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Challenging cases in PH

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ABSTRACT: The requirement for a timely diagnosis of pulmonary arterial hypertension (PAH) to maximise the benefits achieved with appropriate therapy is hampered by the insidious nature of the disease and consequently the late presentation of the majority of patients. Therefore, it is critical to maintain a high index of suspicion in cases of unexplained dyspnoea and to employ a structured and systematic diagnostic strategy.

Pulmonary hypertension (PH) has been classified clinically into PAH, PH associated with left heart diseases, PH associated with hypoxaemia or disorders of the respiratory system, PH caused by chronic thrombotic or embolic disease and PH caused by disorders of the pulmonary vasculature, such as sarcoidosis. These different classes of diseases may have similar presentations despite differing physiologies and aetiologies. Moreover, in some cases, incorrect diagnosis and instigation of an inappropriate course of action can have serious consequences.

This paper illustrates two particularly challenging clinical cases that can be encountered in patients with pulmonary hypertension.

KEYWORDS: Chronic thromboembolic pulmonary hypertension, diagnosis, pulmonary hypertension, pulmonary veno-occlusive disease

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Pulmonary arterial hypertension (PAH) is a life-threatening disease of the pulmonary arterioles, which, in the absence of effective therapy, progresses rapidly to right heart failure and death in many patients. Unfortunately, as a result of the insidious nature of early stage disease, attaining a timely diagnosis is fraught with challenges. Recognising that PAH can occur at any age and thus maintaining a high index of suspicion for PAH in cases of unexplained dyspnoea and employing a structured and systematic diagnostic strategy, are paramount in detecting the condition early and thereby allowing initiation of effective therapies early in the course of the disease.

Although PAH may present with chest pain and syncope, such symptoms only become evident at an advanced stage of the disease. In contrast, the initial symptoms of PAH are all too often unremarkable and nonspecific, with patients typically presenting with dyspnoea during exercise, exercise intolerance and fatigue, symptoms that are associated with a multitude of cardiopulmonary disorders as well as other conditions. Exacerbating the problem is the low incidence of PAH, which means that PAH may not be considered early in the diagnostic process. As a result, diagnosis is often delayed for $\geqslant$2 yrs [1]. Increasing awareness of the condition and the recently published diagnostic algorithm for PAH [2, 3] should help to improve this situation.

Improved knowledge and understanding of disease physiology, natural history and clinical aspects has led to the classification of pulmonary hypertensive diseases. The Evian Classification was developed at the second World Health Organization (WHO) meeting in Evian, France [4], 25 yrs after the first WHO meeting in Geneva, which convened a group of experts in 1973 to standardise the clinical and pathological nomenclature of pulmonary hypertension (PH) [5]. The Evian Classification system, which underwent minor modifications in 2003 during the third World Symposium on PAH, is now well accepted and widely used in clinical practice [6]. PAH represents one category of this classification system and is further divided into idiopathic PAH, familial PAH, and PAH related to other factors, such as connective tissue disease, congenital heart disease, HIV infection and the use of appetite suppressants. The other four categories include: PH associated with left heart diseases; PH associated with disorders of the respiratory system or hypoxaemia; PH caused by chronic thrombotic or embolic disease, such as chronic thromboembolic pulmonary hypertension (CTEPH); and PH caused by disorders of the pulmonary vasculature, *e.g.* sarcoidosis [4].

Despite differences in the physiology and aetiology of these diseases, their clinical presentation may be very similar. A significant challenge thus faced by many clinicians is not only to detect PH

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early, before irreversible pathological changes have occurred, but also to establish an accurate differential diagnosis so that the appropriate treatment regimen can be initiated. It is paramount therefore that the clinician preserves a vigilant approach to the detection of PAH. By maintaining a high index of suspicion and appreciating the potential significance of clinical clues, no matter how small, appropriate lines of investigation to potentially detect PAH in the latent phase of the disease can be initiated.

