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CASE REPORT

Misplaced pulmonary arteries in an adult patient with pulmonary hypertension

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ABSTRACT. Misalignment of pulmonary vessels, with or without alveolar capillary dysplasia, is a rare cause of persistent pulmonary hypertension in the newborn. The prognosis is poor, with virtually all patients succumbing to unremitting hypoxaemic respiratory failure and death during the newborn period. We report the CT and histological findings of misplaced pulmonary arteries in a previously healthy young adult patient who presented with pulmonary arterial hypertension. Contiguous high-resolution spiral CT angiography showed small pulmonary arteries coursing within the interlobular septa and enlarged central pulmonary arteries. Surgical lung biopsy demonstrated anomalous muscularised pulmonary arteries in the interlobular septa. This is, to our knowledge, the first report of misplaced pulmonary arteries presenting in an adult patient and may represent a forme fruste of the neonatal vascular anomaly. A possible association with pulmonary arterial hypertension is also suggested in this case.

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Misalignment of pulmonary vessels, with or without alveolar capillary dysplasia (ACD), is a rare cause of persistent pulmonary hypertension in the newborn [1–5]. The prognosis is poor, with patients usually succumbing to unremitting hypoxaemic respiratory failure and death in early infancy [3–7]. We report the CT and histological findings of misplaced pulmonary arteries in a previously healthy young adult patient who presented with symptoms of pulmonary arterial hypertension. CT of the chest confirmed the findings of pulmonary arterial hypertension and demonstrated small anomalous pulmonary arteries within many interlobular septa. Surgical lung biopsy confirmed the presence of anomalous muscularised small pulmonary arteries in the interlobular septa. To our knowledge, this is the first reported adult patient with a histological diagnosis of misplaced pulmonary arteries in the literature and may represent a variant of misalignment of pulmonary vessels seen in neonates. This finding lends credence to earlier assertions that the distribution of the vascular misalignment, be it patchy or diffuse, may correlate with the phenotypic expression of disease [3, 6, 7]. The finding in an adult without associated ACD would seem to validate previous hypotheses that the anomalies may co-exist or present as mutually exclusive entities [2–5].

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Case report

A 21-year-old previously healthy woman presented with increasing shortness of breath on exertion. Physical examination was unremarkable except for a loud P2 sound consistent with pulmonary arterial hypertension. She had been on oral contraceptives for 3 years and valaciclovir for oral herpes, but reported no other medications. She denied taking appetite suppressants and admitted to smoking marijuana on occasion, but had no history of intravenous or inhaled drug use. Alcohol use had been modest. She had normal laboratory tests, including complete blood count, routine chemistry, urinalysis, immunochemistry, thyroid-stimulating hormone, liver-associated enzymes, virological studies for hepatitis and HIV, arterial blood gas and overnight oximetry, negative rheumatoid factor, extractable nuclear antigen antibodies (including JO-1) and antinuclear antibodies.

Pulmonary function tests showed normal vital capacity and expiratory flows, and a mildly impaired diffusing capacity for carbon monoxide (DL_{CO}) (64% of predicted). She underwent CT angiography in the pulmonary arterial phase on a 64-track multidetector CT scanner with 1 mm image reconstruction at 1 mm intervals. CT angiography revealed no evidence of acute or chronic thromboembolic disease. CT demonstrated an enlarged main pulmonary artery measuring 3.2 cm (Figure 1), peripheral pruning of the vasculature, right ventricular enlargement, straightening of the interventricular septum, and reflux of contrast into the inferior vena cava and hepatic veins — findings consistent with

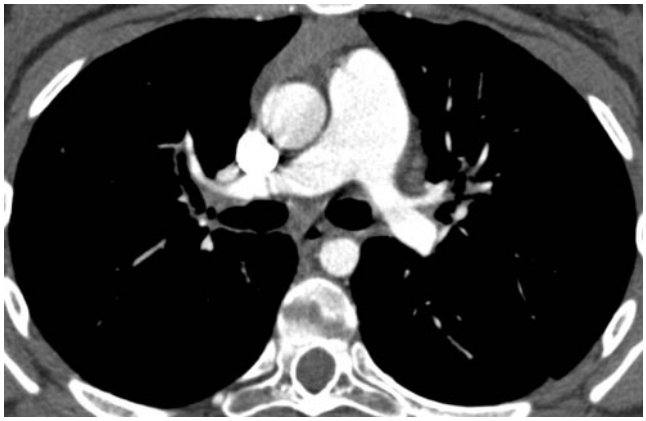

Figure 1. High-resolution CT image demonstrating the enlarged main pulmonary artery compatible with subsequently proven pulmonary arterial hypertension.

pulmonary arterial hypertension. High-resolution CT (1 mm reconstructions) of the lung parenchyma showed mild, patchy, thickening of the interlobular septa. A careful review of the images demonstrated that this pattern was a result of small peripheral pulmonary arteries coursing within the interlobular septa (Figure 2). Focal areas of decreased attenuation and vascularity (mosaic perfusion pattern) were also noted. The CT was otherwise unremarkable. There was no lymphadenopathy or pleural effusion.

