# A rare cause of breathlessness

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Muriel is 51 years old and presents complaining of breathlessness that has been gradually getting worse over a number of years. She thought it was due to 'age' but has now sought help because her activities are becoming more and more limited. She is able to walk 50-100 metres slowly before becoming breathless but is breathless more quickly if she hurries or walks up stairs or inclines. She denies cough, sputum production, chest pain and chest tightness. She has been generally well throughout her life except for an episode of pneumonia 20 years ago.

Muriel takes no regular medication and has never smoked cigarettes. There is no family history of asthma but she remembers her father, who smoked 'a packet a day' had emphysema. She does not remember any other family member as suffering from chest disease. Muriel worked as a clerk in her early 20s but later raised a family at home.

Clinical examination reveals a fit looking woman in no obvious distress at rest. Her blood pressure is 140/85, heart rate 87/min regular, the trachea midline and the jugular venous pressure is not raised. Cardiovascular examination is normal and there is no ankle oedema. Examination of the respiratory system shows she is neither clubbed nor cyanosed and the chest is over inflated but otherwise symmetrical. Chest expansion is reduced, percussion note is increased and auscultation reveals normal vesicular breath sounds but of markedly reduced amplitude.

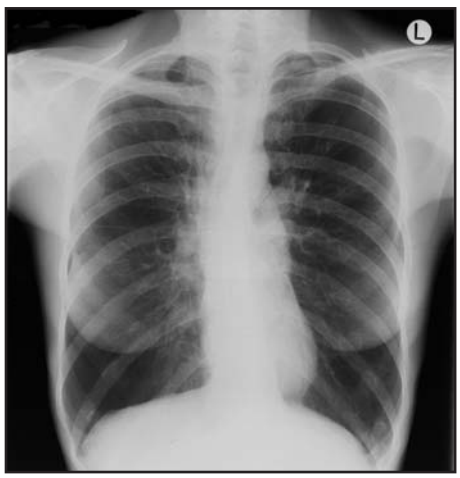


**Figure 1. Chest X-ray**

**Question 1**
What diagnoses would you consider?

**Question 2**
What tests would you perform?

**Question 3**
What do these tests show?

**Question 4**
Is the diagnosis consistent with the test results?

**Question 5**
How would you confirm the diagnosis?

**Question 6**
What do the results show?

**Question 7**
What is the natural history of this condition?

**Question 8**
What advice would you give Muriel?

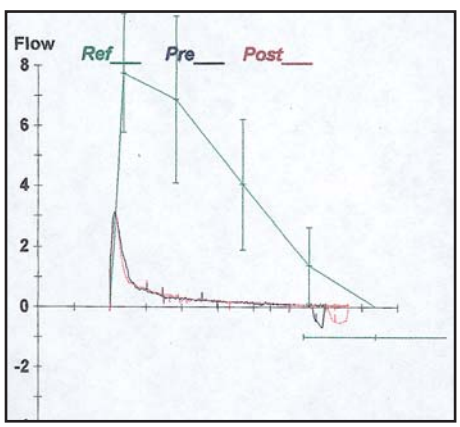


**Figure 2. Lung function tests**

## Answers

**Answer 1**

Clinical examination suggests Muriel is suffering from chronic airflow obstruction (COPD), predominantly emphysema as there is no history of cough and sputum production and no wheezing on examination. Asthma should also be considered.

**Answer 2**

Muriel should have a chest X-ray and respiratory function tests (spirometry and diffusing capacity).

**Answer 3**

The chest X-ray (Figure 1) shows over inflation of the lung fields with flattening of the diaphragms and hyperlucency of the lung fields more prominent at the basal regions. The lung function tests show severe airflow obstruction and a marked reduction in diffusing capacity (Table 1, Figure 2). There is no significant change following inhaled bronchodilator thus making a diagnosis of asthma very unlikely. These results are consistent with severe emphysema.

**Answer 4**

The finding of severe emphysema in a person who has never smoked should prompt the consideration of other causes of COPD. Alpha-1-antitrypsin deficiency and exposure to industrial dusts and fumes should be considered. As Muriel has not had any exposure to the latter a diagnosis of alpha-1-antitrypsin deficiency should be considered.

**Answer 5**

Serum alpha-1-antitrypsin concentration and phenotype should be ordered (Table 1).

**Answer 6**

The results show severe alpha-1-antitrypsin deficiency with a PiZZ phenotype. Thus Muriel has emphysema due to alpha-1-antitrypsin deficiency.

**Answer 7**

Alpha-1-antitrypsin is a protein involved in the protection of the lung against the action of proteinases that cause lung destruction and thus emphysema. Deficiency of alpha-1-antitrypsin may occur as a hereditary process (autosomal codominant inheritance) or be acquired by cigarette smoking. In the latter situation substances contained in cigarette smoke cause inactivation of the alpha-1-antitrypsin molecule by oxidation.

Available overseas data indicates that homozygous PiZZ alpha-1-antitrypsin deficiency (the Z allele imparts severe deficiency) occurs once in every 2500 live births. However, clinical experience suggests this condition is far less common. There is good evidence that only approximately 10-15% of alpha-1-antitrypsin deficient patients develop significant emphysema. This is likely to be due to variable expression of the condition and also it is postulated that some of these patients are protected by other antiproteinases such as secretory leukocyte proteinase inhibitor. It is also recognised that approximately 20% of cigarette smokers develop emphysema. Hereditary alpha-1-antitrypsin deficiency characteristically leads to the early development of emphysema often at quite a young age but usually the condition is detected after patients reach the age of 40 years. However, there appears to be a varying degree of expression of the condition, as some patients do not present until later in life. Cigarette smoking results in a more rapid progression in the development of emphysema of these individuals. Thus patients with this condition must be advised and exhorted not to smoke cigarettes.

**Table 1. Lung function test results**

| Test | Result | | |
|---|---|---|---|
| Chest X-ray (Figure 1) | The chest is over inflated with flattening of the diaphragm and hyperlucency of the lung fields more prominent in basal regions | | |
| Lung function tests (Figure 2) | Flow volume loop | | |
| | | Before bronchodilator | After bronchodilator | Predicted |
| | $FEV_{1.0}$ | 0.73 litres | 0.74 litres | 2.89 litres |
| | Vital capacity | 2.99 litres | 3.32 litres | 3.69 litres |
| | $FEV_1/VC$ | 24 % | 22 % | |
| | Diffusing capacity | 6.7 mL/min/mmHg (25% predicted) | | |
| Serum alpha-1-antitrypsin | 0.33 gm/L | (Normal range: 1.1–2.2 gm/L) | | |
| Phenotype | PiZZ | (Normal phenotype: PiMM) | | |

**Answer 8**

There is no known effective treatment for alpha-1-antitrypsin deficiency. Trials of alpha-1-antitrypsin replacement therapy have shown some promising results but a definitive answer to the question of their efficacy is still awaited. All patients with this condition should be advised not to smoke cigarettes, to actively avoid conditions which may potentially cause lung injury such as working in polluted environments (mines, fumes, dusts) and to seek treatment for respiratory tract infections early. Vaccination for influenza and pneumococcal infection is also advised. As in any patient with emphysema and COPD a trial of steroid and bronchodilator treatment is sensible but should be discontinued if unhelpful. In advanced cases continuous oxygen therapy or lung transplantation should be considered. It is also recommended that family members be screened for alpha-1-antitrypsin status in order to identify deficient individuals so they may be counselled about maintaining good lung health and avoiding smoking.

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