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Plexiform Pulmonary Arteriopathy in a 2 Year-Old Boy

İki Yaşındaki Erkek Çocuğunda Pleksiform Pulmoner Arteriyopati

Sabah BOUDJEMAA[1], Valérie MEAU-PETIT[2], Fazia HALLALEL[2], Aurore COULOMB[1], Jill LIPSETT[3]

Department of [1]Pathology and [2]Reanimation, Hopital Armand Trousseau, PARIS, FRANCE
[3]Department of Pathology, Women's and Children's Hospital, ADELAIDE, AUSTRALIA

ABSTRACT

Idiopathic pulmonary arterial hypertension is a rare disease in children. We report a case of a 2-year old boy admitted to the intensive care unit of our hospital for severe dyspnea and epistaxis. Laboratory investigations showed hemolytic anemia with schizocytes and severe thrombocytopenia. Cardiac investigations diagnosed supra-systemic pulmonary arterial hypertension, which was refractory to maximal medical treatment. On evolution, he had several cardiac arrests and finally died 8 days after admission. Autopsy was performed and showed typical lesions of idiopathic pulmonary hypertensive arteriopathy characterized by plexiform lesions of the interlobular arteries containing numerous disseminated intravascular microthrombi. The rest of the family was screened, DNA was stored, and genetic study of BMPR2 was planned.

Key Words: Child, Pulmonary hypertension, Lung Diseases

ÖZ

İdiyopatik pulmoner arteriyel hipertansiyon çocuklarda ender görülen bir hastalıktır. Hastanemizin yoğun bakım ünitesine şiddetli dispne ve epistaksis şikayeti ile kabul edilen 2 yaşında bir erkek çocuk olgusunu sunuyoruz. Laboratuvar bulgularında şistosit ve şiddetli trombositopeni gözlenen hemolitik anemi mevcuttu. Kardiak araştırmalarda maksimum tıbbi tedaviye dirençli supra-sistemik arteryel hipertansiyon saptandı. Hastalığın seyrinde çok sayıda kardiyak arrest gelişti ve hastaneye yattıktan 8 gün sonra öldü. Otopside çok sayıda yaygın intravasküler mikrotrombus içeren interlobular arterlerin pleksiform lezyonlarıyla karakterize tipik idiyopatik pulmoner arteriyel hipertansiyon izlendi. Ailenin diğer fertleri araştırıldı, DNA'ları alındı ve BMPR2 genetik çalışması planlandı.

Anahtar Sözcükler: Çocuk, Pulmoner hipertansiyon, Akciğer hastalıkları

INTRODUCTION

Idiopathic pulmonary arterial hypertension (PAH) is a rare disease in children. Classical clinical presentation in children is nonspecific as in adults including dyspnea, syncope and chest pain. Plexiform lesions constitute the hallmark of irreversible lung vessel disease, seen in severe, advanced pulmonary hypertension and are associated with a poor prognosis. The pathogenesis of these lesions is not well understood but they appear related to endothelial cells growth deregulation and increased migration and proliferation of smooth muscle cells and fibroblasts leading to structural changes in the pulmonary arterial wall and pulmonary vascular remodeling. We report a case of a 2-year-old boy admitted to the intensive care unit for severe dyspnea and epistaxis. Despite intensive treatment, he had several cardiac arrests and died 8 days after admission. Autopsy was performed and showed typical lesions of idiopathic pulmonary hypertensive arteriopathy characterized by plexiform lesions of the interlobular arteries with numerous disseminated intravascular microthrombi.

CASE REPORT

A 2-year old boy was admitted via the Emergency Department to the Intensive Care Unit of our hospital for severe asthma, and profuse epistaxis. His mother reported that he had experienced recurrent episodes of epistaxis and bronchitis treated with inhaled steroids over the last year. His immunizations were up to date. The current history started with dyspnea that had progressively worsened over a few days.

