Systemic Autoimmune Diseases Case Report Book

Carlos Dias

EASi™
European Autoimmunity Standardisation Initiative
Portugal

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Prefaces

Preface

Dear colleague,

Medicine is, by definition, a multidisciplinary activity where interdependence of expertise, knowledge and different medical specialties is the rule. Autoimmunity is a medical area where this multidisciplinary approach is most evident, with great involvement of Internal Medicine and Rheumatology, but where virtually all other specialties have their presence as a consequence of the specific involvement of the various organs and systems, in several physiopathological situations.

On the laboratory side of autoimmunity a large number of autoantibodies, as well as other analytical parameters of relevance for these diseases, can be identified and quantified. However, in these determinations, the absence of international standardisations is the rule and not the exception. Methodologies can vary between institutions, target antigens may be different in different manufacturers, cut-off criteria and reference range definitions can also be distinct. Some parameters are only applicable under very strict clinical criteria, others are relevant particularly by their negative predictability and very few or none can be used alone as a disease marker.

For these reasons, autoimmunity is perhaps the area of medicine where the detailed knowledge of the methods employed in the laboratory is a must to the enlightened use of its results. Likewise, the interrelation with the experts in laboratory medicine is, as with experts from other medical specialties, absolutely fundamental.

João Pedro Ramos

Preface

Dear colleague,

EASI (European Autoimmunity Standardisation Initiative) is a scientific group of engaged scientists and practitioners from laboratories, clinics or authorities of the health care systems from different European countries, who are interested in collaborating to improve the diagnostics of autoimmune and rheumatic disorders.

Nowadays, it involves ten european countries, including Portugal as the most recent member, formed by three rheumatologists, three lab specialists and three internists, being myself the scientific coordinator.

EASI Portugal hás as the main immediate proposals the elaboration of guidelines on antinuclear antibodies (ANA) methodology, prescription, validation and interpretation, having been accomplished a laboratorial inquiry and a clinical inquiry to rheumatologists, later widened to others, as Internal Medicine. These studies results will be presented soon and discussed in 2010 Medinterna meeting. Beyond this objective it intends to develop other activities, as the essay of new tests, a future creation of a seroteca and an autoimmunity investigation center.

A case reports book on autoimmunity is an important objective, published each two years, compiling the cases presented and discussed in Medinterna annual meeting. This first number hás eight case reports, from Lisbon and Porto, with the most varied pathologies, like autoimmune pancreatitis, sarcoidosis, systemic lúpus erythematosus, catastrophic antiphospholipid syndrome, mixed connective tissue disease, rheumatoid arthritis, Wegener granulomatosis and polyglandular autoimmune syndrome.

This book intends to be to all interested in autoimmunity a study and work tool, specially to residents. Each edition will coincide with the international autoimmunity congress, every two years, where it will be distributed without charge to all participants, as well in Medinterna meeting.

We sincerely hope, with this EASI Portugal initiative, to contibute to a increasing interest and study in the autoimmune diseases.

Carlos Dias

Contents

Case Report 1

Catastrophic antiphospholipid syndrome

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Abstract

Catastrophic antiphospholipid syndrome (CAPS) is a rare variant of APS defined as acute failure of at least three tissues, organs or systems caused predominantly by small vessel thrombosis confirmed by histopathologic evidence. CAPS develops rapidly and leads to death in 50% of cases. The most striking precipitating factor of CAPS is infection. We report a case of a 35 year-old caucasian woman with a 35 weeks of monochorionic biamniotic twin pregnancy who developed a probable CAPS after a respiratory tract infection. At admission she was sleepy, with lentified speech and mild confusion. The laboratorial tests revealed: hepatic failure, acute renal failure and coagulopathy. The results of laboratorial immunological tests revealed elevated IgG anticardiolipin and hipocomplementemia. After hemostatic therapy, urgent caesarian section was performed and two live males were born with Apgar scores of 6/9 and 7/9. The patient was admitted in an Intensive Care Unit. Supportive transfusional therapy with packed red blood cell, platelets, fresh frozen plasma and antithrombin III was given. Intravenous immunoglobulin and steroid therapy was started. In addition, plasma exchange was performed. Despite all therapeutic measures there was a progressive clinical and laboratorial deterioration with death of the patient.

Introduction

Catastrophic antiphospholipid syndrome (CAPS) is characterised by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, with laboratory confirmation of the presence of antiphospholipid antibodies.[1] As a result of CAPS, many organs can be

affected, including the skin, lungs, brain, heart, kidneys, and intestine.

The most striking precipitating factor of the CAPS is infection, ranging from upper respiratory tract infections to gastrointestinal or urinary tract infections. The second most frequent precipitating factor is surgery and other invasive procedures. Fewer cases were associated with drug treatment, obstetric complications, Lupus flares, or withdrawal of anticoagulants.

Differential diagnosis with other microangiopathic syndromes that are capable of producing multiorgan thrombotic events such as, thrombotic thrombocytopenic purpura/haemolytic-uraemic syndrome and HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, must be made.[2]

We report a case of a 35 year-old caucasian woman with a 35 weeks of monochorionic biamniotic twin pregnancy who died from a probable CAPS after a respiratory tract infection.

Case report

A 35 year-old caucasian woman with a 35 weeks of monochorionic biamniotic twin pregnancy presented in our emergency department with asthenia, sleepiness and lentified speech. She was a Gesta 2 Para1, with personal history of normofunctional thyroid nodule. Her first pregnancy took place 3 years before and was uneventful. A caesarian section was performed at term during labor due to intrapartum fever and suspicion of chorioamniotitis. As fever maintained during puerperium and leucopenia was diagnosed, she underwent a a complete work-up, including immunological tests and bone marrow study and she was finally given the diagnosis of idiopathic neutropenia.

The present pregnancy was planned and referred to our outpatient clinic at 7 weeks due to previous history of neutropenia. A diagnosis of monochorionic biamniotic twin pregnancy was made and developed normally, without restriction or discordances of fetal growth or hemodynamic placental abnormalities. Folic acid, iron and magnesium oral supplements were given. She was dismissed from her work as a nurse due to the infectious risk secondary to neutropenia. Gestational diabetes was diagnosed at 24th week and treated with insulin. Mild asthenia developed in the last trimester.

Routine laboratorial analyses were normal, including coagulation tests. A mielogram was also performed and revealed erythroid hyperplasia without excess of blasts.

A week prior to admission (at 34th week pregnancy) she presented with respiratory infection and was treated with amoxicillin. Blood count showed anemia of 10.4 g/dL, leucopenia (2.4 x 109/L, 30% neutrophils, 50% lymphocytes), normal platelet count. Electrolytes, creatinine, urea, liver enzymes levels were normal. Alcaline phospatase and Gama-glutamiltransferase were mildly elevated (between expected ranges during pregnancy). A mielogram was also preformed and revealed erytrroid hyperplasia without excess of blasts.

At admission, the patient was confused. She had icteric skin and mucosa, facial vitiligo (formerly known) and cyanotic ears, without any ecchimosys or pethequiae. Blood pressure was 136/94 mmHg, pulse of 117 bpm, auricular temperature 36,9ºC, eupneic, pulmonary and cardiac auscultations were normal. She had moderate edema of the lower limbs. Laboratorial tests revealed: Hemoglobin-14.1 g/dL, WBC-3.19x109/L (N-35%), PLT-159x109/L, hepatic failure (Total proteins-48.4 g/L; albumin-23 g/L; Bilirrubin total/direct-55.1/33.1 g/L; AST/ALT-115/151 g/L) and acute renal failure (creatinine-2,2 mg/dL). Urinalysis showed mild proteinuria (0.3g/L) and mild erithrocyturia (37,2/uL). Coagulation tests (done 8 hours after admission) showed severe compromise of coagulation (Antithrombin III-0.07 U/mL; APTT-99.1 sec; Prothrombin T-37.7 sec; Fibrinogen <10 mg/dL; d-dimer-156 ug/mL), suggesting a coagulopathy intravascular disseminated. The patient was admitted without a clear diagnosis and termination of pregnancy was decided. After hemostatic therapy (with packed red blood cell, platelets, fresh frozen plasma and antithrombin III), a caesarian section was performed and two live males were born with Apgar scores of 6/9 and 7/9. The operation was uneventful, apart from mild to moderate bleeding.

The patient was admitted in an Intensive Care Unit, drowsy but responsive to verbal stimuli and in spontaneous breathing. Six hours post-surgery, due to confusional state, a cerebral computed tomography scan was performed and was normal. The electroencephalography showed no specific neurologic abnormalities. She spontaneously recovered the state of consciousness. Twenty-four hours post- caesarian section she developed olyguria and mild hypertension. An abdominal ultrasound was performed (to

rule out hepatic hematoma as a complication of an hypothetic pre-eclampsia) and revealed moderate ascitis and left pleural effusion; there was no evidence of sub capsular hematoma nor hepatic or splenic abnormalities. At day 3 she became again confused and was submitted to another cerebral computed tomography scan that revealed blood in the left ventricle and left thalamic intraparenquimatous hematoma. Due to these findings mechanical ventilatory support was started. Supportive transfusional therapy with packed red blood cell and platelets, fresh plasma and antithrombin III kept being administrated. The data of immunologic tests, taken before any transfusional therapy, revealed mildly elevated IgG anticardiolipin (22.2 GPL), mild hipocomplementemia (C3c- 73 mg/dL) and anti-Ro antibody was "borderline". On account of these findings, after a multidisciplinary conference, supposing an antiphospholid syndrome, intravenous immunoglobulin was administered and steroid therapy (dexametasone pulses) were started and later plasma exchange was decided. This last procedure was complicated by an haemoperitoneum. Angiography was performed and revealed an active bleeding from external iliac artery that was successfully embolized. Based on the suspicion of active bleeding and maintenance of active haemoperitoneum, angiography was repeated the next day but didn't demonstrate any active bleeding.

Despite all therapeutic measures, there was progressive clinical and laboratorial deterioration with death of the patient at day 10.

Autopsy revealed extensive thrombi in pulmonary capillaries with alveolar hemorrhage and edema (fig1), renal tubular necroses (fig2), myocardial hemorrhage (fig3), cerebral intraventricular hemorrhage (fig4). Hepatic autopsy was inconclusive because of high grade of autolysis (fig 5).

Lungs

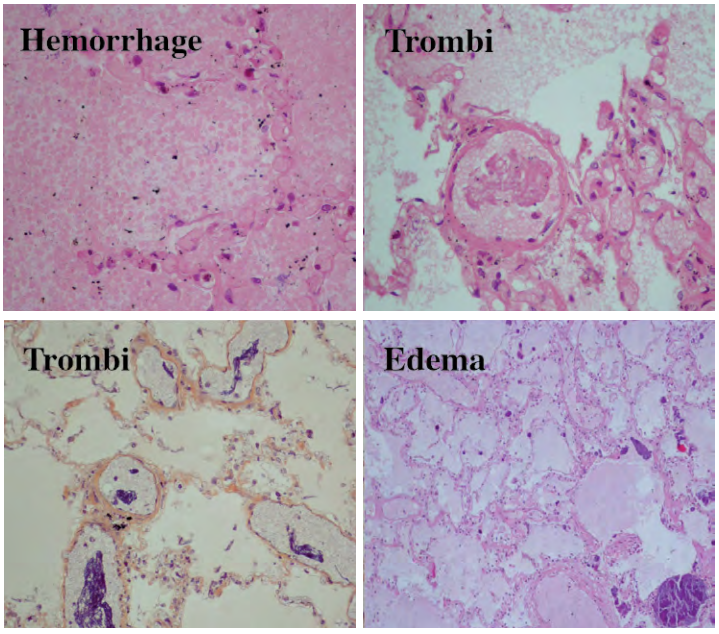

Fig. 1

Kidneys

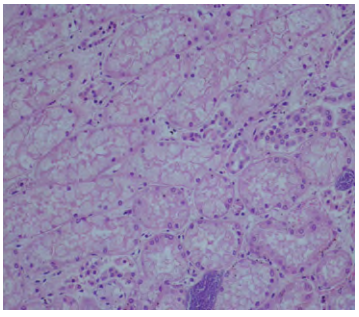

Fig. 2

Myocardium

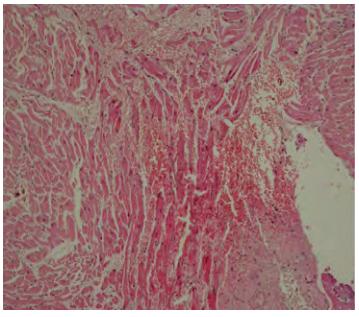

Fig. 3

Brain

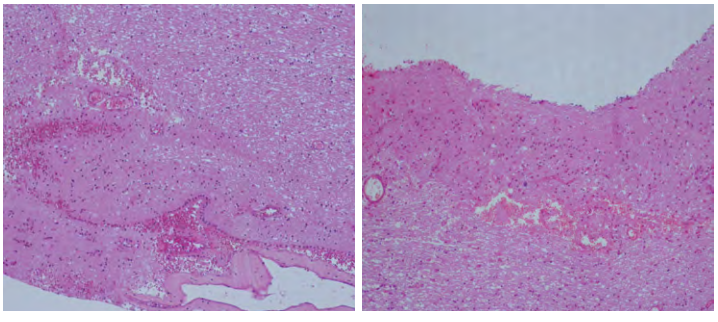

Fig. 4

Liver

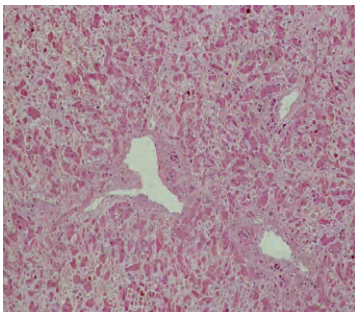

Fig. 5

Discussion

Proposed diagnostic criteria for CAPS are: 1) evidence of involvement of three or more organs, systems and/or tissues; 2) development of manifestation simultaneously or within a week; 3) confirmation of a small vessel occlusion in at least one organ or tissue and 4) laboratory confirmation of the presence of antiphospholipid antibodies. Patients are considered to have definitive CAPS if they fulfil all four diagnostic criteria. Patients are considered to have probable CAPS if they meet all four criteria but only have involvement of two organs or systems or only a single positive determination for antiphospholipid antibodies, or if they meet the first and last criteria , but only one of the two middle criteria.[6]

In our case, the patient presented with central nervous system involvement, hepatic involvement, severe coagulopathy, acute renal failure, and pulmonary involvement. Immunologic tests revealed elevated IgG anticardiolipin, hipocomplementemia and anti-Ro antibody was “borderline”. Autopsy revealed extensive trombi in pulmonary capillaries with alveolar hemmorrhage and edema. These findings suggest a diagnosis of probable CAPS because the patient had only a single positive determination for antiphospholipid antibodies (she died before confirmation).

