Singapore Med J 2012; 53(2) : e24

Rhinoscleroma: a case series

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ABSTRACT Rhinoscleroma is a chronic, slowly progressive, inflammatory disease of the upper respiratory tract. It is associated with *Klebsiella rhinoscleromatis* infection. We present the clinical and pathological features of four patients diagnosed with rhinoscleroma at the National Skin Centre, Singapore between 1997 and 2010. All four patients presented with only cutaneous involvement, and the diagnosis was clinched via histological examination. The patients were treated with a combination of antibiotics. Two patients who were on follow-up at the time of this writing responded positively to the antibiotic treatment, while two were lost to follow-up. Rhinoscleroma is a diagnostic challenge, as it is an uncommon disease in Singapore and Malaysia. We highlight this condition to raise awareness of the disease in order to aid in early diagnosis of patients. Without treatment, this condition can result in significant complications, including involvement of the lower airways. Early diagnosis and appropriate treatment help to reduce morbidity.

Keywords: Klebsiella rhinoscleromatis, Mikulicz cells, Russell bodies, rhinoscleroma
Singapore Med J 2012; 53(2): e24–e27

INTRODUCTION

Rhinoscleroma is a chronic, slowly progressive, inflammatory disease of the upper respiratory tract. "Skleroma" was the Greek name given in 1932, denoting hard tumefaction and emphasising respiratory tract involvement.[1] The lesion was first described in the 1870s by Ferdinando Von Hebra,[2] the histology features by Mikulicz in 1877,[3] and Von Frisch identified the causative agent as *Klebsiella* (*K.*) *rhinoscleromatis* in 1882.[4]

Rhinoscleroma is found predominantly in rural areas with poor socioeconomic conditions. The disease is endemic to regions of Africa, Southeast Asia, Mexico, Central and South America, as well as Central and Eastern Europe. The transmission of this disease is via air-borne routes, and humans are the only identified host. Acquisition of the disease is facilitated by crowding, poor hygiene and malnutrition. It is rarely found in other continents, and infection in non-endemic regions is usually attributed to migration of patients. The sites of involvement commonly include the nasal mucosa (95%–100%), pharynx (18%–43%), paranasal sinuses, trachea and bronchi.[5,6]

Rhinoscleroma is typically classified clinically and pathologically into three stages: catarrhal stage, proliferative stage and fibrotic stage. In the catarrhal stage, patients present with foul smelling purulent nasal discharge and nasal obstruction. There is crusting and atrophy of the nasal mucosa on examination. Histologically, epithelial squamous metaplasia with subepithelial infiltrate of polymorphonuclear cells and granulation tissue are seen. In the proliferative stage, there are usually complaints of epistaxis, nasal deformity, hoarseness, anosmia and epiphora. On examination, bluish red, rubbery granulomatous lesions are seen. The histology is distinguished by the presence of Mikulicz cells (Fig. 1) and Russell bodies. In the fibrotic stage, increased deformity and stenosis, with large amounts of fibrous and scarring tissue on histology, are noted.[7]

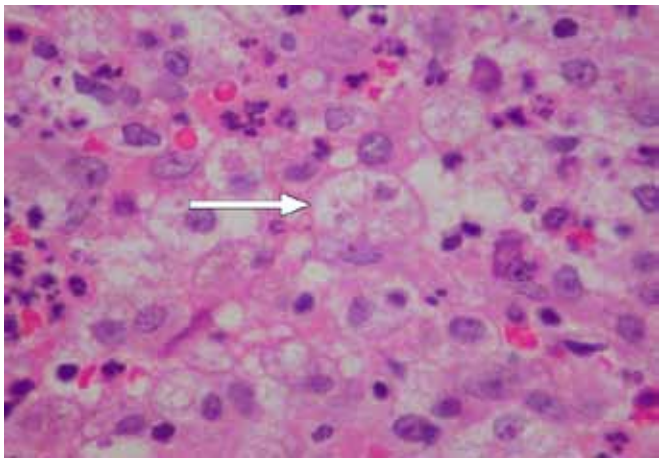

Fig. 1 Photomicrograph shows Mikulicz cells (arrow) (Haematoxylin & eosin, × 600).