Employing a robust and systematic diagnostic approach is crucial. The clinician may have many diagnostic tools at his disposal, so the combination of tools employed for each individual case needs careful consideration. The diagnostic approach for PAH has been defined in recently published guidelines [2, 3] based on the new clinical classification [6]. These guidelines are intended to facilitate an accurate and fast diagnosis *via* an evidence-based algorithm, and are especially useful in helping to avoid the pitfalls that are all too often encountered on the way to attaining a definitive diagnosis.

Following diagnosis of PAH and initiation of appropriate therapy, monitoring of disease progression and response to treatment is essential to inform decisions in patient management. Tailoring therapy to suit the evolving needs of the patient, as well as to initiate appropriate lines of investigation promptly, requires that the physician be constantly on alert. Various parameters such as WHO functional class (WHO FC) and exercise capacity should be assessed at regular intervals. Certain parameters have also been shown to be useful in predicting outcome with a given therapy [2]. In particular the 6-min walk distance (6MWD) has been shown to correlate with survival [7].

In all cases, timely and accurate diagnosis remains a significant clinical challenge. However, in some circumstances, obtaining a definitive diagnosis is even more problematic. During a symposium convened as part of the Annual European Respiratory Society meeting held in Munich during September 2006, the current authors presented two cases to illustrate two of the more challenging clinical pictures encountered in these patients and to highlight a number of key issues that should be borne in mind when evaluating a patient with PH. At various stages during the case presentations, the audience of respiratory physicians was given the opportunity to vote for a particular diagnosis or treatment strategy using an electronic key pad voting system.

CASE STUDIES

Case 1

The first case was that of a 58-yr-old previously healthy female who complained of a 12–month history of dyspnoea on exertion and after assessment by a pulmonologist was assigned to WHO FC II–III. As is frequently the case, her clinical findings and chest radiograph were unremarkable, and pulmonary function tests (PFTs) revealed a forced vital capacity (FVC) of 3,070 mL (96%) and a forced expiration volume in one second (FEV1) of 1,670 mL, representing 54% of FVC. Arterial oxygen tension (P_{a,O_2}) was 7.33 kPa and carbon dioxide arterial tension (P_{a,CO_2}) was 3.87 kPa in the presence of hyperventilation and was indicative of marked hypoxaemia.

Based on this clinical picture, the initial diagnosis made was chronic obstructive pulmonary disease (COPD), and treatment with long-acting β-agonists was initiated. However, although this diagnosis was not necessarily incorrect, an FEV1 value of 54% of FVC in a patient with COPD would not be expected to be associated with such marked functional impairment and it would be even more unlikely for this pattern of blood gases to be present in a patient with COPD.

Nevertheless, therapy was continued with long-acting β-agonists and over the course of the next 2 yrs the patient experienced worsening dyspnoea on exertion, syncope and was hospitalised. At this point, an echocardiogram was performed, which revealed severe PAH and massive enlargement of the right atrium and right ventricle. Doppler systolic right ventricular pressure was calculated to be 110 mmHg. At this point, the diagnosis of PAH was made. Additional tests revealed normal left heart function and stable PFTs and blood gases. A computed tomography (CT) scan showed no evidence of chronic thromboembolic disease and compression ultrasound of arm and leg veins was negative. On right heart catheterisation, mean pulmonary arterial pressure ($\bar{P}_{pa}$) was found to be extremely high at 62 mmHg, pulmonary capillary wedge pressure was in the normal range (7 mmHg), cardiac output was 4.7 $L \cdot min^{-1}$ and pulmonary vascular resistance (PVR) was 935 $dyn \cdot s \cdot cm^{-5}$.

At this point, the audience was asked to refine the initial diagnosis of PAH and was asked whether the clinical profile indicated one of the following: 1) PH due to COPD; 2) idiopathic (i)PAH and COPD; 3) CTEPH; or 4) another form of PH.

The majority of the audience felt that the clinical profile of this patient was indicative of iPAH and COPD (59%) or another form of PH (29%). In agreement with this, the eventual diagnosis arrived at for this patient was iPAH. Oral anticoagulation as background therapy was initiated (international normalised ratio 1.5–2.5) and bosentan was initiated at a dose of 62.5 mg *b.i.d.* increasing to 125 mg *b.i.d.* thereafter. After initially improving, the patient progressively deteriorated and sildenafil was added but without clinical success. Thus, the decision was then what to do once the patient had shown no clinical improvement on combination therapy with bosentan and sildenafil, a therapeutic regimen that offers clinical benefit to many patients with iPAH [8]. The audience was given the following options: 1) starting prostacyclin treatment; 2) performing further diagnostic work-up; or 3) continuing previous combination therapy.

