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Sinonasal Sarcoidosis: Review and Report of Fifteen Cases

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Objectives: **Sinonasal sarcoidosis remains a poorly understood and uncommon chronic granulomatous disease of unclear origin. We have attempted to characterize the main clinical and radiologic criteria for diagnosis and to discuss the treatment.** ***Methods:*** **A retrospective study of 15 cases of chronic, symptomatic, and biopsy-proven sinonasal sarcoidosis and a review of the literature are realized.** ***Results:*** **Among the 15 patients, there were 8 women and 7 men with a mean age of 44 years. The most frequent presentation was a chronic, often crusty, rarely destructive inflammatory rhinosinusitis with nodules on the septum and/or the turbinates. Pulmonary sarcoidosis was associated in 12 cases. Involvement of the nasopharynx, the pharyngolarynx, the skin, the lachrymal and salivary glands, and the liver was associated in some cases. Levels of angiotensin-converting enzyme were elevated in 10 cases and normal in 3 cases. Gallium scan performed in three cases was positive. Radiologic studies showed nodules on the septum and/or the turbinates in 14 cases, complete or subtotal opacification of the sinuses and/or the nasal cavities in 13 cases, and nasopharyngeal or pharyngolaryngeal lesions in 4 cases. Treatment with corticosteroids, methotrexate, azathioprine, and surgery appear globally disappointing in view of the side effects and the relapses during a long follow-up (3–15 yr; mean, 6 yr).** ***Conclusion:*** **On the basis of this study, we propose the following diagnostic criteria: 1) histopathologic confirmation of noncaseating granuloma; 2) chronic rhinosinusitis poorly responsive to conventional treatment and radiologic evidence of rhinosinusitis, often with nodules on the septum and/or the turbinates; 3) elevated level of angiotensin-converting enzyme; 4) positive gallium scan (if performed); 5) frequent evidence of systemic, especially pulmonary, sarcoidosis; 6) no evidence of other granulomatous diseases, such as Wegener granulomatosis.** ***Key Words:*** **Sarcoidosis, sinusitis, sinonasal sarcoidosis, granulomatous disease.**

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INTRODUCTION

Sarcoidosis is a chronic noncaseating granulomatous disease of unknown origin, principally affecting the respiratory tract.[1] Granulomatous involvement of nasal mucosa, already described by Boeck in 1905, is, however, rare. Involvement of sinonasal mucosa could be isolated or a part of multisystem involvement.[2]

MATERIALS AND METHODS

We retrospectively analyzed 15 cases of sinonasal sarcoidosis (SNS), either isolated or associated with multiple organ system involvement, particularly pulmonary sarcoidosis. Ear, nose, and throat (ENT) examination was completed by systematic search for other site involvement, by measurement of angiotensin-converting enzyme (ACE) levels, by sinonasal computed tomography (CT) scan, sometimes by gallium scan, and invariably by multiple biopsies of visible nasal lesions.

The treatment consisted of systemic corticosteroids alone (eight cases), local corticosteroids alone (one case), or combined (five cases), based on the severity of ENT symptoms or on head and neck involvement associated with thoracic lesions. The dose used was 0.5 to 1 mg/kg of prednisolone with gradual reduction. In two cases methotrexate and in one case azathioprine were used in addition to corticosteroids. In one case, therapeutic abstention with clinical follow-up was decided. The duration of corticotherapy was variable, ranging from 6 months to 8 years. The follow-up period ranged from 3 to 15 years (mean, 6 yr).

RESULTS

Clinical, Radiologic, Biologic, and Histopathologic Findings

Among the 15 patients, 8 were women and 7 were men, with ages ranging from 31 to 73 years (mean age, 44 yr). Five patients were of North African origin, four were blacks, and six were Europeans. All patients were symptomatic, and the most frequent symptoms were nasal obstruction (12 cases), rhinorrhea (9 cases), nasal crusts (6 cases), epistaxis (6 cases), anosmia (2 cases), facial pain (5 cases), and intermittent dysphagia and dyspnea (1 case). Other visible localizations were nodular skin lesions (4 cases), lupus pernio (2 cases), cervical and supraclavicular lymphadenopathy (4 cases), ophthalmic involvement (3 cases), and salivary gland involvement (2 cases)

