

Nasal Rhinoscleroma in a Nonendemic Area : A Case Report

Rhinoscleroma is a chronic, granulomatous infectious lesion most frequently affecting the respiratory tract mucosa. This disease is endemic to Africa, Central and South America, South Central and Eastern Europe, the Middle East, and China. We report an extremely rare disease of nasal rhinoscleroma in Korea. The patient was a 63-yr-old man, who suffered from chronic nasal obstruction and septal deviation. Characteristic histology from a nasal biopsy was proven and special stains for bacteria were employed: periodic acid-Schiff, Warthin-Starry silver, Giemsa, and Gram stains. Isolation of *Klebsiella rhinoscleromatis* from a culture of nasal discharge was failed, but ultrastructural examination of numerous phagocytized bacilli in the Mikulicz cells confirmed the diagnosis. The histiocytic nature of the Mikulicz cells was confirmed, using CD 68 and alpha-1 antitrypsin, and by the ultrastructural features of Mikulicz cells. Here, we emphasize the recognition of this rare entity in nonendemic regions, frequently leading to delayed diagnosis.

Key Words : Rhinoscleroma; *Klebsiella Rhinoscleromatis*; Macrophages; Microscopy, Electron

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INTRODUCTION

Rhinoscleroma is a rare, chronic, granulomatous infectious disease in Korea, where only one case has been reported in the history of Korea (1). Without adequate treatment, the disease can potentially spread to the rest of the upper and middle respiratory tract or even rarely intracranially within a few years (2). A life threatening subglottic stenosis requires an immediate surgical intervention.

We describe a case of nasal rhinoscleroma with particular reference to its characteristic histopathology, including ultrastructural findings.

CASE REPORT

A 63-yr-old Korean man presented to the hospital with a 13-yr history of chronic sinusitis, mucopurulent nasal discharge, and nasal obstruction. He was a heavy smoker (40 pack years) who suffered from arteriosclerosis obliterans for 15 yr. He also complained of chronic headache for several months, and brain computed tomography revealed unremarkable abnormalities without cerebrospinal fluid leakage. The right fifth finger was amputated 5 yr ago, as a result of arteriosclerosis obliterans. He had no history of traveling abroad. Laboratory workup, including a complete blood count and electrolyte levels, was normal. Nasal cultures were negative for

mycobacteria and fungi. Examination of the nose revealed a deviated nasal septum, multifocal irregular yellow to brown mucosal polypoid nodules fulfilling the bilateral nasal cavities. The mass was obstructing the right naris, and was pushing into the left nare. Biopsies were taken from the left inferior turbinate to right lateral wall. Grossly, the specimen consisted of small fragments of soft, tan-pink tissue, measuring 1.0 × 0.6 × 0.5 cm in aggregates. The mucosal surface showed intact overlying respiratory or metaplastic squamous epithelium. The underlying submucosa revealed a diffuse infiltration with large, vacuolated histiocytes, i.e. Mikulicz cells (Fig. 1A). Some lymphoplasm cells were present, and some of them contained Russel's bodies (Fig. 1B). A Gram stain showed Gram-negative bacteria, which also stained with periodic acid-Schiff (Fig. 1C) and Warthin-Starry stains. Acid-fast bacilli and Gomori methenamine silver stains were negative for microorganisms. The Mikulicz cells were immuno-reactive for CD68 and alpha-1-antitrypsin, and negative for mucicarmine or pancytokeratin (AE1/AE3). Electron microscopy showed many phagosomes in the cytoplasm of histiocytes and bacilli (Fig. 2). The size of the rod-shaped bacilli was 1-3 μm in average length. A small number of other organelles such as endoplasmic reticulums and lysosomes were squeezed to the side of the cells. There were many granular substances on the surface of the intracellular bacteria, which were not found on the extracellular bacilli. The diagnosis of rhinoscleroma was made. Laryngoscopic examination revealed normal trachea

