Case Report

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Rhinoscleroma – A unique masquerader. A retrospective case series

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Abstract: Objectives: Rhinoscleroma is a rare infectious disease of the upper respiratory tract caused by *Klebsiella rhinoscleromatis*. Apart from mandating an appropriate antibiotic therapy, it poses a unique challenge to the pathologists since it can clinically simulate a malignancy. The main objective was to study the cases of rhinoscleroma of the respiratory tract in a period of 3 years with an emphasis on the clinico-pathologic features.

Methods: We report a retrospective analysis of 7 cases, histopathologically diagnosed at our centre as rhinoscleroma. The topography ranged from nasal mucosa (3), pharynx (2) and larynx (2).

Results: Histopathological examination in all cases showed diffuse aggregates of foamy macrophages (Mikulicz cells) containing intracytoplasmic basophilic organisms; admixed with plasma cells in a fibrotic stroma. The overlying epithelium appeared atrophic to focally hyperplastic. The age ranged from 36–67 years, involving both genders. The significant clinical history included a nasal block without anosmia, atrophic rhinitis with septal perforation to subglottic stenosis, requiring immediate surgical intervention. In 4 of the 7 cases, the working clinical diagnosis was stipulated as a malignancy.

Conclusions: Rhinoscleroma can affect different regions in the upper aero digestive tract. A lack of awareness and a delay in the diagnosis of this disease can lead to complications including upper airway obstruction, physical deformity, and rarely, sepsis. In addition, it must be remembered that the treatment of rhinoscleroma is challenging and requires a prolonged course of antibiotics to achieve a definite cure and avoid relapses.

Keywords: rhinoscleroma, rhinitis, subglottic stenosis, malignancy, complications

1 Introduction

Rhinoscleroma is a chronic granulomatous disease. The causative organism for this disease is a gram-negative bacterium called *Klebsiella pneumoniae* subsp. *rhinoscleromatis*, or more popularly abbreviated as *Klebsiella rhinoscleromatis*. There is established literature pointing towards a higher prevalence of this disease in low-income countries where socio-economic and hygienic conditions play a pivotal role in etiopathogenesis [1]. While the very name of the disease suggests a nasal cavity-based occurrence, there is increasing evidence that other anatomic locations are also involved. These regions include pharynx, laryngeal passage, and the tracheo-bronchial tree [2,3]. Unusual presentations also include middle ear, paranasal sinuses, cervical lymph node, and occasional cases with intra-cranial extension [4–7].

A hallmark of this disease is the tissue appearance of foamy macrophages, also called Mikulicz cells. However, additional ancillary tests such as cytochemical stains and microbiological culture are necessary for corroboration. While antibiotic therapy still remains the mainstay of this disease, the complications can include local pathologies, such as persistent inflammation to scarring, with life-threatening sepsis, and rarely, malignancy. We herein report a case series of rhinoscleroma with an emphasis on its clinicopathological profile and anatomical topography, to highlight the salient features of this disease. The aim was to study the cases of rhinoscleroma of the respiratory tract in a period of 3 years with an emphasis on the clinico-pathologic features.

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2 Materials and methods

The study was retrospective in nature. We evaluated a total of 7 cases diagnosed histopathologically as rhinoscleroma at the Department of Pathology, Kasturba Medical College, Manipal between the years 2017–2020. The reports were retrieved from the electronic software database by typing the keyword for diagnosis (rhinoscleroma, rhinitis, subglottic stenosis, malignancy, complications). Formalin-fixed paraplast-embedded tissue blocks from patients were retrieved from the departmental archives/repository, and sections of 5 μm thickness were stained with Hematoxylin and Eosin (H&E). Additional Periodic Acid Schiff (PAS) stain for identification of the causative microorganism was also performed.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Results

The salient features of the 7 cases are summarized in Table 1. The age ranged from 36 to 67 years, with a mean age of 49.5 years. Males (n=4) and females (n=3) were equally affected and no particular gender predilection was noted. The anatomic locations, where the lesion could be identified based on clinical assessment ranged from the nasal cavity (n=3), the posterior pharyngeal wall (n=2) and the larynx (n=2). The presenting complaints encompassed nasal obstruction with discharge, fever with sore throat, and voice change with significant stridor. In 4 of the cases, the clinician had suspected a possible malignancy due to the presenting complaints and the examination findings. All 7 cases were subject to a guided biopsy which was sent for a histopathologic examination.

