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Sarcoidosis with upper respiratory tract involvement

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Summary The aim of the study was to investigate the upper respiratory tract as a site of extrapulmonary sarcoidosis. Diagnosis of sarcoidosis with upper respiratory tract involvement was performed on the basis of clinical, laboratory, radiographic and histological evidence and by excluding other granulomatous diseases in eight patients followed by the Sarcoidosis Regional Reference Centre pneumologists in collaboration with an experienced ENT specialist at Siena University. In five cases, sarcoidosis was localized in the parotid glands, in the other three subjects larynx, nasopharynx and nose were involved. In four patients parotid gland, nasopharynx and upper respiratory tract mucous membrane involvement was the only clinical manifestation at onset of the disease.

Upper respiratory tract involvement should be suspected in all patients with systemic sarcoidosis and in patients with persistent upper respiratory tract symptoms of unknown cause. What a general practitioner should do as not to miss SURT is underlined. Interdisciplinary management and collaboration are of paramount importance for rapid diagnosis and to avoid the possible complications of this form.

Abbreviations: S, Sarcoidosis; SURT, Sarcoidosis of the upper respiratory tract; ACE, Angiotensin converting enzyme; BAL, Bronchoalveolar lavage; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; HRCT, High-resolution computed tomography; CT, Computed tomography

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Introduction

In sarcoidosis upper respiratory tract involvement (SURT) is uncommon, occurring in approximately 6% of patients. The most characteristic and earliest detectable site is the parotid gland, that encompass a wide variety of clinical syndromes; whereas larynx, nasopharynx and nose localization are less frequent and more difficult to identify.[1–7] The large epidemiological study, A.C.C.E.S.S.[3] recently performed in the USA, reported ear, nose and throat involvement in 22 (2.3%) out of 736 S patients enrolled; in only three it was limited to the nasopharynx.

Diagnosis of SURT without typical lung involvement requires a compatible clinical pattern, histopathologic confirmation of noncaseating granulomas, and exclusion of other diseases with similar histologic or clinical manifestations.[1,8] Differential diagnosis therefore includes tuberculosis, histoplasmosis, blastomycosis, coccidiomycosis, syphilis, actinomycosis, malignant neoplasm, cartilaginous tumours, Wegener's granulomatosis and amyloidosis.[1,6,8]

Here we report the clinical findings of eight patients with histologically proven SURT and describe four of them in greater detail, to show four different types of involvement. In these patients sarcoidosis was diagnosed on the basis of the histology of upper respiratory tract biopsy specimens.

Patients

The subjects were eight patients with SURT: five women and three men ranging in age from 22 to 66 years (mean age 51 years). Their clinical features are summarized in Table 1. In five patients S involved the parotid glands, and in three the larynx, nasopharynx and nose. In all patients, SURT was diagnosed according to histopathological criteria. In four cases, described in more detail below, biopsies of parotid glands, nasopharynx, larynx and nasal mucosa enabled diagnosis of S. In these subjects the upper respiratory tract manifestations were the only clinical evidence at the onset of the disease. All patients with parotid gland involvement had bilateral localization, more evident in the left gland.

Case 1: A 22-year-old man showed a single clinical sign at the onset of the disease, namely bilateral parotid enlargement (more evident on the left side) associated with fever, dry mouth and sweating. Biopsy of the left parotid gland (Fig. 1) led to a diagnosis of S, subsequently confirmed by radiographic findings (stage I in chest X-ray) and liver biopsy. A long course of steroid therapy was maintained. Chest X-ray became normal and the patient is now well. The parotid glands show minimal ultrasonographic evidence of non-homogenous parenchyma.

Case 2: A 62-year-old woman had systemic S (lungs, hilar–mediastinal lymph nodes, ribs) and involvement of the salivary glands and larynx, confirmed by histological examination. At the onset the patient complained of dysphagia with solids and liquids, persistent cough, retrosternal pain and exertion dyspnea. Chest X-ray showed stage II sarcoidosis, BAL documented lymphocytic alveolitis with a CD4/CD8 ratio of 7. ACE and lysozyme serum levels were elevated, together with IgM immunocomplexes. The patient was treated with scalar dose of prednisone (starting at 30 mg/day) and achieved radiological improvement. One year later, she complained of oral discomfort with impaired sense of taste. Parotid sialography showed reduced volume of the glands and rare peripheral duct ramifications. Biopsy of the labial mucosa showed

Table 1 Clinical features.

