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Curable hypoxia in an octogenarian with an undiagnosed inherited condition

Case Report

Case history

An 84-year-old gentleman was referred to the chest clinic with low oxygen saturations on pulse oximetry. He reported breathlessness and wheeze since his retirement as a surveyor 16 years previously. His exercise tolerance was 350 m. He had pre-existing diagnoses of chronic obstructive pulmonary disease and hypertension. He had no avian or occupational exposures, a minimal smoking history while in his teens and had not smoked since, and no history of transient ischaemic attack or cerebrovascular accident.

On examination, he was comfortable with no respiratory distress but had slight peripheral cyanosis and oxygen saturations of 89% on room air. Auscultation of his chest revealed increased vocal fremitus and crackles over the right lower lobe with occasional wheeze.

The patient was investigated using lung function testing, capillary blood gas sampling, a chest radiograph and thoracic computed tomography (CT). His haemoglobin at presentation was 16.1 $g \cdot dL^{-1}$.

Investigations

Lung function

The results of the lung function investigations performed as shown in table 1. Supine and erect spirometry demonstrated oxygen saturations of 93% when lying down and 86% on sitting. There was no significant reversibility to 2.5 mg nebulised salbutamol.

A capillary blood gas taken on air at rest showed an oxygen tension (PO_2) of 8.0 kPa (normal 12.0–15.0 kPa), a carbon dioxide tension (PCO_2) of 4.4 kPa (normal 4.5–6.1 kPa) and pH of 7.44 (normal 7.36–7.42).

CT

CT images are shown in figure 1.

Statement of Interest
None declared.

HERMES syllabus link: module B.5.5, B.15.4, C.1.1, C.1.2, D.2.22, D.3.1

Table 1. *Lung function*

Parameter	Measured	Predicted	% predicted	SR
FEV_1 L	1.64	3.30	50	-3.27
FVC L	4.11	4.47	92	-0.60
FEV_1/FVC %	40	72	55	-4.55
***T*LCO**	5.42	9.67	56	-3.01
***K*CO**	0.91	1.19	76	
RV L	3.94	3.06	129	2.15

SR: standard residual (normal±1.64); FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; *T*LCO: transfer factor of the lung for carbon monoxide; *K*CO: transfer coefficient for carbon monoxide; RV: residual volume.

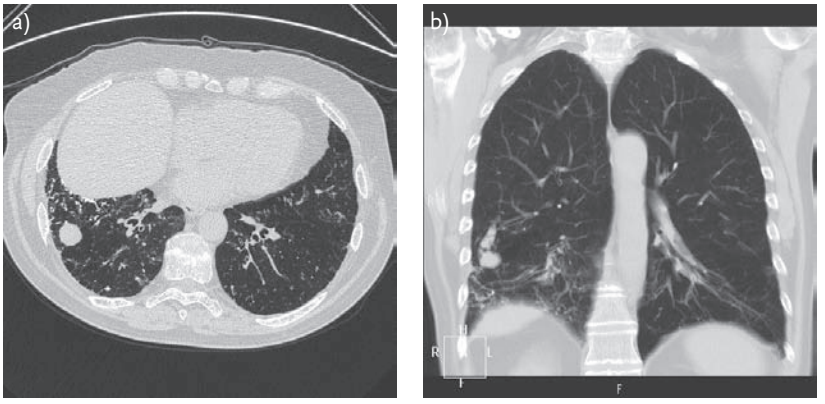

Figure 1
a) Axial and b) coronal CT slice.

Task 1

1) What is seen on the initial CT scan (fig. 1).
2) What conditions can be associated with this?
3) Can you interpret the lung function results (table 1)?

Answer 1

1) There is a 2-cm vascular abnormality in the right lower lobe consistent with a pulmonary arteriovenous malformation (PAVM).
2) PAVMs are most commonly seen with hereditary haemorrhagic telangiectasia (>90%) and post-cardiac surgery for cyanotic congenital heart disease with resultant cavopulmonary shunt. They can occur sporadically, or may very occasionally be secondary to, for example, hepatic cirrhosis or schistosomiasis.
3) The spirometry shows an obstructive picture of moderate severity. Nevertheless, the FEV_1 is relatively well preserved for this degree of desaturation and it was this discrepancy that prompted the initial referral suggesting another contributing pathology. Importantly, this patient demonstrates orthodeoxia, whereby he becomes desaturated when sitting or standing from a recumbent position. This is confirmed symptomatically as his dyspnoea improved when lying flat (platypnoea, a very rare symptom for this condition).

