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Clinical Record

Klebsiella rhinoscleromatis of the membranous nasal septum

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Abstract

Rhinoscleroma is a chronic, infectious, granulomatous disease that may present with mass lesions in the respiratory tract anywhere from the nose to the trachea. The nose is involved in 95–100 per cent of cases. There are three stages of the disease: catarrhal-atrophic, granulomatous (also known as hypertrophic) and sclerotic. The diagnosis is made either by positive *Klebsiella rhinoscleromatis* culture or from the classic histological findings of Mikulicz cells and transformed plasma cells with Russell bodies. Rhinoscleroma is endemic to areas of Africa, South-East Asia, Mexico, Central and South America, and Central and Eastern Europe, and it has been associated with low socioeconomic status. In the past, rhinoscleroma was infrequent in the US population but, with current trends in migration, the incidence of rhinoscleroma may be on the rise. There is often a delay in diagnosis in non-endemic areas such as the US due to unfamiliarity with the disease, the stage-dependent clinical and histological manifestations of disease, and the fact that only 50–60 per cent of cultures are positive for *K rhinoscleromatis*. Such late diagnosis leads to increased morbidity in the form of nasal and airway obstruction and nasal deformity from erosive processes. Rhinoscleroma is difficult to cure and prone to recur. Currently, the recommended treatment consists of a combination of surgical debridement and long-term antibiotic therapy. We present a case report of a culture-positive diagnosis of rhinoscleroma, and we review the existing literature.

Key words: Klebsiella Rhinoscleromatis; Nose; Nasal Septum; Tropical Infection

Case report

A 25-year-old woman who had recently emigrated to the United States from Honduras presented with an eight-month history of bilateral, obstructing, anterior nasal masses. These masses were initially non-tender but had been gradually increasing in size, and the left-sided lesion had recently become painful. The patient felt chronically congested and extremely uncomfortable. She had been treated in the past with various antibiotics for recurrent sinus infections. However, her symptoms of congestion and rhinorrhoea seemed to worsen despite these medications, and the obstructive lesions in her anterior nares made it impossible for her to clear her nose. She denied any similar previous lesions and also any history of intranasal recreational drug use, nasal trauma or surgery. She denied bleeding from these lesions or purulent nasal discharge. She had no hoarseness, voice change, dyspnoea, fevers, chills, lymphadenopathy or weight loss. Her past medical history was unremarkable. She did not have any risk factors for human immunodeficiency virus. No family members or close contacts suffered from similar lesions. She reported no allergies and admitted to smoking one pack of cigarettes per day for one year.

On examination, the patient was found to have tender, fleshy growths from the antero-inferior nasal septum, occluding her nares bilaterally. These masses extended to the columellar skin within the membranous septum (Figure 1). Fiber-optic laryngoscopy revealed a normal glottis and subglottis without evidence of any mass or scarring.

A computed tomographic scan of the paranasal sinuses was performed and showed a predominantly left-sided, soft tissue lesion measuring $20 \times 5 \times 10$ mm along the nasal septum, extending to the lateral aspect of the nasal cavity. There was heterogeneous enhancement with intravenous contrast. Additional, bilateral, polypoid regions of mucosal thickening were also seen within the nasal cavity. There was no evidence of bony erosion. The paranasal sinuses were clear.

A biopsy from the mass in the left nasal vestibule showed squamous mucosa with underlying acute and chronic inflammatory changes and granulation tissue formation (Figure 2). Mycobacterial, fungal and anaerobic cultures were negative. A tuberculin skin test for tuberculosis was also negative. Gram staining and aerobic cultures revealed a '2+' level of *Klebsiella rhinoscleromatis* growth, of the mucoid colony type.

A diagnosis of rhinoscleroma was made. The patient was given four weeks of oral levofloxacin, with good resolution of her symptoms.

