI is the imaging modality of choice because it is more sensitive than CT and can depict a wide spectrum of abnormalities [2, 3]. After administration of contrast the lesions typically enhance when biologically active [2].

In the case reported the patient had a previous diagnosis of sarcoidosis without neurologic involvement for a long period of time. Due to the high

suspicion of neurological involvement according to the symptoms reported by the patient, a basic endocrine study was performed and revealed hypothyroidism, hypogonadism, adrenal insufficiency and diabetes insipidus. Although some of these disorders could be explained by the long term corticosteroids therapy, the brain MRI performed established central nervous system involvement.

Corticosteroids are the drugs of first choice for treatment of neurosarcoidosis [1, 2, 3]. However patients who deteriorate in spite of aggressive corticosteroid treatment, who cannot tolerate or have contraindication to corticosteroid treatment may benefit from cytotoxic agents. This approach was needed in the case reported, because the patient had neurologic involvement despite of being on corticosteroid therapy for six years. Among cytotoxic agents methotrexate and azathioprine are prefered [2]. In this case methotrexate was not used because of liver toxicity and azathioprine demonstrated to be a good choice as after eight months of treatment (full dosage in the last three) the neurological lesions disappeared. Notice that in addition to immunosupression, endocrine deficiencies should be replaced.

The prognosis of patients with neurosarcoidosis varies. The disease may be monophasic or self-limiting, it may come and go, or it may incessantly progress. Apparently, more than two-thirds of patients with this disease respond to treatment and, therefore, do well. In other cases, the progression may be slow and steady. Neurosarcoidosis carries a mortality of 10%, more than twice that of all other manifestations of the disease combined [2].

Conclusion

Management of sarcoidosis is difficult because of its complicated and multidimensional character. The wide range of symptoms and multiple systems involved underline the need for a multidisciplinary approach.

This case illustrates a patient with sarcoidosis with systemic involvement and focus the need for a high suspicion index to diagnose some forms of organ involvement, namely neurologic involvement.

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Case Report 3

Man with Polyarthralgias and Raynaud Phenomenon

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Abstract

The authors describe a clinical case of a male patient of fifty years of age is held in which the diagnosis of Mixed Connective Tissue Disease (MCTD) based on the criteria of Alarcon-Segovia and Villareal. After roughly four years of evolution since the beginning of his illness, he began a framework of nephrotic syndrome and is admitted to the Department of Medicine. After 4 days course of prednisolone pulses suffers a clinical and laboratory improvement and is sent to the Department of Nephrology for renal biopsy that was not performed. The clinical and laboratory improvement compared to treatment suggests a context of renal involvement in MCTD. However after this episode the patient meets criteria for both MCTD and Systemic Lupus Erythematosus (SLE).

To better understand the development and manifestations of systemic connective tissue diseases is needed most prospective studies with a large number of patients, as well as advancements in genetic knowledge on the etiology of these diseases.

Introduction

The precise etiology of most of the rheumatic syndromes and connective tissue diseases (CTDs) is unknown and the clinical manifestations are often overlapping. Management of the connective tissue diseases poses a great therapeutic challenge. These CTDs are characterized by a wide variety of signs and symptoms. As few clinical manifestations are disease specific, the classification of individual patients depends on recognizing certain patterns of

clinical and laboratory features. This is the basis for the classification criteria for CTDs.

This is also true for Mixed Connective Tissue Disease (MCTD). There are four published classification criteria for MCTD.

The initial full-length publication describing MCTD was reported in 1972 by Sharp and colleagues from Stanford University that identified a number of patients with high levels of antibodies against an extractable nuclear antigen (ENA) that was RNase-and trypsin sensitive ribonucleoprotein (RNP) antigen associated with MCTD, and the RNase and trypsin-resistant Smith (Sm) antigen associated with systemic lupus erythematosus (SLE). Now we know that the RNP antigen consists of a complex containing a series of small nuclear ribonucleoproteins (snRNP) including three polypeptides 70 kD, A and C that are linked non-covalently with U1-RNA as part of the spliceosome complex. The first MCTD patients were described as having overlapping features of SLE, scleroderma and polymiositis/dermatomiositis. [1]

These patients were felt to be both immunologically and clinically distinctive based on the presence of antibodies to the RNase and trypsin-sensitive RNP antigen and the absence of serious renal and central nervous system involvement, as well as their favorable initial clinical response to treatment with corticosteroids. However cumulative evidence has suggested that renal involvement is not so rare in MCTD, and it is suggested that more than 10 percent of patients with MCTD develop renal diseases. [1 e 2]

The renal involvement in MCTD can include glomerulonephritis (GN), nephrotic syndrome, scleroderma renal crisis, amyloidosis, and renal infarcts. In one review by Kitridou et al,[3] 11 of 30 patients who had MCTD had renal involvement, and 9 of these 11 patients had nephrotic range proteinuria. Treatment seemed to be successful in 72% of the patients who had nephritis and 62% of patients who were nephrotic had experience resolution or improvement with steroid treatment. [4]

In most instances patients who are diagnosed as having MCTD ar likely to suffer at some time from polyarthritis, myositis, Raynauds phenomenon, puffy hands or mild sclerodactyly, intersticial lung disease, and esophageal dysmotility. Musculoskeletal disease is common. Arthralgias or frank arthritis affect most patients who have diagnosis of MCTD, 50 a 70% are rheumatoid factor positive. [5]

There are four published classification criteria for MCTD and three of these classification criteria have been compared in a study and the criteria published by Alarcon-Segovia and Villarreal showed a sensitivity of greater of 90% and a specificity of greater than 98% when three or more clinical criteria were included along with the presence of anti-RNP antibodies. [1]

	Diagnostic criteria for MCTD (Alarcón-Segovia and Villareal [6])
1 - Serological	Positive high titre anti-RNP
2 – Clinical	Oedema of hands
	Synovitis
	Myositis
	Raynaud s phenomenon
	Acrosclerosis
3 - Requirements	a) Serological
	b) At least three clinical features
	c) Association of hand oedema, Raynaud s phenomenon and acrosclerosis requires at least one other feature

In recent studies of anti-U1RNP-positive patients, these criteria perform well, with high sensitivity and specificity, whether or not patients have evolved features of other autoimmune rheumatic diseases such as SLE or systemic sclerosis. [7]

A prospective study f 32 patients reported by Lundberg and Hedfors [8] who had anti-U1 snRNP antibodies, only 35% of the patients fulfilled the criteria for MCTD and 18 were classified as having undifferentiated connective tissue disease (UCTD). After a mean observation time of 6 years, the diagnosis was changed in 53% (17 cases) of the patients. Of the 18 patients who had UCTD, 15 developed symptoms or signs that were compatible with a defined diagnosis: 11 had MCTD, 2 developed SLE and 2 fulfilled the criteria for MCTD and SLE. From long term follow up Lundberg conclude that approximately one third of patients who have MCTD have a benign course and go into remission, and one third have a more aggressive course with less favorable response to treatment. [9]

Case report

The authors present a clinical case of a male fifty years patient, baker, born and resident in Figueira da Foz.

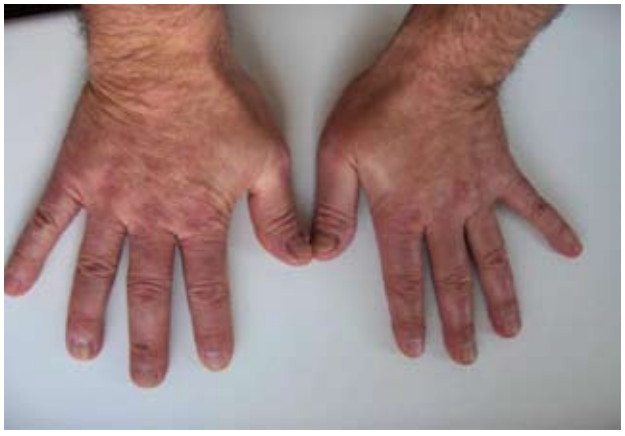
In September 2005 the patient is referred through the emergency room where he appealed in August 2005 for consultation by medical board. The outpatient complaints based on a symptomatology started two months before with symmetrical inflammatory polyarthralgias with morning stiffness more than thirty minutes of the tibio-tarsal (TT) joints, wrists, 2nd and 3rd metacarpo-phalangeal (MCP) proximal and distal interphalangeal (IPD) from hands, shoulders and elbows. Associated to it, he had a swelling of both tibio-tarsal joints. He referred Raynaud phenomenon with an increase of more than ten years.

On general physical examination he showed tenderness and swelling of the wrists joints, 2nd and 3rd MCF and ankles on both sides. He had tenderness of shoulders, elbows, proximal and distal interphalangeal joints.

Laboratory examination showed an erythrocyte sedimentation rate (ERS) of 21 mm/s (<10), positive rheumatoid factor, ANA 1/640 flied pattern, antibodies anti SSB/LA with a low titers and antibodies anti RNP with a high title. The radiography of hands, wrist and tibio-tarsal didn´t show any changes.

In the emergency department he had been treated with metylprednisolone 48 mg i.d. weaned gradually to 8 mg and it was joined in the Medicine attendance sulfasalazine 2 g i.d., nifedipine 5 mg 3i.d. and pentoxifylline 400 mg 2 i.d.

Fig. 1 – **Puffy hands**



In November 2005 he has been evaluated by attending physician without polyarthralgias and morning stiffness. Their hands were similar to those describe as puffy-hands (Fig.1).

The diagnosis of a Mixed Connective Tissue Disease was realized according to the Alarcon-Segovia and Villareal criteria.

In June 2007 in the consultation of autoimmune diseases the patient showed a clinical worsening. He presented polyarthralgias of the hands, elbows, shoulders, knees, ankles and a morning stiffness of more than 30 minutes and tenderness and swelling of the wrists, MCP of the right hand, 2nd, 5th MCP and 2nd and 5th proximal interphalangeal (IFP) of left hand, and left knee. He started methotrexate 10 mg/week, with clinical improvement. He had negative anti CCP and ERS 12 mm/h (<10).

In June 2008 he started edema of the lower limbs, asthenia and arterial hypertension with seven days of evolution.

He presented a normocytic, normochromic anemia (Hb of 9.8 mg/dl), platelets of 127x103, ERS 42 mm/h (<10), protein C reaction 18 mg /dl (<5), total serum proteins of 5,2 g/dl (6,4-8,3), albumin of 3, 1g/dl (3,4-4,8), rheumatoid factor 29,3 Ul/ml (<14). In the summary urine analysis type II, he presented 500mg/dl of proteins 150 Ery/microl, without changes of the urinary sediment and with 6,7g of protein in the 24 hours urine analysis.

During the four days of admission in Medicine department he made prednisolone 250 mg e.v. in the first three days followed by prednisolone 25 mg 6/ 6 h e.v., lisinopril 20mg i.d., furosemide 20 mg 6/6 he.v., enoxaparin 40 mg s.c.i.d. At the D4 he had 1,13 g of proteins in the 24 hours urine analysis. With the therapeutics applied he had a weigh loss of 4,4 kg. The immunologic study was repeated and revealed ANA screening of 34 (>1), Anti-DNAdS 26 Ul/ml/>15), Antibodies Anti RNP >240 U/ml (>10), Antibodies anti SSB/La 17 U/ml/>10), CRP 18,9 mg /L (>5), ERS 42 mm /h, total cholesterol of 231 mg/dl, C3 72 mg/dl (90-180), C4 3,9 mg/dl (10-40).

Underwent an echocardiogram which showed mild pericardial effusion and aortic and mitral regurgitation I II /IV. The renal and abdominal ultrasound showed no changes.

On the 5th day of admission he was transferred to the Nephrology Department to realize a renal biopsy that was not carried out by frank improvement of the clinical and laboratorial situation.

He was discharge in the 12th day with 24 hours proteinuria of 227,7 mg.

The patient was discharged treated with furosemide 20mg i.d., prednisolone 20 mg i.d., folic acid 5 mg, sulfasalazine 2 g i.d., lisinopril 20mg 2 i.d., aspirin 100 mg i.d., rosuvastatin 10 mg i.d., pantoprazole 20 mg i.d.

In February 2009 in the consultation of autoimmune diseases, it was introduced hidroxychloroquine by maintenance of microalbuminuria. He realized capillaroscopy study compatible with connective tissue disease.

Now he is clinically asymptomatic, with mild Raynaud phenomenon.

Immunologically he presents negative anti DNAds and keeps positive antibodies Anti RNP.

Discussion

With this case report, we pretend to demonstrate, according to the literature that the autoimmune diseases, will probably mostly presenting over time distinctly clinical and serological features.

This patient during his disease has criteria for the mixed connective tissue disease fulfilling the serologic condition with titles always high of antibodies anti RNP and three clinical features, hands swelling or puffy hands, the synovitis and the Raynaud phenomenon.

In June 2008 the involvement of kidney disease with clinical presentation of nephrotic syndrome and his quick improvement after corticosteroid therapy lead us to consider that this patient had a renal event into the context of MCTD.

Unfortunately, kidney biopsy was not performed due to markedly patient´s improvement.

That exam would be essential to the histopathological confirmation of the nature of renal involvement. However, considering the renal presentation and clinical and serological expressions of this situation, this patient meets the SLE criteria.

The literature says in prospective studies of small series of patients, and it has been referred previously, there are a minority of patients who meets throughout the course of the disease criteria for MCTD and SLE.

What seems important is the fact that this patient presents clinically asymptomatic after two years and a clear improvement in quality of life, including nearly eviction of Raynaud phenomenon.

