Infections causing central airway obstruction: role of bronchoscopy in diagnosis and management

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Abstract: Central airway obstructive infections (CAOI) are challenging medical conditions that may represent an advanced and complicated process of ongoing infections. The epidemiology of CAOI is unknown as well as the pathophysiology and the mechanism of development. This is due to sparse data in the literature that consists mainly of case reports and retrospective case series. CAOI can be caused by fungal, bacterial, parasitic and viral infections. Most patients with CAOI can be diagnosed clinically and with chest imaging, which demonstrate obstruction of the central airways. However, bronchoscopy is commonly used to confirm and obtain a specific diagnosis to guide specific therapy. In recent years, interventional pulmonology (IP) is becoming widely available and offer a minimally invasive approach for the management of central airway diseases such as cancers, benign strictures, and other conditions. Various bronchoscopic modalities are used to treat central airway obstruction (CAO), such as mechanical debulking, endobronchial laser therapy, electrocautery, argon plasma coagulation, cryotherapy, and airway stenting. In patients with CAOI, the role of therapeutic bronchoscopy is not clearly defined, but many isolated reports in the literature described bronchoscopic intervention in combination with medical therapy as the initial management approach. In this paper, we present cases of CAOI that underwent bronchoscopic intervention as part of their management. We described the infectious etiology, locations, bronchoscopic findings and bronchoscopic modalities for airway management.

Keywords: Central airway obstruction (CAO); infection; bronchoscopy

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Introduction

Central airway obstructive infections (CAOI) are interesting and problematic illnesses that have unusual clinical, radiological, and morphological presentations. They may be caused by common or rare pathogens. Individual immune status and comorbid conditions may allow similar infectious pathogens to cause disease states, which have a unique clinical presentation; unusual anatomic distributions, morphological appearances, and outcomes. To this date, there is no comprehensive review addressing this clinical entity, and the medical literature mainly consists of case reports and cases series, which prompted us to write this paper on CAOI. In this article, we focus on the central
Airway infections causing obstruction and warranting bronchoscopic diagnosis and therapeutic intervention. The PubMed and Embase databases were searched from 1990 to 2016 to identify case reports and case series of central airway infections causing obstruction. We excluded cases of bronchitis or tracheitis caused by common viral or bacterial pathogens that are usually treated medically without any invasive intervention. We also excluded cases of endobronchial tuberculosis (EBTB), as this condition is not uncommon and is considered outside the scope of this paper. We also excluded pediatric cases under the age of 18.

A total of 337 cases of central airway infections diagnosed with bronchoscopy were reported, of which 237 had individual case reports and 100 were in case series. We herein provided an overview of the microbiologic, pathologic, radiologic, and bronchoscopic characteristics of infections affecting central airways. We focused on the bronchoscopic modalities that were used to treat CAOIs, such as rigid bronchoscopy, balloon bronchoplasty, endobronchial laser therapy, cryotherapy, and airway stenting. Additionally, we reported on the immune status of patients and management outcomes.

Epidemiology

There is no epidemiological data that specifies the prevalence, racial or geographical distribution, and age or gender predominance of CAOI. Case reports and case series from reviews of specific pathogens, which causes CAOIs indicate that the immune status of the host plays a crucial role. In one review by Tasci et al. on aspergillosis causing central airway infections, 16 out of 20 reported patients were on immunosuppressive therapy (1). The prevalence of CAOI is expected to increase as the fields of transplant medicine and oncology evolve and particularly with the rapid growth of interventional pulmonology (IP). Tables 1-3 outline case reports of CAOIs who have undergone bronchoscopic management in the last 26 years. Gender, age, immune status of hosts, the location of specific infection, bronchoscopic view, diagnostic and treatment modalities with outcomes are summarized.

Diagnosis

The diagnosis of CAOI can be challenging. An understanding of a patient’s past medical history, clinical presentation, systemic signs of infection, radiologic and microbiologic evidence of infection, and bronchoscopy based modalities must all be assimilated. Procedural skills may include bronchoalveolar lavage (BAL), bronchial washings, protected brush, endobronchial and transbronchial biopsies as well as macroscopic evaluation of lesions. Some cases of CAOI develop at the site of previous disease, anastomosis sites or places where previously inhaled foreign bodies were located. Dicpinigaitis et al. described actinomycosis in a patient with a history of possible chicken bone aspiration. Poor dental hygiene associated with a bony foreign body in the right bronchus intermedius (RBI) caused 90% obstruction (43). In another case, Pornsuriyasak et al. described pseudomembranous tracheobronchitis caused by Aspergillus species (spp.) at the site of previous tracheal stenosis, which had been caused by previous tuberculosis (TB) (4). CAOI can also mimic endobronchial malignancy. In these cases, bronchoscopy with biopsy is indicated for differentiation (44,45).

Clinical presentation

There are no unique clinical symptoms that can distinguish CAOI from other respiratory infections or airway obstruction secondary to other etiology such as malignancy. Dyspnea, cough, fever, and hemoptysis are almost universal presenting signs. Hoarseness and wheezing may indicate large airway involvement with possible obstruction. Suresh et al. reported a case of endobronchial mucormycosis in the left mainstem bronchus (LMB) causing left vocal cord paresis by affecting the left recurrent laryngeal nerve (46). Postobstructive pneumonia is not an uncommon presentation. Rare presentations can be challenging to diagnose, and therefore a high clinical suspicion is required. A cough with expectoration of fungal casts taking the form of the bronchial tree has been observed in fungal obstructing diseases (47). Hemoptysis, although a common presenting symptom of CAOIs, could be a result of broncholiths in the tracheobronchial tree (48), or vascular invasion (47).