On examination, he was conscious and tachypneic (70/min). His central temperature was 39°C and his oxygen saturation on air was 88%. He had bilateral profuse epistaxis. Chest examination showed wheezing, ronchi and a diastolic 3/6 heart murmur. The rest of the examination

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Correspondence: Sabah BOUDJEMAA
Hopital Armand Trousseau, Department of Pathology, PARIS, FRANCE
E-mail: sabah.boudjemaa@trs.aphp.fr Phone: +33 144 73 60 18

was normal. Chest X-ray showed an enlarged pulmonary artery trunk with right heart dilation, while the lungs demonstrated consolidation of the right inferior lobe and diffuse interstitial opacities. Laboratory investigations results were as follow: Arterial gas on 3l/min oxygen: pH 7.45, PCO2 18.4 mmHg, PO2 70 mmHg. Full blood count: hemoglobin (Hb) 9.4 g/dl with 4% schizocytes, platelets (Pts) 18 000/mm3 and white blood cells (WBC) 34 000/mm3 with 80% of neutrophils. Hemostasis: Factor I 4g/l, II 58%, V 51%, VII + X 52%. Haptoglobin was undetectable. C-reactive protein (CRP), ferritin, renal and liver function tests were normal. Myelogram was normal. HIV, HBV, HCV and CMV serologies were negative. Treatment comprised nasal oxygen 3l/min, 4 hourly antibiotics (tazocillin and gentamycin), platelet infusions and intravenous immunoglobulins. Two days after admission, a thoracic and abdominal CT-scan showed intraparenchymal micronodules throughout the lungs, with marked dilation of the main pulmonary artery trunk (35 mm) and the right and left main pulmonary branches (18 mm). There was marked dilation of the right atrium and ventricle, and polysplenia. The Ivemark syndrome was thus suspected. On Day 3, he experienced his first cardiac arrest. He was intubated and ventilated on 100% oxygen. Cardiac ultrasound diagnosed systemic pulmonary hypertension with a right to left shunt through the foramen ovale and confirmed the dilation of the right heart chambers and of the main pulmonary trunk and branches. Right and left ventricular function was impaired. The heart was otherwise anatomically normal.

Nitric oxide and epoprostenol infusion were added to his management but he was unresponsive, experiencing 3 further cardiac arrests and requiring inotropic support with dobutamine and milrinone. He finally succumbed eight days after his admission.

The autopsy confirmed polysplenia with 10 small spleens identified (Figure 1). The liver was abnormal macroscopically with 2 symmetrical lobes located either side of the gallbladder. Basic cardiac anatomy was normal with atrial situs solitus, atrio-ventricular and ventriculo-atrial concordance. The right heart chambers were dilated. The lungs were very dense and dark red/blue (Figure 2). Both lungs were bilobed, with the right lung weighing 211 g and the left lung 165 g. On microscopic examination, the basic underlying pulmonary architecture was normal.

There were generalised severe changes observed involving the muscular pulmonary arteries, most developed in intralobular arterioles. These changes included medial thickening with cellular intimal proliferation and concentric laminar fibrosis in an "onion-skin" pattern that was associated, in some vessels, with complete luminal obstruction. Medial thickening was estimated to be 65% of the external vascular diameter. Intimal changes demonstrated a cellular proliferation between the endothelium and the internal elastic lamina with concentric fibrosis, encroaching on the lumen. Dilatation and plexiform lesions were also observed (Figure 3). The latter were characterized by an angiomatoid, glomeruloid proliferation of small, slit-like vessels within a dilated lumen of arteries that showed destruction of the wall, loss of the elastic lamina and thinning of the media. Dilatation lesions comprised arterioles with thinned walls, clustering into angioma-like proliferations around thickened parent

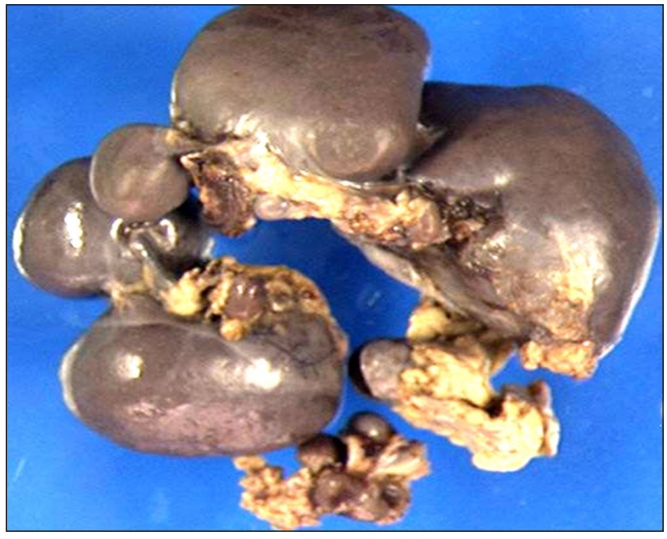

Figure 1: Polysplenia: Presence of about 10 spleens measuring 5 to 60 mm.

