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Original Article

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

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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.

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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 .

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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 \pm 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 $2.5 \times 2 \times 1.5$ 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 structurally 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

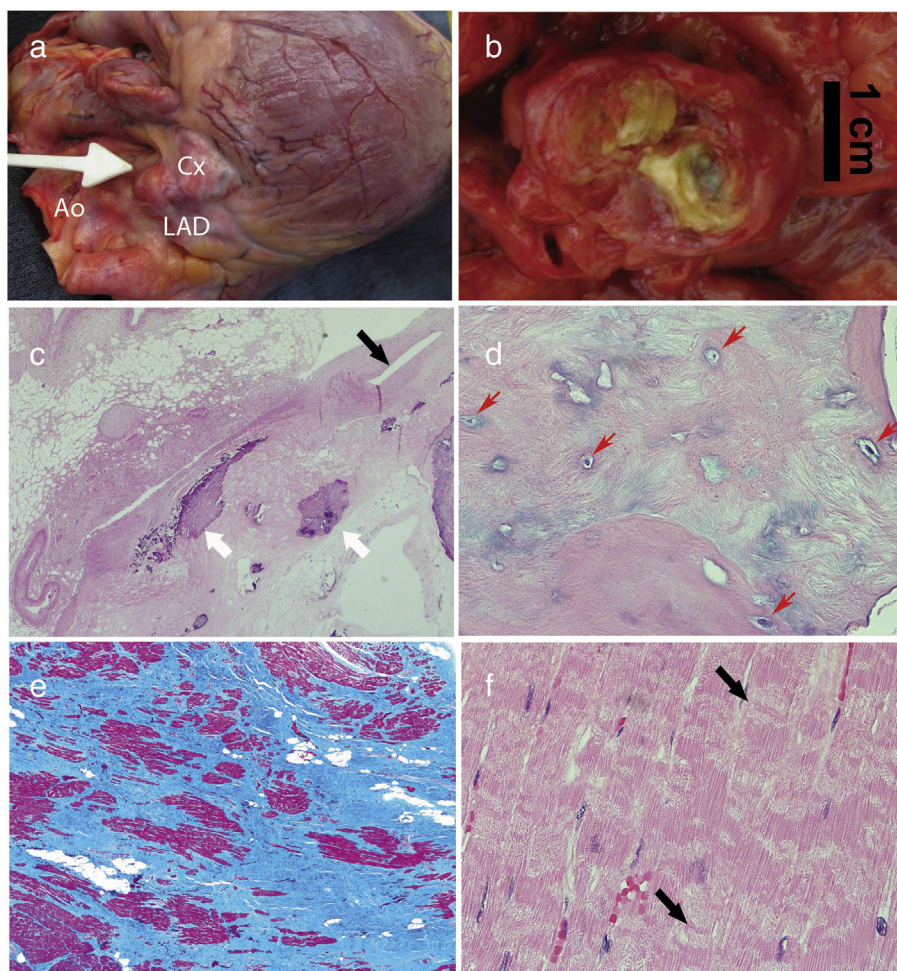


Fig. 1. Case 1: Gross and histological findings. a, Aneurysm at the bifurcation of the LMCA into the Cx and LAD (arrow). b, Section of LAD demonstrating stenosis with calcification. c, Section of left main coronary artery bifurcation aneurysm demonstrating calcifications (white arrows). There are small vascular channels in aneurysm (black arrows) (H&E, 40 \times). d, Section of left main coronary artery bifurcation aneurysm demonstrating calcification with region of chondro-ossification (arrows) (H&E, 200 \times). e, Section of myocardium demonstrating widespread fibrosis (Masson's trichrome, 20 \times). f, Section of papillary muscle demonstrating contraction band necrosis (arrows) (H&E, 400 \times). LMCA: left main coronary artery; Cx: circumflex artery; LAD: left anterior descending coronary artery; H&E: hematoxylin and eosin.

aneurysm with multiple lumina. A soft plaque occluding 75% of the lumen was situated several centimeters distal to the aneurysm. The RCA branched into numerous smaller vessels 1.7 cm from its origin. The Cx artery measured within normal limits. The posterior apical left ventricular myocardium revealed an infarct measuring 2.0 \times 0.8 cm with patchy interstitial fibrosis and pink discoloration. Mural thrombi were not present. The aorta was patent with minimal atherosclerosis.

