

A rare cause of death in infancy: idiopathic infantile arterial calcification

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Key words

Forensic science, autopsy • Generalized arterial calcification • Infancy • Death

Summary

The aim of this paper is to report the autopsy findings of an Idiopathic Infantile Arterial Calcification-new-born male and describe its follow-up. Y.R, a 23-days-old male, hasn't any relevant personal past medical or family history. The baby was weighing 3.2 kg at birth. He was breast fed and appeared to be perfectly normal. In the last 24 hours, he presented to the family doctor with vomits, refuse of feeds without fever or diarrhea. He was diagnosed as having gastroenteritis and was medicated accordingly. A few hours later, he had an hematemese episode associated with facial

cyanosis. Death occurred despite cardio-pulmonary resuscitation. Forensic autopsy was required. The macroscopic examination showed a bilateral pleural liquid effusion without any other abnormalities. Microscopic investigation revealed a generalized arterial calcification of all organs. Idiopathic arterial calcification is primarily a disease of infancy. It is characterized pathologically by generalized arterial calcification within the internal elastic lamina, associated with intimal fibrous proliferation. Death occur often in the first sixth months due to heart failure.

Introduction

Idiopathic Infantile Arterial Calcification (IIAC) is a rare autosomal recessive disorder usually diagnosed at autopsy. To date, the reported cases in literature are about 200¹. It is characterized pathologically by generalized arterial calcification within the internal elastic lamina, associated with intimal fibrous proliferation. Death occur often in the first sixth months of life because of the difficulty of an early diagnosis and the lack of a curative treatment². The aims of this paper are to report a new case of IIAC, to describe its necropsy findings and to describe its follow-up.

Case report

We present the case of a 23-days-old male child, without any personal past medical or familial history. Her birth history was unremarkable. His mother, 32-years-old, had been well during pregnancy with no history of medication or extra vitamin ingestion. The father, 44-years-

old, was well too. This child was the second child of unrelated teenage parents and had a 10-year-old brother who was well. On 23, November 2012, this child presented with vomits and refuse of feeds, without fever or diarrhea for one day. He was crying all the time. He was diagnosed as having gastro-enteritis and was medicated accordingly. A few hours later, he had an hematemese episode associated with facial cyanosis. He was admitted into the emergency room where he developed cardio-respiratory arrest without response to the intensive care resuscitation procedures. A forensic autopsy was requested by authorities.

In necropsy examination, the external examination revealed no dysmorphic features. The biometrical parameters (weight, height and cephalic perimeter) were within normal range (percentile 50). Internal examination showed a bilateral pleural pulmonary effusion (18 cc). The heart weighted 39 grams (normal weight at 3 weeks = 19gr). The wall of the left ventricle was 5 mm thick. The valvular apparatus was macroscopically normal. The coronary arteries showed a normal anatomical pattern. Major arteries (aorta, pulmonary,

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Fig. 1. Coronary arteries showing irregular calcifications (HE x 100).

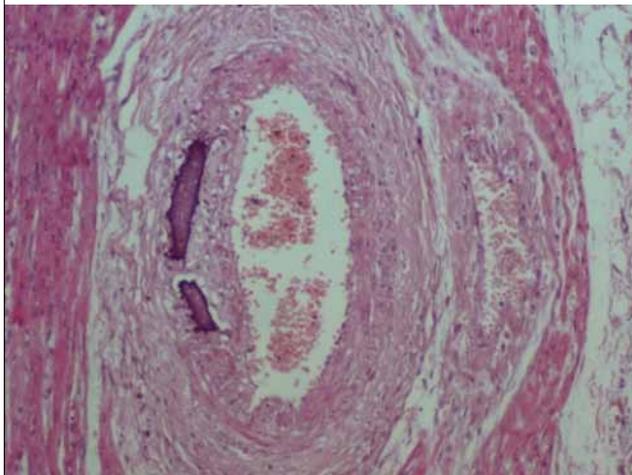


Fig. 2. Pancreatic arteries showing irregular calcifications (HE x 100).

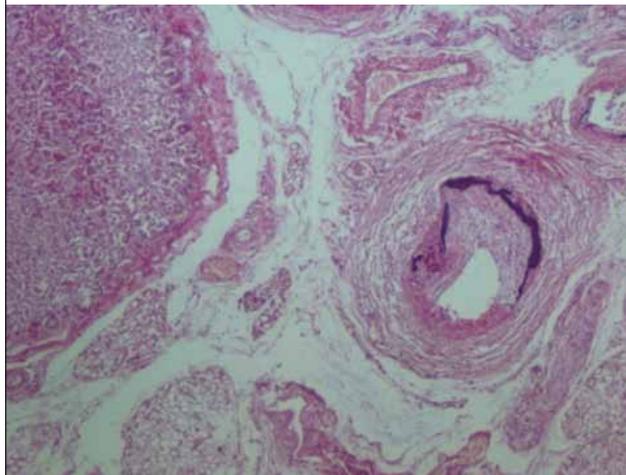


Fig. 3. Pulmonary arteries showing irregular calcifications (HE x 200).

