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The nasal manifestations of sarcoidosis: a review and report of eight cases

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Abstract
We report eight patients presenting to the Department of Otorhinolaryngology between 1990 and 1998 in whom a diagnosis of sarcoidosis was made. The most common presenting symptom was that of nasal obstruction and crusting and the most common site of involvement was the septum and inferior turbinate. These patients differ from the majority of patients who present with the other manifestations of sarcoidosis in that they are older. Where mucosal changes are present within the nose, biopsy gives a high diagnostic yield. The aim of treatment is to gain symptomatic control with the lowest dose of steroids. The majority of patient's nasal symptoms were managed with local measures and topical steroids. Nasal disease tends to follow a prolonged but benign course. Few had other organ involvement. While nasal sarcoidosis remains a rare cause of nasal obstruction, biopsy of abnormal nasal mucosa along with further investigations as dictated by history, examination and histological findings is important if delay in diagnosis is to be avoided.

Key words: Respiratory tract diseases; Nasal; Sarcoidosis

Introduction
Sarcoidosis is a chronic non-caseating granulomatous disease of unknown aetiology with a predilection for respiratory tract involvement. The earliest description of this disease was by Hutchison who subsequently used the term ‘Mortimer’s malady’ in his description of the skin lesions after Mrs Mortimer who was afflicted by these. Subsequently Boeck used the term ‘multiple benign sarkoid’ (Boeck, 1899) to describe the clinical and histological appearance of the skin lesions. In 1905 Boeck described the first case of nasal involvement and in 1937 Kirstner and Robertson confirmed nasal involvement histologically (Kirstner and Robertson, 1938).

The incidence of this condition is estimated to be between six and 10/100 000 with a slight female preponderance. The peak age at presentation is 20-40 years. The reported incidence is greatest in Sweden where the rate is 64/100 000 on chest radiograph. The disease is also more common in black immigrant populations although uncommon in their native countries. In North America the incidence in the Black population is 10-20 times greater than that in Caucasians and in London where the rate has been reported as 27/100 000 in the Caucasian population and 183/100 000 in the West Indian population (Milton, 1985).

The true incidence remains difficult to ascertain due to the high prevalence of asymptomatic pulmonary involvement with over 50 per cent of cases of pulmonary involvement being diagnosed incidentally without symptoms. Furthermore post mortem results in Sweden suggests that the true incidence may be higher still. A study conducted between 1957-1962 on 6707 individuals found evidence of the disease in 43, only three of whom were known to have the disease ante-mortem, representing a prevalence of 671/100 000 (Mitchell, 1998).

The cause remains elusive and there has been little advance in the proposed aetiology in the past 50 years. The most compelling evidence proposes an infective cause such as an atypical mycobacterium.

The typical pathological features comprise epithelioid giant cells with pale round or oval nuclei and lymphocytes

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tbody>
<tr>
<td>OTHER GRANULOMATOUS DISEASES INVOLVING THE UPPER RESPIRATORY TRACT</td>
</tr>
<tr>
<td>Infective</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Leprosy</td>
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<tr>
<td>Aspergillosis</td>
</tr>
<tr>
<td>Actinomycosis</td>
</tr>
<tr>
<td>Blastomycosis</td>
</tr>
<tr>
<td>Histoplasmosis</td>
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<tr>
<td>Rhinoscleroma</td>
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From the Departments of Otorhinolaryngology and Pathology*, Queen’s Medical Centre, Nottingham, UK. Accepted for publication: 8 June 1999.
Hearing loss and approximately 80 per cent and the changes are graded using a simple grading system (Table II) (DeRemee, 1983).

Constitutional symptoms of weight loss, fever, anorexia and malaise occur in approximately one third of patients. The most frequent organ involvement is the lung, being affected in 80-90 per cent of cases although involvement of almost any organ system has been reported.

Overall otolaryngological manifestations occur in 10–15 per cent (Shah et al., 1997). The manifestations are variable with the most common being cervical lymphadenopathy, parotid swelling and facial nerve palsy. Laryngeal sarcoid is estimated to occur in one to five per cent (Spiteri et al., 1997). The most common site is the epiglottis. Hearing loss and peripheral vestibulopathy occur in less than one per cent cases although involvement of almost any organ system has been reported.

