Pseudotumor of the Tracheal-Laryngeal Junction with Unusual Morphologic Features Caused by *Rhodococcus equi* Infection

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Abstract Infectious pseudotumors are unusual proliferations of histiocytes in response to certain microbial organisms. Occasionally this process may involve large airways, producing a mass lesion that may cause respiratory obstruction. Infectious pseudotumors can be confused with malignancy in their radiologic appearance and clinical presentation. We present a case of an aggressive endotracheal pseudotumor associated with *Rhodococcus equi* infection in a patient with advanced HIV disease. Microscopically, the lesion was composed of sheets of epithelioid histiocytes with large, strongly eosinophilic intra-cytoplasmic granules and features of malakoplakia. In this report, we review the literature of these unusual lesions and compare them to cases of conventional malakoplakia involving the large airways. We also explore the pathogenetic mechanisms that may contribute to the distinctive histologic appearance of *Rhodococcus*-associated pseudotumors.

Keywords Malakoplakia · Infectious pseudotumor · *Rhodococcus equi* · Endobronchial mass lesion · Human immunodeficiency virus (HIV)

Introduction

Surgical pathologists encounter a preponderance of neoplastic disease in their every day practice. It is therefore understandable that neoplasia is the first consideration in evaluating mass producing lesions. However, a variety of conditions that are not truly neoplastic can present as tumors and are referred to as “pseudotumors”. Specifically, infectious pseudotumors are mass-forming proliferations of inflammatory cells reacting to an inciting microbiological agent [1]. Here, we describe a patient who came to the emergency room with respiratory obstruction. While the initial clinical impression was that of a malignancy, extensive pathologic and microbiologic studies demonstrated that the lesion was a *Rhodococcus equi*-associated infectious pseudotumor. This case was unusual in several respects that proved a challenge for the clinical and diagnostic teams.

Case Report

A 47-year-old man with a history of poly-substance abuse presented with stridor and non-productive cough. He was found to be HIV-positive with a CD4 count of 32 cells/mm³. On radiologic imaging, an exophytic endotracheal mass that almost completely occluded the airway was detected approximately 5 cm below the vocal cords (Fig. 1a). A cavitary lung lesion in the right upper lobe and hilar lymphadenopathy were also noted (Fig. 1b). The patient was tuberculin purified protein derivative (PPD) negative and induced sputum cultures remained negative for mycobacteria throughout the hospital course. The tracheal lesion was debulked and sent for routine microscopic examination.

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Fig. 1 **a** Sagittal CT scan demonstrates an obstructing mass lesion at the level of the thoracic outlet (*arrowhead*). **b** Coronal CT scan shows a cavitary lesion in the upper lobe of the right lung (*arrowhead*)

Sections of the tracheal mass biopsy showed sheets of epithelioid cells with abundant cytoplasm filled with large, strongly eosinophilic intra-cytoplasmic granules (Figs. 2a, b). Several nuclei were large, with vesicular chromatin and prominent nucleoli. Occasional mitotic figures and apoptotic bodies were identified. No well-formed granulomas or areas of necrosis were present. Acute and chronic inflammatory cells were focally interspersed between the epithelioid cells, but represented a minor component of the overall mass. The little remaining surface and minor salivary gland epithelia were unremarkable.

Given the unusual morphology, a broad differential was initially entertained, including epithelial and mesenchymal oncocyctic neoplasms. The lesional cells were negative for pan-cytokeratin, TTF-1, and thyroglobulin immunostains and for a PTAH special stain for mitochondria. Muscle markers (smooth muscle actin and desmin) highlighted only smooth muscle cell layers surrounding blood vessels, thereby ruling out neoplasms of myogenous origin. The cells were positive for vimentin, CD68 (Fig. 2c), CD45 and focally for polyclonal-CEA, thus identifying them as histiocytes/macrophages. S-100 highlighted interspersed dendritic-type cells. The large cytoplasmic eosinophilic granules stained positive with PAS after diastase digestion (Fig. 2d). The proliferative index (Ki-67) was approximately 10%.