In patients with acquired immune deficiency syndrome (AIDS), the respiratory symptoms may appear after antiretroviral therapy (ART) as a result of immune reconstitution syndrome. Kim et al. described a case of an endobronchial polypoid mass caused by Mycobacterium avium complex (MAC) and occluding the lingular bronchus lumen (49).

Microbiology

CAOIs can be caused by the full spectrum of bacterial,
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Sex/age</th>
<th>Infection type</th>
<th>Location of infection</th>
<th>Bronchoscopic findings</th>
<th>Degree of obstruction</th>
<th>Bronchoscopic treatment</th>
<th>Medical treatment</th>
<th>Immune status</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rojas-Tula et al. 2013 (2)</td>
<td>M/50</td>
<td>Fusarium spp. (mycetoma)</td>
<td>LUL apical segmental bronchus</td>
<td>Large rounded whitish cauliflower type necrotic lesion</td>
<td>N/A</td>
<td>Removal of mycetoma with cryotherapy probe</td>
<td>Itraconazole</td>
<td>Non comp.</td>
<td>Clinical improvement, discharged home</td>
</tr>
<tr>
<td>McGuire et al. 2007 (3)</td>
<td>F/Middle age</td>
<td>Rhizomucor</td>
<td>Right bronchial anastomosis</td>
<td>Darkly pigmented pseudo—membrane and hypertrophic tissue</td>
<td>90% narrowing</td>
<td>Debridement, balloon dilation, later SEMS placement</td>
<td>Amph. B</td>
<td>Comp. (BLT)</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Gonzalez et al. 2013 (5)</td>
<td>M/17</td>
<td>Aspergillus flavus</td>
<td>Distal trachea right lateral wall</td>
<td>15 mm × 15 mm defect on membranous part of right distal tracheal wall communicating with RPC</td>
<td>N/A</td>
<td>Surgical repair then Y shaped silicone stent placement, rigid bronch</td>
<td>Voriconazole</td>
<td>Comp. (ALL)</td>
<td>Clinical and bronchoscopic improvement</td>
</tr>
<tr>
<td>Bentley et al. 2016 (6)</td>
<td>F/65</td>
<td>Cryptococcus neoformans</td>
<td>Bronchi, subglottic area</td>
<td>Extensive polypoid lesions in the subglottic space</td>
<td>&gt;50% airway occlusion</td>
<td>Endobronchial argon plasma coagulation</td>
<td>Amphotericin B, Fluconazole</td>
<td>Comp. (non-Hodgkin lymphoma)</td>
<td>No further respiratory complaints, decannulated</td>
</tr>
<tr>
<td>Paul et al. 2015 (7)</td>
<td>F/23</td>
<td>Mucormycosis</td>
<td>Distal trachea, RMB, LMB</td>
<td>White soft tissue mass, Ball—valve effect</td>
<td>Complete RMB occ.</td>
<td>Rigid bronch. Unsuccessful, right pneumonectomy</td>
<td>Amph. B, posaconazole</td>
<td>Comp. (DM)</td>
<td>Discharge to rehab</td>
</tr>
<tr>
<td>Kim et al. 2000 (8)</td>
<td>M/33</td>
<td>Aspergillus spp.</td>
<td>LLL bronchus</td>
<td>Irregularly shaped yellowish movable mass 1 cm in size</td>
<td>Complete occ.</td>
<td>Basket removal of mass</td>
<td>N/A</td>
<td>Non comp.</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Jung et al. 2013 (9)</td>
<td>M/59</td>
<td>Aspergillus spp.</td>
<td>LLL superior segmental bronchus</td>
<td>Irregular mass —like brownish material and foreign body</td>
<td>Total obstruction</td>
<td>Unsuccessful attempt to remove foreign body by snare</td>
<td>No treatment</td>
<td>Non comp.</td>
<td>N/A</td>
</tr>
<tr>
<td>Yeo et al. 2012 (10)</td>
<td>F/75</td>
<td>Aspergillus spp.</td>
<td>LLB</td>
<td>Broncholith-like calcified endobronchial lesion with irregular yellow and black surface and post obstructive pneumopathy</td>
<td>N/A</td>
<td>Obstructing mass was removed using grasping forceps</td>
<td>Antibiotics NOS</td>
<td>Non comp.</td>
<td>Symptomatic and radiologic improvement</td>
</tr>
<tr>
<td>Author/year</td>
<td>Sex/age</td>
<td>Infection type</td>
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<td>Bronchoscopic findings</td>
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<td>Outcomes</td>
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<tr>
<td>Alraiyes et al./2014 (12)</td>
<td>M/43</td>
<td>Mucormycosis</td>
<td>LMB</td>
<td>Occlusion of LMB</td>
<td>100% LMB occlusion with pinhole opening</td>
<td>Bronchography, fluoroscopic guided balloon dilations</td>
<td>N/A</td>
<td>Comp. (IVIG)</td>
<td>Symptoms improved post intervention</td>
</tr>
<tr>
<td>Pendurthi et al./2016 (13)</td>
<td>M/27</td>
<td>Zygomycetes spp.</td>
<td>LLL bronchus</td>
<td>Endobronchial mass occluding the posterior subsegment of LLL bronchus</td>
<td>N/A</td>
<td>Endobronchial mass was removed using cryotherapy</td>
<td>LAmph. B</td>
<td>Comp. (hematological malignancy)</td>
<td>N/A</td>
</tr>
<tr>
<td>Shameem et al./2010 (14)</td>
<td>M/24</td>
<td>Aspergillus precipitin</td>
<td>RUL posterior segmental bronchus</td>
<td>Ball-like region, with hyperemia movable</td>
<td>Partial occ.</td>
<td>Biopsy, forceps and basket removal of ball</td>
<td>N/A</td>
<td>Non comp.</td>
<td>N/A</td>
</tr>
<tr>
<td>Artinian et al./2010 (16)</td>
<td>M/46</td>
<td>Cryptococcus neoformans</td>
<td>RUL bronchus and RMB</td>
<td>Large glistening, smooth surface mass emanating from RUL into RMB</td>
<td>Almost complete occ. of RMB</td>
<td>Rigid bronch. With electrocautery and snare resection, RMB Dumon stent placement</td>
<td>Fluconazole</td>
<td>Non comp.</td>
<td>Clinical and bronchoscopic resolution</td>
</tr>
<tr>