Microscopic examination of the LAD revealed asymmetric transmurular fibrosis and severe dystrophic calcification causing eccentric narrowing of the lumen that was occluded by acute thrombus (Fig. 2c). The aneurysm wall showed a small focus of calcification (Fig. 2d and e), diffuse fibrosis (blue staining, Fig. 2f), and disrupted internal elastic lamina. The LAD artery adjacent to the aneurysm showed less than 25% stenosis by eccentric non-calcific plaque with amorphous debris and cholesterol clefts. The distal LAD showed intimal hyperplasia with an intact internal elastic lamina. RCA showed re-canalization and multiple lumina lined with endothelial-like cells and elastic lamina (Fig. 2g). Inflammatory cell infiltrates and necrosis were not seen. Microscopic examination of LAD watershed region showed a broad area of fibrosis, focal interstitial fibrosis, and scattered thickened myocytes with enlarged nuclei (Fig. 2h). Other than heart, no remarkable changes were seen.

Death was caused by myocardial infarction secondary to thrombosis of the LAD aneurysm. Interview of the parents revealed a possible KD-compatible illness in childhood at age 6 years diagnosed as scarlet fever. There was no history of tobacco use or other cardiovascular risk factors.

3.3. Review of autopsy cases

We reviewed published reports of autopsies on eight individuals with a history of KD at least 10 years prior to their death (Table 1). Aneurysms were noted in all but one case. The patient who did not have aneurysms died as a result of myocardial infarction associated with CA stenosis. Other pathologic findings were similar to the cases reported here and included luminal myofibroblastic proliferation (LMP) in seven cases, CA wall calcification in seven cases, recanalization of a thrombosed artery in two cases, and atherosclerosis with lipid-laden macrophages in two cases. The paucity of atherosclerotic changes was noted in several of the cases and was also a feature of our cases. These cases highlight the characteristic features of KD vasculopathy in the young adult long after acute KD in childhood, which include luminal myofibroblastic proliferation, thrombosis with recanalization, and calcification with ossification of the arterial wall.

3.4. Immunohistochemical studies

Previously we reported that TGF- β signaling pathway molecules are expressed in the arterial wall from acute KD autopsies in association with myofibroblasts [18]. To investigate the possible role of the TGF- β pathway in vascular remodeling in adults with vascular damage from KD, we stained the coronary arteries from Case 2 with antibodies against the ligand TGF β 2, the receptor TGF β R2, and the activated

