

CASE REPORT

RHINOSCLEROMA: EIGHT PERUVIAN CASES

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SUMMARY

Rhinoscleroma is a rare infection in developed countries; although, it is reported with some frequency in poorer regions such as Central Africa, Central and South America, Eastern and Central Europe, Middle East, India and Indonesia. Nowadays, rhinoscleroma may be erroneously diagnosed as mucocutaneous leishmaniasis, leprosy, paracoccidioidomycosis, rhinosporidiasis, late syphilis, neoplastic diseases or other upper airway diseases. From 1996 to 2003, we diagnosed rhinoscleroma in eight patients attended in the Dermatologic and Transmitted Diseases service of "Cayetano Heredia" National Hospital, in Lima, Peru. The patients presented airway structural alterations producing nasopharyngeal, oropharyngeal and, in one patient, laryngeal stenosis. Biopsy samples revealed large vacuolated macrophages (Mikulicz cells) in all patients. Ciprofloxacin 500 mg bid for four to 12 weeks was used in seven patients and oxytetracycline 500 mg qid for six weeks in one patient. After follow-up for six to 12 months the patients did not show active infection or relapse, however, all of them presented some degree of upper airway stenosis. These cases are reported because of the difficulty diagnosing the disease and the success of antibiotic treatment.

KEYWORDS: Rhinoscleroma; Scleroma; *Klebsiella rhinoscleromatis*; Chronic granulomatous infection.

INTRODUCTION

Rhinoscleroma is a slowly progressive, chronic and granulomatous bacterial disease that usually affects the respiratory tract mucosa. Most of the cases have been reported from poorer regions such as Central Africa, Central and South America, Eastern and Central Europe, Middle East, India and Indonesia. In recent years, some cases in non-endemic areas were reported, explained by the increased migration of the population over the world⁵. Rhinoscleroma is an ancient disease. It is thought that it was frequent in the pre-Columbian Maya civilization in Central America (300 to 600 years AD)²⁰. In 1870, Ferdinand von Hebra carried out a clear description of the disease; some years later, Johann von Mikulicz considered that it was a inflammatory disease and described the typical foamy cells (large histiocytes - Mikulicz cells). In 1882, von Frisch identified the etiologic agent now known as *Klebsiella rhinoscleromatis*²⁹.

Three overlapping stages were described in rhinoscleroma: Catarrhal-atrophic (sometimes called ozaena), granulomatous (proliferative or nodular) and sclerotic (cicatrical or fibrotic). During the catarrhal stage there are foul smelling purulent nasal discharges and nasal obstruction; physical examination may demonstrate atrophy and crusting of the nasal mucosa or hyperemia and exudates in the

respiratory tract mucosa. In the granulomatous stage there are epistaxis, nasal deformity, hoarseness, anosmia and anesthesia of the soft palate; physical examination may find a bluish red and rubbery granulomatous lesion which evolves into a pale hard granulomatous mass. Sclerotic stage symptoms are similar to the previous stage; on physical examination the granulomatous lesions are surrounded by dense fibrotic tissue. Most patients are diagnosed in the granulomatous stage, because they are more symptomatic and other organs besides the nose may be involved⁵.

At present, rhinoscleroma is a diagnostic and therapeutic challenge due to its chronic course and need for prolonged treatment. In addition, the disease may be mistakenly diagnosed as neoplastic disease, mucocutaneous leishmaniasis, leprosy, paracoccidioidomycosis, rhinosporidiasis, late syphilis, etc³⁵.

Herein, we report eight cases of Rhinoscleroma from Peru and review the main aspect of the disease.

PATIENTS AND METHODS

The patients were seen in the Dermatologic and Transmitted Diseases and Otorhinolaryngologic services of "Cayetano Heredia"

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National Hospital from January 1996 to March 2003. All of them were evaluated clinically and by nasopharyngolaryngoscopy. Samples were collected for pathologic and microbiological examinations. Warthin Starry and haematoxylin - eosin stains were used to examine the biopsy samples. Histopathological findings were classified as follows: A) Catarrhal - atrophic stage: squamous metaplasia, subepithelial infiltrate of neutrophils and some granulation tissue. B) Granulomatous stage: atrophy or hyperplasia, showing an infiltrate of chronic inflammatory cells, monocytes, lymphocytes and histiocytes. "Mikulicz cells" could be observed as large histiocytes with numerous vacuoles containing viable or non-viable bacteria. "Russell bodies" were visualized as eosinophilic structures within the cytoplasm of plasma cells. C) Sclerotic stage: large amount of fibrous and cicatricial tissues and few or no Mikulicz cells or Russell bodies. The histologic hallmark for diagnosis of rhinoscleroma is the sub-epithelial presence of Mikulicz cells. Patients were followed up for six months to one year.