Conclusion

Whether MCTD is a distinct disease or a subset of other CTDs is less important and will not be resolved until we have a better grasp of etiology and pathogenesis. More long-term prospective studies of large numbers of serologically well defined patients are required for this as well advances on genetics will contribute for the CTD susceptibility and expression. [1, 7]

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Case Report 4

Pulmonary Thromboembolism as a Manifestation of Recurrent Thrombosis in Antiphospholipid Syndrome

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Abstract

We present a case report of 35 year-old caucasian man diagnosed with Lupus Erythematosus Systemic (LES) presented by Evan's syndrome in 2006 and with Antiphospholipid Syndrome (APS) since 2008 diagnosed after deep venous thrombosis. He began oral anticoagulation with warfarin until June 2009 when he dropped out the consultations. Then, he returned and restarted anticoagulation in September 2010. He was also under corticosteroids (prednisolone 50 mg/day). He presented with anorexia and weight loss since May 2010 and in October 2010 with palpitations and dyspnea at rest. He was tachycardic but normotensive. His arterial blood gasometry showed hypoxemia, hypocapnia and respiratory alkalemia. The international normalized ratio (INR) was in therapeutic ranges (2,68). The d-dimers were one hundred times above the higher limit value (50 ng/mL). The thoracic-CT angiogram revealed signs of acute thromboembolism on the right branch of the pulmonary artery, right ventricular thrombus and several cavitated lesions in both lungs compatible with chronic pulmonar y thromboembolism. The transthoracic echocardiogram showed good biventricular function, without signs of hipokinesis or pulmonary hypertension. The thrombolysis wasn't indicated. He remained stable but with sustained hypoxemia under oxygenotherapy. The treatment choice was the intens ific a t ion of hypocoagulation with warfarin to therapeutic INR ranges of 3-4. Infection was excluded. Other new thrombotic episodes were absent but a portal cavernoma was found on the abdominal-CT.

It's unclear why thrombotic manifestations may occur in patients under anticoagulation within therapeutic ranges. Also, the treatment after recurrent thrombotic episodes is uncer tain and the type of thrombosis should be considered. Thrombotic manifestations including several organs are a risk factor for catastrophic presentation.

Introduction

Antiphospholipid syndrome (APS) is characterized by recurrent venous or arterial thromboses, fetal losses and thrombocytopenia in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or antibodies directed to various proteins, mainly ß$_2$ glycoprotein I (ß$_2$GPI), or all three [1, 2]. The diagnosis is made according the revised Sapporo Classification Criteria: at least one clinical criteria and one laboratory criteria have to be present. [1] Its development may be independent of any underlying disease and this form is termed as "primary". Nonetheless, this syndrome was first recognized in patients with systemic lupus erythematosus (SLE) and later less frequently in those with other autoimmune disorders and this form is termed as "secondary" [2]. This classification becomes artificial because there are no clinical differences between the aPL among patients in these two categories and the aPL profile seems to be more important which to classify these patients into different categories since patients with LA, IgG aCL at high titles or anti-ß$_2$GPI antibodies plus LA or aCL have the highest thrombotic risk[2]. Nonetheless, the LA is the best predictor of thrombotic events.

Any combination of vascular occlusive events may occur int the same individual and the time between them also varies considerably [2]. Deep venous thrombosis, sometimes accompanied by pulmonary thromboembolism, is the most frequent manifestation in this syndrome (reported in 38,9% of patients) [2, 3].

Also, they may develop a broad spectrum of pulmonary disease in which pulmonary thromboembolism and pulmonar y hypertension are the most common complications, but microvascular pulmonary thrombosis, pulmonary capillaritis, and alveolar hemorrhage have also been reported [4]. Recurrent pulmonary emboli may give rise to pulmonary hypertension that may, unusually, in severe cases, be accompanied by isolated tricuspid valve

insufficiency [4]. In some patients the thrombotic obstruction occurs at the level of the large elastic pulmonary arteries [4]. Certain patients with APS present with widespread thrombotic occlusions affecting the small pulmonary arteries or alveolar capillary lumens [4].

There is consensus in treating patients with APS and first venous thrombosis with oral anticoagulation to target international normalized ratio (INR) of 2.0-3.0 [2, 5, 6,] but half of those treated with warfarin to a target INR of less than 3 will present recurrent thrombosis [6]. Repeated thromboses were more frequent and associated with a higher mortality than hemorrhagic complications in patients taking warfarin [6, 7]. Therefore, high intensity oral anticoagulation with warfarin to a target INR of 3 or over should be an option [6, 7].

According to the "Europhospholipid cohort of" 1,000 APS patients, recurrent thrombotic events appeared in 166 of them (16,6%), and the most common were strokes (2,4%), transient ischemic attacks (2,3%), deep-vein thrombosis (2,1%), and pulmonary embolism (2,1%) [2, 3]. A subtherapeutic INR at the time of thrombosis may only represent inadequate anticoagulation and not treatment failure.2 Recurrences were infrequent among patients effectively receiving oral anticoagulation at an INR of 3.0 – 4.0.[2] Therefore, patients with APS with recurrent venous events should be treated with warfarin at an INR of >3.0.[2] In patients who experience recurrent events while receiving oral anticoagulants at an INR of >3.0, adding low-dose aspirin to oral anticoagulation may be a reasonable option in these patients.[2]

Thrombosis may be more frequent when multiple risk factors coexist.[1] The anticoagulation withdrawal or a subtherapeutic INR may not only result in classic APS but also in catastrophic antiphospholipid syndrome.[8]

Case report

A 35 year-old caucasian man, married, unemployed, history of smoking (20 cigars per day over 10 years, cessation in the previous six months), presented in October 2010 with persistent sudden dyspnea, established at at rest, without relieving factors associated with chest pleuritic pain. He didn't have symptoms of respiratory infection, nor arthralgia, pain or asymmetries in the lower limbs.

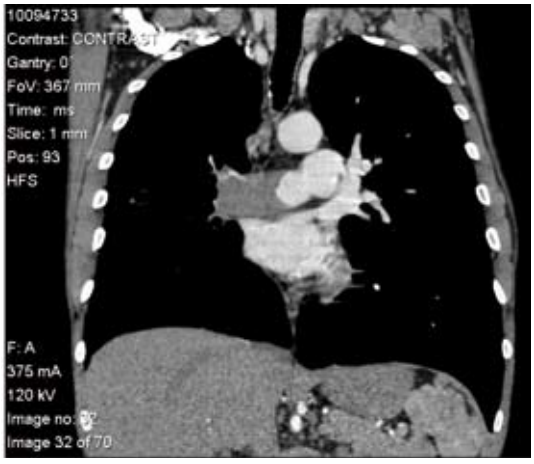
His general condition has worsened since May 2010 and he has already been observed in the emergency room for asthenia, arthralgia and weight loss. At that time, he presented with anaemia and severe thrombocytopenia. Hospitalization was proposed but the patient has refused so he began to be followed in internal medicine consultation. In August 2010 he started corticosteroids (he was under prednisolone 50 mg/day) and in September 2010 he re-started anticoagulation.

At the physical examination he was anxious, with a fine tremor of the hands. Respiratory distress was noted, he was with tachypnoea (27) and with central cyanosis. He had an arterial oxygenation of 91% in air and remained normotensive but tachycardic (110). His heart sounds were decreased and his pulmonary auscultation was normal. His abdominal examination was normal. He didn't have any signs of thrombophlebitis or edema at the lower limbs.

He performed some laboratory tests, his cell blood count revealed a thrombocytopenia ($97x10^9$/L platelets). The erythrocyte sedimentaion rate (ESR) was considered normal (8 mm/1st hour). The autoimmune study revealed IgM ß$_2$ glycoprotein I (ß$_2$GPI) were high and the antinuclear antibodies (ANA's) were negative. The lupus anticoagulant (LA) was not performed.
INR was therapeutic with 2,68. The arterial gasometry revealed hypoxemia (PaO_2 64,8 mmHg), hypocapnia ($PaCO_2$ 28,2 mmHg) and respiratory alkalemia (pH 7,484). He had sinus rhythm and no signs of right ventricular overload on the electrocardiogram. So the d-dimers were requested: the value was 5520 ng/mL, ten times above the upper limit.

A thoracic CT-angiogram was requested and it revealed signs of acute thromboembolism of the right branch of the pulmonary artery with almost total occlusion, right ventricular thrombus and several cavitated lesions in both lungs compatible with chronic pulmonary thromboembolism (Fig. 1, 2 and 3).

Fig. 1 – **Thoracic - CT angiogram showing acute thromboembolism of the right branch of the pulmonary artery with almost total occlusion.**



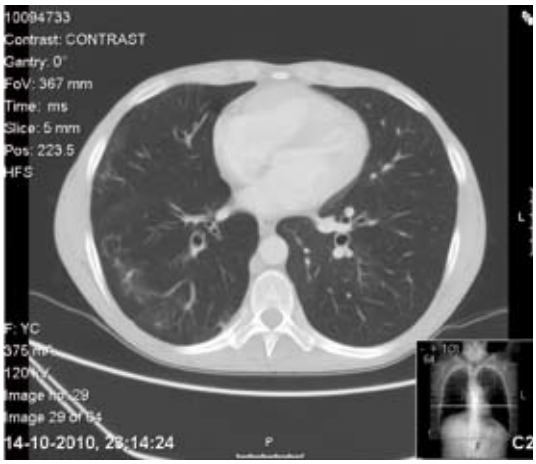


Fig. 2 **– Thoracic - CT angiogram showing right ventricular thrombus.**

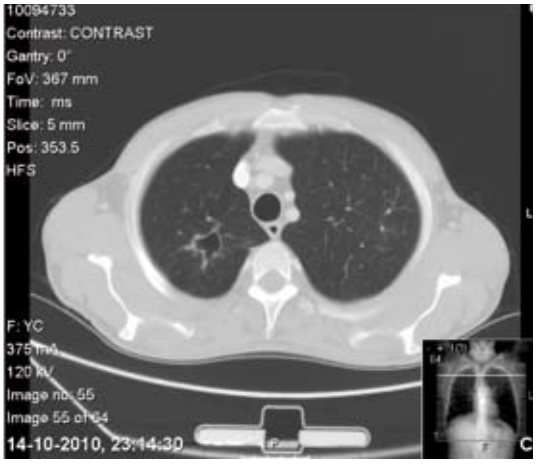


Fig. 3 **– Thoracic - CT angiogram showing cavitated lesions in both lungs compatible with chronic pulmonary thromboembolism.**

In order to manage the pulmonary thromboembolism and stratify the risk he performed an assay of cardiac biomarkers (which were not elevated) and a transthoracic echocardiogram that showed good biventricular function, without signs of hipokinesis or pulmonary hypertension. So, he was only candidate to secondary prevention, either by anticoagulation alone or inferior vena cava (IVC) filter, and was not candidate for thrombolysis. An abdominal-CT was performed and showed hypodense hepatic lesions compatible with hemangioma and an enlarged polylobulated but homogenous spleen.

Nonetheless, as doubts about the nature of the hepatic lesions persisted, an abdominal-MRI was performed and showed a cavernous transformation of

the portal vein compatible with a chronic portal vein thrombosis. (Fig. 4).

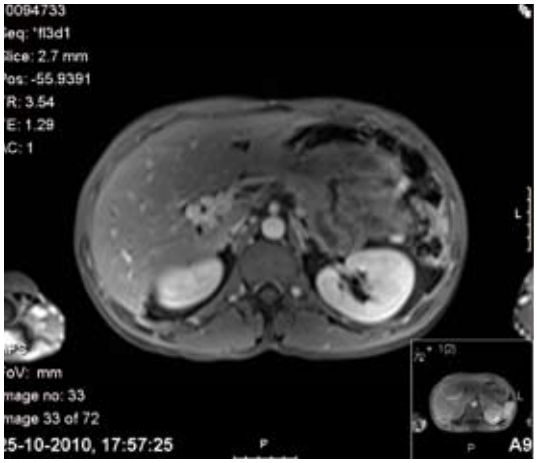


Fig. 4 – **Abdominal - MRI showing cavernous transformation of the portal vein compatible with a chronic portal vein thrombosis.**

His past medical history is crucial for understanding this clinical presentation. It started in June 2006 when he was observed in the emergency room for pleural and pericardial effusion. One month later he was readmitted and observed for arthralgias in his knees and hands and his cell blood count reveled anaemia, which was hemolytic with a polyspecific direct Coombs test positive (12/12) for anti-C3d and IgG and thrombocytopenia. The antinuclear antibodies were positive (1/1000 nucleolar pattern). He was treated with pulses of methylprednisolone and kept the corticosteroids in ambulatory. He started his follow-up in Hematology consultation.

In September 2007 he presented with a spontaneous right ileo-femoro-popliteal deep venous thrombosis and started oral anticoagulation. In March 2008 he presented with a left popliteal deep venous thrombosis. At that time, the diagnosis of antiphospholipid syndrome was established according to the revised Sapporo criteria because beyond the thrombotic manifestations he had positive aPL, namely, lupus anticoagulant (LA), IgG anticardiolipin (IgG aCL) and IgM ß$_2$ glycoprotein I (ß$_2$GPI), and positivity confirmed after twelve weeks for aCL IgG and ß$_2$GPI. He started his follow-up in Thrombophilias consultation.

At October 2008 he had dropped-out the consultations in which he was followed and in June 2009 he abandoned the oral anticoagulation treatment.

In May 2010 his general condition has worsened, he was followed in Internal Medicine consultation since August 2010 and remained stable. The previous value of INR was 3,35.

He was admitted to the Internal Medicine nursery where he stayed for fifteen days. The treatment of choice was the intensification of oral anticoagulation with warfarin to a target INR of 3-4, which was achieved by the fifth day (3,71), without recurrent thrombotic events or hemorrhagic complications and with improvement of the thrombocytopenia (127x10^9/L platelets).

Dyspnea for small efforts remained even under oxygen therapy with 3 L/minute: he had persistent type 1 respiratory insufficiency (ratio PaO2/FiO_2 <300) with PaO_2 of 57,1 mmHg at the time of discharge, respiratory alkalemia and a 6 minute walk test positive for desaturation. So, we prescribed home oxygen therapy, 3 L/minute during 24 hours, expecting the slow resolution of the massive pulmonary thrombosis. He was discharged under corticosteroids (prednisolone 50 mg/day), oral anticoagulation with warfarin for INR target of 3-4 and home oxygen therapy. Two months after discharge he was feeling better, with dyspnea for medium efforts, reduction of the oxygen therapy to 2 L/min and periods without any oxygen, mostly at meal time. The ESR was increased (17 mm/1st hour) and the autoimmunity assays revealed ANA's of 1/1000 nucleolar patter, anti-dsDNA of 25,7 UI/mL and IgG aCL very increased - 115 GPL, normal value <15 (table 1). So, he was started on immunosuppressive therapy with azathioprine and has reduced the corticosteroids for 30 mg/day. One month later he started aspirin at 100 mg/day. After six months he returned to normal daily life, with dyspnea only for great efforts and under oxygen therapy only 8 hours a day during the sleep.