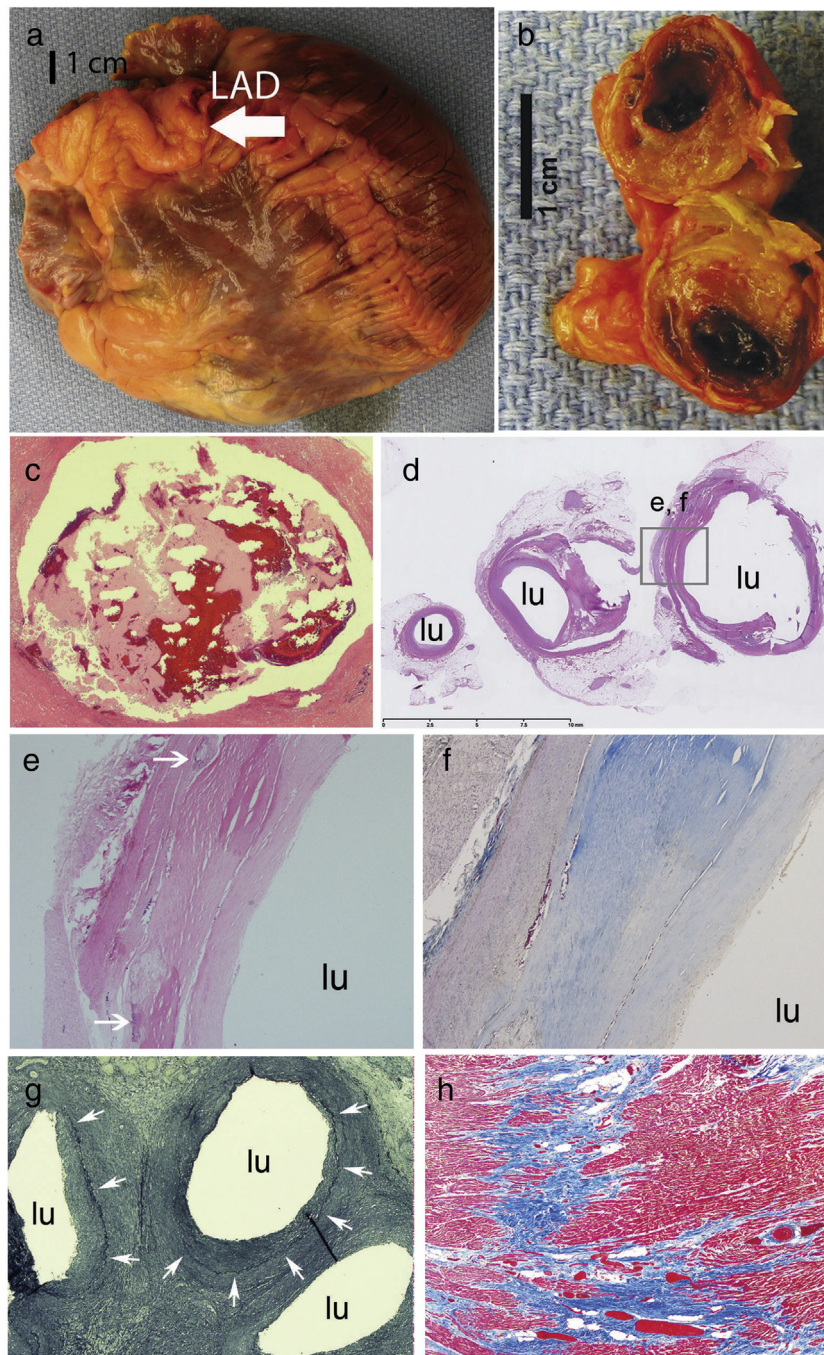


Fig. 2. Case 2: Gross and microscopic findings. a, Aneurysm just distal to the bifurcation of the LMCA (arrow). b, Section of LAD demonstrating calcified aneurysm and thrombus. c, Section of LAD coronary artery demonstrating acute thrombus (H&E, 20 \times). d, Three sections of LAD: section from aneurysmal area (right), adjacent to aneurysm (middle), and distal to aneurysm (left). Boxes denote areas shown in higher magnification in subsequent images (H&E). e and f, Section of aneurysmal LAD with diffusely fibrotic and focally very thin media. Internal elastic lamina is not evident (e: H&E, d: Masson's trichrome, 100 \times). g, Section of right coronary artery aneurysm demonstrating neovascularization with internal elastic laminae (arrows) (Verhoeff–Van Gieson elastic stain, 40 \times). h, Section of myocardium demonstrating an area of fibrosis (Masson's trichrome, 20 \times). LMCA: left main coronary artery; LAD: left anterior descending coronary artery; RCA: right coronary artery; lu: lumen.

signaling molecule pSMAD3. TGF β 2, TGF β R2, and nuclear-localized pSMAD3 were expressed in spindle-shaped cells within the thinned aneurysmal arterial wall (Fig. 3a, e and i). The spindle-shaped cells were α -smooth muscle actin positive and smoothelin negative consistent with a myofibroblast phenotype (data not shown). TGF β 2, TGF β R2, and nuclear-localized pSMAD3 were not expressed in fibrotic myocardium from either case (data not shown).

