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Original Article

Incomplete Kawasaki disease with development of fatal coronary artery thrombosis in a 13-year-old male☆

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ABSTRACT

Kawasaki disease (KD) is among one of the most common causes of vasculitis in children. Since KD was first described in 1967, there have been several reports of patients who did not meet the full diagnostic criteria for KD but who ultimately developed significant coronary artery lesions. Children with incomplete KD are at similar risk of developing coronary artery abnormalities to those with complete Kawasaki.

A previously healthy 13-year-old Asian male was seen at a clinic for fever, pharyngitis, and conjunctivitis. He was given antibiotics for a presumed streptococcal pharyngitis. Two weeks later, the decedent complained of chest pain, collapsed, and was transported by Emergency Medical Services to a nearby hospital where he was pronounced deceased on arrival. A complete autopsy was done by the local medical examiner.

Histologically, all three coronary arteries showed varying degrees of severe transmural lymphoplasmacytic inflammation, marked vascular smooth muscle intimal proliferation, focal destruction of muscular and elastic layers, and luminal stenosis. Some vessels had recent thrombi.

We present an example of incomplete KD in an older child and reiterate the importance of obtaining relevant medical history in sudden death cases that come to the Medical Examiner Office, especially in the pediatric age group.

1. Introduction

Kawasaki disease (KD) is one of the most common causes of vasculitis in children and is a leading cause of acquired heart disease in the pediatric population [1]. KD classically affects children less than 5 years of age but can present in infants, older children, and even adults [2]. Classic KD is a self-limited syndrome characterized by prolonged fever and symptoms of acute inflammation, including rash, nonexudative conjunctivitis, mucosal erythema, and lymphadenopathy. A known and serious sequela of this entity is the formation of coronary artery aneurysms, which has been reported in about 25% of untreated cases [3]. Aneurysms relating to KD have been known to develop in systemic arteries of all sizes as well, but in this disease process, there is a predilection for coronary arteries [4]. Because KD has such a low incidence (about 20 cases per 100,000 children under 5 years of age in the United States [5]), such a heterogeneous presentation, and affects a wide range of age groups, it is difficult for most clinicians to acquire expertise in making this diagnosis on clinical examination. Furthermore, the features listed in the diagnostic criteria typically present asynchronously, requiring careful investigation into a given patient's recent clinical history via direct communication and chart review [3]. In infants less than 6 months old, prolonged fever and irritability may be the only clinical symptoms [3]. Children outside of the typical age range of presentation are at higher risk of delayed diagnosis and of developing coronary artery abnormalities than children in the typical age range (a bimodal distribution of infants less than 6 months old and adolescents) [6].

KD vasculitis is characterized initially by infiltration of vascular walls by CD8-positive T cells, macrophages, and neutrophils. These inflammatory cells originate from both the lumen of the vessel and from the adventitial surface, and there is often extensive edema in the media produced when these two sets of inflammatory cells collide [1]. The disease progresses in three distinct pathologic stages [3]. The first (acute phase) is a necrotizing vasculitis stage, consisting of synchronous neutrophilic inflammation that may progress to destroy the internal elastic lamina of the arterial wall, predisposing to thrombi. In this stage, there may be necrosis of the smooth muscle cells of the arterial wall. The second stage is a subacute/chronic vasculitis with asynchronous infiltration of lymphocytes, IgA-secreting plasma cells, and rarely eosinophils with few macrophages. The third stage (chronic/remote/healing/convalescent phase) is characterized by aneurysmal changes that are associated

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with intimal myofibroblastic proliferation that causes progressive arterial stenosis both proximally and distally to the aneurysm. Recanalization is often seen within aneurysms, and thrombi may appear within the aneurysms and the recanalized channels due to blood flow abnormalities [7]. Both the second and third stages begin in the first 2 weeks after fever onset and can potentially persist for months to years.

