A 24-year-old woman presented to an emergency department with a 1-week history of increasing shortness of breath accompanied with productive cough and wheezing. These symptoms were preceded by those of an upper respiratory tract infection. She had been admitted to hospital recently for a similar presentation and had been discharged home with a diagnosis of asthma and prescribed bronchodilators, an inhaled corticosteroid, supplemental oxygen and a tapering dose of prednisone.

The patient was a current smoker with a 10 pack-year history of smoking. Her medical history included hepatitis C, inhaled cocaine abuse, which she quit a year ago, a mood disorder and a learning disability. She had no history of atopy, sinus disease or gastroesophageal reflux and no family history of asthma. She lived independently with assistance from a local program for people with disabilities.

Over the previous year, she had visited her family physician, walk-in clinics and emergency departments multiple times because of episodes of dyspnea and wheezing, which were becoming more frequent. Her Medical Research Council dyspnea score ranged from 2/5 on good days to 4/5 on bad days. Her list of medications included a combined inhaled corticosteroid and long-acting β-agonist, salbutamol, ipratropium bromide, dextroamphetamine sulfate, risperidone, sertraline hydrochloride, and vitamin D and calcium supplements.

In the emergency department, the patient required 7 L of supplemental oxygen by face mask. Decreased air entry and wheezes were heard bilaterally on auscultation of her lungs. No signs of congestive heart failure were noted; however, a loud pulmonic second sound (P₂) was heard on auscultation. The patient had an elevated body mass index of 33. Arterial blood gas levels on the supplemental oxygen were consistent with mixed respiratory failure: partial pressure of arterial oxygen 75 mm Hg, and partial pressure of arterial carbon dioxide 51 mm Hg. A chest radiograph showed minor atelectasis in the mid–lower zone of the left lung, with no signs of hyperinflation or consolidation. A working diagnosis of difficult-to-treat asthma was made, and treatment with bronchodilators and systemic steroid and antibiotic therapy was started.

On review of the patient’s previous investigations, we noted that when she was relatively well, results of pulmonary function testing showed severe fixed airflow obstruction with air trapping (a ratio of forced expiratory volume in the first second of expiration to forced vital capacity [FEV₁/FVC] of 0.54 and an FEV₁ of 1.50 L [43% predicted], with no substantial change after bronchodilator use). The pattern of the flow-volume loop did not support the diagnosis of extrathoracic, upper airway causes of obstruction. Methacholine challenge had not been done because of severely reduced FEV₁, and the test’s poor specificity in differentiating causes of obstruction. An echocardiogram showed an elevated right ventricular systolic pressure of 40 mm Hg (normal 15–30 mm Hg). High-resolution computed tomography (CT) scans showed a few areas of triangular subpleural opacities, linear atelectasis, mild septal thickening and evidence of small airways disease.

What other diagnosis or diagnoses should be considered?

a. Cystic fibrosis
b. Alpha₁-antitrypsin deficiency
c. Allergic bronchopulmonary aspergillosis
d. Nonadherence to therapy
e. All of the above

Given the patient’s difficult-to-control disease and low diffusion capacity, we entertained other causes of airways obstruction besides severe asthma (e). Workup for allergic bronchopulmonary aspergillosis, cystic fibrosis and α₁-antitrypsin deficiency ruled out these diagnoses. We also ruled out silent aspiration of food and liquid. As for the possibility...
of nonadherence to therapy, the patient’s support worker assured us that the patient had been taking her medications, and her inhaler technique was observed to be adequate.

What additional information will be helpful to establish the diagnosis?

a. Bronchoscopy  
b. Obtain a detailed birth and neonatal history  
c. Lung biopsy  
d. Repeat pulmonary function testing  
e. Have the patient keep a symptom diary

A birth and neonatal history will help to determine the diagnosis (b). No such history had been obtained during our patient’s previous investigations. Her support worker did not have this information. We contacted the patient’s mother, who informed us that the patient had had a complicated neonatal period requiring a prolonged hospital stay. We reviewed the patient’s neonatal medical records, which indicated that she was born at 23 weeks’ gestation and her birth weight was 0.53 kg. She required mechanical ventilation for 2 months and further oxygen therapy for 5 months. Her stay was complicated, with multiple episodes of pneumonia; no pneumothorax was noted in her history. She had feeding difficulties and needed to be fed through a nasogastric tube for a prolonged period. She also had patent ductus arteriosus that was ligated. There was no history of oligohydramnios. The patient was then lost to follow-up until recently, when she started seeking medical help because of shortness of breath and recurrent “asthma” exacerbations.