RESULTS

Patients were born in different cities of Peru, although, seven of them were living in Lima city for several years. The age range was 25 to 66 years and six (75%) were female. The most frequent symptoms were purulent rhinorrhea (six, 75%), some degree of breathing difficulty (five, 62.5%), nasal obstruction (four, 50%), disphonia (four, 50%) and facial pain (three, 37.5%). The symptomatic periods before diagnosis were variable, from six months to 12 years. Endoscopy showed several lesions, granulomatous infiltration in the choanas in four patients (50%), larynx (three, 37.5%) and oropharynx (two, 25%), crusting (four, 50%) and inflamed mucosal inside the nasal cavity (three, 37.5%), and oropharynx (three, 37.5%). Three patients (37.5%) were found with X ray opacity in the paranasal sinus. Histopathologically, six (75%) patients were classified in the granulomatous, one in catarrhal and one in sclerotic stages. Culture was positive in three patients in the granulomatous stage, the isolates were *Klebsiella rhinoscleromatis*, *Klebsiella ozaenae* and *Klebsiella* sp. Mikulicz cells were found in the biopsies of all the patients. Ciprofloxacin, 500 mg bid, for four to 12 weeks (median of six weeks) was prescribed in seven patients and oxytetracycline, 500 mg qid, for six weeks was used in one patient (Table 1). After that, all patients had inactive infection during the follow-up without any relapses. All, however, remained with some degree of upper airway stenosis. After therapy, two patients developed other upper respiratory tract infections by common germs several times and needed additional antibiotics and surgical debridement.

The sixth patient was a pregnant woman who arrived to the emergency service with cyanosis and acute respiratory distress, due to laryngeal obstruction, and that needed an emergency tracheostomy.

DISCUSSION

The accepted of rhinoscleroma causative agent is *Klebsiella rhinoscleromatis*, a Gram-negative rod-shaped bacteria with 2.5 µm in length which, along with *K. pneumoniae*, *K. ozaenae*, *K. oxytoca* and others, belong to the family Enterobacteriaceae. *K. rhinoscleromatis* has a complex capsule cover and many fimbriae, which are responsible for the microorganism's ability to adhere to host cells³³.

Rhinoscleroma always affects the respiratory tract and sometimes

involves other organs nearby. The nose is affected in 95% to 100% of cases, often bilaterally and asymmetrically, the pharynx in 18% to 43%, larynx in 15% to 80%, trachea in 12%, and bronchi in 2% to 7%^{2,22,34}. Other affected organs include the paranasal sinuses², eustachian tubes¹⁹, middle ear¹, orbital tissues²⁶, skin close to the affected mucosae¹⁷, and the brain⁹. Our patients presented similar frequencies; the nose was affected in 87.5%, pharynx in 50%, larynx in 75% and trachea in 37.5%.

Humans are the only identified host of *K. rhinoscleromatis*²³. This bacterium is not a typical resident in the airway tract and the skin microbiota, so that it has been isolated only from lesions of the human airway mucosa¹⁴. Transmission results most probably through large amount of contaminated airborne particles, which are expelled by coughing and sneezing, or by contact with contaminated fomites²².

Several risk factors have been associated with rhinoscleroma. This disease is more frequent among people in the second or third decades of life, living in crowded conditions, rural areas, with poor hygienic and nutritional conditions¹⁹ such as anemia for iron deficiency³ and in women (female:male ratio is 13:1)²¹. The presence of *K. rhinoscleromatis* is not enough for the development of the disease; since contact for many years of a patient with healthy individuals may not necessarily bring about the infection in the latter. This has led to the suggestion that susceptibility of the host is important to develop the disease¹⁸. Cellular immunity is probably impaired. Peripherally there is a reduction in CD4+ lymphocytes and a significant elevation in the numbers of CD8+ lymphocytes, so the CD4/ CD8 ratio into the lesion is decreased, possibly inducing a diminished or altered T-cell response¹⁰. The humoral immunity response does not control the infection, probably due to the intracellular nature and copious mucin coat of the bacteria, or due to the non specific nature antibody of the response of the host. Whether these defects are acquired after infection or already present in predisposed individuals remains uncertain²⁴.

