

Sarcoidosis – case report

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Abstract

Sarcoidosis is a multisystem granulomatous disorder of unknown cause affecting most frequently in young adults with bilateral hilar adenopathy and pulmonary infiltrates.

Although the disease spontaneously resolves in many patients, may also evolve to a progressive and severe outcome. The lack of markers of activity and prognosis, and the lack of treatment protocols, raise many doubts on the decision to treat and to provide optimum therapy to the patient.

We present a 32 year old female patient, who has been followed for 10 years with a diagnosis of sarcoidosis, initially with lung and lymph node involvement.

Despite the good initial response to steroid therapy, the disease appears to be steroid-dependent and progressive, with multisystemic involvement.

The steroids side-effects and the inefficiency of azathioprine as “steroid sparing agent” contribute to the difficulty in monitoring the progression of the disease.

Given the unfavorable progression of sarcoidosis and the desire expressed by the patient to become pregnant, we present this case as a pattern of the challenges posed by this disease.

Key words: sarcoidosis, pulmonary fibrosis, pregnancy.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology, affecting mainly young adults usually displaying bilateral hilar adenopathies, pulmonary infiltrates, cutaneous and ocular lesions. In spite of the preferential lung involvement, it can reach any organ, being therefore a constant challenge and an area of the Internist special interest.

The etiology is unknown, but it is accepted the interaction of two factors, a genetical predisposition and an environmental trigger, namely of an infectious or chemical cause, are found in the origin of this pathology.^{1,2,3}

It is still a motive for discussion whether this is an auto-immune disease. In fact, there are aspects of this disease pointing in this sense, as the overlapping of auto-immune diseases (erythema nodosum, uveitis, thyroiditis, Addison’s disease, Sjögren’s syndrome) and the response to corticotherapy.⁴ However, specific antibodies were not identified and it is not also recognized a true preponderance of this disease in female individuals, as it is an auto-immunity feature.⁵

Sarcoidosis diagnosis is established before clinic-imagiology findings compatible and histopathologic evidence of non-caseous granulomas in the affected organs, excluding other granulomatous diseases as tuberculosis.

The disease can be self-limiting with a spontaneous cure, or chronic with recurrence and episodic remissions, and in such cases may evolve to pulmonary fibrosis and severe systemic disease, and it is still unknown the reason to such diverse manifestations.⁶ However, sarcoidosis course and prognosis are related with the disorder severity and extension at the moment of clinical presentation, being usually associated to a self-limited evolution to an acute beginning, and a progressive fibrosis with a more insidious onset.^{4,5} About two thirds of the patients have a spontaneous resolution and a third will evolve unfavorably. The functional limitation develops itself in 15 to 20% of sarcoidosis patients.⁶

There is not an ideal disease activity marker, several monitoring options have been put forward, as the clinic evolution, imagiology aspect, ventilatory tests, serial angiotensin conversion enzyme (SACE) dosing, gallium scintigraphy and bronchoalveolar wash.⁶ However, the careful use of such tests must be a concern to the physician, not only due to the associated costs, but also by their invasiveness and usefulness while following up the patient. SACE dosing, produced by the granulomas epithelioid cells has a clinic usefulness both as diagnosis support,

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monitoring the response to treatment and detecting recurrence.⁷ However, it is not useful in cases where its initial value is not high (around 30% of cases).⁶

Not all sarcoidosis patients need treatment. This must be reserved for cases with symptomatic and progressive pulmonary disease, hypercalcemia and extrapulmonary involvement (cardiac, neurologic, ocular, upper airways).⁸ Corticotherapy has been used for a long time; however, controlled studies are limited by the reduced number of patients and due to the variability of dose and the treatment duration.^{8,9} In spite of the consistent clinical, radiologic and ventilatory response during the treatment period with corticoids, it was not demonstrated they change long term evolution.¹⁰

There are no defined protocols, if treatment is the option. It is reasonable to start with prednisolone, with a 30-40 mg/day dose, being subsequently reduced according to the symptoms, respiratory functions and radiologic evolution. Treatment should be kept for a minimum of 1 year, but can be prolonged if the dose reduction is followed by a recurrence on the disease activity.^{10,11} Higher doses (60-80 mg/day) may be used in the cardiac, neurologic, ocular and upper airways involvement.

Several alternatives have been proposed to corticotherapy, namely the attempt to limit its secondary effects, as methotrexate, chloroquine, azathioprine and cyclophosphamide. Azathioprine is reserved for refractory cases and occasionally it is effective.¹² Methotrexate shows hepatic toxicity and its use can imply to carry out a biopsy. Also the pulmonary toxicity of this agent can contribute to the diagnosis doubt in patients with a sarcoidosis pulmonary involvement.⁵ Chloroquine is effective in the cutaneous form, but not much interest in the systemic sarcoidosis. Other agents, as pentoxifylline, thalidomide, infliximab, cyclosporine, minocycline and leflunomide, have been a target of a limited clinic use.

