CASE REPORT

An unusual presentation of bronchiolitis obliterans in an adolescent

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KEYWORDS
Bronchiolitis obliterans; Mycoplasma; Adenovirus; Lung transplantation

Summary
Bronchiolitis obliterans usually follows severe lower respiratory tract infection and is a rare complication in children. We present a case of an adolescent who presented in an insidious manner following Mycoplasma pneumoniae infection. Further investigations demonstrated co-infection with adenovirus. Attempts at medical treatment made no difference and she was left with severely reduced lung function (FEV1 23% predicted). She is likely to require lung transplantation at some stage, although the timing and risks of transplantation need careful consideration.

Introduction
Bronchiolitis obliterans (BO) is a chronic, obstructive lung disease characterized by small airways obstruction and fixed bronchoconstriction. The pathological features are inflammation and fibrosis of the terminal and respiratory bronchioles that lead to narrowing or complete obliteration of the airway lumen. It is an infrequent, but distinctive reaction of the small airways to infectious, toxic and immunologic insults.

In children, bronchiolitis obliterans occurs most commonly following an acute severe lower respiratory tract infection. Causative organisms include adenovirus,\textsuperscript{1–5} influenza\textsuperscript{6} and rarely mycoplasma.\textsuperscript{2,7–9} The association with mycoplasma is curious as it is one of the commonest causes of community-acquired pneumonia in children, yet long-term pulmonary sequelae are rare.

Bronchiolitis obliterans also occurs following Stevens–Johnson syndrome,\textsuperscript{10} after allogenic bone marrow transplantation as manifestation of graft-versus-host-disease, and after heart–lung or lung transplantation as organ rejection.\textsuperscript{11}

Clinically, patients with bronchiolitis obliterans present with shortness of breath of varying severity. Findings on chest imaging may include a number of abnormalities
including: areas of hyper-aeration, mosaic ground-glass patterns, areas of vascular attenuation, atelectasis and bronchiectasis. Patients demonstrate severe obstructive lung disease on lung function testing with no or minimal bronchodilator response.

We present a case of bronchiolitis obliterans in an adolescent presenting with a relatively insidious course following an initially proven mycoplasma infection but subsequent testing revealed co-infection with adenovirus.

**Case report**

A previously healthy 14-year-old girl presented to her local doctor with fever, dry cough and lethargy for 2 weeks. A chest X-ray showed left lingular and left lower lobe consolidation. She was commenced on a 2-week course of roxithromycin. Her fevers resolved over 1 week, but she had a persistent dry cough and developed shortness of breath and could only walk short distances, leaving her housebound. She was reviewed by her family doctor 4 weeks later at which time a repeat chest X-ray was unchanged. There was no history of asthma, allergies, recurrent infections, toxic exposures or recent travel. Mycoplasma was confirmed on serum enzyme immunoassay testing.

Eight weeks after the onset of symptoms and with no recovery, she was referred to our institution for assessment. She mobilized in a wheelchair due to respiratory limitation. She was obese (BMI 32). She was afebrile with a respiratory rate of 30 breaths per minute and mild increased work of breathing. There was no digital clubbing and she was not hyperinflated. She had reduced air entry in both lungs with diffuse soft wheeze. There was no clinical evidence of pulmonary hypertension. There was no rash or joint discomfort. Oxyhemoglobin saturation in room air was 92%.

At initial assessment her spirometry demonstrated significant obstructive airways disease with marked airway trapping (see Table 1). Exercise oximetry revealed oxyhemoglobin desaturations into the 80s within 2 min of walking. Overnight oximetry demonstrated desaturations into the high 80s when asleep. The patient was started on 0.5 liters/min supplemental oxygen while asleep.

A high resolution, volumetric CT chest demonstrated markedly hyperinflated lungs, bilateral areas of mosaic attenuation, decreased caliber of pulmonary vessels and air trapping. These changes were consistent with bronchiolitis obliterans. There was no bronchiectasis (see Figure 1).

![Figure 1](image1)

**Table 1** Results of baseline spirometry, post-bronchodilator and 4 weeks following treatment with prednisolone and azithromycin.

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Post-bronchodilator (at baseline)</th>
<th>4 weeks later</th>
</tr>
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<tbody>
<tr>
<td>FVC liters/s (% predicted)</td>
<td>1.12 (27%)</td>
<td>1.33 (32%)</td>
<td>2.16 (55%)</td>
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<tr>
<td>FEV₁ liters/s (% predicted)</td>
<td>0.72 (21%)</td>
<td>0.75 (21%)</td>
<td>0.82 (24%)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% liters/s (% predicted)</td>
<td>0.31 (7%)</td>
<td>0.38 (9%)</td>
<td>0.3 (7%)</td>
</tr>
<tr>
<td>TLC liters (% predicted)</td>
<td>7.14 (139%)</td>
<td>7.18 (141%)</td>
<td></td>
</tr>
<tr>
<td>RV liters (% predicted)</td>
<td>4.44 (393%)</td>
<td>4.46 (398%)</td>
<td></td>
</tr>
<tr>
<td>RV/TLC ratio</td>
<td>62%</td>
<td>62%</td>
<td></td>
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*Apparent improvement in FVC is likely to represent better lung function technique given the absence of improvement in lung volumes.*
To exclude an underlying disease process she underwent further investigations that included: sweat chloride, immunoglobulins and IgG subclasses, T-cell subsets and function, antibody responses to pertussis, tetanus and pneumococcal vaccines which were all normal. Adenoviral IgG (titers 1: 5120) was elevated when compared to measurement on her early blood test (adenoviral titers 1: 128) suggesting recent infection to adenovirus. Serology to influenza, respiratory syncytial virus and parainfluenzavirus viruses were not elevated. Cardiac echocardiogram demonstrated a structurally normal heart and no evidence of pulmonary hypertension.

