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ORIGINAL ARTICLE

CT of the chest in the evaluation of idiopathic pulmonary arterial hypertension in children

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Abstract
Background Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease in children. By definition it is a diagnosis of exclusion, and CT of the chest is primarily performed to exclude other causes. Previous studies have defined CT features suggestive of the diagnosis of IPAH, but these have all been limited to the adult population.
Objective Contrast-enhanced chest CT and high-resolution CT findings in IPAH were evaluated in an attempt to define features consistently seen in children with this condition.
Materials and methods The chest CT scans performed at initial presentation were reviewed in 17 children with echocardiographic or angiographic evidence of IPAH.
Result There were nine boys and eight girls, ranging in age from 1 month to 17 years. The extrapulmonary findings included cardiomegaly with right-sided cardiac enlargement, which was seen in 13 children. The central pulmonary arteries were enlarged in 15 children, with peripheral enlargement in two. In six children this resulted in bronchial compression. In addition, mediastinal and hilar lymphadenopathy was noted in three children. Prominent intrapulmonary features included a peripheral vasculopathy, with enlarged tortuous vessels, seen in eight children. Ill-defined ground-glass centrilobular opacities were also noted in eight children, representing the most common parenchymal abnormality. Other findings included septal lines in five, diffuse ground-glass opacification in four and focal hyperlucent zones in three. Mosaic attenuation was seen in one child.
Conclusion A variety of imaging findings are identified in IPAH. Features particularly consistent with the diagnosis include peripheral vasculopathy and centrilobular opacities in the setting of cardiomegaly and central pulmonary arterial enlargement.

Keywords Chest · Pulmonary hypertension · Imaging · Children

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Introduction

Idiopathic pulmonary arterial hypertension (IPAH), previously known as primary pulmonary hypertension (PPH), is the idiopathic subset of a range of diseases characterized by high pulmonary arterial pressures. Although the pathogenesis of the disease remains unclear, histological changes include medial hypertrophy of the pulmonary arteries, intimal proliferation, small-vessel occlusion and plexiform lesions [1]. These have the combined effect of gradually increasing the pulmonary vascular resistance, with the resultant increase in the right ventricular pressure eventually leading to right-sided heart failure and death [2].

Until recently, IPAH carried an abysmal prognosis. This was particularly true for children, in whom the mean survival was less the 1 year [3]. Although the disease remains incurable, recent significant advances in treatment have dramatically improved survival as well as the quality

of life in these patients [4]. Early recognition is, therefore, essential to initiate therapy while the structural changes are minimal and potentially reversible [5].

The clinical presentation in children is generally nonspecific and varies with the age of the child. Although older children might present with exertional dyspnea similar to the adult patient, infants often present with failure to thrive, lethargy and irritability [3]. Therefore, the diagnostic workup in these patients can often be quite extensive.

As IPAH is a diagnosis of exclusion, CT of the chest is primarily performed to exclude other causes of pulmonary hypertension such as pulmonary embolism, parenchymal lung disease and causes of venous hypertension. However, previous studies have highlighted several intrapulmonary and extrapulmonary abnormalities suggestive of IPAH. The extrapulmonary features include proximal pulmonary artery enlargement, with or without mural deposits [6]. Intrapulmonary abnormalities include mosaic attenuation and bronchial/systemic collaterals [6, 7]. However, all the series available are limited to disease manifestations in adult patients.

In an attempt to define both intrapulmonary and extrapulmonary radiological features consistently seen in children with IPAH, a retrospective review of high-resolution CT (HRCT) and contrast-enhanced CT (CECT) scans of the chest was performed in children referred for evaluation of potential IPAH.

