CASE REPORT

Sarcoidosis – diagnosis difficulties

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ABSTRACT

Sarcoidosis is a granulomatous, multisystem disorder, with an unknown etiology. This pathology mainly involves the lungs and thoracic lymph nodes, but it can affect almost any organs including the central nervous system. We present a case of sarcoidosis evaluated and treated in our ENT department. A short literature review is included regarding the nature of sarcoidosis, the clinical presentation and the treatment modalities.
KEYWORDS: sarcoidosis, pterygomaxillary fossa, corticosteroid therapy

INTRODUCTION

Sarcoidosis is a granulomatous multisystem disorder with an unknown etiology[1]. This pathology mainly involves the lungs and thoracic lymph nodes, but it can affect almost any organs including the central nervous system[1,2]. Nasal involvement occurs in 3-20% of the patients; in this case, we may expect to multiple small polypoid lesions alongside the nasal septum and the turbinates[1,2].

Sarcoidosis occurs throughout the world, affecting all genders and ages[1,2]. Usually, it is asymptomatic, the main symptoms being represented by lethargy, chronic fatigue, anorexia and specific signs related to the organs involved[3]. The disease has a predilection for adults bellow 40 years of age, with a peak between 20 and 29 years[4]. In Scandinavian countries and Japan, there is a second peak incidence in women over the age of 50[4]. Most studies suggest a slightly higher disease rate for women. Sweden, Denmark and USA appear to have the highest prevalence rates in the world[4].

However, in this review, we will focus on non-specific sarcoidosis with multiple organs involving lungs, pterygomaxillary fossa and eyes, but without involving the oculomotor cranial nerve.

CASE REPORT

A 37-year-old man was admitted in our ENT Department for a 2-week history of non-productive cough episodes followed by loss of consciousness, subconjunctival hemorrhage, and pain in the both sides of the retro-orbital region. He had no systemic symptoms. He was a non-smoker, but he worked in a toxic environment. The physical examination was inconclusive. The ophthalmological examination revealed subconjunctival hemorrhage (Figure 1), a result of the intense cough episodes, without a reduction in visual acuity,

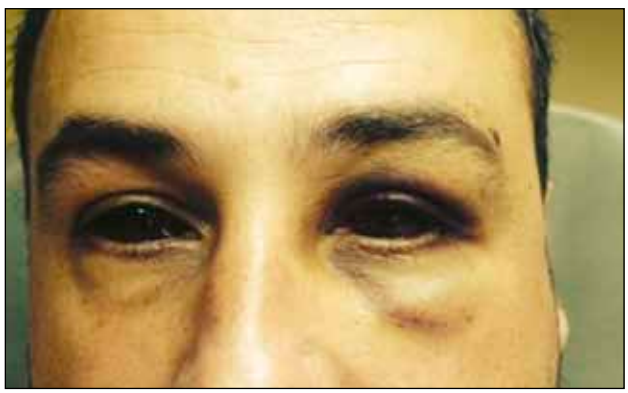

Figure 1 Bilateral subconjunctival hemorrhage

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normal tension on orbital arteries, without ocular motility disorders and no neurological deficits on the oculomotor, trochlear and abducens nerves. Following investigations were normal or negative: complete blood count, blood urea, serum electrolytes, liver function, thyroid function, immunoglobulin electrophoresis, prothrombin time, protein electrophoresis, autoimmune profile blood test for antineutrophil cytoplasmic antibodies (ANCA), both C-ANCA and P-ANCA types.

The thoracic computed tomographic scan revealed an adenopathy in the mediastinum, while the sputum test was negative. After evaluating the case, the pneumophtisiologist recommended a mediastinoscopy to acquire a histological diagnosis and to exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt, and rule out the infection.

The head and neck magnetic resonance imaging revealed left maxillary and left ethmoid sinusitis and an enhancing mass lesion in the left cavernous sinus (Figure 2). The electroencephalogram showed changes compatible with a gross irritative focus in the left temporal fossa. The neurological examination recommendation was angiotensin converting enzyme titration and to perform a biopsy from this tumor mass.

Level of serum angiotensin converting enzyme (ACE) was elevated 70/U/L.