The other microangiopathic syndromes, as well as pre-eclampsia and its possible complications, like HELLP syndrome, were excluded as there was no evidence of haemolysis or thrombocytopenia. In addition, lactic

desydrogenase levels were normal.

The clinical approach of catastrophic APS includes the treatment of any precipitating factor, especially adequate antibiotic therapy for related infections based on the clinical setting, appropriate anticoagulant management and the use of immunosuppressive drugs (especially steroids), plus third line therapy (plasma exchange or intravenous immunoglubulins) for the treatment of the thrombotic and cytokine "storm".[2] Finally, a series of life support measures are needed, such as mechanical ventilation inotropic drugs, and renal supportive therapy.[3]

Our patient was treated with amoxicillin for a respiratory infection one week prior to admission and pregnancy was terminated. Anticoagulant management was not preformed, on a multidisciplinary conference, because the patient presented with active bleeding. Supportive transfusional therapy, plasma exchange, intravenous immunoglobulin and steroid therapy were performed. Despite all therapeutic measures there was progressive clinical and laboratorial deterioration with death of the patient.

This case emphasises that CAPS may present without previous diagnosis of APS and no history of miscarriages or thrombotic events. It is important to maintain a high degree of suspicion of APS in critically unwell patients, particularly with known precipitating factors for CAPS. Early anticoagulation and immunosuppression treatment may give the best chance of improving the 50% mortality rate of the condition.

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Expert Commentary:

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"This is a very interesting case report of a patient with confirmed catastrophic antiphospholipid syndrome".

Case Report 2

Severe multisystemic sarcoidosis

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Abstract

Sarcoidosis is a systemic granulomatous disease usually benign. However, in some cases, it may present as a multisystemic severe lung, CNS, skin, endocrine and other system involvement. The differential diagnosis with other pathologies, particularly with tuberculosis, becomes imperative.

We present the case of a 36 years-old male patient diagnosed with Sarcoidosis since 2000 when he was 30 years. The multisystemic involvement was documented in 2006. Despite all the established immunosuppressive therapy, active disease had evolved. In April 2009 he was admitted with an episode of hyperthermia, without any other complains. A few days later, in UIC, it was documented infection with Mycobacterium tuberculosis with very fast evolution to multyorganic failure despite specific therapy, resulting on the death of the patient.

Introduction

Sarcoidosis is a multisystemic disease characterized histologically by the presence of non-caseating epithelioid granulomas in the affected tissue.

Its etiology is unknown [1]. The high frequency of involvement of lung and intrathoracic lymph nodes raises the possibility of an inhaled causal agent. Several environmental factors have been implicated in the aetiology of the disease by reports of higher incidence in dusty environments and a higher incidence during spring. The ACCESS study, the largest study of sarcoidosis, showed no environmental or occupational agents. Weak associations were found for the use of pesticides in the workplace and exposure to fungi, which suggested a possible microbial aetiology. This study confirmed, also a negative relationship between disease and smoking.

Several authors have linked the disease with an infectious aetiology, based on their similarities in many aspects with tuberculosis. Japanese studies found genomes of Propyonibacterium acnis and granulosum. High titers of antiviral antibodies have been found, which seems to reflect activation of B-cell. The infectious aetiology is supported by the apparent transmission of disease by bone marrow transplantation or transplantation of the heart. Important information to enhance the aetiology of the disease was the observation made in 1940 by A. Kveim. The intradermal injection of sarcoid tissue resulted in a reaction with production of nodular granulomas typical of sarcoidosis after 2-4 weeks.

The demonstration of an infectious agent needs to prove, but many researchers support that certain species of microorganisms can trigger sarcoidosis in individuals with genetic susceptibility. Also, the autoimmunity is unknown, because there are no disease-specific autoantibodies.

However, it is a disease related to activated T lymphocytes. Briefly, there is a systemic accumulation of activated T cells, predominantly expressing the phenotype CD4 and macrophages. The immunopathological final event is the formation of granulomas in response to a specific stimulus that induces a local response mediated by Th1 type T cells, which, by being persistent, results in chronic stimulation of macrophages, which release inflammatory mediators contributing to the maintenance of formation of granuloma. The persistent Th1 response has been associated with fibrosis,usual in sarcoidosis, while a shift to Th2 has been associated with resolution of the granuloma, with or without fibrosis [2]. The histological mark of sarcoidosis is the presence of non-caseating granulomas. The epithelioid cell is the dominant cell believed to be a form of differentiated mononuclear phagocytes. CD4 lymphocytes and macrophages are mature mixed epithelioid in the center, while CD4 and CD8 lymphocytes appear at the periphery of the granuloma. In the lung, granulomas tend to form over areas rich in lymphatic vessels and bronchial submucosa, subpleural and interlobular septal regions, the wall of bronchi and alveoli. Studies have shown increased CD4 lymphocytes in bronchoalveolar lavage.

The prevalence of the disease is estimated at 20-50 per 100,000 of people in Caucasians [3]. It is highest in Scandinavian populations, especially in the form of Lofgren's syndrome, and african-american, with higher incidence of lupus pernio. There is a slight predominance in females. All ages are affected,

but over 80% of cases occur between 20 and 50 years of age. Sarcoidosis is a direct cause of death in <1-6% of cases, usually by pulmonary, cardiac or neurological involvement.

There is substantial evidence for genetic predisposition in sarcoidosis. It occurs in several members of the family in about 5-10% of cases. In the ACCESS study, which compared 706 cases with histological diagnosis of sarcoidosis, was found a higher incidence in twins, and increased susceptibility in Caucasians. The gene HLA-DR3 is associated with increased risk of sarcoidosis in the European population, whereas HLA-DR4 and DR1 are related to the type of presentation of the disease. Some of HLA alleles are also associated with the course more or less benign and with the involvement of certain organs. An American study, SAGA, found no relationship to chromosome 6, in contrast to another study of Germany, probably justified by the mixture of Afro-Americans.

The Sarcoidosis manifests itself in most cases by respiratory symptoms such as dry cough in 30% of cases, extrathoracic locations, mainly peripheral adenopathies, ocular involvement, fatigue in 27% cases, weight loss in 28% cases, fever in 10-17%, nocturnal hipersudoresis and erythema nodosum in 3-44% of cases. The erythema nodosum, usually associated with intrathoracic lymphadenopathies, defines the Lofgren's syndrome, an acute form of presentation of sarcoidosis.

The neurological involvement is a more aggressive form of involvement, but the neurosarcoidosis a rare entity. Retrospective studies have shown the incidence of neurological involvement in cases of systemic sarcoidosis around 5% [5]. The most common presentation is cranial neuropathy with unilateral or bilateral paralysis of the seventh pair (Bell's palsy) and, less frequently, other cranial nerves. This paralysis can resolve with steroids, but usually relapse later. The optical nevritis can result in blurred vision, visual field defects and blindness. The manifestations of the central nervous system can cause masses, aseptic meningitis, hydrocephalus, and pituitary-hypothalamic dysfunction. Seizures, headaches, changes in behaviour, confusion and insipidus diabetes may arise. The compression of the spinal cord is rare, but paraparesis, hemiparesis and leg pain have been described. Peripheral neuropathies may occur in 15% of neurosarcoidosis, as mononeuritis multiplex or primary sensory neuropathy.

The disease can involve other organs, as salivary and lacrimal glands,

with gland enlargement, Sicca syndrome and Heerfordt Syndrome. It may hit bone, joint, liver, with elevated liver enzymes, and cardiac involvement in 5 to 10% of patients. The ocular involvement with unilateral or bilateral anterior uveitis is frequent and often associated with bilateral hilar adenopathy. A chronic uveitis occurs in about 20% of patients with chronic disease. Other less frequent involvement may occur as the achievement of the skin with subcutaneous nodules, erythema nodosum and lupus pernio.

The natural history of disease is variable [6]. Spontaneous resolution occurs in approximately 5 years at 2 / 3 of patients [7]. In a follow-up of a period of 2 years in the ACCESS study, 80% showed improvement or stabilization with no need for treatment [8]. Epidemiological studies have shown that about 5.4% to 10% of cases present with pulmonary fibrosis in early disease. The pulmonary fibrosis carries a mortality rate of 1 to 5% [3]. The most common radiological findings of sarcoidosis include bilateral hilar and mediastinal lymphadenopathy and bilateral nodular infiltrates or reticulonodular.

The diagnosis of sarcoidosis is a diagnosis of exclusion. It is important to differentiate between sarcoidosis and tuberculosis, particularly signs and symptoms of active tuberculosis and progression of the sarcoidosis. It is important to exclude other diseases such as chronic beryllium disease, lymphoma and fungal disease. The diagnosis of sarcoidosis is based on a series of clinical, imaging studies, serological and cerebrospinal fluid and, finally, in the biopsy. The histological confirmation is essential. The local to biopsy is variable and results from the clinical presentation. But it is possible in the lung parenchyma, skin, lips or mediastinal or peripherical lymph nodes. The demonstration of non-caseating granulomas is primordial for diagnosis, though not pathognomonic, as they may arise in normal ganglia and in some tumors. It is important in all patients, to make a chest x-ray, blood tests and kidney function, liver enzymes, serum calcium, ecocardiogram and observation by ophthalmology with slit lamp. Other tests may be useful in the diagnosis of sarcoidosis, such as pulmonary function tests, gallium 67 cintilogram and examination of positron tomography (PET).

Currently the disease staging is based on the radiological presentation of pulmonary involvement (Table I) proposed by Wurm in 1958. The manifestations of radiological intrathoracic involvement are defined by 5 stages (Table I).

Table I

Stage	Features
0	Normal chest Teleradiography
I	Bilateral Hilar lymphadenopathy
II	Bilateral Hilar lymphadenopathy and Pulmonary infiltrates
III	Pulmonary infiltrates
IV	Pulmonary fibrosis

Staging of sarcoidosis based on radiographic findings

The steroids are the main treatment of serious disease or progressive pulmonary or extrapulmonary. They provide a symptomatic relief and may reverse the acute organic disease in more than 90% of patients with symptomatic disease. There is some controversy about the ability of steroids to stop the disease, but there is consensus on the benefits in the initial treatment of acute disease.

There are no consensus recommendations for the treatment of sarcoidosis. It is known, however, that the steroids have the benefit on acute lung granulomas. The recommended treatment is to 20-40 mg / day of prednisone, for 2 to 4 weeks with gradual reduction to a maintenance dose of 5 to 15 mg / day, sometimes on alternate days, for 8 to 12 months. It seems to benefit of initial therapy in cases of symptomatic patients with evidence of lung functional deterioration and radiologic or with extrathoracic involvement. Patients with asymptomatic pulmonary involvement only, usually require no treatment. There is recurrence of the disease in 16 to 74% of cases when therapy is stopped. Inhaled corticosteroids may be used when there is involvement of the upper respiratory tract.

In the specific case of neurosarcoidosis the prednisone dose is superior and in severe cases high doses of intravenous methylprednisolone are necessary. In cases with contraindicated or ineffective corticosteroid therapy, cytotoxic agents such as methotrexate, azathioprine, cyclosporin or cyclophosphamide are suggested [4]. Some recent studies show beneficial results, in selected cases, with infliximab and are based on the role of tumor necrosis factor (TNF) in the formation of granulomas at experimental models. A study with infliximab showed a modest benefit and improved forced vital capacity after 24 weeks.

There are few cases of benefit with adalimumab. The etanercept proved to be ineffective in a small study.

