Cardiovascular Pathology 24 (2015) 310–316

Contents lists available at ScienceDirect

Cardiovascular Pathology

Clinical Case Report

Cardiovascular pathology in 2 young adults with sudden, unexpected death due to coronary aneurysms from Kawasaki disease in childhood

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ARTICLE INFO

Article history:
Received 9 December 2014
Received in revised form 18 February 2015
Accepted 18 February 2015

Keywords:
Kawasaki disease
Sudden death
Coronary artery aneurysm
Myocardial fibrosis
Autopsy
Transforming growth factor beta

ABSTRACT

Purpose: Coronary artery aneurysms (CAA) may remain silent after Kawasaki disease (KD) until adulthood when myocardial ischemia can lead to sudden death. We postulated that there would be young adults with sudden, unexpected death due to CAA from KD who would have a state-mandated autopsy performed by the San Diego County Medical Examiner's Office (SDCMEO).
Methods: We reviewed all autopsy cases <35 years of age from 1997 to 2012 at the SDCMEO with a cardiovascular cause of death (n = 154).
Results: We found 2 cases meeting inclusion criteria. Case 1 was a 22-year-old Korean male with chronic ischemic changes due to a partially occluded and diffusely calcified 15 mm aneurysm at the bifurcation of the left main coronary artery. Interview of the mother revealed that this patient had been diagnosed with KD complicated by giant aneurysms at age two years. Case 2 was a 30-year-old Hispanic male with myocardial infarction due to thrombosis of a calcified left anterior descending artery aneurysm. Histologic findings included diffuse myocardial fibrosis and a recanalized aneurysm in the right coronary artery. Interview of the family revealed a KD-compatible illness in childhood. Immunohistochemical staining showed expression of transforming growth factor β pathway molecules in the aneurysmal arterial wall.
Conclusions: In a medical examiner's office serving a population of approximately 3 million people, 2 of 154 (1.3%) cardiovascular deaths in persons <35 years were attributed to cardiovascular complications of KD in childhood. Antecedent KD should be considered in the evaluation of all cases of sudden, unexpected death in young adults.

1. Introduction

Kawasaki disease (KD) is an acute vasculitis of unknown origin that occurs predominantly in young children. Although the acute illness resolves spontaneously over one to three weeks in the absence of treatment, approximately 25% of untreated children and 5% of children treated with intravenous immunoglobulin (IVIG) develop coronary artery aneurysms (CAA) [1]. Although CAA can remodel in 50%–80% of cases depending on the age of onset, all patients with aneurysms are at risk for ischemic heart disease due to thrombosis or stenosis of the affected coronary arteries [2]. In addition, some degree of myocarditis accompanying the vascular inflammation is universal in KD and may contribute to myocardial fibrosis decades after the acute illness [3–5]. CAA may remain silent after KD until adulthood when myocardial ischemia can lead to sudden death [6–15]. In children in whom the disease is diagnosed and treated, the death rate is less than one per hundred and autopsies are rare [16]. Although suspected KD cases have been reported in the forensic literature, there has been no systematic study to determine the incidence of such cases [8]. In a study from our group, CAA attributed to antecedent KD were present in 5% of young adults (<40 years) evaluated for suspected myocardial ischemia by coronary angiography [17]. We postulated that there would be young adults with sudden, unexpected death due to CAA from KD who would have a state-mandated autopsy performed by the Medical Examiner. We performed a systematic review of young adults with sudden death attributed to a cardiovascular cause. Immunohistochemical studies on formalin-fixed paraffin-embedded (FFPE) tissues from two young

Abbreviations: CAA, coronary artery aneurysm; KD, Kawasaki disease; SDCMEO, San Diego County Medical Examiner's Office; IVIG, intravenous immunoglobulin; TGF-β, transforming growth factor-β.

Funding: This work supported in part by grants from the National Institutes of Health, National Heart, Lung, Blood Institute (HL69413) awarded to JCB and the iDASH grant U54HL108460. We also acknowledge NIH support through the UCSD Neuroscience Microscopy Shared Facility Grant P30 NS047101 and the Biorepository of the UCSD Clinical and Translational Research Institute Grant 1UL1RR031980. The dataset used in this project can be downloaded from the iDASH repository (https://idash-data.ucsd.edu/) by making a request to the authors for access. Database supported by the National Institutes of Health through the NIH Roadmap for Medical Research, Grant U54HL108460.

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http://dx.doi.org/10.1016/j.carpath.2015.02.006
1054-8807/

adults with sudden cardiac death and confirmed or suspected antecedent KD demonstrated expression of molecules in the transforming growth factor (TGF)-β pathway that play key roles in tissue remodeling.

2. Materials and methods

2.1. Database search

A database of 154 cases under age 35 who had a cardiovascular cause of death from 1997 to 2012 was obtained from the San Diego County Medical Examiner's Office (SDCMEO), which serves an area of 4200 square miles with a population of about 3.2 million people (47.6% Caucasian, 32.7% Hispanic, 11.6% Asian, 5.6% African-American and 4.2% mixed population) living in urban (97%) and rural (3%) areas. The population <35 years of age in San Diego county has been consistent between 1997 and 2012 at about 1.5 million (approximately 50% of total population). In San Diego County, every unexplained death in individuals < 35 years of age would be autopsied at SDCMEO. To narrow our search for cases due to antecedent KD, we excluded cases that listed other major medical conditions as contributing to the cause of death including trauma, substance abuse, suicide, cancer, congenital heart disease, morbid obesity, diabetes, hypertension, and severe hyperlipidemia. Then we reviewed the SDCMEO records for demographic data, clinical history, and gross and histologic autopsy findings. For the two cases classified as KD, the parents of the decedents were interviewed following written informed consent. This protocol was approved by the Institutional Review Board at UCSD.