She was treated with a 4-week course of prednisolone (50 mg daily) and azithromycin (500 mg daily). At the end of the treatment, she remained significantly breathless with limitation in her activities of daily living. Repeat spirometry demonstrated no improvement (see Table 1). She was subsequently weaned from prednisolone and azithromycin.

Given her poor quality of life, she was referred for psychological counseling and review by a rehabilitation physician. She has been immunized with influenza and pneumococcal vaccine. The family was keen to pursue discussions about lung transplantation.

Discussion

Bronchiolitis obliterans in children most commonly follows severe lower respiratory tract infections. It is more common in infants (but not those <6 months) and young children.\textsuperscript{5,14,15} The course of patients with bronchiolitis obliterans varies from mild, asthma-like symptoms to rapidly progressive deterioration and death. There are three points to highlight in this case. Firstly, mycoplasma is a rare cause of bronchiolitis obliterans and co-infection with adenovirus should always be suspected. Secondly, the insidious manner of presentation is unusual and therefore subjects with unexplained shortness of breath following respiratory tract infections should be referred to respiratory care as soon as possible. Thirdly, bronchiolitis obliterans following lower respiratory tract infection is not restricted to infants and children, but can also occur to adolescents.

We reviewed the medical literature (Medline 1966–2007) and found scattered case reports of bronchiolitis obliterans following mycoplasma infection.\textsuperscript{7,8} Chan et al. (2000) reported three cases of bronchiolitis obliterans attributed to mycoplasma infection (based on a two-fold increase in paired serological titers), but there was no mention of adenoviral co-infection.\textsuperscript{15} In a larger series of bronchiolitis obliterans by Kim et al. (2001), two subjects were included who had co-infection with both mycoplasma and adenovirus.\textsuperscript{7} We have previously reported a case of bronchiolitis obliterans thought to be caused by respiratory syncytial virus, but re-examination of available serum implicated adenovirus.\textsuperscript{16} Not all adenovirus infections result in bronchiolitis obliterans, but serotypes 3, 7 and 21 are thought to be the principal sub-types.\textsuperscript{3,17,18} While we were not able to serotype the adenovirus in our case, identification of adenovirus facilitated the diagnosis in this unusual presentation.

The other features of our case that were typical of bronchiolitis obliterans were the fixed airways obstruction and the high-resolution CT appearances. This was important to us as it avoided the need for lung biopsy.\textsuperscript{12,13}

The treatment of bronchiolitis obliterans remains unsatisfactory. The use of corticosteroids in the early phase of the illness may be beneficial in modifying the inflammatory cascade.\textsuperscript{2} In our patient, the use of high dose prednisolone for 4 weeks was commenced well beyond the acute phase of the illness and made no clinical or lung function improvement. The use of bronchodilators are common among patients with bronchiolitis obliterans, but of no value in patients with fixed airway obstruction.\textsuperscript{2} The use of macrolides are unproven in this case, despite the literature suggesting some benefit post-lung transplant. Their effect post-transplant may be due to infection with atypical organisms or a non-specific anti-inflammatory effect.\textsuperscript{19} By the time we saw this patient, it is likely any active airway inflammation had evolved to fibrosis.

The development of pediatric lung transplantation has given some children with end-stage lung disease, including bronchiolitis obliterans, an opportunity for improved quality of life and survival. From January 1991 to June 2006, the international registry for heart and lung transplantation lists only 35 children with bronchiolitis obliterans who have been transplanted (3.6% of total pediatric lung transplants).\textsuperscript{20} There are no survival figures individualized to bronchiolitis obliterans. Of some concern, perhaps theoretical, is the risk of bronchiolitis obliterans being more likely to happen in the transplanted lung if the original diagnosis was also bronchiolitis obliterans. The adolescent we presented was keen to explore the possibility of lung transplantation to improve her quality of life. The difficulty we have recommending this treatment is the fact that her pulmonary function may remain the same for many years. It may not be until she reaches 25 years of age, another 10 years, that her lung function starts to decline. While the average yearly decline of FEV\textsubscript{1} from 25 years of age is around 25 ml/year for women, it could be faster in her.\textsuperscript{21} We have recommended weight loss as a way of improving the balance of her metabolic requirement and poor lung function along with a pulmonary rehabilitation program. Advice regarding avoidance of active smoking was given and assistance to quit smoking offered to her mother.

In conclusion, we have presented a case of an adolescent with bronchiolitis obliterans secondary to concurrent mycoplasma and adenovirus infection. This case is unusual because of its insidious presentation and the age group of the patient. We recommend further testing to identify adenovirus in all cases of post-infectious bronchiolitis obliterans. This case highlights the lack of effective interventions for the treatment of bronchiolitis obliterans and the difficult decisions around lung transplantation for this condition.

Conflicts of Interest

Dr. Andrew Tai and has A/Prof John Massie has no conflicts of interest with relation to this work.

References