The exact mechanism of orthodeoxia is unclear but is different to cardiac disease. One contributing factor to the orthodeoxia is that most PAVMs are at the lung bases and right-to-left shunting increases on standing because of the effects of gravity. The normal anatomical right-to-left shunt is less than 2% but is increased in patients with PAVMs. The size of the shunt influences arterial oxygen tension and saturation, and occlusion of the PAVM increases saturation. When there is co-existing lung disease, ventilation–perfusion mismatch may also be a contributing factor [1].

Case management and outcome

Following the diagnosis of a PAVM, the patient underwent percutaneous radiologically guided embolisation with improvement in his exercise tolerance to 800 m. Post-procedure, his oxygen saturations on air were 97% when sitting and 95% when supine.

On closer questioning, he reported frequent nosebleeds over a number of years and was seen by the ear, nose and throat team who confirmed the rhinological appearances were compatible with hereditary haemorrhagic teleangiectasia (HHT).

Despite his age at presentation, the diagnosis had not been previously considered. Subsequently, his daughter and grandsons reported recurrent nose bleeds, and were advised to seek screening for HHT.

Discussion

PAVMs are direct communications between branches of the pulmonary artery and vein allowing blood to pass from one to the other without traversing the pulmonary capillary bed, resulting in the pulmonary arterial blood passing through these right-to-left shunts without being oxygenated. As the normal pulmonary capillary bed also prevents bacteria and emboli from reaching the systemic circulation, bypassing this system can potentially lead to both septic and embolic events.

PAVMs due to HHT account for at least 90% of cases and these develop over time. HHT is an autosomal dominant disorder of the vasculature resulting in AVMs and telangiectasia. PAVMs in HHT may be present in childhood but grow and, in some, possibly many cases, develop *de novo* in puberty.

Acquired PAVMs are far less common and have been reported to occur most frequently following thoracic surgery for congenital valvular heart disease [2]. Lesions have been classified as simple (with one feeding artery), complex (with more than one feeding artery) and diffuse (rare but with hundreds of malformations) [3].

Presentation

The cardiorespiratory clinical picture depends on the size of the shunt and associated clinical parameters, such as concurrent cardiopulmonary disease and iron deficiency. Shunts over 20% of the cardiac output can lead to cyanosis, clubbing and polycythaemia. Large shunts commonly cause minimal or no clinical symptoms even when associated with clinical signs such as cyanosis, clubbing or polycythaemia. As the hypoxaemia is due to a right-to-left shunt, the cyanosis may only partially correct with oxygen therapy. More acute presentations are due to paradoxical emboli causing stroke, or due to rupture of the AVM with resultant massive pulmonary haemorrhage or haemothorax. A 2:1 female

Table 2. *Presenting features of pulmonary arteriovenous malformations*

Symptoms	Signs
Asymptomatic	Cyanosis
Breathlessness	Clubbing
Haemoptysis	Telangiectasia (if associated with HHT)
Focal neurological deficit (stroke/brain abscess)	Polycythaemia
	Pulmonary bruit (exacerbated by the Müller manoeuvre)
	Focal neurological deficit (stroke/brain abscess)

preponderance has been reported in older series.

As most cases are associated with HHT, there may be a history of epistaxis or neurological symptoms (due to paradoxical emboli) but many PAVMs are asymptomatic.

Presenting features of PAVMs are shown in table 2.

Complications of PAVMs

PAVMs carry significant risks [4]. Neurological complications are most commonly reported (up to 59% of patients) and are due to paradoxical emboli *via* pulmonary circulation. The most common neurological manifestation is migraine but there is significant risk of stroke (1% per annum) and brain abscess (0.5% per annum) with the risk being unrelated to the size of the lesion [5]. Pulmonary complications are rare with one study showing an incidence of 8% in a group of patients referred for interventional radiology. These complications are more common in women, particularly when pregnant. Prevention of these complications is the main rationale for prophylactic treatment due to the potentially catastrophic nature of stroke and haemorrhage.

Investigations

Full history and examination is required to elicit any personal or family history of any symptomatology suggestive of HHT.

A chest radiograph may demonstrate a localised abnormality (as it did in this case) but contrast-enhanced CT is more accurate in diagnosis and determining the anatomy. Pulmonary function tests, pulse oximetry and demonstration of orthodeoxia all add to the overall clinical picture. A bubble contrast echocardiogram will demonstrate a right-to-left shunt but not identify the cause or the extent of the defect. Of note, bubble contrast echocardiography can be positive in control subjects. Pulmonary angiogram allows definition of the vasculature during embolisation [2] while CT angiogram has better resolution for small PAVMs.