Table 1 – **Antibody profile at pulmonary thromboembolism presentation and after discharged during follow-up.**

Cell Blood Count	October 2010	January 2011	Reference Values
ESR (mm/1ª hour)	8	**17**	4.4-6.0
Platelets (x10^9/L)	**97**	380	180-500
Auto-immunity Assays			
ANAs	<1/100	**1/1000 Nucleolar**	<1/100
Anti-dsDNA (UI/mL)	<20	**25.7**	<20
Anti-cardiolipin IgG (GPL)	<1.0	**115.0**	<15
Anti-cardiolipin IgM (MPL)	1.9	6.2	<15
β2-glicoprotein I IgG (SGU)	5.2	9.0	<15
β2-glicoprotein I IgM (SMU)	**45.4**	5.2	<15

Discussion

The withdrawal of anticoagulation and corticosteroids and the time without any follow-up was crucial for the magnitude of thrombotic presentation in this patient., not only with an extensive acute pulmonary thromboembolism but also with signs of thrombosis in

multiple organs (signs of peripheral chronic pulmonary thromboembolism, liver, heart,).

In 2006 he already had four criteria for the establishing the diagnosis of LES, according to he criteria of the American College of Rheumathology: polyserosite, arthritis, hematologic disorder (anaemia and thrombocytopenia) and ANA's positive. Back then, the LES presented by an Evan's Syndrome but the diagnosis was not established definitly and the patient only did corticosteroids in a short period of time.

The revised Sapporo criteria according to the aPL profile classify this patient has having a type 1 APS (there are four types) because he had positive results after twelve weeks for two aPL, namely aCL IgG and $ß_2$GPI. This finding means that this patient has an aPL profile that confers a higher thrombotic risk. This classification is more useful in studies to help in selecting patients with similarthrombotic risk and also with similar prognosis turning the populations comparable and the results valid. So, the consequences of not being treated with oral anticoagulation and corticosteroids are even more dramatic in this patient as the risk of thrombosis is higher. In the management of pulmonary thromboembolism we should use the modified Wells criteria for stratifying the probability of pulmonary thromboembolism, our patient scored six point which means that the pulmonary thromboembolism was likely. So, the d-dimers assay was unnecessary and he should have done the thoracic angiogram right away. These patient was not candidate to thrombolysis even with a massive thrombus in the pulmonary artery because he didn't have any signs of right ventricular dysfunction and even if he was in an intermediate probability area he had relative contraindications to this treatment, namely oral anticoagulation. The shunt effect caused by that huge pulmonary thrombus was very important and one of the main causes of the indication for oxygen therapy. He was only candidate to secondary prevention and the best secondary thromboprophylaxis in patients with definite APS, that is those who have suffered thrombosis and at least two positive determinations of aPL is long-term anticoagulation. The anticoagulation strategy in patients with pulmonary thromboembolism already under oral anticoagulation is uncertain: either heparin or warfarin may be used. In this case, as there was a APS we preferred to increase the intensity of oral anticoagulation. The thrombus resolved with oral anticoagulation and so the indication of oxygen therapy temporary. He has performed a trans-thoracic echocardiogram at six months to evaluate the development of pulmonary hypertension, which had no

functional tricuspid insufficiency neither estimated PSAP. In terms of pulmonary manifestations he only had ar terial thromboses and microvascular pulmonary thrombosis and no life-threatening complications have developed. Patients with APS with recurrent venous events should be treated with warfarin at an INR of >3.0. The INR aimed for this patient should be 3-4, even before the pulmonary thromboembolism since he already have signs of recurrent venous thrombosis: two episodes of deep venous thrombosis. Repeated thromboses were more frequent and associated with a higher mortality than hemorrhagic complications in patients taking warfarin, so the treatment of choice in this patient is high intensity oral. As the thrombotic risk is high and the recurrent events are probable in this patient, low-dose of aspirin was added to oral anticoagulation. The immunosuppressive therapy was started assuming that there was a lupus flare. The thrombotic manifestations in this patient involve multiple organs but mainly large vessels, which differs from the predominant involvement of small vessels in the catastrophic presentation. The prognosis is hard to establish because in order to do that the disease should be predictable which is not the case of the APS and also no control trials exist. We know that the mortality is usually higher in patients with LES. Also, this patient presents many possible precipitating factors of catastrophic presentation including the previous oral anticoagulation withdrawal and the possibility of lupus flares.

Conclusion

The d-dimers assay should depend on the clinical probability of pulmonary thromboembolism estimated by the Wells criteria because if this diagnose is likely, the thoracic. CT angiogram should be the gold standard for the diagnose. In the case of patients already under oral anticoagulation the management of pulmonar y thromboembolism may be the intensification of oral anticoagulation. When considering the thrombolysis, the signs of gravity like the hipokinesis of the right ventricule or hypotension may determine the treatment indications. The classification of the APS according to the aPL profile is more useful in the investigation field. The LA is the best predictor of thrombotic events and should be performed in every patient where there is a high suspicion to the APS diagnosis even in the absence of other aPL positive results. The most frequent manifestation is the deep venous thrombosis. The withdrawal of oral anticoagulation may have serious was the main conditioning of the thrombotic potential and of the risk of

recurrent events aggravating the prognosis which was already poor. Now, this patient has thrombosis in multiple organs and the the best treatment option is long-term oral anticoagulation with warfarin for INR target of 3-4 associated with lowdose aspirin because repeated thromboses were more frequent and associated with a higher mortality than hemorrhagic complications in patients taking warfarin. Of course that this conclusions are mainly based in small studies and there is the need of more trials in order to treat efficiently this spectrum of thrombotic manifestations. Close follow-up of this patients is needed. Usually they are young patients with a severe disease who not always accept well their diagnose. The adherence to the therapeutic strategy is one of the most important factors to prevent worsening the prognosis.

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Case Report **5**

Systemic Sclerosis in the Elderly

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Abstract

Systemic sclerosis is a connective tissue disease characterized by fibrosis of the skin and internal organs, pronounced changes in the microvasculature and frequent cellular and humoral immunity abnormalities. It is a disease more commonly seen in women, frequently ocurring until the fifth decade. SSc diagnosis in advanced age is not frequent and may be associated with malignancy.

The authors describe three clinical cases diagnosed after 75 years of age, in which, neoplastic causes were excluded and enhance that despite being a rare clinical entity it should be considered in the diagnosis of elderly patients.

Introduction

Systemic sclerosis (SSc) is an uncommon multisystem autoimmune disease characterized by immune abnormalities, fibrosis of the skin and internal organs, and an obliterative vasculopathy. It is a heterogeneous disease ranging from mild limited cutaneous features to widespread skin thickening. Internal organ involvement can be minimal, with mild gastroesophageal reflux, subtle skin changes, and Raynaud's phenomenon (RP) as the sole manifestations [1].

It is a disease more commonly seen in women in a 4:1 ratio to men, frequently ocurring until the fifth decade. Early in life, the female to male ratio is 7:1 while the ratio narrows to 2:1 after the fifth decade. The diagnosis after the age of 75 is unusual [2].

SSc has an increased association with certain malignancies and it can present as a paraneoplastic syndrome, mainly in elderly. On the other hand, in

cases not associated with malignancy, late-age onset SSc usually represents a milder form of disease, with limited morbidity and minimal skin and internal organ involvement [3-4].

Antinuclear antibodies (ANAs) are found to be present in > 90% of patients with SSc and the immunofluorescence pattern of ANA is most commonly nucleolar. A positive anticentromere antibody is seen more commonly in patients with limited cutaneous disease (35-80%). A positive anti-Scl-70 antibody is associated with increased risk for the development of diffuse skin disease (20-40%) and with interstitial lung disease (ILD) [5-6]. High serum titers of antinuclear antibodies are rarely found in SSc associated with neoplasia [4-7].

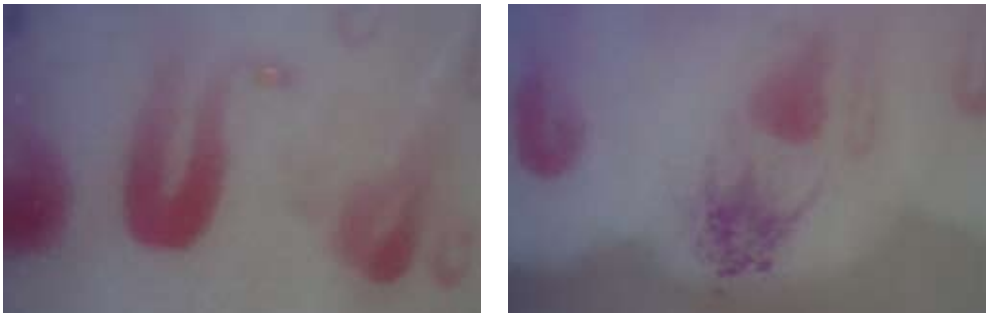
The authors describe three case reports diagnosed after 75 years of age, in which, paraneoplastic syndrome was excluded, all of them with high titers of antinuclear antibodies.

Clinical Case 1

Female, 76 years-old. Patient was admitted in our rheumatology department with a history of sudden onset of Raynaud's phenomenon and dyspnea for moderate exertion with 2 months of evolution. No other systemic complaints. Physical examination revealed Raynaud's phenomenon, digital pits in 2nd, 3rd and 4th finger of right hand and the 2nd and 3rd finger of left hand, digital ulcers in 2nd finger of the right hand, puffy fingers, facial edema and telangiectasia on the face and neck. Laboratory findings revealed positive ANAs (titer 1/640 with centromeric pattern by immunofluorescence) positive anticentromere and negative anti-Scl-70. High resolution CT scan and echocardiogram were normal. Nailfold videocapillaroscopic showed frequent giant capillaries and frequent capillary microhemorrhage changes compatible with scleroderma pattern (active pattern).

Neoplastic causes were excluded and a diagnosis of limited cutaneous Systemic Sclerosis (lSSc) was established. Treatment with hiyroxychloroquine and vasodilators was started with clinical improvement and in the follow-up, there was no progression of the disease.

Fig. 1 - **Nailfold videocapillaroscopic – scleroderma pattern (active pattern): frequent giant capillaries, frequent capillary microhemorrhages, moderate loss of capillaries, absent or mild ramified capillaries with mild disorganization of the capillary architecture).**



Clinical Case 2

Male, 79 years-old. Patient followed in our Rheumatology Department for a limited cutaneous Systemic Sclerosis. Onset complaints were Raynaud's phenomenon, dyspnea for moderate exertion, dysphagia, asthenia and anorexia. On general physical examination, he presented puffy hands, pedal edema on lower limbs, Raynaud's phenomenon, skin thickening on the face and extremities, telangiectasia on the face, neck and chest. Chest examination showed crackles at the lung bases.

ANAs in a titer 1/320 with speckled pattern by immunofluorescence, positive anti-SL70 and negative anticentromere were the relevant findings in lab exams. High resolution CT revealed interstitial thickening at the lung bases, evidence of ground-glass opacification and lung fibrosis areas. Echocardiographic examination showed a high estimated pulmonary artery systolic pressure and a low ejection fraction, but the right-sided heart catheterization excluded pulmonary arterial hypertension. The upper endoscopy revealed esophagitis. After excluding a paraneoplastic syndrome, treatment with hydroxychloroquine, vasodilators and corticosteroids was started with clinical improvement of the skin and the Raynaud's phenomenon. Treatment with diuretics and ACE inhibitors also was started for the heart failure. After 5 years of follow-up, there was no progression of the disease.

Nailfold videocapillaroscopic showed absent giant capillaries and microhemorrhages but severe loss of capillaries with extensive avascular

areas, ramified/bushy capillaries, and intense disorganization of the normal capillary array, changes compatible with scleroderma pattern in the late phase (Fig. 2).

Fig. 2 - **Nailfold videocapillaroscopic – scleroderma pattern (late pattern): almost absent giant capillaries and microhemorrhages, severe loss of capillaries with extensive avascular areas, ramified/bushy capillaries, and intense disorganization of the normal capillary array.**

Clinical Case 3

Male, 77 years-old. Patient was admitted in our rheumatology department with a history of sudden onset Raynaud's phenomenon. No systemic complaints were referred. Physical examination revealed sclerodactly, telangiectasia on face and neck and subcutaneous calcinosis. Laboratory assessment showed positive for fluorescence ANAs (titer 1/320, exhibiting centromeric pattern) and a positive anticentromere. High resolution CT

revealed mild peripheral subpleural lung fibrosis areas and echocardiogram was normal.

Nailfold videocapillaroscopic showed frequent giant capillaries and moderate loss of capillaries, changes compatible with scleroderma pattern in the active phase (Fig. 3).

Fig. 3 - **Nailfold videocapillaroscopic - - scleroderma pattern (active pattern): frequent giant capillaries and moderate loss of capillaries.**

A diagnosis of limited cutaneous Systemic Sclerosis (lSSc) was established and treatment with hydroxychloroquine and vasodilators was started with clinical improvement and stabilization of the disease.

Discussion

SSc is rarely considered in elderly patients. The diagnosis of SSc may be overlooked in elderly patients, due to the minor nature of the skin changes and the best favourable course. To date, few reports of SSc in elderly patients have been published [8]. In the absence of skin changes, the diagnosis is less frequently considered especially in the elderly in whom multiple symptoms such as dysphagia, dyspnea and arthralgia may be attributed to multiple pathologies rather than a multi-system disorder. Furthermore, in this subgroup of patients, there is an increased risk of malignancy, so the paraneoplastic syndrome should be excluded [9].