The diagnosis depends upon an appropriate clinical history with demonstrable non-caseating granulomas on biopsy along with exclusion of other granulomatous diseases (Table I) with negative serology, stains and culture for relevant infectious agents and normal anti-neutrophil cytoplasmic antibody levels. Chest radiographs (CXR) changes are present in approximately 80 per cent and the changes are graded using a simple grading system (Table II) (DeRemee, 1983).

The most common CXR appearance is that of bilateral hilar lymphadenopathy present in approximately 50 per cent (Clarke et al., 1994). Angiotensin-converting enzyme (ACE) levels although elevated in sarcoid in somewhere between 30–90 per cent are also increased a variety of other conditions including hepatitis, Gaucher’s disease, leprosy, berylliosis, mycobacterial infection, silicosis, histoplasmosis, lymphangiomyomatosis and farmer’s lung. Elevated levels of ACE return to normal following treatment and so may be used as a marker of disease activity and in detecting clinical relapse. It is not however useful as a prognostic determinant or in determining need for treatment.

We report on eight patients presenting to our ENT Department with nasal symptoms between 1990 and 1998 not known at the time of presentation to suffer from sarcoidosis who subsequently had the diagnosis established in order to highlight the condition and its protean manifestations along with the difficulties in establishing a definitive diagnosis.

Subjects and methods

The case notes of these patients were reviewed retrospectively and the presenting symptoms and signs along with demographic details and results of investigation and treatment are recorded (Table III).

The patient details were either obtained in the majority of cases by identifying pathology specimens of nasal biopsies with granulomata (Figure 1) and reviewing the case notes of these patients to establish those with sarcoidosis or, from a diagnostic index of the senior author. All but one of the patients underwent nasal biopsy that was positive in all but one.

The age range of the patients was 21–70 with an average age of 44 years. The female to male ratio was 3:1.

### Table II

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal CXR</td>
</tr>
<tr>
<td>1</td>
<td>Hilar lymphadenopathy only</td>
</tr>
<tr>
<td>2</td>
<td>Hilar lymphadenopathy with parenchymal involvement</td>
</tr>
<tr>
<td>3</td>
<td>Parenchymal involvement only</td>
</tr>
</tbody>
</table>

### Table III

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Race</th>
<th>Symptoms</th>
<th>Signs</th>
<th>CXR</th>
<th>ACE</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>ESR</th>
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</thead>
<tbody>
<tr>
<td>MG</td>
<td>F</td>
<td>43</td>
<td>C</td>
<td>Obstruction</td>
<td>Congested mucosa</td>
<td>Stage 0</td>
<td>Negative</td>
<td>Betamethasone Douching</td>
<td>4</td>
<td>Persistent</td>
<td>Elevated</td>
</tr>
<tr>
<td>MGri</td>
<td>F</td>
<td>44</td>
<td>C</td>
<td>Obstruction</td>
<td>Mucosal hypertrophy</td>
<td>Stage 0</td>
<td>Elevated</td>
<td>Betamethasone</td>
<td>3</td>
<td>Improved</td>
<td>None</td>
</tr>
<tr>
<td>AMR</td>
<td>F</td>
<td>21</td>
<td>C</td>
<td>Obstruction</td>
<td>Crusting Perforation</td>
<td>Stage 0</td>
<td>Elevated</td>
<td>Naseptin</td>
<td>10</td>
<td>Improved</td>
<td>Elevated</td>
</tr>
<tr>
<td>EB</td>
<td>F</td>
<td>70</td>
<td>C</td>
<td>Obstruction</td>
<td>Polyps</td>
<td>Stage 0</td>
<td>Upper limit</td>
<td>Betamethasone Douching</td>
<td>2</td>
<td>Resolved</td>
<td>None</td>
</tr>
<tr>
<td>PH</td>
<td>M</td>
<td>39</td>
<td>C</td>
<td>Obstruction</td>
<td>Crusting</td>
<td>Stage 1</td>
<td>Upper limit</td>
<td>Betamethasone Steroids</td>
<td>24</td>
<td>Resolved</td>
<td>Elevated</td>
</tr>
<tr>
<td>HH</td>
<td>F</td>
<td>41</td>
<td>A</td>
<td>Obstruction</td>
<td>Granular Mucosal hypertrophy</td>
<td>Stage 0</td>
<td>Elevated</td>
<td>Beclomethasone</td>
<td>1</td>
<td>Improved</td>
<td>None</td>
</tr>
<tr>
<td>JH</td>
<td>M</td>
<td>48</td>
<td>A</td>
<td>Obstruction</td>
<td>Granular mucosa</td>
<td>Stage 0</td>
<td>Elevated</td>
<td>Steroids</td>
<td>61</td>
<td>Improved</td>
<td>Elevated</td>
</tr>
<tr>
<td>ST</td>
<td>F</td>
<td>46</td>
<td>C</td>
<td>Obstruction</td>
<td>Crusting</td>
<td>Stage 1</td>
<td>Negative</td>
<td>Steroids</td>
<td>18</td>
<td>Improved</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Age is at first presentation.
Follow-up is from time of diagnosis in months.
A = Afro-Caribbean, C = Caucasian.
The nasal manifestations of sarcoidosis: a review and report of eight cases