The development of granulomas or fibrosis and its resolution is unpredictable, since the disease has a large variability. It is reported that 60% of patients have spontaneous remission, both radiological and clinical. In 2 years, 20% resolves with treatment and 10 to 20% occurring on corticotherapy. Poor prognosis is registered in afro-american population, cases of initial presentation, particularly insidious, with multiple extrapulmonary lesions, radiographic stages III and IV and low CD4/CD8 ratio (<3.5).

Case report

Male, 36 years-old, healthy until 30 years, which after excision of a cervical adenomegaly for esthetical reasons had the diagnosis of sarcoidosis. At that time he also had Lofgren´s syndrome with erythema nodosum, fever and bilateral thoracic adenopathies.

The patient reported at the time an episode of Bell's palsy resolving with non steroid anti-inflammatories. He denied any respiratory symptoms. He was observed by Internal Medicine and treated with prednisolone 40 mg / day in a reducing gradually dose but we don't know the initial dose, because he was initially accompanied in another hospital. He also initiated methotrexate 15 mg / week in that hospital.

The chest x-ray was compatible with stage II sarcoidosis.

Despite the treatment he remained with complains of purulent rhinorrhea and nasal obstruction until 2006. At this year the patient had three admissions, the first in January 2006 by sepsis associated with cellulitis of the right leg, treated with vancomycin 1 g and ceftriaxone 1g with resolution in 7 days. In the same hospital, he presented with dyspnoea for small efforts, persistence of mucopurulent rhinorrhoea, seizures, parotid swelling and sarcoid nodules. So, it was decided to do a new staging of the disease on imaging studies.

In the endocrine studies we noted a decrease of gonadotrophins, hyperprolactinemia and euthyroidal hipotiroxinemia (Table II).

He initiated bromocriptine 1.5mg/day and testosterone, which dosis is unknown.

He performed the following imaging tests:

Table II - Endocrinological study

	Reference values	Results
FSH	1.1-13.6 mUI/mL	0.49 ↓
LH	1.1-8.8 mUI/mL	<0.07 ↓
TSH	0.35-4.94 UI/mL	1.20
Thyroglobulin	0.0-55 ng/mL	14.40
Free T3	1.71-3.71 pg/mL	1.68 ↓
Free T4	0.70-1.48 ng/dL	0.84
Prolactin	2.6-18.1 ng/mL	69.1 ↑
Total testosterone	1.7-8.4 ng/mL	1.54 ↓
PTH	10-65 pg/mL	61.4
ECA	< 52 U/L	14
Estriol	> 11-44 pg/mL	51.4
DHEA-S	80-560 g/dL	7.0 ↓
Free cortisol (urine)	36-137 g/dia	29.7 ↓
ACTH	< 46pg/mL	24.7

CT and MRI brain – nodular lesions temporal with contrast captation in the right side attributed to neurosarcoidosis lesions with other areas of collection of contrast adjacent to the III ventricle (Figure 1), the cerebellum and the level of callosum corpus and cerebral peduncles.

Thoracic CT (Figure 2) – nodularities forming bronchovascular pseudomasses in the pleura and subpleural gap, hilar and mediastinal nodal formations bilaterally and increased size of 41mm of the pulmonary artery trunk, which suggests pulmonary hypertension.

CT perinasal sinus – diffuse thickening of the lining mucosa and marked reduction of permeability.

MRI hands – thickening tissue, which preferentially evoke an infiltrative / inflammatory type of synovitis.

Abdominal CT scan – hepatomegaly by infiltration with diffuse steatosis.

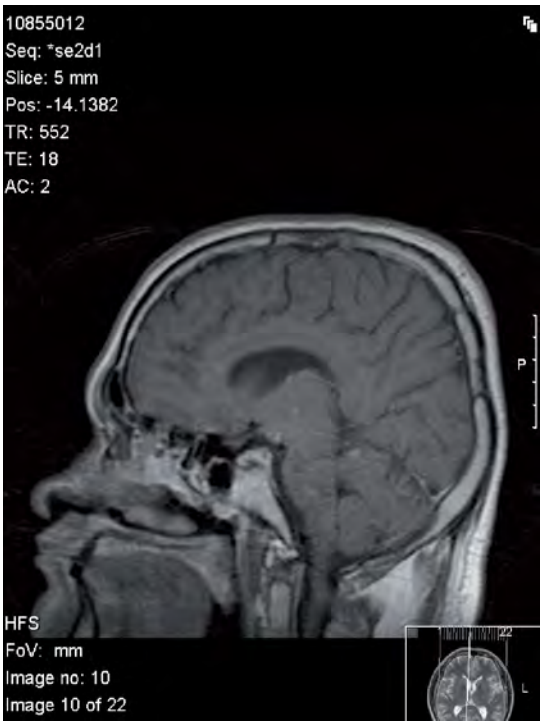
Tilt Test – vagal dysautonomia.

Respiratory function tests – restrictive ventilatory syndrome.

In 2006 he had another two admissions by respiratory infection and acute CMV infection.

In April 2007 owing to maintain activity of the disease he stopped methotrexate and initiated oral cyclophosphamide. In December 2007 the disease remained in an active form and refractory to therapy with maintenance of the framework of neurosarcoidosis, dyspnoea for medium and small efforts, purulent rhinorrhea. It was decided to start anti-TNF alpha (Infliximab).

Fig 1 - **MRI Brain**

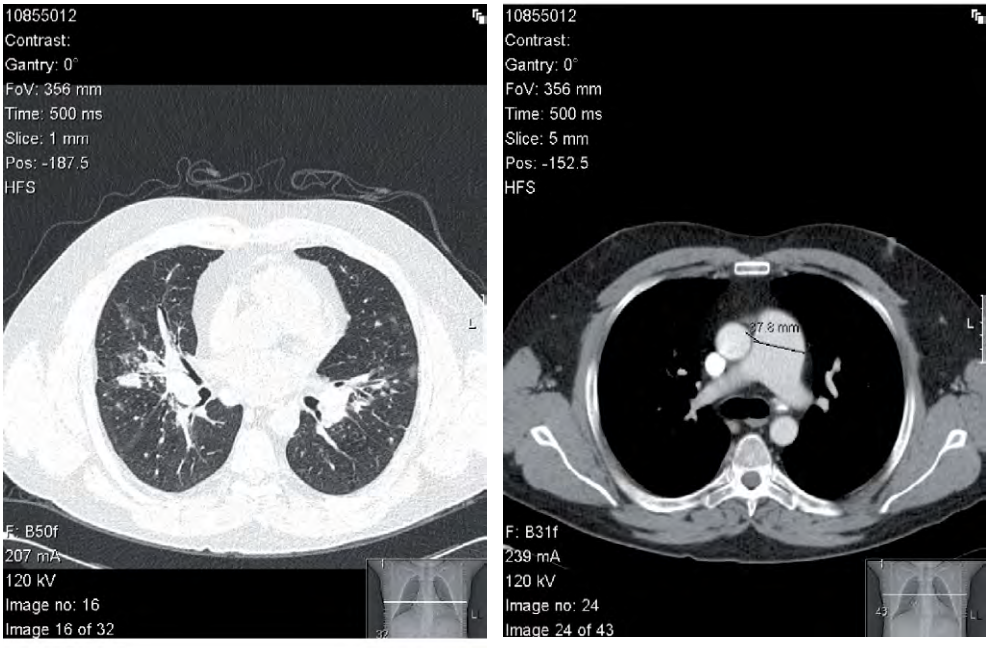


Later there were other hospitalizations: one in April 2008 due to erysipela of the right leg and another in May 2008 for cellulitis of the right leg.

Despite therapy with Infliximab the symptoms of easy fatigue, subcutaneous nodules, dyspnoea with exertion and lupus pernio remained.

In January 2009, the patient stopped all therapy on his own initiative, maintaining only the Infliximab. In the last administration of infliximab, at March 2009, probably, he was in a febrile syndrome, but he had however obscured this fact.

Fig 2 - **TC Torax**



At the end of March 2009, he was admitted for persistent high fever, without any other complaints. It was excluded any infection. The chest teleradiography showed no new changes. The clinical picture was interpreted as activation of the disease and restarted the corticotherapy with 60 mg / day, with fever resolution and he left apiretical.

At home, it occurred new episodes of fever and he was admitted again for hyperthermia at the end of April 2009. On admission he had temperature of 39.8 º C, was conscious, cooperative, oriented in time and space, and normotensive and normocardical. Lung examination showed crackles in pulmonary bases. In blood tests was observed type 1 respiratory failure and oxygen therapy was instituted.

In the 2nd day of admission was observed worsening of their clinical condition with severe difficulty breathing. Radiological opacities were noted in both lung fields from the apex to the pulmonary base. He was transferred to the Intensive Care Unit (ICU) where he began invasive mechanical ventilation and broad-spectrum antibiotics for possible bacterial nosocomial infection with linezolid + meropenem + sulfamethoxazole + trimethoprim and azithromycin. On suspicion of tuberculosis initiated isoniazid + rifampicin + pyrazinamide + ethambutol. At the 4th day of hospitalization were observed MT bacillis on bronchial secretions. He suffered hemodynamic instability with sustained hypotension although sympathomimetic amines support. During the treatment he also showed liver and kidney dysfunction. It was decided to initiate continuous dialysis technique. The patient developed persistent acidosis with lactacidemia and maintained high continuous vasopressor support. Radiologically there was a progressive worsening bilateral infiltrates, with a picture of ARDS, as shown in Figures 3 and 4.

Fig 3 - **Chest x-Ray**

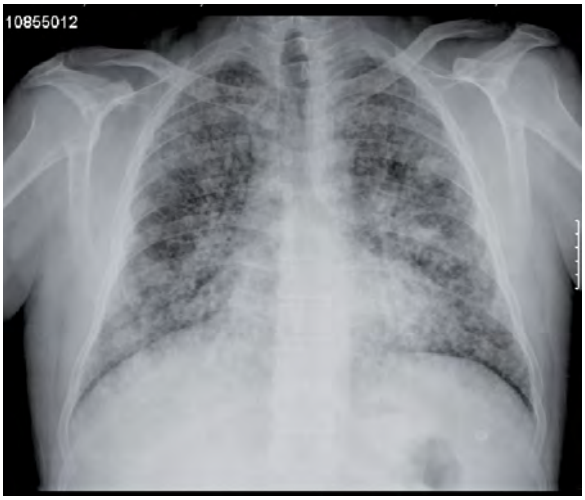
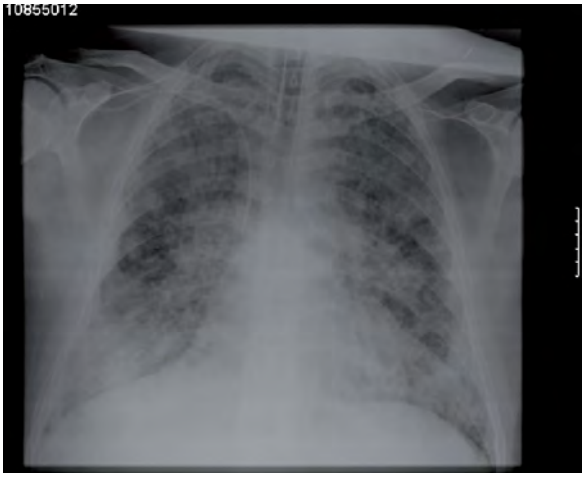


Fig. 4 - **Chest x-Ray, Day 3 at UCI**



The patient died at 6th day of hospitalization. No autopsy was performed.

Discussion

The history of Sarcoidosis dates back to 1899, when the Norwegian dermatologist Caesar Boeck, used the term to describe skin nodules characterized by involvement of epithelioid cells with large pale nuclei and giant cells, initially designated as multiple benign skin lesions [9].

Sarcoidosis is a multisystemic granulomatous disease that may involve several systems and organs, like lungs, skin, CNS, osteoarticular apparatus, gastro-intestinal tract and eyes. Particularly in the case described, the patient has pulmonary sarcoidosis with stage IV and pulmonary hypertension described in CT chest with pulmonary fibrosis and increased size of the pulmonary artery trunk. He also suffered from a restrictive ventilatory syndrome reported in pulmonary function tests and neurological achievment with hypogonadism secondary to hypothalamic granulomatous involvement, hyperprolactinemia, autonomic neuropathy, euthyroidal hipotiroxinemia and dermatological hit with lupus pernio, sarcoid nodules and erythema nodosum. It was also observed sarcoid arthropathy in the form of chronic arthritis with tenosynovitis of the flexor side of the metacarpals and a cyst on

5th right metacarpal and Lofgren's syndrome. The patient also had chronic rhinosinusitis with otorhinolaryngological achievement. In addition to the severe multisystemic involvement of sarcoidosis the patient also had adrenal insufficiency secondary to an iatrogenic Cushing, with marked osteopenia, abnormal anthropometric and mellitus diabetes 2; macrovesicular hepatic steatosis secondary to chronic disease and iatrogenic (steroid and methotrexate) and finally a metabolic syndrome with abdominal obesity, hypertension, hypertriglyceridemia and hyperglycemia.

He was initially treated with steroids and methotrexate followed by cyclophosphamide and, finally, infliximab. The last administration of Infliximab was done in March 2009. At this time he had, however, hided it.