<td>Husari et al./1994 (17)</td>
<td>M/56</td>
<td>Mucormycosis</td>
<td>LMB</td>
<td>Endobronchial mass, firm, well circumscribed with smooth erythematous mucosa</td>
<td>LMB obstruction</td>
<td>Nd-YAG laser endobronchial therapy</td>
<td>IV Amph. B</td>
<td>Comp. (DM)</td>
<td>Clinical and radiographic improvement</td>
</tr>
<tr>
<td>al-Majed et al./1992 (18)</td>
<td>M/44</td>
<td>Mucormycosis (Rhizopus)</td>
<td>RLL bronchus distal to the origin of superior segment</td>
<td>White cheese like mass</td>
<td>Occlusion of RLL bronchus</td>
<td>Rigid bronchoscopy and removal of mass</td>
<td>IV Amph. B</td>
<td>Comp. (DM)</td>
<td>Clinical and bronchoscopic resolution</td>
</tr>
<tr>
<td>Zhou et al./2013 (19)</td>
<td>M/44</td>
<td>Cryptococcus neoformans</td>
<td>RMB</td>
<td>Mass over RMB orifice</td>
<td>Occlusion of RMB orifice</td>
<td>Tracheal endoscopic mass ablation, tracheal stent</td>
<td>Itraconazole Voriconazole LAmph. B.</td>
<td>Non comp.</td>
<td>Radiologic and bronchoscopic resolution of the mass</td>
</tr>
<tr>
<td>Radunz et al./2013 (20)</td>
<td>F/47</td>
<td>Aspergillus fumigatus</td>
<td>Mid trachea</td>
<td>Thick white mucous coverings</td>
<td>Tracheal stenosis subtotal</td>
<td>Stent placement</td>
<td>Voriconazole</td>
<td>Comp. (OLT)</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Fabbri et al./2013 (21)</td>
<td>M/49</td>
<td>Cryptococcus</td>
<td>Proximal trachea</td>
<td>Exophytic mass arising from posterior tracheal wall</td>
<td>Subtotal obstruction of trachea</td>
<td>Nd-YAG laser resection</td>
<td>Fluconazole</td>
<td>Comp. (RTP)</td>
<td>Clinical and bronchoscopic resolution</td>
</tr>
<tr>
<td>Zuil et al./2001 (22)</td>
<td>M/46</td>
<td>Mucormycosis</td>
<td>RBI</td>
<td>Whitish yellow mass</td>
<td>Complete obstruction of RBI</td>
<td>Rigid bronchoscopy, cryotherapy</td>
<td>IV Amph. B, LAmph. B, then right pneumonectomy</td>
<td>Comp. (DM)</td>
<td>Expired due to pulmonary edema</td>
</tr>
<tr>
<td>Author/year</td>
<td>Sex/age</td>
<td>Infection type</td>
<td>Location of infection</td>
<td>Bronchoscopic findings</td>
<td>Degree of obstruction</td>
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<tr>
<td>Rachel et al. /2002 (23)</td>
<td>F/33</td>
<td>Mucormycosis</td>
<td>Carina, LMB</td>
<td>LMB occluded by a gelatinous adherent material, purulent pseudo-membranes entire length of LMB</td>
<td>Near complete occlusion of LMB</td>
<td>Stent placement, APC</td>
<td>IV and nebulized Amph. B, endobronchial instillation of Amph. B</td>
<td>Comp. (RTP)</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Nathan et al. /2000 (24)</td>
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</tr>
<tr>
<td>Case 1</td>
<td>M/F 49.9+/−9.9</td>
<td>Aspergillus fumigatus</td>
<td>RMB</td>
<td>Exuberant granulation tissue Pseudomembranes</td>
<td>Endobronchial narrowing</td>
<td>Endobronchial Laser therapy</td>
<td>Itraconazole/ Amph. B</td>
<td>Comp. (lung transplant)</td>
<td>Improvement in FEV₁</td>
</tr>
<tr>
<td>Case 2</td>
<td>–</td>
<td>Aspergillus fumigatus</td>
<td>LMB</td>
<td>Exuberant granulation tissue Pseudomembranes</td>
<td>Endobronchial narrowing</td>
<td>Stent placement</td>
<td>Itraconazole/ Amph. B</td>
<td>Comp. (lung transplant)</td>
<td>Improvement in FEV₁</td>
</tr>
<tr>
<td>Case 3</td>
<td>–</td>
<td>Aspergillus fumigatus</td>
<td>LMB</td>
<td>Exuberant granulation tissue</td>
<td>Endobronchial narrowing</td>
<td>Stent placement</td>
<td>Itraconazole/ Amph. B</td>
<td>Comp. (lung transplant)</td>
<td>Improvement in FEV₁</td>
</tr>
<tr>
<td>Case 4</td>
<td>–</td>
<td>Aspergillus fumigatus</td>
<td>LMB</td>
<td>Exuberant granulation tissue</td>
<td>Endobronchial narrowing</td>
<td>Stent placement</td>
<td>Itraconazole/ Amph. B</td>
<td>Comp. (lung transplant)</td>
<td>Improvement in FEV₁</td>
</tr>
<tr>
<td>Case 5</td>
<td>–</td>
<td>Aspergillus fumigatus</td>
<td>Right middle lobe bronchus</td>
<td>Stricture Pseudomembranes</td>
<td>Endobronchial narrowing</td>
<td>Balloon dilation</td>
<td>Itraconazole/ Amph. B</td>
<td>Comp. (lung transplant)</td>
<td>Improvement in FEV₁</td>
</tr>
<tr>
<td>Case 6</td>
<td>–</td>
<td>Aspergillus fumigatus</td>
<td>LMB</td>
<td>Exuberant granulation tissue</td>
<td>Endobronchial narrowing</td>
<td>Stent placement</td>
<td>Itraconazole/ Amph. B</td>
<td>Comp. (lung transplant)</td>
<td>Improvement in FEV₁</td>
</tr>
<tr>
<td>Argento et al./2015 (25)</td>
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<tr>
<td>Case 1</td>
<td>M/68</td>
<td>Aspergillus fumigatus</td>
<td>Trachea RMB</td>
<td>Endobronchial mass with extrinsic compression</td>
<td>Significant obstruction</td>
<td>Debridement by rigid bronchoscopy</td>
<td>Voriconazole/ micafungin Amph. B</td>
<td>Comp. (Heart transplant)</td>
<td>Development of tracheal fistula</td>
</tr>
<tr>
<td>Case 2</td>
<td>M/62</td>
<td>Aspergillus fumigatus</td>
<td>Main carina RMB, RBI</td>
<td>Necrotic mass Pseudomembranes</td>
<td>Progressive stenosis of bronchus intermedius</td>
<td>Debridement by rigid bronchoscopy balloon dilations stent placement</td>
<td>Voriconazole/ micafungin</td>
<td>Comp. (AIDS)</td>
<td>Alive after 30 months</td>
</tr>
</tbody>
</table>