The main atypical clinical features that help differentiate these forms from idiopathic conditions are: age at onset over 50 years, sclerodactyly, progressive skin sclerosis extending to the neck and trunk, and acute onset of Raynaud's phenomenon. By contrast, the absence of Raynaud's phenomenon with a normal capillaroscopy pattern can be another distinguishing feature of

cancer induced systemic sclerosis. Although infrequently, high serum titers of antinuclear antibodies may be found in the absence of an autoimmune disease [4].

In the clinical cases described, besides age, the patients presented clinical characteristics, including sudden onset Raynaud's phenomenon and pulmonary involvement that could be part of SSc of a paraneoplastic syndrome. On the other hand, the presence of a high titer of ANAs and nailfold videocapillaroscopic alterations compatible with a sclerodermic pattern suggested a case of idiopathic Systemic Sclerosis. A neoplastic cause was excluded in the 3 patients and after the start of treatment with vasodilators and hydroxychloroquine there was a clear improvement in their condition. It should also be noted that in all the patients, in the follow-up there was a stabilization in the evolution of their condition, which is characteristic of idiopathic forms in this age group in which the disease has a less aggressive clinical course. The authors thus seek to highlight the fact that despite of being a rare clinical entity and even less frequent among the elderly, systemic sclerosis should always be considered in the differential diagnosis whenever justified by the condition. Immunology and capillaroscopy are very useful in the differential diagnosis between idiopathic forms and associated malignancy forms.

In elderly patients, the limited cutaneous Systemic Sclerosis subset (lSSc) is more prevalent than the diffuse cutaneous SSc subset (dSSc). Pulmonary and cardiac sclerodermic involvement are more prevalent in aged patients, and these systemic manifestations appear sooner after the disease diagnosis in this subgroup [9].

In the clinical cases described, a diagnosis of lSSc was established in all patients. Raynaud phenomena and pulmonary involvement were more frequent. It is important to point out that knowledge of the disease characteristics of this subgroup of patients and their differences compared with younger patients can help to improve its management, decreasing morbidity and mortality [9].

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Case Report **6**

A Clinical Case of Behçet's Disease

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Abstract

Behçet's disease is a multisystemic relapsing inflammatory disorder of unknown cause. Neurological manifestations of Behçet's disease (neuro-Behçet's disease) occur in about 5% of cases and are classified into parenchymal and nonparenchymal categories.

The authors present a case of a 28 year old woman with an infrequent and severe parenchymal CNS involvement as the second manifestation of Behçet's disease (the first one being recurrent oral ulcers).

Introduction

Behçet's disease (BD) is a chronic multisystemic inflammatory disorder, characterized by recurrent oral and genital ulcers and ocular lesions, as well as several manifestations of cutaneous, neurologic, vascular, articular, gastrointestinal, renal or cardiopulmonary involvement. Mucocutaneous features are the most common presenting symptoms of BD; ocular, vascular and neurological involvements are the most serious. [1, 2, 3, 4]

BD was first described by the Turkish Hulusi Behçet in 1924 and its prevalence and incidence are higher along the old Silk Road, extending from the Mediterranean to Asia. The prevalence in Europe is 1 case per 15,000-500,000 population.[5] The usual onset of BD is in the third decade and although both genders are equally affected, it is more severe in men and in the young. [1]

The underlying cause of BD remains unknown but theories behind its pathogenesis currently point toward an autoimmune etiology. Current research suggests that exposure to some antigens and organisms may trigger a cross-reactive immune response (heat shock proteins, streptococcal antigens,

herpes simplex virus, helicobacter pillory, parvovirus B19). Genetic influences include association with certain human leukocyte antigens (HLA), including HLA-B51, but also non-HLA genes may play a role. There is evidence of both cellular and humoral immune activation and, in the later stages of the disease, circulating autoantibodies against α-enolase of endothelial cells and ASCA are found to be present. [1, 5, 6, 7]

Vasculitis is usually considered to be the central pathological feature in BD and it is remarkable for involving blood vessels of all sizes and both arterial and venous (mainly these last ones). Many (but not all) clinical manifestations of BD are believed to be vasculitic. [2, 6]

As there are no specific symptoms and signs and no specific laboratory findings, the diagnosis of BD is based on the recognition of a group of clinical features.[1, 7] In 1990, the International Study Group (ISG) published a set of diagnostic criteria – International Criteria for BD (ICBD), which were revised in 2004 by the International Team for the Revision of ICBD and published in 2008. Oral aphthosis, skin manifestations, vascular lesions and positive pathergy test get each 1 point. Genital aphthosis and ocular lesions get each 2 points. 3 or more points are necessary for BD. The overall result showed a sensitivity of 96.1%, specificity 88.7% and accuracy 93.8% and the new ICBD has gained 13.7% sensitivity and 7.1% accuracy over ISG criteria. [8]

The treatment of BD aims to suppress inflammation and involves the use of immunosuppressives (systemic corticosteroids, azathioprine, cyclosporine A, infliximab, interferon-α, cyclophosphamide, thalidomide…) for treatment of serious organ-related issues such as ocular, vascular and neurological involvements. By contrast, the aim in the management of self-limiting manifestations such as mucocutaneous and joint involvement is usually suppression of symptoms (use of local corticosteroids, sucralfate suspension, colchicine…). [9, 10, 11]

The severity of the syndrome usually abates with time. Apart from the patients with neuro-Behçet disease (NBD) and major vessel disease, the life expectancy seems to be normal and the only serious complication is blindness. [7]

Case report

The authors present the case of a 28 year old woman, who was referred to their outpatient clinic with a suspicion of BD, on March 2011. She was previously healthy until April 2010, except for some episodes of migraine, and she was only medicated with oral contraceptive pill. She smoked 10 cigarettes a day.

On April 2010, the patient presented a first episode of exuberant oral ulcers, with no other symptoms, which was treated with antibiotics by a Dentist doctor. On June 2010, she complained of an itchy pain on the sole of her feet, that worsened when she walked and relieved with ibuprofen and diclofenac. On August 2010, she got erythematous lesions on the palms of her hands and she felt a "stingy" sensation on the tip of her fingers. On September 2010, she had a second less severe episode of oral ulcers, again treated with antibiotics by a Dentist doctor and a genital burning sensation (with no genital ulcers being observed by her or by a doctor), this time associated with pain on the palm of the hands, periungueal point-sized lesions and pain on both knees. She was prescribed an oral daily dose of 40 mg prednisone, progressively tapered until December 2010, and she started colchicine, that she didn't tolerate because of nausea. On January 2011, she had a third episode of oral ulcers and she was prescribed 3 day course of 30 mg oral deflazacort, with relief; since January, she had daily frontal headaches migraine-like, sometimes associated with nausea, which relieved with ibuprofen.

On February 2011, she complained about decreased visual acuity on her left eye, associated with headache; ocular movements were painless. She consulted an Ophthalmologist who documented papilledema and atrophy of the retinal posterior pole of the left eye, consistent with the findings of an optic neuropathy. She was not prescribed any medication nor sent to any Urgency Department.

She was first observed by the authors ten days later. General physical examination was normal except for the evaluation of visual fields – she had decreased visual acuity on the right inferior quadrant. Her weight was 52Kg and height 152 cm. She had normal blood pressure and was apyretic. She had some blood tests and results from previous exams: X-ray and echocardiography from July 2010 – normal; ESR from September 2010 – 32 mm; ANCA, ANA, RA test – negative; pathergy test – negative. She was sent to the Urgency

Department and she was evaluated by an Ophthalmologist. She had visual acuity of 0.2 on her left eye and papilledema, cotton-wool exudates, tortuous veins, micro-hemorrhages and stasis on left fundoscopy. She was admitted to the Neurology Department for treatment and study of a probably vasculitic optic neuropathy.

She was given a 5 day course of methylprednisolone 500 mg/day.

She had normal blood count and coagulation, normal ionogram, normal hepatic, renal and thyroid function; C reactive protein and ESR remained normal. B12 vitamin and folic acid were normal. ACE was normal. She had a hypercholesterolemia (313 mg/dl) and hypertriglyceridemia (212 mg/dl). Cardiac enzymes were negative.

Serum immunoglobulins, k/lambda and protein immunoelectrophoresis were normal. C3c, C4 and CH50 were normal. ANA were positive 1/1000 (nucleolar pattern), with negative anti-dsDNA and anti-PCNA. Anti-nucleosome, ANCA, anti-cardiolipin, anti-centromer, circulating immunocomplexes, ASMA, anti-CCP, ARPA, RA test, anti-neuronal and anti--ENA were normal or negative.

C protein and activated C protein resistance were slightly increased; S protein, antithrombin III and lupus anticoagulant were normal or negative. The CSF study showed no relevant changes.

The serologic and microbiologic blood, urine and CSF tests were all normal or negative.

The electrocardiogram was normal as well as the ecocardiography. The cervical and transcranian eco-doppler showed no relevant findings. The evocated visual potentials were consistent with the diagnosis of left optic demyelinating neuritis. The retinal angiography showed left typical neuroretinitis and right papillitis.

At day 6, she developed a sudden left hemiparesia, with ipsilateral hemihiposthesia and central facial paresia that spontaneously partially recovered after a few hours and no thrombolysis was needed. Cerebral CT scan was normal but cerebral MRI showed an acute ischemic vascular lesion at temporo-insular right hemicortex and a flow decrease on the ipsilateral medium cerebral artery at the angio-MRI.

She was given 60 mg of oral prednisone. Due to the fact that she had not recovered from the loss of her visual acuity and according to the recent episode of stroke, it was decided to add cyclophosphamide 50 mg daily to the

steroid therapy.

The patient was discharged three weeks later with the diagnosis of a systemic vasculitis – probable Behçet's disease - and dyslipidemia. She was given oral prednisone 50 mg daily, oral cyclophosphamide 50 mg daily, rosuvastatin 10 mg daily, omeprazole 20 mg daily.

The patient has been clinically stable until now. She has migraine, resistant to anti-inflammatory drugs, and she started crescent topiramate prophylaxis with good result. She has no oral or genital ulcers, no neurologic deficits, no skin changes, no arthritis and no gastrointestinal symptoms. She has loss of visual acuity, with 0.5 of visual acuity on her left eye but only minor changes on fundoscopy.

Oral prednisone was tapered to 10 mg daily and cyclophosphamide increased to 75 mg daily.

She started primary prophylaxis with trimethoprim-cotrimoxazole, cholecalciferol-calcium carbonate and acetylsalicylic acid.

Discussion

According to the New ICBD [8], this patient gets 2 points for ocular lesions, 2 points for oral aphthosis and 1 point for central nervous system involvement – a total of 5 points – consistent with the diagnosis of BD.

The patient's earliest manifestation of the disorder was the most common for BD: mucocutaneous involvement, with three recurrent episodes of painful and multiple oral ulcers, in less than 12 months. She also had a history of genital complaining, but no ulcers have been directly observed.

After the second episode of oral ulcers, she also had a history of probable cutaneous and articular involvement, with erythema on the palms of the hands and pain on both knees. These were all only minor manifestations and colchicine could have been the initial therapy but it was not tolerated by the patient. Systemic steroids, progressively tapered, were a right choice on this case.[10, 11] A 3-day course of oral corticosteroids is not considered in the literature. Non-steroidal anti-inflammatory drugs have not shown benefit in the only randomized controlled trial with azapropazone [9], although the patient reported some pain relief with ibuprofen, diclofenac and etoricoxib.

Headache is the most common neurologic symptom seen in BD (prevalence ~80%) and may be independent from neurologic involvement;

nevertheless, NBD must be meticulously investigated in BD patients who present with headache.[12, 13] A few studies have approached the prevalence and characteristics of different types of headache in patients with BD: the most frequent one was migraine, as in the case of our patient. This form of headache is not specific for this disorder, but may be explained by a vascular headache, triggered by the immunomediated disease activity in susceptible individuals – it can be exacerbated with systemic BD flare-ups, and some patients had migraine attacks triggered only by systemic BD activation, which showed a good response to the treatment of systemic inflammation.[12, 14] The patient took ibuprofen for acute symptoms and recently started topiramate prophylaxis.

Ocular disease occurs in 50% of patients with BD, and the most common form is a pan-uveitis.[1, 3] Optic neuropathy is a rare form of parenchymal CNS involvement in BD. It can be related to an inflammatory neuropathy, a stasis papilledema complicating a benign intracranial hypertension or an ischemic neuropathy. Early recognition of this entity and treatment with high-dose systemic corticosteroids and immunosuppressive drugs may limit the degree of permanent visual loss. However, the optimal treatment has not been established.[2, 15, 16]

In this case, the first doctor who diagnosed this problem neither referred the patient to an Urgency Department nor implemented any medication and this may have worsened the prognosis in terms of permanent loss of visual acuity. Fundoscopy, evocated visual potentials and retinal angiography findings were consistent with neuroretinitis – an inflammatory neuropathy. For parenchymal CNS involvement, EULAR recommends high dose of pulsed corticosteroids. Usually 3-7 pulses of IV methylprednisolone 1g/day, is given during attacks, followed by maintenance oral corticosteroids which are tapered over 2-3 months.

Immunosuppressives may also be given to prevent recurrences and progression.[10] The patient completed 5 IV pulses of 1g methylprednisolone with no improvement on visual acuity.

After that, she sudden developed left hemiparesia, a more common finding of parenchymal CNS involvement in BD (on a study of 200 patients with NBD, > 50% had hemiparesia, > 90% unilateral)[2], from which she totally recovered along the next days; the MRI showed an acute ischemic vascular lesion on the right hemicortex.

NBD is the constellation of neurologic manifestations as a direct consequence of BD, usually confirmed by imaging studies and/or CSF analysis.[17] It has a prevalence of about 5%, is more common in men and is one of the most serious manifestations of BD, causing both increased morbidity and mortality.[1, 4] It is classified into parenchymal and non-parenchymal categories.[18]

Although this patient presented with papilledema and headache, MRI showed no non-parenchymal disease and she had not intracranial hypertension or dural sinus thrombosis.

