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Infectious Pseudotumors: Red Herrings in Head and Neck Pathology

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Abstract Infectious pseudotumors are tumor-like growths caused by specific microbial organisms. Proliferating histiocytes in these lesions may show atypical cytology with nuclear pleomorphism and increased mitotic activity, erroneously suggestive of malignancies including carcinoma, sarcoma, and lymphoma. Specific and nonspecific immunohistochemical staining profiles may lead to the consideration of a wide range of benign and malignant neoplastic processes. Two such cases are reported. The first is an obstructive endotracheal mass in an AIDS patient caused by *Rhodococcus equi* infection. The proliferating histiocyes were cytologically atypical with deeply eosinophlic granular cytoplasm leading to the consideration of oncocytic carcinoma, Hurthle cell carcinoma, and pleomorphic rhabdomyosarcoma. The second case is a nasal mass with a microscopic and immunohistochemical profile suggestive of chordoma and paraganglioma. Special microbial stains revealed intracellular bacilli consistent with *Klebsiella rhinoscleromatis.* In both cases, microbial virulence factors affecting phagocytosis prolonged their intracellular survival and resulted in active histiocytic proliferation. It is of importance that the surgical pathologist be conscious that some infectious processes can clinically and microscopically mimic malignant neoplasms. Accurately identifying these lesions and the specific causative agent is of particular significance since they can be successfully treated with antibiotics.

Keywords Infectious pseudotumors · Histiocytes · Oncocytic carcinoma · *Rhodococcus equi* · Lysosomes · Phagosomes · *Rhinoscleroma* · *Klebsiella rhinoscleromatis* · Chordoma · Mikulicz cells · Michaelis-Guttmann bodies

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Introduction

Infectious pseudotumors of the head and neck are non-neoplastic tumerous lesions resulting from unusual histiocytic proliferation caused by specific microbial infections. They may be clinically and microscopically aggressive, mimicking malignant neoplasms. Varied Immunohistochemical profiles with specific and nonspecific staining results can be misleading and suggest the consideration of a wide differential diagnosis including carcinomas, sarcomas, and lymphomas. Two such cases are reported here, one presenting as an obstructive upper tracheal mass caused by *Rhodococcus equi*, and the other a tumerous nasal lesion caused by *Klebsiella rhinoscleromatis* infection.

Case 1

A 47-year-old man presented to the emergency room with stridor and respiratory obstruction. Radiographic imaging showed an exophytic mass near the tracheo-laryngeal junction that almost completely occluded the airway. The mass was debulked and sent for routine microscopic examination. The lesion recurred shortly after the initial excision and another debulking was performed. The patient was later found to be positive for HIV with a viral load of 475 copies/mL and a CD4+T-cell count of 32 cells/mm. This time, the excised material was sent for bacterial culture and the sample grew *R. equi.*

Microscopic Examination

Sections of the initial biopsy specimen showed sheets of large epithelioid cells with large nuclei and prominent

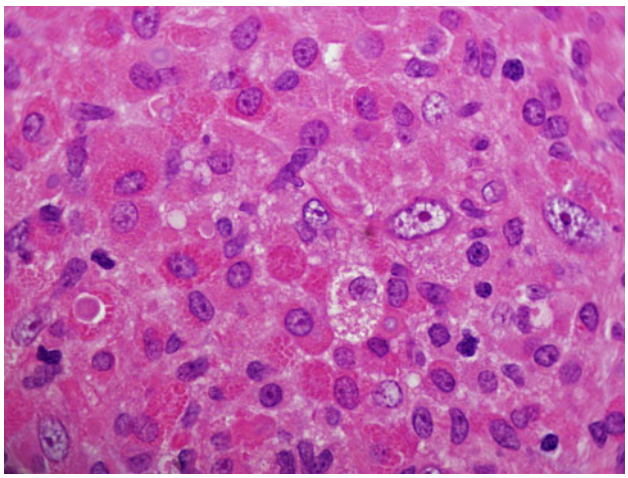

Fig. 1 *R. equi* infectious pseudotumor: sheets of atypical epithelioid histiocytes with abundant, deeply eosinophilic and coarsely granular cytoplasm