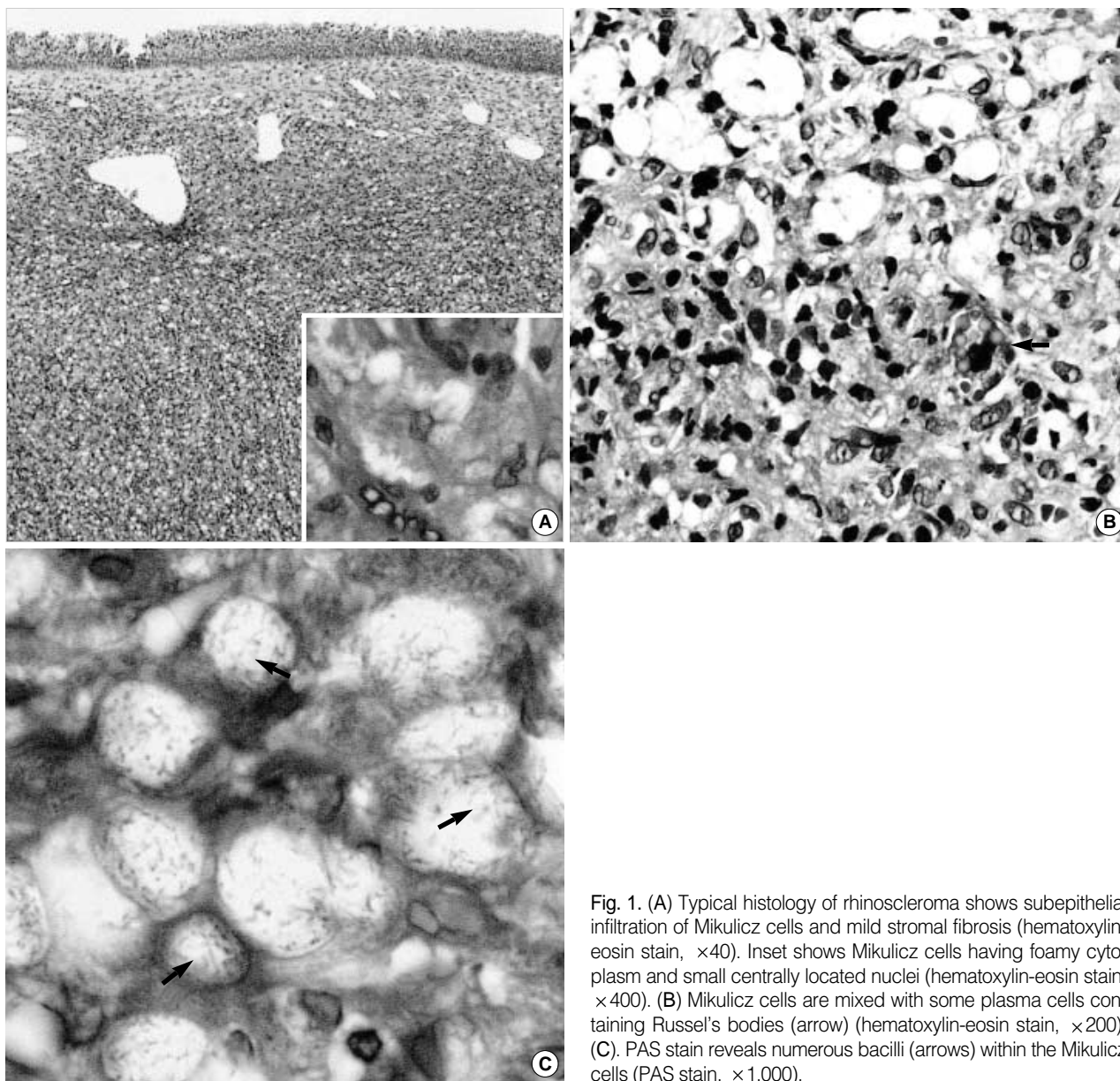


Fig. 1. (A) Typical histology of rhinoscleroma shows subepithelial infiltration of Mikulicz cells and mild stromal fibrosis (hematoxylin-eosin stain, $\times 40$). Inset shows Mikulicz cells having foamy cytoplasm and small centrally located nuclei (hematoxylin-eosin stain, $\times 400$). (B) Mikulicz cells are mixed with some plasma cells containing Russell's bodies (arrow) (hematoxylin-eosin stain, $\times 200$). (C) PAS stain reveals numerous bacilli (arrows) within the Mikulicz cells (PAS stain, $\times 1,000$).

and larynx. Treatment with tetracycline for 3 months was followed by significant symptomatic improvement.

