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Sarcoidosis of the submandibular gland: A systematic review

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Abstract

Introduction: Submandibular gland sarcoidosis is rare and little is known about its clinical presentation besides the usual neck swelling. The aim of the study was to extract clinical knowledge on submandibular sarcoidosis from the literature.

Methods: A systematic review was performed using a search in Medline with the key-words "sarcoidosis," "submandibular," "submaxillary."

Results: Forty-six articles fitting the search criteria were found, whereas 31 had to be excluded because they did not report submandibular gland sarcoidosis. Twenty cases of submandibular gland sarcoidosis were considered suitable for analysis. Almost all reported cases concerned female patients. In some cases submandibular gland's swelling is the first and only manifestation of the disease.

Conclusion: Sarcoidosis should be considered in the differential diagnosis of all progressive and painless swellings of the submandibular gland, especially in women. Rarely, it may be the first manifestation of the disease.

1. Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Almost all systems of the human body may be affected and there is a great variety in the presenting symptoms. Consequently, the range of otolaryngological manifestations of the disease is wide. Submandibular gland swelling is commonly seen in daily ear, nose, and throat outpatient clinics and the differential diagnosis ranges from infectious, traumatic, congenital, and malignant to inflammatory causes. However, sarcoidosis in this gland is rather uncommon and more often seen in parotid swelling. Thus, there are no clinical characteristics which could draw the physician's attention to suspect more particularly sarcoidosis. The present systematic review aimed to extract the available knowledge on submandibular gland sarcoidosis to identify possible common clinical presentation characteristics. Besides the reported cases in the literature, we also added a recent case of submandibular gland sarcoidosis treated in our department.

2. Material and methods

2.1. Systematic review: materials and methods

A search was performed in MEDLINE (from 1950 to February 2009) using the terms: "sarcoidosis," "submandibular," "submaxillary," and "gland." These terms were combined using Boolean operators. Searches were restricted to English-, French-, or German-language articles. Reference lists from identified articles were searched and cross-referenced to obtain further relevant articles. The authors searched for articles of submandibular gland sarcoidosis independently and blinded from each other. Patients' characteristics such as age, sex, affected side and organs, symptoms, investigations, as well as treatment and evolution were extracted and recorded when available. In case of

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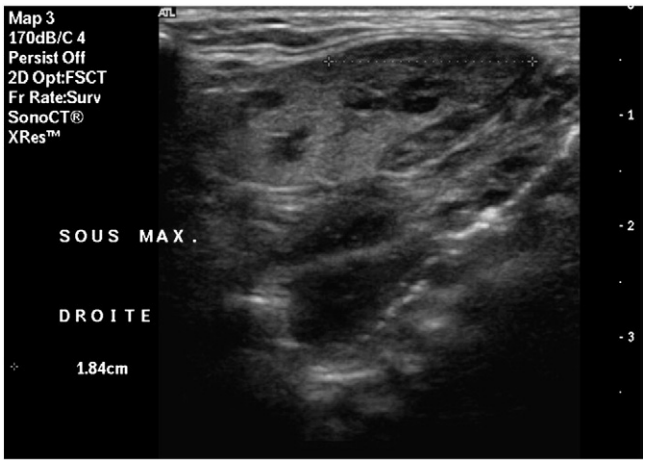

Fig. 1. Heterogeneous texture and hypoechoic nodules were demonstrated in the right submandibular gland's ultrasound.

discrepancies, agreement was reached through discussion. Cases of submandibular lymph node sarcoidosis without submandibular gland involvement were excluded.

2.2. Case report

A 60-year-old woman presented to our outpatient clinic with a progressive swelling of the right submandibular area for the last 6 months. She had a 2-year history of sarcoidosis limited to the chest (radiological stage 2). One year after the initiation of oral corticosteroid treatment, the patient had a complete remission of the disease, and her pneumologist had decided to interrupt it. She was otherwise healthy, and the only other noteworthy disease in her medical records was a melanoma of the lower limb, excised more than 15 years ago.