We report a case series of four patients with rhinoscleroma. It is interesting that the patients were all middle-aged females from Singapore and Malaysia with no significant travel history. Our patients considerably differed from reported cases in the literature in terms of epidemiology and presentation of solely cutaneous manifestations of the disease. This article aims to raise awareness of this condition among physicians and aid in early diagnosis so as to reduce morbidity. The discussion also highlights treatment challenges and complications associated with rhinoscleroma.

CASE REPORTS

This case series comprises four female patients aged 30–69 years. The duration of disease manifestation to presentation at the National Skin Centre was 1–5 years. The patients only had cutaneous manifestations of the disease, and they were otherwise asymptomatic and had no associated cervical lymphadenopathy. All four patients had no abnormalities

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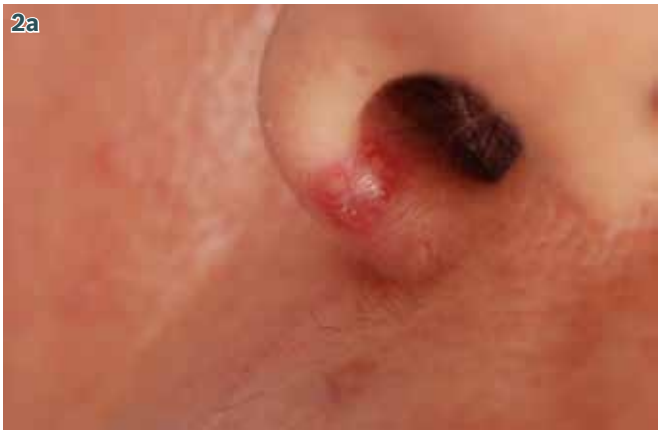
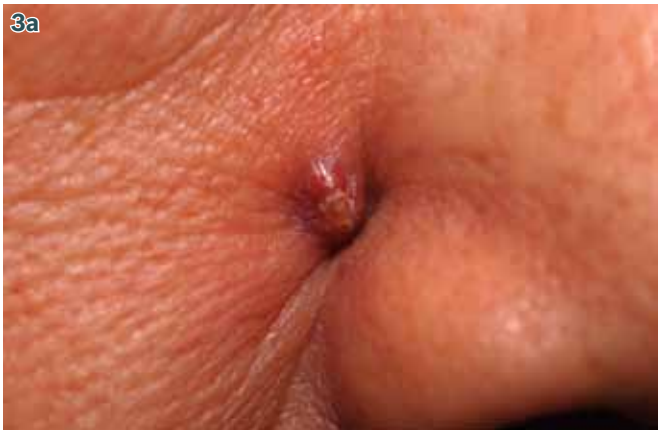


Fig. 2 Photographs show (a) a red-yellowish mass over the patient's right nostril prior to treatment and (b) clearance of lesion after treatment.



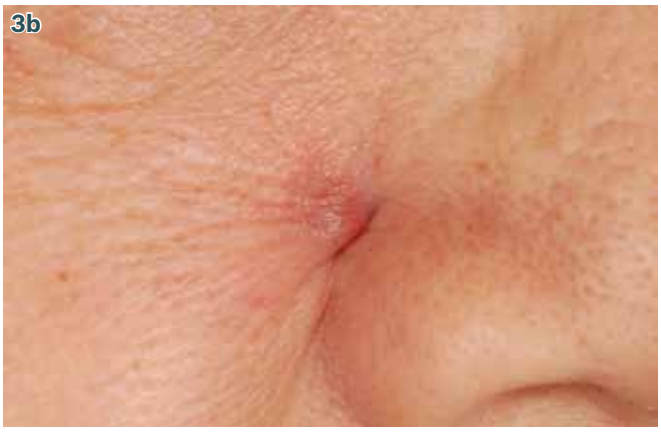


Fig. 3 Photographs show (a) an erythematous papule on the patient's right cheek prior to treatment and (b) clearance of lesion while on treatment.

detected on otorhinolaryngological examination by an ear, nose and throat (ENT) doctor with a nasoscope. They did not require further reviews with the ENT doctor. There was histological confirmation of the diagnosis in all four cases. Mikulicz cells – large histiocytes with numerous vacuoles containing viable or nonviable bacteria, and Russell bodies – eosinophilic structures within the cytoplasm of plasma cells, were present. The presence of intracellular organisms was demonstrated by positive Periodic acid-Schiff (PAS) and Giemsa stains. *K. rhinoscleromatis* infection was confirmed with silver impregnated Warthin-Starry stain.