2.2. Review of autopsy cases

To understand pathological findings unique to KD, a comprehensive review of the current literature in English and Japanese was performed using PubMed and the Japan Medical Abstracts Society with "Kawasaki Disease," "Mucocutaneous and lymph node syndrome," "aneurysm," "pathological study," and "autopsy" as the search terms. KD cases with an interval between onset and pathologic examination of at least 10 years were reviewed. Only cases in which KD was diagnosed during childhood or retrospectively diagnosed at autopsy were included. We excluded papers and abstracts without details of the pathology and histology at the time of autopsy.

2.3. Histology

Formalin-fixed paraffin-embedded (FFPE) cardiac tissues prepared at the time of necropsy were obtained from the SDCMEO with consent of the next-of-kin. Only one new tissue block from Case 1 was made from the left main coronary artery that had been fixed and stored in formalin for about three years. Coronary artery control tissue from a 20-year-old male with no cardiovascular history was obtained from the UCSD Pathology archives. Histochemical staining with hematoxylin–eosin (H&E), Verhoeff–van Gieson (VVG), and Masson trichrome stains was performed using standard techniques.

2.4. Immunohistochemical staining

IHC staining was performed as previously described [18].

3. Results

Among 154 cases with sudden cardiac death under age 35, 122 cases met exclusion criteria. There were no cases with CAA on the reports for the 122 excluded cases. Of the remaining 32 cases reviewed, two (6.25%) had CAA described in the necropsy report. For those two cases, families were interviewed regarding a KD-compatible illness during childhood, and detailed histologic studies were performed.

3.1. Case 1

A 22-year-old Korean male collapsed while exercising on a treadmill and was found unresponsive. Aggressive resuscitative efforts were unsuccessful and the body was referred to the ME office for necropsy. The body was well-developed, well-nourished, and measured 173 cm in length and weighed 93 kg. The heart weighed 430 g (heart weight for healthy adult men: 233 to 383 g [19]) with smooth epicardium and a ventricular wall measuring up to 1.6 cm in thickness (mean ± SD for left ventricle thickness for adult male (mean age 62 years) with BMI 30–34.9: 1.57 ± 0.3 cm [20]). At the bifurcation of the left main coronary artery (LMCA) into the circumflex (Cx) and left anterior descending (LAD) arteries, there was a calcified, nonocclusive aneurysm measuring 2.5 × 2 × 1.5 cm (Fig. 1a). The adjacent LAD appeared to be very small and was partially occluded where it transitioned into the aneurysm (Fig. 1b). Associated with this coronary artery occlusion was a region of subendocardial pallor in the anterior left ventricular wall adjacent to and partially including the septum up to 4 cm in length. The Cx had a larger caliber than the LAD and was patent distal to the aneurysm. The proximal right coronary artery (RCA) had a normal to slightly dilated caliber (0.4 cm) with a small, discrete aneurysm proximally (about 0.6 cm). The distal RCA, proximal to the posterior descending artery, was also dilated (about 0.6 cm) compared to the adjacent segment (0.3 cm).

Microscopic examination of the LAD showed adventitial sparse cellular fibrosis, extensive dystrophic calcification (Fig. 1c), and regions of chondro-ossification (Fig. 1d). Within these regions there were small vascular channels representing apparent recanalization of organized thrombus (Fig. 1c). There were occasional lymphocytes, but no evidence of active vasculitis or necrosis. Patchy, but fairly widespread fibrosis with compensatory hypertrophic changes in adjacent myocytes was present (Fig. 1e). In addition, there were small clusters of darker, more intensely staining myocytes suggestive of acute ischemia. The papillary muscle showed striated variation in staining consistent with contraction band necrosis (Fig. 1f). Other than the heart, no remarkable changes were seen except general congestion of viscera with marked pulmonary edema and congestion, and few small cutaneous injuries.

Sudden cardiac death was associated with chronic ischemic changes due to a partially occluded 15 mm aneurysm at the bifurcation of the LMCA and LAD with diffuse calcification.

Interview of the mother revealed that this young man had been diagnosed with KD and had been followed by a pediatric cardiologist for his giant aneurysms. Review of his medical record revealed that he was diagnosed with KD at 2 years and 9 months and treated with IVIG twice, followed by aspirin and dipyridamole. Giant aneurysms in both the LAD and RCA were found. Cardiac angiography at age 14 revealed an LMCA aneurysm (1 cm) and complete occlusion of the LAD with calcification and extensive collateral circulation. Activity restriction was advised. The patient had been maintained on aspirin and dipyridamole under the care of a cardiologist until he left home at age 20. No information was available regarding traditional cardiovascular risk factors for atherosclerotic disease.

3.2. Case 2

A 30-year-old Hispanic male was found unresponsive in the locker room after a boxing work-out and resuscitation attempts were unsuccessful. The body was well-developed and well-nourished, measuring 175 cm in length and 93 kg in weight. The non-dilated heart weighed 410 g, (heart weight for healthy adult men: 233 to 383 g [19]) was structually normal with normal ventricular wall thickness, and a smooth epicardial surface. The coronary arteries had normal origins and were normally distributed. However, a saccular aneurysm in the LAD measuring 1.6 cm in length and 1.0 cm in diameter arose immediately distal to the origin of the LAD and Cx coronary arteries (Fig. 2a). The LAD wall was thin and calcified and the lumen was filled with a layered occlusive thrombus (Fig. 2b). The RCA showed a re-canalized