The principal presenting nasal symptoms were remarkable only in that three had epiphora. Obstruction was present in seven of eight cases, three had nasal discharge, one had an external deformity, one had epistaxis and one had anosmia.

Principal signs of nasal disease were of a granular appearance to the mucosa of the inferior turbinate and/or septum and of crusting present in half the patients (see Figure 2). A variety of other signs were demonstrated including an atypical congested mucosa (three), external deformity (one), nasal polyps (three), adhesions (one) and a septal perforation (one).

CXR changes were present in only two of eight patients, while ACE levels were elevated or at the upper limit of normal in six of the seven patients who had this investigation. Four of eight patients had evidence of systemic disease either at time of presentation or during follow-up.

The time from presentation to diagnosis was on average five months, with a range from one to 18 months.

Of the eight patients described, three required systemic steroids in order to control their symptoms. Of these one had a short course of systemic steroids lasting only five days at 30 mg/day, another had 20 mg/day for four months then 15 mg/day for a further four months before being lost to follow-up and the final patient has had prolonged treatment with steroids over 15 months ranging in dose between 10 and 20 mg/day principally for systemic disease. The remaining patients were managed with betnesol drops, emollients and douching for symptomatic relief. In three patients their symptoms improved, in two they were symptom-free on review, two were lost to follow-up but on last review one had improved symptoms and the other’s symptoms had resolved. One patient felt no improvement in her symptoms.

Follow-up from time of diagnosis was on average 15 months ranging from one to 61 months.

There is no single pathognomonic symptom, sign or investigation that allows a definitive diagnosis of sarcoidosis. Based on the World Association for Sarcoidosis and other Granulomatous Disorders Criteria a compatible clinical history and/or radiological picture along with positive histology and exclusion of other diseases by culture and special staining techniques and serology allows a confident diagnosis. Elevated ESR and ACE, while supportive if present, are not diagnostic.

While the best diagnostic criterion is histological evidence, two patients in this series did not have positive histology. In one no nasal biopsy was taken and, in the other, the specimen was felt to be too superficial and was not repeated. For a diagnosis of sarcoidosis to be made in these circumstances it is recommended that there be radiological evidence, complementary investigations e.g. ACE, gallium scan, extrapulmonary involvement compatible with sarcoidosis if any, exclusion of other differential diagnosis and follow-up for perhaps six months or longer (Hosada et al., 1997). In the two patients (Cases 2 and 3) who did not have positive histology neither had radiological changes compatible with sarcoidosis but both had elevated ACE, both had extrapulmonary involvement compatible with the disease, with Case 2 having an external nasal appearance typical of lupus pernio along with manifestations of pituitary involvement and Case 3 having swelling of her interphalangeal joints and rash. Both had clinical observation for greater than six months and other diagnoses excluded. Thus there is strong substantive evidence for the diagnosis without the criteria being fully met.

Of the remaining six cases all had positive histology with typical non-caseating granulomas with the exclusion of bacteria and fungi by culture and staining. Two patients (Cases 5 and 8) had typical radiological changes and therefore the diagnosis was established. Case 5 also had elevated ESR supporting the diagnosis.
Discussion