4. Discussion

This is the first study to use a review of records from a Medical Examiner's Office to identify young adults dying suddenly and unexpectedly from sequelae of apparent KD in childhood. Notable findings were diffuse myocardial fibrosis and expression of molecules in the TGF β pathway by spindle-shaped cells expressing α -SMA in the wall

Table 1

Literature review of pathological findings in the coronary arteries of young adults with a history of KD in childhood

	Case #	Age at death (y)	Age at KD (y)	Interval until death (y)	Intimal thickening	CA Aneurysms	Calcification	Atherosclerosis/lipid-laden macrophages	CA stenosis/occlusion	Re-canalization	References
Review of pathological findings of autopsies performed at least 10 years after the onset of KD	1	17	1.4	15	+	+	+	ND ^a	+	–	Pounder 1985 [12]
	2	19	4	15	ND	+	+	ND	+	–	Wreford 1991 [9]
	3	21	3	18	+	+	+	ND	+	–	Fineschi 1999 [10]
	4	24	0.5	24	+	+	+	+	+	+	Kojimahara 2000 (Japanese) [13]
	5	19	3	16	+	+	+	–	–	–	Takahashi 2001 [31]
	6	20	4	16	+	+	+	+	+	+	
	7	22	3	19	+	–	–	–	+	–	Oreinstein 2012 [23]
	8	30	4	26	+	+	+	–	+	–	Okura 2013 [11]
SDCMEO cases	Case 1	22	2.75	20	ND	+	+	–	+	–	Present study
	Case 2	30	6.0	23	+	+	+	+/-	+	+	Present study

^a ND: no data

of the coronary artery aneurysms. Of the cases from the SDCMEO, which serves a population of approximately 3.2 million people, 2/154 (1.3%) primary cardiovascular deaths in persons <35 years over a fifteen-year period could be attributed to cardiovascular complications of KD in childhood.

Coronary artery aneurysms that form during the acute phase of KD can remodel, remain unchanged, or thrombose. In a study of 594 untreated KD patients followed over a period of 10–21 years, 146 (25.0%) developed aneurysms [21]. Of those patients, 28 (19.2%) developed arterial stenosis, 11 (7.5%) suffered a myocardial infarction, and 5 (3.4%) died during the follow-up period. A Japanese longitudinal study of 6576 KD patients (maximum age 39 years) found 46 deaths during a period of 27 years. The most frequent cause of death was KD-related cardiovascular sequelae (13 subjects, 0.2%) followed by malignancy (7 subjects, 0.1%), trauma (7 subjects, 0.1%), and suicide (7 subjects, 0.1%). There were 1003 subjects with cardiac sequelae of KD in this cohort and seven (0.6%) died of suspected or confirmed cardiovascular causes over the 27-year period of the study [16]. Only the mortality rate among Japanese with cardiac sequelae due to KD was significantly higher than that of the general population. During the time period of our study, we are aware of only one KD autopsy performed in San Diego on one of our patients who died 15 years after KD of cardiovascular complications directly attributable to his KD.

A study of the medical histories and coronary angiograms of young adults (<40 years) who underwent coronary angiography for evaluation of suspected myocardial ischemia found definite or presumed coronary artery sequelae of KD in 13 of 261 (5%) cases [17]. The US National Registry of Sudden Death in Athletes reported that five of 1049 (0.5%) young athletes who had sudden cardiovascular deaths died due to complications of KD [22]. As more children with a history of KD reach young adulthood, the incidence of acute ischemic events and cardiac arrest caused by the cardiovascular sequelae of KD is likely to increase.

It remains unclear if antecedent KD is associated with the potential for accelerated development of atherosclerosis in the regions of vessel wall damage. Only one of our two cases had cholesterol crystals adjacent to the aneurysm area. Although Oreinstein et al. reported that there were no histological features of atherosclerosis in remote KD deaths in their study, there were only two autopsy cases with an interval of at least 10 years between KD onset and death [23]. Case reports of autopsies on young adult KD patients often lack detailed history regarding traditional risk factors for atherosclerosis, thus making it difficult to assess the relative contribution of KD to the development of atherosclerosis. A larger sample of KD autopsies with a well-characterized medical history for atherosclerotic risk factors will be needed to evaluate the risk of atherosclerosis associated with coronary aneurysms associated with KD. Based on the current limited data, there is no evidence that KD vasculopathy leads to accelerated atherosclerotic changes. In KD vasculopathy, atheroma or lipid-laden macrophages or SMCs (foam cells) are rare. Hyaline degeneration, thrombosis with re-canalization, and calcification with ossification of the vessel wall are characteristic autopsy findings in the late convalescent stage of KD.