Echocardiography demonstrated a dilated right ventricle with interventricular septal motion and mild tricuspid regurgitation, and confirmed the elevated right-sided pressures. There was no shunt evident on contrast saline injection. Right heart catheterisation showed elevated right atrial pressures of 6/3 mmHg, normal pulmonary capillary wedge pressures of 11/13 mmHg, and elevated pulmonary artery pressures of 65/18 mmHg, with a mean pressure of 36 mmHg and mean capillary wedge pressure of 9 mmHg. There was no significant drop in the pulmonary vascular resistance in response to inhaled nitric oxide at concentrations up to 80 parts per million.

Surgical biopsy of the right lung was performed. Histopathology confirmed the vascular manifestations of pulmonary arterial hypertension, with medial arterial

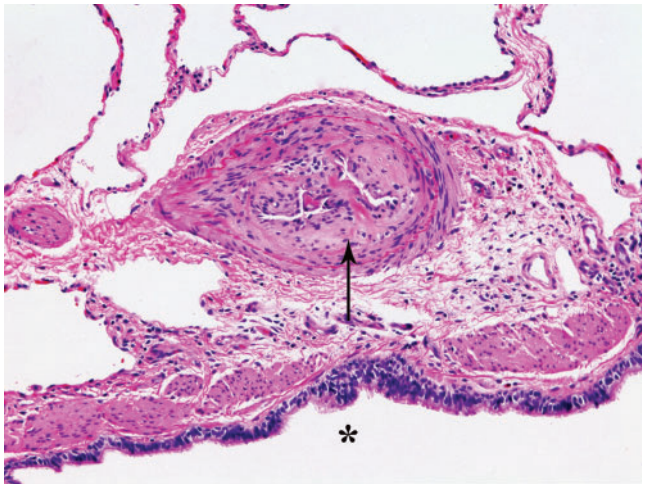

Figure 3. Photomicrograph of a histopathological specimen shows a pulmonary artery with intimal hyperplasia (arrow) and slit-like narrowing of the lumen. The asterisk (*) denotes the adjacent bronchiole (haematoxylin and eosin stain, $\times$100 original magnification).

thickening and intimal hyperplasia (Figure 3). The most unusual finding was that of abnormally situated pulmonary arteries, with some branches observed within the interlobular septa, isolated from the airways (Figures 4 and 5). The arteries displayed both internal and external elastic lamina, distinguishing them from normal bronchial arteries within the subpleural septa. There was no overt abnormality insofar as the apparent density or morphology of the capillaries within the alveolar septa was concerned. Morphologically normal pulmonary vessels were also identified in their normal position within the bronchovascular sheath. In a number of instances, the major bronchovascular vessel displayed histological features intermediate between an artery and a vein (Figure 6), and the true nature of these structures was difficult to determine. A number of small airways demonstrated thickening with accompanying changes of smooth muscle hyperplasia, consistent with chronic bronchiolitis. No vascular plexiform or dilation lesions were identified. Prominent bronchial arteries were noted both within the bronchovascular bundle and within the pleura.

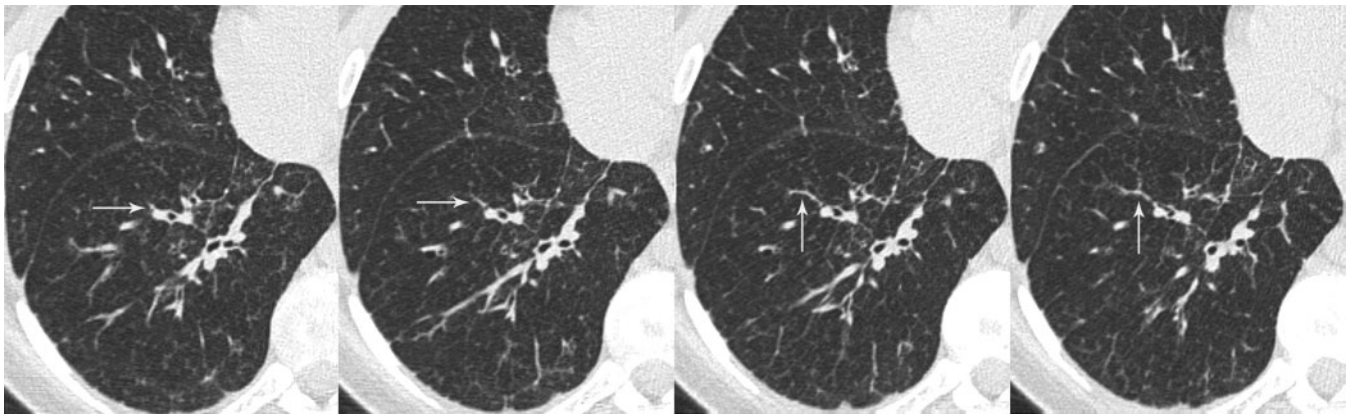

Figure 2. Sequential magnified views of the right lower lobe from a 64-track multidetector row CT pulmonary angiogram demonstrate a small subsegmental pulmonary artery coursing within the interlobular septa (arrows). Also noted is mild interlobular septal thickening.