Discussion

Rhinoscleroma is a chronic, infectious, granulomatous disease that may present with mass lesions in the respiratory

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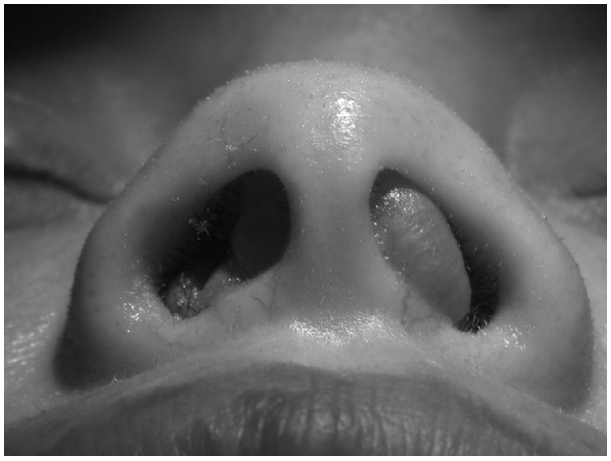

FIG. 1
Bilateral, tender, fleshy growths from the membranous septum.

tract anywhere from the nose to the trachea. The nasal cavity is most often affected (95–100 per cent) but lesions may also involve the: larynx (15–40 per cent); nasopharynx (18–43 per cent); oral cavity; paranasal sinuses (26 per cent); soft tissues of the lips and nose; trachea (12 per cent); bronchi (2–7 per cent); and, rarely, the orbit or middle ear.[1] The condition is often indolent, progressive, prone to recurrence and extremely difficult to cure. The infectious agent, *K rhinoscleromatis* (of the Enterobacteriaceae family), was first described by von Frisch in 1882.[2] This Gram-negative, non-motile, encapsulated, facultative, glucose-fermenting, intracellular diplobacillus is hosted by humans alone. No racial predilection exists, but females are slightly more affected than males (about 1.3 to one) and patients are commonly afflicted in the second and third decades of life.[3]

Although the infectious agent has been well characterised, the mechanism of infection and the pathophysiology of disease progression are poorly understood. Transmission is proposed to occur via direct inhalation or inoculation by respiratory droplets, but only after prolonged contact. Rhinoscleroma is more common in developing countries and rural areas and is endemic in Africa, South-East Asia, Mexico, Central and South America, and Central and Eastern Europe.[1,3] There appears to be an association between poor hygiene, poor nutrition, crowded living conditions and the development of rhinoscleroma.

Host factors may play a role in development of the disease. Cellular immunity is impaired in affected patients, but humoral immunity remains intact.[4,5] Studies in patients with rhinoscleroma have shown alterations in the ratio of CD4-positive lymphocytes (Helper T cells) to CD8-positive lymphocytes (Cytotoxic T cells) with a marked increase in the latter type. Patients have also shown an impaired response of their CD4 lymphocytes to interleukin-2 and also a diminished proliferative response to Concavalin A, a T-lymphocyte mitogen.[6]

The bacterium itself contributes to the host's ineffective cellular immune response. It is widely accepted that the mucopolysaccharide in the capsule of *K pneumonia* protects the bacteria by effectively inactivating macrophages so they cannot phagocytise bacteria.[7] *Klebsiella rhinoscleromatis*, because of its close biochemical relationship, is proposed to share this defense mechanism. Ineffective phagocytosis of the organisms by macrophages results in the characteristic Mikulicz cells, large macrophages with clear cytoplasm and intracellular bacilli (Figure 3). This ineffective phagocytosis may be responsible for the chronicity and granuloma formation seen with this disease.

Canalis and Zamboni have elucidated this process by examining the structural changes occurring in *K rhinoscleromatis* infection.[8] According to their work, the majority of events leading to chronic infection occur in the subepithelium. First, *K rhinoscleromatis* invades the subepithelium, multiplies and incites capillary proliferation. Next, many polymorphonuclear cells enter into the subepithelium in response. They are able to phagocytose the bacteria but die at an accelerated rate without completing digestion of the organism. Finally, macrophages (histiocytes) enter the area and phagocytose the decaying polymorphonuclear cells and klebsiella organisms. Their phagosomes undergo massive dilation and at this point they become the characteristic Mikulicz cells. These macrophages are effective in lysing decaying polymorphonuclear cells but are unable to destroy the klebsiella bacteria. Eventually, these macrophages rupture and release both active and inactivated organisms into the interstitium, and the cycle continues.

