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Rhinoscleroma in Three Siblings

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Abstract: **Rhinoscleroma is a chronic, granulomatous infectious disease that responds poorly to treatment. In recent years an increasing number of cases have been reported in nonendemic areas, explained largely by major migratory movements. We describe rhinoscleroma in three siblings. They had ulcerated but painless lesions, which bled spontaneously, and hemorrhagic scabs or crusts in their noses. In one child, the lesions had destroyed the entire left nasal ala and alar cartilage and most of the right. Dermatopathologic study identified the Mikulicz macrophages that contained organisms. It is possible that disposing factors could have been the neutropenia common to the three children and their poor living conditions. They were treated with a combination of trimethoprim-sulfamethoxazole and cefalexin, for a period of 3 months. We present this unusual case history of three siblings affected by a process that is relatively infrequent in our area of practice and is not considered very contagious. It is important to recognize the clinical signs characteristic of this disease, the diagnosis of which is not easy. Improvements in living conditions, hygiene, and health standards are essential prerequisites for its control and prevention.**

Rhinoscleroma is a chronic, granulomatous infectious disease that responds poorly to treatment. It is moderately contagious and is produced by *Klebsiella rhinoscleromatis*. Von Hebra first described it in 1870 (1) as a sarcoma. Subsequently both Geber (1872) and Mikulicz (1876) believed that it constituted an inflammatory process, but the bacillus was not identified until 6 years later by Von Frisch (2).

This disease is characterized by the formation of asymptomatic, hardened nodules or tumors, often ulcerated, of reddish color and variable size, that invade the mucous membranes of the upper respiratory tract and the skin of the nose, lips, and even the neck. Initially it affects the nasal fossa and from there invades the upper respiratory tract and the lacrimal apparatus, where a granulomatous infiltrate is produced; this causes a marked tendency toward sclerosis and subsequent obstruction. It passes through three stages of development: the rhinitic, infiltrative, and cicatricial stages, during the course of which the airways become progressively obstructed (3).

CASE REPORTS

Patient 1

A 9-year-old girl had, between the ages of 2 and 5 years, relapsing outbreaks of ulcerated but painless lesions, with spontaneous bleeding and hemorrhagic scabs or crusts, in the right nostril. At the time of the consultation, she had a cicatricial lesion that was associated with

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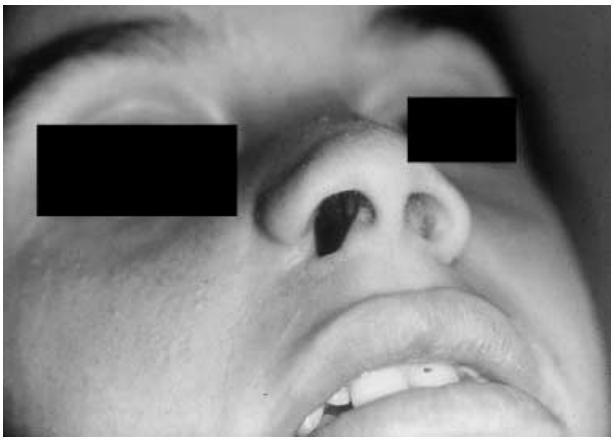

Figure 1. Cicatricial appearance of the lesion with loss of the left nostril tissues in patient 1.

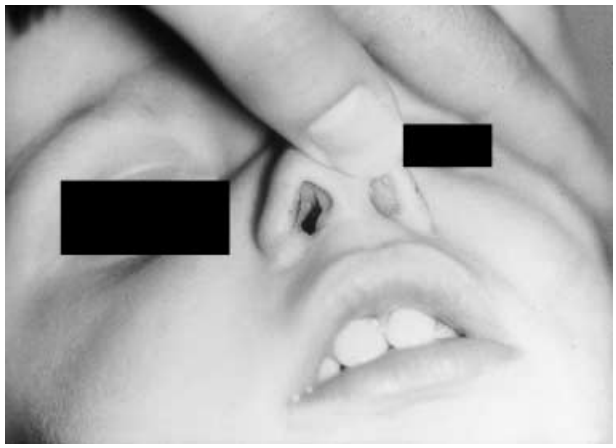

Figure 2. Patient 2. Painless, ulcerated lesion with spontaneous bleeding and hemorrhagic crusts.

the release of a substance from the affected nasal ala, with destruction of the alar cartilage (Fig. 1). In the analysis performed, a slight neutropenia (1.480 cells/µl) and decreased IgA levels (87.7 mg/dl) were observed. The culture was positive for *Staphylococcus aureus*. In the dermatopathologic study, the presence of an intense inflammatory infiltrate, predominantly mononuclear, with plasma cells was confirmed. This was associated with slight acanthosis of the overlying epidermis and the presence of a very small number of histiocytes in the papillary and reticular dermis.