There was an almost even split between opting to start prostacyclin therapy (43%) and performing further diagnostic work-up (52%). Not surprisingly, only 4% elected to continue with previous therapy, since as previously indicated, it is rare for a patient with iPAH to show no response to combination therapy with bosentan and sildenafil. Either of the two alternative options would be valid approaches to take. However, when an unexpected response to treatment is observed, the most appropriate approach is likely to be to use alternative techniques to gain additional diagnostic clues to drive appropriate treatment. Consequently, a ventilation/perfusion (V'/Q') scan was performed.

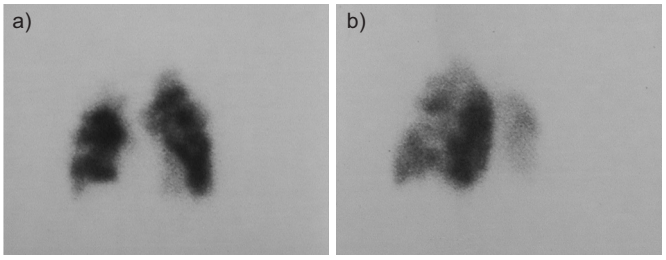

FIGURE 1. a, b) Abnormal ventilation/perfusion scan in a patient diagnosed with idiopathic pulmonary arterial hypertension showing irregular perfusion indicative of chronic thromboembolic pulmonary hypertension.

The resulting scan clearly showed bilateral subsegmental and segmental perfusion defects, which are indicative of CTEPH (fig. 1). Re-examination of the chest CT scan did not provide any clear evidence of vessel abnormalities that would have been suggestive of chronic thromboembolic disease (fig. 2), highlighting the importance of performing several diagnostic tests to gain an accurate picture of disease. The CT pictures, however, were obtained with an older generation scanner and not with a modern multi-slice CT scanner.

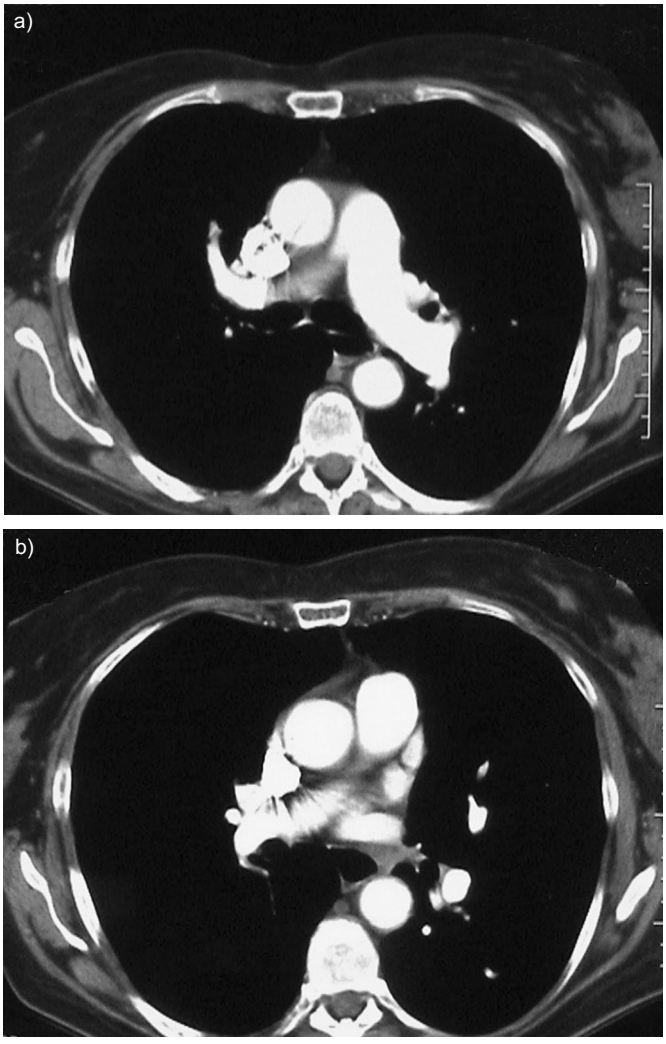

FIGURE 2. a, b) Computed tomography scan showing no clear evidence of vessel abnormalities indicative of chronic thromboembolic disease.

