Cardiovascular Pathology 36 (2018) 15–19

Contents lists available at ScienceDirect

Cardiovascular Pathology

Case Report

Coronary pathology of inherited generalized arterial calcification of infancy: a case report

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ARTICLE INFO

Article history:
Received 21 March 2018
Received in revised form 26 April 2018
Accepted 14 May 2018
Available online xxxx

ABSTRACT

Generalized arterial calcification of infancy (GACI), or idiopathic infantile arterial calcification, is a rare autosomal-recessive disease recognized aAs an inherited disorder characterized by severe pathologic calcification of large- and medium-sized arteries accompanied by smooth muscle cell (SMC) hyperplasia leading to vascular obstruction [1]. The prognosis is extremely poor, with 85% of affected infants dying within the first 6 months of life. Loss-of-function mutations in the ectonucleotide pyrophosphatase phosphodiesterase 1 (*ENPP1*) gene is recognized as the main defect associated with GACI [1]. The underlying pathogenesis of osteogenic transition leading to calcification and severe stenosis in GACI, however, is poorly understood. Herein, we present a case of a GACI patient with cardiac complications who exhibited extensive vascular disease at autopsy.

1. Case

An 8-month-old boy, second son of consanguineous parents of Turkish nationality, was admitted to the hospital (Papa Giovanni XXIII Hospital, Bergamo, Italy) in cardiogenic shock. An electrocardiogram showed evidence of myocardial ischemia in anteroseptal and inferolateral regions of the left ventricle (LV). Coronary angiography revealed severe multivessel disease with diffuse stenosis of the left anterior descending artery (LAD). His older sister had died of sudden cardiac arrest at the age of 3 months. Genetic testing revealed a mutation of the *ENPP1* gene confirming the diagnosis of GACI. The patient died after a short period of relative clinical stability.

Gross examination of the heart demonstrated prominent coronary arteries (CAs), especially the distal segment of LAD (Fig. 1). The LV showed hypertrophy with dilatation along with a circumferential subendocardial healed myocardial and a transmural infarction of the posterior LV and ventricular septum. Radiographic imaging of the dissected CA revealed focal to diffuse calcification involving all major CAs (Fig. 1).

Histological examination of major CAs showed focal disruption of internal elastic lamina (IEL) with mild to severe intimal thickening composed of SMCs, extracellular matrix, and chronic inflammatory cells, especially in highly calcified lesions. The hallmark of GACI phenotypic change is represented by calcification involving disrupted fragments of IEL, at the intimal-medial border. (Fig. 2). Severe intimal thickening from SMC hyperplasia along with disruption and reduplication of IEL close to the lumen was also common (Fig. 3). The progression of calcification involved the gradual disruption and loss of IEL with a parallel increase in hydroxyapatite deposits. Initially, SMCs were the predominant cell-type bordering regions of calcification, but as the mineral deposits enlarged and encroached on the lumen, there were infiltrates of chronic inflammatory cells mainly consisting of T lymphocytes and macrophages (Fig. 3). Remarkably, the intramyocardial arteries were always spared without evidence of disease. Moreover, other vascular beds, such as aorta and its major branches, similarly showed early calcification accompanied by an SMC-rich neointima (Fig. 4).

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https://doi.org/10.1016/j.carpath.2018.05.001
1054-8807/

