Difficult asthma:
Consider all of the possibilities

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Most patients with asthma are easily diagnosed and respond to standard therapy that includes short acting inhaled beta 2-agonists as needed for symptom control and maintenance treatment with inhaled corticosteroids. However, approximately 5% of patients do not respond to this treatment approach and, thus, require additional investigation to determine the reason for this failure. Difficult asthma is often defined as a failure to achieve control with the maximum recommended doses of inhaled therapy (1). Several factors may contribute to a poor response to standard therapy, and it is important to consider these in a systematic fashion to identify those that are relevant to the particular patient. Questions that should be addressed under these circumstances include: does the patient definitely have asthma or is there alternative pathology masquerading as asthma; are medications being delivered to the lungs at appropriate doses (including issues...
of proper use of delivery devices and compliance); are there unidentified exacerbating triggers in the environment; are there potential aggravating factors or comorbidities (eg, smoking, chronic obstructive pulmonary disease, cardiac disease); and has the patient followed a strict treatment plan for six months or more? (1,2). This paper presents and discusses a case referred for control of difficult asthma to illustrate the importance of this systematic approach to a patient with ostensible asthma.

**CASE PRESENTATION**

A 35-year-old female presented with a history of cough, wheezing and dyspnea of four years’ duration. She was born in Sri Lanka, grew up in England and immigrated to Canada at age 35 years. She had no history of respiratory problems, including asthma, as a child. She did have a history of eczema as a child that resolved spontaneously. She had a seven pack-year smoking history but had stopped smoking five years previously. Four years before her first visit to the Asthma Centre at the Toronto Western Hospital, she developed intermittent episodes of dyspnea, wheezing and cough after an upper respiratory tract infection. She was evaluated by her family physician, and a presumptive diagnosis of asthma was made, but no spirometry was obtained. Treatment with an inhaled beta2-agonist was instituted, giving partial relief of her symptoms. Two years before her visit, she was evaluated by an ear, nose and throat surgeon because of postnasal drip and sinusitis. No polyps were seen on rhinoscopic examination, and the patient underwent septal rhinoplasty. The episodes of dyspnea become more frequent and of longer duration. In the year preceding her evaluation, the dyspnea and wheezing became continuous. Treatment with high dose, inhaled corticosteroids (fluticasone 1000 mcg/day), zafirlukast, theophylline and salmeterol did not improve her symptoms. Throughout the preceding year, she made multiple visits to the emergency department, some with subsequent hospitalization. During this time, she was assessed by several specialists including respirologists. Spirometry demonstrated mixed defect, with a combination of reduced vital capacity and mild airflow limitation with improvement after bronchodilator (Table 1). She was given several courses of oral corticosteroids (50 mg prednisone/day for two to three weeks) with a minimal improvement in symptoms. Two months before her initial evaluation, she was admitted to a community hospital for an asthma exacerbation, and received treatment with intravenous methylprednisolone and antibiotics but did not resolve her symptoms. At this time, she was referred to the Asthma Centre at the Toronto Western Hospital for the further evaluation of asthma that was considered to be difficult to control.

Physical examination revealed a woman in no respiratory distress. Abnormal findings included inspiratory and expiratory wheezes that were heard diffusely but were loudest over the central airways.

The initial differential diagnoses included steroid-resistant asthma, allergic bronchopulmonary aspergillosis, vocal cord

### TABLE 1

<table>
<thead>
<tr>
<th>Pulmonary function test</th>
<th>September 1997</th>
<th></th>
<th>Post BD (L)</th>
<th>August 1998</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre BD (L)</td>
<td>% predicted</td>
<td>Post BD (L)</td>
<td>Pre BD (L)</td>
<td>% predicted</td>
</tr>
<tr>
<td>Forced vital capacity (FVC)</td>
<td>2.16</td>
<td>62</td>
<td>2.54</td>
<td>2.25</td>
<td>65</td>
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<tr>
<td>Forced expiratory volume in 1 s (FEV1)</td>
<td>1.64</td>
<td>55</td>
<td>1.91</td>
<td>1.61</td>
<td>54</td>
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<tr>
<td>FEV1/FVC (%)</td>
<td>76</td>
<td>89</td>
<td>76</td>
<td>83</td>
<td>102</td>
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<tr>
<td>FEF50</td>
<td>2.44</td>
<td>70</td>
<td>2.29</td>
<td>2.03</td>
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<tr>
<td>Total lung capacity (TLC)</td>
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<tr>
<td>Functional residual capacity of lungs</td>
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<td>1.88</td>
<td>70</td>
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<tr>
<td>Respiratory volume (RV)</td>
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<td></td>
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<tr>
<td>RV/TLC (%)</td>
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<td></td>
<td></td>
<td>49</td>
<td>166</td>
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<tr>
<td>Carbon monoxide diffusing capacity of the lungs</td>
<td>18.44</td>
<td>97</td>
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<td></td>
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</tr>
</tbody>
</table>