As a presenting symptom nasal symptoms are uncommon, occurring in one per cent of patients with sarcoidosis (McCaffrey and McDonald, 1983). Nasal involvement can also occur concurrently or manifest later in the disease process in between one to six per cent of cases (Neville et al., 1976; McCaffrey and McDonald, 1983). A number of previous studies have investigated the prevalence of nasal symptoms and signs in those known to suffer from sarcoidosis. Wilson et al. (1988) in a prospective study over two years of 750 patients known to have sarcoidosis found nasal involvement in 27 patients, confirmed by histology in 21. In a further series of 2319 patients with sarcoid a retrospective review showed only 17 with histologically-proven nasal involvement and a further seven with nasal symptoms recorded over a 31-year-period (McCaffrey and McDonald, 1983). James et al. (1982) reported on 818 patients with sarcoidosis and found nasal involvement to be the sole presenting symptom in 33 patients. There are, however, few studies that examine patients who present with nasal symptoms and signs in whom a diagnosis of sarcoidosis is made as a result. Shikowitz and Alvi (1993), and Busutill and Hopkinson (1981) both report on three cases who were diagnosed with sarcoid as a result of presenting with nasal symptoms. Milton (1985) reported on eight patients over a 21-year-period and Krespi et al. (1995) record 28 patients over an undetermined period whose ‘primary manifestation’ was sinonasal tract symptoms. The paucity of reports and small numbers involved highlights the relative rarity of this condition presenting initially with nasal disease.

Symptoms of nasal disease in sarcoidosis are varied and non-specific. The most common presenting symptom in this series was found to be nasal obstruction that was present in all but one of the patients. As this was a retrospective series the presenting symptoms and signs are dependent on accurate and full documentation. This is in keeping with previous published reports with 14 of 17 (McCaffrey and McDonald, 1983), 24 of 27 (Wilson et al., 1988) and three of three (Shikowitz and Alvi, 1993) complaining of this symptom. Another prominent symptom in our patients was epiphora not reported in other series. This is partially attributable to the referral patterns with a large number of endoscopically-assisted laser dacrocystorhinostomies being performed in the hospital. Epistaxis, crusting, rhinorrhoea, post-nasal drip and anosmia all occurred in addition in this series of patients which are recognized presenting symptoms of this condition.

Nasal pain that has also been previously described (McDonald, 1993) was not noted in any patients. The patient may return after failure on topical steroids and two patients in the series had failed on topical medication prior to referral.

The age of presentation of patients with nasal disease was noticeably older than for sarcoidosis in general. Of five studies involving 138 patients the average age was 38–43 years (James et al., 1982; McCaffrey and McDonald, 1983; Milton, 1985; Wilson et al., 1988; Krespi et al., 1995) and in the current group the average age was 48 years. In all these studies as in our series there was a female preponderance except in the series reported by Milton (1985) when there was an equal sex distribution.

Signs of nasal disease seen were atypical hypertrophic mucosa, nasal polyps and masses, crusting, septal perforation and adhesions and external deformity. Septal perforation is rare, occurring in one patient and was noted in other series as one of 27 (Wilson et al., 1988), one of 13 (Milton, 1985) and in a case report (Patey et al., 1990). The typical submucosal nodules are described as tiny elevated yellowish lesions that become confluent to form diffuse infiltrates and can become superficial to form yellowish wrinkled plaques with mucosal hypertrophy lending a corrugated appearance to the mucosa. Large nodules up to 4 mm in diameter have been reported (Falkoff and Schatz, 1986). The nasal mucosa may appear friable or show atrophic rhinitis or fibrous thickening or polypoid changes.

The most common sites of involvement in our series were the septum and inferior turbinate. Two patients had polypoid changes (Figure 3) yielding positive biopsies. The inferior turbinate is the most commonly involved site with the nasal septum and paranasal sinuses also being affected in most other series. Of note, the nasal mucosa typically fails to shrink following application of a topical decongestant such as phenylephrine (McDonald, 1993).

Nasal polyps seen at endoscopy subsequently demonstrating non-caseating granulomas consistent with sarcoidosis.
The external appearance of the nose may change through involvement of the nasal cartilage causing saddle deformity although this is felt to be unusual (Allen, 1978; Bull, 1983). Involvement of the nasal bones and subcutaneous tissues is the least common manifestation (Schikowitz and Alvi, 1993) but can lead to swelling and widening of the nasal bridge. Sarcoid affecting the skin and subcutaneous tissues of the external nose can occur as small discrete raised papular lesions, as large flat plaques, as a large conglomerate mass protruding a little and involving the subcutaneous tissue or as a combination of these (Israel and Sdnes, 1958). Lupus pernio describes the chronic violaceous skin lesions typically affecting nose, cheeks, fingers and ears. These range in size from small nodules to large plaques (Figure 4). This manifestation is uncommon occurring in 35 of 818 presenting with sarcoidosis in one series (Spiteri et al., 1985). Lupus pernio is more common with increasing age of onset of disease and is associated with chronic disease. Ninety-five per cent had positive nasal biopsies and 54 per cent had symptomatic nasal disease in the above series. Typically in long-standing disease granulomas may occur at the mucocutaneous junction of the upper lip and in the region of the nasal alae, vestibule and columella (Figure 5) (Krespi et al., 1995).