Ear, nose, and throat examination showed nasal crusts in eight patients, polyps of the middle meatus in two patients, small, often pale or erythematous nodules or

granulations on the turbinates and/or the septum in 14 patients, inflammatory mucosa in nine patients, turbinoseptal synechiae in two patients, saddle nose deformity from septal and nasal bone sarcoid involvement in one patient, sarcoid localizations in the buccal cavity, rhinopharynx, pharynx, and larynx in four patients, with a pseudotumoral aspect of nasopharynx in one patient and involvement of the maxillary sinuses detected by biopsy during sinusoscopie in two patients. Thus, the most frequent presentation was a chronic inflammatory rhinitis or rhinosinusitis with occasional, though rarely destructive, crusting, with often nodular lesions on the septum and/or turbinates (Fig. 1).

Among 13 determinations, ACE levels were elevated in 10 patients and normal in 3 patients.

Gallium scan performed in three patients showed hepatosplenic involvement in one patient, sinonasal involvement in two patients, and involvement of lachrymal and salivary glands in one patient.

The CT scan showed different types of lesions:

Nodular lesions of the septum in 13 patients and of the inferior turbinates in 10 patients (Fig. 2).

Mucosal thickening and complete or subtotal opacification of ethmoidal, maxillary, and/or sphenoid sinuses in nine patients; obstruction of the ostiomeatal units in two patients and of the upper part of the nasal cavities in two patients.

Turbinoseptal synechiae in two patients.

Destruction or erosion of turbinates in two patients, of nasal bones in one patient, and of septum, ethmoid air cells, and sphenoid sinus in one patient.

Nasopharyngeal and/or pharyngolaryngeal involvement in four patients with pseudotumoral aspect of the rhinopharynx in one patient, lachrymal glands involvement in three patients, salivary glands involvement in two patients, and optical perineuritis in one patient.

Consistent histopathologic examination of multiple biopsy samples of nasal or sinusal mucosa showed noncaseating granulomatous lesions in all 15 cases.

Pulmonary and mediastinal involvement was considered as a stage II of sarcoidosis in 11 cases and as a stage III in one case. Bronchoscopic biopsies in seven cases and biopsy of mediastinal lymphadenopathy via mediastinoscopy in one case confirmed the diagnosis of sarcoidosis suspected on radiologic findings. In four other patients, the radiologic findings were compatible with thoracic sarcoidosis and were associated with increased levels of ACE and abnormalities in pulmonary function tests. The search for mycobacteria was always negative. The diagnosis of sarcoidosis was also confirmed by cervical lymphadenopathy biopsy in two cases, by skin biopsy in three cases, and by liver biopsy in one case.

Our 15 cases of SNS can therefore be classified as follows:

Association of sinonasal and pulmonary sarcoidosis in 12 cases, 3 cases among them also manifesting nasopharyngolaryngeal involvement.

One case of SNS associated with hepatosplenic sarcoidosis.

One case of SNS associated with pharyngolaryngeal sarcoidosis.

One case of isolated SNS.

Results of Treatment and Follow-Up

We noted complete failure after treatment with hydroxychloroquinine in two patients who initially refused corticosteroids and two failures after surgery. These four patients later received systemic corticosteroids. In one case, all intensive medical treatments (corticosteroids, methotrexate, azathioprine) failed, with several relapses of nasal, cutaneous, and pulmonary lesions as well as evolution to respiratory insufficiency.

In eight cases, relapse appeared after 1 year of corticotherapy with decreasing steroids doses (relapse for 40 mg prednisolone daily in two cases, 30 mg in three cases, 15 mg in two cases, and 5 mg in one case) and required a renewed increase of corticosteroid doses.