She had some poor prognostic factors – parenchymal CNS involvement, earlier development of NBD in the course of the disease. The good prognostic factors included a normal CSF, one only attack and independence at admittance and discharge. For parenchymal CNS manifestations of NBD, first-line drugs include corticosteroids, azathioprine, methotrexate, and cyclophosphamide. Second-line drugs are TNF-α blocking drugs, interferon-α, chlorambucil, and mycophenolate mofetil. [17] In this case, attending to the severity of the neurological presentation, with parenchymal CNS involvement in a recent-diagnosed BD patient, it was decided to add cyclophosphamide to systemic corticosteroids.

After 4 months, she has reduced the steroid dose and maintained daily oral cyclophosphamide. She still has loss of visual acuity on her left eye – the delay on introducing the proper treatment may have possibly contributed to this or perhaps it is just the consequence of the severity of the neuropathy. She has only migraine symptoms for now. The prognosis for this patient might not be favorable, as she is young and her BD (NBD) presented in an infrequent and severe way. Furthermore, she may have permanently lost her normal vision on her left eye.

Conclusion

This case illustrates an infrequent and severe presentation of BD in a young woman – the neurologic involvement in the early course of the disease, with different CNS manifestations, appearing almost subsequently. It is fundamental to immediately and aggressively treat the rare event of optic neuropathy in BD, with high-dose systemic corticosteroids and immunosuppressive drugs, in order to prevent permanent loss of visual acuity.

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Case Report 7

Multiple lymphadenophaties - - difficulties in diagnosis

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Abstract

The authors report the case of a patient 48 years of age with constitutional symptoms, arthritis and multiple lymphadenopathies.

After the study, we concluded that he met criteria for classification of SLE. However, many other diagnoses should be considered, namely lymphoma, as well as the possibility of co-existing two distinct diseases, which in our case, was not an easy task.

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic multisystem disease of complex pathophysiology that may involve any organ or system, leading to a wide variety of clinical manifestations. Its ethiopathogenesis remains unknown, although it is acknowledged that genetic and environmental factors combine to generate the autoimmune response. The diagnosis is not always easy and requires the exclusion of many other medical conditions that may mimic it, turning the whole process often a challenge.

Case report

The authors present a case of a 48 year old previously healthy man, admitted in our department of Rheumatology refering asthenia, anorexia, weight loss and fever for 6 months. Subsequently initiated symmetrical polyarthritis of wrists, metacarpophalangeal and proximal interphalangeal joints of the 2nd, 3rd fingers and multiple enlarged lymph nodes appeared in

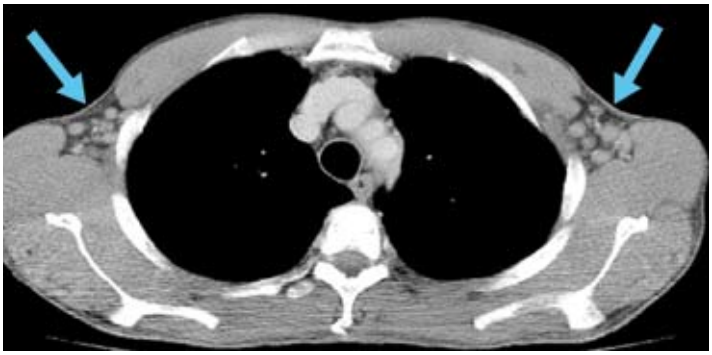
the cervical and axillary chains. The physical examination revealed, besides the previously described, an aortic systolic murmur without radiation.

Laboratorial tests revealed normocytic and normochromic anemia (hemoglobin 8.5 g/dl), positive direct Coombs, elevation of inflammatory parameters (ESR 82 mm/1ªh and CRP 2mg/dl); DHL and remaining biochemistry were normal. Urinalysis showed active urinary sediment and proteinuria of 1g in 24 hours.

Immunological study revealed positive antinuclear antibody (ANA 1/640) and positive anti-ds DNA, anti-SSA, anti-SSB antibodies with hypocomplementemia (C3- 48 mg/dl and C4 -7 mg/dl). Blood and urine cultures were negative, serological markers for HIV, HBV, HCV, CMV, EBV, HSV and Treponema pallidum were negative. Tuberculin skin test was 0 mm.

Echocardiography excluded signs of endocarditis. The study by thoraco-abdominal CT scan confirmed the presence of multiple mediastinic and axillary adenopathies, the largest measuring 17 mm in diameter.

Fig. 1 **- CT torax: there were several axillary adenopathies (marked by arrows)**



Excisional biopsy was performed in an axillary node, and the result revealed pathological findings compatible with follicular hyperplasia, without evidence of atypical proliferation.

Although treated with prednisolone 15 mg/ day he presented no improvement of signs and symptoms. We decided to review the histology of axillary node excised, for definitive exclusion of lymphoproliferative disease. In this second study, morphological and immunohistochemical findings compatible with classical Hodgkin lymphoma were described.

So, at the end, the patient fulfilled criteria for diagnosing SLE but it

was necessary to consider the possibility of a lymphoproliferative disease. Thus, we referred the patient to the department of Onco-hematology in the Portuguese Institute of Oncology (Oporto) where lymphoma was excluded.

The patient started treatment with azathioprine 150 mg/ day in combination with 1 mg/Kg/day of prednisolone and hydroxychloroquine 400 mg/day showing gradual improvement and is currently asymptomatic.

Discussion

A patient with constitutional symptoms, lymphadenopathy, arthritis, hemolytic anemia, abnormal urinary sediment and immunological changes with positive ANAs and other auto-antibodies such as anti-dsDNA, meets criteria for diagnosing SLE.

However, it can only be established after exclusion of other diseases, including malignancies, particularly lymphoproliferative disorders, the Kikuchi-Fujimoto disease and certain infections, since in all these pathologies, systemic symptoms such as asthenia, anorexia, weight loss and fever as well as multiple lymphadenopathies may be present.

Some studies have shown that positive ANA can be found in numerous clinical conditions such as SLE, systemic sclerosis, idiopathic thrombocytopenic purpura, rheumatoid arthritis, several cancers (including lymphoproliferative diseases), as well some chronic infection and healthy individuals, in some cases with high titers.[1]

Even the positivity of anti-dsDNA, autoantibodies considered specific of SLE, in a patient with constitucional symptoms and multiple adenopathies, do not definitively exclude a lymphoproliferative disease.[2, 3]

Moreover, it is known that patients with SLE have a higher risk of developing lymphoproliferative diseases (in particular, B cell lymphoma), diseases that may also present with positive autoantibodies. The mechanism responsible for this possible association is not entirely clear, however, several hypotheses have been suggested.

One theory is that the high accumulation of B and T lymphocytes, could be responsible for an abnormal immune response.[4]

In immunomediated established diseases, the immunosuppressive therapy has often been pointed to a possible risk factor in increasing the risk of lymphoproliferative diseases, although more recent studies show that risk

was not statistically significant when compared with controls with treatment. [5]

Other studies consider that some infections may be important for this association. In the pathogenesis of some lymphomas, persistent infections by viruses, including EBV have been implicated. In patients with SLE, due to a deficiency of cytotoxic response mediated by T cells, EBV infection may persist, predisposing to a malignant transformation. [6]

In the case presented, the co-existence of both clinical situations in such short time would be less likely. Although in this patient the histological results were not easy to interpret, histology still plays an essential role in the differential diagnosis between these diseases.

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Case Report **8**

Approach to Neurologic Manifestations of Antiphospholipid Syndrome: Cerebral Venous Thrombosis

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Abstract

We present a case report of 28 year-old caucasian woman in the puerperium with an history of migraine without aura and an anxiety disorder since childhood. Her pregnancy was complicated by gestational diabetes and pre-eclampsia. She was treated with diazepam 10 mg/day. Two weeks after delivery she presented with persistent headache and vomiting. She was observed at the emergency room and she was treated with analgesics (paracetamol, lysine acetylsalicylate) and anti-emetics (domperidone). Antibiotic (sulfamethoxazole with trimethoprim) was started by the suspicion of an urinary tract infection. After 24 hours she didn't experience any relief, presented with fever and with a deviation of labial commissure. At the neurologic exam she presented a left facial central paralysis and hemiparesis of the left arm (NIHSS = 4). She had signs of mild papilledema on examination of the fundus. The cerebral-CT revealed two heterogenous lesions in a cortical-subcortical localization, bilaterally in the frontal brain parenchyma, with a hemorrhagic content and edema. The cerebral-MRI angiogram showed thrombosis of the anterior third of the superior sagittal sinus. She was admitted in an intermediate care unit. The auto-immune assays were positive for antiphospholipid antibodies (aPL) namely lupus anticoagulant (LA) and β_2 glycoprotein I (β_2GPI) IgM and IgG. The oral anticoagulation with warfarin was started to an INR target of 2-3. The diagnose of Antiphospholipid Syndrome was established then by the confirmation of the presence of β_2 glycoprotein I

(β_2GPI) IgM and IgG more than twelve months after. She remained stable without hemorrhagic complications. The symptoms improved, the neurologic exam was normal at the time of discharge and a control cerebral-CT showed reduction of the hemorrhagic lesions. A thrombotic stroke occurring in a young patient with no overt risk factors for cerebrovascular disease is the classicsetting in which to suspect antiphospholipid syndrome. An ischemic stroke may be an expression of in situ thrombosis. Pregnancy is a common cause of cerebral venous thrombosis and symptoms usually occur during the puerperium. Also, the antiphospholipid syndrome is associated with cerebral venous thrombosis which tend to be recurrent.

Introduction

Antiphospholipid syndrome (APS) is characterized by recurrent venous or arterial thromboses, fetal losses and thrombocytopenia in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or antibodies directed to various proteins, mainly β_2 glycoprotein I (β_2GPI), or all three [1, 2]. The diagnosis is made according the revised Sapporo Classification Criteria: at least one clinical criteria and one laboratory criteria have to be present [1]. Its development may be independent of any underlying disease and this form is termed as "primary". Nonetheless, this syndrome was first recognized in patients with systemic lupus erythematosus (SLE) and later less frequently in those with other autoimmune disorders and this form is termed as "secondary" [2]. This classification becomes artificial because there are no clinical differences between the aPL among patients in these two categories and the aPL profile seems to be more important to classify these patients into different categories since patients with LA, IgG aCL at high titles or anti-β_2GPI antibodies plus LA or aCL have the highest thrombotic risk [2]. Nonetheless, the LA is the best predictor of thrombotic events.

Any combination of vascular occlusive events may occur int the same individual and the time between them also varies considerably [2]. Cerebrovascular accidents - either stroke or transient ischemic attacks - are the most common arterial thrombotic manifestations [2].

Since description and designation of the antiphospholipid (Hughes) syndrome, the links between aPLs and diseases of the nervous system have been

considered of major importance [3]. Since the first report by Hughes in 1983, the cerebral symptoms in APS patients have become more important.[3] The main neuropsychiatric presentations in the context of APS are: cerebrovascular disease (either transient ischemic attacks, ischemic strokes, acute ischemic encephalopathy and cerebral venous thrombosis), epilepsy, headache, chorea, multiple sclerosis, transverse myelitis, idiopathic intracranial hypertension, cognitive dysfunction, dementia, psychiatric disorders such as depression or psychosis or other neurologic syndromes such as sensorineural hearing loss, Guillain-Barré syndrome, transient global amnesia, ocular syndromes and dystonic Parkinson.[3] These presentations are not solely explained by hypercoagulability and may have had more complex origin. The aPLs may bind neurons or glial cells and disrupt their function. Also, there is evidence that the aPLs may interfere with endothelial cell function and promote the procoagulant activity of endothelial cell function and promote the procoagulant activity of endothelial cells [3].

Cerebrovascular disease is the most frequent neurologic manifestation in aPL-positive patients [4, 5]. It was also suggested that aCL and LA represent a kind of aPLs leading to cerebral vascular injury and thrombosis resulting in cerebral infarction. The cerebral ischemia, which is mainly focal, can be transient or permanent. The risk of recurrent stroke appears to be increased in APS patients. Generally, the territory of the middle cerebral artery is more commonly affected. A chronic multifocal disease can produce multi-infarct dementia. The association between livedo and ischemic stroke - *Sneddon's Syndrome*, occasionally with hypertension, has been known since 1965.[6] Recurrent ischemic events in aPL-positive patients are related to aCL at the time of the initial stroke. These relationships are probably more relevant to younger populations with evidence of prothrombotic tendencies and little other risk of stroke. Acute ischemic encephalopathy has also been observed but is a rare feature in systemic lupus erythematosus (SLE). Cerebral venous thrombosis (CVT) is another uncommon appearence in APS but it may be involved in a range of hypercoagulability states, especially in young women.

According to one study were 113 cases of CVT were reviewed, this presentation was more common in young adults and in women. Most of them had risk factors for CVT like the use of oral contraceptives, thrombocytosis, secondary polycythemia, circulating lupus anticoagulant, protein S deficiency, arteriovenous malformation and metastatic carcinoma. The most

frequent presentation symptoms were the headache, seizures, focal signs and consciousness disorders. The most frequent neurologic findings were: headache, focal signs, consciousness disorders, seizures, bilateral pyramidal signs, papilledema, nuchal rigidity and isolated intracranial hypertension. The neuroradiological exams were normal or showed signs of cerebral venous thrombosis or parenchymal lesions. The cerebral magnetic resonance imaging (MRI) was able to identify more signs of venous thrombosis and parenchymal lesions. In that study was found a high frequency (70%) of parenchymal lesions (venous infarcts and intracerebral hemorrhages) that manifested as focal neurological signs, epileptic seizures, disorders of consciousness, intracranial hypertension, nuchal rigidity, and hemorrhagic cerebral spine fluid. [7]

A wide variety of well-known conditions may cause or predispose to CVT, and their relative importance may vary in different areas of the world. In a study. 60% of cases were associated with pregnancy and puerperium. [7]

Case report

We present a case report of a 28 year-old caucasian woman, student, in the puerperium, with a pregnancy complicated by gestational diabetes and pre-eclampsia. She had an history of migraine without aura and an anxiety disorder since childhood. She was a non-smoker and she didn't drink alcohol. She was treated with diazepam 10 mg/day, magnesium, folic acid and iron supplies. She wasn't under oral contraceptives. Two weeks after delivery she presented with persistent headache and vomiting. She was observed at the emergency room and she was treated with analgesics (paracetamol, lysine acetylsalicylate) and anti-emetics (domperidone). Antibiotic (sulfamethoxazole with trimethoprim) was started by the suspicion of an urinary tract infection. After 24 hours she didn't experience any relief, presented with fever and with a deviation of labial commissure. She was hemodynamically stable (arterial blood pressure of 119/70 mmHg), her radial pulse was rhythmic (heart rate of 99 bpm). Afebrile. Her cardiac and pulmonary auscultation was normal. The abdominal exam showed no alterations. At the neurologic exam she presented somnolence, a left facial central paralysis and hemiparesis of the left arm (NIHSS = 4). She had signs of mild papilledma on examination of the fundus.