An infectious etiology underlying this histiocytic proliferation was then investigated. A CMV immunostain was negative and in situ hybridization for Epstein-Barr virus-encoded RNA (EBER) showed non-specific staining. Special stains for acid fast bacilli (Ziehl-Neelsen) and atypical mycobacteria (Fite) were negative. Warthin-Starry and GMS stains were also negative for spirochetes and fungal organisms, respectively, but stained intracellular

bacteria (Fig. 2e). A tissue Gram stain highlighted Gram-positive coccobacilli within the cytoplasmic granules of the histiocytes (Fig. 2f). An iron stain showed focal inclusions within the macrophages (Fig. 2g) and a von Kossa stain identified numerous calcified intracellular spherules (Fig. 2h). The iron- and calcium-laden inclusions were consistent with Michaelis-Gutmann bodies, considered pathognomonic for malakoplakia. Taken together, these results were interpreted as an infectious pseudotumor with malakoplakic features, produced in response to the coccobacilli seen within the histiocytes.

The patient was started on HAART therapy and broad-spectrum antibiotics, but the tracheal mass persisted necessitating another debulking operation. This time, material was also sent for bacterial culture and the sample grew *Rhodococcus equi*. However, antibiotic susceptibility studies were not performed. Cultures, serologic studies and PCR assays for Bartonella, Mycobacteria, Histoplasma and Blastomycoses were all negative. Empirically, the patient's antibiotic regimen was changed to vancomycin, meropenem and azithromycin based on known susceptibilities of *R. equi*. During his hospitalization, he continued on HAART therapy and his HIV viral load consequently dropped from 475 copies/ml at presentation to <48 copies/ml (undetectable) at discharge. Concurrently, his CD4 count increased from 32 to 83 cells/mm³. Even though the patient was symptomatic, a complete resection of the pseudotumor was not considered feasible due to considerable potential morbidity. An attempt to stent the trachea was also unsuccessful and the patient underwent a tracheostomy operation to protect his airway. The patient was discharged after a six-week course of intravenous antibiotic treatment without significant improvement. Oral antibiotic therapy was continued with azithromycin and rifampin. Six months

Fig. 2 **a** An H&E stained section shows sheets of epithelioid cells with eosinophilic cytoplasm. **b** Higher magnification of H&E stained section shows coarse eosinophilic cytoplasmic granules. **c** A CD68 immunostain identifies the epithelioid cells as macrophages. **d** The coarse eosinophilic cytoplasmic granules stain with PAS after diastase digestion. **e** A GMS stain is negative for fungal organisms but highlights coccobacilli within the macrophages. **f** A tissue Gram stain

demonstrates Gram-positive coccobacilli within the macrophages. **g** A Prussian blue iron stain is focally positive in rounded structures within the macrophages. **h** A von Kossa stain for calcium highlights Michaelis-Gutmann like bodies within the lysosomes of histiocytes. (600 $\times$ original magnification for all panels except panels b, e and f, which are at 1,000 $\times$)

after the initial diagnosis, the patient returned with stridorous symptoms. CT imaging showed an interval increase in size of the pseudotumor requiring another endoscopic debridement. This most recent specimen was microscopically identical to the initial diagnostic biopsy.

Discussion

Our patient's acute presentation with stridor and radiologic findings initially prompted an evaluation for malignancy. On routine-stained sections, the eosinophilic coarse granular cytoplasm of the lesional cells led us to consider oncocytic epithelial or mesenchymal neoplasms. However, the immunostain panel that we performed ruled out these entities. When the pseudotumor was cultured, it grew *Rhodococcus equi*, an opportunistic pathogen of immunocompromised hosts [2]. In HIV-infected patients, *R. equi* infection usually presents as cavitary pneumonia with hilar lymphadenopathy [3], but in the case of our patient, it uncharacteristically produced an intraluminal mass.