At present, the limited experience, the non-existence of controlled studies and the unsatisfactory results of these new agents, imply that the steroids remain the pillar of medical treatment.¹⁰ Last, the organ transplant can be an alternative in patients with cardiac, liver and pulmonary disease.

Clinical Case

Female patient, 32 years of age, followed since 1996 in the Medicine Service of Figueira da Foz District

Hospital, referred by the Emergency Service due to the appearance of multiple cervical and supraclavicular adenopathies. On the anamnesis, he referred the condition starting about 2 months earlier, identifying a right submaxillary adenopathy, which has suffered no change after non-steroidal anti-inflammatory medication suggested by the assistant physician. The clinical deterioration, appearing multiple cervical and supraclavicular adenopathies, has implied that the patient attended the Emergency Service and after that the Medicine consultation.

The patient denied any change regarding systemic complaints, and in her personal history only to be mentioned a tonsillectomy in childhood. She has been a smoker of 5 number of pack years and takes regularly an oral contraceptive. Besides a grandmother with chronic obstructive pulmonary disease, the remaining family history was irrelevant.

At the objective exam, she was aware, cooperative, oriented in time/space, with an apparent age coinciding with her real age. She was afebrile and eupneic, without showing any alteration on her skin and mucosa, as well as vital signs. She weighed 62 Kg and body mass index of 21 Kg/m². Thyroid was impalpable and no changes were recorded on the cardiopulmonary auscultation, abdominal palpation and a summary neurologic exam. The breast observation and palpation showed no changes. Ganglionic chains palpation has identified: two right cervical adenopathies and another one left supraclavicular, all pericentric, two right axillary adenopathies, with a 1.5 cm diameter. No inguinal adenopathies were palpable. All identified adenopathies showed an elastic consistency, normal mobility and were unpainful.

Several diagnosis hypothesis were raised, namely a cytomegalovirus or Epstein-Barr virus mononucleosis syndrome, an acute retroviral syndrome due to human immunodeficiency virus, tuberculosis, toxoplasmosis, neoplasm of hematologic origin (Hodgkin's disease, non Hodgkin lymphoma and leukemia), lung cancer and sarcoidosis.

The initial hemogram showed leukopenia and relative monocytosis; the peripheral blood smear has enabled the identification of vacuolated mononuclear cells, and some of a cleaved core. The erythrocyte sedimentation rate was 18 mm in the 1st hour. The blood biochemistry did not show any changes on the hepatic and kidney function tests, glucose, lactate dehydrogenase and C-reactive protein and recorded



Initial thoracic X ray.

FIG. 1

an increase on the serial calcium of 2.7 mmol/L. Calciuria was 9 mmol/24h (normal interval, respectively: 2.2 – 2.6 mmol/L, in the blood and 2.5 to 8.8 mmol/24 h, in the urine). Paul-Bunnell test was negative and serology have shown immunity for the TORCH group and B hepatitis, and negative for A and C hepatitis and HIV₁ and ₂. Immunoglobulins Ig G, A and M dosage, as well as the electrophoretic proteinogram, did not record any changes. Thorax X ray has shown hilar adenopathies and bilateral diffuse parenchymatous infiltrates, these more evident in the lower fields (Fig 1).

The patient has undergone a right axillary ganglionar exeresis, that identified a granulomatous lymphadenitis, and this can mean either a tuberculosis or sarcoidosis. The first hypothesis was eliminated after the tuberculin intradermoreaction and bacteriologic sputum exam, both negative.

SACE dosage was 76 U/L (upper limit: 52U/L) and the study of the bronchoalveolar wash liquid, obtained by bronchofibroscopy, has shown a slight increase on the cellularity (180/mm³), with macrophages 80%, lymphocytes 20%, neutrophils 0%, with a Thelper/suppressor ratio of 14.83, compatible with sarcoidosis without fibrotic activity.

Having the sarcoidosis diagnosis been reached

with pulmonary involvement in stage II, ganglionar and hematologic, the patient was subject to ophthalmology screening, which has shown no alterations, and to ventilatory tests with a restrictive light pattern and a small reduction on the alveolocapillary diffusion.

Afterwards, for 2 years, there was a surveillance period of the disease activity, where it was seen the adenopathies growth, now with a painful expression, dyspnea for small efforts and asthenia, symptoms associated to a growing titulation of SACE levels, with a maximum of 213 U/L. The bronchoalveolar wash (Table I) made at the time, has shown a strong increase on cellularity (1,200,000/mm³), with macrophages 48%, lymphocytes 47%, neutrophils 5%, with a Thelper/suppressor ratio of 15, i.e., a neutrophilic alveolitis predictive of a fibrotic activity evolution. The patient has started a corticoid treatment, with prednisolone in conventional doses (40mg/day), with a response detected by the quick SACE decrease for normal values.