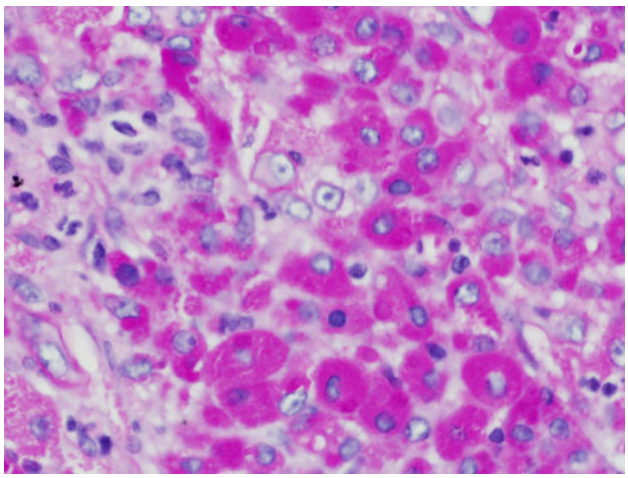

Fig. 2 *R. equi* infectious pseudotumor: PAS stain after diastase digestion (PAS/D) showing positive granular cytoplasm

nucleoli. The cells were distinguished by abundant, deeply eosinophilic coarsely granular cytoplasm. Occasional mitotic figures and apoptotic cells were identified (Fig. 1).

The epitheliod cells were positive for PAS stain after diastase digestion (PAS/D) highlighting coarsely granular cytoplasm (Fig. 2). However, they were negative for phosphotungstic acid hematoxylin (PTAH) stain. A panel of immunohistochemichal stains was performed and the cells reacted positively for vimentin, S100 protein, CEA, CD31, CD45, and CD68. The Ki-67 score was approximately 20% (Fig. 3). The cells were, however, negative for cytokeratins AE1/AE3, CAM 5.2, CK7, and CK20. They also reacted negatively to epithelial membrane antigen (EMA) and the muscle markers, Desmin, muscle specific actin (MSA), and myoglobin. Melan A, TTF-1 and thyroglobulin were also negative.

Special stains for acid fast bacilli (Ziehl-Neelsen) and atypical mycobacteria (Fite) were negative. Warthin-Starry and Gomory methenamine silver (GMS) stains were negative for spirochetes and fungal organisms, respectively. However, a tissue Gram stain highlighted Gram positive intracytoplasmic coccobacilli (Fig. 4). Based on these findings and the bacterial culture results, a diagnosis of *R. equi* infectious pseudotumor was rendered.

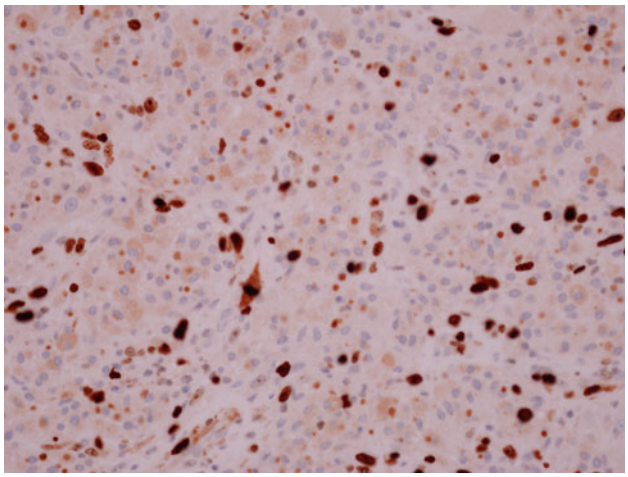

Fig. 3 Ki-67 immunostain showing positive nuclear reactivity in more than 20% of the cells, in some parts of the *R. equi* pseudotumor