Rare cases of endobronchial infectious pseudotumors have been reported in HIV-infected patients [4]. A wide variety of inciting microbial agents have been associated with these pseudotumors, including CMV [5], HSV2 [6], atypical mycobacteria [7], and *Pseudomonas* [8], to name a few. However, to our knowledge, only five previous reports have described an endobronchial infectious pseudotumor linked to *Rhodococcus equi* [9–13]. Malakoplakia can also rarely produce plaque-like or tumor-like lesions in the upper airways of immunocompetent hosts. The clinicopathologic features of the five previously reported *R. equi* pseudotumors and the current case, as well as four representative cases of endobronchial malakoplakia, are summarized in Table 1.

Some generalizations can be made from this data. First, there does not appear to be a particular site within the upper airways that is particularly susceptible to pseudotumor formation—lesions can be seen from the epiglottis and pyriform sinus all the way down to the lobar bronchi. Second, endobronchial pseudotumors associated with *R. equi* are found exclusively in patients with advanced HIV disease/AIDS. Third, immunocompromised patients seem to have an aggressive disease course despite antibiotic therapy or localized resection of infected tissue. In one report, the patient died of disease, and our own patient has had a prolonged course without significant improvement despite extended antibiotic therapy and repeated interventions. By comparison, in conventional malakoplakia, the mass of the pseudotumor seems to be smaller and the prognosis is better. Fourth, all of these lesions are

histologically characterized by sheets of histiocytes with somewhat variable cytoplasmic characteristics. Notably, only our and one other case of *R. equi*-associated pseudotumor showed Michaelis-Gutmann bodies, which are required for the diagnosis of malakoplakia [10]. Similarly, besides the current case, only one other report of a *R. equi*-associated pseudotumor describes eosinophilic granules in the cytoplasm of the histiocytes [9]. In the other four cases, no additional qualitative characteristics of the granular cytoplasm were described. Interestingly, infection with *Tropheryma whippelii* can produce an infiltration of foamy macrophages with cytoplasmic PAS-positive granules. However, *T. whippelii* usually involves the digestive tract, though it has been reported to affect the upper airways [14]. Also, in Whipple disease, the macrophage cytoplasm has a foamy character on H&E stained sections rather than being filled with coarsely eosinophilic granules as seen in this case. As discussed below, the virulence factors of *R. equi* may lead to this distinctive microscopic appearance.

Malakoplakia is an abnormal proliferation of macrophages that forms a plaque-like lesion in immunocompetent hosts. The majority of cases occur in the genitourinary tract, especially in the bladder. Infrequently, malakoplakia can affect the gastrointestinal tract or the pulmonary parenchyma [15]. Interestingly, *R. equi* has been associated with all known cases of malakoplakia affecting the pulmonary parenchyma in HIV patients [16]. *R. equi* directly interferes with phagosomal acidification and delays phagosome maturation into lysosomes [17–19]. Virulent *Rhodococcus* strains carry extrachromosomal plasmids expressing a variety of virulence genes in the *Vap* family (*VapA-G*). In vitro studies suggest that *VapA* may prevent acidification of the phagolysosome [20]. As a result, the bacterium is able to survive and proliferate within an almost neutral intracellular compartment. In immunocompromised hosts, *R. equi* may more easily survive in macrophage phagolysosomes due to the reduced activation of macrophages by CD4 + T-cells. In our patient, we speculate that the neutralization of the pH in phagolysosomes by *R. equi* and its proliferation within these organelles produced the coarse eosinophilic granules seen on H&E stained sections.

In summary, we present a case of an infectious pseudotumor due to *R. equi* presenting as an obstructing mass at the junction of the larynx and trachea of a patient with AIDS. The lesion had some of the features of malakoplakia but was distinguished by the presence of epithelioid histiocytes with strongly eosinophilic, coarsely granular cytoplasm. The virulence factors of *R. equi* that prevent phagolysosomal maturation may contribute to this striking histologic appearance.