DISCUSSION

Rhinoscleroma, chronic specific granuloma of the nose and upper respiratory tract, is a rare disease that mainly occurs among people of low socioeconomic status. Korea is a nonendemic area where rhinoscleroma occurs sporadically (1), and a low index of suspicion in nonendemic areas could explain the extreme delay in the diagnosis, as seen in our patient. Nasal rhinoscleroma should be considered in patients complaining of severe nasal obstruction or atrophy/polyposis exhibiting

significant adherence to the nasal septum and relative sparing of the sinus. Under light microscope, we first raised the possibility of metastatic mucinous carcinoma from an unknown primary site, rather than the infection itself. The histologic hallmark in the diagnosis of rhinoscleroma is the subepithelial presence of Mikulicz cells, containing rod shaped bacilli highlighted by Warthin-Starry silver, Giemsa or periodic acid-Schiff stains (2). The phagocytized bacillus is *Klebsiella rhinoscleromatis*, which is a Gram-negative, facultative intracellular bacteria. The organism is an encapsulated, nonmotile, and diplobacillus member of the family of Enterobacteriaceae. Its tumor-like appearance and local-spread arouse the suspicion of malignancy. However, differential diagnosis of rhinoscleroma also includes fungal infections and numerous granulo-

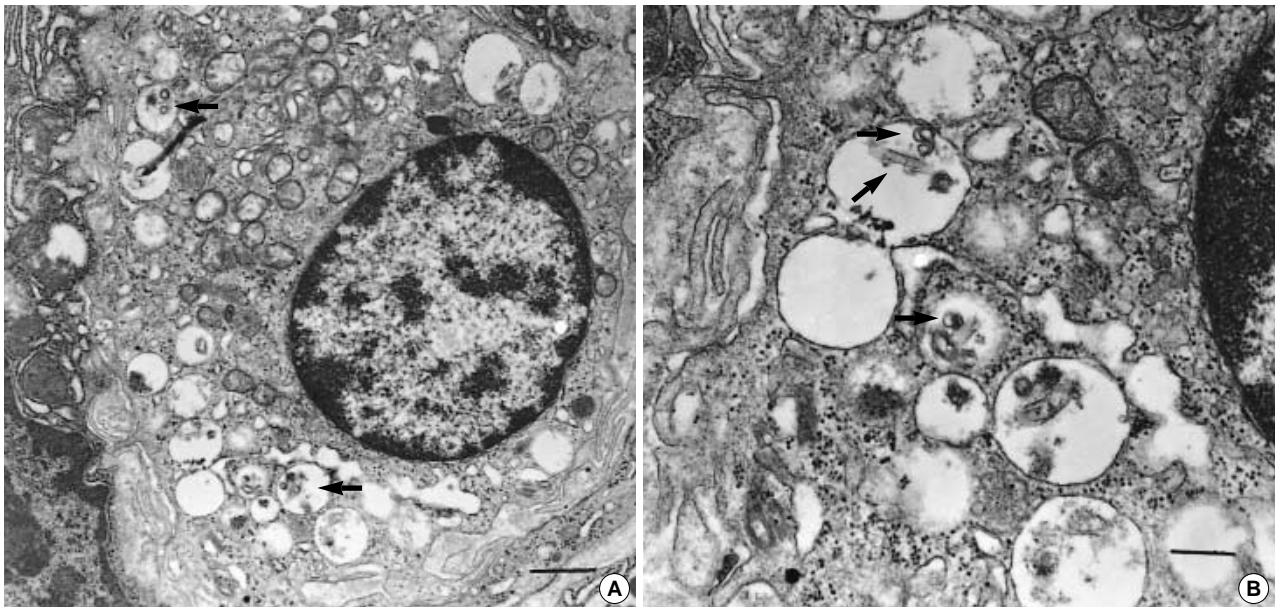


Fig. 2. (A) Electron microscopy reveals numerous small vacuoles containing fine granular material (arrows) are seen inside Mikulicz cells (original magnification $\times 8,000$, bar represents 1,000 nm). (B) Higher magnification reveals that intact intravacuolar bacilli (arrows) usually have a slime layer and appear surrounded by a corona of radially oriented fibrillar cilia (original magnification $\times 20,000$, bar represents 800 nm).