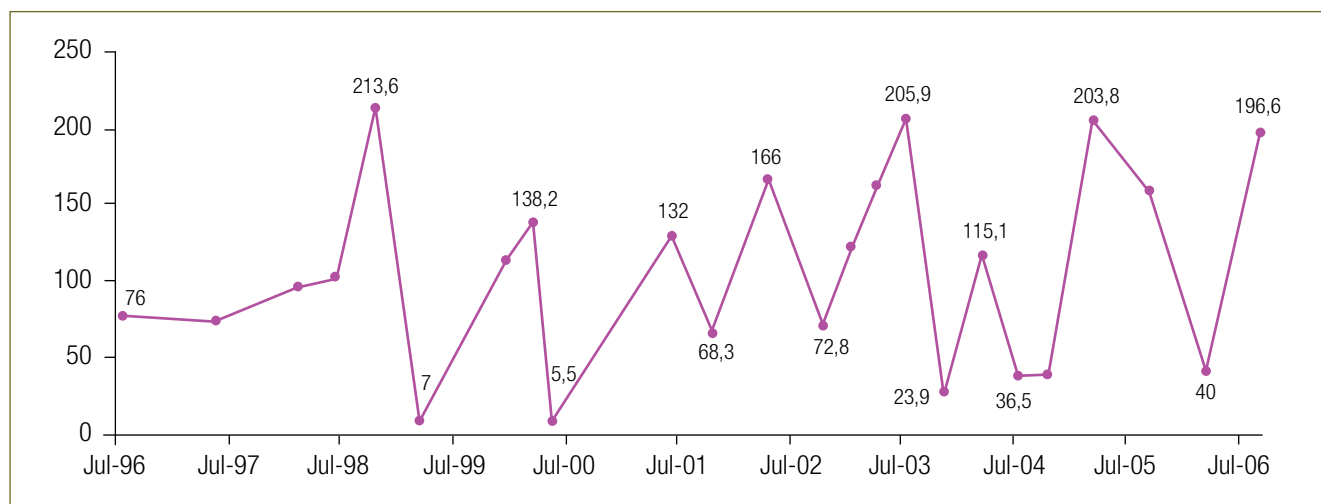
However, the corticotherapy secondary effects were apparent, namely with weight gain, cushingoid facies, dyslipidemia and recurrent respiratory infections, associated to the secondary depressive mood to the changes in the body esthetic, what made difficult steroid administration in the recommended time treatment.

Thus, the patient has been undergoing, for the last 10 years, several therapy cycles, alternating between the clinical complaints associated to SACE high values and periods of clinical and laboratorial remission linked to the corticotherapy secondary effects (Fig. 2). The attempts of using a steroid sparing agent, as azathioprine in the dose of 1 mg/Kg/day, inhaled cor-

TABLE I

Evolution of the bronchoalveolar wash results

LBA	Jul/96	Dec/98	May/99	Units
Cells	180.000	1.200.000	1.200.000	/mm ³
Neutrophils	0	5	3	%
Lymphocytes	20	47	22	%
Macrophages	80	48	75	%
Total lymphocytes	36.000	560.000	26.000	/mm ³
Helper/Suppressor	14,83	15	3,62	



SACE evolution.