With this additional birth and neonatal history, we diagnosed bronchopulmonary dysplasia (BPD). Over the course of a week in hospital, the patient’s condition improved and she was discharged. She is taking an inhaled corticosteroid and long-acting β-agonist, with short-acting bronchodilators as rescue medication. She has stopped smoking and was advised to lose weight. She will not likely be a good candidate for lung transplant because of her developmental disability and poor social support.

Discussion

Although most patients with obstructive airways disease have asthma or chronic obstructive pulmonary disease (COPD), less common pulmonary conditions can present in a similar manner1,2 (Box 13,4). Uncommon features such as atypical disease progression or a poor response to standard treatment should encourage clinicians to seek other causes of airflow limitation by taking a thorough history and requesting other tests as indicated. A diagnosis of difficult-to-treat asthma should be considered, and factors such as medication adherence, inhaler technique, exposure to allergens, smoking status and comorbidities such as sinusitis and gastroesophageal reflux should be explored. If the more common diagnoses of asthma and COPD are ruled out, rarer causes of obstruction should be considered.12

Obtaining a complete birth and neonatal history should be standard practice in all cases of obstructive lung disease. In the case we have described, such a history proved be a vital part of our investigations and helped with the diagnosis.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD), a chronic lung disease affecting premature neonates, is defined as continued dependence on supplemental oxygen for more than 28 days after birth.3 It is mainly seen in neonates born before 30 weeks’ gestation with a birth weight of less than 1500 g.

The disease is classified as mild, moderate or severe depending on the duration and amount of

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**Box 1: Causes of obstructive airways disease**

**Upper airway**
- Vocal cord dysfunction
- Trauma (e.g., subglottic stenosis after intubation)
- Infection (e.g., tuberculosis, papillomatosis)
- Inflammatory and autoimmune diseases (e.g., granulomatosis with polyangiitis, sarcoidosis, rheumatoid arthritis)
- Upper airway tumour
- Congenital malformation (e.g., tracheal stenosis, complete tracheal rings)
- External compression (e.g., thyroid, vascular structures, lymph nodes)
- Idiopathic

**Lower airway**
- Common causes
  - Chronic obstructive pulmonary disease
  - Asthma
  - Bronchiectasis (including cystic fibrosis)
  - Endobronchial tumour
  - Foreign-body aspiration
- Rare causes
  - Bronchiolitis (e.g., viral infection, inhalation of toxic fumes)
  - Endobronchial granulomatous infection and inflammation (e.g., tuberculosis, sarcoidosis)
  - Bronchomalacia
  - Bronchiolitis obliterans
  - Diffuse panbronchiolitis
  - Bronchopulmonary dysplasia
  - Congenital malformation (e.g., congenital bronchomalacia)
  - External compression (e.g., vascular structures, lymph nodes)
oxygen required near term. It is also classified as
old or new depending on the use of surfactant
treatment and the timing and extent of lung
injury due to mechanical ventilation. Detailed
diagnostic criteria and severity grades of this
condition have been developed.2

About 60 000 premature infants are born
annually in the United States, 20% of whom will
have BPD.3 The epidemiologic features among
adults with the disease are less clear. Up to 25%–
71% of those with BPD who survive into adult-
hood will continue to have respiratory symptoms
at that time.3

Pathogenesis
Old BPD occurs in slightly premature neonates not
given surfactant who are exposed to aggressive
mechanical ventilation and supplemental oxygen
treatment. This management leads to intense
inflammation and massive parenchymal disruption
in surfactant-deficient lungs. The incidence of old
BPD has declined substantially because of ad-

ances in ventilation modalities and use of steroids
that affects very premature neonates given sur-
factant. The underdeveloped lungs of these
neonates are exposed to various insults, which
leads to impaired alveolization and vasculariza-
tion. The result is simplification of lung architec-
ture, with fewer and larger alveoli. Airways are
relatively spared, and inflammation is milder
than in the old form of the disease.6