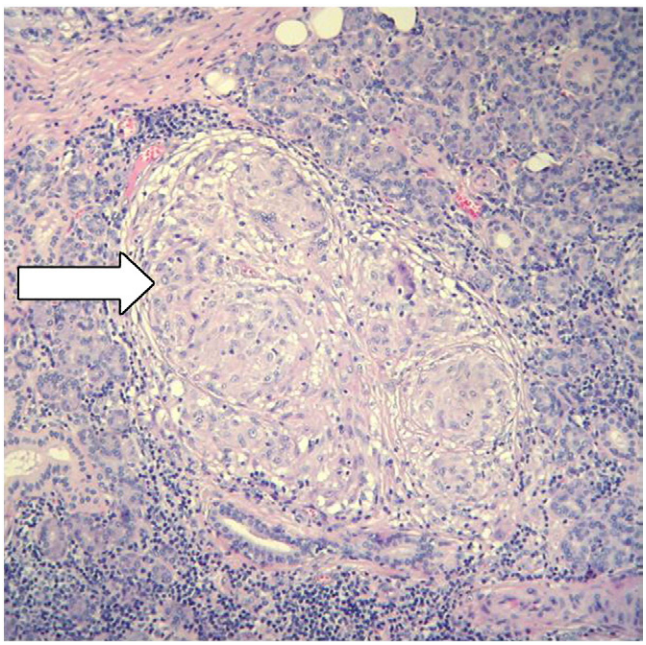

Fig. 2. Hematoxylin and eosin staining (original magnification ×100) of the submandibular gland removed, showing a noncaseating granuloma (arrow).

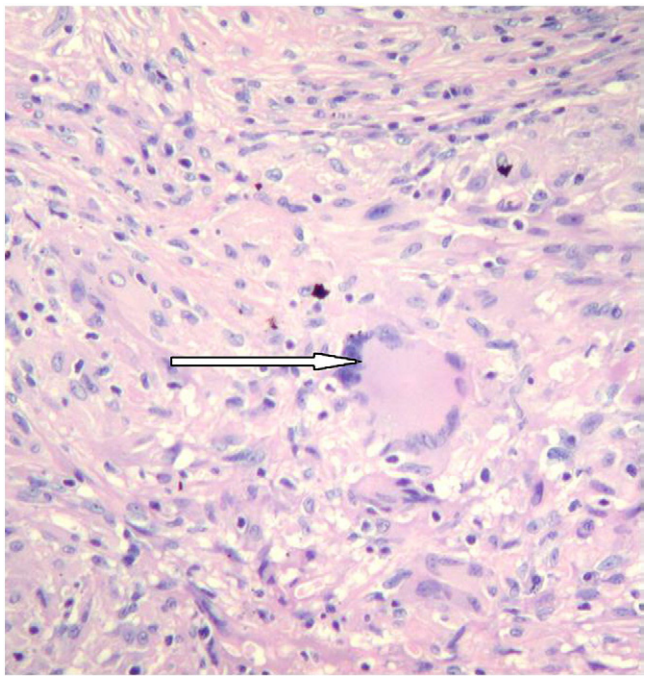

Fig. 3. High power detail (original magnification ×400) of a giant cell. Arrow indicates hematoxylin and eosin staining.

Physical examination revealed an elastic, mobile, and painless mass of the right submandibular region measuring 3 × 2 cm. The rest of the ear, nose, and throat examination was normal. Cervical ultrasound showed hypoechoic lesions in both submandibular glands (Fig. 1). No diagnosis could be established by fine needle aspiration biopsy since the aspirated material was insufficient for cytological examination. In order to establish a diagnosis and to rule out malignancy, a resection of the right submandibular gland was performed. The pathology revealed multiple intraglandular noncaseating granulomas (Fig. 2) with multinuclear giant cells (Fig. 3), compatible with a sarcoidosis. The patient was referred to her pneumologist and further workup didn't show any other lesions. An attitude of clinical surveillance was decided.

3. Results

We identified 46 articles, of which 13 were eliminated because of the language criterion or they did not focus on sarcoidosis. Eighteen more articles were excluded as reviews with no cases of sarcoidosis reported or as reports of sarcoidosis without submandibular gland involvement (see flow chart; Fig. 4). Only 15 reports were fulfilling our systematic review's inclusion criteria (see Table 1) [1-16]. These articles were including 20 cases of submandibular gland sarcoidosis, to which our case was added (see details on Table 1). Most of the articles was written in English, each one of them reporting 1 or 2 cases. There was only one article reporting 4 cases [3].

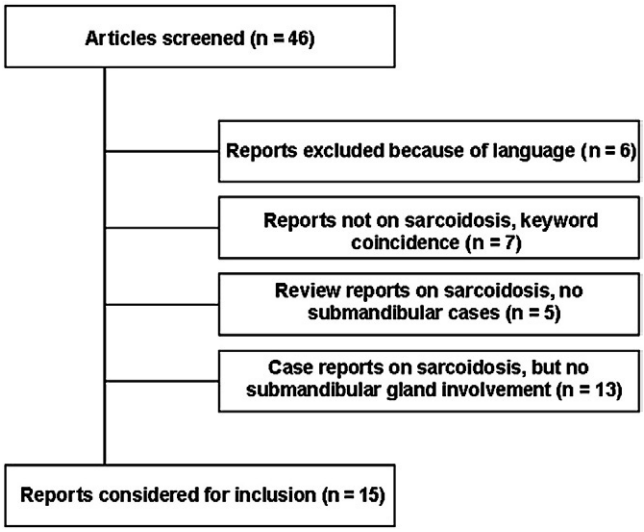

Fig. 4. Flow chart of screened, excluded, and considered reports.