The surgical approach involved an endoscopic septoplasty to enlarge the operative field, uncinectomy and a wide maxillary antrostomy to provide maximum exposure of the posterior maxillary sinus wall (Figure 3a). Careful opening of the posterior wall of the maxillary sinus and underlying periosteum provided ready access to the pterygomaxillary space in an atraumatic approach. Biopsy specimens were taken-off under direct endoscopic visualization, using biopsy forceps (Figure 3b).

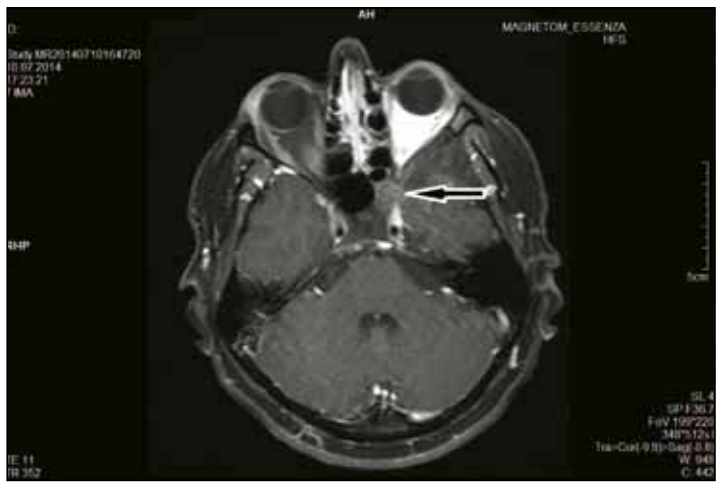

Figure 2 Cranial MRI, axial scan, showing: fibrous dysplasia of the greater and lesser wings of the left sphenoid sinus that diminished the left orbital volume, which hallmark the lateral rectus muscle. Retrobulbar orbital left edema.

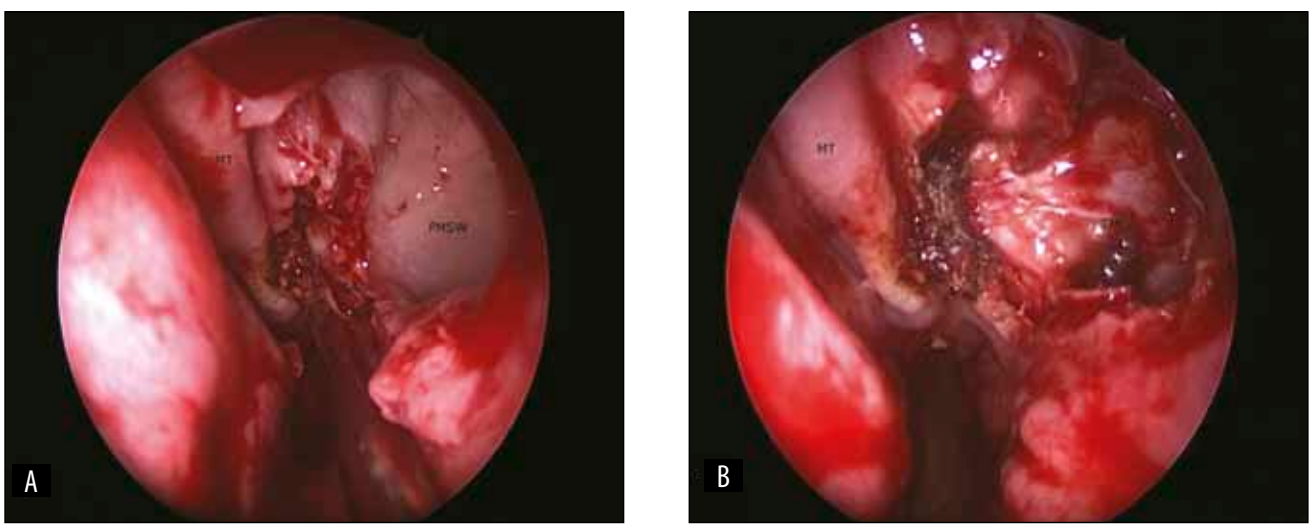

Figure 3 Intraoperatory view - MT-middle turbinate; PMSW-posterior maxillary sinus wall; TM-tumor mass from the pterygomaxillary fossa; SA- Sphenopalatine artery

The histological examination revealed a non-caseating granuloma specific for sarcoidosis.