The patient was hospitalized in April 2009 due to hyperthermia that was initially interpreted as central termoregulator disfunction. He did septic screening and chest X-ray. Radiologically there were nodular infiltrates in both lung fields. Due to difficulty breathing syndrome he was admitted to the UCI where invasive mechanical ventilation was initiated associated with broad-spectrum antibiotic, tuberculostatic and sympathomimetic amines support. Although all the therapeutical measures perfomed, the patient developed multiorganic failure and died at 6th day of hospitalization.

About 5% of patients with sarcoidosis have clinical involvement of the nervous system, although the incidence of subclinical neurosarcoidosis being much higher. The hypothalamus is the endocrine gland most commonly involved. The sarcoidosis and other granulomatous diseases lead to an infiltration of the hypothalamic-pituitary, manifested by morbid obesity, dysregulation of body temperature, changes in behaviour, syndrome of inappropriate secretion of antidiuretic hormone, hyperprolactinemia, insipidus diabetes, hipoadrenalism and hypothyroidism [10]. Some of these features were presented in our patient.

The corticosteroid is the standard treatment. However there are adjuvant therapies with anti-malarial agents, cytotoxic agents and anti-TNF-alpha. Increasing evidence suggest that TNF-alpha has an important role in the inflammatory cascade triggered by the disease. Recent observations suggest a favorable response in cases of refractory systemic sarcoidosis with the use of infliximab, monoclonal antibody directed against TNF-alpha,[11] with immunosuppressive activity. Patients under treatment with infliximab, however, have an increased risk of developing lymphomas, viral infections

and others such as tuberculosis, histoplasmosis, coccidioidomycosis and cryptococcal infections. Of particular interest and concern is the association with increased reactivation of tuberculosis [12]. It is essential the differential diagnosis between the exacerbation of sarcoidosis itself and possible association with concomitant presence of tuberculosis.

In our case the use of infliximab when he was hiding a febrile syndrome had contributed to the fatal outcome, because he had concomitantly with the active disease an infection by Mycobacterium tuberculosis contributed to the spread of it.

Conclusion

The case described illustrates that although sarcoidosis had usually a benign course, there are cases where it occurs in a multisystemic severe form.

This case also demonstrates the importance of high index of suspicion and the differential diagnosis between sarcoidosis and tuberculosis, so in the past was considered as one of the etiologies of sarcoidosis. The treatment with infliximab, probably, contributed to the development of active and aggressive tuberculosis and the evolution to multiorganic failure.

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Comment

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Sarcoidosis is a disease which, most of the times, does not lead directly to death.

In this case, death was also not caused directly by Sarcoidosis. Nevertheless, the patient had, since the beginning, signs and symptoms of a more serious illness and never had a real remission. So, second-line medications had to be prescribed and infliximab may have reactivated a past tuberculosis infection not known or reported by the patient, as the authors say.

The indication for treatment with an anti-TNF alpha in this case may be controversial, but the disease was severe and all other medications had not led to remission, besides there are some reported cases of Sardoidosis with favorable response to infliximab.

It is interesting to point out that, this case, illustrates well the multisystemic features of this disease and the need for a broad approach in what concerns diagnosis and treatment, as it was done by Internal Medicine

specialists.

It is also important to realize that, although regarded as a benign condition, in some cases Sarcoidoisis can have a severe multiorganic involvement and so, more studies on the etiology and pathogenesis of the disease are needed so that we can predict earlier its prognosis and have more consistent therapies.

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This report exemplifies a very complex clinical case of sarcoidosis, with multisystem involvement, particularly with significant neurological, cutaneous and thoracic clinical features. Although a clinical presentation with erythema nodosum usually associated with a good prognosis, the patient had progress to a chronic form of the disease. Furthermore, the clinical case describes and motivates the discussion about some of the therapeutic agents used in sarcoidosis. From all data about this patient I'd like to focus my comments on three following details.

Patients with erythema nodosum (EN) tend to be young, female and have an acute onset of sarcoidosis with arthritis or arthralgia of the ankles and early stage pulmonary disease, usually bilateral hilar lymphadenopathy although lung infiltrates are occasionally present. This condition was originally described by Löfgren in 1952 and constitutes a different form of sarcoidosis with a distinct and characteristic clinical presentation. A genetic association with a particular CCR2 haplotype and HLA DRB1*03 has been described. Usually, the patients with EN have self-limiting disease and spontaneous remission occur during the first two years after the diagnosis. However in a small number of patients, the disease may remain active or recur long after its onset. Recently Johan Grunewald and colleagues described a clinical implication of HLA DRB1*03 in the disease course, with almost every DRB1*03-positive patients having disease remission within 2 years, but 49% of the DRB1*03-negative patients developed a chronic form of the disease, suggesting DRB1*03 as a potential prognostic marker.

Neurological involvement by sarcoidosis is relatively rare occurring in less than 10% of patients. Any portion of the central or peripheral nervous system can be affected, so signs and symptoms are variable, depending on

location and size of granulomas. However neurosarcoidosis has a predilection for the base of the brain and cranial neuropathies are the most common manifestation. Peripheral seventh nerve palsy (Bell's palsy) is the single most common cranial nerve lesion and this was also one of the first manifestations of the disease in this patient. Other neurological manifestation occurred during the course of disease was tonic-clonic seizures. This usually indicates a progressive or relapsing clinical course and a poor prognosis. Less frequently granulomatous lesions are found in the hypothalamus and/or pituitary gland and may cause several endocrine manifestations such as diabetes insipidus, adenopituitary failure, amenorrhoea-galactorrhoea syndrome or hypothalamic hypothyroidism isolated or in various combinations. This patient had hypogonadism, hyperprolactinemia and hypothyroidism which were refractory to the prescribed therapeutics causing persistent symptoms and related depression and lack of self esteem.

There are several reports in literature showing anti-TNF therapeutic efficacy for diverse manifestations of sarcoidosis. Despite some records related with etanercept and adalimumab, most of data is addressed to infliximab. Moreover two double blind randomized trials have been published showing benefit for infliximab in chronic pulmonary sarcoidosis. Failure response to conventional therapy or the presence of intolerable side effects from steroids are the main indications to prescribe anti-TNF agents and these both features were present in this clinical case. In addition, all three anti-TNF agents are associated with increased risks for opportunistic infections, especially tuberculosis, with higher risk for infliximab. Screening for prior tuberculosis infection is absolutely required previous to anti-TNF therapy administration. The Portuguese Society of Rheumatology and the Portuguese Society of Pulmonology have update in 2008 guidelines for the diagnosis and treatment of latent tuberculosis infection (LTBI) and active tuberculosis in patients that are candidates to this therapy. A detailed history, tuberculin skin testing and chest x-ray is mandatory for all patients. If the induration is higher than 5 mm, tuberculin skin test is considered positive and implicates LTBI treatment. However the accuracy and reliability of tuberculin skin testing is significantly affected by immunosuppressive therapy, so in this context LTBI treatment should be offered during 1 to 3 months before starting anti-TNF therapy according with guidelines. Nevertheless should be considered that LTBI is a relative contraindication to anti-TNF therapy since chemoprophylaxis may

not prevent emergence of active tuberculosis during this therapy. Actually active tuberculosis during anti-TNF treatment is usually associated with disseminated presentation and extrapulmonary involvement more frequently than other cases and can also be refractory to anti-tuberculosis therapy. These features can cause a calamitous clinical evolution, as this clinical case illustrates.

Case Report 3

Wegener's granulomatosis with tracheal stenosis

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Abstract

The Wegener's granulomatosis (WG) is a systemic autoimmune disease characterized by granulomatous vasculitis of medium and small vessels with significant tissue necrosis. Among the most common manifestations are the involvement of the upper/lower airway and renal achievement. Tracheal stenosis occurs in about 17% of cases. The authors describe a case of a patient of 33 years old who in 2007 started complaints of nasal and oral ulcers. Radiologically lung nodules were detected and analytically ANCA +. The diagnosis of Wegener's granulomatosis was established. There wasn´t renal achievement. The patient remained treated with azathioprine 100 +75 mg / day and esomeprazole 20 mg / day. 3 months later she started dyspnea with stridor. It was detected tracheal stenosis. She underwent rigid bronchoscopy with stent placement tube. In 2008 a new stridor episode has occurred and in its sequence a stenosis above the prosthesis was detected. It was tried its repositioning but without success due to mucosal edema and purulent secretions in high quantity. It was left an artificial airway and the patient started prednisolone 150 mg intravenous(IV). She was admitted in the Intensive Care Unit (ICU) and the prosthesis was removed in the 2nd day. The stenosis was about 6cm long. New prosthesis was placed without complications.

This case illustrates that the tracheal stenosis should be considered in all patients presenting with WG with worsening of dyspnoea, cough and dysphonia so it´s crucial the early diagnosis.

Introduction

In 1936 Friedrich Wegener, German pathologist, identified three

patients with approximately 30 years of age with a benign clinical presentation, suggestive of common cold. In seven months they had all died of systemic inflammatory disease that culminated in uremia. He later described the disease as "a peculiar rhinogenic granuloma with particular involvement of the arterial system and the kidney. Goodman and Churg set out the key features of Wegener's granulomatosis: necrotizing granulomas of upper and/or lower respiratory tract, necrotizing vasculitis of arteries and veins and segmental glomerulonephritis, associated with necrosis and thrombosis of capillary loops, with or without granulomatous lesions.

Wegener's Granulomatosis (WG) is one of the most common forms of systemic necrotizing granulomatous vasculitis which affects small and medium-sized arteries, involving mostly the upper and lower respiratory and kidney [1]. The cause is unknown, but the granulomatous inflammation suggests a hypersensitivity response to one or more unknown antigens [1]. WG is a vasculitis associated with anti-neutrophil cytoplasm (ANCA), usually directed against proteinase-3 (PR3), a constituent of cytoplasmic granules of polymorphonuclear (PMN) and monocytes [2]. The mechanism by which ANCA may induce vascular damage involves the interaction of PMN with endothelial cells via cell adhesion molecules, with release of mediators (cytokines) and subsequent necrotizing inflammation of the vessel wall. Granuloma formation depends, probably, on an hyperactivity of T cells Renal lesions and lung have CD4 + T cells and macrophages. The CD4 + T cells express Th1 cytokines, which stimulate cell-mediated response. American studies show a prevalence of three cases per 100,000 people. The average age of diagnosis is between 20 and 40 years and males are more affected than females by a ratio of 1.5/1.0 [2]. It affects all races, but with a higher prevalence in individuals of northern Europe.

The initial signs and symptoms are not very specific and time to diagnosis can be quite prolonged, especially in cases of more indolent evolution.

The initial general symptoms are fever, anorexia, weight loss and asthenia.

Classic WG involves upper respiratory tract, lungs and kidneys but may also occur in the eyes, ears and other organs. The upper respiratory tract is involved in 70 to 100% of cases [3]. Nasal manifestations may be bleeding, ulcers, nasal crusting and obstruction. Inflammation of the cartilage can lead

to perforation of the septum, known as deformation in saddle nose. This involvement often affects the development of secondary infections.

Sometimes, WG can involve only the involvement of the upper airway. The tracheal stenosis, subglottic usually occurs in about 17% of cases [4] and is one of the potentially fatal complications of the disease and of difficult treatment. It results from inflammation of the scar region of the trachea below the vocal cords. Is often asymptomatic and sometimes is manifested only by hoarseness, but usually presents with subacute onset of stridor. Over time scar occurs accompanied by narrowing of the trachea. Severe cases may require tracheostomy and respond poorly to immunosuppressive agents. The most effective therapy in cases of stenosis, is the mechanical dilatation and, eventually, stenting, combined with local application of steroids or mitomycin-C, through the submucosa or the mucosa.

There may be involvement of the ears, with hearing loss by granulomatous inflammation of the middle ear or vasculitic neuropathy. Ocular involvement is also frequent, with masses retroorbitary, scleritis, episcleritis, keratitis, uveitis, conjunctivitis or lacrimal obstruction. The achievement of the lung is more frequent with bilateral granulomatous infiltrates, easily evidenced by biopsy. At X-ray it may shows bilateral infiltrates, with multiple bilateral nodules, often with cavitation.

Renal involvement is the most serious manifestation characterized by segmental necrotizing glomerulonephritis associated with formation of crescents. Clinically it presents with hematuria, red cylinders, non-nephrotic proteinuria and progressive renal failure, which, with appropriate therapy, may return in weeks, but often with progression to terminal renal failure and dialysis dependency. The diagnosis is based on clinical, radiological, serological and pathological findings. The current recommendation of the American Academy of Rheumatology is the fulfillment of the diagnostic criteria published in 1990 - oral or nasal inflammation, nodules, fixed infiltrates, or cavities on plain chest radiograph, microscopic hematuria, or more than five erythrocytes per field, and / or inflammation granulomatous biopsy. Patients who have at least two of these four criteria can be diagnosed as having Wegener's granulomatosis, with reported sensitivity and specificity, respectively of, 88.2% and 92% in relation with other vasculitides.