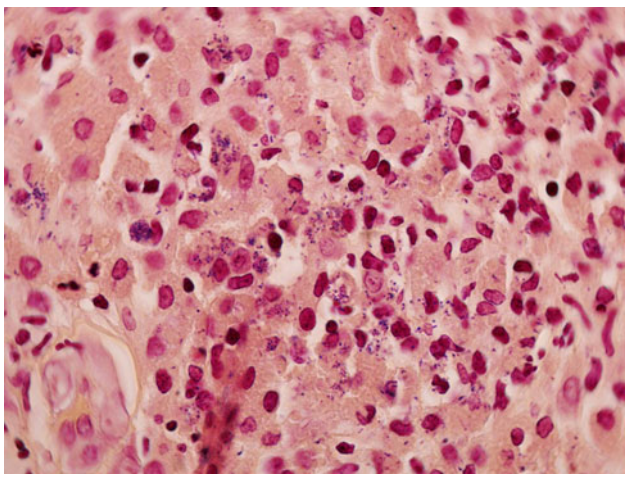

Fig. 4 Tissue Gram stain highlighting intracellular Gram-positive coccobacilli of *R. equi*

Discussion

The aggressive clinical presentation of an obstructive endotracheal mass combined with worrisome microscopic features initially suggested the consideration of a malignant neoplastic process. The differential diagnosis of a lesion with large epithelioid cells and prominent, deeply eosinophilic granular cytoplasm located in the upper trachea

included oncocytic carcinoma, Hurthle cell carcinoma, and pleomorphic rhabdomyosarcoma.

Oncocytic carcinoma is a rare malignant salivary gland neoplasm that affects predominantly the major glands, particularly the parotid, and rarely the minor mucoserous glands of the upper aerodigestive tract. The cells of oncocytic carcinoma have large nuclei and prominent nucleoli. Their eosinophilic cytoplasm is finely granular as a result of accumulation of excessive number of mitochondria. Phosphotungstic acid-hematoxylin (PTAH) stain is usually positive in oncocytic carcinoma. PTAH stains the mitochondria-rich cytoplasm a dark blue hue. The stain was negative in the current lesion, thus arguing against this entity.

Hurthle cell carcinoma is an oncocytic variant of follicular carcinoma of the thyroid. The tumor may rarely show extra-thyroidal extension into the trachea. The cells have large nuclei, prominent nucleoli and deeply eosinophilic granular cytoplasm. Hurthle cells stain positively for thyroglobulin, TTF-1 and may or may not be positive for keratin. Like oncocytic carcinoma, the cytoplasmic granularity is caused by excessive accumulation of mitochondria and is, therefore, PTAH positive. Thyroglobulin, TTF-1, and PTAH were all negative in the lesion.

Pleomorphic rhabdomyosarcoma is a rare neoplasm affecting adults, more commonly male patients, usually in the muscles of the extremities but may rarely occur in the head and neck. Immunohistochemical stains for myogenous differentiation such as desmin, muscle specific actin (MSA) and myoglobin are generally positive. These were all negative in the current lesion.

PAS-positive diastase-resistant cytoplamic granules were identified in the lesion. Typically, PAS-positive diastase-resistant material identifies zymogen granules in acinic cell carcinoma. However, unlike the current lesion, the cytoplasmic granules in acinic cell carcinoma are basophilic. Lastly, while the vimentin and S100 inmmunoreactivity may suggest malignant melanoma, the deeply eosinophilic granular cytoplasm seen in this lesion makes it unlikely; moreover, a Melan-A immunostain was negative.

Immunoreactivity for CD45and CD68 identified the cells as histiocytes/macrophages. With the additional history of HIV disease, an infectious etiology for this histiocytic proliferation was investigated. Special stains for acid fast bacilli (Ziehl-Neelsen) and atypical mycobacteria (Fite) were negative. The Warthin-Starry stain was negative for spirochetes. GMS stain was negative for fungi but highlighted bacterial organisms. A tissue Gram stain highlighted gram positive intracytoplasmic coccobacilli (Fig. 4). Bacterial culture confirmed these organisms as *R. equi.* Cultures, serologic studies, and PCR assays for Bartonella, Mycobacteria, Histoplasma and Blastomyces were all negative. The patient was started on HAART therapy in addition to an antibiotic regimen including vancomycin, meropenem, and azithromycin, based on known susceptibility *of R. equi* [1].