Before the surgical procedure, the patient has received methylprednisolonum 500mg for 5 days and, after biopsy, Dexamethasone 16 mg for 5 days with real benefits, the headache and the cough episodes were diminished in intensity. The steroid dose was tempered down and shifted to oral methylprednisolonum 32 mg for the next week.

The follow-up cranio-facial MRI performed ten days after the surgical procedure revealed short dimensional remission compared to the previous exam (Figure 4).

DISCUSSIONS

Etiology and genetics of sarcoidosis

Sarcoidosis is a chronic systemic granulomatous disease involving many organs in the body, like lymphatic system, lungs, liver, spleen and bones[2,5]. Sinonasal involvement is considered an uncommon disease manifestation of sarcoidosis[6].

The new staging system for sinonasal sarcoidosis, first implemented by Krespi, divided the disease into three categories regarding the extent and reversibility[7]:

- Stage I - sinonasal sarcoidosis patients usually suffer from limited, reversible partial nasal obstruction as a result of hypertrophic turbinates and edema of sinus mucosa.
- Stage II - sinonasal sarcoidosis is characterized by moderate and reversible encrustations, epistaxis, adhesions, limited single sinus involvement or mucoperiosteal thickening.
- Stage III - sinonasal sarcoidosis is characterized by irreversible septal perforation, intranasal synechiae, nasal stenosis, saddle shape deformity or extensive sinus involvement.

In sarcoidosis, the lung is the most frequently involved identified organ. The lung disease, which occurs in >90% of patients with sarcoidosis, can be categorized into four stages using the Scadding classification system[8]:

- stage I - hilar adenopathy alone;
- stage II - hilar adenopathy with pulmonary infiltrates;
- stage III - pulmonary infiltrates alone;
- stage IV - pulmonary fibrosis.

The pathogenesis of sarcoidosis results from exposure to environmental agents in a genetically susceptible host. The most commonly associated genes are class I HLA-A1 and –B8 and class II HLA-DR3, the inheritance being polygenic. The disease begins with an alveolitis consisting of T cells that elaborate chemotactic factors that attract monocytic cells, which will transform into epithelial cells[9,10]. These cells form the granuloma that may lead to fibrosis[10]. This granuloma has not a specific histologic feature, similar ones occurring in tuberculosis, berylliosis, leprosy, hypersensitivity pneumonitis, fungal disease and chronic inflammatory processes[11,12].

Externally, nasal involvement may present as raised, papular lesions on the nose that can coalesce to form bluish-red swellings. These lesions are firm and elastic when palpated and involve the entire thickness of the dermis[13].

Another form of nasal sarcoidosis known as *lupus pernio* is the most characteristic cutaneous lesion of sar-

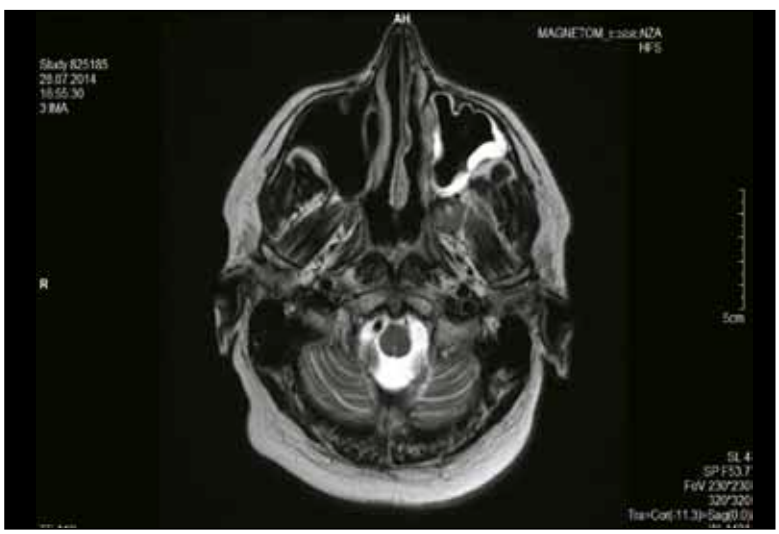

Figure 4 A follow-up MRI investigation evidentiates diffuse thickening in intensive hyposignal T2,T1, discrete hypersignal swelling on narrow areas and minimum contrast amprenting, that withholds the sphenoid wing on the left side, with volumetric growth of the bony mass without destruction in the bony cortical tissue, small volumetric diminishing of left middle cerebral fossa, with no effraction into the left orbit or the left intraorbital structures – short dimensional remission compared to the previous exam.