RUL, right upper lobe; LUL, left upper lobe; RBI, right bronchus intermedius; RMB, right main stem bronchus; LMB, left main stem bronchus; LLL, left lower lobe; occ., occlusion; DM, diabetes mellitus; RTP, renal transplant patient; BLT, bilateral lung transplant; LAmph. B, Liposomal amphotericin B; Amph. B, Amphotericin B; NOS, not otherwise specified; N/A, not applicable; Comp., compromised; SEMS, self-expandable metallic stent; bronch., bronchoscopy; BLT, bilateral lung transplant; OLT, orthotopic liver transplant; BMT, bone marrow transplant; ALL, acute lymphoblastic leukemia; IVIG, intravenous immunoglobulin; RPC, right pleural cavity; TB, tuberculosis; FEV₁, forced expiratory volume in 1 second; APC, argon plasma coagulation; Nd:YAG laser, neodymium-doped yttrium aluminum garnet laser; spp., species; M, male; F, female; AIDS, acquired immune deficiency syndrome.
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Sex/age</th>
<th>Infection type</th>
<th>Location of infection</th>
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<th>Medical treatment</th>
<th>Immune status</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folliet et al./2015 (26)*</td>
<td>N/A</td>
<td>Actinomyces meyeri</td>
<td>RMB</td>
<td>Endobronchial tumor</td>
<td>Complete occ. RMB</td>
<td>Rigid bronchoscopic debridement, Y shaped stent placement</td>
<td>Antibiotic therapy NOS</td>
<td>Non comp.</td>
<td>Complete regression of obstruction expired after stent removal due to massive hemoptysis</td>
</tr>
<tr>
<td>Kebbe et al./2016 (27)</td>
<td>F/57</td>
<td>Finegoldia magna (formerly Peptostreptococcus magnus)</td>
<td>RUL, Trachea, RMB LMB</td>
<td>Dynamic airway collapse and significant tracheal edema</td>
<td>Narrowing of b/l proximal mainstem bronchi</td>
<td>Deploying a silicon Y-stent in the distal trachea and b/l proximal mainstem bronchi</td>
<td>N/A</td>
<td>Comp. (chemotherapy)</td>
<td>Asymptomatic the stent was removed 5 weeks after using rigid bronchoscopy</td>
</tr>
<tr>
<td>Guerrero et al./2014 (28)</td>
<td>F/39</td>
<td>Corynebacterium spp.</td>
<td>Proximal trachea</td>
<td>Pseudomembranes, severe tracheal inflammation with multiple mucosal, plaque-like lesions</td>
<td>95% obstruction of proximal trachea obstruction recurred with complete obstruction</td>
<td>Mechanical debridement recurrence: rigid bronchoscopy, dilatation with percutaneous dilatation tracheostomy</td>
<td>Clindamycin for recurrence imipenem and vancomycin</td>
<td>Non comp.</td>
<td>Surgical tracheal resection</td>
</tr>
<tr>
<td>Colt et al./1991 (29)</td>
<td>M/54</td>
<td>Corynebacterium pseudodiphtheriticum</td>
<td>Trachea</td>
<td>Circumferential inflammatory process, with ulcerations, thin membranes and necrosis</td>
<td>Partial occlusion of trachea</td>
<td>Rigid bronch and Mechanical debulking</td>
<td>IV penicillin</td>
<td>None comp.</td>
<td>Resolution of inflammatory process</td>
</tr>
<tr>
<td>Manali et al./2005 (31)</td>
<td>M/58</td>
<td>Mycobacterium kansasii</td>
<td>Carina, LMB and RMB</td>
<td>Fungating mass, ulcerated carina and narrowing of mainstem bronchi</td>
<td>Partial occ. LMB and RMB</td>
<td>Laser resection and balloon bronchoplasty b/l mainstem bronchi</td>
<td>INH, rifampin, EB</td>
<td>Non comp.</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Henderson et al./2009 (32)</td>
<td>M/48</td>
<td>Streptococcus pyogenes</td>
<td>Trachea, RMB LMB</td>
<td>Diffuse pseudomembranes</td>
<td>Near complete obliteration of LMB</td>
<td>Cryo-adhesion therapy to remove pseudomembranes</td>
<td>NOS</td>
<td>Non comp.</td>
<td>Recovery Discharge</td>
</tr>
<tr>
<td>Gorbett et al./2013 (33)</td>
<td>F/52</td>
<td>MAC</td>
<td>RBI</td>
<td>Endobronchial mass</td>
<td>Near complete occ. RBI</td>
<td>Biopsy, debulking bronchoscopy with cryotherapy</td>
<td>MAC therapy</td>
<td>Comp. (CLL)</td>
<td>Clinical improvement</td>
</tr>
</tbody>
</table>