However, some characteristics typical of CTEPH were evident on close examination of the scan. Areas that had been mistaken previously as air trapping due to COPD were in fact patterns of mosaic perfusion, which is almost pathognomonic of chronic thromboembolic disease (fig. 3). Consequently, the patient underwent pulmonary angiography, which duly showed large areas of the lungs that were not perfused due to the presence of obstructive lesions. Vessels were occluded or, in some areas, completely obliterated and most of the vessels of the lower lobe were absent (fig. 4). This type of image showing obvious proximal CTEPH is a clear indication for surgical pulmonary endarterectomy (PEA). A year after PEA, the patient fulfilled criteria of WHO FC I–II and was able to climb three flights of stairs without issue. The patient's 6MWD increased to 550 m, which is not far short of the 600 m distance considered to be normal. On echocardiography, the patient's right ventricle showed a near normal diameter and a residual estimated pulmonary arterial pressure of 45 mmHg.

Key learning points

The learning points from the case are simple. Chronic thromboembolic PH can occur in the absence of clinically overt venous thromboembolism, as is the case in 30–50% of patients [9]. Even in the era of many advanced imaging techniques, including multi-slice CT scanners and magnetic resonance angiography, the simple technique of V'/Q' scanning remains a useful diagnostic and screening tool for CTEPH.

Case 2

The second case was that of a 29-yr-old female who had been experiencing dyspnoea on exertion for a short period of ~3 months. Disease progression was rapid and at presentation she fulfilled the criteria of WHO FC III–IV and echocardiography indicated severe PH. Her V'/Q' scan and multi-slice

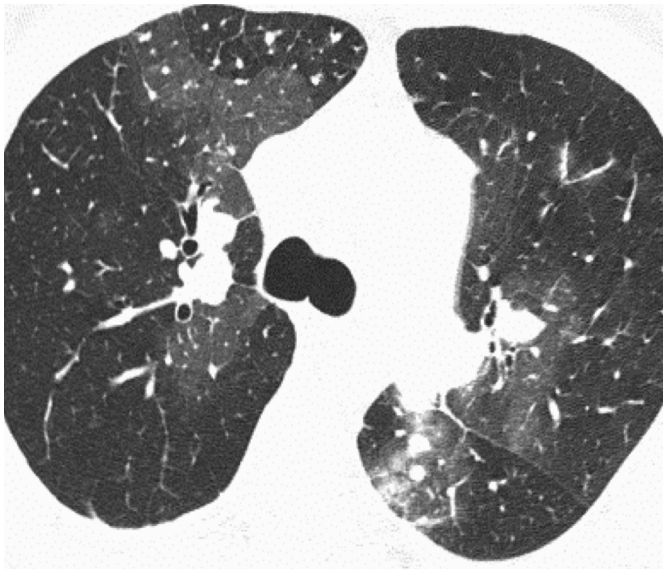

FIGURE 3. Characteristic patterns of mosaic perfusion.

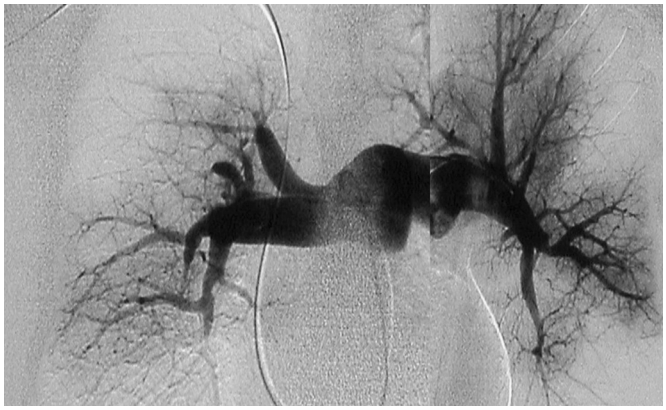

FIGURE 4. Pulmonary angiogram of a patient with chronic thromboembolic pulmonary hypertension.

