An Adolescent with Kawasaki Disease

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Kawasaki disease is an acute vasculitis of unknown etiology that predominantly affects children <5 years of age. The incidence and the severity of myocarditis in this disease is variable and depends upon the stage of the disease, acute or chronic. Acute-stage Kawasaki disease shows relatively high incidence of myocarditis, but almost all cases are clinically mild. We describe teenage boy presenting with atypical/incomplete manifestations of Kawasaki disease and developing fulminant myocarditis within a week of illness resulting in death. The case underscores the importance of suspecting Kawasaki disease in a young child presenting with features of myocardial ischemia.

Keywords: *Complications, Incomplete Kawasaki disease, Morbidity, Myocarditis*.

Kawasaki disease is an acute febrile mucocutaneous lymph node syndrome with multisystem vasculitis affecting infants and children less than 5 years of age [1]. The diagnosis is established clinically by the presence of six principal symptoms, including fever of unknown etiology persisting for ≥5 days, redness/desquamation of palms and soles, polymorphous exanthema, conjunctival congestion, strawberry tongue and cervical lymphadeno-pathy [2]. Children suspected of having Kawasaki disease with clinical or laboratory features suggestive of the illness but who do not fulfil diagnostic criteria (i.e., have less than four signs of mucocutaneous inflammation) are said to have 'incomplete' or 'atypical' Kawasaki disease [2-4]. The presentation in these patients is varied and not always straightforward, leading to under-diagnosis or missed diagnosis. As there is no available diagnostic test with sufficient specificity and sensitivity for Kawasaki disease, in the absence of 'classical' clinical symptoms, the diagnosis of Kawasaki disease requires a high index of suspicion.

CLINICAL PROTOCOL

History: A 14-year-old boy presented with complaints of sudden onset chest pain and shortness of breath of one day duration. The chest pain was left sided precordial, non-pleuritic severe, squeezing and associated with sweating. It increased with exertion and lying down but reduced with rest. This was associated with shortness of breath (Class IV) and orthopnea. Shortness of breath was followed by vomiting containing undigested food particles and an episode of watery, loose stool. There was no history of fever, cough, syncope, joint pain, sore throat, trauma, or drug intake. The past, family and personal histories were non-contributory.

Clinical examination: He was afebrile, conscious, but disoriented. He had a pulse rate of 120/min that was low volume. All his peripheral pulses were palpable. His blood pressure was 90/60 mmHg (right arm), respiratory rate of 26/min with SpO_2 91% on room air. There was no pallor, icterus, cyanosis, clubbing, or adenopathy. He had pedal edema and raised jugular venous pressure (JVP). There were subconjunctival hemorrhages in both eyes. Chest and cardiovascular system examination was within normal limits. Liver and spleen were not palpable, though ascites was present. Central nervous system examination was normal. Troponin T was positive and creatine kinase-MB was 197 unit on the day of admission; Lactate dehydrogenase was elevated at 2215 unit on day 2. Serum cholesterol, Low-density lipoprotein and triglycerides were normal. Blood and urine cultures were sterile, Widal was negative; and peripheral smear for malaria parasite was negative. Serology for Epstein-Barr Virus, Cytomegalovirus, leptospira, Rickettsia and Dengue was negative. Antinuclear antibody (ANA) was negative.

Radiology: Ultrasonography showed liver size of 15.1 cm, with normal echotexture, spleen size of 5.2 cm, and both kidneys normal size and echotexture with moderate ascites.

Computed tomography pulmonary angiogram (CTPA) showed a normal main pulmonary artery with all its branches. Inferior vena-cava was dilated. Cardiac

sections of CT showed ballooned out right atrium. The left atrium was morphologically normal, the left ventricle wall revealed concentric hypertrophy. Minimal pericardial effusion was noted along the right atrium and right ventricle. Pulmonary artery was dilated which was suggestive of pulmonary arterial hypertension (PAH). No obstruction or mural thickening of the aorta was noted. Bilateral pleural effusion was seen. No lymphadenopathy was noted.

Electrocardiogram (ECG) revealed following findings on three consecutive days: Day 1 and 2- ST elevation in V_1, q waves in lead I, aVL. No right ventricular hypertrophy (RVH) identified. Pure R wave were noted in aVL. No R waves identified in V_4 V_5 and V_6. Day 3- Right bundle branch block (RBBB) was noted.