Patients with GW whose symptoms are life threatening involving vital organs should be treated with an immunosuppressive agent, usually

cyclophosphamide and high doses of corticosteroids. The stable forms should receive conventional treatment with prednisolone 1 mg / kg for four to six weeks, with gradual reduction to the complete reduction in 6 months. It can be joined methotrexate at a dose of 0.3 / kg / week in an attempt to avoid the side effects of cyclophosphamide. It has been growing the experience with combination of corticosteroids and methotrexate, but the remissions are rare and recurrence after discontinuation of drugs is usual. The usual dose of cyclophosphamide is 2-3 mg / kg / day, a dose that should be adjusted according to the number of leukocytes, always above 4.000/mm3. Cyclophosphamide should be removed one year after disease remission. Given the cytotoxicity of conventional scheme, several studies have been conducted with other drugs. The use of azathioprine (2 mg / kg / day) in place of cyclophosphamide in the maintenance treatment after induction of remission was proposed by a recent study.

The severe forms with alveolar hemorrhage, involvement of the central nervous system or rapidly progressive glomerulonephritis should be aggressively treated with pulses of methylprednisolone (500 to 1,000 mg / day for three days) and cyclophosphamide (2 to 3 mg / kg / day) for 3 6 months followed by azathioprine for more than 18 months. The performance of plasmapheresis may be an option in some refractory cases [5]. The Trimethoprim-sulfamethoxazole should be involved in patients with Wegener's granulomatosis, particularly with nasal and pulmonary involvement, to reduce the number of relapses and also as prophylaxis for Pneumocystis carinii pneumonia during immunosuppression. The clinical course is marked by a tendency to frequent relapses after treatment discontinuation.

The morbidity and mortality of Wegener's granulomatosis are associated with the presence of severe disease of the lower respiratory tract and rapidly progressive glomerulonephritis. Clinical treatment with immunosuppressants and corticosteroids increases the survival of these patients.

Case report

Female patient, 33 years old, married, born and resident in Porto manager. In past medical history she had cholecystectomy for cholelithiasis at 16 years old and splenectomy at the same age of unknown cause. She also had carpal tunnel surgery at age 29 and tabagic habits of 10 units per year.

Alprazolam and Diclofenac in SOS were her usual medication.

She was followed in Otorhinolaryngology (ENT) by complaitns of otalgia and hearing loss in the right ear . CT was performed and revealed cystic lesions in the nasopharynx. It was complemented by MRI that was consistent with cancer of the nasopharynx, but the biopsy revealed a benign lesion.

The patient was admitted at the emergency room (ER) of HSJ in 5th September of 2007 by intense asthenia and arthralgias especially in the lower limb joints since 1 month with progressive worsening. She was treated with ibuprofen, with no effect. Simultaneously were emerged oral ulcers, gingival swelling, papulopustular lesions in the right eyebrow and olecranon and right inguinal and vulvar region.

No complaints of fever, respiratory, gastro-intestinal or urinary tract symptoms.

Physical examination revealed no signs of joint inflammation but were observed oral nodular lesions along the insertion of some of the teeth. Was evaluated by ENT who prescribed antibiotic ciprofloxacin by infected lesion of the nasopharynx. She was then admitted in Internal Medicine internment for study.

On admission she had fever of 38.5° C, was confined to bed, with hearing impaired at right oral candidiasis, oral ulcers, in the right thigh, papulopustular lesions and supraciliary region and also in right olecranon.

Was made a skin biopsy of ulcer of the thigh and flare of the right elbow, consistent with "process begins with features that raise the possibility of systemic vasculitis, highlighting the presence of vascular lesions in small vessels of venous type, in the absence of injury granulomatous".

Given the suspicion of Behçet's disease, was made pathergy test that was negative.

Serum specimens were tested for viral and immunological study (Table I).

The patient was observed by Ophthalmology to exclude damage to eyes and Gynecology, showing no characteristic lesions of Behçet's disease.

Suspicion of inflammatory intestinal disease was asked but upper and lower endoscopy were negative.

She was also observed by dentist and lesions in the oral cavity corresponded to aphthous lesions on the lips and tongue granulomas.

Fever was maintained during admission with complaints of dysphagia. In D8 it was made a biopsy of the nasopharynx.

In D9 was reviewed by Dermatology with report of solid-papular lesion painful in right eyebrow, the metacarpophalangeal joint of 3rd finger of left hand similar to the lesions in elbows, and a large ulcer in the right suprainguinal region. Was also observed an erythematous lesion - exudative in the edge of the navel and a brown painless papule at the top of the inner right thigh.

A biopsy was performed which showed lesions of the skin flap with representation from ulcer exudate consisting of fibrinoleukocytic and granulation tissue involving the whole thickness of the flaps with lesions of leukocytoclastic vasculitis.

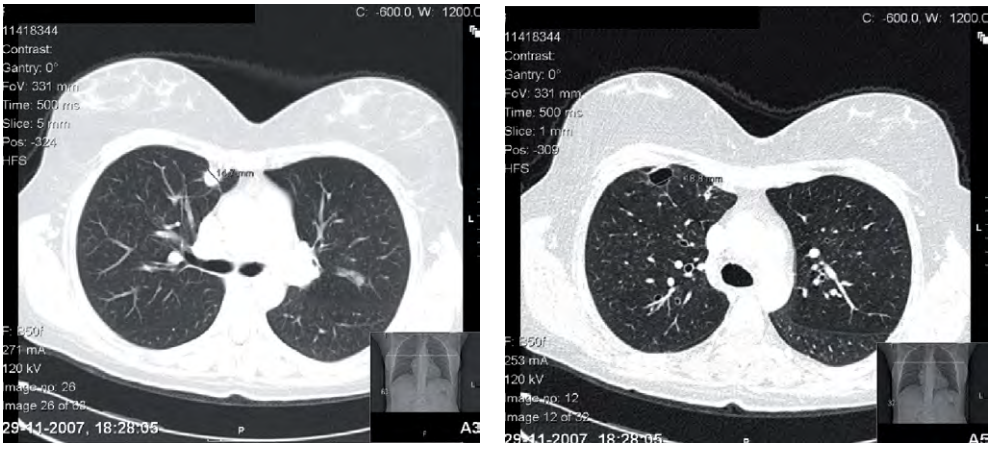
Analytically the immune study (Table I) showed high PR3 ANCA (99 U / mL) and increasing fractions of complement.

Table I - Immunology

Imunology	Results	Reference values
C3	↑202	83-177 mg/dL
C4	↑39	12-36 mg/dL
C5	↑24	4.9-20.5
CH50	135	63-145 UA
ANCA PR3	↑99	<20
ANCA MPO	<20	<20

Given the analytical results joined with symptoms the diagnosis of ANCA + vasculitis was performed, probably Wegener's granulomatosis, with an infectious process superimposed. The abdominal ultrasound revealed no changes and chest CT showed cavitation subpleural about 18 mm in largest diameter and a nodule with 14 mm (Figure 1).

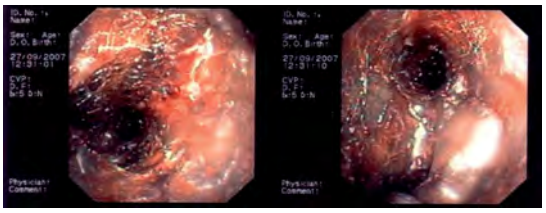
Fig. 1 **- CT chest - cavitation subpleural about 18 mm in diameter and a larger nodule with 14 mm of diameter.**



Was scheduled renal biopsy that was never done.

In D11 of admission the patient maintained fever and had a productive purulent cough .The lung auscultation with audible rhonchi billaterally. Analitically was registed anemia with blood transfusion necessity. By D13 was observed a difficult in breathing, aphonia, inability to swallow, polypnea with mild supraclavicular draft, auscultation with audible breath sounds bilaterally with inspiratory and expiratory rhonchi and prolonged expiratory time. The Gasometry revealed hypoxemia. Radiologically was showed infiltrates nbut wothout pneumonic pneumonic. She was evaluated by ENT without stridor,. For impossibility of flexible bronchoscopy realization due to nasal ulcers and indirect laryngoscopy due to lesions of the tongue was made a rigid bronchoscopy that showed abundant thick secretions with parcial glottal obstruction.

Fig. 2 **- Bronchoscopy – The distal trachea carina with the mucosa covered throughout its length by a brownish film resulting from necrosis of the mucosa.**



And antibiotic therapy was started with ciprofloxacin and metronidazole. By keeping the impossibility of swallowing was considered gastrostomy feeding, which was not needed. In D15 of admission she was transferred to the Intermediate Care Unit due to respiratory

insufficiency (RI) type 1. At the entrance to IR problems had type 1this time she had Wegener's granulomatosis (PR3 ANCA +, skin and lung granulomas, nasal ulcers) and impossibility of aspiration of secretions. She began Piperacillin / Tazobactam + vancomycin, fluconazole IV and methylprednisolone 1 g IV over 3 days.

Due to exhaustion, tachypnea, abundant bronchial secretions and edema of the nasopharynx, was admitted in the next day on the ICU for invasive ventilation. Was performed a rigid bronchoscopy wich revealed extensive areas of necrotic mucosa and narrowing of the lumen (Figure 2).

It was then placed an endoluminal prosthesis.

The patient was also evaluated by Physical Medicine and Rehabilitation for possible early respiratory physiotherapy but due to high risk of bleeding it was only performed classical physiotherapy. For active urinary sediment and proteinuria in renal function was thought to do a renl biopsy, wich was not performed because it would not alter the course of therapeutics.

Was made a Bronchoalveolar lavage (BAL) to microbiology (Viruses, P.jiroveci, BK, fungi and bacteriology) and Staphylococcus aureus was isolated. In Thoracic CT was showed an image suggestive of pneumonia in the left lower lobe and it was added Imipenem. She repeated bronchoscopy about a week later consistent with friable mucosa but with no bleeding, no evidence of areas of necrosis.

Repeated chest CT at D10 ICU that showed two nodular lesions in the right upper lobe qith a cavitation with a 36 mm diameter. Were completed seven days of imipenem, 16 days of Vancomycin and fluconazole. For isolation of Pseudomonas aeruginosa multiresistant she also started Colistin. At D20 patient was extubated successfully. She returned to UCIM 2 days after and completed 22 days of Colistin, 13 days of fluconazole and 8 days of Ciprofloxacin (after five days of Imipenem). Was made lung biopsy of the cavitation showed in Fig.1 (Fig. 1).

She was transferred to the ward of internal medicine at D13 UCIM. She was in D24 of of Colistin, 10 days of ciprofloxacin, without complaints, including shortness of breath or chest pain or pain in the mouth.

Tests of respiratory function ere carried out and revealed mild respiratory disease. Trans-thoracic echocardiogram compatible with aortic insufficiency and mild mitral minimum systolic left ventricular function generally kept with EF of 56%.

The lung biopsy performed "pulmonary parenchyma with preservation of architecture with areas of septal thickening and lesions capillaritis. There are still pockets of necrosis and hemorrhage. Was observed vessel wall with lesions of vasculitis - aspects that are consistent with the diagnosis of Wegener's granulomatosis.

In D50 in HSJ the patient had an episode of deep vein thrombosis documented by Doppler echocardiography that showed venous intraluminal with signs suggestive of recent deep vein thrombosis of superficial femoral veins bilaterally and in the popliteal veins bilaterally.

Was observed by Vascular Surgery. And was decided to keep low Molecular Weight Heparin in therapeutic dose and as soon as possible, start hypocoagulability oral.

With no complaints the patient went home in D60 of admission.

In December 2007 she started complainints of stridor and was diagnosed after bronchoscopy, stenosis of the trachea (2-3 cm below the vocal cords) and sheunderwent rigid bronchoscopy with a stent placement tube.

In 2008 a new stridor episode has occurred and in its sequence was detected stenosis above the prosthesis. Was tried it´s repositioning but without success due to mucosal edema and purulent secretions in high quantity So it was left an artificial airway and the patient started prednisolone 150 mg intravenous(IV). She was admitted in the Intensive Care Unit (ICU).

The prosthesis was removed in the 2nd day. Was observed stenosis with about 6cm long. New prosthesis was placed without complications.

In September 2009 she is mantained in our external consulation of Internal Medicina- Autoimmune Diseases with immunosuppressive medication with Lepicortinolo 5 / 10 mg on alternate days and azathioprine 175 mg / day.

Discussion

Essentially all patients with WG have involvement of the upper airways and lungs and the great majority have both. Symptoms of upper airway initially dominate the clinical picture but the pulmonary and renal involvement occurs later in 80 to 90% of patients. The three histopathological features are (1) necrotizing granulomas in the upper respiratory or lower, (2) necrotizing

vasculitis involving both arteries and veins and (3) glomerulonephritis.

Renal involvement may be manifested by acute renal failure and proteinuria with erythrocyturia. Renal biopsy shows a segmental necrotizing glomerulonephritis [5] with few immune deposits on immunofluorescence or electron microscopy.