Chronicity of the disease is still not well understood. After mucosal invasion by the bacteria, the acute inflammatory response is inefficient, the neutrophils phagocytize *Klebsiella*, but appear to die too soon, before digestion finishes, releasing viable bacteria. Histiocytes continue with phagocytosis, and their phagosomes undergo massive dilatation. They thus become Mikulicz cells, which are unable to destroy *K. rhinoscleromatis*, and eventually rupture, releasing the bacteria into the interstitium¹². The altered proportion of CD4+ and CD8+ lymphocytes in the lesion may produce disabled macrophages, allowing bacterial multiplication inside them and an ineffectual delayed type hypersensitivity response²³. *K. rhinoscleromatis* possess several important resistance characteristics such as a complex capsule covered by fimbriae, pleomorphism and the ability to grow vigorously both intra and extracellularly¹².

Specific diagnosis is made by the bacterial isolation by culture on blood or MacConkey agar (positive in 50% to 60%) and by identification of histopathologic features and bacilli in biopsied lesions biopsies, using periodic acid-Schiff (PAS), Giemsa and Warthin - Starry stain⁵. These stains combined with immunoperoxidase staining using *Klebsiella* capsular type 3 antiserum increase accuracy and specificity of both histological and bacteriological diagnoses²⁹. Radiography, computed tomography or resonance imaging rarely lead to diagnosis

Table 1

Characteristics, clinical presentations and findings in the diagnostics procedures and treatment of eight patients with rhinoscleroma in Peru, assisted in "Cayetano Heredia" national hospital from 1996 - 2003

Cases	Age		Time from disease	Symptoms	Paranasal X rays	Culture	Histopathologic diagnosis	Treatment
1	60 yr	Female	10 yr	Mucopurulent rhinorrhea, cough with mucous expectoration, dysphagia, hoarseness, foreign body sensation in the pharynx and laryngeal stridor.	Diffuse opacity in all the paranasal sinuses	<i>K. rhinoscleromatis</i>	Granulomatous	Ciprofloxacin, 500 mg bid, for 12 weeks
2	30 yr	Male	1 yr	Foul smelling purulent rhinorrhea, slight breathing difficulty due to nasal obstruction and sporadic cough with expectoration.	—	<i>K. ozaenae</i>	Granulomatous	Oxytetracycline, 500 mg qid, for six weeks
3	31 yr	Female	6 mo	Purulent rhinorrhea, nasal obstruction, hyposmia and slight morning facial pain.	Opacity of both maxillary sinuses and right frontal sinus	Negative	Catarrhal	Ciprofloxacin, 500 mg bid, for four weeks
4	34 yr	Male	8 yr	Foul smelling purulent rhinorrhea with nasal obstruction and slight breathing difficulty. Pain in the infra-orbital region, dysphonia and right otalgia.	Opacity of right maxillary sinus	<i>Klebsiella</i> sp.	Granulomatous	Ciprofloxacin, 500 mg bid, for six weeks
5	25 yr	Female	6 mo	A sense of right nasal obstruction and intranasal tumor, deformation of the nasal pyramid, mild epistaxis and, occasionally, frontal headache.	—	Negative	Granulomatous	Ciprofloxacin, 500 mg bid, for six weeks
6	30 yr	Female	12 yr	Cough with mucopurulent expectoration, dysphonia, larynx stridor, cyanosis and acute respiratory distress.	—	Negative	Granulomatous	Ciprofloxacin, 500 mg bid, for six weeks
7	46 yr	Female	5 yr	Purulent nasal discharge, slight breathing difficulty and dysphonia.	—	Negative	Sclerotic	Ciprofloxacin, 500 mg bid, for eight weeks
8	66 yr	Female	6 mo	Dry cough, slight breathing difficulty and dysphonia. Without rhinorrhea.	—	Negative	Granulomatous	Ciprofloxacin, 500 mg bid, for five weeks

of rhinoscleroma, although they are helpful in defining the extension of the disease²⁵.

Rhinoscleroma treatment involves prolonged antibiotic therapy, in the attempt to eradicate *K. rhinoscleromatis*, because the relapse rate is high. *In vitro*, these bacteria are inhibited by clinically achievable concentrations of amoxicillin - clavulanate, chloramphenicol, trimethoprim - sulfamethoxazole, cephalosporins, streptomycin, tetracyclines and ciprofloxacin³². However, *in vivo*, antibiotics with demonstrated efficacy are streptomycin, doxycycline, tetracycline, rifampicin, second- and third-generation cephalosporin, sulfonamides, clofazimine, ciprofloxacin¹¹ and ofloxacin³¹. Because *K.*