Patients' age ranged from 26 to 68 years, with a mean age of 48 years. Almost all cases where sex data were available concerned female patients. Twelve cases concerned women while only one case concerned a male patient. Unfortunately, no sex data could be extracted from the reports in seven cases.

The main symptom of submandibular gland's involvement was a progressive and painless swelling, unilateral or bilateral. To a far lesser degree, symptoms occurred such as xerostomia, fever, fatigue, reduced appetite, and weight loss. The most often simultaneously affected organ was the parotid gland, followed by the lungs, the accessory salivary, and the lacrimal glands. In 3 cases, the submandibular gland swelling was the first and only manifestation of sarcoidosis. Most patients have either received oral corticosteroids or had a watchful waiting attitude. All cases had a favorable evolution. Chest x-ray was normal in 5 cases and pathological in 4. The angiotensin converting enzyme (ACE) serum levels were elevated in 2 cases and normal in 2 others.

4. Discussion

The main findings of the present systematic review are that submandibular gland sarcoidosis: (1) presents as a painless swelling which is occasionally accompanied by parotid enlargement, (2) seems to have a strong female preponderance, and (3) is often not accompanied by pathological chest x-ray or elevated ACE serum levels.

The exact prevalence of submandibular gland sarcoidosis is not known. Although our review cannot provide any prevalence data, some clinical characteristics of this localization of sarcoidosis could be established. The major manifestation seems to be a painless swelling of the submandibular gland, occasionally associated to a parotid enlargement. Unilateral and bilateral localizations are equally often reported. Although most patients had a simultaneous affection of other organs, there were 3 cases of isolated manifestations from the submandibular glands. The review further revealed that with the exception of one case; all the other reports of submandibular gland sarcoidosis concerned female patients. This suggests that submandibular gland involvement has probably an even greater female preponderance than sarcoidosis in general. These results have to be considered with caution because the small number of submandibular cases did not allow for statistically significant conclusions, and a bias may be due to the fact that gender information has been omitted by the authors in 7 cases. However, it is highly unlikely that all these cases concerned male patients.

In a considerable number of patients, chest x-rays and ACE serum levels were normal. However, since these tests were not systematically performed, no conclusion can be made concerning their sensitivity and sensibility. Nevertheless, ACE serum levels and chest X-ray may be more valuable than so far reported in the investigation of cervical masses [17]. Another diagnostic tool to be considered in submandibular gland swelling is fine needle aspiration [3]. Unfortunately, submandibular gland resection is often inevitable in order to establish diagnosis and to rule out malignancy.

The prevalence of sarcoidosis in Europe and the United States is about 10 to 40 per 100 000 inhabitants, with a peak between 20 and 40 years of age. Women are affected slightly more often but the female: male ratio is rarely reported over 3:2 [18-20]. The disease may affect all organs, whereas most frequently affected are the lungs, the lymph nodes, the eyes, and the skin. Less frequent localizations include the exocrine glands, the spleen, the kidneys, the bone marrow, the muscles, the nervous system, the heart, and the intestines [21].

The presenting symptoms depend on the organs affected and vary considerably from vertigo to fatigue and unexplained fever to joint pain [22,23]. In some cases, the disease is discovered incidentally by abnormal chest x-ray in asymptomatic individuals [19]. Autopsies of sarcoidosis patients reveal that many organs may be affected subclinically [21].

The main targets in the head and neck region are the lymph nodes, the skin, the nose, the oral mucosa, the palatine tonsils, the larynx, the trachea, the cranial nerves, and the salivary glands [24]. Salivary gland involvement is most frequent in the parotids (macroscopically) and the accessory salivary glands (microscopically), in 5% and 50% of all cases, respectively [14]. A rare pattern of salivary gland involvement is seen in the Heerfordt syndrome where parotid enlargement is accompanied by facial nerve paralysis and uveitis [21].