Case no.	Sex	Age (yr)	Chest radiological stage	ACE (UI/ml/min)	% BAL lymphocytes	CD4/CD8 ratio	SURT localization	SURT biopsy	Therapy
1	M	44	1	74 ↑	n.d	n.d.	Parotid	+	Steroids
2	F	66	1	49	73.5	5.8	Parotid	+	Steroids
3	F	62	2	67 ↑	50	10	Larynx	+	Steroids
4	F	64	3	105 ↑	55	5	Parotid	+	Steroids
5	F	39	1	56 ↑	n.d.	n.d.	Rinopharinx	+	Steroids
6	M	22	2	62 ↑	45.5	6	Parotid	+	Steroids
7	F	62	2	67 ↑	43	2.8	Parotid	+	Steroids
8	M	49	3	n.d.	32	2.3	Nose	+	Surgery Steroids

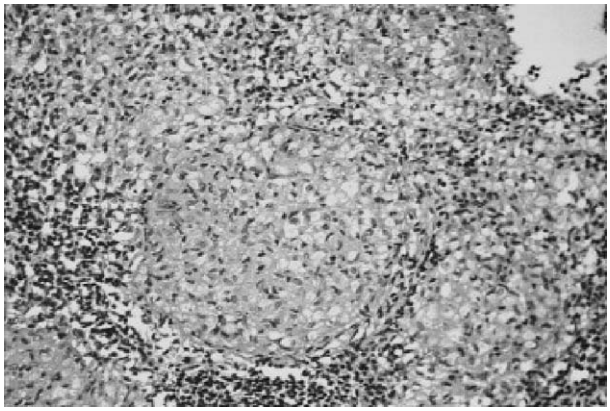

Figure 1 Biopsy of the right parotid gland. Note non-necrotizing epithelioid granuloma (hematoxylin–eosin, × 20).

epitheliod granulomas without necrosis, consistent with S. Dysphonia and pyretic pharyngodynia manifested about 2 years later, together with relapse of S (chest X-ray stage II). ENT examination revealed marked hypomobility of the right hemilarynx with swelling of the right false vocal cord and laryngeal vestibule. Biopsy (Fig. 2) showed Ziehl–Nielsen-negative, epithelioid giant-cell granulomatosis and a subsequent bronchial biopsy confirmed these histopathological findings. BAL showed lymphocytosis (59%) with a CD4/CD8 ratio of 3.1. The patient was treated with scalar doses of prednisone starting at 40 mg/day and achieved significant clinical and radiological improvement. Three months later, while on 20 mg/day prednisone, the patient complained of dysphonia and purulent discharge. Routine laboratory tests revealed ESR 65 mm/1 h, CRP 5.7 mg/dl, microhematuria, and hypogammaglobulinemia. Chest X-ray showed non-homogeneous parenchymal infiltrate with cavity lesions. *Mycobacterium tuberculosis* complex was found in sputum. After several months of antitubercular and low dose steroid therapy, the patient's condition improved considerably and dysphonia disappeared. Chest X-ray showed an absence of tubercular lesions but relapse of S (stage III) associated with an increase in serum levels of ACE and lysozyme. After 11 years the disease is still in active phase and the patient continues low dose steroid therapy.

Case 3: A 39-year-old female complained of chronic maxillary sinusitis, documented by CT. ENT examination showed mucosal swelling occluding 1/3 of the nasopharyngeal cavum. Nasopharyngeal biopsy showed granulomas compatible with S. Chest CT revealed mediastinal lymphoadenopaties. Corticosteroid treatment was started and continues. The nasopharyngeal swelling decreased but has not disappeared.

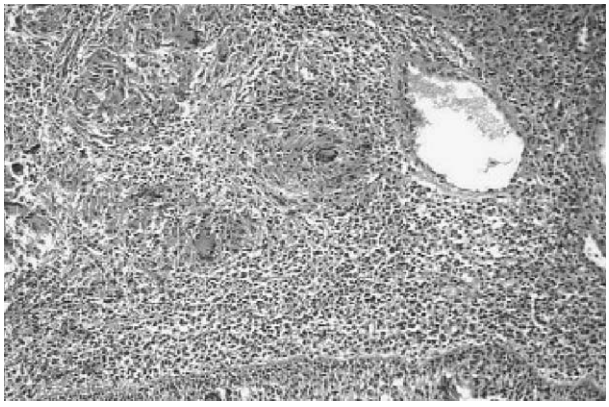

Figure 2 Biopsy of the vocal fold with sarcoid lesion (hematoxylin–eosin, × 10).

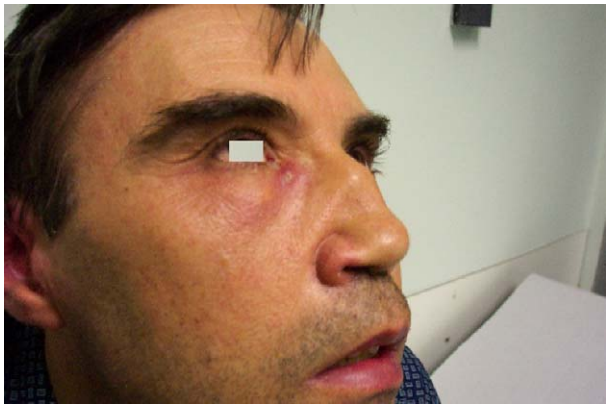

Figure 3 Nasal pyramid deformation in Case 4.