Luminal myofibroblastic proliferation (LMP) has been reported in KD autopsies not only in aneurysmal lesions but also in non-aneurysmal coronary arteries and other medium-sized, muscular arteries [23]. In a study of seven KD patients not known to have aneurysms who died from non-cardiac causes 60 days to 14 years after KD onset, thickening of the intima, thinning of the media, and stretched or focally interrupted internal elastic laminae were noted in five patients [24]. However, detailed information regarding echocardiographic findings during the acute illness was not available. Arteries were stained for expression of PDGF-A, TGF- β , and VEGF and no increased expression was seen in comparison to controls. Immunohistochemical staining for TGF- β pathway molecules showed expression in spindle-shaped cells with a myofibroblast phenotype in the wall of the aneurysm (Fig. 3). It is well-established that the TGF- β pathway is important for endothelial/epithelial-to-mesenchymal transition and the creation of myofibroblasts, which have been detected in the arterial wall of KD aneurysms [18]. Thus, increased expression of molecules in the TGF- β signaling pathway may be a unique feature of coronary artery damage in KD patients who develop aneurysms.

Diseases associated with coronary artery aneurysms include autoimmune disorders (e.g. systemic lupus erythematosus), trauma, and connective tissue diseases such as Ehlers Danlos Type IV, Marfan and Loeys–Dietz syndromes [25–27]. KD is clearly the leading cause of coronary artery aneurysms in otherwise healthy young adults. Therefore, we incorporated this term as one of our inclusion criteria. However, in reviewing published autopsy reports (Table 1), one case was described as having “CA stenosis/occlusion” but not aneurysms. So both “aneurysm” and “CA stenosis/occlusion” should perhaps be used as criteria when reviewing autopsy series for missed KD.

The cases reported here manifested diffuse, patchy myocardial fibrosis. In general, myocardial fibrosis is related to either replacement fibrosis after myocardial infarction or interstitial fibrosis as a sequela of myocardial inflammation, which is universally present during acute KD according to endomyocardial biopsy studies from Japan [4,5,28]. A systematic study of 29 KD patients who died within the first 40 days after fever onset demonstrated myocarditis with varying degrees of infiltration of inflammatory cells in all cases [29]. Whether myocarditis during the acute phase of KD is responsible for the diffuse, patchy fibrosis seen in our two cases is unknown.

We recognize both strengths and limitations to our study. The SDCMEO serves a large population with diverse ethnicities with 50% of individuals under the age of 35 years. However, because KD is over-represented among Asian populations and San Diego County has a relatively large Asian population (11.6%), this could increase the incidence of deaths due to KD compared to other regions. In contrast, there is a relatively small African American population in San Diego (5.6%), which is another group with increased susceptibility to KD [30].

The limited sample size precludes any precise estimation of the prevalence of KD-related sudden death. The pathologic studies were limited to available archival tissues that precluded systematic evaluation of the