Submandibular gland involvement is considered to be rare and only few cases have they been reported. The differential diagnosis of a submandibular gland swelling should include acute and chronic sialadenitis (bacterial or

Table 1
Details of the included reports

Author	Language	No of cases	Age	ACE levels	Chest X-Ray	Sex	Manifestations and side	Other organs affected	Treatment	Year	Article type
Mahmood [7]	English	1	38	Normal	Normal	F	Neck lump (bilateral), xerostomia	Parotid	Steroids (per os)	2007	Case report
Vairaktaris [2]	English	2	68, 66	No	Normal	F	Painless lump left side	none	Steroids (per os)	2005	Case series
Alyas [13]	English	1	No	No	No	No	Painless lump left side	Lung	No	2005	Review
Howlett [9]	English	1	No	No	No	No	Painless lump right side	Parotid	No	2004	Review
Odenheimer [5]	German	1	54	Elevated	No	F	Xerostomia, Neck lump (bilateral), weight and appetite loss	None	Steroids (per os)	2002	Case report
Ohtsuka [4]	English	1	63	Normal	Path	m	Neck and parotid swelling right side	Parotid	Minocycline	2001	Case report
Wiemeyer [15]	German	1	35	Elevated	Normal	F	Weight loss, fatigue, nausea, bilateral	Accessory salivary glands, hypercalcemia	Steroids (per os)	1996	Case report
Mandel [6]	English	1	42	No	Path	F	Neck lump (bilateral)	Accessory salivary glands, Lung	No	1994	Case report
Aggarwal [14]	English	1	57	No	Path	F	Joint stiffness, Submandibular enlargement (bilateral), Intermittent fever	Lung	No	1989	Case report
Bruneton [12]	English	1	No	No	No	No	No	No	No	1985	Case series
Lubat [8]	English	1	27	No	No	F	Nausea, fever, bilateral	Liver, Parotid	No	1985	Case report
Hillerup [10]	English	1	57	No	Path	F	Submandibular and parotid swelling (bilateral), Xerostomia, Weight loss	Lung, Parotid	No	1976	Case report
Gupta [11]	English	1	26	No	Normal	F	Upper lid, Neck and parotid swelling, right side	Parotid and lacrimal gland	Steroids (per os)	1974	Case report
Mandel [16]	English	1	34	No	No	F	Submandibular swelling right side	No info	No	1962	Case report
Tambouret [3]	English	4	No	No	No	No	No	No	No	2000	Fine needle biopsy study
Our case	English	1	60	No	Normal	F	Submandibular swelling right side	Lung	No therapy	2007	Systematic review
Summary	English (n = 14) German (n = 2)	20	48 y	Normal (n = 2) Elevated (n = 2) No info (n = 16)	Normal (n = 5) Path (n = 4) No info (n = 11)	F (n = 12) m (n = 1) No info (n = 7)	Mass (n = 13) Xerostomia (n = 3) Weight/appetite loss (n = 3) Fever/fatigue (n = 2) Bilateral (n = 7) Unilateral (n = 8)	No other manifestation (n = 3)* Parotid (n = 6)* Lung (n = 5)* Acc. salivary and lacrimal glands (n = 3)*	Oral steroids (n = 6) No info (n = 18) No therapy (n = 2) Minocycline (n = 1)		Mostly case reports

No, No info; Path, pathological; F, female; M, male. Data are expressed as means ± SEM.

* For further details, see the Results section.

fungal), swellings secondary to lithiasis or Wharton's duct stenosis, benign tumours, primary or metastatic malignant tumours, Sjögren's disease, lymphomas, hematomas, as well as granulomatous diseases other than sarcoidosis.

A causal treatment is not yet available because the etiology of sarcoidosis is unclear. Once the diagnosis is established, other organs potentially affected have to be assessed, since multiple localizations change the attitude and influence the prognosis. Oral corticosteroids are frequently prescribed [22], although the possibility of a wait-and-see attitude may sometimes be an alternative. For most of the patients, the prognosis is good and frequently without significant sequelae. Approximately half of all patients with sarcoidosis have some stable, mild, permanent organ dysfunction. The disease remains active or recurs intermittently in 15% to 20% of all patients. In the long run, complications and consequences of the disease is the cause of death in only 1 of 10 affected patients.

The present study establishes, through a systematic review of the literature, the clinical characteristics of this unusual localization of submandibular sarcoidosis. This might help physicians confronted to an unexplained submandibular swelling. The main shortcoming of this review is the fact that some of the variables analyzed are lacking from the individual reports included.

5. Conclusion

The involvement of submandibular glands in sarcoidosis is rare; nevertheless, it should be taken into account in the differential diagnosis of all progressive and painless swellings of the gland, particularly in female patients. It may occasionally be the presenting and only manifestation of the disease.

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