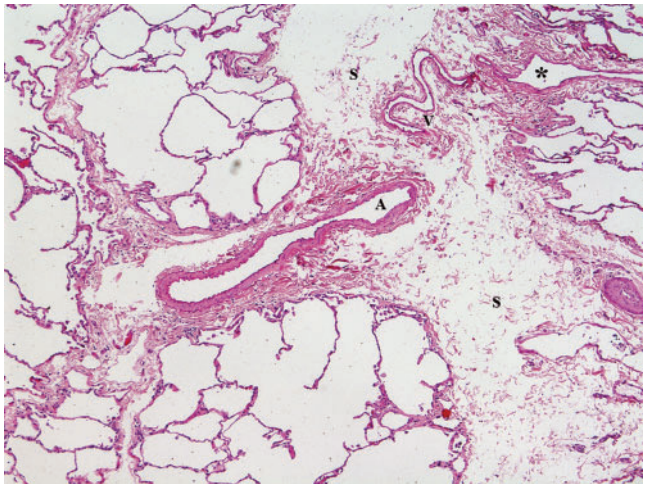

Figure 4. Higher power view demonstrating a pulmonary artery (A) independent of any bronchioles, extending into an interlobular septum (S). The interlobular vein (V) and adjacent tributary (*) are also present (haematoxylin and eosin stain, ×40 original magnification).

The patient was started on warfarin (5 mg bid) and bosentan (62.5 mg bid, and subsequently 125 mg po bid), with monthly liver function tests. The oral contraceptives were discontinued. On follow-up 6 months after initiating drug therapy, she showed improved exercise tolerance and reported no recent pre-syncopal episodes or chest pain. She had an improved cardiopulmonary performance on exercise testing compared with that before bosentan therapy was initiated. Her peak oxygen consumption was 27.4 ml kg^{-1} min^{-1}, compared with 21.5 ml kg^{-1} min^{-1} 6 months earlier. A repeat echocardiogram 2 years after the initial assessment showed an improvement in systolic pulmonary artery pressures from 65 mmHg to 43 mmHg.

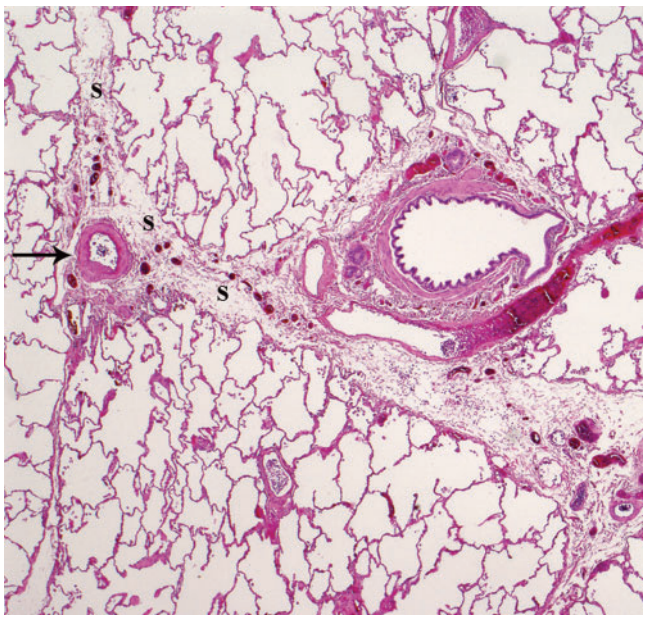

Figure 5. Low magnification photomicrograph showing the pulmonary artery (arrow) situated within confluent interlobular septa (S) (haematoxylin and eosin stain, ×40 original magnification).