The laryngeal obstruction may present clinically as hoarseness, dyspnea, laryngeal stridor and in severe cases, acute respiratory failure. Early diagnosis prevents serious complications in most cases. It is observed that stenosis is often associated with pulmonary pathology [6]. The diagnosis of subglottic stenosis in Wegener's granulomatosis is made by visualization of laryngeal narrowing of the lumen, concentric in diffuse form or restriction to the posterior wall of this in the localized form, limited to the subglottis, without important distal extension. The mucosa is often erythematosus. Ulcerations are common. A biopsy of the laryngeal tissue, unlike lung tissue samples, rarely confirms the diagnosis of Wegener's granulomatosis . Histopathologic results revealed only chronic inflammatory tissue in these cases, with absence of key elements such as the presence of vasculitis and granulomas in the material studied. The lungs correspond to the point of maximum positivity in anatomical pathology tests. Medical treatment can sometimes be delayed due to the difficulty of confirming the diagnosis, either by the absence of the classical or complementary methods reliable.

The treatment of stenosis is done with dilation, laser resection with carbon dioxide, the use of intralesional injections of corticosteroids and laryngo-tracheal reconstruction.

In our clinical case was detected tracheal stenosis 3 months after the diagnosis of WG. The patient underwent rigid bronchoscopy in December 2007 with the placement of endotracheal prosthesis. A year later stridor and respiratory distress has coccured and a re-stenosis above the graft with about 6 cm long was observed. New prosthesis was placed without complications.

The patient never showed renal involvement by WG so far.

Conclusion

This case illustrates that the stenosis should be considered in all patients presenting with GW worsening of dyspnoea, cough and dysphonia.

This complication may present a spectrum of clinical manifestations that varies from asymptomatic cases to cases of severe dyspnoea with impairment of the patient's life. It is therefore crucial its early diagnosis.

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Case Report 4

Mixed Connective Tissue Disease

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Abstract

We report a case of a 32 year old woman suffering from mixed connective tissue disease (MCTD). She showed symmetric arthritis, especially in her finger joints with great limitation of daily life activities. Although the clinical picture resembled a rheumatoid arthritis the laboratory findings were characteristic of MCTD.

The diagnosis and treatment of this autoimmune disorder remains a challenge for the physician.

Introduction

Patients with signs and symptoms suggestive of systemic autoimmune disease but not fulfilling the classification criteria for defined diseases are common in clinical practice.

Mixed connective tissue disease (MCTD) was described initially by Sharp et al. in 1972 as an overlap syndrome with features of lupus, scleroderma, and poly/dermatomyositis (PM/DM) in patients who had antibodies to extractable nuclear antigen with ribonucleoprotein (RNP) specificity.

Since then much controversy has arisen concerning this new clinical identity. Its resemblence with other autoimmune disorders brought many physicians to disagree with the idea that this is a different disease.

Many diagnostic criteria were proposed since then and even now many difficulties are still present when it comes to performing such diagnosis.

But the challenge gets even bigger when it comes to the therapeutic approach for such patients.

How to treat this mixed disorder that resembles more than one

autoimmune disorder?

We report a patient suffering from MCTD that presented great disease related incapacity.

The therapeutic approach for this patient is the most challenging aspect of such disease.

Case report

We describe the case of a 32 year old female, cooker, resident in Peniche, Portugal.

The patient was admitted to our Hospital in 2004, at the age of 28, with complaints of difficulty in moving fingers, joint pain and malaise. Two years before she had noticed bilateral knee pain with morning stiffness that resolved during the day. Since then more joints got involved, always in a bilateral and addictive pattern – shoulders, elbows, wrists and fingers.

She also complained of color changes in her fingers and swelling of her hands and referred sporadic episodes of malar rash.

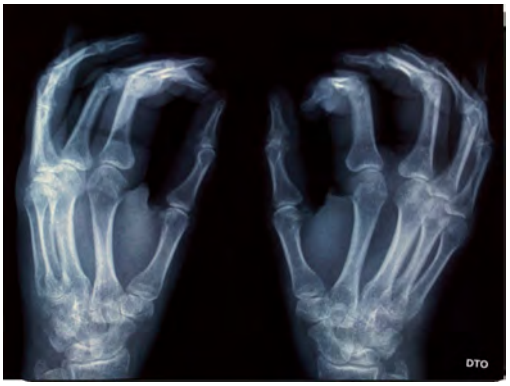
When she was admitted the functional incapacity was so important that she couldn't fulfill the simplest daily tasks.

On general physical examination, she showed bilateral swelling and tenderness of the metacarpo-phalangeal and wrist joints, limitation on wrist and finger extension and puffy fingers.

The remaining joints didn't show any inflammatory signs.

There was no skin change characteristic of connective tissue diseases but Raynaud phenomenon was observed by the attending physician.

Fig. 1



Laboratory examination revealed mild anemia and erythrocyte sedimentation rate (ESR) elevation (58 mm/h). Serum myogenic enzymes (lactic dehydrogenase and creatine kinase) were normal.

On immunological examination there was serum Immunoglobulin G elevation and positive Anti-RNP antibodies (title >100).

Anti-dsDNA antibodies and rheumatoid factor were negative.

Finger joint X-rays (Figure 1) showed signs of osteopenia and reduced interarticular spaces but no destructive changes characteristic of rheumatoid arthritis.

MCTD was diagnosed based on the combined clinical and laboratory findings characteristic of rheumatoid arthritis and systemic lupus erythematosus, and positive anti-RNP antibody.

On the 1st day of admission, oral prednisolone (40 mg/day) and hidroxychloroquine (400mg/day) where initiated. An intensive Rehabilitation Program was started which included active and passive joint mobilization, hand massage, strengthening exercises and hand muscular stretching.

There was remarkable improvement and the patien was discharged by day 8, with the same medication plus diclofenac 100mg/day, alendronate 70mg/week, vitamin D and oral calcium.

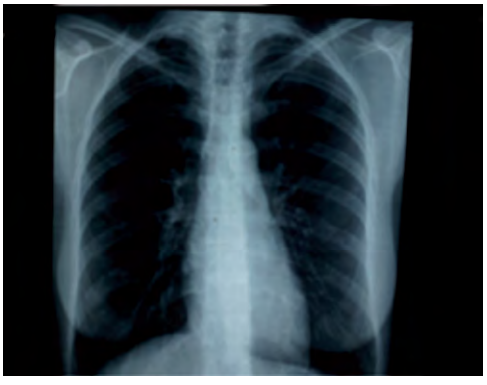
She also maintained the Physiotherapy rehabilitation program.

During follow-up she maintained a progressive regression of the symptoms – joint swelling and pain disappeared and ESR normalized in a few months.

By 2004 the patient complained of wrist pain and parestesias of the right hand fingers. An electromiogram was performed and a carpal tunnel syndrome diagnosed. The proposed treatment was wrist ionization with prednisolone, with marked improvement.

By 2005 the finger joint pain got worse and methotrexate 7,5mg/week was initiated followed by a slow dose increase to 20mg/week, with good tolerance and symptom improvement.

Fig. 2



The disease remained stable until 2007. Meanwhile the anti-CCP antibodies were checked but came out negative.

By the spring of 2007 the patient started complaining of persistent dry cough, without fever or dyspnea. The chest X-Ray (Figure 2) was normal, no signs of interstitial pneumonia or fibrosis were found in chest computed tomography and findings

of pulmonary hypertension were not confirmed by echocardiography.

There was a moderate reduction 6,78 (expected 8,99) of carbon monoxide diffusing capacity (DLCO).

A lung specialist consultation was asked and eventual methotrexate toxicity was admitted, and so the therapy was switched to azathioprine.

The cough resolved without any other specific treatments and DLCO stabilized.

Since then the disease remained under control except for a few months in 2008 when the patient referred finger joint pain. This complains were concomitant with a reactive depression caused by the loss of a loved one.

Diclofenac was used and the pain disappeared as soon as her humor got better.

She now keeps regular follow up at our outpatient clinic and remains symptom free and there as been no progression of lung disease.

The patient was retired from work because of incapacity related to her disease.

Discussion

The discussion about MCTD is still far from ending, as many articles published in the past few years came to show us.

The mixed presentation of this autoimmune disorder as well as its evolution and prognosis make it a permanent challenge for physicians. In this case, the patient had many manifestations that could fulfill the diagnostic criteria for rheumatoid arthritis but the immunological studies didn't confirm that hypothesis. One can only speculate if someday more specific RA auto-antibodies will turn positive in this patient? And also, if this patient would ever benefit of a biologic agent? Besides its common manifestations with other rheumatic diseases some studies have already shown that biological agents aren't the most efficient weapons for treating MCTD patients.

On the other hand a more important role has to be given to Rehabilitation and Physiotherapy. By the enormous disability that this diseases cause in mostly young and professional active patients their complete rehabilitation becomes even more important. A well designed Physiotherapy program has many benefits and changes drastically the prognosis of such diseases, in some series with results as good as the pharmacologic agents and

with fewer side effects.

Another important aspect of such chronic diseases is the psychological wellbeing of the patient and the strict correlation that one can find between the emotional state and the clinical manifestations of disease. Many times, just like we described in our patient, an emotional stress can be the explanation for a sudden aggravation of symptoms in a previously well controlled patient. The bio-psycho and social aspects interact in the sense of well being and this is especially true for chronic diseases and even more for rheumatic diseases.

One last word to an eventual bias that determined the course of therapy.

While analyzing our patient clinical records we've realized that the DLCO was calculated using the estimated hemoglobin for this patient, and not the real one. As you probably remember our patient had a mild chronic anemia that remained stable since diagnosis, but in the referred exam the hemoglobin used for the calculations was 2g/dL higher than real and so the expected DLCO level in each exam was probably lesser than the ones obtained. Eventually there was no methotrexate toxicity but an incorrect calculation of DLCO that drove us to a wrong diagnosis.

Conclusion

Many aspect of MCTD have been studied and clarified; however, there is no agreement on the best way to identify patients with MCTD after the onset of their disease.

One of the challenges of studying a rare condition is the small number of patients who have this diagnosis at any center. The literature on MCTD is based on relatively small case series, with very few multicenter studies. Hopefully one day there might be registries or multicenter cohorts established to better address the pathogenesis, diagnosis, prognosis and treatment of this condition.

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Comment

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Although it was first described in 1972, the diagnosis of MCTD is still a challenge.

This clinical case report illustrates the overlapping features of such clinical entity, the difficulty of its diagnosis and also the evolution which can be very different from patient to patient.

In this case, the diagnosis was made mainly on the basis of clinical and laboratory characteristics of Raynaud Phenomenon, edema of the hands, arthritis, Systemic Lupus Erythematosus and positive anti-RNP antibody, although synovitis or myositis was not demonstrated.

The finding of a reduction of carbon monoxide diffusing capacity (DLCO) could also be the sign of pulmonary hypertension, which is the primary cause of death in these patients and should be a reason for concern and early treatment.

As the authors point out it is very interesting the relationship of emotional stress and disease flare, which is common to many other observations seen in most autoimmune diseases.

MCTD is not, any more, considered a benign condition as it was thought in the beginning. So, it is very important to have more efficient and specific therapeutical means based on strong clinical assays so that we can be more aggressive in treatment and contribute to a better prognosis.

Marta Mosca
Assistant Professor of Rheumatology at the Rheumatology Unit,
University of Pisa, Pisa, Italy

"I found your case very interesting and frankly I do not have any comment. It is indeed very important that MCTD/overlap syndromes are not confused with undifferentiated diseases".

Case Report 5

Is it just Rheumatoid Arthritis?

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Abstract

The authors report the case of a 59-year-old female who developed a malignant-like syndrome after initiating etanercept for Rheumatoid Arthritis (RA) unresponsive to classic disease-modifying anti-rheumatic drugs (DMARD). After 18 months of etanercept therapy, the patient started complaining of asthenia and fatigue. Skin lesions of Dermatitis Herpetiformis (DH) appeared at the third year of therapy, followed by multiple axilar and mesenteric lymphadenopathies at the sixth year of etanercept.

After exclusion of malignant and infectious causes of these symptoms, etanercept was withheld and the switch to rituximab was made. A complete symptomatic relief and radiologic regression followed this switch, suggesting that these symptoms were caused by systemic involvement of RA.

RA is a systemic disease frequently associated with other autoimmune diseases and anti-TNF **α** therapy has showed evidence of capacity for modifying the natural history of this disease, albeit it can increase the frequency of infectious diseases and also malignant ones such as lymphoma.

Introduction

Rheumatoid arthritis (RA) is a symmetric, peripheral polyarthritis of unknown etiology that untreated or if unresponsive to therapy, typically leads to deformity and destruction of joints through the erosion of cartilage and bone.

Although RA develops its central pathology within the synovium of diarthrodial joints, many nonarticular organs become involved, particularly

in patients with severe joint disease.

Systemic or extra-articular manifestations are very common. The prevalence of systemic manifestations reported in studies of RA is approximately 8% to 12%; this excludes studies that do not include cardiovascular disease as a manifestation of RA [1-4]. Systemic symptoms include fatigue, fever and weight loss.

Many of the extra-articular manifestations of RA are associated with increased disease activity and with markers of inflammation, such as high levels of rheumatoid factor (RF) and C-reactive protein (CRP). [4-7] This suggests that early aggressive treatment of RA with effective therapies should lower the risk and severity of systemic manifestations associated with RA.