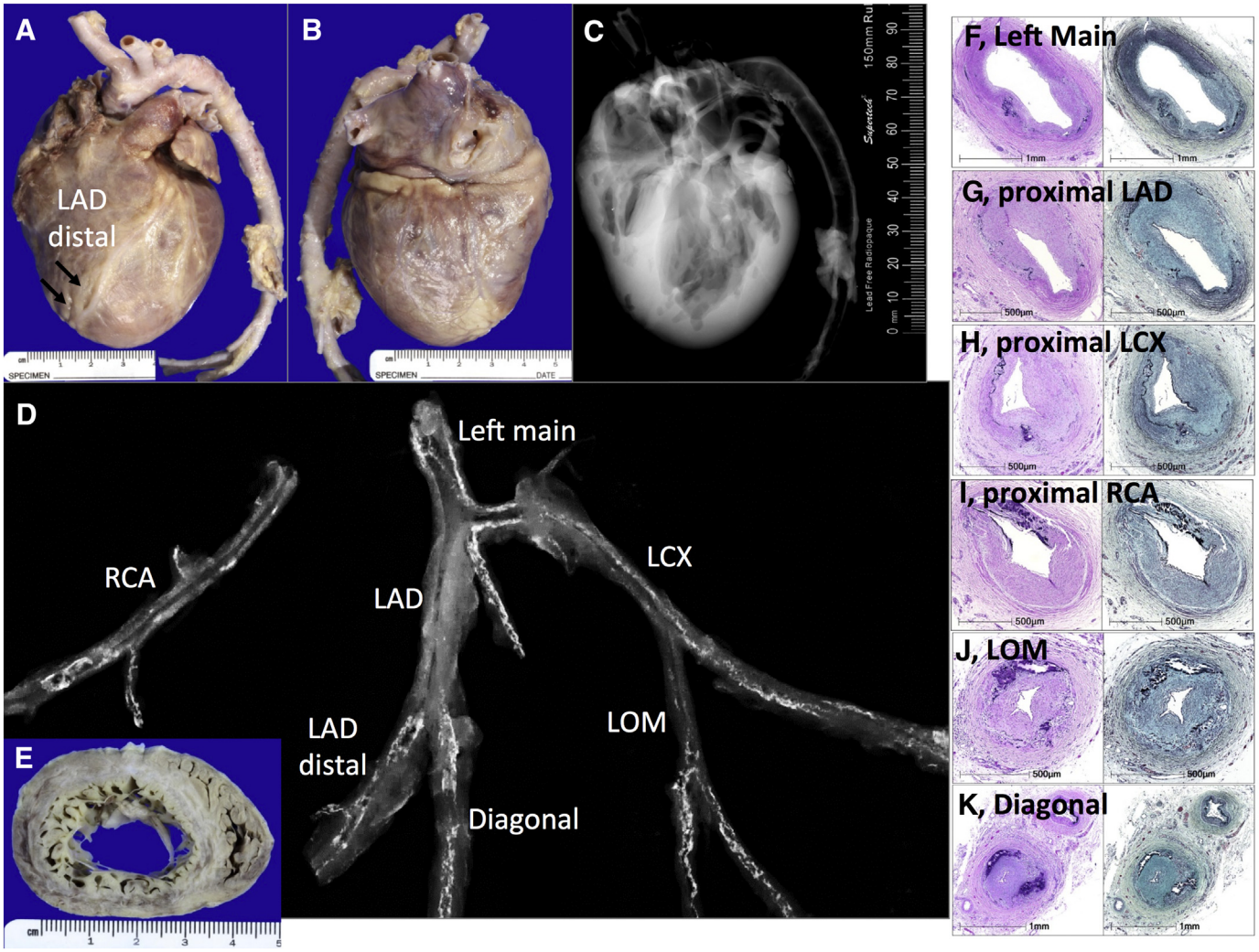

Fig. 1. Gross, radiographic, and histologic images of heart and CA. Gross and radiographic images of a heart with attached aorta (A–C) shows calcification of the major CAs and branches. Note that calcification is most prominent in distal LAD (panel A, black arrows) and diagonal arteries with mild overlying epicardial thickening. Radiographs of excised CAs (D) demonstrate focal calcification of all major branches [left main, LAD, left circumflex artery (LCX), and right CA (RCA)]. (E) Mid-LV slice demonstrates dilatation and subendocardial circumferential healed myocardial infarction along with transmural scarring of the posterior septum and posterolateral wall. (F–K) Hematoxylin and eosin-stained (left) and Movat pentachrome-stained (right) sections of the major CAs and branch vessels clearly demonstrate moderate to severe luminal narrowing with varying degrees of calcification and near circumferential disruption of IEL (LOM: left obtuse marginal).

2. Discussion

Mutations in the *ENPP1* gene represent the underlying abnormality of the rare, incurable autosomal-recessive disorder of GACI accounting for more than 75% of the affected cases [2]. There is, however, a considerable phenotypic overlap with a related calcification disorder, pseudoxanthoma elasticum (PXE; prevalence, approximately 1:25,000) also characterized by elastin fragmentation, reduplication, and mineralization, whereby dystrophic calcification of soft connective tissues including the skin and eyes, and arterial media is linked to a different genetic mutation in gene *ABCC6* [1]. Evidence suggests that *ABCC6* may also be a relevant candidate gene in some cases of GACI without mutations in the *ENPP1* gene, and GACI may be an atypical and severe end of the vascular phenotype spectrum of PXE [3]. In a series of 30 patients reported with GACI, *ENPP1* mutations were identified in 28, although nearly half also exhibited *ABCC6* mutation [3]. In comparison with GACI, PXE is a late-onset, slowly progressing disease; however, PXE and GACI are considered to reflect two ends of a clinical spectrum of ectopic calcification and other organ pathologies, rather than two distinct disorders. Despite a reasonable understanding of genetic inheritance, the precise physiologic substrate(s) of *ENPP1* and *ABCC6* underlying the widespread dystrophic calcifications of PXE and GACI remains largely unknown.

One contention for widespread arterial calcification in GACI suggests that the primary defect involves fragmentation of elastic fibers inciting secondary calcification, while others implicate abnormalities in calcium metabolism [1]. *ENPP1* is a cell surface enzyme generates inorganic pyrophosphate (PPi), a known inhibitor of hydroxyapatite crystal deposition. Inactivating mutations in *ENPP1* in GACI restrict PPi generation leading to hydroxyapatite deposition, through inorganic phosphate (Pi), which is a component of hydroyapatite crystal growth [4].

Our case exhibited a spectrum of early to late calcification of CAs beginning with linear deposits colocalized to areas of focal IEL fragmentation in plaques with limited SMC hyperplasia.