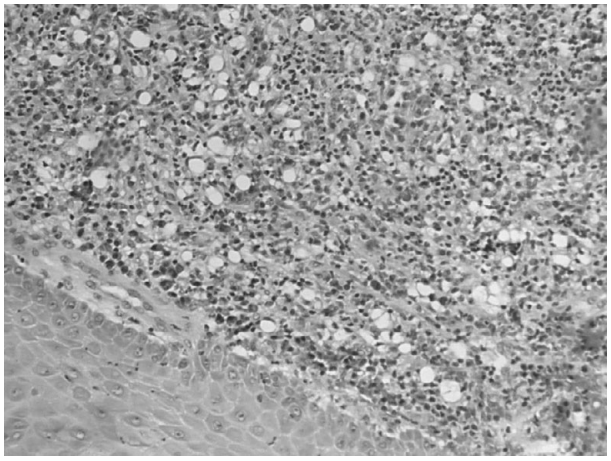

FIG. 2
Histology: squamous mucosa with underlying acute and chronic inflammatory changes and granulation tissue formation (H&E; ×10).

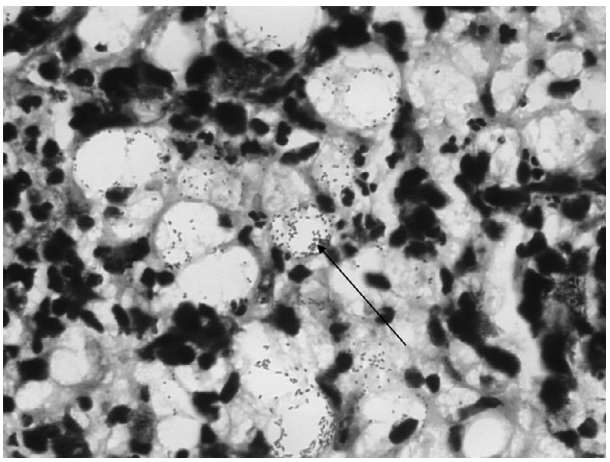

FIG. 3
Mikulicz cells (arrow), large macrophages with clear cytoplasm and intracellular bacilli (Gram; ×40).

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Infection and subsequent mass lesions occur in areas of transition between squamous and ciliated respiratory epithelium, such as the nasal vestibule and the subglottic area. Iron deficiency has been proposed as a risk factor for rhinoscleroma and may contribute to this site predilection by altering epithelial regeneration and causing squamous metaplasia.[9] This may explain the association of rhinoscleroma with poor nutrition, and also why menstruating and pregnant women have been anecdotally observed to have a more severe course than other rhinoscleroma patients.

Classically, there are three clinical and histological stages of rhinoscleroma: catarrhal-atrophic, granulomatous and sclerotic. The catarrhal-atrophic stage may last weeks to months and may begin with a non-specific rhinorrhoea. This may evolve to a foul-smelling, purulent rhinorrhoea with crusting and nasal obstruction. Patients with this presentation are often treated for recurrent sinusitis. Histologically, squamous metaplasia of the epithelium is seen, with an underlying infiltrate of polymorphonuclear cells and some granulation tissue.

The granulomatous or hypertrophic stage is usually the point at which the clinical and histological findings are most easily recognised. Patients present with bluish-red or polypoid, anterior nasal masses which are non-tender, rubbery and may be prone to bleed. These masses most often affect the antero-inferior septum, but sometimes the maxillary antrum may be involved and act as a reservoir for infection. Nasal deformity is not uncommon as destruction of the nasal cartilages occurs to form a classic hebra nose (Figure 4). The destructive process of the disease may leave the patient with anosmia, anaesthesia of the soft palate, enlargement of the uvula, dysphonia or various degrees of airway obstruction. The soft palate may appear thickened at its junction with the hard palate. Histologically, there is pseudoepitheliomatous hyperplasia, Mikulicz cells and evidence of chronic inflammation with many monocytes, lymphocytes and macrophages present. Russell bodies are eosinophilic structures within the cytoplasm of plasma cells and are found characteristically during the granulomatous stage (Figure 5). In addition, sometimes the inflammatory infiltrate is found to be angiocentric and causes a vasculitis-like picture, with hyalinisation of the vessels.