matous diseases, as well as malignant lymphoma (2, 3). Nasal granulomatous diseases such as leprosy, tuberculosis, vasculitis and Wegener's disease should be distinguished from the granulomatous stage of rhinoscleroma. From the viewpoint of pathologic diagnosis, histologic findings differ according to the stages of the disease; catarrhal/atrophic, granulomatous and sclerotic stages (4), and the pathologic stages correspond well to the clinical stages of the disease. In the catarrhal stage, subepithelial infiltration by the bacilli was followed by the proliferation of capillaries. At this stage, purulent nasal discharges predominate. Subsequently, neutrophils and histiocytes are accumulated in the subepithelium. Plasma cells may predominate in the chronic stage. Finally, the formation of granulomas and extensive fibrosis in the bacilli-infiltrated regions are the major cause of tissue injury. Electron microscopy is also helpful for the diagnosis. Ultrastructurally, many Mikulicz cells containing large phagosomes filled with bacilli are found, as they were surrounded by a finely granular or fibrillar material in radially arranged mode (5). Accumulation of antibodies on the bacterial surface and appear as electron-dense granular and fibrillary substances on electron microscope is called as "type A" granules. Type B granules are less electron-dense substances, representing bacterial antigen composed of mucopolysaccharides surrounded by antibodies, i.e. type A granules. Humans are the only identified hosts of *K. rhinoscleromatis*. Because the bacteria is not found in normal nasal secretions, demonstration of *K. rhinoscleromatis* through culture is diagnostic. However, routine cultures in MacConkey agar reveal positive results among 50-60% of the patients (6, 7).

The pathogenesis of the rhinoscleroma is regarded as the

sole etiologic role of *K. rhinoscleromatis* is unclear. The observation that contacts with a patient may not necessarily bring about the infection in healthy individuals supported the suggestion that the susceptibility of the host plays an important role in the development of disease. Cellular immunity is impaired in affected patients, while the humoral immunity is preserved. The CD4/CD8 ratio within the lesion is altered, showing decreased CD4 lymphocytes and increased CD8 lymphocytes, possibly inducing a diminished or altered T-cell response. In one experimental study of intravenous injection of *K. rhinoscleromatis* in albino rats, positive histopathological diagnosis of scleroma was reported in the nose of 66.7% of rats, the larynx of 46.7%, the lungs of 26.7% and the liver of 20% of rats (6). Based on these results, this disease might be induced by the organs' variable susceptibility or interaction of bacilli and inflammatory cells including neutrophils, histiocytes and plasma cells. In the infiltrative (catarrhal) stage, subepithelial infiltration of *K. rhinoscleromatis* was followed by its active multiplication and proliferation of capillaries. Subsequently, neutrophils delivered into this space actively phagocytized the organisms but appeared to have died without completing the digestion of the microorganisms. Lastly, the histiocytes are collected and engaged in unrestrained phagocytosis of destroying the bacilli, neutrophils, and their debris. The histiocytes' phagosomes are dilated, thus becoming Mikulicz cells. Factors leading to the transformation of histiocytes into Mikulicz cells are unknown. Autophagic process may contribute to phagosome distention, and to the rupture of the vacuolar membranes and cell wall. These Mikulicz cells cannot consistently kill the bacilli, and thus eventually ruptured,

releasing them into the interstitium, implying that immunologic protection of macrophage is incomplete. Prompt treatment with tetracycline, ciprofloxacin or rifampin is necessary due to the high recurrence rate. Surgery and laser therapy are often required to treat airway compromise and severe deformity.

In order to avoid delayed treatment in our country, it is important to keep in mind this rare entity in long-standing nasal obstruction and significant adhesion to the nasal septum.

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