In contrast, new BPD, considered a develop-
mental disorder, is a milder form of the disease
that affects very premature neonates given sur-
factant. The underdeveloped lungs of these
neonates are exposed to various insults, which
leads to impaired alveolization and vasculariza-
tion. The result is simplification of lung architec-
ture, with fewer and larger alveoli. Airways are
relatively spared, and inflammation is milder
than in the old form of the disease.6

Recently, genetic research in BPD suggested
that abnormalities in the genes involved in angio-
genesis, inflammation and immune factors such
as surfactant, tumour necrosis factor α and anti-
oxidants may play a role in predisposing patients
to BPD.8

The effects of prolonged intubation and oxy-
gen therapy are not only limited to the small air-
ways and alveolar space but can also cause
trauma to the upper and central airways. The
trauma may be the result of intubation or fre-
frequent suctioning. This can lead to tracheo-
bronchomalacia, which can further worsen the
obstructive physiology of BPD.

Sequelea in adulthood
Although BPD during infancy has been studied
extensively, only a few studies have looked at the
long-term sequelae of BPD. It is clear, however,
that adults with BPD have an increased incidence
of respiratory symptoms, including cough, wheez-
ing and asthma. Northway and colleagues9 studied
pulmonary outcomes in 26 young adults with
BPD and found that 25% of the patients had re-
current respiratory difficulties, including wheez-
ing, episodes of pneumonia and limited exercise
capacity.

Lung function
Results of pulmonary function testing of patients
with BPD will show persistent airway obstruc-
tion, airway hyperresponsiveness and hyperinfla-
tion of the lungs.9–11 In a study of the effect of
preterm birth on pulmonary function at age
7 years, preterm children with BPD had signifi-
cantly reduced FVC and FEV1, compared with
healthy children who were born at term.11 These
abnormalities may persist into adulthood.9 Not
only is lung function worse in patients with
BPD, but the rate of decline is faster than nor-
mal. In a study involving 147 people who had a
birth weight of less than 1500 g and who under-
went pulmonary function testing at a mean age
of 18.9 years, those who had BPD in the neonat-
al period had clinically significant reductions in
airflow and deterioration in pulmonary function
since the previous evaluation at 8 years of age.13
Birth weight13 and results of pulmonary function
testing at 2 years of age14 appear to be reasonable
predictors of long-term pulmonary outcome,
with low birth weight and abnormal test results
indicating a poorer prognosis.

Contrary to the above-mentioned findings of
abnormal lung function persisting into adulthood
in people with BPD, Narang and colleagues15
have proposed that lung function can be regained
over time in patients with BPD. However, they
acknowledged that limitations in the study may
have contributed to this finding.15

Pulmonary hypertension
Another feature of BPD is the development of
pulmonary hypertension.16 Pulmonary hyperten-
sion develops early during infancy and is a pre-
dictor of poor survival. Bronchopulmonary dys-
plasia results in a reduced pulmonary capillary
bed and increased vascular tone, which leads to
increased pulmonary arterial pressures. Small
airways obstruction may also contribute to pul-
monary hypertension in these patients. Those
with BPD and pulmonary hypertension who sur-
vive infancy usually show improvement in pul-
monary pressures over time.16

Radiographic findings
Persistent radiographic changes are observed in
patients with BPD.15 In adults, the most common
findings on high-resolution CT scans include lin-
ear and triangular subpleural opacities, emphy-
sema and thickening of the bronchial wall.11
Other findings include mosaic perfusion and air
trapping. These findings can exist even in the

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absence of overt clinical symptoms. The duration of oxygen therapy during infancy seems to be an important predictor of structural abnormalities on high-resolution CT scans seen later in life.\textsuperscript{11}

**Nonpulmonary changes**

There are nonpulmonary long-term consequences of BPD, especially in the areas of cognitive and motor development. A recent systematic review identified 2 studies that reported developmental delay and learning difficulties in adults with BPD compared with those born prematurely without BPD.\textsuperscript{17} Although not seen consistently, anthropometric data from patients with BPD implies growth failure in adulthood.\textsuperscript{17}