Materials and methods

Approval for the study was obtained from the research ethics board of our institution. In the 6-year period from 1999 to 2005, a total of 30 children were referred for a CT scan of the chest for pulmonary hypertension of unknown cause. On further evaluation a hemodynamically significant atrial or ventricular septal defect was identified in nine patients, who were therefore excluded. On the basis of the CT examination, pulmonary veno-occlusive disease (PVOD) was suggested as the underlying diagnosis in two children. This was subsequently confirmed at autopsy, and these children were also excluded. Two other patients were excluded from the study, as significant motion artifact rendered the examination nondiagnostic.

The diagnosis of IPAH was based on echocardiographic and angiographic evidence. Eight children had angiography with pressure measurements performed within 1 month of the CT examination. The remainder had echocardiography performed within 1 month of the CT study. Of the latter group, two patients had the diagnosis previously established by angiography and two more underwent angiography in the following year, with confirmatory angiographic and pressure findings.

In all of the patients the CT scan was performed at initial presentation, before initiation of therapy. One child had the CT examination performed on a single-slice helical HiSpeed scanner while the remainder of the studies were performed on an eight-slice LightSpeed scanner (both General Electric Medical Systems, Milwaukee, Wis.). A CECT scan was performed in all 17 of the included patients, with selected HRCT images also obtained in 13 of these patients. Contiguous nonoverlapping images were obtained for the CECT with a slice thickness of 5 mm, beam collimation of 20 mm, pitch of 1.35 and table speed of 27 mm per rotation. The examinations were performed with a kV of 120 with the mAs adjusted according to the weight of the child (range 80–150 kg). Omnipaque 300 was used as contrast material, with a total of 2 ml/kg administered up to a maximum of 100 ml. The HRCT images were obtained with 1-mm thick sections at intervals of 10 mm.

All of the examinations were reviewed independently by two staff pediatric radiologists and one fellow in pediatric radiology. In instances of discrepancy, a final decision was reached by consensus. The findings were divided into intrapulmonary and extrapulmonary features. The lungs were divided into central, middle and peripheral thirds, as well as upper and lower zones. In patients with intrapulmonary findings, the extent of lung involvement and distribution was noted. In the absence of any discernible predominance in distribution, the findings were designated as random.

Ground-glass shadowing was defined as hazy increased lung opacity with no obscuration of underlying vessels. Focal areas of hyperlucency were also noted. Where the patchy areas of hyperlucency were accompanied by attenuation of the pulmonary vasculature the pattern was termed “mosaic perfusion.” Septal lines were defined as abnormal thickening of the interlobular septa. Round, at least moderately well-defined opacities were noted as nodules and termed centrilobular if they conformed to the lobular core. Finally, the presence of abnormal or collateral pulmonary vasculature was also documented.

The extrapulmonary features recorded included the presence or absence of cardiomegaly, which was assessed subjectively but independently by the three reviewers. Pulmonary arterial enlargement was defined as a main pulmonary artery diameter to thoracic aorta diameter ratio greater than 1 [8]. This was then subdivided into central or peripheral enlargement, with or without compression of the adjacent bronchi. The diameters of the right and left pulmonary arteries were measured at their widest portion and the artery diameter to main bronchus diameter ratios calculated. Other findings such as venous abnormalities, mediastinal or hilar lymphadenopathy and pericardial or pleural effusions were also noted.

Patient charts, as well as angiography and echocardiography findings, were reviewed. Note was made of the predominant presenting symptoms. Mean pulmonary arterial pressure (MPAP) at the time of initial evaluation was also documented. The correlation between MPAP and individual imaging findings was then calculated using the Spearman rank correlation test. In cases where the other variable was dichotomous (i.e. presence or absence of a finding), the point-biserial correlation coefficient was calculated. A two-tailed *t*-test was then used to determine the probability.

Results

The 17 children included in the study ranged in age from 1 month to 17 years (mean±SD, 9.1±6.2 years). There were eight girls and nine boys. The intrapulmonary findings are summarized in Table 1 and the extrapulmonary findings in Table 2.