Case 4: A 49-year-old male patient complained of recurring dacryocystitis in the right eye and nasal obstruction. Chest X-ray was normal. ENT examination showed a deformation of the nasal pyramid considered post-traumatic (Fig. 3) with substenotic deviation of the nasal septum, marked rhinorrhea and clinical evidence of maxillary sinusitis. After unsuccessful pharmacological treatment with local and systemic antibiotics, the patient underwent septoplasty, inferior turbinoplasty and bilateral endoscopic enlargement of the natural maxillary ostium. Histological examination of biopsies of mucosa of the nasal septum and inferior turbinates indicated S. Chest CT subsequently showed diffuse bilateral nodular opacities. BAL indicated lymphocytic alveolitis with a high CD4/CD8 ratio. Transbronchial biopsy was positive for epithelioid granulomas, in line with the initial diagnosis. The patient was treated with prednisone, starting at 0.5 mg/kg, with much improvement in symptoms. Long-term steroid treatment was undertaken. Nasal symptoms and recurrent dacryocystitis have now disappeared. Retrospective evaluation of nasal morphology makes nasal bone sarcoid involvement more likely than trauma.

Discussion

Diagnosis of upper respiratory tract involvement in sarcoidosis may require the co-operation of pneumologists and ENT specialists, as demonstrated in the cases described here.

Case 1 with parotid gland involvement represents the most frequent and easily diagnosed localization of SURT. Parotid gland biopsy made diagnosis possible. This kind of biopsy is seldom indicated, though the need to confirm suspected S may justify it, particularly if minor salivary gland biopsy is negative or inconclusive. Case 2 was particularly difficult to diagnose because of the rarity of sarcoid vocal cord involvement and of subsequent tubercular lung complications. The histopathology of the laryngeal lesion, recovery with anti-tubercular treatment and persistence of steroid sensitive laryngeal involvement confirmed the diagnosis of SURT. In this localization, symptoms may be mild, but supraglottal granuloma may cause severe airway obstruction.

The third patient had nasopharyngeal involvement. This localization is rare, especially in children and difficult to suspect.[9] The fourth case had aggressive involvement of the lachrymal glands and sinonasal tract without other symptoms. The saddle nose deformity, reported as post-traumatic, was actually due to nasal cartilage localization of sarcoidosis. Septal perforation, nasal bone osteoporosis or destruction and cartilage destruction with nasal deformity have been described in patients with severe disease.[10,11] Braun and colleagues [12] recently reported 15 cases of sinonasal S and proposed two diagnostic criteria, namely poor response to conventional treatments and radiological evidence of rhinosinusitis, often with nodules on the septum and turbinates.

The general practitioner should obtain an accurate clinical history and examine all patients with chronic undiagnosed and progressive upper airway involvement (particularly sarcoidosis patients). If he suspects SURT, he should refer the patient to an ENT specialist expert in S. The ENT specialist examining the patient for the first time must carefully assess any chronic rhinosinusitis that responds poorly to conventional treatment, and examine the mucosa of the nasal septum, turbinates and nasopharynx for abnormal crusting, swelling or nodules. Diagnosis of SURT is particularly difficult in the absence of symptoms or when upper respiratory involvement is the first manifestation, because this site is rare and differential diagnosis with respect to many other causes is difficult. In these patients, a panel of tests (X-rays, CT scan) and a biopsy are necessary to confirm diagnosis and evidence of other organ localization should be sought.[6,13–16]

Early recognition of SURT helps prevent severe complications, such as upper airway obstruction in laryngeal S, anosmia and erosion of septal cartilage with nasal collapse and deformity in nasal involvement, facial palsy in cranial nerve involvement, and persistent enlargement of the parotid glands with dry mouth in salivary gland involvement.

There have been no studies in large series of SURT patients as to the effectiveness of pharmacological treatment, although international guidelines suggest that systemic or intralesional corticosteroids are indicated when critical organs are involved or when S is severe.[1] Topical steroids alone may be effective in SURT and intralesional steroid treatment has been proposed, particularly for patients with laryngeal S.[3,17] In chronic patients with symptomatic SURT, steroid treatment is generally used. Immunosuppressive and cytotoxic drugs, such as methotrexate, azathioprine and in some cases cyclophosphamide, have been administered in difficult cases.[6,18,19] In patients with chronic refractory sarcoidosis, new anticytokine agents that block TNF have been proposed. These therapies include pentoxifylline, thalidomide and more recently infliximab.[6,18,20] Use of thalidomide is limited by its toxicity and more clinical control trials are necessary to confirm its efficacy.[18] Infliximab is a chimeric antibody, which specifically inhibits TNF alpha.[21] It has been successfully used in patients with persistent symptomatic sarcoidosis.[6,19,20] In patients 2 and 4, treatment with infliximab was considered, but it was not given due to pulmonary tuberculosis lesions and dacryocystitis, respectively. Sharma reported the effectiveness of antimalarial agents (such as chloroquine and hydroxychloroquine) in treating selected patients with sarcoidosis.[6,22] Surgery is useful for intranasal management of complication and airway obstruction. Septoplasty may be complicated by septal perforation. We have no personal experience with radiotherapy in laryngeal S, but failures seem to outnumber successes.[23]

In conclusion, the present experience suggests that collaboration between pneumologists and ENT specialists is necessary for early diagnosis of SURT and to reduce its complications.

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