**Association with asthma**

The underlying pathophysiology of asthma differs from that of BPD. However, these conditions may present in a similar manner clinically. In the study by Northway and colleagues,\textsuperscript{9} symptoms, signs and findings on pulmonary function testing similar to those of asthma were reported in up to 50% of the participants with a history of BPD in infancy. The incidence of airway hyperreactivity is higher among children with a history of BPD than among those without such a history.\textsuperscript{9} Several other studies have noted an increased history of asthma among young adults with BPD, but the reported rates have varied.\textsuperscript{7} Lack of standardization of the diagnostic criteria for asthma in these studies could explain the observed variation. It has also been suggested that, because of a substantial overlap between asthma and BPD symptoms, some children are imprecisely labelled as having asthma.\textsuperscript{6,14}

**Diagnosis**

Because BPD shares symptoms with other obstructive airways diseases, it can be clinically challenging to diagnose it. Furthermore, as with other childhood-onset diseases, BPD may be forgotten and not included in the differential diagnosis of obstructive airways disease in an adult patient. Several clues, however, should raise suspicion of BPD. The most important is the birth and neonatal history. A history of low birth weight, prematurity, prolonged use of supplemental oxygen and the need for mechanical ventilation upon birth supports the inclusion of BPD in the differential diagnosis. Other clues include unusual severity of the obstructive airways disease for the patient’s age and a lack of smoking history. Although commonly associated with asthma, the prevalence of atopy or a family history of asthma was not increased among children with BPD compared with controls in the study by Northway and colleagues.\textsuperscript{9}

On investigation, the airflow limitation in BPD may be only partially reversible after use of a bronchodilator.\textsuperscript{13} There are also differences between findings of asthma and BPD on high-resolution CT scans. Scattered parenchymal fibrosis and distortion of the lung architecture, common findings in BPD, are rarely seen in asthma. The role of sputum analysis is established in asthma, but its role in BPD is unclear. In a study involving 31 children with BPD, the levels of exhaled nitric oxide, a marker of eosinophilic inflammation, were significantly lower in those with BPD than in age-matched children with asthma.\textsuperscript{19} In complex cases with added elements of cigarette smoking and drug abuse, such as the case with our patient, it is particularly challenging to diagnose BPD.

**Treatment**

Although there has been much interest in the treatment of BPD in premature neonates around the time of birth, the optimal therapy in adults with BPD is not known. Bronchopulmonary dysplasia is considered to be a developmental disorder, and our current understanding of its pathophysiology does not support the use of systemic corticosteroid therapy. In the absence of evidence-based studies, such treatment may be harmful. Because there are no forthcoming guidelines for the management of BPD in adults, we suggest that long-term steroid therapy be avoided and the cause of acute exacerbations be investigated and treated accordingly. Furthermore, the role of inhaled corticosteroid therapy is unclear. In a study involving 15 children of low birth weight, regular use of inhaled corticosteroids did not alleviate symptoms or improve lung function.\textsuperscript{20}

The use of intravenous immunoglobulin has been reported to be of benefit in infants with recurrent infection; again, there are no data to support this treatment in adults.\textsuperscript{21} Bronchopulmonary dysplasia is an indication for lung transplant in infants, and there is a case report of lung transplant in a 19-year-old patient with BPD.\textsuperscript{22} With improvements in the understanding of mechanisms of lung repair and inflammation in BPD, new treatment strategies are being explored. Enzyme, gene, cytokine, antioxidant and antiprotease therapies as well as stem cell treatment are being developed in animal models of lung injury.\textsuperscript{10}

Every effort should be made to minimize further insult to the lungs. These include smoking
cessation and regular vaccinations. In our pa-
tient, we believe that the cause of her frequent
exacerbations was cigarette smoking. The patient
was duly counselled and has quit smoking.

Although it might appear that there is no ther-
apeutic advantage to diagnosing BPD, it is never-
thelss important to patient care. Making the right
diagnosis will not only discourage physicians
from pursuing more aggressive investigations, it
may also minimize potential adverse effects of
treatments such as long-term systemic steroid
therapy that may have little added clinical benefit.

Conclusion

With advances in the care of premature neonates,
more children with BPD will reach adulthood and
will present with symptoms shared by more com-
on obstructive airways diseases such as asthma
and COPD. The case we have described high-
lights the importance of taking a thorough med-
ical history, including a birth and neonatal history.
Furthermore, it also illustrates that childhood-
set diseases can have sequelae in adulthood and
should be included in the differential diagnosis in
adults presenting with chronic dyspnea.

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