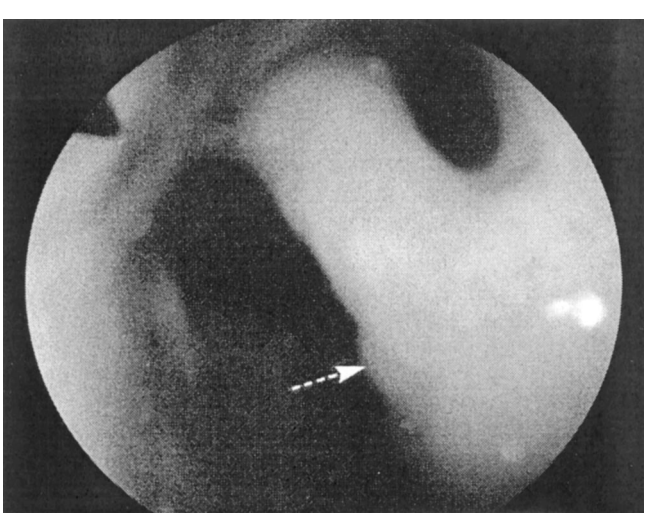

Fig. 1. Nasal sarcoidosis, endoscopic view. Sarcoid nodule on the inferior turbinate (arrow).

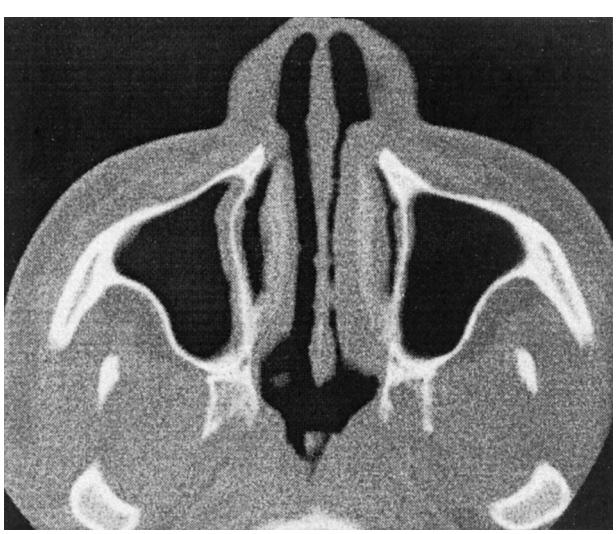

Fig. 2. Nasal sarcoidosis, axial computed tomography scan. Sarcoid granulomas on the nasal septum and inferior turbinates.

Satisfactory control of symptoms was achieved in two patients after stopping the corticosteroids and was maintained for up to 2 years. In one patient with severe sarcoid lesions of the nose and the rhinopharynx, it was possible to withdraw systemic corticosteroids after 8 years without clinical or CT relapse, and the patient remains well 3 years later. In one case of isolated SNS, the nasal lesions remained stable for up to 3 years with a simple follow-up.

Two patients were lost for follow-up, one due to death related to intercurrent illness.

The untoward side effects of corticotherapy were relatively frequent. In one case, methotrexate was stopped because of toxic hepatitis.

DISCUSSION

From the literature, it is difficult to estimate the incidence of sarcoidosis and especially that of SNS. It is probably underestimated in the absence of methodical ENT examination in thoracic sarcoidosis. The overall incidence of sarcoidosis can be estimated to be between 6 and 10 per 100,000, with a slight female preponderance and with geographical and ethnic variations.[2–5] Wilson et al.[5] described 27 cases of sarcoidosis (21 biopsy-proven cases) with head and neck involvement among 750 case of sarcoidosis. In a study from the Mayo Clinic, 220 patients out of 2319 cases of sarcoidosis (9%) had head and neck involvement and only 1% had isolated involvement of nose and sinuses.[6]

The clinical signs are that of a chronic rhinitis or of a chronic inflammatory rhinosinusitis, sometimes with crusting, and poorly responsive to conventional treatment. SNS diagnosis should be evoked and nodules and granulomatous lesions carefully looked for to guide biopsy, as only this has a real diagnostic utility. Consequently, within this context any atypical or unusual lesion may represent a granulomatous lesion, and in these cases biopsy should therefore be performed systematically. Blindly performed nasal biopsy was negative in 12 of 13 cases but biopsy of abnormal mucosa gave a high diagnostic yield, with positive results in 19 of 21 cases.[5] Biopsy-proven involvement of sinuses seems to be rarer than nasal involvement, usually with concomitant pulmonary and extrapulmonary sarcoidosis.[1,6]