Magnetic resonance angiography is an option for younger patients where the radiation risk is of greater concern but may not identify all clinically significant lesions.

Treatment

PAVMs were previously treated with surgical resection but now embolisation with coils and plugs is the treatment of choice. PAVMs should be embolised if technically feasible, which is generally possible with feeding arteries of 2 mm or more. Treatment of PAVMs by embolisation is a safe and effective way to reduce lifetime risk of embolic events and abscess formation as well as treating haemoptysis and improving oxygenation [6].

Screening

Following identification of a patient with a PAVM, consideration needs to be given to screening of family members due to the autosomal dominant inheritance of HHT. The diagnostic criteria (Curacao criteria) for HHT are outlined in table 3. HHT can be definitively diagnosed when three or four of the criteria are met.

There is no clear consensus on the optimal screening tool. In some centres, the demonstration of a right-to-left shunt by contrast echocardiography has a reported sensitivity and negative predictive value >95% [7]. The low specificity (62%) may indicate microscopic PAVMs that are too small to be recognised on CT imaging. Other

Table 3. *Curacao diagnostic criteria for HHT*

Recurrent spontaneous nosebleeds
Mucocutaneous telangiectases at characteristic sites (fingertips, lips and oral mucosa)
Visceral AVMs (pulmonary, gastrointestinal, cerebral and hepatic)
Family history of first-degree relative affected

3–4 criteria: definite HHT; 2 criteria: possible HHT; 0–1 criterion: unlikely HHT.

centres opt for chest radiography proceeding to contrast CT if any abnormality is detected and using contrast echocardiography if the chest radiograph is normal [8]. Genetic screening may of benefit to asymptomatic family members of a known HHT patient but, in the general patient population, the Curacao criteria are a more sensitive diagnostic tool.

Special considerations: pregnancy and pulmonary hypertension

PAVMs can become more problematic in pregnancy as the increase in cardiac output and blood volume can cause dilatation of the vasculature. The risk of PAVM rupture is difficult to quantify but is significantly higher in pregnancy. Therefore, women with known PAVMs need to be carefully counselled pre-pregnancy with emphasis on treatment prior to conceiving.

Overall maternal mortality in the UK is 4.67 per 100,000 maternities [9] but in women with PAVMs mortality is 1% with all deaths occurring in women without pre-pregnancy diagnosis of their PAVM [10]. Current UK recommendations [10] propose that, although the risk remains low and most pregnancies have no complications, the significant increase means that these patients should be managed as high-risk pregnancies. Therefore women with known PAVMs need to be carefully counselled pre-pregnancy and screened for PAVMs with emphasis on treatment prior to conceiving. Screening for cerebral AVMs should also be considered in those HHT patients with a family history of cerebral haemorrhage and, for those wanting regional anaesthesia, a spinal magnetic resonance imaging scan may be considered to exclude spinal AVMs. Antibiotic prophylaxis is required during delivery.

Patients with co-existing PAVMs and pulmonary hypertension can be difficult to manage, although the treatment options remain the same. Embolisation will preferentially correct areas with lower vascular resistance and paradoxically increases the risk of focally elevated pulmonary artery pressure with potentially disastrous consequences. In this group of patients, the risk of embolic events diminishes with the rise in pulmonary artery pressure and some patients fail to obtain symptomatic relief following embolisation. Therefore, it has been suggested that the risks of PAVM embolisation in patients with co-existing pulmonary hypertension may outweigh the benefits [6].

Follow-up and patient education

Patients with PAVMs require long-term follow-up. While embolisation may cure the malformation, up to 60% of patients have evidence of residual disease due to PAVMs too small to treat. Residual defects may also increase in size following embolisation of the larger vessels. Additionally, there is a risk of recanalisation over time of up to 20%, either through the embolic device or from the development of collateral feeding arteries. Following treatment, patients will be regularly followed up but with urgent review and further CT assessment if their condition changes. Patients need to be given education regarding antibiotic prophylaxis for routine medical and dental procedures, the need for air filters on intravenous infusions, and the risks of decompression sickness in scuba diving [12].

As most PAVMs are associated with HHT, a thorough assessment of the patient in this regard is required and familial screening may be indicated.

Further reading

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