Treatment was begun with a combination of trimethoprim-sulfamethoxazole and cefalexin for a period of 3 months. Mupirocin was included for treatment of the underlying infection.

Patient 2

Patient 2 was the youngest sister of patient 1, who at the time of consult was 1 year old. When she was 2 months old, she developed a lesion at the level of the right nasolabial sulcus, that was ulcerated but not painful, which occasionally bled spontaneously and was covered by hemorrhagic scabs. This lesion was destructive of the affected tissue (Fig. 2).

Again, the analysis demonstrated moderate neutropenia (1.110 cells/µl) and a decreased level of IgA (23.5 mg/dl), although in this case the culture was positive for *Streptococcus pneumoniae*. In the dermatopathologic study, the presence of a dense inflammatory infiltrate, predominantly of mononuclear and plasma cells, was confirmed; this was associated with acanthosis in the zones where the overlying epidermis had not been destroyed by intensive necrosis. At the level of the papillary and reticular dermis, a larger number of histiocytes with cytoplasmic debris could also be observed, which showed a positive reaction to periodic acid-Schiff (PAS) stain, although the responsible organism was not identified.

Treatment was begun with a combination of trimethoprim-sulfamethoxazole and cefalexin, and was given for a period of 3 months. Mupirocin was included for treatment of the underlying infection.

Patient 3

The 3-year-old brother of the two girls developed a lesion similar to those of his sisters at the age of 2 years. In his case, however, the lesion was more extensive and affected both nasal fossae. Again, the lesions were ulcerated, painless, occasionally bled spontaneously, and were covered with hemorrhagic scabs, but in this case were more extensive, causing nasal obstruction. At the time of consultation, the entire left nasal ala and alar cartilage, and most of the right, had been destroyed (Fig. 3). Again, there was moderate neutropenia (1.000 cells/µl) and a decreased IgA (38.3 mg/dl), and the culture was positive for both *S. aureus* and *S. pneumoniae*.

In the dermatopathologic study, a strong inflammatory infiltrate, predominantly mononuclear and rich in plasma cells, was found. In the zones where the overlying epidermis had not been destroyed, there was extensive necrosis, with areas of pseudoepitheliomatous hyperplasia. At the level of the papillary and reticular dermis, a considerable number of histiocytes with a cytoplasmic content that showed a positive reaction to PAS staining could be seen. With Gram stain, it was confirmed that these cells corresponded to large vacuolized and occasionally multinucleated macrophages in the cytoplasm in which gram-negative bacilli could be identified. At greater magnification with Giemsa staining, this intracytoplasmic component corresponded to accumulations

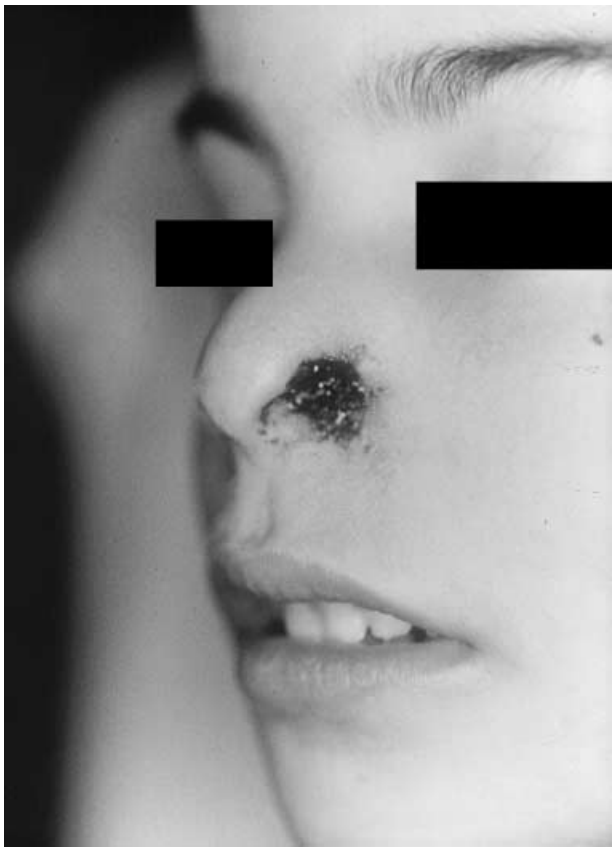

Figure 3. Patient 3. Almost complete destruction of the wing of the nose and the left lesser alar cartilage as well as a great part of the right cartilage.