The biopsy findings (Figures 1 and 2) showed a lining epithelium to be either normal or attenuated. The submucosal stroma in all cases showed diffuse aggregates of foamy macrophages (Mikulicz cells) containing intracytoplasmic basophilic organisms; admixed with numerous plasma cells, lymphocytes and few neutrophils in a variably fibrotic stroma. PAS stain in 5 cases showed intracellular tiny amphophilic organisms, whose morphology was suggestive of *K. rhinoscleromatis* (Figure 3). In 2 remaining cases, the staining was equivocal. Also, staining for acid fast bacilli (AFB) excluded the possibilities of both leprosy and tuberculosis.

Microbiological studies (staining and culture) were performed on only 4 cases, with 2 showing an evidence of *K. rhinoscleromatis*. All barring one case were treated with doxycycline-based antibiotic therapy with added ciprofloxacin for 6–8 weeks. In the immediate follow-up weeks, the symptoms had subsided in all 6 cases. One case however, developed a sudden deterioration in voice quality with progressive stridor. This patient apparently had a two-week history of an upper respiratory tract

Table 1: The salient clinicopathological features of the cases

Particulars	Anatomic location of the lesion	Presenting complaints	Clinical (working) diagnosis	Ancillary tests
Case-1, 36yr/Female	Left nasal cavity mass	Nasal obstruction and occasional bouts of epistaxis	Malignancy	PAS stain: positive for bacillus Culture: not done
Case-2, 43yr/Male	Posterior pharyngeal wall	Sore throat with nocturnal bouts of dry cough	Pharyngitis	PAS stain: positive for bacillus Culture: negative
Case-3, 51yr/Female	Right nasal cavity mass/polyp with septal perforation	Nasal discharge with sinusitis and epistaxis	Sinonasal polyposis, secondary to inflammation	PAS stain: positive for bacillus Culture: not done
Case-4, 55yr/Male	Left nasal cavity	Nasal obstruction with a sore throat	Deviated nasal septum with rhino-sinusitis	PAS stain: negative for bacillus Culture: not done
Case-5, 67yr/Male	Left sided false vocal cords	Hoarseness of voice with low grade fever	Malignancy	PAS stain: positive for bacillus Culture: positive
Case-6, 54yr/Female	Bilateral true vocal cords with subglottic extension	Stridor, dry cough and fever	Malignancy	PAS stain: positive for bacillus Culture: negative
Case-7, 40yr/Male	Posterior pharyngeal wall	Sore throat with low grade fever	Malignancy	PAS stain: negative for bacillus Culture: positive

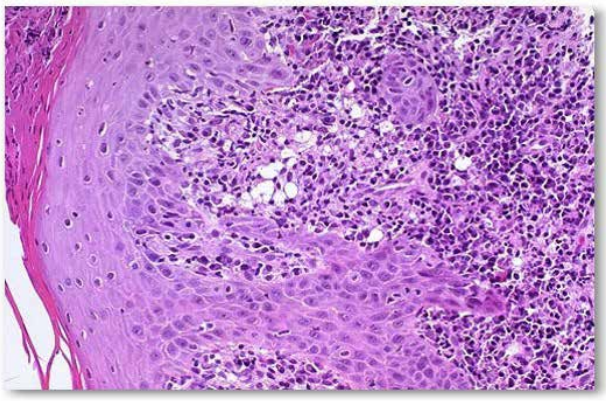

Figure 1: Laryngeal biopsy showing submucosal aggregates of foam cells and a mononuclear inflammatory infiltrate (H&E; 100x)

infection and was refractory to an initial dose of antibiotics. The information on the nature of the medication taken was not retrievable. The laryngoscopy showed a subglottic stenosis with adhesions which necessitated active surgical intervention. The patient recovered in two weeks' time with additional antibiotic coverage and noted marginal improvement in quality of voice and subsiding of symptoms. At the time of submission of this article, no further follow-up was available on that case.

Latest follow-up was available for only 3 patients, all of whom had reported an improvement in general health and symptoms. The remaining 4 patients were lost to follow-up.