In previous studies, nasal biopsy of abnormal mucosa gave a high diagnostic yield, 19 of 21 were positive in one series (Wilson et al., 1988), 28 of 28 were positive in another (Krespi et al., 1995). Of note, the yield in nasal mucosa which appears normal is very poor with one of 13 positive (Wilson et al., 1988) and two of 26 with BHL positive (Postma et al., 1984). The high yield and ease of obtaining tissue for histology from the nasal mucosa make it important to note nasal disease in patients with sarcoidosis. It is noteworthy that two patients with a presumptive diagnosis of sarcoidosis during retrieval of the notes were subsequently diagnosed as lymphoma and TB. This highlights the importance of establishing the diagnosis of sarcoid early to allow appropriate treatment and follow-up and also to exclude other potentially serious differential diagnoses (Table II).

In the current series nasal biopsy was performed in each case. We perform nasal biopsy in all cases where the mucosa appears atypical and in addition all nasal polyps are routinely submitted for histological examination. Further investigations are determined as necessitated following histological analysis.

The diagnosis of sarcoidosis may prove difficult to establish conclusively. Indeed, in a previous report of granulomatous nasal polyps no diagnosis was established in six of 19 patients (Coup and Hopper, 1980). Treatment of nasal disease is based on the severity of the symptoms and other organ involvement. Topical treatment with nasal steroids along with nasal douching and simple emollients to relieve the discomfort of crusting may be sufficient. For more severe symptoms intralesional injection of steroids may be used. If there is severe disease with destructive changes then systemic steroids may be indicated.

Whilst laser therapy with CO₂ to ‘debulk’ intra-nasal mass has been advocated it did not alter the natural history of the disease (Frederiksen and Jorgensen, 1996). We advocate medical treatment as surgery can result in atrophic changes and a higher incidence of septal perforation.

In those in whom a diagnosis of sarcoidosis is established routine referral to a respiratory physician is recommended to establish the extent of the disease and initiate any systemic therapy required. The mainstay of therapy is steroids balancing therapeutic benefit against side-effects. The principles of treatment are to treat any recent (within three months) deterioration in pulmonary function tests (PFTs) or
other critical organ involvement, to minimize steroid exposure and to stop treatment if the patient is stable on low dose for six months (Hull & Caghaeke, 1997). The severity of the CXR changes or PFTs do not in themselves justify treatment as they may represent inactive ‘burnt out’ disease. A minority of patients cannot be tapered off high dosage steroids or rarely may be resistant to high dose steroids and in these circumstances methotrexate, chloroquine or increasingly pulsed cyclophosphamide may be considered as adjuvants under close medical supervision.

External nasal deformity which is primarily confined to the skin may resolve in time with adequate medical treatment (Milford et al., 1990). Spontaneous remission of lupus pernio has been reported but this becomes less likely if the disease has been present for over two years (Spiteri et al., 1985). The majority of cases of lupus pernio show improvement in lesions within a matter of weeks of commencing steroid therapy although a third flare-up on a reducing dose. Intralesional steroids only give short-term improvement and lead to thinning of the skin leaving it liable to ulcerate (Spiteri et al., 1985). Rhinoplasty in patients with nasal deformity secondary to sarcoidosis should only be performed when the disease is quiescent. Interestingly grafted skin may become involved (as also may grafted cartilage) in the disease process (Scott et al., 1992).

Conclusions
Sarcoidosis is a diverse disease, that can involve almost any organ in the body. Nasal involvement is uncommon as a presenting manifestation of the disease and the symptoms and signs are highly variable. These factors taken together make the diagnosis, in those patients presenting solely with nasal disease, very difficult and a high degree of clinical vigilance is required. Nasal mucosal biopsy has a high yield in patients with sarcoidosis when mucosal changes are evident and as a general rule biopsy should be performed in all cases where the mucosa appears atypical as should all polyps be submitted routinely for histology. Subsequent investigations may then be performed based on the histological findings. It is important to exclude multisystem disease through close co-operation with the respiratory physicians although this was unusual in this series. The first line treatment for localized nasal disease is topical nasal steroids retaining oral steroids and ‘steroid-sparing’ agents for more resistant cases.

References

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