coidosis[14]. The lesion is typically described as red to purple (due to increased vasculature), swollen, with shiny skin changes on the nose, cheeks, lips or ears. It is particularly resistant to both surgical and medical therapy[15].

Diagnosis methods

To make the diagnosis of sarcoidosis, three criteria must be fulfilled: the compatibility of the clinical and radiographic findings with sarcoidosis, non-caseating granulomas and other causes for granulomatous changes excluded[16].

- Biochemical data involves elevated serum or urinary calcium and elevation of angiotensin-converting enzyme (ACE). ACE converts angiotensin 1 in angiotensin 2 and is correlated with the clinical activity of sarcoidosis in 83% of cases. Therefore, it is useful for both the diagnosis and the monitoring of sarcoidosis. It is important to know that ACE levels can also be elevated in tuberculosis, lymphoma, leprosy and Gaucher's disease[17].
- Histologic findings confirm the clinical diagnosis by the presence of non-caseating granulomas in the nasal mucosa[5].
- Sinus CT and X-ray are abnormal, as well as the pulmonary x-ray that may reveal hilar lymphadenopathy or pulmonary fibrosis[8]. Gallium-67 uptake is elevated in the nasal mucosa because the isotope is taken up in the inflammatory tissues and accumulates there, remaining yet nonspecific[7,17].
- Kveim test

Kveim test is a skin test that was introduced by A. Kveim in 1941[18]. This investigation consists in intradermal injection of 0.15-0.20 ml of a suspension in saline of material from a granulomatous lymph node that was prelevated from a patient with active disease. It takes 4-6 weeks to develop; a positive reaction appears as a firm nodule of 3-8 mm in diameter[18]. The histological examination revealed a collection of epithelioid cells in small tubercles associated with multinucleate giant cells and lymphocytes[19].

A positive Kveim test is generally accepted as evidence of sarcoidosis, the mechanism being not yet known. At present, there is virtually no evidence to support the view that a positive reaction is based on an immune response to a unique etiological agent, though this was presumably the theoretical basis of the original test[18,19]. The reliability of the test depends largely on the test material itself, and batches prepared in apparently identical fashion may vary widely in their activity. It is therefore essential that any material used for diagnostic purposes to be adequately standardized against material of known activity[20].

The contribution of the Kveim test to diagnosis can be assessed in the light of knowledge of the proportions of patients with sarcoidosis at various stages and with various leading manifestations that give a granulomatous response to the suspension used for the test and the clinical picture of the patient tested[20]. In a patient with a clinical picture compatible with sarcoidosis, a granulomatous response increases and a non-granulomatous one diminishes the probability of this diagnosis to a degree varying with the apparent stage of the disease[21].

For this case we do not propose the histology of Kveim reaction except to comment that, in our view, reports of the results of this test should be in terms of histological appearances[19-21]. This does not, of course, exhaust the possible variations, and in some instances reports should refer to mixed reactions, or to such features as the presence of large numbers of giant cells, foreign material, especially birefringent, and necrosis. This histological report should be made for all patients from affected tissue[22].

Differential diagnosis

Differential diagnosis for sarcoidosis requires the exclusion of alternative diseases and it is usually harder to get in absence of biopsy from the affected tissue[5]. Many systemic disorders offer the same clinical aspects[23]. Neurological diseases (multiple sclerosis, acute demyelinating encephalomyelitis), infectious diseases[24] (tuberculosis, cryptococcosis, neurosyphilis), neoplasms (lymphoma, en plaque meningioma, metastatic carcinoma, primary CNS tumor), and vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome)[25] can be included in the differential diagnosis. In the table below, we offer some specific investigations[25,26] (Table 1).

Treatment

The management of sarcoidosis consists of systemic corticosteroids[27].