chest CT were normal as were all other techniques employed to rule out secondary causes of PH. Right heart catheterisation duly confirmed the echocardiographic suggestion of PAH and the patient was found to have severe PAH with a measured $\bar{P}_{pa}$ of 54 mmHg, a cardiac index (CI) of 1.5 L·min^{-1}·m^{-2} and a PVR of 1,306 dyn·s·cm^{-5}.

On the basis of these findings, a diagnosis of iPAH was made and background treatment was initiated with oxygen and warfarin. Targeted combination therapy with bosentan (125 mg *b.i.d.*) and a higher than the currently approved dose of sildenafil (50 mg *t.i.d.*) was initiated concomitantly. This combined therapeutic approach did not result in clinical improvement; in fact, the patient's hypoxaemia worsened, with P_{a,O_2} of 6 kPa and P_{a,CO_2} of 3.47 kPa on room air, and she went into right heart failure with a right atrial pressure of 18 mmHg and a CI of 1.1 L·min^{-1}·m^{-2}. Given this information, the audience was asked how they would choose to proceed. They were given the choice of the following: 1) increasing the sildenafil dose; 2) adding inhaled iloprost; 3) commencing *i.v.* prostacyclin; 4) performing an atrioseptostomy; or 5) referring for lung transplantation.

Approximately equal proportions of the audience chose to start *i.v.* prostacyclins (31%) or to refer for lung transplantation (37%). A substantial minority opted for atrioseptostomy (19%). Opting for increasing the dose of sildenafil in this situation is unlikely to be the most appropriate course of action since an additional effect would be unlikely in a patient already unresponsive to relatively high doses of 50 mg *t.i.d.* and in cases of such severe PAH, inhaled iloprost is likely to offer limited additional benefit. It is important to emphasise that atrioseptostomy in this patient should not be performed under any circumstances. The patient is in severe right heart failure and hypoxaemic, and would not be expected to survive this procedure. Lung transplantation could be necessary here and the patient should be put on the transplantation list immediately. However, she also needs appropriate management prior to availability of a suitable donor organ and this may include the use of an *i.v.* prostanoid.

After initiation of this therapy, right heart function improved immediately (right atrial pressure 11 mmHg, CI 2.8 L·min^{-1}·m^{-2}) but hypoxaemia continued to deteriorate (P_{a,O_2} 6.4 kPa, P_{a,CO_2} 3.73 kPa) on 10 L·min^{-1} oxygen *via* a non-rebreathing mask. The patient subsequently required intubation and mechanical ventilation for respiratory failure.

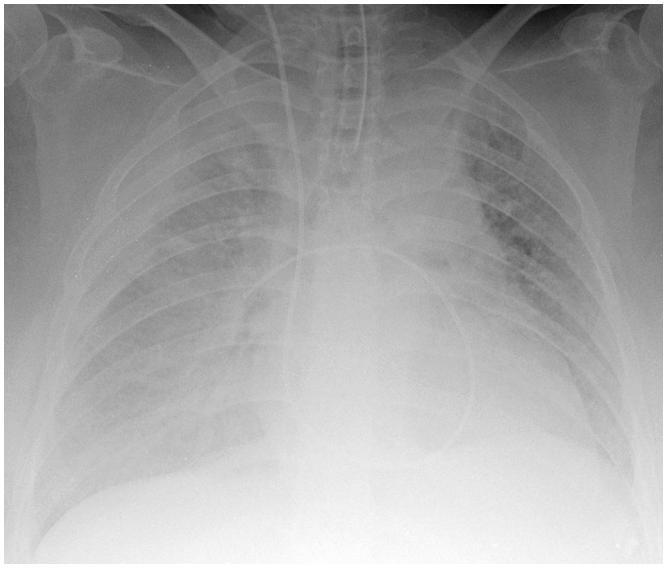

FIGURE 5. Chest radiograph showing pulmonary oedema after institution of *i.v.* prostanoid treatment.