FIG. 4
Hebra nose. Reproduced with permission.[10]

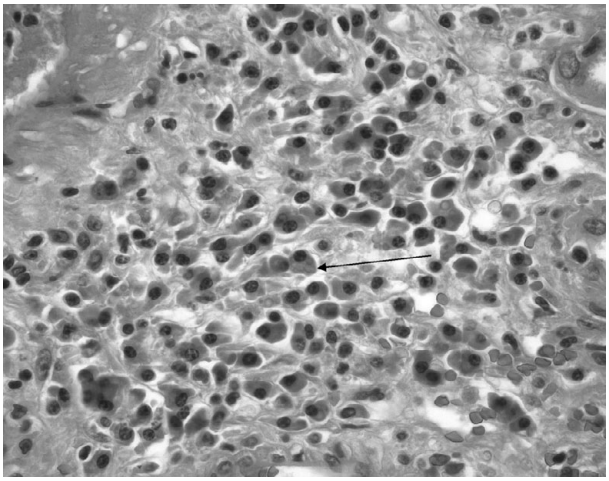

FIG. 5
Russell bodies (arrow), eosinophilic structures within the cytoplasm of plasma cells (H&E; ×20).

Finally, in the sclerotic stage, former masses are replaced by extensive scarring, deformity and stenosis. Few Mikulicz cells or Russell bodies are found during this stage.

Patients may present at any of these three stages and with a host of non-specific complaints, including: nasal obstruction, rhinorrhoea, epistaxis, dysphagia, nasal deformity, anaesthesia of the soft palate, difficulty breathing or stridor, dysphonia, and anosmia. On examination, the diagnosis of rhinoscleroma should be considered if the patient comes from an endemic area and has nasal lesions involving the nasal septum with relative sparing of the sinuses.

Other granulomatous, neoplastic and infectious lesions must also be considered in the differential diagnosis. These include sarcoidosis, Wegener's granulomatosis, lethal midline granuloma, vasculitis, lymphoma, basal cell cancer, verrucous carcinoma, actinomycosis, paracoccidioidomycosis, leishmaniasis, leprosy, tuberculosis, sporotrichosis, syphilis, rhinosporidiosis, nasopalatine duct cyst and Rosai–Dorfman disease.

Establishing the diagnosis is often challenging. When rhinoscleroma is suspected, a brush biopsy specimen of the nasal or respiratory tract mass or an incisional biopsy of an easily accessible lesion should be sent for cytology and culture. A positive culture of *K rhinoscleromatis* on blood or MacConkey agar is diagnostic of rhinoscleroma, but only 50–60 per cent of patients are culture-positive.[1] The bacteria may also be seen using periodic acid-Schiff, Giemsa, Gram or Warthin–Starry silver stains. The histology changes according to the stage of the disease but characteristically is marked by subepithelial Mikulicz cells and transformed plasma cells with Russell bodies. These pathologic findings, along with pseudoepitheliomatous hyperplasia, are usually present in the hypertrophic or granulomatous stage. An immunoperoxidase technique for the K capsular antigen has been shown to increase the specificity of histological findings in culture-negative cases.[1,11]

Imaging studies are somewhat helpful in determining the extent of disease but should not be relied upon for diagnosis. On computed tomographic scans, rhinoscleroma

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appears as a homogenous, non-enhancing mass with distinct margins. Occasional bony or cartilaginous erosion may be seen, but adjacent fascial planes are not usually invaded. Magnetic resonance imaging may show masses obstructing the osteomeatal complexes and may also show high signal intensity on T1- and T2-weighted images in the hypertrophic stage.