In children younger than 3 years cyanosis was the predominant presenting symptom, seen in three of four children. Older children were more likely to present with one or more of the following symptoms: dyspnea on exercise (6/14), chest pain (4/14), syncope (3/14) and cyanosis (2/14). The MPAP varied between 21 and 74 mmHg (mean±SD, 15.6±16 mmHg).

The most common parenchymal abnormalities were ill-defined ground-glass centrilobular opacities, which were noted in eight children. These were random in distribution from the center to the periphery, with no evidence of zonal predominance (Fig. 1). A prominent vasculopathy was also noted in six children with enlarged tortuous vessels seen in the periphery of the lungs and extending to the pleura (Fig. 2). There was no evidence of a zonal distribution. Small septal lines with a predominantly subpleural distribution were seen in four children (Fig. 3). Diffuse ground-glass opacification was identified in four children and was uniform in distribution (Fig. 4). Randomly distributed focal areas of hyperlucency were noted in three children (Fig. 5), and "mosaic perfusion" was identified in one child (Fig. 6).

The most common extrapulmonary finding was central pulmonary arterial enlargement, which was seen in 15 children (Fig. 7). In six of these children this resulted in bronchial compression, although there was no correlation between bronchial artery compression and focal areas of hyperlucency. The main pulmonary artery diameter measured 1.1–4.8 cm (mean±SD, 2.6±1 cm). Enlarged segmental pulmonary arteries were also noted in two children. Cardiomegaly, with predominantly right-sided cardiac enlargement, was seen in 13 children (Fig. 8). In addition, mediastinal and hilar lymph node enlargement was identified in two children. There was no evidence of pericardial thickening in any of the children, and pericardial effusion was seen in only one child. The left pulmonary artery-to-left main bronchus ratio ranged from 1.2 to 3.4 (mean±SD, 2.5±1.2). Similarly, the right pulmonary artery-to-right main bronchus ratio varied from 1.4 to 3.1 (mean±1 SD, 2.1±1.6). There was a weak nonlinear correlation between the MPAP and the pulmonary artery diameter (r=0.53, P=0.03). No other significant correlation was identified between the MPAP and other imaging findings.

Table 1 Intrapulmonary CT findings in children with IPAH

Finding	Number	Percent (%)
Centrilobular opacities	8	47
Peripheral vasculopathy	6	35
Ground-glass opacification	4	24
Septal lines	4	24
Hyperlucent zones	3	18
Mosaic perfusion	1	6

Table 2 Extrapulmonary CT findings in children with IPAH

Finding	Number	Percent (%)
Enlarged pulmonary arteries	15	88
Cardiomegaly	13	76
Lymph node enlargement	3	18
Pericardial effusion/thickening	1	6

Discussion

The diagnosis of idiopathic pulmonary hypertension is, by definition, one of exclusion. At the World Pulmonary Hypertension Symposium in 2003, the name of the condition, previously known as primary pulmonary hypertension, was officially changed to IPAH to reflect the unknown underlying cause.

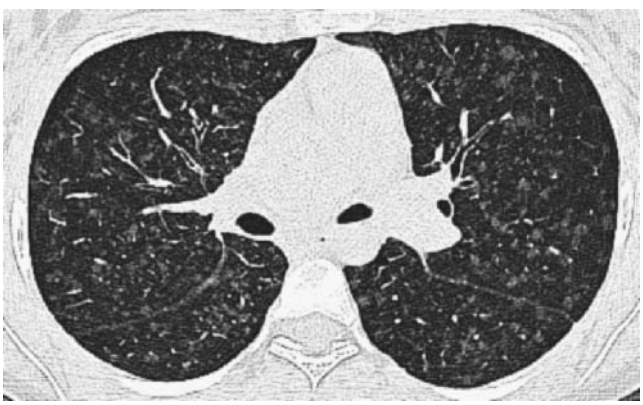

Fig. 1 HRCT in a 15-year-old girl who presented with dyspnea and chest pain. Diffuse centrilobular opacities are seen bilaterally