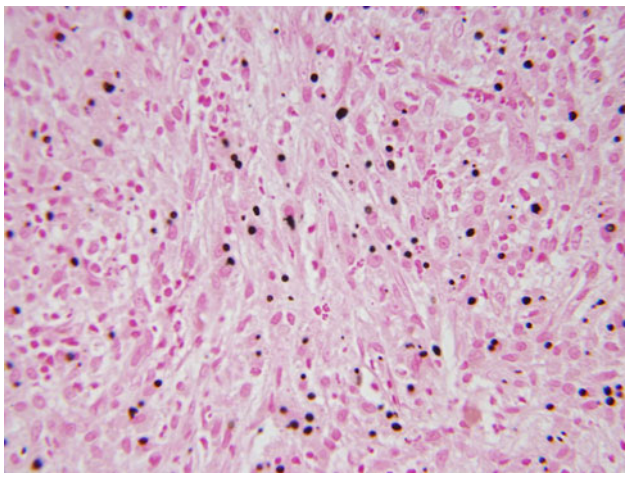

Fig. 5 A von Kossa stain for calcium demonstrating rounded Michaelis-Guttmann-like bodies within the histiocytes in *R. equi* pseudotumor

R. equi is a Gram positive coccobacillus soil organism that has long been known as a pulmonary pathogen that causes pneumonia in foals, and more recently, in AIDS patients [2]. It is an intracellular pathogen that persists within the host cells by arresting the normal pathway of phagosome maturation and normal phagocytosis. *R equi* can survive the phagolysosomal microenvironment in macrophages by suppressing acidification of the phagolysosomes [3]. Virulent *Rhodococcus* strains carry extrachromosomal plasmids expressing a variety of virulent genes in the Vap family *(VapA-G). Vap A* protein has been shown to stabilize the phagosomal membrane, thus suppressing its acidification by lysosomes. As a result, the bacterium is able to survive and proliferate within an almost neutral phagolysosomal environment [4, 5]. The high pH in these organelles may also explain their strong eosinophilia [1]. Some cases of *R. equi* pseudotumors show Michaelis-Gutmann bodies analogous to those that are diagnostic of malakoplakia [6] [Fig. 5]. In the latter condition however, unlike the current case, the lysosomal abnormality is believed to be an inherent rather than acquired one. The abnormality has been shown to be due to an intra-cellular cyclic-GMP deficiency, which is correctable by cholinergic agonists [7].

Case 2

A 44-year-old male patient had a polypoid lesion of the nasal cavity. The lesion was biopsied and the frozen section diagnosis was carcinoma. A panel of immunohistochemical

stains was performed on the biopsy specimen and the case was received as a consult with a differential diagnosis including paraganglioma and chordoma.

Microscopic Examination

The sections showed a hypercellular lesion composed of epithelioid cells intermixed with plasma cells showing numerous Russell bodies. The epithelioid cells formed sheets and nests in a fibromyxoid stroma. In focal areas, the cells demonstrated prominent cytoplasmic vacuolization producing a foam cell appearance (Fig. 6). Occasional multinucleated cells were observed.

A panel of immunohistochemical stains was performed and showed that the lesional cells were positive for vimentin, S100 protein, NSE, calretinin, and CD68 (Fig. 7). EMA showed cytoplasmic, nonmembranous staining (Fig. 7). The cells were, however, negative for AE1/AE3, CK5/6, and MSA.

A tissue gram stain was negative and the Steiner stain showed a few bacillary organisms but was difficult to interpret because of background staining. A GMS stain was negative for fungi, however, it highlighted numerous bacillary organisms within the vacuolated cells, consistent with *K. rhinoscleromatis* (Fig. 8). A diagnosis of rhinoscleroma was rendered. No microbial culture was done and the patient is reportedly doing well after surgery and antibiotic treatment.