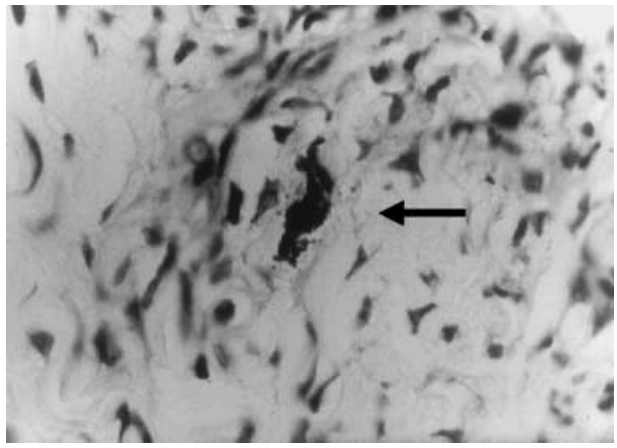

Figure 4. Mikulicz cell.

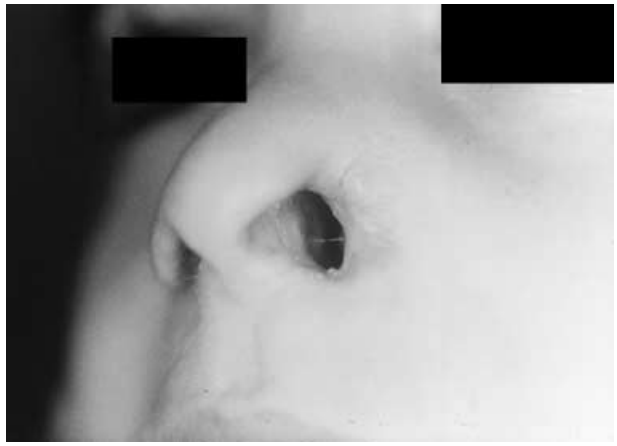

Figure 5. Disappearance of the ulcerated, crusty lesions in patient 3 after treatment.

of a Giemsa-positive stippling that was related to the presence of very short intracytoplasmic bacilli (approximately 3 μm in length) that had not been destroyed in the interior of the histiocytes. In this way the Mikulicz cells were identified (Fig. 4). Similarly, at the level of both the reticular and the papillary dermis, it was possible to differentiate anucleated intracytoplasmic structures that showed an intense eosinophilia and corresponded to Russell bodies.

After establishment of the diagnosis of rhinoscleroma, the three siblings were treated with a combination of trimethoprim-sulfamethoxazole and cefalexin for a period of 3 months. Mupirocin was included for the treatment of the underlying infection. Despite the chronic state of the process, this treatment led to the disappearance of the ulcerated and scabbed lesions in all three children (Fig. 5).

DISCUSSION

Rhinoscleroma is a characteristic disease of certain endemic regions, such as the countries of the former Soviet Union, Central Europe, Mexico, Central and South America, India, Indonesia, north Africa, and more recently China, central Africa, and east Africa (4). In addition, in recent years an increasing number of cases have been reported in nonendemic areas, explained largely by major population migratory movements (5).

This disease is contracted by direct or indirect contact with a patient during the stage of secretory rhinitis – "rhinorrhea." It is endemic in certain well-defined areas where transmission takes place within families and communities. The disease is more common where people live in poor conditions, predominantly in poor and primitive rural communities and in slums (6). Hence the predisposing factors are a rural location, immunodepression, malnutrition, and poor hygienic conditions. In our patients, it is possible that the predisposing factors could have been the neutropenia common to all three children and the poor hygiene of their living conditions. This was due in part to the low education level of their parents and because their house was situated on a rubbish dump. The

fact that three siblings in the same family were affected may be related to an immunologic or genetic predisposition, a factor in the appearance of this infectious disease suggested by some authors (7).

There has been considerable discussion of the pathogenic mechanisms of this disease. The bacteria are disseminated during the rhinitic phase and seem to be confined to close-living groups. The microorganism shows a particular predilection for the rhinopharyngeal mucous (8), and the disease possibly begins in the transition zone between the stratified squamous epithelium of the nasal vestibule and the respiratory epithelium of the nose. The mucopolysaccharides of the bacteria capsule may be specifically responsible for most of the lesions.