**Table 2 (continued)**
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Sex/age</th>
<th>Infection type</th>
<th>Location of infection</th>
<th>Bronchoscopic findings</th>
<th>Degree of obstruction</th>
<th>Bronchoscopic treatment</th>
<th>Medical treatment</th>
<th>Immune status</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shih et al./1997 (34)</td>
<td>F/34</td>
<td>MAI</td>
<td>RMB, LMB, RBI</td>
<td>Multiple polypoid tumors</td>
<td>Near complete occlusion of RMB,</td>
<td>Nd, YAG laser therapy</td>
<td>Ofloxacin, clarithromycin, rifampin</td>
<td>Non comp.</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Ling et al./2011 (35)</td>
<td>F/60</td>
<td>Pseudomonas aeruginosa staphylococcus aureus</td>
<td>Trachea RMB LMB</td>
<td>Multiple pink lobulated polypoid bronchial lesions (fibroepithelial polyps), some of which were up to 10 mm in diameter</td>
<td>Partial obstruction of segmental bronchi</td>
<td>Argon plasma coagulation biopsy</td>
<td>Ciprofloxacin Azithromycin</td>
<td>Non comp.</td>
<td>Resolution of symptoms and polyps</td>
</tr>
<tr>
<td>Bigi et al./2016 (37)</td>
<td>F/46</td>
<td>Klebsiella rhinoscleromatis</td>
<td>Proximal trachea, Subglottic</td>
<td>Subglottic mucosal hypertrophy arising in the cricoid</td>
<td>Tracheal stenosis to 7 mm in diameter</td>
<td>Endobronchial CO$_2$ laser therapy</td>
<td>Ofloxacin</td>
<td>Non comp.</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Buls et al./2011 (38)</td>
<td>F/71</td>
<td>MRSA</td>
<td>Trachea</td>
<td>Mass of granulation tissue</td>
<td>Tracheal obstruction</td>
<td>Rigid bronchoscopy, mechanical debulking and placement silicone stent</td>
<td>Antibiotics NOS</td>
<td>Non comp.</td>
<td>Stent removal in 2 months. No stenosis in 2 years</td>
</tr>
<tr>
<td>Case 2 F/76 Pseudomonas aeruginosa</td>
<td>Trachea</td>
<td>Mass of granulation tissue</td>
<td>Tracheal obstruction</td>
<td>Rigid bronchoscopy, mechanical debulking, argon plasma coagulation</td>
<td>Antibiotics NOS</td>
<td>Non comp.</td>
<td>Procedure repeated in 3 weeks. No recurrence afterwards</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*, foreign language article, RUL, right upper lobe; LUL, left upper lobe; RBI, bronchus intermedius; RMB, right main stem bronchus; LMB, left main stem bronchus; MAC, Mycobacterium avium complex; MAI, Mycobacterium avium intracellulare; INH, isoniazid; TMP, trimethoprim; SMX, sulfamethoxazole; EB, ethambutol; Comp., compromised; occ., occlusion; NOS, not otherwise specified; N/A, not applicable; bronch., bronchoscopy; MRSA, methicillin-resistant Staphylococcus aureus; b/l, bilateral; Nd:YAG laser, neodymium-doped yttrium aluminum garnet laser; M, male; F, female; spp., species.
Table 3 Cases of central airway infection caused by viruses and parasites with respective bronchoscopic findings, intervention, and outcomes

<table>
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<tr>
<td>Aventura et al.2011 (39)</td>
<td>M/55</td>
<td>CMV</td>
<td>LMB stent site</td>
<td>Granulation tissue proximal and distal to stent</td>
<td>N/A</td>
<td>Rigid bronchoscopy placement of new stent</td>
<td>IV ganciclovir, IV CMV immune globulin</td>
<td>Comp. (BLT)</td>
<td>Improvement in FEV,</td>
</tr>
<tr>
<td>Naber et al.2005 (40)</td>
<td>M/57</td>
<td>CMV</td>
<td>RBI</td>
<td>Polyp 1.5 cm</td>
<td>NOS</td>
<td>Bronchoscopic polyp removal</td>
<td>Ganciclovir</td>
<td>Comp. (lung transplant)</td>
<td>Reactivation expired</td>
</tr>
<tr>
<td>Chaaban et al.2015 (41)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>M/69</td>
<td>HSV</td>
<td>LLL lateral segment</td>
<td>Narrowing of bronchus</td>
<td>80 % narrowing</td>
<td>Balloon dilation</td>
<td>Valacyclovir</td>
<td>Comp. (lung transplant)</td>
<td>Improvement of lumen narrowing to 100%</td>
</tr>
<tr>
<td>Case 2</td>
<td>M/67</td>
<td>HSV</td>
<td>LUL bronchus</td>
<td>Stenotic lesion, pinpoint</td>
<td>Almost complete collapse on exhalation</td>
<td>Bare metal stent</td>
<td>Valacyclovir</td>
<td>Comp. (lung transplant)</td>
<td>Oxygen requirements returned to baseline</td>
</tr>
<tr>
<td>Zhang et al.2014 (42)</td>
<td>F/40</td>
<td>Leech infestation</td>
<td>Upper trachea</td>
<td>Brown worm-like moving foreign body 2 cm below the glottis surrounded with granulation tissue</td>
<td>N/A</td>
<td>Rigid bronch. and forceps extraction</td>
<td>N/A</td>
<td>Non comp.</td>
<td>Clinical improvement</td>
</tr>
</tbody>
</table>