1.1. "Complete" or classic KD

The diagnosis of KD is based on criteria established by the Japanese Kawasaki Disease Research Committee and the American Heart Association (AHA) [8,9]. The diagnostic criteria for KD established by the AHA include a fever (≫38°C) lasting at least 5 days without any other explanation and at least four of the following criteria: polymorphous exanthema (rash of any kind), bilateral bulbar conjunctival injection without exudates, erythema of the oral mucosa (including lips, pharynx, or tongue), peripheral extremity changes (including erythema of palms or soles and/or swelling of hands or feet), and cervical lymphadenopathy (with at least one lymph node ≫1.5 cm in diameter). The Japanese Kawasaki Disease Research Committee guidelines are the same as those set out by the AHA, except that there is no requirement for cervical lymph node size [8–10].

1.2. Incomplete KD

Since Kawasaki first described this eponymous syndrome in Japan in 1967, there have been several reports of patients who did not entirely meet the full diagnostic criteria for KD but who ultimately developed significant coronary artery lesions [6,11–14]. For this reason, the diagnosis of "incomplete KD" was proposed by the Japanese Society of Kawasaki Disease and the AHA in 2004 to help identify those patients who did not meet the full criteria for a diagnosis of classic or "complete KD" but who might still benefit from treatment [8,9].

Of all the symptom criteria, prolonged fever appears to be the only consistent finding among reports of both complete KD and incomplete KD. The diagnosis of incomplete KD is considered in individuals in the vulnerable age groups who present with ≥5 days of fever and at least two of the clinical criteria for KD, and whose overall clinical picture is consistent with KD, or in infants with fever for ≥7 days without explanation after ruling out all other possible etiologies [8,9].

Children with incomplete KD are at similar risk of developing coronary artery abnormalities as those with complete KD, perhaps in part because children with an incomplete presentation are more likely to have a delay in diagnosis and treatment [3,15–17]. Complete and incomplete KDs are now considered a spectrum of the same pathologic process.

We present an autopsy case of a sudden death in a 13-year-old boy who, in retrospect, we feel had clinically unsuspected incomplete KD.

2. Materials and methods

The decedent was a 13-year-old Asian male with no prior significant medical history. Two weeks prior to his death, he had presented at a pediatric clinic with complaints of fever of unspecified duration, pharyngitis, and conjunctivitis. On examination, he was febrile (99°F), he had injected conjunctivae, his tongue was pale, and there was erythema of the pharynx without exudate. He had no skin exanthema or lymphadenopathy. He was given antibiotics for a presumed streptococcal pharyngitis. On repeated interview, the parents related a history of several (2–3) weeks of illness with fever and pharyngitis before presentation to clinic.

On the day of his death, the decedent had been feeling well and went to school as usual. Around noon that day, he had one episode of syncope from which he recovered. His mother was called and she took him home immediately. The decedent declined to be taken to the hospital at that time because he "felt better". Approximately 4 h after his arrival at home from school, the decedent complained of chest pain that radiated to his left arm. His mother called 911. The decedent then reported a sudden increase in chest pain, collapsed, and lost consciousness. When Emergency Medical Services arrived, the patient was unresponsive. He was rushed to a nearby hospital where he was pronounced deceased on arrival.

The body was sent to the local County Medical Examiner's Office for a complete autopsy using standard autopsy procedures.

3. Results

The decedent was a well-developed teenager (height: 170 cm; weight: 62.6 kg; body mass index: 21.7). There were no skin lesions, evidence of trauma, or any other external abnormalities. There was no localized cervical or generalized lymphadenopathy.

The significant gross autopsy findings were confined to the 330-g heart. There was a mild resolving epicarditis with delicate fibrous adhesions between the epicardial surface and thickened pericardium. All four cardiac chambers were dilated. The myocardium was pale tan in color. It was firm and had no identifiable abnormalities.

Both the right and left coronary arteries and their major branches arose normally from the aorta. Serial sectioning of the vessels showed that their walls were thickened by firm tan tissue resulting in luminal stenosis (Fig. 1). No focal mural dilations were observed.