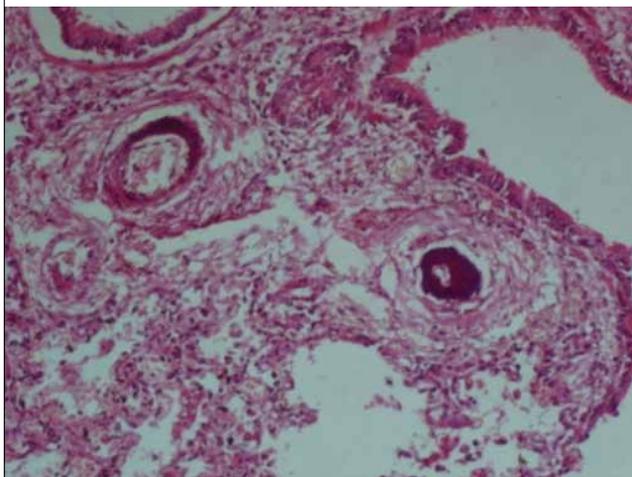
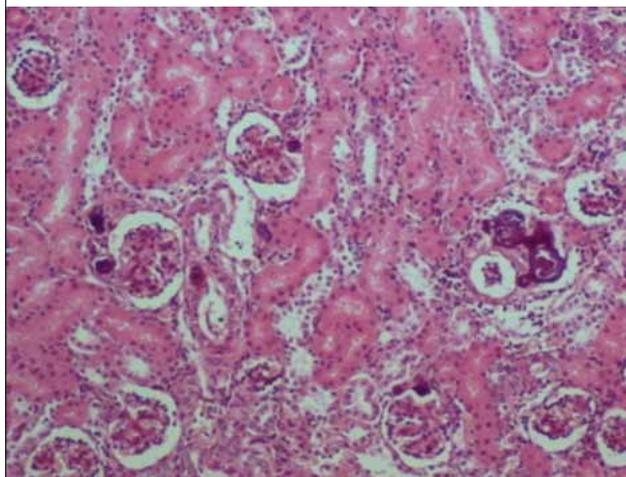


Fig. 4. Renal arteries showing irregular calcifications (HE x 200).



carotid, and renal arteries) were unremarkable. The pericardium, pulmonary, and systemic venous drainage were normal.

Histological tests revealed a widespread calcification in the intima and media of large and medium-sized arteries of several organs (coronary, pancreatic, renal, pulmonary and thymic arteries) (Figs. 1, 2, 3, 4). The lungs were oedematous and there was also hypertrophy of left ventricle myocardium without any signs of acute infarction or fibrosis. The toxicological screening was negative. Genetic examination of the parents and surviving sibling was not made because they were out of sight.

Discussion

Generalized arterial calcification is an idiopathic variety of arterial calcification that is well described in infancy and childhood. It is a rare autosomal recessive disease³.

This is usually a fatal disease. The incidence of IIAC is unknown but over 200 cases have been described in literature. The incidence of this disease is approximately equal for males and females⁴.

Several theories explaining this pathologic condition have been presented in the literature like a disorder of connective tissue⁵, a defect of the endothelium which may promote the intimal proliferation⁶, an alteration in iron metabolism⁷ or a hemodynamic perturbation secondary to a stress sustained in utero may prime the arteries for later development of idiopathic infantile arterial calcification⁸.

Inactivating mutations of the ecto-nucleotide pyrophosphatase/phosphodiesterase 1 gene (ENPP1) were reported in 80% of the cases with IIAC. Some patients have late manifestations of the disease without mutations in the ENPP1 gene, probably due to alterations of other still unknown gene(s)⁹. In our case, it was not possible to evaluate ENPP1 gene alterations.

The most common symptoms are respiratory distress,

with cyanosis and tachycardia, usually in a previously healthy infant. However, some infants present with gastrointestinal symptoms, especially vomiting and refusal to feed, such in our case, followed by poor weight gain, lethargy and convulsions. Most patients have died between the first few days of life and one year, the majority dying in the first 6 months¹⁰, like our case. Death is usually attributed to acute cardiac failure or myocardial ischemia, due to changes in the coronary arteries. These changes were secondary to intimal thickening². In our case, histological testing revealed a calcification in the wall of coronary arteries and a left ventricle hypertrophy without signs of myocardial infarction. Those findings lead to suggest that death was probably attributed to rapidly progressive heart failure with refractory hypertension. Both clinicians and pathologists must be aware of this entity when they are presented with a suggestive clinical background.

The histopathological features include an intimal fibroblastic proliferation of medium and large-sized vessels with extensive calcifications. This results from the deposition of calcium hydroxyapatite in the internal elastic lamina layer.

Differential diagnosis arises with arterial calcifications associated with anomalies of the heart and great vessels, hypervitaminosis D, primary or secondary hyperparathyroidism and also sepsis with myocarditis or endocarditis². The diagnosis is almost always made in postmortem. The frequent autopsy findings are myocardial hypertrophy, like our case, subendocardial fibrosis and tortuous coronary arteries. Moran and Becker⁴ in their review found 5 cases with thrombosis of coronary vessels, 14 with definite myocardial infarction, and 10 with myocardial fibrosis.

The gold standard for diagnosis is arterial biopsy, but this invasive technique can be replaced by some standard imaging techniques: foetal ultrasonography, usually showing hyperechogenicity of the walls of major arteries and signs of fetal hydrops with heart chamber hypertrophy and cardiomegaly. This test is recommended in future pregnancies of the affected families^{11, 12}. However, there is no evidence that early detection can improve the prognosis of this disease. So far, there are fourteen long-term survivors reported in literature, most of them with an early diagnosis¹³. Diphosphonate has been successful in minor (not advanced) cases. In more severe cases, it has been reported to improve the degree of vascular calcification but it does not prevent lethal progression of intimal vascular occlusion^{14, 15}.

In conclusion, idiopathic arterial calcification is a disease of infancy. This condition should be suspected in

any child presenting with heart failure, hypertension and signs of ischemia. Because of the genetic etiology, once the diagnosis is made, the family should be informed and genetic counseling must be made. In our case, genetic examination of the parents and surviving sibling was not made because they were out of sight.

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