LUL, left upper lobe; RBI, bronchus intermedius; LMB, left main stem bronchus; LLL, left lower lobe; bronch., bronchoscopy; BLT, bilateral lung transplant; Comp., compromised; NOS, not otherwise specified; occ., occlusion; N/A, not applicable; FEV₁, forced expiratory volume in 1 second; CMV, cytomegalovirus; HSV, herpes simplex virus; IV, intravenous; IG, immunoglobulin; M, male; F, female.
viral, fungal and parasitic pathogens. In contrast to other common respiratory tract infections with highly virulent pathogens causes bronchitis or pneumonia, the host immune status in CAOIs is usually compromised, and even common respiratory tract colonizers or saprophytes can cause serious illness. Microbiological tests differ for each group of pathogens. In all cases, routine blood work, human immunodeficiency virus (HIV) status, blood and sputum cultures require examination. Bronchoscopic specimen including biopsy should be sent for histopathological analysis, cytology, histochemical staining and fungal/mycobacterial stains. BAL and bronchial wash for fungal, bacterial, mycobacterial and viral cultures should also be obtained. Specific testing, which may include polymerize chain reaction (PCR) for viral or mycobacterial pathogens, may be needed if the clinical suspicion is high.

**Radiology**

Chest radiography (CXR) is universal for patients presenting with most respiratory symptoms and is the first step in the radiologic workup. CXR findings are not specific and may be helpful if lobar atelectasis or unilateral lung collapses are seen and indicate main stem bronchial, lobar or segmental bronchi obstruction. Pulmonary infiltrates may be suggestive of major airway involvement depending on suspected pathology. Lee et al. showed that in 121 patients with EBTB, the CXR showed parenchymal infiltration in 58.7% and loss of volume in 34.8% (50). In another study by Qingliang et al., only one out of 22 patients diagnosed with EBTB had a normal chest radiograph (51).

Chest computed tomography (CT) is more informative to localize the abnormality and to assess the severity of obstruction. Chest CT findings of “tree in bud,” focal consolidation with “halo sign,” and many centrilobular small nodules may all be indirect signs of tracheobronchial involvement with infection. The chest CT may show endobronchial or tracheal mass with luminal narrowing, mural thickening, intramural air, and even fistula formation (52). Airway obstruction caused by broncholithiasis or a foreign body with surrounding granulation tissue, due to superimposed infection can be visible on chest CT imaging. Chest CT is more specific for endobronchial actinomycosis as it can show proximal obstructive calcified endobronchial lesions caused by actinomycosis associated with broncholithiasis (43,53,54). Chest CT can be a useful tool prior to bronchoscopic intervention as it can delineate the extent of disease in central airways, give information about the degree of obstruction, and show the presence or absence of fistulae (55).

**Pathology**

Many patients with CAOI present with the same clinical, radiologic and bronchoscopic findings and tissue sampling is routinely needed to confirm the specific diagnosis. In this paper, we present the CAOI cases by infectious etiology, and we grouped them into fungal, bacterial, viral and parasitic infections. Fungal infections are usually diagnosed using various techniques such as histopathological examination, silver stains, tissue cultures, Periodic Acid-Schiff (PAS), or mucus carmin (56-59). Bacterial and viral CAOI are usually diagnosed using real-time PCR, monoclonal antibodies, immunohistochemical staining, gram stain, Ziehl-Neelsen stain and other available tests (40,60).

**Bronchoscopy**

The role of bronchoscopy is invaluable for the diagnosis of CAOI, however its role in CAOI management and post-treatment surveillance in not well defined. Clinical presentation and imaging are essential for the diagnosis of airway obstruction but bronchoscopy is frequently required to obtain specific diagnosis through direct airway inspection, and tissue sampling using endobronchial biopsy, brush, fine needle aspiration and bronchial washing (51,61). Immunocompromised patients may present with nonspecific respiratory symptoms, and routine bronchoscopy of these patients may help in the diagnosis of endobronchial disease. In the study by Calpe et al., seventy bronchoscopies were performed on 59 HIV patients with respiratory symptoms. Pulmonary TB was diagnosed in 25 patients, six of whom were found to have EBTB (62).