Her cell blood count examination showed normocytic normochromic anemi a (hemoglobin of 10,1 g /dL) , without thrombocytopenia (205x10^9/L) and with high erythrocyte sedimentation rate (75 mm/1st hour). The ddimers were high: 2930 ng/mL. The cerebral-CT revealed two heterogenous lesions in a cortical-subcortical localization, bilaterally in the anterior portion of frontal brain parenchyma, in both cerebral hemispheres, with an hemorrhagic content and edema, bigger in the right with 40x50x45mm, conditioning mass effect under the right frontal horn and a 5 mm deviation of the median structures to the left. The cerebral-MRI angiogram showed thrombosis of the anterior third of the superior sagittal sinus with venous frontal infarcts with an hemorrhagic content more evident at the right, with mass effect under the median structures, the lateral horn and corpus callosum.

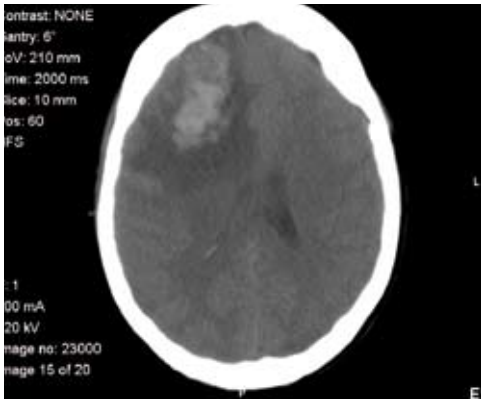

Fig. 1 – **Cerebral - CT showing heterogenous lesions in a cortical-subcortical localization.**

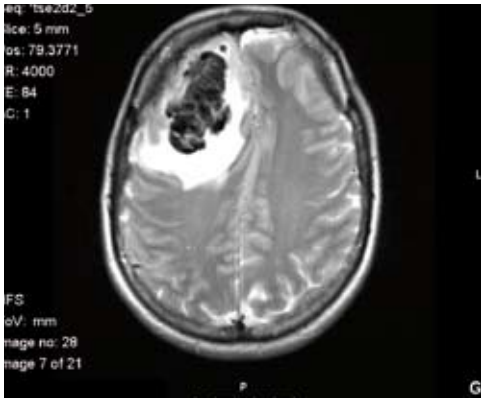

Fig. 2 – **Cerebral - MRI angiogram showing thrombosis of the anterior third of the superior sagittal sinus with venous frontal infarcts with an hemorrhagic content.**

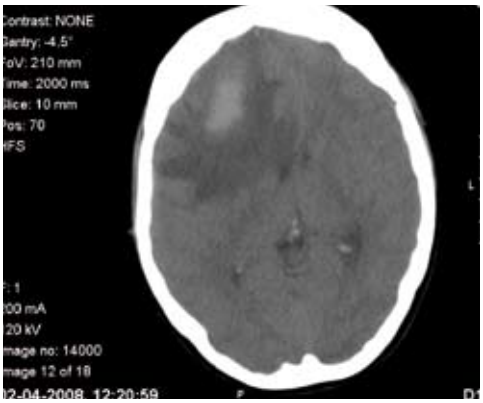

Fig. 3 – **Cerebral - CT showing reduction of the hemorrhagic lesion.**

She was admitted in an intermediate care unit. Her thyroid function was normal. The auto-immune assays were positive for antiphospholipid antibodies (aPL) namely lupus anticoagulant (LA) and β_2 glycoprotein I (β_2GPI) IgM and IgG. She was heterozygous to the mutation of the gene of MTHFR. She was treated with anti-edematous medications (mannitol). She started bromocriptine for the inhibition of lactation. She started anticoagulation initially with enoxaparin and then with warfarin to an INR target of 2-3. The diagnose of Antiphospholipid Syndrome was established then by the confirmation of the presence of β_2 glycoprotein I (β_2GPI) IgM and IgG more than twelve months after.

She remained stable without hemorrhagic complications. The symptoms improved (she had discharge two months after the event), the anemia has resolved, the neurologic exam was normal at the time of discharge and a control cerebral-CT (twelve days after) showed reduction of the hemorrhagic lesions. She made an electroencephalogram that showed slowed cerebral function in a frontotemporal localization with important cerebral dysfunction.

She was treated at home with enoxaparin and warfarin (until target INR of 2-3), alprazolam 0,25 mg, zolpidem in SOS and esomeprazole 40 mg.

She started the follow-up in the Internal Medicine Autoimmune Diseases consultation. She showed warfarin resistance and the oral anticoagulation was switched to acenocoumarol. She has been stable for two and a half years, without any thrombotic recurrence or hemorrhagic complication. We have established a INR target of 2,5-3,5, the last INR was 2,85. The autoimmune assay shows a mild elevation of β_2 glycoprotein I IgM and IgG.

Discussion

This is a typical presentation of a cerebral venous thrombosis in a patient with an under lying antiphospholipid syndrome: a young woman who presented initially with headache and then with neurological focal signs and indirect signs of intracranial hypertension. Also, the puerperium is a risk factor for hypercoagulability states and this state may have been the trigger to the event.

At the time of presentation, this patient was positive for antiphospholipid antibodies (aPL) namely lupus anticoagulant (LA) and β_2 glycoprotein I (β_2GPI) IgM and IgG. The LA represent one kind of aPL more related with cerebral vascular injury and thrombosis resulting in cerebral infarction. Also, LA is the best predictor of thrombotic events. In this case, the thrombotic potential was high. The LA became negative and maybe this is protective against recurrence. The diagnosis of APS was then established the by the confirmation of the presence of β_2 glycoprotein I (β_2GPI) IgM and IgG more than twelve months after.

It is also of note that this patient was heterozygous to the mutation of the gene of MTHFR. Venous blood clots occur in approximately 1 in 1000 individuals per year. [9] It is also important to consider this factor as a potential contributor factor.

The parenchymal lesions, as venous infarcts and intracerebral hemorrhages, are frequent imaging findings in cerebral venous thrombosis as in this case.

Current standard practice for patients with APS is to recommend indefinite anticoagulation with warfarin. This is derived from a limited experience with ar terial thrombosis, a much larger and more definitive experience with venous thrombosis and the observations by many groups that these patients are prone to recurrent cerebrovascular events which, in principle, should be preventable. In these studies venous and arterial disease is not clearly separated and comparison between different forms of recurrence prevention is limited.[10] Patients with definite APS with a first venous thrombosis should be treated with prolonged oral anticoagulation at a target international normalized ratio (INR) of 2.0–3.0 and those with an arterial event at an INR of 3.0–4.0. So, because we find this patient prone to

both kind of events, we have chosen an intermediate interval to target the INR ideal value for the oral anticoagulation: 2,5-3,5. [2]

As the thrombosis resolved with anticoagulation and the hemorrhagic component was reabsorbed (as documented by the cerebral-CT scan), the symptoms improved. This is not surprising because in the case of thrombosis (arterial or venous) the symptoms may be transient if the anticoagulation is effective.

Conclusion

There is a strong association between aPLs and cerebrovascular disease, headache, cognitive dysfunction, and seizures. Testing for aPLs should be recommended not only for patients with autoimmune diseases and neuropsychiatric syndromes but also for younger patients (age < 40 years) without an underlying autoimmune disease who develop ischemic cerebral events. During brain MRI, such young individuals with multiple hyperintensity lesions without other known causes should also undergo testing for aPLs.[3]

Neurological diseases, possibly due to vascular-ischemic (occlusive) disturbances, are the most life-threatening conditions, especially in catastrophic APS (CAPS) and/or when recurrences appear.[3]

Life-long oral anticoagulation at a target INR interval depending on wether there is an arterial or venous event is the treatment of choice.

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Case Report 9

Churg Strauss Syndrome Manifesting as Acute Coronary Syndrome

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Abstract

Churg-Strauss Syndrome is a rare disorder characterized by asthma, eosinophilia and systemic vasculitis. The most commonly involved organ is the lung, however, it can affect any organ system. Cardiac involvement is present in up to 60% of patients and it is related to worse prognosis.

The authors describe a case report of a 55-year-old woman who presented with recurrent chest pain at rest over the last two months. She was admitted with acute coronary syndrome and based on her past medical history (asthma, eosinophilia, chronic rhinitis and transient pulmonary abnormalities), Churg-Strauss Syndrome was diagnosed.

Keywords: Churg Strauss Syndrome, eosinophilia

Introduction

Churg-Strauss Syndrome (CSS) is defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract, coupled with necrotizing vasculitis affecting small-to-medium-sized vessels, and is associated with asthma and eosinophilia [1].

It is a rare disorder with an incidence between 2.7 and 3.4 cases per 1 000 000 patients per year [2]. The mean age at the time of diagnosis is 52 years, with no significant gender difference [3].

Three different phases can be recognized in CSS. A prodromal phase, characterized by asthma and atopic allergies, is common and may last several years. The second phase is heralded by peripheral eosinophilia, and may be associated with additional organ involvement. In the third phase, symptoms

and findings of a systemic vasculitis are present [4].

The most commonly involved organ is the lung, however, CSS can affect any organ system, including the cardiovascular, gastrointestinal, renal and central nervous system. Vasculitis of extrapulmonary organs is largely responsible for the morbidity and mortality associated with CSS [5].

The authors describe a case of Churg–Strauss Syndrome manifesting as acute coronary syndrome due to coronary vasospasm.

Case Report

A 55 year-old-woman presented to our emergency department with epigastric pain radiating to her chest and left arm, with no relation to effort, associated with shortness of breath, hypersudoresis, nausea and vomiting. Similar episodes had occurred over the previous two months. On admission, physical examination did not reveal abnormalities. Laboratory findings revealed leukocytes of 8.17×10^9/L, with a high level of eosinophils (26,7% of total leukocytes, corresponding to an absolute value of $2,18\times10^9$/L), urea 60mg/dL and creatinine 1,5 mg/dL. C-reactive protein was negative. Electrocardiography showed no signs of ischemia but there was an elevation of cardiac biomarkers (troponin I 0,2ng/mL). The patient was admitted to our department with the diagnosis of acute coronary syndrome.

Her past medical history revealed arterial hypertension, asthma, chronic renal insufficiency and ischemic cardiopathy. Asthma was diagnosed eight years before and she was medicated with bronchodilator and inhaled corticosteroids. There were no documented allergies, desensitization program or history of antileukotriene agents. She had a history of one hospitalization ten months before because of acute coronary syndrome. The study included coronary angiography that showed normal arteries and echocardiogram which revealed preserved ventricular function. Cardiac nuclear magnetic resonance was inconclusive for cardiac ischemia.

During her period in the hospital, the patient complained of recurrent chest pain at rest, during 30 minutes, that relieved spontaneously and without electrocardiographic changes or elevation of cardiac biomarkers. In this context, she started nifedipine 30 mg/day with the hypothesis of Prinzmetal Angina. The next day, the patient experienced another attack of severe chest

pain at rest that partially relieved with sublingual nitrates. Electrocardiogram showed a mild ST-segment elevation in leads DII, DIII and a mild depression in ST-segment in V2-V4. The maximum troponin I level was 6,91 ng/mL. Echocardiography did not reveal abnormalities. Coronary angiography revealed a distally occluded left anterior descending and left circumflex arteries, the occlusion being reversible after nitrates.

Autoimmune parameters, including antineutrophil cytoplasmic antibodies, were negative. IgE was elevated 1070 kU/L (reference value <114 kU/L) and eosinophilia achieved its maximum level (29,3% of total leukocytes).

The images of several thoracic computed tomographies performed in the last year were reviewed, and they were consistent with transient abnormalities, including pulmonary densifications, ground-glass opacities, bronchial wall thickening and consolidation.

A bronchofibroscopy with bronchoalveolar lavage was performed and it revealed 2,8% of eosinophils (under corticotherapy).

The patient was undergone an otolaryngology examination that confirmed chronic rhinitis and nasal polyposis.

The presence of asthma, hypereosinohilia >10%, chronic sinusitis and transient pulmonary infiltrates were suggestive of CSS. Oral corticosteroids were applied with an initial dosage of 50 mg prednisolone per day (1mg/kg/d), being continuously tapered to a dosage of 5mg/day.

After initiating corticosteroid therapy, symptomatology improved and no further angina attacks occurred during the patient's stay in hospital. Eosinophilia, IgE count and Troponin I decreased to normal range.

At six-month follow-up, there were not further chest pain episodes, and the eosinophilia was between normal values.

Discussion

Despite the continuous redefinition of diagnostic criteria for CSS, diagnosis remains a clinical one. The American College of Rheumatology (ACR) classification of CSS includes six criteria: asthma, eosinophilia of >10% white blood cell count, migratory or transient pulmonary opacities on chest radiographs, mononeuropathy or polineuropathy, paranasal sinus

abnormalities and extravascular eosinophils on biopsy. According to this classification, the presence of four or more of these criteria allows a diagnosis of CSS to be made with a sensitivity of 85% and a specificity of almost 100% [6].

In the case presented, the diagnosis was suggested by the presence of adult-onset asthma associated with allergic rhinitis and the elevation of peripheral-blood eosinophil count. The diagnosis is typically missed initially, because asthma and associated sinus disease are very common, and they can precede onset of vasculitis by many years. Although asthma is typically associated with eosinophilia, eosinophil count greater than 10% of the total white-cell-count should prompt consideration of Churg-Strauss Syndrome [7].

