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Case Report

A sheep in wolf's clothing? Herpes-simplex-virus endobronchial pseudotumor

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ABSTRACT

Central airway obstruction (CAO) is generally defined as airflow limitation due to >50 % occlusion and is most commonly due to malignant etiologies. However, benign etiologies, including herpes-simplex-virus (HSV) endobronchial pseudotumor, can occur. Due to the rarity of HSV causing airway obstruction, an evidence-based approach to the bronchoscopic resection and standardization of therapy after removal are lacking. Herein, we present a case of HSV pseudotumor successfully managed by argon-plasma-coagulation (APC) debulking via bronchoscopy and medical management with intravenous foscarnet due to failed treatment with acyclovir for previous HSV lesions.

1. Introduction

Central airway obstruction (CAO) was first described in 1898 when Gustav Killian used a "bronchoscope" to remove a piece of pork bone from a farmer's trachea [1]. CAO is generally defined as airflow limitation due to >50 % occlusion, as quantified on imaging by decreased cross-sectional area or diameter of the trachea, main stem bronchus, bronchus intermedius or lobar bronchus [1,2]. Malignant etiologies are more prevalent than benign etiologies, which include granulation tissue resulting from prior endotracheal/tracheostomy tubes, airway foreign bodies, and trachea- or bronchomalacia.

Primary tumors of the airway are relatively uncommon, with an estimated incidence of 600–700 cases per year. Most primary tracheal tumors are squamous cell carcinoma or adenoid cystic carcinoma. Carcinoid tumors, however, account for most primary airway tumors distal to the carina. Herpes-simplex-virus (HSV) endobronchial pseudotumor is an extremely rare phenomenon with only eight prior case reports to date. Herein, we present a case of HSV pseudotumor successfully managed by argon-plasma-coagulation (APC) debulking via bronchoscopy and medically managed with intravenous foscarnet due to the patient's previous HSV-2 lesions having resistance to acyclovir.

2. Case presentation

49-year-old African American male with a past medical history of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), originally diagnosed in 1996, with most recent CD4 of 320/mm^3 and HIV RNA of 80 copies/mL, currently receiving anti-retroviral therapy, prior herpes simplex virus-2 (HSV-2) infection of the lip and penis, previously treated mycobacterium avium infection (MAI), prior secondary spontaneous pneumothorax, chronic obstructive pulmonary disease (COPD) with bronchitis and emphysema, and ongoing tobacco abuse who presented to our center's emergency department (ED) with a three-day

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history of dyspnea, cough with congestion, nausea, and vomiting. Upon initial evaluation, the ED providers noted that he was extremely tachypneic and had dysphonia and inspiratory and expiratory stridor. He received a one-time dose of racemic epinephrine (racepinephrine 2.25 %, 0.5 mL) and an intravenous dose of 10 mg of dexamethasone.

Laboratory results were notable for metabolic panel showing sodium 136 mmol/L, potassium 3.9 mmol/L, chloride 110 mmol/L, bicarbonate 24 mmol/L, anion gap 9 mmol/L, blood urea nitrogen 9 mg/dL, creatinine 0.95 mg/dL, glucose 144 mg/dL, calcium total 8.5 mg/dL. Liver function tests revealed an aspartate aminotransferase 21 units/L, alanine aminotransferase 13 units/L, alkaline phosphatase 58 units/L, total bilirubin 0.8 mg/dL, total protein 7.1 gm/dL, and albumin 3.3 gm/dL. Complete blood count (CBC) showed a white blood cell count (WBC) 9.5 k/cumm, hemoglobin (Hgb) 13.4 gm/dL, and platelets 449 k/cumm. A venous blood gas showed pH 7.47, pCO2 30 mmHg, pO2 73 mmHg, base excess (BE) −1 mmol/L, bicarbonate 21.6 mmol/L, O2 sat 96 % on 0.40 FIO2. Other laboratory results obtained included lactate 1.0 mmol/L, thyroid stimulating hormone (TSH) 0.428 mcU/mL, free T4 (FT4) 1.3 ng/dL, urine streptococcus antigen and urine legionella antigen negative, MRSA polymerase chain reaction (PCR) negative, CD4 count of 119/mm^3, and HIV RNA viral load <20 copies/mL.

He underwent computed tomography (CT) imaging of his chest showing a background of emphysematous changes along with mediastinal lymphadenopathy and left-sided tree-in-bud and ground glass opacities, consolidation, infiltrate, mucus plugging and impaction of the left mainstem bronchus (red arrow, Fig. 1). The abdomen and pelvis revealed no acute pathology to connect to his nausea and vomiting. The patient also underwent a flexible fiberoptic nasolayngoscopy for stridor by otolaryngology showing limited vocal cord mobility, vocal fold edema, and edematous aryepiglottic folds and arytenoids. Unfortunately, he was intubated for respiratory distress and admitted to the intensive care unit (ICU).