Echocardiography revealed aortic velocity 1.1, Pulmonary velocity 1.0, and mild to moderate mitral regurgitation (MR) (eccentric jet), moderate to severe tricuspid regurgitation (TR), RVSP=RAP+34, and global hypokinesia. Estimated left ventricular ejection fraction was 35-40%. There was mild pericardial effusion.

Course: The boy presented with acute onset respiratory failure which was attributed to cardiac cause. He was initiated on supportive care, which included sequential addition of vasopressors and subsequent ventilation. He was started on intravenous antimicrobials. He had one episode of generalized tonic-clonic seizure during the stay. Injection heparin was started on day 2 of illness. He started developing fever spikes on day 3 of admission. However, his condition progressively deteriorated and he succumbed to his illness. The postmortem blood culture grew *Acinetobacter boumanii* which was sensitive to imipenem and colistin.

Unit's Final Diagnosis: Viral myocarditis with cardiogenic shock.

Discussion

Clinical discussant: We have a 14-year-old boy who presented with complaints of acute chest pain and biventricular failure. He initially had left ventricular failure (LVF) (marked tachycardia, marked tachypnea, hypotension and hypoxemia) and later developed right ventricular failure (RVF) (hepatomegaly, raised JVP, dilated RA and RV, and ascites). ECG showed lateral wall changes along with elevated CPK-MB, increased troponin-T and increased LDH. During his hospital stay, he had mild elevation of AST which increased significantly likely due to systemic hypotension. He had one episode of seizure which was most likely secondary to hypoxia, and pre-terminally developed febrile illness with worsening hemodynamics.

Acute onset chest pain with biventricular failure, ECG evidence of myocardial ischemia, elevated CPK-MB, and increased toponin-T point to myocardial ischemia as the predominant pathophysiology in this child. Myocardial ischemia in children and adolescents is rare and can occur due to the following causes:

- Aortic stenosis: Absence of aortic stenosis on ECHO and LVH on ECG go against this diagnosis.
- Congenital coronary artery abnormalities

Anomalous left coronary artery from the pulmonary artery (ALCAPA): ALCAPA usually presents in infancy, but 10-15% patients will present late with myocardial dysfunction and with ECG showing typical features of Q waves in lead I, T wave inversion in lead I, aVL and poor R wave in V_4, V_5 and V_6. This is an important cause of left sided myocardial ischemia in children and should be thought of any child who presents with ischemic changes in left sided leads.

Anomalous origin of left coronary artery from right coronary sinus: This left coronary artery after origin from right coronary sinus courses between aorta and pulmonary artery which can cause ischemia. Clinical presentation is generally with arrhythmia and acute LVF is usually not seen. Still it should be considered in any young person with chest pain as a remote possibility.

TABLE I RESULTS OF HEMATOLOGICAL AND BIOCHEMICAL INVESTIGATIONS IN THE INDEX CASE

Investigations	Day 1	Day 2	Day 3
Hemoglobin (g/dL)	13.9		10.4
Total leukocyte count (10^9/L)	10.1		13.2
Platelets (10^9/L)	393		220
Serum sodium (mEq/L)	138	140	141
Serum potassium (mEq/L)	4.9	3.8	4.2
Blood urea (mg/dL)	37	60.7	62.7
Serum creatinine (mg/dL)	0.67	0.84	0.73
*AST (IU/L)	360	1441	1507
#ALT (IU/L)	286	1241	1572
Alkaline phosphatase (U/L)	271	256	195
Serum bilirubin total (mg/dL)	1.85	2.9	2.7
Serum bilirubin conjugated (mg/dL)	0.31	0.6	0.53
Serum calcium (mg/dL)	10.1	8.01	
Serum phosphorus (mg/dL)	5.4	3.44	
Serum total proteins (g/dL)	5.84	6.43	
Serum albumin (g/dL)	3.9	4.5	

**Aspartate aminotransferase; #Alaline aminotransferase.*

Other coronary artery abnormalities like coronary artery fistula are very rare and are difficult to diagnose clinically. Coronary fistula is usually asymptomatic at this age. These patients do not present acutely unless a catastrophe like thrombotic occlusion occurs. An easily audible continuous murmur helps in the diagnosis.