Table 1 Characteristics of *R. equi*-associated endobronchial pseudotumors compared to cases of mass-forming endobronchial malakoplakia

Endobronchial pseudotumors associated with <i>R. equi</i>									
Age	Sex	Immune Status	Location	Endobronchial appearance	Lung findings	Culture results (site)	Histologic features	Outcome	Reference
15	Female	HIV/AIDS	Left main stem bronchus, near carina	Occlusive masses	Cavitary lesion, necrotizing pneumonia	<i>R. equi</i> (PBL)	Sheets of PAS-positive foamy macrophages filled with Grampositive coccobacilli	Death	[11]
32	Male	HIV/AIDS	RML bronchus	Occlusive mass	RML consolidation	<i>R. equi</i> (PBL, BAL, pseudotumor)	Histiocytes with associated lymphocytes, plasma cells and neutrophils; malakoplakia like features	RML lobectomy	[10]
30	Female	HIV/AIDS	LUL bronchus, LUL	Partially occlusive endobronchial mass, lung mass	LUL mass lesion	<i>R. equi</i> (Bronchial aspirate, BAL, tissue)	Sheets of histiocytes with eosinophilic, faintly granular cytoplasm	LUL lobectomy, resolution	[9]
25	Male	HIV/AIDS	Left main stem bronchus	Partially occlusive mass	Cavitary left lower lobe lesion	<i>R. equi</i> (Bronchial aspirate)	Sheets of epithelioid histiocytes	Resolution	[12]
33	Male	HIV/AIDS	Posterior commissure right ventricle	Granulomatous nodules	RUL infiltrates	<i>R. equi</i> (Laryngeal mucosa)	Histiocytic lesion with necrosis and true granulomas	Resolution	[13]
47	Male	HIV/AIDS	Trachea	Occlusive mass with erosion to esophagus	Cavitary RUL lesion	<i>R. equi</i> (Laryngeal pseudotumor)	Sheets of histiocytes with eosinophilic, coarsely granular cytoplasm	Persistence requiring tracheostomy	Current case
Endobronchial malakoplakia									
32	Female	Immune competent	Arytenoid cartilage, false vocal cord, trachea	Tumor-like nodules and plaques	RLL pneumonia, lingular infiltrate	<i>E. coli</i> (Trachea), <i>MAI</i> (Bronchial aspirate)	Sheets of histiocytes with finely granular, vacuolated cytoplasm	Lost to followup	[21]
76	Male	Immune competent	Left pyriform fossa ulceration, submandibular mass	Tumor-like soft tissue mass with necrosis	N.D.	<i>E. coli</i> (Trachea)	Sheets of histiocytes with PAS and von Kossa positive cytoplasmic inclusions	Resolution	[22]
45	Female	Immune competent	Epiglottis	Nodular lesion	N.D.	N.D.	Sheets of histiocytes with eosinophilic, coarsely granular cytoplasm	Resolution	[23]
61	Male	Immune competent	False vocal cord, pyriform fossa	Smooth plaque/nodule	N.D.	N.D.	Sheets of histiocytes with granular, pale cytoplasm	Resolution	[24]
<i>RUL</i> right upper lobe, <i>RML</i> right middle lobe, <i>RLL</i> right lower lobe, <i>LUL</i> left upper lobe, <i>PBL</i> peripheral blood, <i>BAL</i> bronchioalveolar lavage, <i>MAI</i> <i>Mycobacterium avium</i> intracellular complex, <i>N.D.</i> not done									

RUL right upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *LUL* left upper lobe, *PBL* peripheral blood, *BAL* bronchioalveolar lavage, *MAI* *Mycobacterium avium* intracellular complex, *N.D.* not done

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