In the ICU, he underwent an urgent bedside fiberoptic flexible bronchoscopy revealing a white, fleshy, nodular mass with mucus impaction (Fig. 1). At the time of the bronchoscopy, the overnight team left the tumor undisturbed as the tumor was felt to be friable and would bleed easily. Bronchoalveolar lavage (BAL) was performed and sent for gram stain, aerobic and anaerobic cultures, viral cultures, acid fast bacilli (AFB), pneumocystis DNA PCR, fungal antigen studies including histoplasmosis, blastomycosis, and aspergillus, and cytology. The aerobic and anaerobic culture was positive for group B streptococcus but all other tests were negative. Coccidioides antibody by complement fixation (CF) and IgG/IgM were not detected. Galactomannan and (1,3)-beta-D-glucan (Fungitell) were both negative. With the concern for primary neoplasm, we consulted our interventional pulmonologist (RW) to aid with biopsy and tumor debulking. Diagnostic flexible bronchoscopy with endobronchial forceps biopsies were performed on the left mainstem mass a few days after ICU admission, and rapid-on-site-evaluation (ROSE) touch preps did not reveal any obvious neoplasm (Fig. 2). Tumor debulking of the endobronchial mass was performed with APC to pre-specified pulmonary settings (40 W, 0.8 L/min) in concert with large forceps for further debridement. At the end of the case, there was substantial improvement of the left mainstem lumen patency and was estimated to be 80 % (Fig. 3).

Surgical pathology was reported three days after the first biopsy and revealed fragments of bronchial mucosa with extensive necrosis, acute inflammatory infiltrate with dense neutrophilic clusters, fibrin exudates and cellular debris, patchy lymphoplasmacytic aggregates and no evidence of lymphoma. AFB and grocott-methenamine silver (GMS) special stains were negative for acid fast bacilli and fungal organisms. Immunohistochemical stains showed nuclear staining positive for HSV-1 and HSV-2 but negative for cytomegalovirus (CMV) and adenovirus.

After reviewing the results, we consulted the infectious disease team. The patient had a history notable for HSV-2 resistance to acyclovir. To avoid treatment failure, the infectious disease team promptly started the patient on a two-week course of intravenous foscarnet. Two weeks after the results came back, the patient then underwent a repeat fiberoptic flexible bronchoscopy. The patency of the lumen was noted to be 85 % (not published). To definitively exclude malignancy, we performed additional forceps biopsies of the distal leading edge of the prior lesion site. Additionally, we performed endobronchial ultrasound (EBUS) with fine-needle-

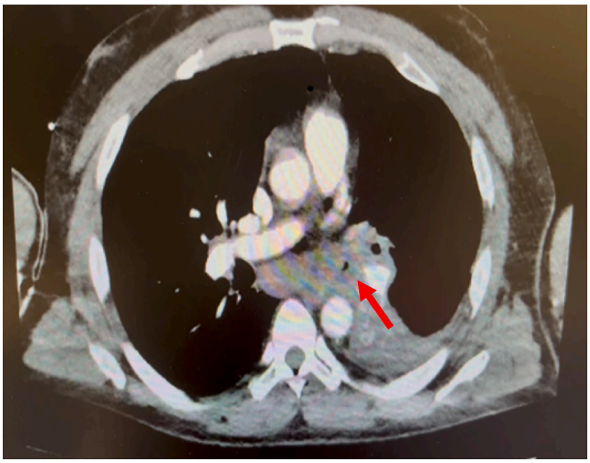

Fig. 1. A CT Chest that was obtained before intubation. This demonstrated left sided consolidation, infiltrate, mucus plugging and impaction of the left mainstem bronchus (red arrow), which was suspicious for a post-obstructive process secondary to possible neoplasm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

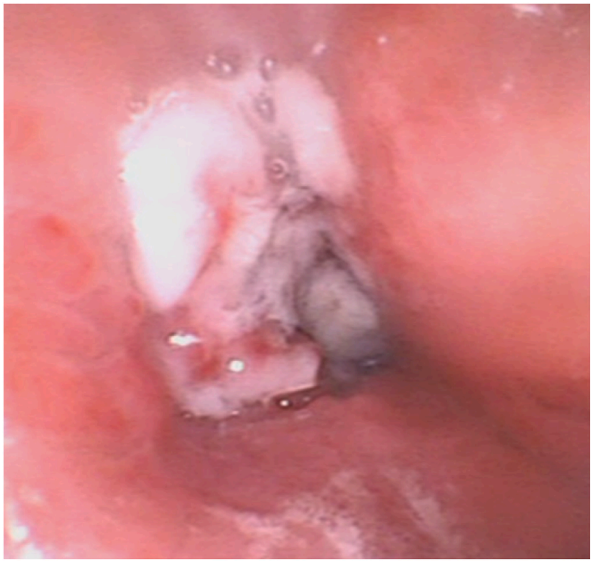

Fig. 2. Initial fiberoptic flexible bronchoscopy via GlideScope shortly after urgent endotracheal intubation. This was performed by overnight critical care revealing a white, fleshy, and nodular mass with mucus impaction. Biopsy not done due to concern for malignancy and to avoid additional bleeding.