Case report

A 59-year-old female started the follow-up for Rheumatoid Arthritis in the outpatient clinic of our department in 2002. This disease had been diagnosed for 4 years and, by 2002, she had a moderate activity score (4,64) according to DAS 28 (Disease Activity Score) in spite of therapy with Hydroxychloroquine 400mg per day. A methotrexate trial had been made before with 10mg weekly but the patient developed hepatotoxicity. The physical examination revealed symmetrical arthritis of wrists, proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the 2nd and 3rd fingers with morning stiffness of 30 to 40 minutes. The blood sample analysis showed anemia of chronic disease (hemoglobin, Hb 11,7g/dL), elevated erythrocyte sedimentation rate (ESR 46 sec.), mild elevation of aminotransferases (AST 41 UI/L, ALT 68 UI/L) and also gamma-glutamiltransferase (74 UI/L) and alkaline phosphatase (131 UI/L). The RA test was strongly positive with high serum values (over 600). The plain radiographic exams of the affected joints showed joint space narrowing and osteopenia but no bone erosions.

It was decided to start an anti-TNF α agent, and etanercept was chosen on the dose of 50 mg weekly combined with nonsteroidal anti-inflammatory drugs (NSAID). At the third month of ongoing therapy with etanercept, the patient had a partial remission of symptoms with clinical significant reduction of DAS 28 score: the patient scored 1.99, compatible with inactive disease.

At the 18th month of therapy, she started complaining of asthenia and

fatigue. No signs of heart failure, infectious disease or other serious systemic disease were found and all the exams were normal. These included plain chest X-ray, complete blood analysis, electrocardiogram, echocardiogram, pelvic ultrasound and mammography. We assumed these symptoms were caused by anti-TNF **α** therapy but we decided not to withhold it once those were not severe side effects and the RA was clinically inactive.

During the 3rd year of ongoing therapy, multiple papulo-vesicular skin lesions appeared on the patient's buttocks, limbs and abdomen, associated with severe pruritus. These lesions had symmetrical distribution and preference for extensor surfaces. Some were infected; reason why etanercept was stopped and systemic antibiotics were started. These lesions did not disappear and there was a relapse of RA with DAS 28 score of 5.77 (very active disease).

The histopathological exam of the skin lesions was compatible with Dermatitis Herpetiformis (DH) with negative immune-fluorescence test so a digestive endoscopy with biopsy to exclude asymptomatic celiac sprue was performed and no abnormal changes were found. The laboratory results revealed positive serum IgG antitransglutaminase antibodies but negative antigliadin antibodies. We decided to perform a dapsone trial with complete remission of these lesions.

Etanercept was withheld during 6 months and, meanwhile, methotrexate and corticosteroids were prescribed to the patient with no clinical or laboratory response. After exclusion of an adverse effect of etanercept, this drug was again prescribed on the previous dose but with lower efficacy: the patient maintained a DAS 28 score of moderate activity with increasing daily doses of glucocorticosteroids.

During the sixth year of ongoing therapy with etanercept, the patient complained of weight loss of 4 Kg in 2 months, associated with the appearance of severe asthenia and axilar lymphadenopaties. The laboratory results showed worsening of anemia (Hb 9.7 g/dL) and erythrocyte sedimentation rate of 120 sec. A CT-scan was performed that revealed multiple axilar and mesenteric lymphadenopathies (with maximal diameter of 20mm and 15 mm, respectively). No mediastinic lymphadenopathies were found. The histopathological exam of one of these lymph nodes revealed reactive follicular hyperplasia and the bone marrow exam was normal. After lymphoma, an infectious disease or other serious systemic disease were excluded, it was decided to start higher dose of glucocorticosteroids (prednisolone on a daily

dose of 30 mg), stop etanercept and make a switch to rituximab.

On the third month on rituximab, the patient had an inactive RA, the lymph nodes were normal but still had anemia and elevated ESR.

Discussion

The important clinical features of this case are the development of diffuse generalized lymphadenopathy, with systemic symptoms such as weight loss and fatigue, and the onset of Dermatitis Herpetiformis.

The development of Dermatitis Herpetiformis could be related to gluten sensitive enteropathy or other endocrinological, connective tissue, liver, lung, or skin diseases.

In a 10 year cohort study by Reunala and Colin [8] of 305 patients with DH, 9.5% of patients developed various autoimmune diseases and of this 0.7% developed rheumatoid arthritis. Other reports describe as- sociation of DH with systemic lupus erythematosus by Moncada [9] and Davies, [10] thyroid disease, dermatomyositis and Sjogren's syndrome by White and Tesar [11] and rheumatoid arthritis by Rothwell [12]. It could also be a cutaneous side-effect in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists [13].

In our case we presume that DH was related to the baseline disease: etanercept interruption didn't modify the course of the lesions, Immunoglobulin (IgG) G-based antigliadin (AGA) test was negative and no changes were observed on duodenal mucosa histology.

Lymphadenopathy is common in rheumatoid arthritis, affecting up to 75% of patients at some stage of their disease. [14] It may occur in nodes draining an inflamed joint but can also be generalized. [15]

The differential diagnosis consists of complications of this patient's autoimmune disease or its treatment, including infections and lymphoproliferative disorders, as well as conditions that may mimic or be associated with autoimmune disorders. A proportion of such patients undergo lymph node biopsy to exclude these disorders.

Our patient lymph node biopsy showed reactive follicular hyperplasia and in fact, with the switch to Rituximab, with control of the disease, the lymphadenopathies disappear (showed by computerized CT).

This case illustrate that autoimmune diseases are systemic disorders

with a very different course, which can be modified by treatment. Every patients with autoimmune disease required tight control, particularly those on classic Disease-modifying antirheumatic drugs and on the recent anti-TNF therapy.

The course of the presented case makes one wonder if all these symptoms and clinical changes were caused plainly by RA with bizarre presentation or other unknown clinical condition.

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Case Report 6

Autoimmune Pancreatitis

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Abstract

Autoimmune pancreatitis is a chronic idiopathic pancreatitis with clinical, morphological, serologic and histological characteristics. Its manifestations may mimic pancreatic cancer, acute pancreatitis, chronic pancreatitis, inexplicable exocrine insufficiency, cholangiocarcinoma or primary sclerosing cholangitis. A main pancreatic duct with diffuse and irregular stenosis associated with elevated serum IgG4, presence of certain antibodies and lymphocytic infiltration in the pancreas are the key to diagnosis.

A correct diagnosis can avoid unnecessary surgery. It is characterized by a rapid and effective response to steroids.

Case report

The authors present the case of a 49 year old previously healthy man, which presented with abdominal and obstructive jaundice in January 2008; His General Practitioner asked a CT scan which showed an abdominal cefalopancreatic mass. He was submitted to a partial pancreatoduodenectomy in February 2008. Histology of the mass showed "lymphoplasmacytic sclerosing pancreatitis accompanied by sclerosing cholangitis of the extrahepatic bile ducts and lymphoplasmacytic chronic cholecystitis". The patient was discharged and referenced to the Surgery outpatient clinic without specific therapy. In May 2008 he complained of bilateral red eye and decreased visual acuity. He was observed by Ophthalmology and was diagnosed with a non specific bilateral scleritis. His Ofthalmologist referenced him to our Autoimmune Disease's outpatient clinic.

When he was first seen the only complaints he had were unpainful bilateral red eye, decreased visual acuity, bilateral sporadic and arthralgia of wrists and hands. On physical examination he had, bilateral red eye, unpainful and non itchy erythematous papular skin lesions in nose, ears, forearms and trunk, which could suggest panniculitis.

Laboratory tests showed hyperglycemia, IgG4 frankly increased (> 2xN) and positive anti-SSA and anti-SSB antibodies. Abdominal CT scan showed mild dilatation of the intrahepatic bile ducts in left lobe and biliary tract, with no changes in body and tail pancreas or ectasia of Wirsung. The patient started therapy with prednisolone 0.5 mg/ kg/day with good clinical response (disappearance of the red eye, skin lesions and arthralgia) and analytical (normalization of Ig G4 and negativity anti-SSa and anti-SSb antibodies). He had persistent hyperglycemia and was started on insulin.

Discussion

A few cases of autoimmune pancreatitis are described in the literature. The disease is more common in middle aged men. The most common clinical presentation is obstructive jaundice and abdominal pain but it can also manifest as pancreatic insufficiency or as part of the clinic spectrum of other systemic diseases which can be associated. The differential diagnosis must include the possible causes of chronic pancreatitis including pancreatic mass. There are serious therapeutic implications related to its underdiagnosis because it is a reversible disease when the correct treatment instituted.

Imaging is characterized by a diffuse increase of the pancreas ("sausage like") and main pancreatic duct with diffuse and irregular stenosis. Histologically it is characterized by dense periductal lymphocytic infiltration, fibrosis and venulitis obliterans. The inflammatory infiltrate consists mainly of lymphocytes and plasma cells (IgG4 positive) and occasionally macrophages, neutrophils and eosinophils. Immunophenotyping shows predominantly CD4 + and CD8 + lymphocytes and few B- lymphocytes.

Analytically it is characterized by high levels of IgG4 which is one of the diagnostic criteria proposed by the Japan Pancreas Society, recently modified. It may also present autoantibodies (ANA's antinuclear antibodies, rheumatoid factor RF, antilactoferrin ALF, anti-carbonic anhydrase II-ACA II).

Initially, the diagnosis of autoimmune pancreatitis had to include the imaging and histological or serological criteria. Presently and according to the most recent Mayo Clinic diagnostic criteria the presence of histological criteria is sufficient to make diagnosis of this disease.

If there is demonstration of multifocal fibrosis with the same histopathological features in the salivary glands, peripancreatic tissue, extrahepatic bile duct and gallbladder we can say that it is a pancreatic manifestation of a systemic IgG4 associated disease. There is occasional association with other autoimmune conditions such as diabetes mellitus, sclerosing cholangitis, Sjogren's syndrome, interstitial nephritis, rheumatoid arthritis, and retroperitoneal fibrosis. Only about 10% of diabetes mellitus cases are associated with type 1 diabetes. In these cases it is more common the presence of ALA and ACA-II.

This patient presented clinical, histological and serological criteria and there is a probable association with other autoimmune conditions, such as Sjögren's syndrome (he had anti-SSa and anti-SSb antibodies without dry eyes or dry mouth) or Diabetes Mellitus.

The clinical and analytical outcomes were good with treatment with prednisolone 40 mg/day. The serum IgG4 normalized and he had no radiological evidence of recurrence of disease. He is on current treatment with insulin because of persistent hyperglicemia.

Conclusion

This case illustrates one of the most common presentations of autoimmune pancreatitis - pancreatic mass suspected of malignancy - and the excellent response to steroids. The low level of suspicion led, in this case, to an unnecessary surgery.

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Case Report 7

Young female with Systemic Lupus Erythematous and antiphospholipid syndrome

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder of unknown cause, associated with the presence of a wide spectrum of auto-antibodies reactive against sub-cellular structures [1], which affects predominantly females. Presentation may range from rash and arthritis through anemia, thrombocytopenia, serositis, nephritis, seizures, and psychosis [2,3]. According to well defined criteria [4] (Table 1), and its clinician course is characterized by periods of both, active disease and remission.

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* b) Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	a) Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed *OR* b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance

9. Hematologic Disorder	a) Hemolytic anemia--with reticulocytosis *OR* b) Leukopenia--< 4,000/mm^3 on ≥ 2 occasions *OR* c) Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions *OR* d) Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	a) Anti-DNA: antibody to native DNA in abnormal titer *OR* b) Anti-Sm: presence of antibody to Sm nuclear antigen *OR* c) Positive finding of antiphospholipid antibodies on: 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Table 1 - Adapted from The 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

The determination of prognosis is determined by disease development, activity, severity and development of major organ involvement [5].

Antiphospholipid syndrome (APS) is defined by the association of arterial and/or venous thrombosis, recurrent miscarriages, and anti-phospholipid (aPL) antibodies. Criteria for defining this syndrome have been published in 2006 on Sydney Consensus Statement on Investigational Classification Criteria for the APS and are listed in Table 2.

Clinical criteria:
Vascular thromboses:
1. One or more documented episodes of arterial, venous, or small vessel thrombosis—other than superficial venous thrombosis—in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
Pregnancy morbidity:
a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, or Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria:
1. Lupus anticoagulant (LAC) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LACs/phospholipid-dependent antibodies). 2. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. 3. Anti-ß $_2$ glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

*APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Table 2 – Adapted from summary of the Sydney Consensus Statement on Investigational Classification Criteria for the APS

This syndrome may be idiopathic or associated with other autoimmune disease [6] being SLE the autoimmune disease mostly associated with APS [7]. SLE patients with idiopathic APS have a multiorgan involvement witch cannot be explained neither by the thrombophilic state per se, nor to

well known clinical manifestations associated with SLE. This suggests that these apparently different diseases are somehow related [8]. Positivity of aPLs in SLE patients, may lead to antiphospholipid syndrome development. SLE related APS is clinically similar to idiopathic APS, with vascular thrombosis, pregnancy morbidity or both 9. Up to 20 to 40% of SLE patients have positive blood test for aPL antibodies [9]. There are a few reviews that suggests that SLE related APS syndrome is actually more common than idiopathic APS.