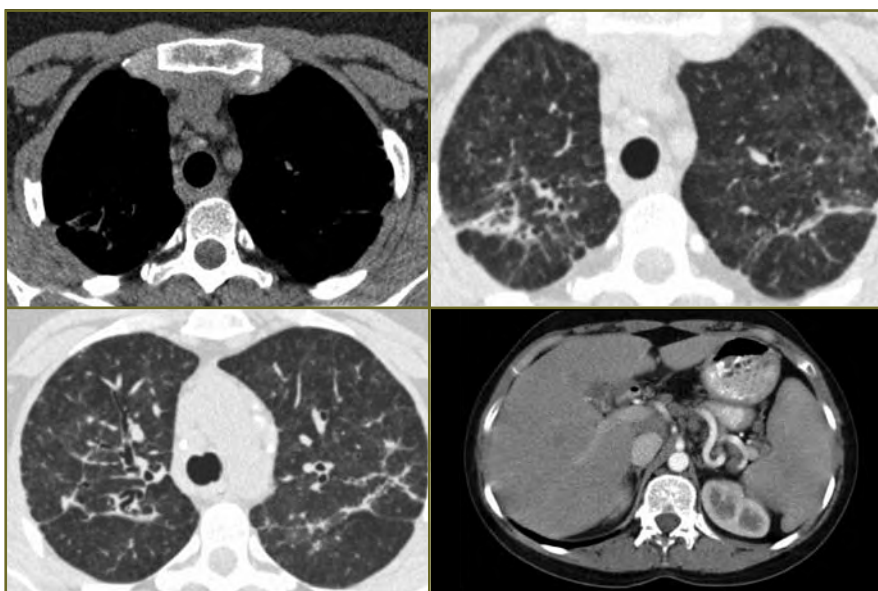
FIG. 2

ticoid, an alternative steroid with a deflazocort, and prednisolone but with increasing time intervals, did not show effective in the disease definitive control which has shown corticoddependency in high doses (0.4 mg/Kg/day).

Recently, the patient now 32 years of age and with a 10 years of disease evolution, has shown the will to get pregnant. Subject to a clinical re-valuation, it was verified a SACE frank increase to 196.6 U/L and a change in the hepatic tests (AST 33 U/L, ALT 66 U/L, γ -glutamyl transferase 306 U/L, alkaline phosphatase 207 U/L). The thoraco-abdominal CAT Scan has shown multiple adenopathies in the mediastine and hilar chains, cylindrical bronchiectasis in both upper lobes, diffuse increase on the pulmonary parenchyma density with multiple milimetric nodular opacities and retractile aspect opacities. It was also identified, at abdominal level, a volume hepatosplenomegaly and multiple lateral-aortic adenopathies (Fig. 3). The ventilatory tests have kept their restrictive features with a moderate change on the alveolocapillary diffusion

and the last bronchoalveolar wash made, confirmed the maintenance of the parenchyma fibrotic activity (cellularity 490,000/mm³, macrophages 66%, lymphocytes 32%, neutrophils 2%, Thelper/suppressor ratio 3.5) (Table I).

The patient has started a new cycle of corticotherapy and was advised to delay pregnancy to a period of clinical remission.



Images of the thoraco-abdominal CAT scan.

FIG. 3

Discussion

This case presents us a young female patient, in fertile age, with a diagnosis of corticoid-dependent sarcoidosis evolving for 10 years, with a multisystemic compromise, pulmonary predominance in stage IC, with a possible liver involvement (a biopsy was not made for a definite diagnosis), corticotherapy multiple secondary effects and an absence of response to azathioprine.

Thus it represents, regardless of the therapeutic action, a minority of sarcoidosis cases evolving unfavorably with a chronic progression and multisystemic compromise. Besides this situation, corticoid-dependency, steroid iatrogen and the consequent difficulty in fulfilling the recommended therapeutic cycles, as well as the azathioprine as steroid sparing agent, contributing also to the difficulty on controlling the disease progression.

Added to this, a pregnancy hypothesis brings us new challenges. As it affects a population preferably young, sarcoidosis coincides with women child bearing age. It is unknown any change on fertility caused by disease. The diagnosis during pregnancy is harder, as symptoms overlap in pregnant women and radiology tests must be avoided.¹³ The current procedures during pregnancy and labor should not be changed.¹⁴

It is a consensus that pregnancy should be avoided, as in this case, in periods of higher disease activity, as well in a situation of respiratory insufficiency, cardiac insufficiency, pulmonary hypertension and a central nervous system disease.¹⁵ Previously, a general evaluation should be made to define the pregnancy risk, determining chronicity, pulmonary capacity, inflammatory activity, imagiological staging and response to the treatment. Visible pulmonary parenchymatous lesions in the thoracic radiography, advanced radiologic stage, extrapulmonary sarcoidosis, low inflammatory activity, need for another medication apart of corticotherapy and advanced maternal age make the worst prognosis factors,¹⁶ and several of these are represented in the current case.

In general, pregnancy in women with controlled sarcoidosis does not bring any problems, either to the mother or to the embryo/fetus. Pregnancy does not change the disease progression, but is common a recurrence 3 to 6 months after labor, therefore patients benefit from a clinic and radiologic follow-up. Indications for the treatment are the same, and

corticotherapy is kept as the therapy of choice, as methotrexate, azathioprine and chloroquine are not recommended in pregnant women, due to the risk of teratogenesis.¹⁷

Corticosteroids cross the placenta barrier, but due to its quick metabolization, fetal serial concentration is of 10% of maternal concentration, without evidence of teratogenesis risk or suppression of the hypothalamus-hypophysary-adrenal axis. To the pregnant woman, corticotherapy can increase the risk of complications related with pregnancy, as an early membrane failure, gestational diabetes and arterial hypertension. In spite of small amounts of glucocorticoids being transferred to the maternal milk, maternal breastfeeding is considered safe.¹⁸ ■

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