Discussion

The microscopic features of this nasal lesion, in combination with the initial immunohistochemical profile, were misleading. The epithelioid nesting pattern of the histiocytes in some areas (Fig. 6) and a positive reactivity to NSE and calretinin (Fig. 7) suggested the diagnosis of paraganglioma (PGL). Unlike the current lesion, PGLs are highly vascular and are composed of two types of cells: epithelioid chief cells and spindled sustentacular cells. The epithelioid cells are arranged in a characteristic alveolar or Zellballen pattern and contain neurosecretory granules that stain positively for neuroendocrine markers, including NSE and calretinin. The sustentacular cells are devoid of neurosecretory granules and are located at the periphery of the Zellballen. These cells react positively with S100 protein antibodies. In the current lesion, the epithelioid cells were positive for S100 protein and no sustentacular cells were identified, effectively ruling out PGL as the diagnosis.

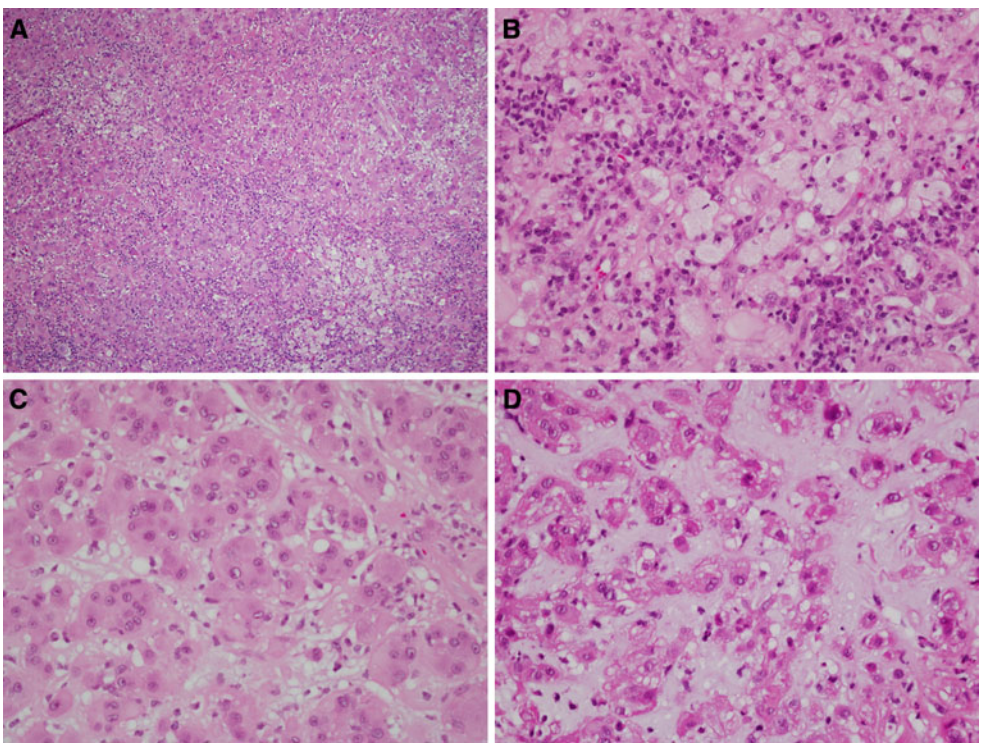

Fig. 6 Rhinoscleroma: **a** Sheets of epithelioid histiocytes mixed with plasma cells and vacuolated Mikulicz cells and occasional multinucleated giant cells. **b** Higher magnification illustrating Mikulicz cells and plasma cells, many of which have Russell bodies. **c** Cell nesting is observed in some parts of the lesion. **d** Vacuolated Mikulicz cells in a myxoid stroma resembling the "physaliferous" (*bubbly*) cells of chordoma