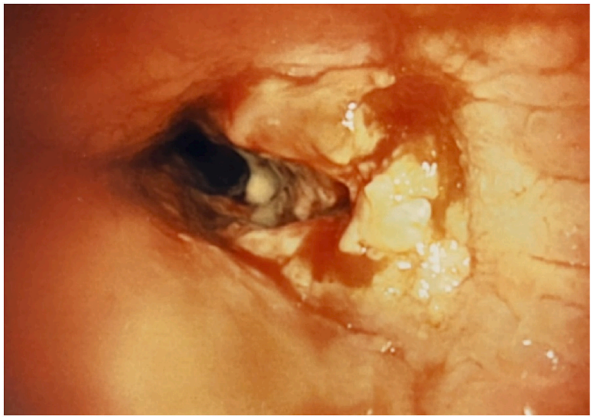

Fig. 3. Follow-up fiberoptic flexible bronchoscopy was performed a few days after initial endotracheal intubation and flexible bronchoscopy. This image shows a white, nodular tumor suspicious for malignancy after multiple forceps biopsies and before APC debulking.

aspirations (FNA) of a station 7 subcarinal lymph node. Surgical pathology again demonstrated similar findings as before and were negative for carcinoma and additional viral or fungal etiologies. The FNA cytology revealed a reactive lymph node. The patient was discharged 17 days after admission with planned follow up with infectious disease and interventional pulmonology as well as otolaryngology, who deemed his vocal fold edema to be due to either the HSV or from co-infection with another virus.

3. Discussion

HSV infection of the respiratory tract is more common in immunocompromised individuals, although there have been case reports of immunocompetent patients developing infection [3]. Tracheobronchitis and pneumonia have been described in patients with solid organ transplants, both solid tumor and liquid malignancies, AIDS or corticosteroid usage [4,5]. The pathophysiology of how HSV invades the lower respiratory tract is not established but is suspected due to aspiration, propagation after reactivation in the oropharynx or deposited in the lower airways after endotracheal intubation. HSV endobronchial lesions are typically described as white, plaque-like or exophytic in nature, and their etiology remains poorly delineated. Possibilities for the lesions' origin include secondary to extensive, local necrosis with formation of abundant granulation tissue in the subepithelial zone as a reaction to epithelial inflammation, from repeated local microtrauma, from previous infections that determined squamous metaplasia, or even local distant reactivation [5,8].

In our case, the patient initially underwent a CT chest that revealed dense lung consolidation causing concern for a post-obstructive process. The differential diagnosis at the time of evaluation by the overnight critical care team included typical and atypical infectious causes, foreign body impaction, and neoplasm. Thus, bronchoscopy with APC debulking was necessary. The patient's

suboptimal control of his HIV further prompted a workup that included bronchoscopy and biopsy looking for atypical infectious or neoplastic causes of the endobronchial pseudotumor. We performed an additional bronchoscopy and biopsies given the strong suspicion of cancer, which was not always performed in the case reports described. Histopathology revealed dark, nuclear inclusions that were positive for HSV-1 and HSV-2 for both procedures. As we used APC to relieve the CAO, we wanted to compare our approach to the available literature for bronchoscopic treatment of HSV pseudotumor.

To date, there have been eight prior case reports that have described endobronchial HSV pseudotumor and mentioned bronchoscopic techniques for diagnosis or treatment of the pseudotumor obstruction [5–12]. The first case of endobronchial pseudotumor from HSV was reported in 1995 by Armbruster et al. about a 52-year-old male with a history of HIV and AIDS who was found to have a right upper lobe lesion. On bronchoscopy, he had a necrotizing tracheobronchitis and exophytic tumor causing obstruction of the apical segment of the right upper lobe which was subsequently biopsied [5]. Histopathology revealed HSV-2, and the patient received a two-week course of ayclovir. The patient died six weeks later after the original diagnosis and underwent autopsy showing no residual bronchial tumor.

The next case of pseudotumor was by Upadya et al. [6]. They published a case of a 68-year-old female with severe restrictive lung disease caused by kyphoscoliosis who presented with a one-week history of dyspnea at rest, right-sided chest pain and swelling of the right lower extremity. She underwent a bronchoscopy revealing extensive inflammation of bronchial mucosa with a 3 × 2 cm white, fungating mass near the ostium of the right middle lobe (RML). The lesion was brushed and biopsied with the touch preparation negative for cancer and cytologic exam positive for epithelial cells with inclusions positive for HSV-1 and HSV-2. No endoscopic treatment was done due to the severity of her illness, and the family opted to withdraw life support. The authors concluded that the pseudotumor contributed to her morbidity but not overt mortality.