Case 1 was a 59-year-old Chinese woman who presented with a red-yellowish mass over her right nostril. A nasal swab for culture for *K. rhinoscleromatis* was negative. Treatment was commenced with a combination of ciprofloxacin 500 mg twice a day and doxycycline 100 mg twice a day. Definitive clinical improvement was seen after three weeks of antibiotics. Ciprofloxacin was reduced to 250 mg twice daily after three months, and the patient went on to complete a total duration of six months of antibiotics with good resolution of clinical lesion. Upon completion of antibiotic therapy, she remained asymptomatic with no clinical evidence of recurrence after 12 months (Fig. 2).

Case 2 was a 69-year-old Chinese woman with an erythematous papule on her right cheek. She was initially started on ciprofloxacin 500 mg twice a day. Doxycycline 100 mg twice a day was added to the treatment regime one month later. There was good clinical response to the antibiotics, and the patient was still on treatment when this paper was being written, with an aim to complete six months of antibiotics in total (Fig. 3).

Case 3 was a 47-year-old Chinese woman who presented with a lesion over the right side of her nose, which recurred despite four excisions. Nasal pyogenic organism, tuberculosis and fungal cultures were all negative. She was initially treated with monotherapy using ciprofloxacin 500 mg twice a day for six weeks but had a relapse of the lesion. The patient was then switched to monotherapy with doxycycline 100 mg twice a day with clinical improvement and flattening of the lesion. However, she was subsequently lost to follow-up in 2007.

Case 4 was a 30-year-old Chinese woman. She presented with a lesion over the right side of her nose, which was recurrent despite two excisions. She was treated with a variety of antibiotics over a nine months period, including ciprofloxacin (8.5 months), doxycycline (six months), co-trimoxazole (six weeks), dapsone (six weeks) and rifampicin (six weeks), with no significant clinical response. There was eventual response to intralesional gentamicin 0.1 ml (40 mg/ml) with resolution of the lesion. However, it recurred three years later, and the patient was treated with a combination of electrocautery and cephalexin with some clinical response. The patient was subsequently lost to follow-up.

Table I. Demographics, clinical presentations, investigations other than histology, and treatment data.

Demographic	Case 1	Case 2	Case 3	Case 4
Age (yrs)	59	69	47	30
Gender	Female	Female	Female	Female
Race	Chinese	Chinese	Chinese	Chinese
Country of origin	Singapore	Singapore	Malaysia	Malaysia
Duration of cutaneous lesion prior to presentation (yrs)	1	3	4	1
Site and characteristics of lesion	Red-yellowish mass over the right nostril	Erythematous papule on the right cheek	Recurrent erythematous noduloplaque on the right side of the nose	Recurrent lesion over the right side of the nose
Investigations	Nasal swab for culture was negative	Magnetic resonance of nasal sinuses revealed no abnormalities	Nasal pyogenic organism culture, tuberculosis culture and fungal culture were all negative	Nil
Treatment	Ciprofloxacin and doxycycline (6 months)	Ciprofloxacin and doxycycline (6 months)	Failed monotherapy with ciprofloxacin, clinical improvement with doxycycline	Failed a variety of antibiotics, with response to intralesional gentamicin and subsequently to electrocautery and cephalexin

The demographics, clinical presentations, investigations other than histology, and treatment data of the patients are summarised in Table I.

DISCUSSION

Rhinoscleroma is a diagnostic challenge. It is an uncommon disease and not usually found in the list of differentials when physicians encounter patients with nasal lesions. Most of the cases reported in the literature originated or migrated from endemic regions, and this makes the patients in our case series interesting, as they had no significant travel history. Cases reported in the literature have had respiratory tract involvement and complications from rhinoscleroma; however, in our case series, our patients presented with only cutaneous manifestations of the disease. Their conditions did not progress further to involve the respiratory tract, and the patients did not require any further reviews with an ENT.