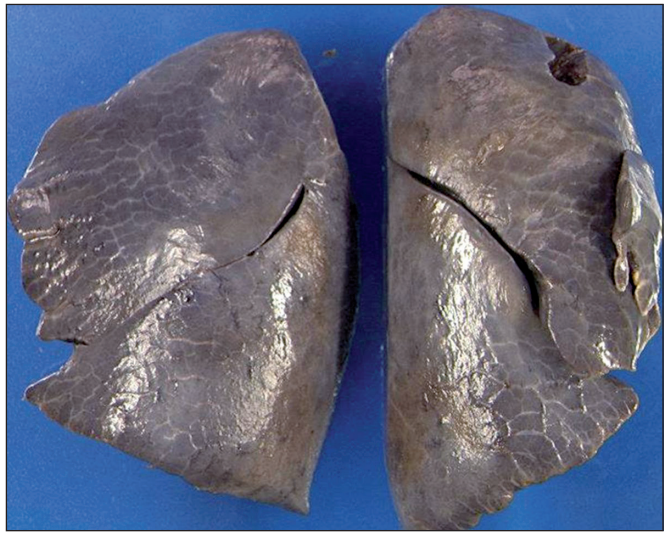

Figure 2: Both lungs were bilobed, with dense and dark red/blue appearance and firm consistency.

arterioles. Numerous microthrombi were seen within the lumina of these lesions (Figure 4). The presence of medial hypertrophy and the extension of the lesion outside the lumen of the parent artery ruled out recanalized thrombi (colander-like lesions).

There was no veno-occlusion and no hemosiderin deposition evident. Focally there were numerous capillaries with a pseudo pulmonary capillary hemangiomatosis pattern. These lesions were not associated with inflammatory cells. Numerous megakaryocytes could be identified throughout the lung parenchyma. There was alveolar edema and congestion related to the multivisceral failure. Airways appeared normal and hilar lymph nodes showed vascular transformation.

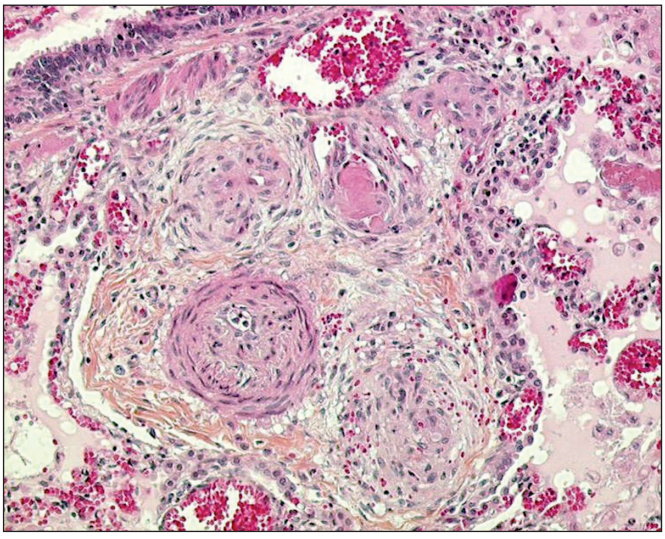

Figure 3: Plexiform lesions consisting in: stenotic muscular arteries (onion skin pattern), proliferation of endothelial cells in stenotic muscular arteries (angiomatoid proliferation) and distal network of dilated thin-wall vessels (dilatation lesions) (H&E; x400).

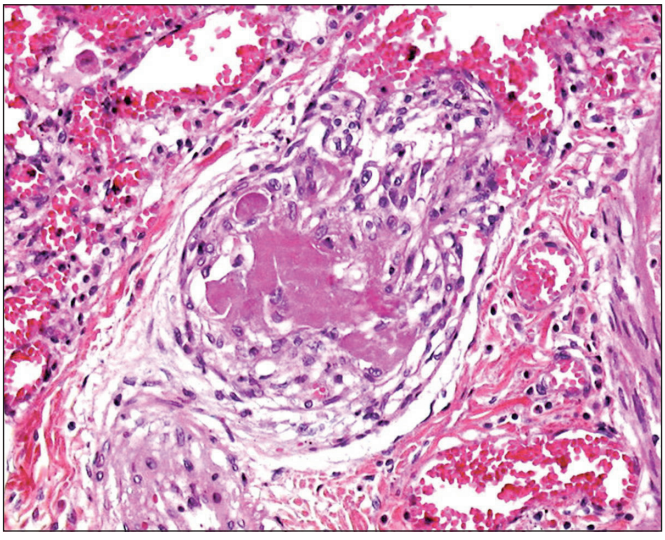

Figure 4: Microthrombi occluding the lumina of arteries (H&E; x400).