Histologically, all three coronary arteries showed varying degrees of inflammation extending from the intima into the adventitia. The inflammation consisted mainly of lymphohistiocytic infiltrates with prominent plasma cells and rare eosinophils. The intensity of the inflammation varied from moderate to severe in sections of the same vessel (Fig. 2). Some sections showed only intimal thickening by prominent proliferating vascular smooth muscle cells (VSMCs) with intact muscular and elastic layers, and with luminal stenosis but no thrombosis (Fig. 3). Immunostaining with smooth muscle actin confirmed that the proliferating cells in the coronary arterial intima were VSMCs (Fig. 4). This finding indicates a relatively acute vascular injury as could be elicited by a severe inflammatory, possibly viral, process. Other sections showed varying degrees of muscular layer destruction and loss of elastic tissue (Fig. 5). Some vessels had recent thrombi (Fig. 6). No giant cells or aneurysms were seen. The muscular layers of all three coronary arteries examined showed varying degrees of destruction with replacement by fibrosis in some sections. The adventitia in all three coronary arteries examined was edematous and infiltrated by mononuclear cells including lymphocytes and prominent collections of plasma cells.

The myocardium was globally edematous with foci of wavy fiber changes but showed no features of an acute myocardial infarction or active myocarditis. Three microscopic foci of healing infarctions,

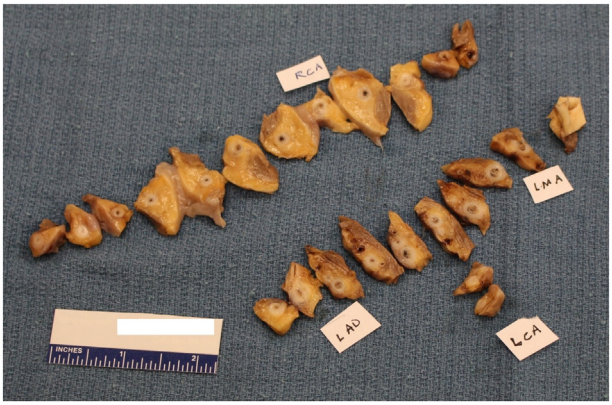

Fig. 1. Gross appearance of the left main, left anterior, circumflex, and right coronary arteries. All vessels were focally stenotic with luminal thrombi. No focal dilations were observed.

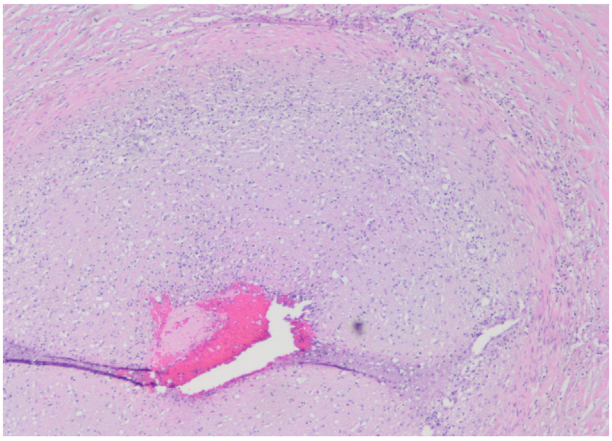

Fig. 2. Left anterior descending coronary artery showing lymphohistiocytic infiltrates in the muscular layer and adventitia with luminal thrombosis [hematoxylin and eosin (H&E)].

consistent with at least 1-week duration, were seen near the atrioventricular node but did not directly affect the node.

The aorta and its major branches in the neck, chest, and abdomen arose normally, followed the usual distribution, and were free of atherosclerotic lesions or other abnormalities. On both gross and microscopic examination, inflammation or other abnormalities of the aorta and its ostia were not identified.

The 690-g right lung and 590-g left lung were markedly edematous and congested and had intra-alveolar hemorrhage. On microscopic examination, the lungs were free of inflammation or vasculitis. The liver was severely congested and had mild mononuclear cell infiltrates surrounding the portal tracts.