- Acquired causes of coronary artery involvement: Among the acquired causes of myocardial infarction, Kawasaki disease, coronary arteritis and coronary artery dissection are known to occur in young children. Drug abuse also remains a possibility.

Kawasaki disease is the most important cause of myocardial ischemia in children. A past history of Kawasaki disease can easily be mistaken as a viral illness. Upto 25% of untreated children with Kawasaki disease will develop coronary artery abnormalities. Giant coronary aneurysms with complications like thrombosis, stenosis and rupture are well known. So, this possibility should always be considered in such a child. ECHO can pick up coronary abnormalities and help in diagnosis.

Coronary arteritis has been described with many systemic illnesses like Systemic lupus erythematosus (SLE) and Polyarteritis nodosa (PAN). This is a possibility; however, there are no clinical features to suspect these conditions. Spontaneous dissection of coronary artery is more common in young pregnant females. There have been case reports in young children who present with sudden onset of symptoms. Drug abuse causing coronary vasospasm and resultant MI remains a possibility, though there is no such history available.

Besides coronary abnormalities, myocardial ischemia can be caused by myocardial diseases; hypertrophic cardiomyopathy being the commonest. Absence of septal hypertrophy on echocardiography and LVH on ECG go against this diagnosis.

Myocarditis should also be considered in such a setting, as it can masquerade acute coronary events. Elevation of muscle enzymes is well known and diffuse ECG changes like ST elevation in lead I, aVL, and ST depression in lead III, aVF, and poor R waves are well described in myocarditis. Echocardiography finding of global hypokinesia is also seen in myocarditis. With a short history, elevated enzymes and ECG changes, it remains a strong possibility. Fulminant myocarditis can have a similar presentation and important causes include infections, toxins, hypersensitivity myocarditis, immune mediated disorders, necrotizing eosinophilic myocarditis and giant cell myocarditis. Clinically, it is practically impossible to pinpoint a specific cause of myocarditis.

Besides left ventricular failure, this child also had ascites and edema along with right atrial and right ventricular dilatation, severe tricuspid requrgitation and no pulmonary embolism. It is difficult to explain prominent right ventricular failure based on myocarditis or myocardial ischemia. So the question is whether this child had an underlying right ventricular dysfunction which was asymptomatic till date and manifested with myocardial ischemia/myocarditis.

Among the myocardial diseases responsible for right ventricular dysfunction, arrhythmogenic right ventricular dysplasia commonly presents with arrhythmia. There were no clinical features to suggest Fabry's disease. Uhl's anomaly is a rare disorder that can present in infancy with RVF. It seems likely that this child did not have a myocardial cause for his RVF. Right ventricular ischemia remains an important cause for RVF in adults. Index child did not have ECG evidence of RV infarction. ECHO did not show evidence of tricuspid regurgitation or stenosis either. It is possible to miss sinus venosus type of atrial septal defect (SVC ASD) on routine echocardiography. Sinus of Valsalva aneurysms can present at this age with bi-ventricular failure, but this entity is marked by a continuous murmur and this child did not have one.

Pressure overload situations like severe pulmonary artery hypertension and pulmonary embolism have been ruled out by CT scan. Right ventricular outflow tract obstruction (RVOT) has been ruled out by echocardiography. So, pulmonary vascular diseases seem unlikely. He did not have any features of RVH. Pericardial diseases can present with biventricular failure, however, it seems unlikely in this child.

Pre-terminally, he had healthcare-associated infection with persistent fever and positive blood culture.

So, my final diagnosis is acute fulminant myocarditis, likely viral or myocardial infarction with premature coronary artery disease like dissection or giant coronary artery aneurysm and cause of death is healthcare-associated infection.

Clinician in-charge: This child presented a diagnostic challenge of acute onset bi-ventricular failure with predominant RVF features. Most likely it was an acute on chronic event. Looking at the fulminant presentation, viral myocarditis was the first possibility based on which intravenous immune globulin (IVIg) was given to this child. It was not clear whether there was any underlying congenital or acquired myocardial disease.

Chairman: This child played football the previous evening, meaning thereby that even if he had an underlying heart disease, it was fairly well compensated and an acute event caused decompensation.