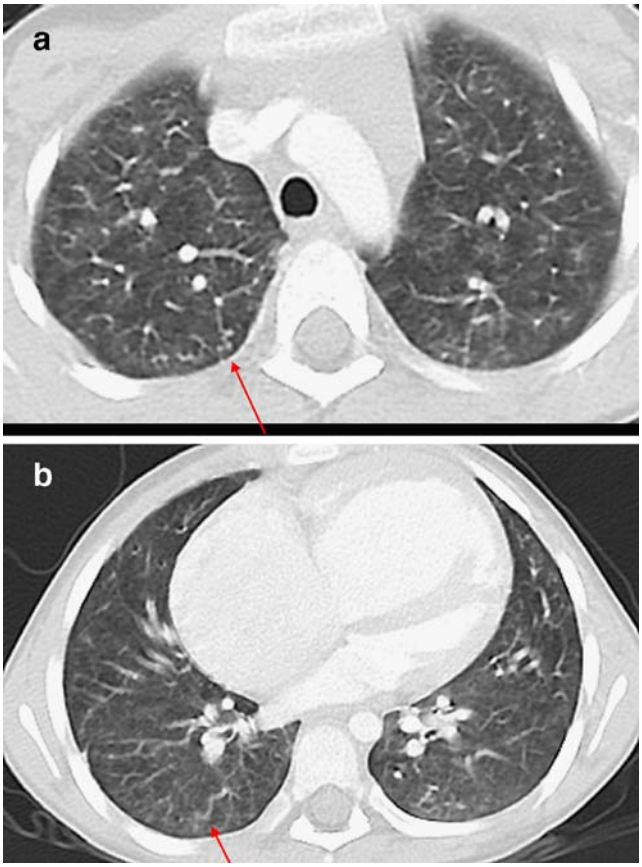

Fig. 2 CECT in a 7-year-old boy with a history of dyspnea on exertion. **a** A tortuous dilated peripheral vessel is seen extending to the periphery of the right lower lobe (*arrow*). **b** CECT in 6-year-old boy presenting with syncope. A small tortuous vessel is again seen in the periphery of the right lower lobe (*arrow*)

IPAH is a rare disease, although the exact frequency in the pediatric population remains unknown [3]. Including all ages, IPAH has an incidence of 1–2 cases per million in the general population [2], and reports suggest that the occurrence of IPAH in children is higher than previously recognized [3]. The definition in children is the same as in adults: MPAP ≥25 mmHg at rest or ≥30 mmHg during exercise. Pathologically, in children the characteristic plexiform lesions are less common, but pulmonary vascular medial hypertrophy is seen more frequently [2]. It has been suggested that pulmonary vasoconstriction leads to medial hypertrophy early in the course of the disease, with subsequent development of fixed vascular changes such as plexiform lesions [9].

The increased reactivity of the vascular bed in children also predisposes these patients to acute pulmonary hypertensive crises that can be triggered by any respiratory infection that results in a ventilation perfusion mismatch [3]. However, recent major advances in therapy, including the use of prostaglandin analogues, endothelin receptor antagonists and phosphodiesterase inhibitors have significantly improved survival and quality of life in these children [3, 10].

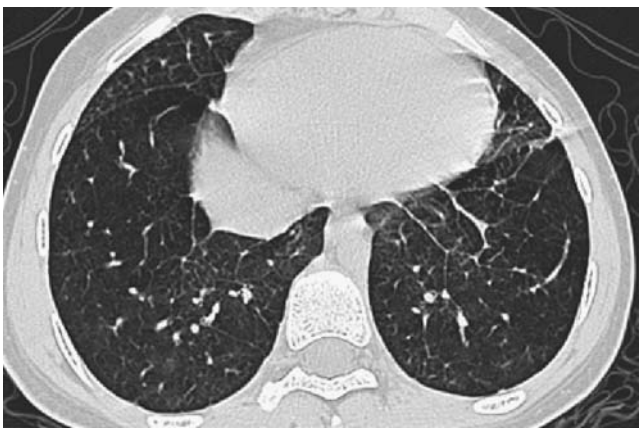

Fig. 3 HRCT image in a 7-year-old girl with exertional dyspnea. Smooth septal thickening is seen in the left lower lobe