rhinoscleromatis is an intracellular bacteria prolonged courses of rifampicin and fluoroquinolones would theoretically be most effective, due to their high concentration in macrophages^{22,37}. BORGSTEIN *et al.*(1993), reported that 89% of culture of the biopsy of the lesion was negative two months after the use of ciprofloxacin for four weeks, and after six months clinical improvement was significant and the relapse rate was low¹¹. However, the duration of antibiotic therapy with ciprofloxacin has not been established, different author recommend using for six weeks to six months or longer, until repeated cultures and histological examination are negative³⁰. Long-term follow-up is required to identify early relapse^{8,22}. Topical antibiotics such as acriflavine 2% or rifampin have been used with significant results^{7,19}. Most of our

patients used ciprofloxacin 500 mg bid for a period of four to 12 weeks with good results and no one relapsed during six to 12 months of follow-up, which agrees with other reports from Latin America^{15,28}.

Granulomatous tissue, crusting and fibrotic scarring are lesions that produce several degrees of airway obstruction and cosmetic deformity, so that surgical therapy is indicated in some cases³⁶. Surgical procedures must be postponed until no residual disease activity is evident in the tissues to be debrided; otherwise there is high risk of relapse or iatrogenic dissemination²². Carbon dioxide surgical laser showed to be of value²⁷. Tracheobronchial stenosis could be managed by bronchoscopic dilatation¹³. Severe acute respiratory failure could require emergency tracheostomy, close observation and oral or intravenous corticosteroids^{4,38}. Pregnant women could be a special group affected with serious airway obstruction by granulomatous infiltration into the laryngotracheal mucosa⁶. The only severe case in our report was a pregnant woman with long-standing disease (12 years) involving glottal stenosis who needed tracheostomy.

After therapy, patients remain with some sequels which vary in seriousness that depend on the organs affected, such as hoarseness and stridor because of glottal/subglottal stenosis, dysphonia due to fibrosis of the vocal folds fibrosis, olfactory disorders produced by nasal mucosa scarring. Early diagnosis and prolonged therapy are critical to avoid their late sequelae⁴. Case fatality is extremely low in rhinoscleroma³⁸.

Prophylaxis is based on the improvement of sanitary conditions and general living conditions of poor people in endemic areas¹⁶.

CONCLUSION

Rhinoscleroma is a multifactorial disease with some identified risk factors, more frequent in middle aged women, living in rural areas with poor hygiene and nutritional conditions. Patients show a deficient immuno-cellular response which could be acquired by the infection or to other associated risk factor such as malnutrition, or could be constitutional. It is a long-standing disease that begins in the nasal mucosa and extends to other respiratory tract organs, producing airway obstruction and sometimes threatens the patient life. Early diagnosis and treatment are important to eradicate *K. rhinoscleromatis* and limit the fibrotic scarring sequelae. Fluoroquinolones are well-tolerated drugs with low incidences of adverse effects when used for long periods. There is no evidence of relapse after quinolone treatment, indicating that they are good therapy, although there have been no formal clinical trials to evaluate their efficacy.

RESUMO

Rinoscleroma: oito casos peruanos

O rinoscleroma é uma infecção rara nos países desenvolvidos, no entanto, tem sido relatado com alguma frequência nas regiões pobres da África Central, América Central e do Sul, Europa Central e Oriental, Oriente Médio, Índia e Indonésia. A doença pode ser erroneamente diagnosticada como leishmaniose mucocutânea, hanseníase, paracoccidiodomicose, rinosporidiose, sífilis tardia, neoplasias ou outras doenças que afetam a via respiratória superior. No período de

1996 a 2003, foram diagnosticados oito casos de rinoscleroma no serviço de Doenças Dermatológicas e Infecciosas do Hospital Nacional "Cayetano Heredia", em Lima, Peru. Os pacientes apresentaram alterações estruturais das vias respiratórias, caracterizadas por estenose da nasofaringe e orofaringe, e em um paciente, a nível da laringe. As biópsias mostraram macrófagos com grandes vacúolos (células de Mikulicz). A ciprofloxacina 500 mg de 12/12 horas por quatro a 12 semanas foi usada em sete pacientes e oxitetraciclina 500 mg de 6/6 horas por seis semanas em um paciente. Durante o acompanhamento por seis a 12 meses todos os pacientes apresentaram cura clínica, sem recaída, embora exibissem algum grau de estenose na via respiratória superior. O motivo do relato deve-se ao fato desta doença constituir um grande desafio diagnóstico e pelo sucesso alcançado com o tratamento antibiótico.

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Received: 23 November 2005

Accepted: 27 April 2006