Prior to institution of prostanoid therapy, a further CT scan was performed, which was normal. However, a further chest radiograph performed a few days after initiation of prostanoid therapy showed bilateral pulmonary opacification (fig. 5). Having reviewed this radiograph, the audience was asked to make a diagnosis from the following: 1) left heart failure; 2) fluid overload; 3) pulmonary veno-occlusive disease (PVOD); 4) hypersensitivity pneumonitis; or 5) another lung disease.

PVOD was diagnosed by 62% of the audience, with the majority of the rest diagnosing either left heart failure (16%) or fluid overload (10%). The physicians treating this patient also

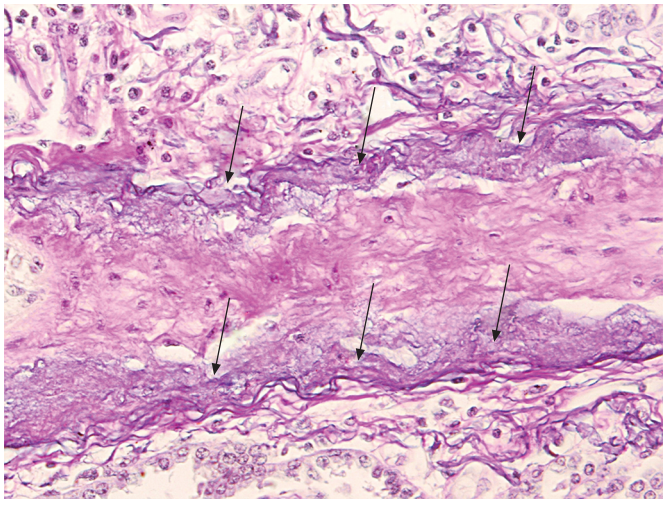

FIGURE 6. Histological specimen of explanted lungs showing typical findings of pulmonary veno-occlusive disease with complete obliteration of small pulmonary veins (arrows).

diagnosed PVOD and opted to refer the patient for highly urgent lung transplantation, rather than opting to increase the dose of prostanoids, to use high-dose steroids or to perform atrioseptostomy. It is highly typical of patients with PVOD that as soon as they are administered *i.v.* prostacyclins they rapidly develop pulmonary oedema, as was evident on the radiograph (fig. 5). The reasons that contraindicate atrioseptostomy have already been discussed. Stopping prostanoid therapy would improve oxygenation but this patient was dependent on prostanoid therapy and would have gone into right heart failure if it had been withdrawn. Increasing the dose of prostanoids would have led to worsening of oxygenation and high-dose steroids have been shown to be ineffective in patients with PVOD. For this patient, urgent lung transplantation was the only option available. The patient subsequently underwent heart and lung transplantation and has fully recovered. Histological examination of the explanted lungs confirmed the diagnosis of PVOD (fig. 6).

Key learning points

Pulmonary veno-occlusive disease is probably the most malignant form of pulmonary hypertension and is found in ~10% of patients initially diagnosed with idiopathic pulmonary arterial hypertension. Typical findings on chest radiograph include increased septal markings and patchy ground-glass opacities. Bronchoalveolar lavage may be helpful as it may identify occult alveolar haemorrhage, a feature of pulmonary veno-occlusive disease. In bronchoalveolar lavage fluid, haemosiderin-laden alveolar macrophages comprise ~40% of the total cells in pulmonary veno-occlusive disease patients, compared with just 3% in idiopathic pulmonary arterial hypertension patients. In pulmonary veno-occlusive disease, pulmonary oedema is common during prostacyclin therapy and some institutions use prostacyclin-induced pulmonary oedema as a diagnostic technique for pulmonary veno-occlusive disease. Unfortunately, pulmonary veno-occlusive disease is notoriously unresponsive to medical therapy and in most cases of suspected pulmonary veno-occlusive disease urgent lung transplantation should be considered.

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