Discussion

Misalignment of lung vessels (MLV) is a developmental anomaly of the pulmonary vasculature [1–5]. It has only been described in full-term newborn infants who present after a variable length of time postnatally with clinical features of persistent pulmonary hypertension of the newborn. Originally described in 1981 [1], it is usually associated with ACD [2]; however, the two terms are occasionally used synonymously [3]. It has been suggested in several reports that ACD may exist separately [4, 5]. More than 80 paediatric cases of MLV have been reported to date in the English literature. The majority of cases are sporadic, with fewer than 10 examples of familial cases in the literature, suggesting the possibility of a genetic cause [6–8]. An autosomal recessive pattern of inheritance is most likely in familial cases [9, 10]. Despite a transient improvement in symptoms with pulmonary vasodilators, such as nitric oxide and prostacyclin therapy, in addition to extracorporeal membrane oxygenation and mechanical ventilatory support, the condition has been described as universally fatal, with a maximum reported survival of 2–3 months [11, 12].

A diagnosis is usually confirmed at autopsy in more than 80% of cases, with the remainder diagnosed ante mortem [13–16]. However, one recent retrospective analysis reported that diagnoses were made prior to death in 86% of confirmed cases [17]. Histological findings of ACD–MPV include (i) anomalous pulmonary veins coursing within or adjacent to the bronchoarterial sheath alongside the pulmonary arteries and bronchi; (ii) medial hypertrophy of the small pulmonary arteries; (iii) muscularisation of the small intra-acinar arterioles; (iv) a paucity of capillaries adjacent to the alveolar epithelium; and (v) immature alveolar development with thickened alveolar septa. Only the first two features were demonstrated in our patient. Involvement of the lung may be diffuse or patchy in distribution [4, 17–19]. Several authors have suggested that variability in the clinical presentation, such as the onset of symptoms and the

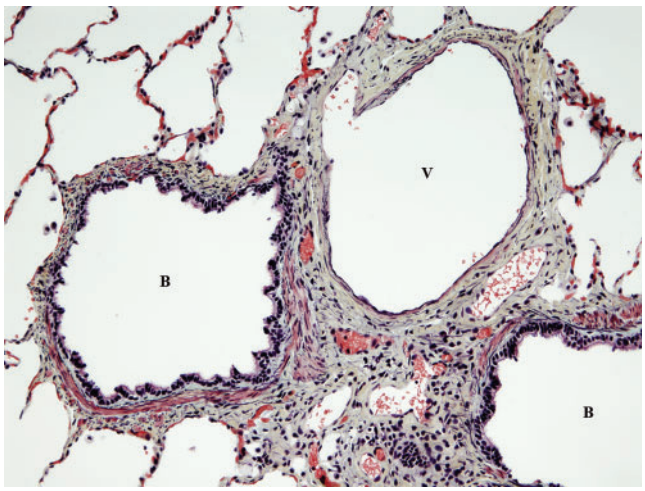

Figure 6. Higher power magnification showing a vessel with venous characteristics (V) situated adjacent to two bronchioles (B) (Movat pentachrome stain, ×100 original magnification).

severity of pulmonary hypertension, may correlate with the extent of involvement of the lungs [3, 6, 7]. Focal involvement without associated changes in the maldeveloped alveolar–capillary interface may account for the extended survival into adulthood in our patient.

The precise aetiology of the anomaly is unknown. Development of the pre-acinar vessels coincides with that of the airways; genesis of the intra-acinar vessels occurs at the same time as alveolar growth [20]. The proximal lung vessels develop by angiogenesis (outgrowth of new vessels from pre-existing ones), whereas the peripheral vasculature develops by vasculogenesis (mesenchymal growth from blood lakes) [21–23]. A mutation or insult during embryogenesis to the governing mechanism for angiogenesis has been suggested in cases of MLV without ACD [2, 20]. Vascular endothelial growth factors have also been implicated as a potential mechanism [24, 25]. Arterial muscularisation may be a primary anomaly related to abnormal vascular development [26] or secondary to regional hypoxaemia resulting from intrapulmonary shunting via gas exchange through the arteriovenular wall [19, 27]. Cullinane et al [28] proposed that the arterial changes were the primary abnormality, possibly caused by a teratogenic exposure *in utero*, with pulmonary vasoconstriction leading to failure of normal angiogenesis.

In the patient presented in this report, the prominent arteries in the interlobular septa display the histological characteristics of pulmonary arteries, with readily identifiable internal and external elastic laminae. It is possible, however, that some of these vessels are bronchial arteries that have acquired a distinctive external elastic lamina. Bronchial arteries may demonstrate compensatory enlargement in the setting of maldevelopment of the pulmonary arterial circulation, as seen in the setting of pulmonary atresia [24].

In summary, we present the CT findings and accompanying histology of an adult patient diagnosed with misplaced pulmonary arteries, which to our knowledge has not been described in the literature to date. The histological findings are similar morphologically to those described in full-term neonates who present with persistent pulmonary hypertension of the newborn, and may represent a forme fruste of the vascular anomaly identified in neonates. The finding of a newly diagnosed vascular anomaly in the setting of pulmonary arterial hypertension raises the possibility of an association between the two entities.

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