No vasculitis was seen in other organs. The cause of death was deemed as "Complications of Atypical Kawasaki Disease," and the manner was natural. Subsequent studies of heart tissue sent to the Centers for Disease Control and Prevention (CDC) were negative by immunohistochemistry and polymerase chain reaction (PCR) for enterovirus. Parvovirus B19 was detected by PCR.

4. Discussion

The differential diagnosis for KD in this age group includes those conditions that may have similar clinical presentations and may or may not be associated pathologically with a vasculitis. Among these are polyarteritis nodosa (PAN), Takayasu's arteritis, adenovirus infection, and parvovirus B19 infection.

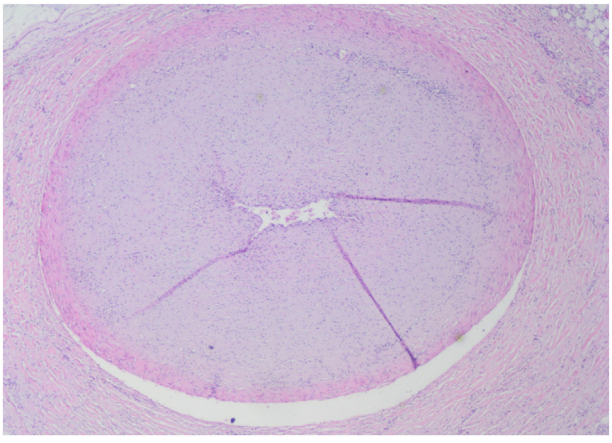

Fig. 3. Left anterior descending coronary artery with marked myofibroblastic intimal proliferation and luminal stenosis (H&E).

4.1. PAN

PAN is a segmental transmural necrotizing vasculitis of small- to medium-sized arteries that is classically associated with aneurysm formation. It typically affects young adults but can affect children as well. Clinical features vary greatly depending on the organs affected, but typical features include rapidly accelerating hypertension, abdominal pain and bloody stools, diffuse myalgias, and peripheral neuritis. The Eular/Printo/Pres classification criteria for childhood PAN require a biopsy of a small- or medium-sized artery demonstrating necrotizing vasculitis OR angiography showing aneurysms, stenosis, or occlusions not associated with intimal myofibroblastic proliferation and at least one out of five of the following features: skin lesions such as subcutaneous nodules, purpura, plaques, blistering, or necrosis; myalgias; hypertension; peripheral neuropathy; or renal involvement [18,19]. The vasculitis is usually widely scattered and affects multiple organs rather than presenting as an isolated coronary vasculitis. The most common affected organs include the kidneys, heart, liver, and gastrointestinal tract. Histologically, the acute phase is characterized by a mixed infiltrate of neutrophils, eosinophils, and mononuclear cells, and fibrinoid necrosis. Thrombosis of the vascular lumen can also occur in the acute stages. Following the acute phase, there are fibrosis and thickening of the vessel wall, and typically, many ages of vascular lesions are found. Our case would not meet these criteria, as none of the main criteria were met and none of the five possible associated clinical features were present.

4.2. Takayasu's arteritis

Takayasu's arteritis is a chronic vasculitis that typically affects women ages 10–40 years [20,21]. Clinical features include nonspecific symptoms such as fatigue, weight loss, and fever. Vascular symptoms such as systemic hypertension, reduced peripheral pulses, ocular disturbances, and neurologic deficits begin to appear with later progression of the disease. Takayasu's arteritis classically affects the aorta but can also affect the pulmonary, renal, and coronary arteries. Coronary artery involvement usually occurs at the ostia and can lead to myocardial ischemia and infarction. Histologically, Takayasu's arteritis is characterized by granulomatous inflammation with and without giant cell granulomas, mononuclear infiltrates, marked intimal thickening, destruction and fibrosis of the media, and adventitial fibrosis [22]. This is in contrast to KD, where giant cell granulomas are not seen and there is full-thickness inflammation as opposed to inflammation focused on the media. There may also be aneurysm formations in Takayasu's arteritis, which have been shown to regress in some cases.