In conclusion, the appearances were typical of idiopathic pulmonary arteriopathy characterized by plexiform lesions involving interlobular arteries containing numerous disseminated intravascular microthrombosis. DNA was stored and genetic study of BMPR2 was planned.

DISCUSSION

Pulmonary arterial hypertension (PAH) is rare in childhood. A clinical classification of PAH for both adults and children was proposed in 1998 at Evian, France and was revised in 2003 in Venice (1). International diagnostic and management guidelines were published in 2004 (2). The most common causes of PAH in children are idiopathic or familial PAH, congenital heart disease with left-to-right shunt, chronic hypoxia (chronic lung disease of prematurity) and persistent pulmonary hypertension of the newborn. Connective tissue disease, chronic thrombo-embolism, HIV, portal hypertension, sarcoidosis, sickle cell disease and anorexigen related PAH are mainly observed in adults. A Swiss registry established in 1999 categorised 23 children over a 7-year period and showed a high prevalence of congenital heart disease (52%), with idiopathic PAH (34%) and PAH associated with pulmonary disease (13%) (3).

To achieve the best outcomes, PAH in children should ideally be recognised early so as to institute life-saving treatment, and minimize complications. In this case the child presented with asthma and epistaxis. The clinical presentation of PAH in children and adults is notoriously non-specific and includes dyspnea, syncope and chest pain. In children, the main differential diagnosis is asthma but the respiratory signs do not resolve with bronchodilatators. In addition this child presented with epistaxis related to thrombopenia. Hemolytic anemia with schizocytes and thrombopenia can be explained on the basis of numerous microthrombi within the plexiform lesions and sequestration of the numerous megakaryocytes in the lung parenchyma. Epistaxis at presentation, related to intrapulmonary platelet sequestration has not been described before in PAH.

Cardiac catheterization remains the "gold standard" for diagnosis, assessing the severity of PAH, determining prognosis and thus establishing the appropriate treatment regime. PAH in children is characterized by increased acute vasoreactivity when compared to adults, thus permitting more responsive treatment with calcium channel blockers.

Recent therapeutic advances have dramatically improved the prognosis of PAH. These advances include the use of intravenous prostacyclin derivatives, including epoprostenol and targeted therapy with endothelin-receptor antagonists (bosentan) and phosphodiesterase type 5 inhibitor (sildenafil). Some of these treatments have been used in children. In children with syncope, atrial septostomy may be performed. For this patient, clinical evolution was acute and the child didn't respond to vasodilatator treatment with nitric oxide and epoprostenol.

In this observation, pathological examination ruled out secondary causes of PAH. There was no evidence of veno-occlusive disease, pulmonary capillary hemangiomatosis, interstitial or alveolar lung disease, chronic thrombotic or embolic disease. Post-mortem examination showed no heart anomalies except a distended right heart without any shunts. Polysplenia was identified but without situs inversus.

Plexiform lesions represent the hallmark of this disease. It is speculated they develop in areas of fibrinoid necrosis in association with spastic vasoconstriction (4). Research into the molecular pathways triggering the remodeling process is incomplete but studies have shown an important role for the TGF family in modulating extracellular matrix synthesis (5). In a recent study (6) performed to assess whether matrix cross-linking enzymes played a role in experimental pulmonary hypertension, all 5 lysyl oxidases were detected in concentric and plexiform vascular lesions. Lox, Lox1, Lox 2 and Lox 4 expression was elevated in lungs of patients with idiopathic PAH. Lysyl oxydases seem then to play a role in experimental pulmonary hypertension and may represent an interesting therapeutic target.

Genetic abnormalities are thought to account for 10% to 20% of all patients with idiopathic PAH within half of whom mutations in BMPRII gene have been identified encoding one of the TGF superfamily receptors (7). In this case, there was no family history of pulmonary hypertension and prospective screening of the whole family, the parents and three older sisters, confirmed no other cases. The presence of other abnormalities noted at autopsy, including abnormalities of lung, liver lobation and polysplenia lend support to an underlying genetic developmental basis. The parents were counselled and consented to DNA extraction, storage and investigations including BMPRII mutation analysis.

In conclusion, pediatric idiopathic pulmonary arterial hypertension is a rare disease with usually nonspecific symptoms. The pathognomonic histological pattern (plexiform lesions) of this disease should be known by pathologists to allow an early diagnosis and a precocious management of these children.

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