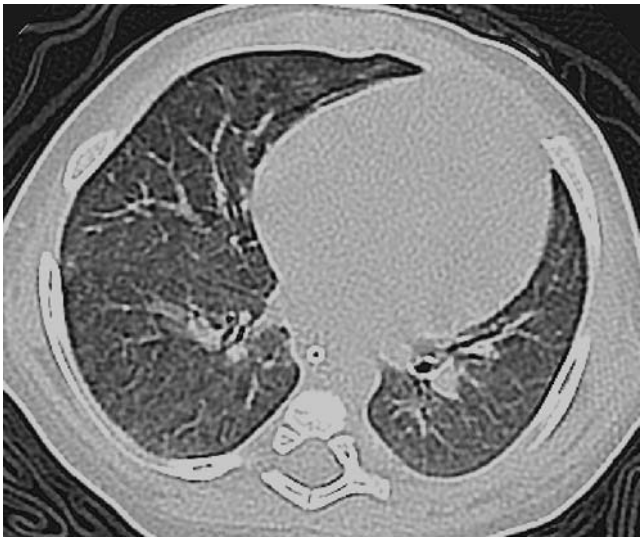

Fig. 4 HRCT image in a 3-month-old girl with cyanosis. Diffuse ground-glass opacification of both lungs is seen

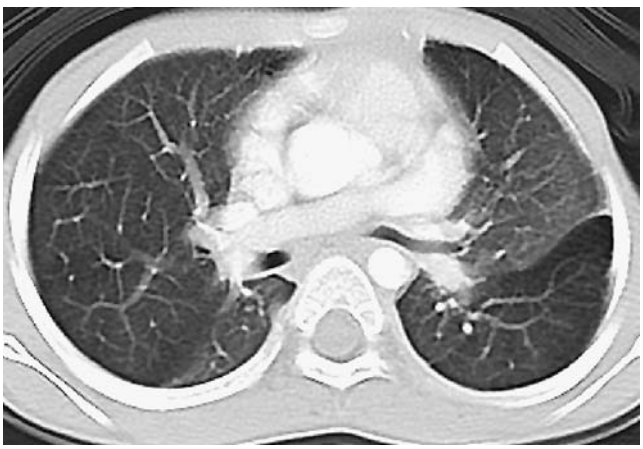

Fig. 5 HRCT in a 6-year-old boy presenting with cyanosis and syncope. Focal areas of hyperlucency are noted, with no significant attenuation of the pulmonary vessels

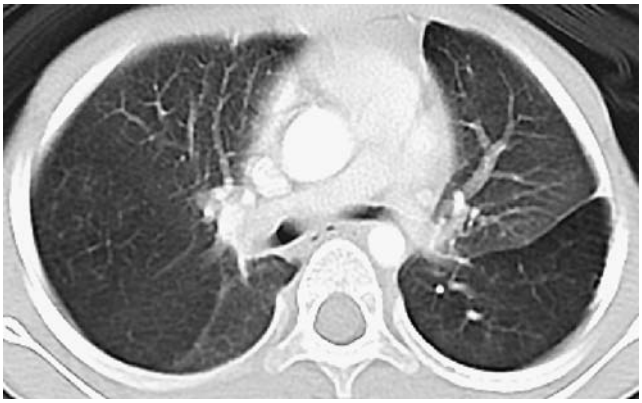

Fig. 6 HRCT image in an 8-year-old girl presenting with exertional dyspnea. Focal areas of hyperlucency are seen with attenuation of the pulmonary vasculature, giving a pattern of "mosaic perfusion"

The clinical presentation is often nonspecific and varies according to the age of the child [2]. As in our series, infants and toddlers generally present with failure to thrive or cyanosis, while older children are more likely to complain of dyspnea on exertion. Chest pain, from right ventricular ischemia, is also seen in older children and might account for crying spells in infants [9].