4.3. Adenovirus infection

Adenovirus infection is another entity that should be considered in the differential of KD, as it may present with similar symptoms. These include purulent conjunctivitis, pharyngitis, and fever [23]. Adenovirus infections can be diagnosed using PCR, viral culture, and/or serology. Adenovirus and other viral pathogens have been reported to be associated with cases of KD and have been investigated as potential causative agents, although no specific viral cause has been shown [24,25].

5. Summary

The patient presented in this case report had history of prolonged fever, erythema of the oral mucosa, and nonpurulent conjunctivitis in the weeks preceding his death, all of which are part of the clinical criteria of presentation of KD. The microscopic findings of lymphohistiocytic coronary vasculitis and intimal VSMC proliferation with luminal stenosis are also consistent with the subacute/chronic phase of Incomplete KD.

The significance of the results of the viral studies done at the CDC is somewhat equivocal, as parvovirus B19 can frequently be detected in

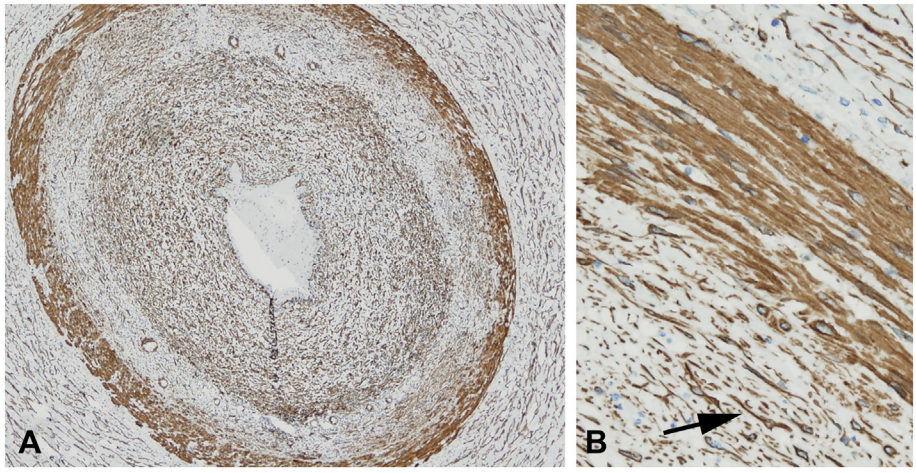

Fig. 4. Immunostain of epicardial coronary artery for smooth muscle actin demonstrates the extreme intimal proliferation and predominance of vascular smooth muscle cells. (A) Note staining of arterial media. (B) Higher power shows positivity of proliferating cells in intima (arrow) and normal media.

heart tissue with no clinical or histopathologic evidence of myocarditis [26,27].

In 2017, the AHA published an update to its 2004 scientific statement that included an algorithm for the evaluation and treatment of children with suspected KD who did not meet the full classic diagnostic criteria [3]. The algorithm included a set of six supplemental laboratory criteria that can help support the diagnosis of incomplete KD, including albumin ≤3.0 g/dl, anemia for age, elevation of alanine aminotransferase, platelets after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine with ≥10 white blood cells/high-power field [3]. For patients who fulfill three or more supplemental laboratory criteria, treatment can be initiated before echocardiography.

The diagnosis of complete or incomplete KD is confirmed if evidence of coronary artery abnormalities is shown on echocardiography; these abnormalities, in addition to aneurysm formation, include increased perivascular brightness, vascular ectasia, lack of tapering of the coronary arteries, and a *Z* score (diameter normalized against body surface area) of the left anterior descending coronary artery or right coronary artery ≥2.5. Associated findings may include decreased left ventricular function, mitral valve regurgitation, and/or pericardial effusion [3]. A normal echocardiogram within the first week of illness does not rule out a diagnosis of KD, as coronary aneurysms typically do not develop until after this time [3]. Such aneurysms may also resolve with time.