*FEF50 Forced expiratory flow after 50% of vital capacity has been expelled*
dysfunction, subglottic stenosis and other types of large airway obstruction, such as a foreign body or tumour in the central airways. Pulmonary function testing demonstrated a reduced vital capacity with evidence of gas trapping. There was no improvement after bronchodilator administration (Table 1). A flow volume loop demonstrated no evidence of extrathoracic obstruction (Figure 1). During subsequent visits, additional diagnostic studies were performed. Methacholine testing was negative but inspiratory stridor was noted during the test. There was no blood or sputum eosinophilia. Direct laryngoscopy demonstrated no evidence of vocal cord dysfunction or subglottic stenosis. A chest x-ray (Figure 2) revealed a filling defect in the right main stem bronchus extending into the proximal trachea. A computed tomography scan demonstrated the presence of an intrabronchial mass (Figure 3). During evaluation she developed acute dyspnea, and physical examination demonstrated tracheal deviation to the right, markedly diminished movement of the right hemithorax and diminished breath sounds on that side compatible with atelectasis of the right lung. Ventilation perfusion lung scanning revealed markedly diminished ventilation and perfusion to the right hemithorax. Urgent rigid bronchoscopy demonstrated a tumour completely occluding the right main stem bronchus extending into the proximal trachea.

The working diagnosis was a bronchial tumour, most likely a carcinoid. The patient underwent a right pneumonectomy with a sleeve resection of the trachea. The final pathological diagnosis was mucoepidermoid carcinoma of intermediate grade with spread to one of three interlobar lymph nodes (Figure 4). The final staging was as follows: T3 (tumour diameter greater than 5 cm), N1 (ipsilateral node involvement), M0 (no evident metastases). The patient improved dramatically after the surgery and has remained disease free at year one of follow-up.

**DISCUSSION**

This woman had evidence of reversible airflow limitation consistent with asthma early in the course of her disease. However, the primary basis for her refractory symptoms was not difficult asthma but rather an endobronchial tumour obstructing a major airway. This case illustrates the importance of a comprehensive approach to the evaluation of such patients. The evaluation at our centre yielded observations that...
were inconsistent with a diagnosis of ‘difficult’ asthma. First, physical examination demonstrated both inspiratory and expiratory wheezes that were loudest over the central airways. Second, pulmonary function testing revealed a reduced vital capacity and gas trapping without evidence of significant reversible airflow limitation. In retrospect, the gas trapping was likely due to a check valve effect of the endobronchial tumour, with complete occlusion on expiration. Finally, the lack of blood and sputum eosinophilia were atypical of asthma (3,4), although a lack of sputum eosinophilia in asthmatics may predict a lack of benefit to corticosteroids (5).

It is important to consider alternative diagnoses when assessing patients labelled as having ‘difficult to manage asthma’. Chronic obstructive pulmonary disease may present with certain features of asthma, and there is often substantial overlap between these conditions. Against this diagnosis were the patient’s age, her minimal smoking history and the restrictive pattern on pulmonary function testing. Another possibility is vocal cord dysfunction; patients with this syndrome exhibit episodic wheezing and dyspnea as a result of paradoxical laryngeal adduction during both inspiration and expiration. This upper airway phenomenon can mimic classical asthma, and may result in multiple emergency department visits, hospitalizations and even intubations. It is often associated with multiple diseases or psychological disturbances, and the diagnosis is notoriously difficult to confirm (6). Individuals with vocal cord dysfunction often have an inability to perform spirometric tests reproducibly, which suggests a problem of upper airway closure (2). The gold standard for diagnosis is laryngoscopy during an acute episode, either spontaneous or induced, demonstrating inappropriate vocal cord motion with adduction of the vocal cords on inspiration or expiration with a small anterior ‘chink’ remaining for airflow.

With respect to this patient, data suggestive of the diagnosis of vocal cord dysfunction included the referring diagnosis of difficult to treat asthma, multiple emergency department visits and hospitalizations, wheezing and dyspnea unresponsive to bronchodilators and steroids, and wheezing on inspiration (stridor) and expiration heard loudest over the central airways. However, direct laryngoscopic examination did not support this diagnosis.

Upper airway obstruction due to diverse causes can present with features that mimic certain aspects of asthma (Table 2). Many of these obstructions are potentially life threatening but eminently treatable if recognized early. Neoplasms of the upper airway, while less common, are clearly an important consideration in patients with features atypical of asthma. Bronchogenic or metastatic (eg, breast, renal cell carcinoma, melanoma) carcinomas are the most frequent. Carcinoid tumours, although less common, tend to be less aggressive and are often amenable to complete resection.

Mucoepidermoid carcinoma of the tracheobronchial tree, a rare tumour comprising only 0.1% to 0.2% of primary lung malignancies, is thought to originate from the minor salivary glands lining the tracheobronchial tree (7-12). Prominent symptoms experienced by these patients include cough, hemoptysis, wheezing, dyspnea and chest pain (7,13,14). However, patients may also be asymptomatic (13,14). Possible radiographic abnormalities include a solitary nodule or mass, with or without findings of postobstructive pneumonia or atelectasis (7,12,14). The tumour usually appears as a sharply margined or lobulated airway mass on computed tomography scans (14), although it may adapt to the branching features of the airways. Treatment primarily involves surgical resection, if possible, and, occasionally, chemotherapy and/or radiation (7-9,15).

CONCLUSIONS

Although this case presented with some clinical features suggestive of asthma, several features on physical examination and laboratory testing were not consistent with this diagnosis. When patients do not respond to conventional therapy, it is important to keep an open mind and consider all the possibilities to avoid misdiagnosis and delays in appropriate treatment.

REFERENCES