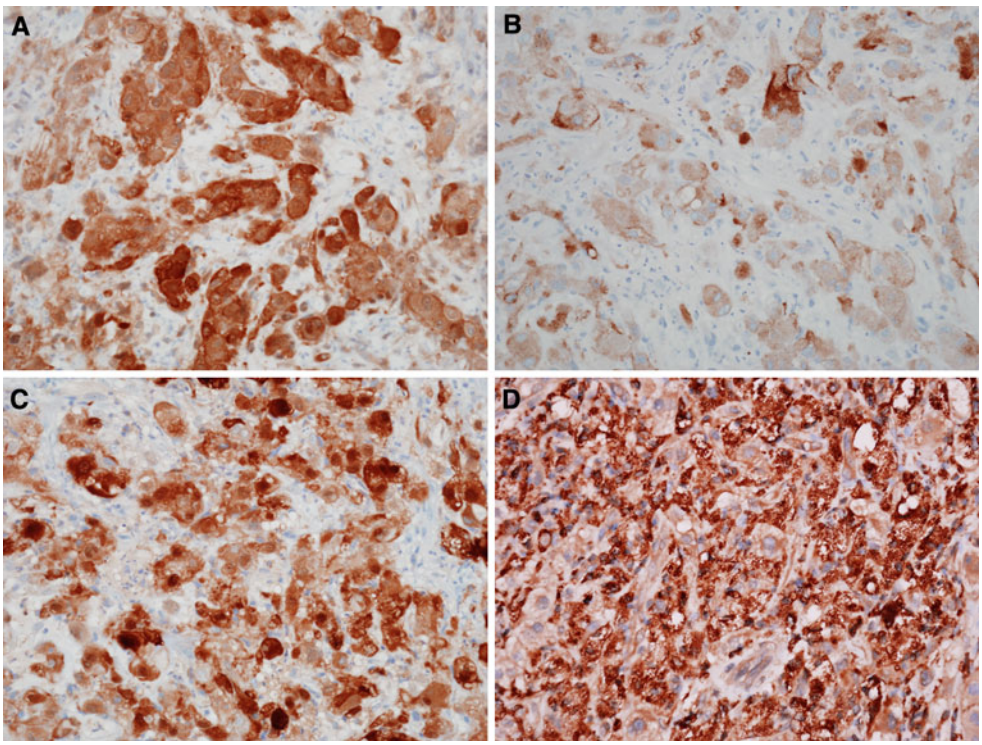

Fig. 7 Rhinoscleroma: **a** A neuron-specific enolase (NSE) immunostain showing positive reactivity in the epithelioid cell nests. **b** Epithelial membrane antigen (EMA) immunostain showing nonspecific cytoplasmic staining. **c** S100 protein stain. **d** CD68 immunostain identifying the epithelioid cells as macrophages

Moreover, in the head and neck, PGLs typically arise in the carotid body, middle ear, jugular bulb, or the vagus nerve. Much less frequently, PGLs occur in other sites such as the larynx, thyroid, and rarely the sinonasal tract.

Chordoma was another differential diagnosis that was considered. In the head and neck, chordomas typically present as an osteolytic lesion arising in the sphenooccipital region. However, they have rarely been reported in the sinonasal tract. Microscopically, this lesion had some features in common with chordoma. It showed aggregates of epithelioid cells arranged in nests and sheets dispersed throughout a fibrous and myxoid stroma. Many of the cells had prominent cytoplasmic vacuoles [8] (Fig. 6). In chordoma, these cells are referred to as "physalliferous" (bubbly or vacuolated) cells, while in rhinoscleroma they are known as Mikulicz cells. Positive reactivity to S100 protein and EMA in the present lesion (Fig. 7) added further support to the misdiagnosis of chordoma. However, the histiocytic nature of the cells was eventually confirmed by CD68 reactivity (Fig. 7) and special microbial stains, which highlighted bacillary microorganisms, many of which were intracellular and associated with Mikulicz cells (Fig. 8).