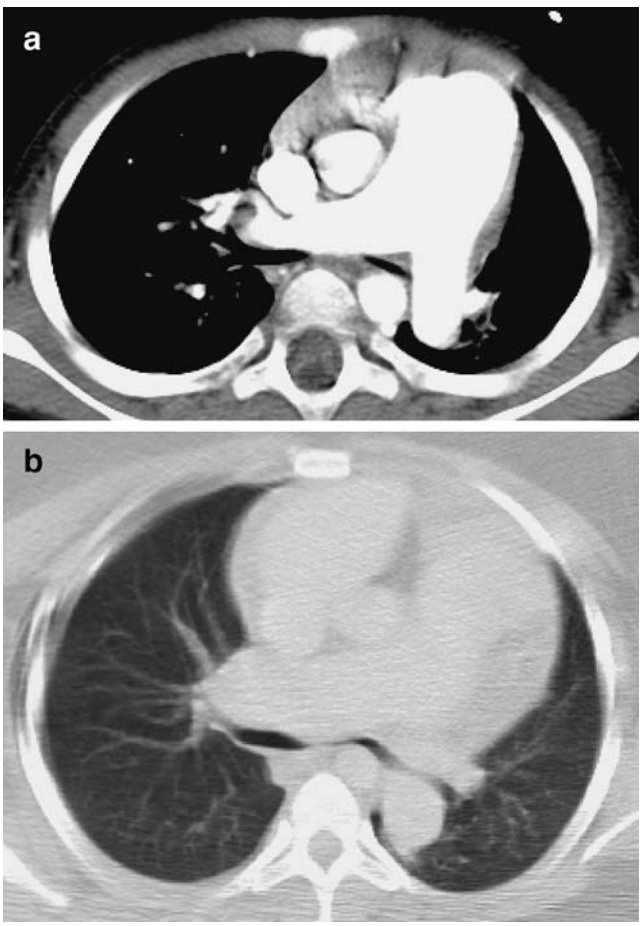

Fig. 7 CECT in a 2-year-old boy with cyanosis. **a** A grossly enlarged pulmonary trunk is seen, with the main pulmonary artery significantly larger in diameter than the thoracic aorta. **b** CECT (lung windows) in a 17-year-old boy with exertional dyspnea and chest pain. The enlargement of the main and left pulmonary arteries has resulted in compression of the left mainstem bronchus

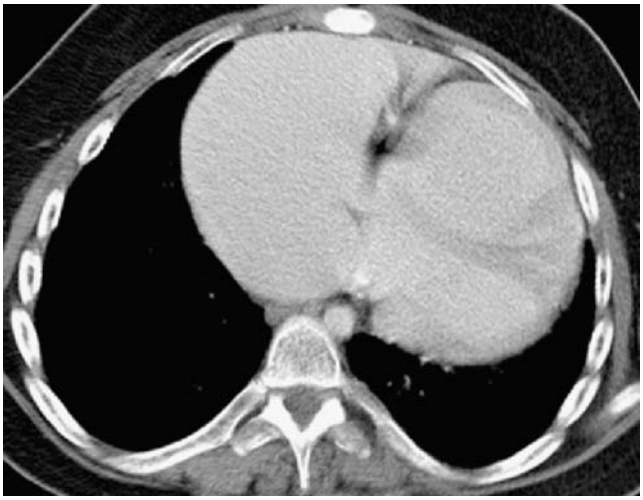

Fig. 8 CECT in a 13-year-old boy with exertional dyspnea and chest pain. An enlarged right ventricle is seen with gross dilatation of the right atrium

The initial investigations in these children are aimed at uncovering potential causative or contributory factors [3]. To this end a CT scan is often performed during the initial evaluation, together with chest radiography, electrocardiography and echocardiography. Previous studies in adults have identified features on HRCT and CT angiography that are consistent with pulmonary hypertension and in some cases suggestive of IPAH [6].