Physician 1: This child had leucocytosis, edema, ascites, sub-conjunctival hemorrhage, transaminitis and anemia. A possibility of leptospirosis could be considered but the odd points are the absence of fever and absence of renal involvement.

Chairman: The absence of fever is a very important finding. As we know, leucocytosis is an acute phase response which can occur in multiple conditions including non-infectious like myocardial ischemia.

Physician 2: In view of the global involvement of myocardium as demonstrated by echocardiogram, I would consider myocarditis as the possibility rather than myocardial ischemia which will cause a focal involvement.

Cardiologist: There is discordance between the history, clinical examination and the investigation. With this acute illness, ECG and echocardography showing global involvement, myocarditis remains the first possibility but leptospirosis has to be looked for.

Pediatrician 1: A young boy coming with myocarditis or MI like presentation, Kawasaki disease remains as one of the most important possibility. Atypical and incomplete presentations are well described in the literature.

Radiologist: With myocardial thickening and RA, RV dilatation, possibility of myocarditis is strong.

PATHOLOGY PROTOCOL

A partial autopsy was carried out. Externally, the deceased was noted to be thin-built. There was pericardial effusion and pleural effusion with 50 mL and 500 mL of straw-colored fluid, respectively. The peritoneal cavity was within normal limits. The findings in the heart were remarkable with biventricular dilatation and bifid apex. Thrombus was noted in the right auricle. All the chambers were dilated. The right and left ventricular wall thickness measured 0.6 cm and 1.6 cm, respectively. On gross examination, there was transmural haemorrhagic discoloration of ventricular wall involving papillary muscle and major portions of RV (***Fig.* 1**). All the four valves were within normal limits. On microscopy, there was fibrinous pericarditis, extensive interstitial myocarditis with a neutrophil-rich infiltrate and perivasculitis involving major portions of both ventricles (***Fig.* 2**). Features of myocardial ischemia with loss of nuclei, hyper-eosinophilia and significant inter-myocyte edema were detected in major portions of left and in parts of right ventricle (***Fig.* 2d**). Coronaries and other medium-sized vessels (***Web Fig.* 1**) (superior mesenteric and right external iliac artery) demonstrated extensive disruption of internal elastic lamina (IEL) with irregular heaping of intima. Fibrinoid necrosis and significant medial inflammation were not detected within the vessel walls. No aneurysms were identified. The polymerase chain reaction (PCR) for Coxscakie and entero-viruses performed on the DNA extracted from the post-mortem heart and kidney tissue was negative. Lungs revealed features of early bronchopneumonia with focal alveolar hemorrhages. The rest of the organs examined both grossly and microscopically were within normal limits.

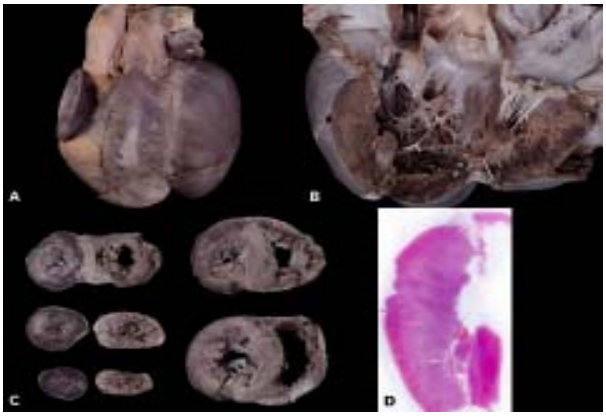

FIG. 1 *(a) Gross appearance of heart from anterior surface with bifid apex. (b) Dilated left ventricle with transmural haemorrhagic discoloration of ventricular wall and endocardial sclerosis. (c) Serial horizontal slices of heart from apex to base with transmural haemorrhagic discoloration involving both ventricles and portions of interventricular septum. (d) Scanner view of left ventricle (LV) demonstrates large areas of coagulative necrosis of its myocardium and papillary muscle.(Color images at website)*