Rhinoscleroma remains a difficult entity to cure, and relapses are common. Currently, the recommended treatment of rhinoscleroma consists of a combination of surgical debridement and long-term antibiotic therapy. Treatment is also stage-dependent. Streptomycin was initially widely accepted as the drug of choice for treatment of rhinoscleroma. Tetracycline soon became the preferred antibiotic, with its potential for oral administration and avoidance of the vestibulotoxic side effects of streptomycin. However, the need for a prolonged course of therapy resulted in poor compliance. The use of tetracycline was further limited by its contraindication in children and pregnant women. Ciprofloxacin, trimethoprim–sulphamethoxazole, topical and systemic rifampin, and topical acriflavine have also been used with some success. A shorter course (four to 12 weeks) of ciprofloxacin 500 mg twice daily, along with nasal lavage twice daily, has been stated in a number of case reports to be an effective and affordable option.[12–15] None of these case reports offer a suggested duration of treatment, but they all continued treatment for at least a month after clinical resolution had been documented. Despite its high overall cost, ciprofloxacin for four weeks was found to be more cost-effective and clinically efficacious than the standard six-month combination of rifampin and co-trimoxazole normally used at one institution in an endemic area.[12] Increased compliance, due to shorter duration of treatment, twice-daily dosing and a low side-effect profile, makes ciprofloxicin an appealing drug of choice. Moreover, ciprofloxacin achieves superior tissue penetration and is concentrated within macrophages.[16] In one *in vitro* study, ciprofloxacin was found to have the greatest bacteriocidal activity against *K rhinoscleromatis* of any agent, when compared with streptomycin, tetracycline, rifampin, trimethoprim–sulfamethoxazole and broad spectrum cephalosporins.[13] Trimethoprim–sulphamethoxazole remains a good, inexpensive alternative in developing countries.

- **Rhinoscleroma is a chronic, granulomatous disease affecting the respiratory tract from the nose to the trachea**
- **The nasal cavity is involved in 95–100 per cent of cases**
- **The disease is endemic to areas of Africa, South-East Asia, Mexico, Central and South America, and Central and Eastern Europe, and has been associated with low socio-economic status**
- **Lack of awareness when the disease presents in developed countries often leads to delay in diagnosis**

There are several indications for surgery in rhinoscleroma, including relief of airway obstruction and reconstruction of cicatricial defects. Bronchoscopy can be used for small, early lesions in the lower airway. Tracheostomy should be considered for laryngeal obstruction in either the granulomatous or sclerotic stages. Reconstructive surgery is needed for nasal or lower airway stenosis from scarring or imperforation. For tracheal lesions, the laryngofissure approach is recommended for patients without evidence of subglottic stenosis. Carbon dioxide laser is currently the most effective surgical method for eradication of clinical and histological disease. In one study, patients at the sclerotic stage faired better with CO_2 laser resection than did those with granulomatous disease, as their tissue involvement was often more limited and easier to resect completely.[17] However, both subsets showed a favourable initial clinical response, and only at long-term follow up (18 months) did about 50 per cent of the granulomatous patients show histological recurrence. Uvulopalatopharygoplasty is recommended to address palatal scarring and thickening.

Recurrence is common in patients with rhinoscleroma, and they should be followed regularly with nasal endoscopy and nasal cytology. In addition, a prolonged course of antibiotic therapy, lasting weeks to months, may stave off recurrences.

Conclusion

In the past, rhinoscleroma was rare in the US population, but its incidence may be on the rise with current trends in migration and travel abroad. There is often a delay in diagnosis in non-endemic areas due to: unfamiliarity with the disease; the stage-dependent clinical and histological findings; and the fact that only 50–60 per cent of cultures are positive for *K rhinoscleromatis*. Although rhinoscleroma is rarely lethal, late diagnosis leads to increased morbidity in the form of nasal and airway obstruction and nasal deformity from erosive processes. Rhinoscleroma must remain in the differential diagnosis for all otolaryngologists and infectious disease physicians confronted with airway obstruction and symptoms mimicking prolonged sinusitis. Early recognition is important in order to avoid airway compromise, to quell extensive tissue destruction and scarring, and to control spread to other individuals.

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