Other bronchoscopic techniques such as balloon radial endobronchial ultrasound (R-EBUS) can help to identify the extent of the endobronchial lesions, the invasion depth and the involvement of surrounding structures such as mediastinal vasculature. Using advanced diagnostic bronchoscopy techniques can help the proceduralist in planning the diagnostic as well as the therapeutic procedure and prevent serious complications such as airway perforation or life-threatening bleeding (57,63). In the case described by Handa et al. utilizing bronchoscopy with narrow band imaging (NBI) showed opaque vessels in bronchial subepithelium in the ulcerative lesion. The biopsy of that area revealed Cryptococcus neoformans (64).
Bronchoscopic findings in fungal CAOI

Denning et al. classified airway aspergillosis into four distinct types: pseudomembranous aspergillus tracheobronchitis (ATB), ulcerative ATB, obstructing and invasive ATB (65). The endobronchial appearance of infection can present with wall edema, pseudomembranes, necrotizing pseudomembranous lesions, ulcerative lesions, whitish or yellowish plaques, endoluminal masses and vegetations (Figure 1) (57,58,66-73). Mucor and Rhizopus are the most commonly reported pathogens of mucormycosis. The endoscopic appearance most commonly seen are mucoid plugs, yellowish or whitish in color, endobronchial mass or polypoid lesions, white cheese like masses, plaques, and areas of necrosis (18,46,59,74-78). In patients with airway cryptococcal infections, the bronchoscopic appearance has been reported as whitish or yellowish masses, mucous plugs, red or white thrush-like plaques, mucosal granularity, white granulation tissue, elevated ulcerated lesions, and polypoid masses (Figure 2) (6,44,64,79-81). Endobronchial histoplasmosis disease is rare but submucosal grayish nodules, ulcers, vesicular lesions as well as masses have been described (82-85). Endobronchial disease with stenosis due to fibrosing mediastinitis has also been reported (86). Coccidioides immitis usually presents as a pulmonary disease, and endobronchial disease is rare. Two mechanisms of endotracheal and endobronchial disease described by Polesky
include direct invasion of airways and erosion into the airways from lymph nodes, but the latter is less common (87). Endobronchial involvement can be seen as an obstructing mass, sessile nodular lesions, granular lesions, hyperemic patches and as cobblestoned mucosal involvement (87-89). Other fungal infections such Penicillium marneffei and Fusarium can cause endobronchial disease that may appear as whitish endobronchial masses, large whitish cauliflower necrotic lesion, large polypoid lesions, and granulomatous nodules (2,90-93).

**Bronchoscopic findings in bacterial CAOI**

Mycobacterium TB is well known to cause endobronchial diseases. The incidence of EBTB has been reported to be from 4.1% to as high as 20% of TB patients (50,94).

In contrast to EBTB, endobronchial disease caused by non-tuberculous mycobacteria (NTM) is rare. Awareness and early diagnosis using bronchoscopic techniques are important.

Most endobronchial NTM infections have been reported to be caused by MAC and Mycobacterium kansasii. In cases of MAC, the bronchoscopic appearance varies and can present as polypoid lesions (34,95-100), endobronchial masses, multiple nodular lesions (101), ulcerative lesions with bronchial strictures (102,103), caseating endobronchial lesions (104) and as white-yellow irregular mucosal lesions. Mycobacterium kansasii has been reported as endobronchial masses, sessile polypoid lesions, mass with ulcerations and nodular lesions (31,105-109). Actinomycosis has been reported in the central airways and can be associated with foreign body and broncholiths. The endobronchial appearance has been described as white and yellow exophytic masses, large broncholith conglomerates and even circumferential ulcerative lesions (43,48,110,111). Other bacterial infections, such as Nocardia can present with endobronchial disease and may present as obstructing tumor-like masses, polypoid lesions, white friable lesions, white ulcerative lesions and necrotic endobronchial masses (112-116).

Klebsiella rhinoscleromatis has also been reported to cause tracheobronchial disease and were previously described as diffuse polypoid lesions, subglottic tracheal tumor—like mass, or mucosal hypertrophy depending on the stage of granulomatous inflammation (36,37,117,118).

Staphylococcus aureus and epidermidis have rarely been reported to cause isolated central airway obstruction (CAO) (119-121). Corynebacterium central airway infection has rarely been reported. Only three cases of major airway infection caused by Corynebacterium spp. were described in the literature. They presented as mild airway erythema, circumferential ulcerations, pseudomembranous plaque-like lesions, and severe obstruction of the trachea (28,29,122).

**Bronchoscopic findings in viral CAOI**

Cytomegalovirus (CMV) has been reported to cause CAO. Naber et al. reported a case series of three patients with CMV central airway disease. All presented as endobronchial polypoid lesions (40). Imoto et al. reported CMV tracheal disease presenting as an exophytic mass with almost complete obstruction of the distal trachea (123). CMV bronchitis can also be seen as mucosal edema and ulcerations (124). Aventura reported a case of CMV endobronchial infection in a bilateral lung transplant patient presenting as granulation tissue at the site of the left main bronchus stent (39). Herpes simplex virus (HSV) infection localized to the respiratory tract and especially tracheobronchial tree is also not common. Both HSV I and HSV II have been reported to cause central airway disease. It is usually discovered during bronchoscopic examination done for evaluation of respiratory symptoms in immunocompromised patients. In one study by Ben-Izhak, herpetic tracheitis was found in three out of 56 patients who underwent tracheostomy after prolonged intubation (125). Endobronchial findings of central airway disease caused by HSV include fungating and endobronchial masses, polypoid lesions, mucosal irregularities, and ulcerations causing airway stenosis. Necrotic and vesicular blistering lesions have also been identified (60,126-132). The clinical significance of herpetic tracheobronchial disease is unknown as these patients tend to be critically ill with a high overall morbidity and mortality. Similar to HSV, central airway disease caused by varicella zoster virus (VZV) can occur in immunocompromised and in immunocompetent patients and is usually seen with varicella pneumonia. A report of 24 patients with varicella central airway infection by Inokuchi et al. showed a male predominance (19 males and 5 females), and age range of 24 to 60 years. Two patients were immunocompromised and only one patient died (133).