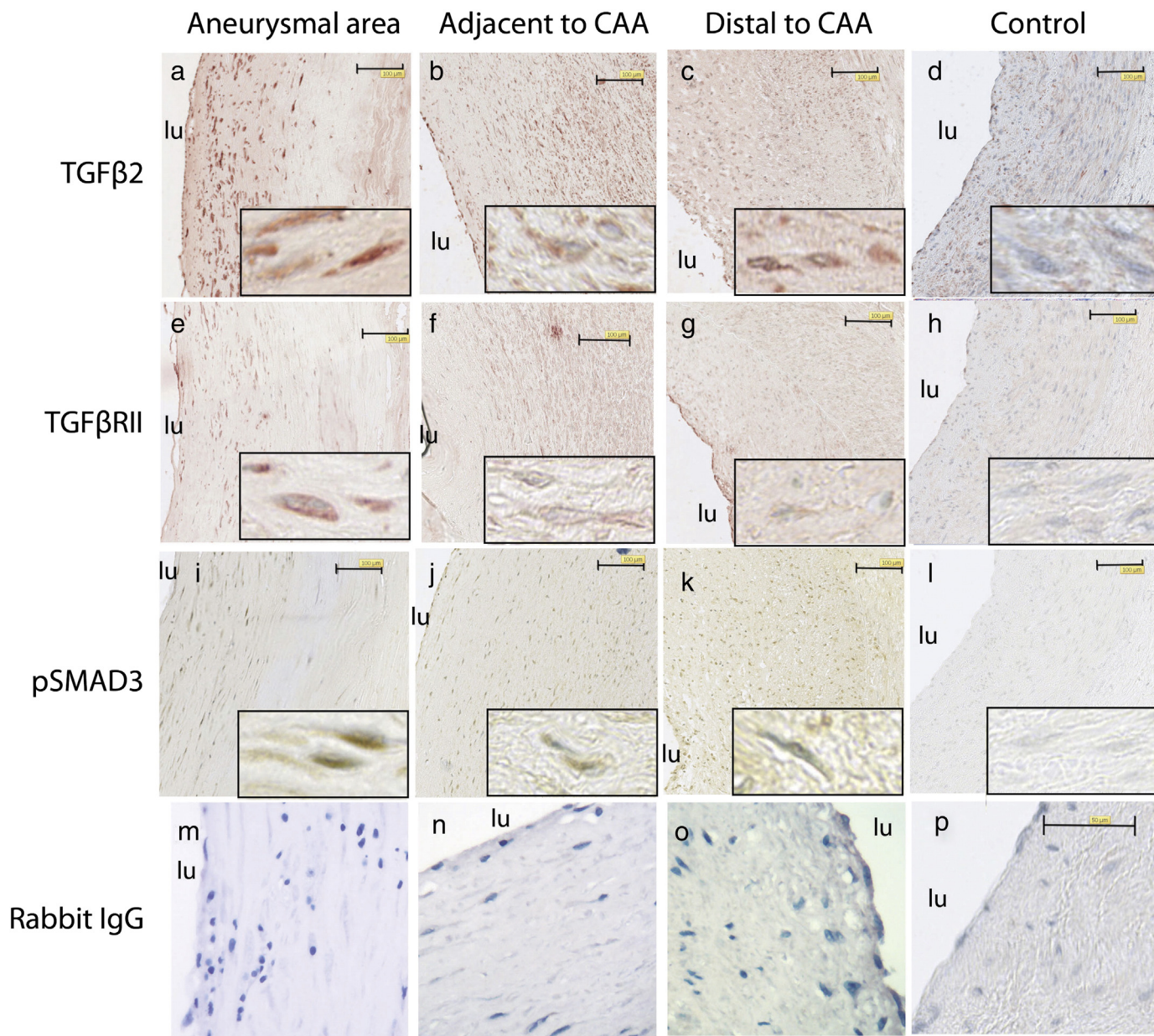


Fig. 3. Immunohistochemical study of left anterior descending coronary artery (LAD) from Case 2. Three sections of LAD (Fig. 2d) and a normal control coronary artery were stained for TGF- β pathway molecules: TGF β 2 (a–d), TGF β RII (e–h), phosphorylated (activated) signaling molecule pSMAD3 (i–l), and rabbit IgG as negative control (m–p) (100 \times , representative staining of spindle-shaped cells is shown in inserted boxes at higher magnification (original \times 600)). Aneurysmal wall (a, e, i, and m.) Note that TGF β 2, TGF β RII, and nuclear localized pSMAD3 were expressed in the spindle cells within the thinned aneurysmal arterial wall and endothelial cells. Adjacent (b, f, j, and n) and distal (c, g, k, and o) to the aneurysm, TGF β 2, TGF β RII, and nuclear localized pSMAD3 were stained in endothelial cells. Rabbit IgG staining was used as negative control in all samples (m–p). Coronary arterial wall from the control autopsy (d, h, l, and p) showed constitutive expression of TGF β 2, TGF β RII was only expressed in the endothelial cells, and pSMAD3 was not expressed in endothelial cells or in cells within the thickened intima. TGF β 2: transforming growth factor- β 2, TGF β RII: TGF β receptor II, pSMAD3: phosphorylated SMAD3.

coronary pathology including sections proximal and distal to the aneurysms as well as the transition zones.

5. Conclusions

Unexpected sudden cardiac death in young adults may be caused by coronary artery and myocardial sequelae of antecedent KD. Medical examiners should have a high index of suspicion of KD in young adults with coronary artery aneurysms and luminal myofibroblastic proliferation.

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