Another case of pseudotumor was published by Plowman and colleagues and involved a 31-year-old male with HIV and AIDS found to have an obstructive bronchial lesion due to HSV-2 infection, who responded promptly to endoscopic resection and oral treatment with acyclovir [7]. Unfortunately, we did not have access to this article so we were unable to provide further details of the case. Another case described by Dantas and colleagues concerned a 76-year-old male with chronic lymphocytic leukemia (CLL) who presented with fever, cough and dyspnea for four days [8]. A chest CT demonstrated a mass-like lesion causing obstruction of the respective lobar bronchus. Bronchoscopy demonstrated polypoid lesions occluding the left upper lobe (LUL) bronchus. BAL was negative for neoplastic cells. However, histopathology revealed metaplastic and mature squamous epithelial cells with cytopathic changes and were compatible with viral infection. Repeat bronchoscopy had epithelial cells that demonstrated nuclear inclusion bodies consistent with HSV infection. Molecular testing using PCR identified HSV-1 and HSV-2 in the tissue specimen. The treatment included APC debulking and oral acyclovir for six weeks. Chest CT after treatment revealed regression of the lesion with re-expansion of the LUL. Katsenos et al. also published a case on a 75-year-old male who presented with hoarseness and found on bronchoscopy to have a mid and distal tracheal mucosal thickening that was also positive for HSV-1 and HSV-2 that responded to several weeks of acyclovir [9].

The last few cases were published at national meetings and include Hamera and colleagues' description of a 68-year-old immunocompetent female with COPD who was found to have a large right effusion secondary to a large right lower lobe (RLL) mass on CT chest [10]. She was intubated and underwent bronchoscopy showing an endobronchial lesion and underwent biopsy and BAL. Biopsy results were positive for HSV-1. The patient completed a course of acyclovir and improved. Additionally, Russell and colleagues described a case of a 71-year-old male who presented with one week of dyspnea, cough, and sputum production with a chest x-ray revealing a RLL pneumonia and respiratory culture with group C streptococcus [11]. Bronchoscopy revealed an endobronchial lesion in the bronchus intermedius. Results from forceps biopsy showed suspected squamous cell carcinoma (SCC). Rigid bronchoscopy was performed for tumor debulking and staging with pathology revealed pseudoepitheliomatous hyperplasia associated with HSV inclusions in ground glass nuclei in submucosal nests of atypical squamous cells with overlying squamous metaplasia. Lastly, Martinez et al. presented a case of a 46-year-old HIV positive male who presented with dyspnea, chest pain, and dry cough for two weeks and was subsequently intubated for respiratory failure secondary to bilateral pneumonia on chest x-ray [12]. Bronchoscopy was done demonstrating a large, pale, lobulated mass arising from the anterior main carina and was partially blocking the lower trachea, along with a second lesion blocking the right mainstem. The biopsy revealed atypical cells suspicious for lung cancer but was not definitive so a cryobiopsy and concomitant APC debulking was performed. The biopsy revealed HSV-1, and the patient was also treated with acyclovir after discharge with unclear duration. The follow up CT after discharged showed resolution of the airway lesion.

In three of the eight cases, tumor debulking was done via bronchoscopy. Of the three that were done, two were done via APC. No adverse events or complications were reported with these cases. All cases reported resolution of the obstruction. Thus, APC appears to be safe and effective when debulking HSV pseudotumor causing airway obstruction.

4. Conclusion

In conclusion, this case represents another in a collective and ever-expanding series of patients with endobronchial pseudotumor secondary to HSV. As supported by our case and the available case reports, clinicians should have a heightened suspicion for HSV pseudotumor if they have an immunocompromised individual with a white, nodular, and fleshy tumor in the airway and histopathology is not initially suggestive of malignancy but has presence of nuclear inclusions. We summarized all the available cases to date and from doing so, it is evident that antiviral therapy is tantamount to the treatment of endobronchial pseudotumor. However, central airway obstruction is not always co-existent and thus represents an additional challenge when present. The standardized approach and management of this particular entity is not well delineated in this population and should further encourage both interventional pulmonologists and infectious disease physicians to determine a more uniform approach to this disease, including bronchoscopic modality and duration of antiviral therapy. Furthermore, this case highlights the importance of a multidisciplinary approach to pseudotu-

mor caused by HSV. We posit that this case further provides additional evidence that outcomes with bronchoscopic debulking with APC followed by medical treatment with antiviral therapy are excellent, and this approach may be the benchmark going forward in managing these patients.

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CRediT authorship contribution statement

Alan Hyslop: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Robert Weller:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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