Moderately well-defined centrilobular opacities are commonly seen in pulmonary occlusive small vessel diseases [11] and represented the most frequent finding in our study. However, these remain relatively nonspecific and have also been described in PVOD, sickle cell anemia and chronic postembolic disease [12–14]. Diffuse micronodules, thought to represent cholesterol granulomas, have also been described in IPAH [11] but were not identified in any of our children. Inhomogeneous panlobular ground-glass opacification was seen in a small number of children, together with focal areas of hyperlucency. Although this pattern can also be seen in PVOD, there is usually significant accompanying diffuse septal thickening. In contrast, the septal thickening seen in children with IPAH is less marked and restricted to the periphery.

The peripheral vasculopathy seen in six of our patients has not previously been described with IPAH. Seen as tortuous vessels extending to the periphery, these are of uncertain origin and significance. Possible etiologies include neovascularization or enlarged collateral vessels. The fact that mosaic perfusion was an uncommon finding is consistent with published results of studies in adults, in whom it is more often suggestive of chronic postembolic disease [7].

Central pulmonary arterial enlargement is a reliable feature of pulmonary arterial hypertension. The distal main

pulmonary artery width exceeding the diameter of the ascending aorta has a specificity and positive predictive value of greater than 90% [8]. The degree of pulmonary arterial dilatation has a nonlinear correlation with the mean pulmonary arterial pressure [15]. Consistent with previously published adult data the ratio of right and left pulmonary arteries to right and left main bronchi was greater than 1:1 in all patients, with a mean greater than 2:1 [16]. The majority of our patients also had evidence of cardiomegaly with predominantly right-side cardiac enlargement. Lymph node enlargement was also a relatively uncommon finding, consistent with results in adults, in whom it is seen more consistently with PVOD [12]. However, while pericardial thickening and effusion have been described as a frequent finding in adults with PAH [17], this was identified in only one of our patients. Similarly, while mural calcific deposits in the pulmonary arteries have been described in 23% of adult patients [6], they were not identified in any of the children in our series.

Limitations of our study include the relatively low number of patients. However, pediatric IPAH remains a very rare disease and we are not aware of any previously published series describing the imaging features in this group. A further limitation is that four of the children in our series did not have an HRCT scan performed. Evidence suggests that certain intrapulmonary findings, such as ground-glass shadowing, are still significantly better assessed on HRCT images rather than thin slices reconstructed from volumetric data [18]. A final significant limitation is the lack of a definite pathologically proven diagnosis in the majority of patients. Autopsy and post-transplantation pathology findings were available in three children, while the remainder either did not have an autopsy performed or had graduated to adult services. However, all children in the study underwent extensive investigation, with no other underlying cause identified.

Conclusion

IPAH presenting in childhood is a rare progressive condition, but early recognition and treatment can significantly alter the natural history of the disorder. IPAH remains a diagnosis of exclusion, and CT of the chest is often undertaken in an attempt to identify other underlying causes. However, the diagnosis should be considered in the setting of central pulmonary arterial enlargement and cardiomegaly without mediastinal lymphadenopathy. Intraparenchymal findings consistent with the diagnosis include centrilobular opacities, patchy ground-glass shadowing and a peripheral vasculopathy in the absence of diffuse septal thickening.

Reflecting the important clinical and pathological differences from adult-onset disease, there do appear to be some significant differences in imaging appearance. Pericardial thickening and mural calcific deposits are frequently noted in adults, but appear to be rare in children. Conversely, a peripheral vasculopathy appears to be much more common. Therefore, while angiography remains the gold-standard investigation for diagnosis, CT represents a useful non-invasive modality in the initial evaluation of IPAH.

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