4 Discussion

Rhinoscleroma is a specific chronic granulomatous disease of the upper respiratory tract. The initial confirmed report of this disease has been credited to Von Frisch in 1882 who described the microbiological structure [8]. This disease occurs predominantly in the eastern hemisphere, with cases reported from impoverished areas of Africa, Central and South America and South-East Asia. In the Indian sub-continent, cases are attributed to low levels of hygiene in an increasingly crowded habitat. The mode of transmission is hypothesized to be contaminated airborne particles, which are expelled by coughing and sneezing or by contact with fomites. Interestingly, a genetic association has also been reported. The haplotype HLA-DQA1*03011-DQB*0301 has been reported to be associated with the development of this disease [9]. In the present case series, no familial tendencies were noted. As for the background of the patients, they ranged from low-income households to middle-class family individuals, although

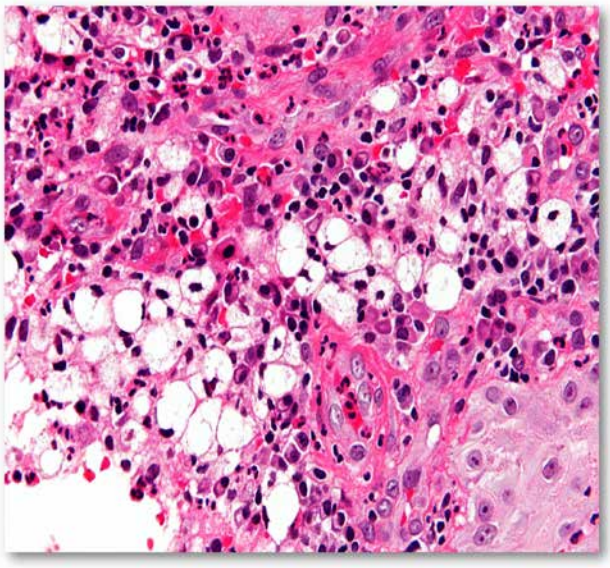

Figure 2: Biopsy showing foam cells, some with intracytoplasmic bacilli (Mikulicz cells) and a plasma cell infiltrate (H&E; 400x)

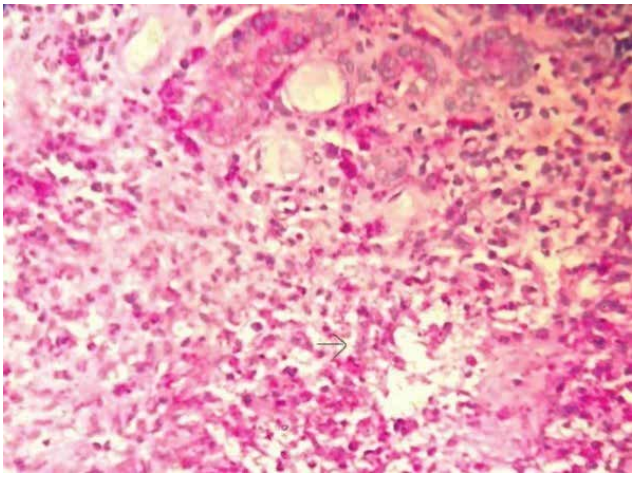

Figure 3: PAS stain demonstrating intracellular bacilli (arrow) (PAS; 400x)

co-morbidities such as diabetes mellitus and obstructive respiratory diseases were documented in 4 cases.

This infection charts a typical course which has been widely reported in literature, into three distinct, yet overlapping stages [10]. An initial catarrhal/rhintic phase is augured by non-specific rhinitis that can last for weeks to months and often evolves into purulent rhinorrhea with crusting. This leads to a second stage: granulomatous/florid, with a bluish red nasal mucosa and intranasal nodules or polyps. This phase may also see additional features such as epistaxis, nasal deformities, and destruction of the nasal cartilage. The sclerotic/cicatricial phase is characterized by extensive fibrosis leading to extensive scarring and possible nasal/laryngeal stenosis. The time-

line between the above-mentioned phases may range from several days to months, and more importantly perhaps, overlap too. In the present case series, most cases could be slotted into the catarrhal phase, purely on the clinical index of suspicion. The one case showing laryngeal stridor is clearly the final sclerotic phase, which necessitated a surgical intervention in addition to the pre-existing antibiotic regimen.

The nasal cavity and nasopharynx are sites of predilection for rhinoscleroma. This was noted in 5 cases in the present case series. But a plethora of other sites of involvement have been reported [2,3]. Of relevance to this article, a study showed pharyngeal rhinoscleroma in only 9 (10%) patients, whereas a laryngeal involvement occurred in 19 (21.5%) cases [11]. Involvement of the trachea was only reported in 1 (1%) case in the same study. In our series, the topographical involvement is similar to the above stated study with one solitary case with laryngeal involvement.