Pulmonary involvement is nearly universal in CSS. Asthma is present in 96-100% of patients and pulmonary abnormalities are present in 70,6%-100%. Changes are nonspecific and the most common radiologic findings are parenchymal opacities and consolidations. Additionally, micronodules, bronchial wall thickening and pleural effusions were described [8,9].

Recent studies suggest that the clinical characteristics of patients with CSS differed according to their antineutrophil cytoplasmic autoantibody (ANCA) status. Cardiomiopathy predominated in ANCA-negative patients and necrotizing glomerulonephritis was more often observed in ANCA-positive patients [10].

Cardiac involvement is one of the most serious manifestations of CSS and is present in 62% of patients [11]. Clinical manifestations include myocarditis, heart failure, cardiac tamponade, myocardial infarction or pericardial effusion. Myocardial damage is caused by vasculitis leading to coronaritis and coronary occlusion, by the release of toxic mediators by activated eosinophils causing direct myocardial damage, or by replacement of the myocardium with granulomas and scar tissue [11-14]. Cardiac involvement is the major cause of mortality, accounting for 48% of deaths due to CSS [15].

The absence of abnormalities in the epicardial coronaries suggested small vessel vasculitis-related ischemia. This fact, in association with hypereosinophilia and asthma were the key to establish the diagnosis.

The treatment decision was based on the severity of disease, using the "five-factors score" (FFS) [16]. Therapy with oral prednisolone was started at dosage of 1 mg/kg per day, in association with inhaled asthma medication.

Conclusion

Churg-Strauss Syndrome is a rare diffuse vasculitis that is almost invariably associated to asthma and can affect any organ. Heart involvement is associated with worse prognosis. Vasospastic angina is an unusual clinical manifestation of CSS, but this diagnosis should be considered when there is coronary vasospasm associated with eosinophilia.

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Case Report **10**

Rowell's Syndrome

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Introduction

Rowell's syndrome (RS) is a distinctive syndrome, described in 1963 by Rowell et al [1]. It consists in erythema multiforme-like lesions associated with lupus erythematosus. Zeitouni et al. recently redefined the major and minor diagnostic criteria. Major criteria are systemic lupus erythematosus (SLE), erythema multiforme-like lesions (EM) and speckled pattern of antinuclear antibody. Minor criteria are chilblains, positive anti-La (SS-B) or anti-Ro (SS-A) antibody and reactive rheumatoid factor.

We report a case of an 18-years-old-woman, with erythema multiforme-like lesions associated with systemic lupus erythematosus. We believe that our patient meets the criteria for this rarely reported entity.

Case report

Female patient, 18-years-old at the time of admission, caucasian, student, born and resident in Portugal. In February 2008 was refered to the Emergency Room with fever for about 3 weeks of evolution associated with generalized headache with photophobia, asthenia, anorexia, weight loss (measured at about 10 kg in 3 months), night sweating and arthralgia at the metacarpal joints, without arthritis.

She had been treated with multiple antibiotics regimens, anti-inflammatory and analgesic, without any improvement.

As past history, she refered only recurrent tonsillitis in childhood,

without relevant family history and without any usual medication. The patient was admitted in the Department of Medicine for clinical investigation.

The analytical study carried out showed: leukopenia with lymphopenia (3.770/uL-870/uL); normochromic normocytic anemia (Hb: 8.6g/dL) regenerative (reticulocytes 5%); peripheral blood smear with anisopoikilocitosis, many elliptocytes, rare tears cells and rare schizocytes; low iron, folic acid and B12 vitamin normal; normal haptoglobin; direct Coombs test positive; normal thyroid function; transaminases elevation (with values 3-4 times higher than normal); LDH 578 U / L; total bilirubin, G-GT and alkaline phosphatase normal; erythrocyte sedimentation rate of 120mm/hour, RCP negative; low complement (C3: 26.1 and C4: 3.0); high IgG (3200), normal IgA and IgM; anti-Nuclear antibodies (title 1 / 1280), homogeneous + speckled pattern; double-stranded DNA antibodies positive; anti- Ro (SS-A) antibodies positive; anti-histone positive; rheumatoid factor negative; anti-SCL70 negative; viral markers (HIV 1 and 2, HBV and HCV) were negative; Syphilis serology, CMV, rubeola, toxoplasmosis, and HSV I and II were negative, serodiagnosis of infectious mononucleosis and Weil-Felix reaction negative; Urine 24-hour proteinuria normal. Negative blood and urine cultures as well as research of BK in urine and gastric juice.

About imagiologic tests: thoracic X-ray was normal; echocardiogram showed "chambers with dimensions and normal wall thickness, normal valvular structures, globally preserved systolic ventricular function with a mean EF of 59% without changes in segmental contractility, normal pericardium, without effusion, normal pulmonary blood flow without intracardiac mass or vegetation"; abdominal ultrasound with an "enlarged liver (16.5cm), small accessory spleen with the splenic hilum, with the two elements adenopathy hepato-duodenal ligament 2x0.7cm, without other changes"; cervico-thoracic-abdominal-pelvic tomography showed "small bilateral axillary lymphadenopathy, with the largest 2 cm without lymph node enlargement in size in mediastinal and hilar regions; homogeneous hepatomegaly, slightly prominent spleen, no changes in density, multiple formations abdomino-pelvic ganglion chains peri-celiac, hilar, renal, lumbar-aortic, mesenteric, common iliac and external inguinal; small volume ascitis, located in the posterior fornix".

By presenting anti-nuclear antibodies positive (title 1/1280, homogeneous and speckled pattern), double-stranded DNA antibodies positive, anti- Ro (SS-A)

antibodies positive, anti-histone positive, low complement, leucopenia and anemia we suspected of connective tissue disease. So we started pulses of methylprednisolone on the 2nd day of admission.

Seven days after hospitalization, the patient presented extensive skin lesions with large bubbles in the hands, forearms, knees and feet, associated with intense itching and disabling articular pain, but without arthritis. Skin biopsy was compatible with erythema multiforme ("epidermal keratinocytes necrosis, formation of micro-abscesses containing predominantly eosinophils blistering and epidermal-dermal inflammatory cells, including eosinophils are identified, the underlying dermis is the site of mild to moderate inflammatory peri-vascular infiltration").

The patient showed good progress, sustained apyrexia after 4th day, improvement of general health, analytical parameters and skin lesions regression. At the time of discharge the patient was asymptomatic. The adenopathy and ascites also disappeared after steroid therapy.

She was discharged, oriented to Outpatient Internal Medicine - Autoimmune Diseases, treated with prednisolone and hydroxychloroquine. Kept following the consultation of Autoimmune Diseases with no skin lesions, treated with prednisolone 5mg/day, hydroxychloroquine 400 mg/day and azathioprine 50 mg /day.

Conclusion

Rowell's syndrome diagnosis is supported on clinical and immunologic features. The speckled pattern of ANA is the most consistent laboratory feature of this syndrome [2, 3], and it was present in our patient additionally to a positive anti-Ro. Clinical condition of RS include Lupus Erythematosus (systemic, discoid or subacute), EM-like lesions and chilblains.

The association of SLE with EM was originally documented by Scholtz in 1922 But, Rowell's syndrome (RS) as a distinctive syndrome, was first described in 1963 by Rowell et al (1). Although this syndrome was described in a discoid erythematous lupus (DEL) patient by Rowell [1] in 1963, other cases with cutaneous LE, subacute (SCLE) or systemic (SLE) were reported [4].

Classical EM is not associated with any specific auto-immune

serological abnormality [2]. EM is precipitated by trigger factors such as infectious agents (Mycoplasma pneumoniae and Herpes simplex) or drugs (antibiotics, non steroid anti-inflammatories and anti-convulsants), although other causes including connective tissue or malignant diseases have been associated with this condition. In our patients no identifiable precipitating factor was identified.

The early EM- like lesions in Rowell's syndrome begin as erythematous papules and progress to ring shaped lesions with a vesicular edge; bullae and necrosis occur in severe cases. Histopathologically these lesions show changes characteristic of erythema multiforme. Patients with this syndrome also frequently have perniotic lesions, that was not present in our patient. Although oral, eye and vulval lesions are infrequent features of RS, mucosal involvement has been demonstrated in some cases.

The clinical and histology in EM and SCLE may be difficult to differentiate [4, 5, 6]. Necrotic keratinocytes may be found in SCLE lesions [3] as in EM, early SCLE lesions with annular-polycyclic pattern may resemble EM. Herrero et al described the presence of necrotic keratinocytes in 6 of 13 (54%) SCLE patients [7]. As some clinical, histological and immunological findings seem to overlap RS and SCLE, it has been suggested by some that lupus eythematosus with EM-like rash designated as RS represent a subset of SCLE with targetoid lesions, rather than a distinct entity [4, 8, 9].

Although most case reports do not mention the presence or absence of chilblains, Zeitouni et al. considered that chilblains should be included as a minor diagnostic criteria [2]. It has been hypothesized that the speckled ANA factor may be part of the immunologic disturbance contributing to the formation of chilblain lesions [4] and some patients with chilblains often have a positive rheumatoid factor (RF). It is possible that both the speckled ANA pattern and RF are actually associated with perniosis [4, 10]. In fact chilblains are one of the more common cutaneous manifestations in the spectrum of LE, and speckled ANA and RF are strongly associated with the chilblain lupus variant and should not be considered as a specific criteria [11].

Zeitoni at al reviewed diagnostic criteria for Rowell Syndrome[2] and proposed three major and three minor criteria. The major criteria consist in the presence of LE (systemic, discoid or subacute), EM-like lesions (with or without involvement of mucous membranes) and speckled pattern of antinuclear antibodies. The minor criteria includes chilblains, anti-Ro and/or

anti-La antibodies and positive RF. All three major criteria and at least one minor criteria are required to establish the RS diagnosis [2, 4, 11, 12].

Our patient had all the three major and one minor criteria (anti-Ro antibody), thus fulfilling the requirements for diagnosis.

RS patients are, in the literature, predominantly middle-aged women, however it as also been described in younger women (as our patient) and even in pregnant women. RS has been rarely described in male population.

Patients with lupus erythematosus may develop coincidental erythema multiforme[3], but if characteristic serological abnormalities are present and there is no obvious precipitating factor, RS should be considered [2, 12].

With corticosteroids and antimalarials therapy patients have a very good response [2, 4, 5, 6, 8, 10, 13, 14, 15], with only a few complications related to LE or EM [3]. Zeitoni at al described a case of RS responding to dapsone [2]. In our patient the lesions completely resolved after methilprednisolone pulses and followed by oral prednisolone and hidroxichloroquine. We started azathioprine because other manifestations of SLE persisted although corticoid therapy.

Mandelcorn at al in a recent publication described a more severe variant of Rowell syndrome characterized by an acute progression to toxic epidermal necrolysis in two patients [14].

Rowell's syndrome is rare. As more cases are reported, the existence of this entity will be further clarified [2, 12]. It should be suspected and screened in all patients with LE and EM-like lesions, that have no evidence of a precipitating factor.

Our patient has been without lesions for more than three years and is followed in the consultation of Autoimmune Diseases.

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Case Report 11

Severe Inflammatory and Vascular Activity in Primary Sjögren´s Syndrome

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Abstract

Sjögren´s Syndrome is an auto-immune disease characterized by glandular dysfunction, presented by symptoms like xerophtalmy and xerostomy, but with potential to affect any organic system.

We report a clinical case of a 45 year old woman with Primary Sjögren´s Syndrome, with extra-glandular multi-organic effects and a progressive 8-year clinical evolution; with the developing of GI lesions, pulmonary pathology and a permanent inflammatory state, with difficult clinical and laboratorial management.

Facing the serious and worrying evolution, we consider which therapeutic options should be used, according to the imunossupressor therapy already in course with little success till now.

Keywords: Sjögren´s Syndrome; Extra-glandular; Inflammation; Renal Failure; Vasculitis.

Introduction

Sjögren´s Syndrome (SS) refers to a long term inflammation which affects mainly the salivary and lacrimal glands. It may occur in isolated form (Primary SS) or in association with other autoimmune pathologies, especially LES or AR (Secondary SS).

Both forms (primary or secondary form) are characterized by "sicca" complex, xerophtalmy and xerostomy by definition[1].

SS etiology is still unknown, although genetic factors are considered to

be important, especially when influenced by environmental factors (infectious) and neuro-humoral factors. The major histo-pathogenic characteristics are the invasion of the exocrine gland by T lymphocytes and stimulation of B lymphocytes, which generates a lymphoplasmocytic CD4 cell infiltration on glandular tissue, causing progressive destruction and hypofunction. In consequence cytokines, INF-γ and IL-2 are released, leading to hyperactivation of B cells with massive production of auto-antibodies and possible malignant proliferation, which occurs in 2.5% of the patients with SS [2].

The clinical manifestations may be classified as glandular (30%) or extra-glandular (20% - 70%) [6], conditioning a wide multisystemic spectrum.

It affects mainly pre-menopausal women, in a female:male ratio of 12:14 for each man. It may occur at any age, but mostly in the 4th and 6th decades of life and the first symptoms are related to "sicca" syndrome.

In moderate stages we may find small amounts of auto-antibodies and slight symptoms of asthenia, myalgia and cognitive dysfunction.

In more advanced stages a severe salivary gland hypertrophy may be observed, in addition to adenopathies, presence of SSA/SSB auto-antibodies, cryoglobulinemias, hypocomplementemia and a higher probability to develop LNH.

In patients with extra-glandular presentation, the glandular manifestations may be discrete [3], so diagnosis has to be completed by serology, immunology and histology.

Cutaneous involvement is common and the frequency of vascular cutaneous inflammatory disease is estimated around 20% to 30%. Among cutaneous vasculitic forms, the most predominant is palpable purpura and chronic urticaria [4].

Renal insufficiency is not frequent and may be related with a severe form of interstitial nephropathy, or less commonly with glomerulopathy. The most frequent lesion is an interstitial mononuclear infiltrate of variable intensity with tubular atrophy and the presence of fibrosis [5].