The prevalence of epileptic seizures in SLE patients is about 11,2%, and they may precede the appearance of other serological or clinical evidence of the disease by many years [5, 10]. There is a relation between epileptic seizures at onset of SLE and aPL antibodies and stroke [11].

Case report

The authors present the case of a seventeen year-old caucasian female, that was admitted to a private clinic because of cutaneous fotossensibility, nephrotic syndrome and a lupus like immunologic study. Renal biopsy suggested a membranous glomerulonephritis. Therapy with prednisolone, ciclophosphamide and azathioprine was begun. Four years later, she presented to emergency department with menometrorrhagia lasting 1 month, asthenia and pale face. She was under deflazacort 6 mg every other day. She was conscient and colaborant, pale and with palpebral edema. A systolic murmur could be heard on the pulmonary focus; hepatomegaly and limb edema were evident on fisical examination. Blood sample analysis demonstrated anemia (4,2 g/dl), with increased reticulocytes percentage, increased DHL - 525 UI/ml (N – 135 – 225), decreased haptoglobin, thrombocytopenia (72 x 10^9/l) renal failure (acute vs deterioration of chronic renal failure) and hiperkaliemia (6,31 mEq/l). Coagulation study was normal. Direct coombs was positive. Vaginal exam revealed blood lost from vaginal ostium and she was admited to Ginecology ward. Estrogen thepapy and corticotherapy with prednisolone (1,5 mg/Kg/day) was started. There was improvement with decreasing blood losses.

On the 5th day she was admitted on emergency room, with acute lung edema. The transthoracic ecocardiogram raised the possibility of mitral endocarditis and the transesophageal ecocardiogram confirmed the presence of small sessil masses adherent to the mitral valve. Left ventricular function

was preserved. Blood cultures were negative. Mitral valve was replaced for a biological prothesis. Aspirin® therapy was started. Laboratory studies revealed nephrotic proteinuria (4,42 g/day), with positive lupic inhibitor, and results of immunologic study was unknown. Patients improved and was discharged with metilprednisolone 16 mg fd;

Assintomatic for the next 4 years, followed by internal medicine hospital care, with decreasing doses of corticoid, she began azathioprine and hidroxichloroquine. Laboratory studies revealed no disease activity, with normal complement and anti Ds-DNA, decreasing daily proteinuria and positive aPLs were documented in one medition. Intrauterine device was inserted.

In 2001, she started to refer matinal frontal headaches, without fever, photophobia or phonophobia, nauseas or vomiting. A cerebral CT scan revealed small bilateral hypodensities on corona radiata, probably ischemic and vascular lesions. The electroencephalogram revealed no epileptiform activity. From laboratory work, there was anemia (9,6 g/dl), increased sedimentation velocity (88 mm/1ªh). Immunological study revealed complement: C3c – 77 mg/dl (N – 83 – 177); C4 – 15 mg/dl (N – 12 – 36); serum haemolytic capacity – 40 UA (N – 63 – 145), Anti Ds – DNA - 29,0 UI/ml (N < 20); positive lupic anticoagulant; aPLs were positive (anticardiolipin IgG – 89,9 (N < 15); ß$_2$ glycoprotein > 150 (N < 15)). The patient kept therapy with Aspirin®.

About 8 months later, on routine follow up, patient presented haemolytic anaemia (Hb – 8,2, g/dl; direct Coomb – 12; DHL – 450 UI/ml), renal failure (PUr – 0,98 g/l; Cr – 2,7 mg/dl), increased sedimentation velocity (122 mm/1ª h), increased anti-Ds DNA (588 UI/ml) and hypocomplementemia (C3 – 59 mg/dl; C4 – 8 mg/dl; serum haemolytic capacity – 19 UA). Interpreted as lupus "flare", patient started metilprednisolone pulses (1 g/day, for 3 days), not stopping azatioprine, with renal improvement and decreased activity disease inflammatory markers. She didn't performed renal biopsy. Five months latter, the patient performed an exodontia, with significant haemorrhage. Laboratory studies showed anemia (Hb – 7,4 g/dl), thrombocytopenia (100 x 10^9/l), increased inflammatory markers (VS – 127 mm/1ªh; 24-hour urine proteins (5,8 g) , anti Ds DNA (715 UI/ml) and hypocomplementemia (C3 – 68 mg/dl; C4 – 12 mg/dl; serum haemolytic capacity – 33). She was admitted to internal medicine ward and pulses of cyclofosfamide were begun, with improvement.

Two years later, December 2005, patient was admitted to emergency department because of confusional state lasting a few hours, dysnomia and lentification, without focal neurological deficits or fever. A cerebral CT scan was performed, with bilateral small hypodensities on corona radiata that were probably ischemic and vascular lesions, similar to previous imaging exam. A lumbar puncture was performed and cerebrospinal analysis revealed 1 cell/mm3; low proteins (0,07 g/l) and normal glucose (0,66 g/l). Cultures of cerebrospinal fluid were negative. The initial evaluation included also an electroencephalogram that revealed paroxystic epileptiforme activity on left temporal lobe and carbamazepine therapy was started. Immunological study revealed increased anti-Ds DNA (499,3 UI/ml) and hypocomplementemia (C3 – 56 mg/dl; C4 – 9 mg/dl; serum haemolytic capacity – 51 UA) as well as increased aPLs (anticardiolipin IgG – 70 (N < 15); $ß_2$ glycoprotein > 150 (N < 15). Further investigation also included a cerebral Magnetic Resonance Imaging with multiple bilateral ischemic areas. Metilprednisolone pulses therapy was started as well as hypocoagulation, keeping imunossupression with azatioprine. Patient was discharged from hospital, clinically improved.

In 2006, during internal medicine hospital care follow-up, it was detected on routine lab studies, sub-clinical hypothyroidism, with high anti-peroxidase antibodies, and therapy with levothyroxine was begun.

At this moment, patient is under corticotherapy, 5 mg prednisolone per day, azathioprine, hydroxychloroquine and hypocoagulation. Laboratory studies reveal stable haemoglobin (10,4 g/dl), stage II chronic renal failure (Cl – 58 ml/min/1,73 m^2), normal anti DsDNA (6,1 UI/ml) and no hypocomplementemia.

Discussion

This patient was diagnosed with SLE, based on following criteria: cutaneous fotossensibility, nephrotic syndrome, renal biopsy with membranous glomerulonephritis and compatible immunologic study. The presence of antiphospholipid antibodies in SLE patients is related with an increased risk for thrombo-occlusive incidents [5]. The finding of ischemic lesions on cerebral CT scan, with the presence of antiphospholipid antibodies made us think about SLE related - APS. Secondary prevention was needed but clinical decision was

a difficult step to take because of previous hemorrhagic complications. The effectiveness of oral anticoagulation over aspirin is known [5], so patient started treatment with warfarin.

Cardiac involvement with sterile valvular lesions, which occurred in our patient, and that can lead to valvular insufficiency and subsequent valve replacement need, is a recognized complication of SLE and APS 12. Neurological manifestations were initially related to "lupic flare" but positive aPLs antibodies and no activity disease markers as well as ischemic lesions on imaging cerebral studies were suggestive of APS.

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Case Report 8

Polyglandular autoimmune syndrome subtype 3 – seven clinical reports

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The polyglandular autoimmune syndromes (PAS) are rare polyendocrinopathies characterized by the association of two or more endocrine disorders mediated by autoimmune mechanisms usually leading to a hypofunctional state. Circulating organ- and cell-specific autoantibodies are frequently detected in patients with the syndrome and may be markers of organ failure. In rheumatology it is particularly relevant the PAS subtype 3, which is defined by the presence of autoimmune thyroid disease in association to other autoimmune disorders, especially rheumatic diseases. The authors describe seven clinical cases of patients with polyglandular autoimmune syndrome subtype 3.

Table 1

PAS **type 1** Chronic candidiasis, chronic hypoparathyroidism, Addison´s disease (at least two present)
PAS **type 2** Addison´s disease (always present) and thyroid autoimmune diseases and/or type 1 diabetes mellitus
PAS **type 3** Thyroid autoimmune diseases associated with other autoimmune diseases (excluding Addison´s disease and/or hypoparathyroidism)
PAS **type 4** Combination of organ-specific autoimmune diseases not included in the previous groups

Clinical case 1.

Female, 48 years-old. Previous diagnosis of **pernicious anaemia** (antral gastritis, low vitamin B12 levels and anti- parietal cells antibodies). Haemoglobin normalization after supplementation with parenteral vitamin

B12 was achieved.

Concomitantly, diagnosis of Sjogren's syndrome was established: clinically with dry eyes and dry mouth, presence of anti-SSA and anti-SSB autoantibodies, hypergammaglobulinaemia and suggestive minor salivary gland biopsy.

In the follow up a diagnosis of autoimmune hypothyroidism was also established (TSH elevated and anti-thyroid antibodies positive).

Clinical case 2.

Female, 57 years-old. Female with a history of excessive somnolence, polyarthralgia, leg oedema, alopecia, dry eyes and dry mouth and rarefact eyelids.

Laboratory with normochromic normocytic anaemia, leucopenia, ESR and CRP□, ANA 1/160, homogeneous, positive anti-SSA and anti-SSB autoantibodies, hypergammaglobulinaemia, diminished T3/T4 and elevated TSH with positive anti-thyroid antibodies (antiperoxidase and antimicrossomal). Positive Shirmer´s test.

A diagnosis of **Sjogren`s syndrome and autoimmune hypothyroidism** was established.

Treatment with hydroxychloroquine and levothyroxine was started with clinical improvement.

Clinical case 3.

Female, 43 years-old. Previous diagnosis of **rheumatoid arthritis** (with RF, WR and anti-CCP antibodies +) involving joints of the wrists, hands and feet in treatment with metotrexate, hydroxychloroquine and salazopyrin.

Investigation of an intense fatigue and alopecia revealed an **autoimmune hypothyroidism** with diminished T3/T4 and elevated TSH and positive anti-thyroid antibodies.

Treatment with levothyroxine lead to a favourable clinical response.

Clinical case 4.

Female, 45 years-old. Previous diagnosis of long lasting **rheumatoid arthritis** – clinically controlled with methotrexate and low dose corticosteroids.

After evaluation of an atrial fibrillation *de novo* a thyroid hyperfunction was detected. The study showed diffuse goiter with positive anti-thyroid antibodies – diagnosis of **autoimmune hyperthyroidism** was established.

Clinical case 5.

Male, 46 years-old. Presence of vitiligo in the extremities for several years. Admitted in our rheumatology department for important wasting weight and an addictive symmetrical polyarthritis involving shoulders, knees, wrists, hands and feet, with functional impotence.

Laboratory investigation revealed, normochromic normocytic anaemia, leucopenia, FR, WR and anti-CCP+. T3/T4 elevation with TSH suppression and positive anti- thyroid antibodies. Antinuclear antibodies were negative. Thyroid ultrasonography revealed a diffuse goiter.

Diagnosis of **rheumatoid arthritis, Grave´s disease and vitiligo** were established**.** Treatment with propylthiouracil, low doses corticosteroids, hydroxychloroquine and methotrexate was followed by great clinical and laboratory improvement.

Clinical case 6.

Female, 48 years-old. Patient followed in our rheumatology department for a seropositive **rheumatoid arthritis** with 2 years of evolution in treatment with methotrexate and low dose corticosteroids.

Although asymptomatic, a thyroid dysfunction (T3/T4□and TSH□) with positive anti-thyroid antibodies (anti-peroxidase and anti-thyroglobulin antibodies) and diffuse enlargement of thyroid were detected.

The association of **rheumatoid arthritis** and autoimmune hypothyroidism allowed the diagnosis of **autoimmune polyglandular syndrome type 3.**

Clinical case 7.

Female, 39 years-old. Long standing clinica history of **hypothyroidism** without definitive diagnosis. Admitted to our rheumatology department presenting fever, symmetrical polyarthritis predominantly of hands and feet and serositis involving the pericardium. A diagnosis of seropositive **rheumatoid arthritis** (anti-CCP +) was established. Treatment with methotrexate was followed by a good clinical response. By that time, our study revealed positive anti-thyroid antibodies with extremely elevated levels which lead to the diagnosis of **autoimmune hypothyroidism.**

Conclusion

All patients had autoimmune thyroid disease (hypo or hyperthyroidism) and concomitantly one **rheumatic disease** (2 patients with **Sjogren´s syndrome** and 5 with **rheumatoid arthritis).** Additionally, one had vitiligo and another pernicious anemia. Taking into account all these associated autoimmune disorders, we assume that our patients suffered from a variant of type 3 PAS.

Organ-specific autoimmune endocrine disorders may occur in association with autoimmune polyglandular syndromes. **Up to one quarter of patients** with evidence of hypofunction in one gland have evidence of other endocrine disease. Although **some of these disorders are often asymptomatic,** it is important to consider the diagnosis of potentially life-threatening disorders. These cases illustrate the need for clinical awareness of PAS also in patients with an inflammatory rheumatic disease, particularly rheumatoid arthritis and Sjogren´s syndrome.

PAS should be considered in patients with one or more of the disorders constituting the syndrome; this should facilitate early diagnosis and perhaps even prevention of other components of the disease. Early recognition and replacement therapy can be life-saving, particularly when there is adrenal or thyroid insufficiency.

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