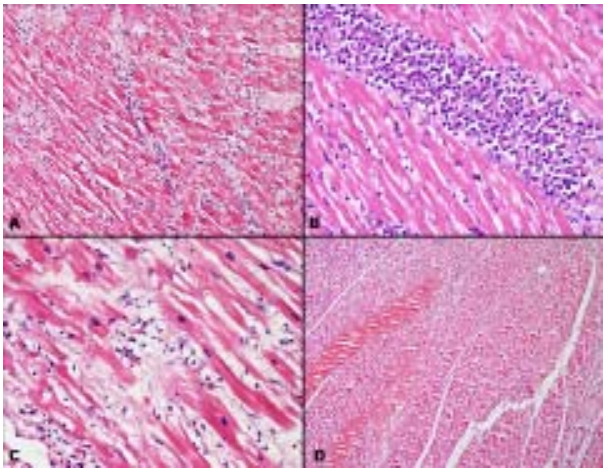

FIG.2 *(a) Interstitial myocarditis with a neutrophil predominant infiltrate and interstitial oedema (H&E×100), (b) Dense interstitial collection of inflammatory cells (H&E×200), (c) Inflammatory cells with myocyte destruction (H&E×400), (d) Large areas of infracted myocardium with loss of myocyte nuclei, loss of striations and hypereosinophilia of fibres (H&E ×100). (Color images at website)*

Final Autopsy Diagnosis: Kawasaki disease with early bronchopneumonia and pleural effusion

OPEN FORUM

Pediatrician 1: Myocarditis is a universal feature in Kawasaki disease as documented in many previous autopsy series. So, myocarditis accompanied by vasculitis and infarction, I think Kawasaki disease remains a strong possibility.

Pathology discussant: The findings which favoured a diagnosis of Kawasaki disease were myocardial ischemia and involvement of coronaries, i.e. the destruction of the internal elastic lamina which is a key feature and an early event for the aneurysm formation. The history lasted only three days and had he lived long, we could have found other features as well.

Chairman: In a young child or adolescent presenting with features of heart failure and ischemia, possibility of Kawasaki disease should be considered more frequently.

DISCUSSION

Kawasaki disease is an important childhood systemic vasculitis with potentially major cardiovascular implications, especially if the diagnosis is missed, and if timely and appropriate treatment is not given. The incidence of incomplete Kawasaki disease is unknown [5,6]. In a retrospective report of 242 Japanese children with Kawasaki disease treated at a single center over a nine-year period, 10 percent of patients were diagnosed with incomplete Kawasaki disease [5]. The incidence appears to be greater in infants younger than six months of age [6,7].

Pathological studies over the years on Kawasaki disease have mostly focused on arterial lesions with changes mostly affecting the coronary arteries [8-10]. Ischemic cardiac lesions due to stenosis, thrombosis or aneurysmal dilatation of coronary artery have been well described within the spectrum of acute or chronic-phase Kawasaki disease [10]. Myocarditis frequently occurs in the acute phase of disease; however almost all cases are clinically mild [2,11]. Fulminant fatal myocarditis during the acute-phase of the disease is rarely reported in the literature. While the clinical presentation in the teenager boy was atypical or incomplete for Kawasaki disease, the presence of subconjunctival hemorrhages was the positive clinical clue which was unfortunately missed. Histologically, presence of acute interstitial myocarditis accompanied by coronary arteritis is considered to be characteristic myocardial lesion in Kawasaki disease [12]. Myocarditis in Kawasaki disease have been described to develop prior to development of epicardial coronary arteritis as early as on the sixth day of onset of illness in a recent study on autopsied hearts [12]. The inflammatory infiltrate in Kawasaki disease chiefly comprises of neutrophils and monocytes/macrophages and few lymphocytes, in contrast to viral myocarditis wherein the infiltrate is mostly composed of lymphocytes accompanied by necrosis of individual myocardial cells or myocardial fibre bundles [13].

Coronary arteritis as seen in this case is characterized by irregular thickening of the initima along with breakage of the internal elastic lamina, which is the key feature for aneurysm formation noted in 20-25% of cases [14]. The rapidly fulminant fatal course perhaps preluded the development of aneurysms in the teenager boy. The differential diagnoses include common childhood febrile illnesses like measles, scarlet fever and viral fever. Coronary artery abnormalities (CAA) that occur in Kawasaki disease can lead to long term consequences in the form of thrombosis, stenosis or occlusion leading to MI, ischemia or sudden death. There have been multiple reports and studies reporting patients who had coronary events as long term sequelae attributable to childhood Kawasaki disease [15-18].

The case underscores the importance of suspecting Kawasaki disease in a young child presenting with features of myocardial ischemia.

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