SS treatment is glandular substitution therapy, although there isn't one capable of changing the gland's pathologic evolution. The extra-glandular involvement requires specific treatment for the organ and immunosuppressive therapy proper to aggressiveness of the disease [4].

The authors present a case report of Sjögren syndrome, of a woman with progressive extra-glandular involvement of increasing severity. Cutaneous,

pulmonary, gastrointestinal and renal involvement was added along with exuberant constitutional symptomatology and permanent inflammatory expression refractory to immunosuppressive upgrading therapy.

Case report

45 years old woman, caucasian.

Clinical history of smoking, depressive syndrome and essential hypertension.

The patient was presented in 2003 to the Autoimmune Diseases Department of Internal Medicine, due to myalgia and major articulations arthralgia with inflammatory character. She also showed progressive xeroftalmia and xerostomy for two years of evolution.

The patient presented dry oral mucosa, tibiotarsal synovitis and *reticular livedo* on the thighs. There was no parotid glands injury, hepatoesplenomegaly, peripheral edema, or alteration of cardiac auscultation and arterial pressure was stable.

Analytically, a normochromic and normocytic anemia (Hb 11.6g/dl) was observed, but there was no variations on leucocytes or platelet count; ESR of 106mm; positive ANA´s and antiSSA with negative ANCA, negative ds-DNA, rheumatoid factor, anti-CCP e anti-Sm and no complement consumption, hyperproteinemia, raised IgG (3480), normal renal function, negative serological markers for viruses and normal thyroid function. Positive Shimer test, salivary gland biopsy was consistent with acute sialoadenitis.

Considering clinical and analytical context primary SS was assumed and therapy with prednisolone 10mg/ day was initiated, with a good response.

In April 2005 she presented a recrudescence in arthralgia, no synovitis, and progression of xerostomy with lesions in the oral and nasal mucosa, rising ESR without other analytical changes. Therapy was optimized by association with hydroxicloroquine (HCQ) 400 mg/day and NSAIDs to corticotherapy already initiated (Prednisolone 10 mg/day).

Due to fatigue and incapacitating arthralgia, the prednisolone dose was increased to 30 mg/day, in the attempt to withdrawing to 10 mg/ day, but without success justified by the persistent inflammatory polyarthritis.

After 6 months of therapy with NSAIDs, prednisolone 30 mg,

hydroxicloroquine 400 mg/ day presented active disease with polyarthralgia, aggravation of anemia and increase in ESR and C-Reactive Protein, which justified the introduction of Methotrexate (MTX) 15 mg/ day and the attempt to withdraw the corticoids.

In November 2007, 9 months after MTX introduction the patient presented escalation of the disease with polyarthritis, dysphagia, asthenia, weight loss (4Kg), aggravation of anemia and "de novo" renal failure.

Assuming extra glandular progressive involvement and refractory to instituted immunosuppression the investigation was re-evaluated.

Analytically, it was discovered an aggravated anemia (Hb 10.6 g/dl), an ESR 123 mm, a creatinine 1.4 mg/dl, without proteinuria, a creatinine clearance of 43 ml/min; an autoantibody progression, with positive SSB and RF, with negative anti-CCP, ENA's and ANCA's, complement consumption, hypergammaglobulinemy (IgG 4740 mg/dl), and negative cryoglobulin assay.

Endoscopy showed chronic gastritis with focal intestinal metaplasia in the antrum.

Renal failure was admitted either in iatrogenic form due to abusive use of NSAIDs versus to disease progression, so it was decided to suspend NSAIDs, start ACEI and increase prednisolone, deferring renal biopsy.

One year later (Nov/2008), a new flare of the disease, with diffuse petechial rash on lower limbs and associated edema, aggravation of renal function with decreased creatinine clearance to 36.3 ml/ min, proteinuria of 375 mg and IgG monoclonal peak with hemoglobin decrease.

Myelogram showed 2% plasmocytes, 30% lymphocytes, raising the suspicion of LNH of the marginal zone with renal involvement. Renal biopsy showed tubular-interstitial nephritis with plasmocyte tubular diffuse infiltrate, assumed as tubular-interstitial nephritis secondary to SS. LNH was not confirmed by bone biopsy, due to immunohistochemical results marking anti-CD20 antibodies and revealing scarce well differentiated lymphocytes marking. Cutaneous biopsy showed leukocytoclastic vasculitis. Pulmonary CT showed perihilar bronchiectasis and functional respiratory tests demonstrated slight obstruction syndrome and no alterations on bronchoalveolar lavage.

Faced with severe disease with renal, hematological and vascular progression, assuming the possibility of medullar toxicity was decided to suspend the use of MTX and introduction of azathioprine 1.5 g/Kg/day. The

following 18 months, the patient presented symptomatic and laboratorial improvements. However, the inflammatory parameters (ESR and hemoglobin decrease) were high. In May 2010 a new flare of the disease appeared with disperse petechial purpura on lower limbs with diffuse edema and polyarthritis. Before severe articular and cutaneous involvement with refractory vasculitis, an immunoglobulin cycle was performed (120g/day) with transitory success.

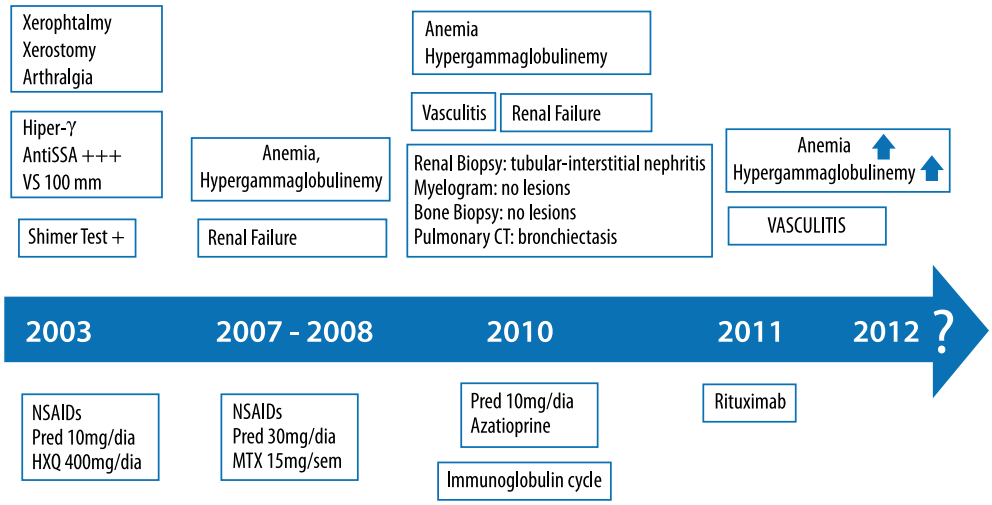
During the following months, despite improvements on articular scenario the patient maintained active vasculitis and inflammatory activity parameters of disease, dependent of high doses of prednisolone, reason why was introduced Rituximab (used in November of 2010) and maintenance therapy with MTX 12.5 mg/week.

On April 2011 the patient showed significant clinical improvement, denying pain, and without vasculitis or arthritis. There was analytically a normal CBC, ESR of 100 mm, creatinine of 1.3 mg/dl and creatinine clearance of 38 (III class) with decreasing hypergammaglobulinemy.

Summary

A 45 year-old woman, diagnosed with Sjögren Syndrome in September 2003, has sicca symptoms, 2 years of progressive arthralgia, compatible analytical alterations (positive ANA's, AntiSSA and AntiSSB; IgG hypergammaglobulinemia, increased ESR), positive Shimer's test and compatible major gland biopsy.

During 8 years the patient showed disease progression with successive symptomatic therapy adjustments (NSAIDs and pain killers) and immunomodelatory/ immunosuppressive (Prednisolone, Hydroxicloroquine, Methotrexate, Azathioprine and Immunoglobulins), with persistent inflammatory disease activity, uncontrolled and exuberant (high values of anemia, VS and PCR), and with progressive organ involvement (glandular, hematological, IG, pulmonary and vascular).



Discussion

This is a case report of primary Sjögren Syndrome because it comprises clinical and analytical evidence, and absence of other autoimmune pathology, where is obvious the glandular involvement with "sicca" and multi-organic extraglandular manifestations, namely articular, IG, hematological, vascular and renal.

There is persistency of the disease, with progressive aggravation of inflammatory parameters (anemia, CPR and high ERS) and immunological parameters (increase in antibodies antiRo-SSA, hyperglobulinemia, and complement C4 clearance values).

The initial treatment for symptomatic control, with non-steroid anti-inflammatory drugs, corticosteroids, hydroxicloroquine and latter methotrexate, as described in international guidelines, proved to be partly efficient in symptomatic control but inefficient on solving the inflammatory clinical picture and disease control [5].

The progression of the cutaneous involvement secondary to an exuberant and refractory vasculitis raised the suspicion to LNH. According to bibliography this cutaneous manifestation happens in about 10% of patients with Primary SS, being related with higher probability of extra-glandular complications including lymphoma[1].

In most patients vasculitis involves small blood vessels such as capillaries, arterioles and venules. Palpable purpura is the most common

cutaneous sign and is generally associated with the presence of anti-Ro/SSA antibodies, hyperglobulinemia and positive RF assay, as verified in this patient. In 5% of the situations injuries occur in medium blood vessels. Urticarial, papules and blot lesions are present and may evolve into small ulcers. Lower limbs are mostly affected. The association between cutaneous lesions and cryoglobulins values is well< described, and in this case these values were negative in several controls. However there are no records about prognostic value of this form of manifestation of disease.

Progression of hyperglobulinemia was registered, concerning IgG progression and lymphocyte hyper activation. The monoclonal gammophathies are present in 22%, with higher prevalence to IgG and then IgM. Generally, it is correlated with high ESR and presence of cryoglobulinemias.

In literature the triad: Sjögren Syndrome, Cryoglobulinemia and rheumatoid factor can identify patients at increased risk of developing B-cell lymphoma, described in 6 patients of an 18 patients sample, yet in another sample with 380 patients this relationship wasn't verified [1].

Nevertheless a negative rheumatoid factor after having had a positive register is suggestive of malignant transformation of B-cells [7].

Another concern in this case report is the renal involvement that progressed to renal failure class III and recently to class IV of CKD. It is known that nephropathy by SS is not frequent and when occurs indicates severity of underlying disease, generally in the form of interstitial nephritis/ tubulo-interstitial or less commonly as glomerulonephritis.

The renal context in this patient raises some questions due to prolonged use of NSAIDs for arthralgia control which may have resulted in nephropathy by NSAIDs. However the eosinophilia assay in the sediment was negative and biopsy was not consistent with this hypothesis. Given the evolution of the disease that always presented refractoriness to the instituted therapy concerning inflammatory control we can infer about the AINEs role in a constantly affected kidney by permanent inflammatory status, assuming CKD in the context of a shared responsibility.

Finally and alarmingly we are witnessing an evolution that will ultimately flourish in lymphoma. Most lymphomas present with a general malaise, hepatosplenomegaly and generalized lymphadenopathy, relating to advanced disease. There is a documented relationship between presence of lymphoma with extra-glandular manifestations (cutaneous vasculitis, CNS

involvement, among others) and the presence of monoclonal immunoglobulins and cryoglobulines in several bibliographical studies.

The development of a lymphoproliferative disease is the major complication that can emerge throughout the evolution of SS and there are also some predictive clinical factors known as the persistent parotiditis, fever, adenomegalies, monoclonal transformations, the rising of cryoglobulins as well as the detection of a B monoclonal population on salivary glands that may indicate malignant transformations.

Through literature reviews it becomes apparent predilection of lymphoma by certain solid organs: salivary glands (95%); pulmonary (23%); gastric (20%).

The possibility of lymphoma appear in any organ where is lymphoid tissue creates a variety of clinical presentation in patients with SS renal failure with hyperuricemia or hyperkalemia, neurological injury (usually high-grade lymphomas), renal or ovarian masses. From a series of 2311 patients with SS only 4% (98 patients) evolved to lymphoma after 5 years of follow up.

Some authors suggested that the existence of certain analytical alterations may be associated with higher risk of developing lymphoma, namely the significant reduction in the value of hypergammaglobulinemia, elevetated β2 microglobulin, elevated soluble IL-2 receptor and negative RF.

Chromosomal changes translating the association of SS with lymphoma have been described, namely translocations t(14:18) or t(11:14) not verified in this patient´s karyotype; and some other changes as trisomy 3; mutations of p53 gene or accumulation of O6-methylguanine-DNA in the lymphocytes.

Rituximab has been a powerful weapon in the treatment of lymphomas and has been used to treat autoimmune diseases. It was approved by FDA (Federal Drug Administration) as an additional chemotherapy drugs in rheumatoid arthritis, autoimmune thyroiditis, SLE, among others.

It's a chimeric monoclonal antibody mouse/human that specifically binds to the transmembrane antigen CD20 contained in pre-B lymphocytes and mature B-lymphocytes, but not in mother cells, pro-B cells, normal plasma cells or other normal tissues. The antigen is present in more than 95% of all B-cells from non-Hodgkin's lymphoma (NHL). After antibody binding, immunological reactions begin leading to B-cell lysis. The average count of peripheral B-cells decrease significantly below normal after the first dose, starting 6 months after their recovery and returning to normal between the

next 9 to 12 months after completion of treatment.

The first studies with anti CD20 and SS report to 2005 and covered secondary SS patients. In 2007 new studies were developed involving patients with primary SS.

A study performed in 15 patients with primary SS, 4 of whom under Rituximab treatment for lymphoma, showed B-cell depletion with glandular functional improvements; however those 4 patients with a lymphoma developed anti-rituximab antibodies [8].

The use of Rituximab opens new therapeutic perspectives, but there are still no studies that prove its long term use in patients with SS.

Conclusion

The authors exposed a case report of Sjögren Syndrome, with severe systemic manifestations and refractory to conventional therapy.

Despite the absence of other severity criteria indicating malignant transformation, there are records of patent inflammatory status with evolution of renal and hematological disease, which may respond to anti-CD20 therapy, preventing lymphoproliferative progression to B lymphoma, also achieving the control of vascular disease.

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