The diagnosis of rhinoscleroma rests on a combination of histopathologic features and microbiology studies. The hallmark histologic feature is most certainly the Mikulicz cells (Figures 1 and 2). These cells are transformed/activated histiocytes recruited from the bone marrow by signals generated by interleukin-10 (IL-10) to the localized zone of inflammation, forming large foamy macrophage aggregates with numerous enlarged vacuoles [12]. The vacuoles may or may not contain the gram negative bacteria. In the present series, only two cases showed paucicellular bacilli. PAS stain may be required to underscore the presence of the bacilli. While the catarrhal phase may demonstrate only neutrophils with granulation tissue, the pathognomonic Mikulicz cells are reported predominantly in the granulomatous phase, accompanied by an interspersed mixed inflammatory infiltrate, composed of lymphocytes and plasma cells. In the lone case belonging to the sclerotic phase in this case series, these inflammatory infiltrates were sparse. Apart from the special stains, only 4 cases had a concurrent microbiology evaluation by culture, to establish the presence of the bacillus. It has been reported that demonstration of type III *Klebsiella* antigen by immunohistochemistry and tissue culture yields positive recognition of *K. rhinoscleromatis* in about 50% of cases, specifically in the granulomatous stage of the disease [13]. It is pertinent to bear in mind that mimickers of foamy histiocytes in a tissue biopsy are readily seen in other granulomatous lesions of the head and neck region. With the Indian subcontinent in particular, one cannot discount the possibilities of leprosy and tuberculosis. Rare considerations also include Wegener's granulomatosis and sarcoidosis. In the present cases, no particular clues in histology were available corresponding to these diseases.

The severity and chronicity of the disease is seemingly determined by the virulence factors, that mediate in the pathogenesis of *K. rhinoscleromatis*. The capsule polysaccharide (CPS) inhibits the deposition of complement components onto the bacterium, thus avoiding adhesion and phagocytosis of the bacterium by macrophages and epithelial cells [14]. The discrepancy in the numbers of Mikulicz cells, which vary across the three phases, could possibly be explained by the hypothesis drawn by Corelli and colleagues, who in their study in animal models, have determined that CPS it is not required to induce the formation of Mikulicz cells [1].

The failure of formation of granulomas, despite the chronic course of the disease, has also been debated. Researchers such as Berron et al. demonstrated attenuated cell-mediated immunity, evidenced by a reduced CD4/CD8 T cell ratio and a consequent poor T cell response in rhinoscleroma [15]. As we understand from literature, helper T cells are necessary to secrete interleukins which recruit the histiocytes and facilitate their transformation into the pathognomonic epithelioid cells, endowed with phagocytic and defensive effects against microorganisms. Poor cell-mediated immunity may very well be the culprit for the lack of tissue granuloma formation in rhinoscleroma. No granulomas were noted in the seven cases. Elsewhere, it has been demonstrated that humoral immunity is the predominant response against *K. rhinoscleromatis*; evidenced by the numerous plasma cells and lymphocytes in the stromal tissue [16]. The same was reflected in our cases as well.

The management of rhinoscleroma includes a combination of antibiotics coupled with surgical debridement. The latter may be necessitated in case of complications of a cosmetic disfigurement. Since *K. rhinoscleromatis* is an intracellular gram negative bacterium, the antibiotics that can achieve high concentrations within macrophages have been deemed effective. In the paper by Fawaz et al., the authors proposed the use of rifampin, trimethoprim-sulfamethoxazole, or ciprofloxacin for at least 2–3 months [11]. There has been experimentation with other antibiotic drugs as well. Six of the seven patients in our case series were given a combination of ciprofloxacin and doxycycline for 6–8 weeks. One case, however, developed a sudden deterioration in voice quality with progressive stridor. Laryngoscopy showed a subglottic stenosis with adhesions which necessitated active surgical intervention. Zhong and co-workers, in their exhaustive case series involving 40 patients, with an available follow-up of over three decades, reported that 27 patients remained relapse-

free 1 to 10 years following treatment with antibiotics supplemented in some cases with surgery or radiotherapy [17]. Elsewhere, Tan and colleagues have recommended an antibiotic regimen consisting of a combination of ciprofloxacin and doxycycline for at least 6 months [18]. In more recent works, Jage and co-workers in India and Guatemalan researchers: Mariz and colleagues have reported recovery by using doxycycline and long-term trimethoprim and sulfamethoxazole combination, respectively [19,20].

5 Conclusions

Rhinoscleroma can affect different regions in the upper aero digestive tract. A lack of awareness and a delay in the diagnosis of this disease can lead to complications including upper airway obstruction, physical deformity, and, rarely, sepsis. In addition, it must be remembered that both diagnosis and treatment of rhinoscleroma is challenging and requires a prolonged course of antibiotics to achieve a definite cure and avoid relapses.

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Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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