The pathophysiology of rhinoscleroma is speculative, likely related to impaired cellular immunity in patients with a reversal of CD4:CD8 ratio. The altered proportion of CD4 and CD8 lymphocytes may produce disabled macrophages, allowing bacterial multiplication within them and leading to ineffective delayed hypersensitivity response.[6] Genetic susceptibility is likely to predispose to infection, as mutations affecting genes encoding components of nicotinamide-adenine-dinucleotide-phosphate oxidase complex cause susceptibility to *K. pneumoniae* infection in mice,[8] and HLA-DQA1*03011-DQB*0301 haplotype has been found to be a strong risk factor for the development of respiratory rhinoscleroma.[9] It would have been remarkable if we had managed to investigate for ineffective macrophages or genetic mutations in our patients.

The diagnosis of rhinoscleroma is usually clinched with histological confirmation, as demonstrated in all four patients, with characteristic findings of Mikulicz cells, Russell bodies and positive Warthin-Starry stains. Routine cultures on blood or MacConkey agar are positive for *K. rhinoscleromatis* in 50%–60% of patients in the granulomatous stage. Our patients only had cutaneous manifestations, which may account for the negative culture results in two out of the four patients. It is not possible to differentiate subspecies by molecular biology, as sequences exhibited 98.2%–99.7% 16S rDNA sequence similarity and 99.4%–100% rpoB sequence similarity. Serologic tests such as complement fixation tests, immunofluorescence staining assays with high titres of IgA have been described in the literature, but these tests have cross reactions and are therefore difficult to interpret.[10] Imaging studies can be used to delineate the extent of involvement. Radiography, computed tomography or magnetic resonance imaging rarely lead to a diagnosis but would be able to demonstrate lesions and affected sites.

Differentials to keep in mind include bacterial causes such as tuberculosis, actinomycosis and leprosy, which can produce granulomas in the upper airways. Fungal infections, including histoplasmosis, blastomycosis and sporotrichosis, should also be considered. Other differentials consist of mucocutaneous leishmaniasis, malignancy such as lymphomas, inflammatory lesions such as sarcoidosis and Wegener's granulomatosis.

Treatment is challenging, as it is difficult to eradicate the disease and recurrences are common. As seen in Case 2 and 3, there were several recurrences despite various treatment modalities. *In vitro*, *K. rhinoscleromatis* is inhibited by clinically achievable concentrations of amoxicillin-clavulanate, chloramphenicol, trimethoprim-sulfamethoxazole, cephalosporins, streptomycin, tetracyclines and ciprofloxacin. *In vivo*, antibiotics with demonstrated efficacy include streptomycin, doxycycline, tetracyclines, rifampicin, second and third generation cephalosporins, sulfonamides, clofazamine,

ciprofloxacin and ofloxacin. *K. rhinoscleromatis* is an intracellular bacterium; it responds well to prolonged courses of rifampicin and fluoroquinolones, as these antibiotics can achieve high concentrations in macrophages. Fluoroquinolones are recommended for their excellent activity against Gram-negative bacilli, intracellular efficacy and low toxicity profile.[11] Recommendations for duration of therapy vary; we currently recommend a treatment regime consisting of a combination of ciprofloxacin and doxycycline for at least six months. Combination therapy is preferred due to the high relapse rates of the disease, as seen in our third and fourth patient with recurrences while on monotherapy. Our first patient completed a six-month course of antibiotics, and remained recurrence-free for 12 months. We acknowledge that the recurrence-free period is short and that close follow-ups are needed in order to detect future recurrences.

Surgical debridement could also be considered if there is significant airway obstruction or cosmetic deformity. Relapses in rhinoscleroma are common, hence the need for prolonged antibiotic treatment and close follow-up to detect early recurrences. Other rarer complications to keep in mind include stenosis leading to respiratory obstruction, haemorrhage, intracranial invasion and malignancy transformation.

In conclusion, rhinoscleroma is an intriguing disease, with further research needed in order to gain a better understanding of its pathophysiology and to improve treatment regimens so as to prevent relapses and associated complications. Our case series serves to highlight that rhinoscleroma can present with only cutaneous manifestations, and we hope to raise awareness of this disease among physicians.

ACKNOWLEDGEMENT

We wish to acknowledge Dr Joyce SS Lee from the National Skin Centre, Singapore for her help with histology.

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