In stage 1 of pulmonary involvement, the "watchful waiting" with periodic examination is indicated. Many patients can get spontaneous remission[28].

Patients with stage 2 and 3 disease, with no spontaneous improvement, who show worsening at 6 months after diagnosis, will usually require treatment - 10 to 40 mg per day of prednisone will control the symptoms[28,29]. The oral dosage may be reduced by using intranasal steroids[28].

Non-steroid treatment is indicated when patients have adverse effects over corticosteroid treatment[29,30].

Methotrexate is a successful alternative treatment[31], while cyclophosphamide is rarely used with modest benefits[32].

Chloroquine, due to its immunomodulating properties, can be used for cutaneous lesions, neurological sarcoidosis and bone lesions[33]. Cyclosporine, known with lymphocyte-suppressive properties, can also be used on skin sarcoidosis[34].

Table 1
Differential diagnosis of sarcoidosis

Type	Specific Disorders	Specific Investigation
Rheumatologic disorders	Juvenile idiopathic arthritis (juvenile RA) Kikuchi-Fujimoto disease (lymph nodes only) Necrotizing sarcoid granulomatosis RA Sjögren syndrome[26] Granulomatosis with polyangiitis (Wegener granulomatosis)[19]	Blood test for antineutrophil cytoplasmic antibodies (ANCA). Of 2 types: C-ANCA and P-Anca Chest CT scan Sinus CT scan Biopsy of affected tissue
Hematologic cancer	Castleman disease (a lymphoproliferative disorder associated with infection by HIV or human herpesvirus 8) Hodgkin lymphoma Non-Hodgkin lymphoma Splenic lymphoma	HIV tests Biopsy of affected tissue (fine needle aspiration samples) Liver function and serum protein CT scan
Fungal infection	Aspergillosis Blastomycosis Coccidioidomycosis Cryptococcal infection Histoplasmosis	Eosinophilia Positive skin test to Aspergillus spp. Elevated Serum Immunoglobulin E (IGE) CT scan MRI scan Positive serology for different kinds of fungus. Biopsy of affected tissue
Other infections	Brucellosis Cat-scratch disease (lymph nodes only) Mycoplasmal infection Pneumocystis jirovecii infection Syphilis	VDRL test Treponemal enzyme immunoassay (EIa) T. Pallidum chemiluminescent assay. CT scan MRI scan Biopsy of affected tissue Cerebrospinal fluid analysis.

Infliximab proved to be an effective treatment for patients with hepatic sarcoidosis and neurosarcoidosis[35].

Complications

There are a lot of important problems when sarcoidosis is not diagnosed at the proper time. It can lead to complications that may affect different parts of body[36,37]:

- Lungs - untreated pulmonary sarcoidosis can lead to irreversible damage of the tissue between the air sacs and also to pulmonary fibrosis[36];
- Eyes - can affect almost any part of the eye, can eventually cause blindness[37];
- Kidney - glomerular disease, obstructive urophaty and end stage renal disease (ESRD)[38,39];
- Heart - advanced heart block, arrhythmias, congestive heart block[40];
- Nervous System – inflammation in the facial nerves can cause irreversible facial paralysis[37].

Follow-up

Usually, sarcoidosis spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration[41]. These patients can be followed with CT scan, MRI scan, serial X-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (routine renal and liver function testing, annual slit-lamp ophthalmologic examination). The frequency of follow-up testing is determined by the severity of disease[42].

CONCLUSIONS

Sarcoidosis is a systemic disorder characterized by non-necrotizing granulomatous inflammation, with varying degrees of concomitant fibrosis[1]. For the ENT domain sarcoidosis, minimally aggressive biopsy is desirable; surgical resection of intracranial granulomas is only indicated in life threatening situations or when medical treatment is insufficient. The gold standard treatment for all types of sarcoidosis is the chronic administration of corticosteroid. In patients unresponsive to corticosteroids or if there are contraindications to the use of systemic corticosteroids, methotrexate may be used[29,31].

The peculiarity of this case is represented by the subconjunctival hemorrhage and loss of consciousness without sphincterian incontinence during cough episodes, the symptomatology being remitted under corticosteroid anti-inflammatory treatment, without clear determination of a certain etiology.

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