Although in our three patients a significant decrease in immunoglobulin A was observed, other studies have demonstrated that these patients have a normal humoral response; however, alterations in cellular immunity do exist. In fact, the granulomas of rhinoscleroma are granulomas of inefficient histiocytes in which the macrophages are inactivated and are unable to digest or kill the bacteria (9). Thus the Mikulicz cells phagocytose a large proportion of the bacilli, retaining them within the vacuoles, but are incapable of destroying them. Therefore, as the number of phagocytosed bacilli increasingly accumulate, there comes a moment when the cell membrane bursts and the bacilli are again released. On patients under treatment, microorganisms in the division phase inside the Mikulicz cells have been observed, and these bacilli, when released, are morphologically viable.

The first manifestations of the disease are nasopharyngeal, this being the area for which the microorganism has a special predilection, and which is initially affected in 98% of all cases (10). Since the disease develops relatively slowly but progressively, the lesions are painless and the general health condition is not usually affected. Therefore the patient does not usually consult a doctor until the disease has been present for a period of years. Our patients were brought for consultation only because the condition of the male sibling alarmed the parents, although the elder sister had recidivist outbreaks of lesions since she was 2 years old (i.e., for 7 years). Thus we were able to identify the disease in all three siblings.

From the clinical perspective, the evolution of the disease has been divided into four successive stages. The rhinitic phase commences with the symptoms of a common cold associated with a malodorous nasal secretion, which in some cases has been confused with an ozena. In this phase, it is difficult to see the microorganisms in the histologic sections due to their being hidden by the strong inflammatory component (11).

Next is the granulomatous phase, characterized by the appearance of exuberant, friable, and granulomatous tissue, with the formation of scabs and hardening, which then extends to the pharynx and larynx. When the larynx is affected, changes occur in the voice (12). In this stage, it is much easier to see the pathogenic agent (13). The male child, at 3 years of age, was at this phase of evolution, while his 1-year-old sister was just beginning to develop the disease, and therefore the identification of the bacilli was much more difficult in her case.

The nodular phase is essentially the extension of the preceding stage toward the nasal lobe and the upper lip, often leading to a nasal deformity known as the nose of Hebra (tapir nose). In a few rare cases the bone and cervical ganglia may be affected (14).

Lastly, the fibrotic or sclerotic stage represents the cicatrization of the lesions, leading to anatomic distortion and stenosis of the affected structures during the proliferative phase (15).

The dermatopathologic findings in these patients may aid diagnosis when a granulomatous infiltrate is observed that is characteristically rich in plasma cells and, in addition, contains a characteristic structure: the Mikulicz cell. Mikulicz cells are large, rounded, and vacuolated histiocytes, with a pale-colored, reticulated, and ill-defined cytoplasm and an eccentric nucleus. The Giemsa and Gram stains and silver impregnation enabled numerous bacilli in the cytoplasm of some of the Mikulicz cells to be seen. The PAS stain facilitates demonstration of the intracellular organisms. The best technique for identifying the pathogenic agent is Warthin-Starry stain.

The Russell bodies are elliptical, nonnucleated structures, much smaller than the Mikulicz cells that are believed to be plasmocytes that are undergoing hyaline degeneration. The homogeneous cytoplasm is extremely eosinophilic, dyes bright red, and is refringent under light. The Russell bodies can be seen in any disease with plasma cells and are common on mucous membranes even without this disease.

Rhinoscleroma is a chronic disease with a very slow course. It is rare for a spontaneous cure to occur, but clinical remissions and relapses can be very frequent. The prognosis is very grave in a minority of cases (5–10%) in which the lower part of the trachea and the bronchi are affected. In fact, patients who are not treated can die as a consequence of respiratory obstruction, additional infection, hemorrhage, or intracranial invasion.

Currently the most useful antibiotics are trimethoprim-sulfamethoxazole, tetracycline, chlortetracycline, chloramphenicol, cephaloridine, and rifampin, although reports exist that describe other effective therapeutic agents such as streptomycin, triacetyloleandomycin, kanamycin, and gentamicin. The cephalosporins are effective in many cases, which may serve to differentiate *Klebsiella* from organisms of the *Enterobacter* genus. The penicillins are

not efficacious (16). Corticosteroid therapy in combination with antibiotics has given good results in some cases. Nasal washes with an aqueous solution of acriflavine at 2% (a mixture of 2,8-diaminoacridine and 2,8 chloride of diamino-10-methylacridinium) used for 2–3 months may help in some cases (17).

Whichever antibiotic is selected, it should be administered over a prolonged treatment period of 3 months or more without interruption. Unfortunately the majority of patients relapse, and require clinical and bacteriologic controls for several years even after an apparent cure. In general, patients can be treated as outpatients.

The prophylaxis is based on the improvement of sanitary conditions and the general living conditions of poor people. It is for this reason that this disease has become less frequent in, for example, central Europe and Russia since the beginning of the 20th century. Education in elementary hygiene is essential in the endemic zones.

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