According to the literature,[1–9] ENT examination and guided biopsy enables confirmation of the diagnosis of pulmonary sarcoidosis suspected on radiological examination of chest or leads to complementary investigations, as sarcoidosis can be a multisystemic disease. Levels of ACE were increased in 80% of cases in our study. This emphasized the interest of its measurement during the investigation of a granulomatous disease as reported in the literature.[1–5]

Although sinonasal CT scan was rarely precisely evaluated in the different studies,[1–4,8–11] we tried to appreciate its usefulness in diagnosis as well as in differential diagnosis. The granulomas or nodules are visible only to expert eyes and constitute a frequent and helpful diagnostic criteria of sarcoidosis. Interpretation of other CT features such as opacification of paranasal sinuses, ostiomeatal units, or nasal cavities or involvement of nasopharynx, lachrymal and salivary glands or optic nerve depends on clinical context as they are nonspecific radiologic features. Destructive lesions or bone erosions need to be differentiated from other systemic granulomatosis. Thus, depending on the site and type of lesions, other granulomatous diseases, such as tuberculosis, aspergillosis, actinomycosis, Wegener granulomatosis, Churg-Strauss syndrome, or even rare ENT localizations of Crohn disease, should be considered in the differential diagnosis.[1–4,7–10]

Due to variable evolution of SNS and to their presentation (isolated or associated with multisystem sarcoidosis), the treatment of SNS remains poorly codified in the literature. Different treatments have been proposed:

Simple follow-up in view of stability or spontaneous regression of the lesions.[2–5]

Local nasal corticosteroids and/or oral corticosteroids[2–6,8,11,12] and/or intralesional injections of corticosteroids.[2,3,9]

Endoscopic sinus surgery or laser surgery.[8,9,11,13]

Hydroxychloroquine, methotrexate, azathioprine, thalidomide, pentoxifylline, or infliximab to decrease the doses of oral corticosteroids.[4,5,8,12]

Thus, for Krespi et al.,[2] local corticosteroid therapy gave good results (50%) in cases of limited and reversible SNS (stage I, 6 patients). In cases of moderate but still potentially reversible SNS (stage II, 21 patients), improvement was 90% when it was associated with intralesional injections of long-acting corticosteroids. Nevertheless, improvement was very poor with corticosteroids (40–60 mg of prednisolone per day) in cases of severe and irreversible SNS (stage III, 4 patients). The endoscopic sinus surgery may be used to treat only "identifiable symptomatic anatomic blockage" for Kay et al.[11]

Our long-term results clearly appear to be not as good as those reported by Krespi et al.,[2] even though our results were impressive in the beginning of the treatment with high-dose corticosteroids. These therapeutic results, globally disappointing in the long term, and the frequent evolution toward pulmonary fibrosis when head and neck and thoracic lesions are associated or when sarcoidosis of upper respiratory tract is associated with lupus pernio,[7,8] require a careful and long-term follow-up as well as interdisciplinary management. In our experience, response rates to treatment of symptomatic biopsy–proven SNS vary from no improvement to complete remission. According to the literature,[5,8,9] our patients with histopathologic evidence of SNS were generally more difficult to check compared with patients presenting with sarcoidosis without sinonasal involvement.

CONCLUSION

Sinonasal sarcoidosis can be isolated or associated with a multisystemic, particularly pulmonary granulomatous disease. The prevalence of SNS remains difficult to estimate. When nodules are visibly noted by ENT specialists or radiologists, the diagnosis of SNS is evoked and may lead to nasal biopsy. Consequently, guided biopsy, ACE measurement and CT findings are the main diagnostic criteria. The natural history and the course of SNS are unpredictable despite symptomatic and biopsy-confirmed sinonasal involvement, which seems to be a factor in chro-

nicity and poor prognosis. The treatment is poorly codified. Corticosteroids remain the cornerstone of therapy. Other immunosuppressive agents and/or endoscopic sinus surgery can have some effectiveness in selected cases. Despite an often long and aggressive treatment, relapses and chronicity are frequent after tapering or discontinuing the corticosteroids and require a long follow-up and interdisciplinary management. Further studies are indicated to determine the effectiveness of the different treatments, to evaluate the prognostic factors, and to access the natural history of SNS.

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