Rhinoscleroma is a chronic progressive infectious disease that is endemic to areas in Africa, South East Asia, and Central and South America. The incidence in the USA

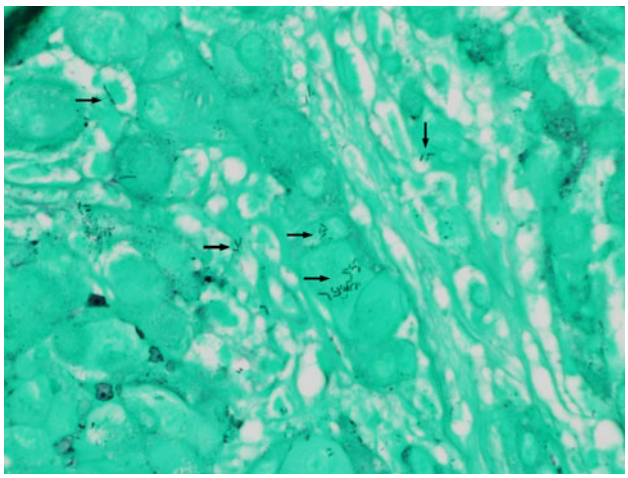

Fig. 8 Rhinoscleroma: GMS stain showing intracellular bacillary microbial organisms (*arrows*)

appears to be increasing, usually among emigrant populations [9, 10]. The causative bacterium is a Gram negative bacillus known as *K. rhinoscleromatis*. Increased incidence among family members and household contacts has been reported and genetic predisposition has been suggested. The organism has low infectivity; transmission is believed to be by airborne secretions [11]. Rhinoscleroma affects predominantly the nasal cavity and, less commonly, the

nasopharynx, larynx, nasal sinuses, and oral cavity. It has been suggested that the term "scleroma" is more appropriate [12]. Progression of the nasal disease leads to deformity and destruction of the nasal cartilage.

Three clinicopathologic stages characterize the disease: First, an initial "rhinitic/catarrhal" phase associated with red atrophic mucosa; Second, a proliferative phase in which the characteristic microscopic features are well-expressed [13]. The final stage is characterized by fibrosis and thus called the fibrotic or sclerotic phase, which may lead to stenosis and disfigurement.

The lesion in the proliferative phase is typically composed of an inflammatory cell infiltrate with histiocytes mixed with lymphocytes and plasma cells. Mikulicz cells, which are foamy macrophages with prominent vacuolated cytoplasm, are abundant at this stage. *K. rhinosclermatis bacilli* are found within the cytoplasm of these cells. In addition to the bacteria, the vacuoles contain accumulated mucopolysaccharides derived from the polysaccharide capsule of *K. rhinoscleromatis* [13]. The capsule is a virulent factor that prevents adequate phagocytosis. Tissue Gram stain is usually negative, but silver impregnation methods often demonstrate the organism [14]. Tissue culture for *K. rhinoscleromatis* may be positive in only 50% of the cases [10].

Treatment involves surgical debridement and antibiotic therapy. Ciprofloxacin and rifampin are shown to be effective drugs [11].

Other examples of microbial infections that may cause nongranulomatous histiocytic proliferation and pseudotumor formation in the upper aerodigestive tract (UADT) include histoplasmosis and lepromatous leprosy. *Histoplasma capsulatum* microorganisms appear in routine sections as small spherical intracellular and extracellular hematoxylinophilic structures surrounded by a small halo. The organism also stains with GMS and PAS special stains. Lepromatous leprosy may manifest in the UADT prior to the development of skin lesions. A Fite stain demonstrates the acid fast bacilli of *M leprae.*

In summary, two cases are presented in which bacterial infection by *R. equi* and *K. rhinoscleromatis,* respectively, resulted in the development of tumorous masses. An aggressive clinical presentation, worrisome microscopic features, and varied immunohistochemical staining profiles lead to the consideration of a variety of neoplastic processes. In both cases, microbial virulence factors affecting phagocytosis prolonged their intracellular survival and resulted in active histiocytic proliferation. In the case of *R. equi* infection, reduced acidification of phagosomes interfered with proper phagocytosis and resulted in increased pH and consequent cytoplasmic eosinophilia. In the second case, the polysaccharide capsule of *K. rhinoscleromatis* prevented phagocytosis. Accumulation of the organism within the infected cells produced the vacuolated cytoplasm.

While infectious pseudotumors are rarely encountered in the practice of surgical pathology, it is of Importance to realize that infectious processes can closely mimic neoplastic lesions. Identification of these processes and the causative organisms is of particular significance since they can be cured by antibiotic therapy.

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