**Bronchoscopic findings in parasitic CAOI**

Parasitic CAOIs are extremely rare, and there are a few isolated case reports. There is a lack of experience with parasitic CAOIs. Findings are usually incidental during bronchoscopy. Zhang et al. described a case of tracheal leech
infection. The patient underwent an evaluation for long-standing dyspnea and hemoptysis. A 5-cm living leech was removed by rigid bronchoscopy. The leech was surrounded by granulation tissue (42). Visceral leishmaniasis with pulmonary involvement and endobronchial disease was described by Kotsifas et al. in immunocompetent patient who presented with a cough and hemoptysis. Bronchoscopy showed mucosal polypoid lesions and biopsy was consistent with leishmania infection (134). A case report of Strongyloides stercoralis causing CAO resulted in death from hemoptysis. Bronchoscopy described yellowish mucosa with multiple nodules with partial obstruction of the airway (135). Lophomonas blattarum is a protozoan that causes infection mainly in immunocompromised hosts (136). Zeng et al. reported a case of Lophomonas blattarum in a patient with chronic obstructive pulmonary disease (COPD) who presented with frequent exacerbations without response to treatment. Lophomonas blattarum was diagnosed by bronchoscopy. Macroscopic diffuse swelling, congestion of bronchial mucosa, and purulent secretions were seen (137). These case reports suggest that bronchoscopy may be a useful diagnostic modality for the treatment of resistant respiratory symptoms when parasitic infection is in the differential diagnosis.

Management

Medical management

The treatment of CAOI depends on bronchoscopic findings, laboratory results, and the disease severity. Central airway infections have a propensity to affect the immunocompromised hosts. Broad-spectrum antibiotic coverage is usually required with antibacterial, and sometimes antifungal or antiviral agents. In addition to establishing a specific diagnosis, bronchoscopic interventions may be indicated to relieve airway obstructive symptoms. Treatment of tracheobronchial fungal diseases with long term antifungals (Amphotericin B and its lipid formulations) is most commonly used in critically ill patients (1). Voriconazole, posaconazole, and itraconazole are used when oral therapy is appropriate for long-term treatment. Fluconazole can be used as maintenance therapy for cryptococcal disease and coccidioidomycosis.

CAOI caused by NTM is usually treated with a macrolide, ethambutol, and rifampicin or rifabutin. Some case reports describe quadruple therapy with the addition of amikacin (100,138,139). Actinomycosis usually responds to penicillin therapy. The most commonly used antibiotics for central airway actinomycosis are intravenous (IV) or oral penicillin, amoxicillin/clavulanic acid, or amoxicillin (43,48,54,140,141).

The treatment of choice for nocardial disease is trimethoprim-sulfamethoxazole (TMP-SMX), but minocycline and imipenem have also been successful (142). HSV and VZV tracheitis and endobronchial diseases have been conventionally treated with acyclovir and valacyclovir (60,127,128,130). Endobronchial CMV infection is usually treated with ganciclovir (39,123,124).

Surgical management

Surgical treatment has been commonly pursued in patients with mucormycosis, actinomycosis, endobronchial aspergillosis, and nocardial infection. Indications for surgical management include failed medical and bronchoscopic treatment, massive hemoptysis or the concern of massive hemoptysis after bronchoscopic intervention due to the angioinvasive nature of some infections, tracheal obstructions due to mass lesions and inability to ventilate the patient (7,75,110,115,129,143-149). In these latter cases, tracheal resection with removal of the mass and tracheostomy placement was necessary (150).

Timely surgical management may be curative and should be considered in patients with delayed or partial response to medical treatment, or in patients with a high risk of life-threatening hemoptysis.

Bronchoscopic management

Therapeutic bronchoscopy for CAOI is not clearly delineated in the literature, and it is mainly found as scattered case reports and series. The airway management of CAOI is essentially similar to cases of malignant airway obstructions and consist of endobronchial debulking, balloon bronchoplasty, endobronchial laser therapy, argon plasma coagulation, cryotherapy and airway stent placement (151-153). Both flexible and rigid bronchoscopies can be used to treat CAOI. Other techniques such as removing endobronchial lesions using the grasping forceps, baskets and snares have been reported.

In Tables 1-3, we present cases of CAOI that were treated bronchoscopically, and we described the types of infection, locations, bronchoscopic findings and reported outcomes of these patients.
Outcomes

The outcomes of patients who have undergone bronchoscopic intervention to treat CAOIs depend on multiple factors. These include the overall condition of patient, severity of symptoms, immune status, specific infection type and location of infection, degree of airway obstruction, and the response to medical treatment. Whether the type of bronchoscopy procedure affects outcome remains to be determined. Most reported deaths were in the immunocompromised patients with aspergillosis. Favorable outcomes were observed in patients with clinical and radiological improvement on follow-up visits, improvement or resolution of bronchoscopic findings during follow-up repeat bronchoscopies, and improvement of obstruction as measured by spirometry. Table 1-3 detail reported outcomes in patients who underwent bronchoscopic intervention for CAOI.

Conclusions

Central airway infections causing obstruction are probably rare. Awareness of their existence and the possibility of bronchoscopic intervention for rapid relief of obstructive symptoms or treatment of persistent airway obstruction are important. This article supports the notion that bronchoscopic intervention for CAOI is feasible and similar to interventions for CAO related to other etiologies such as malignant and benign diseases. The literature lacks data about the safety, effectiveness, and outcomes of CAOI treated by bronchoscopic intervention compared to medical therapy alone or with surgical management. Given the unknown epidemiology of CAOI, conducting prospective studies is challenging, and it is currently reasonable to extrapolate data from managing CAO caused by noninfectious etiology to treat patients with CAOI.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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