The treatment of both complete and incomplete KD is aimed at reducing arterial damage and preventing thrombosis of affected arteries [3]. The primary treatment is intravenous immunoglobulin, which has been shown to reduce coronary artery abnormalities when administered in the acute phase [1,3,11,16]. Acetylsalicylic acid (ASA) has also been traditionally used in treatment, but its use has not been shown to reduce frequency of coronary artery abnormalities [3,28]. Its efficacy is based primarily on its antiplatelet activity for the prevention of thrombosis formation. Development of Reye syndrome has been associated with high-dose ASA treatment for a prolonged period of time, although low-dose therapy has not been associated with Reye syndrome [29–31].

It is now recognized and accepted that children with incomplete KD may present with only a few of the classic symptoms and that these children have similar risk of developing coronary artery abnormalities as children who do meet the full diagnostic criteria for KD. In the case presented, the patient was older than the typical age group and showed an incomplete presentation, and therefore, the diagnosis of KD was not made when he presented at the pediatric clinic.

Pathologically, this case demonstrates important features relative to KD. First the striking intimal proliferation by VSMCs most likely represents acute endothelial injury. Such intimal proliferative lesions are found in experimental situations, such as following acute endothelial injury in the rat [32] or transplant vasculopathy in rabbit [33]. In these animal models, the intense vascular smooth muscle cell migration to the intima occurs in a time frame of 2–3 weeks postinjury, causing remarkably stenotic lesions which, after additional time, in the experimental

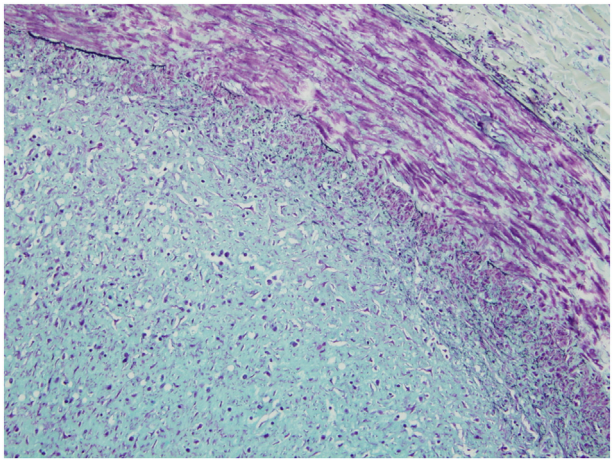

Fig. 5. Left main coronary artery showing significant destruction of muscular layer and loss of elastic laminae (Masson's Trichrome).

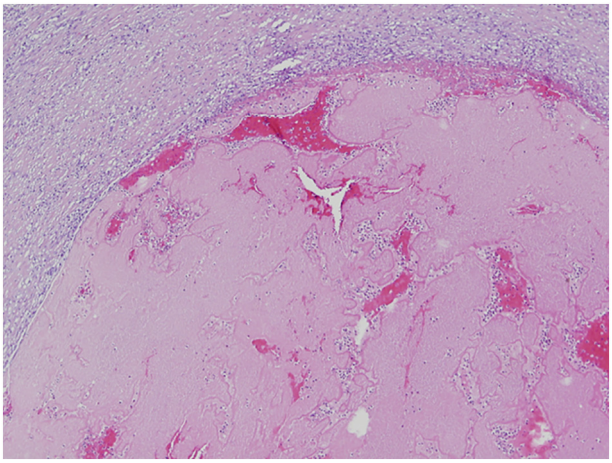

Fig. 6. Left main coronary artery showing occlusive luminal thrombosis (H&E).

situation of acute endothelial injury can largely resolve. Further, the lesions of KD seen in this patient indicate that the pathogenetic sequence of the disease is a severe pan-coronary arteritis progressing from acute to chronic plasmacytic that underlies the later development of coronary arterial aneurysms. We present this case as an example of incomplete KD in an older child and reiterate the importance of obtaining as complete and relevant medical history as possible in sudden death cases that come to the Medical Examiner Office, especially in the pediatric age group.

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