Unexpected late-onset aortic valvulitis and moderate regurgitation during longitudinal evaluation of atypical infantile Kawasaki disease: The heart beyond coronaries!

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ABSTRACT

Kawasaki disease (KD) is the most common pediatric vasculitis with coronary involvement feared as the most serious complication. The reported case describes a child presenting initially with atypical KD and coronary artery aneurysms. He was treated with intravenous immunoglobulin and aspirin. In spite of adequate compliance and no clinical recurrence, serial echocardiography revealed nonregression of aneurysm and new-onset moderate aortic regurgitation (AR) in the subacute phase produced by prolapse of noncoronary cusp of the aortic valve. AR without aortic root dilatation from persistent inflammation of the valve leaflets in KD is a rare phenomenon. This case demonstrates unusual cardiac manifestations of KD and reoriented our protocol for long-term surveillance in infantile KD.

Keywords: Aortic regurgitation, aortic root, atypical Kawasaki disease, coronary aneurysms, extracoronary involvement, late-onset aortic valve prolapse

INTRODUCTION

Kawasaki disease (KD) is an acute febrile illness with mucosal inflammation, cutaneous changes, nonexudative conjunctivitis, and cervical lymphadenopathy recognized most often in children younger than 5 years of age.¹,² Valvar dysfunction occurs in ≈ 25% of patients, most commonly affecting the mitral valve. Acute mitral regurgitation (MR) coexists with pancarditis, whereas late MR is produced by ischemic insult to mitral valve apparatus. Aortic regurgitation (AR) was reported in only 1% of patients associated commonly with aortic root dilatation.¹,²,³

The index child presented initially with atypical clinical features of KD and coronary artery aneurysms on echocardiography. He was treated with intravenous immunoglobulin (IVIG) and aspirin as per the American Heart Association (AHA) protocol.¹⁴ In spite of good compliance and no clinical recurrence, serial echocardiography demonstrated persistent aneurysm with new-onset significant AR with prolapse of noncoronary cusp (NCC) of the aortic valve without aortic root dilatation possibly due to persistent inflammation from Kawasaki sequelae.

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CLINICAL SUMMARY

A 5-month-old male child, weighing 6.5 kg, presented with 7 days of intermittent high-grade pyrexia, irritability, and nonexudative conjunctivitis with limbal sparing. Clinical examination did not reveal any focus in central nervous system, abdomen, respiratory system, bones, joints, genitourinary tract infection, skin, or mucosa. He was hemodynamically stable. Initial hemogram on day 7 of illness revealed hemoglobin 11.1 g/dl, total leukocyte count 9350/cumm (neutrophils 52.1%, lymphocytes 29%), and borderline platelet counts (430,000/cumm). Acute-phase reactants (erythrocyte sedimentation rate [ESR] 82 mm in first hour, C-reactive protein [CRP] 96 mg/L) were elevated with normal liver and renal function profiles. Sepsis panel was negative. Blood and urine cultures were sterile, and he tested negative for dengue, malaria, typhoid, and rickettsia. Echocardiography was requested to exclude cardiac etiology of pyrexia (endocarditis, myocarditis, rheumatic fever, arteritis, vasculitis, etc.).

Sedated echocardiography was done with echo machine EPIQ 7, Philips Healthcare, Andover, USA, with broad band cardiac transducer (S3, S8, and S12). It excluded structural congenital heart disease, vegetation, cardiac dysfunction, myocarditis, valvular regurgitation, and pericardial effusion. Coronary artery imaging with high-frequency transducer (S12) in the parasternal short axis view revealed fusiform aneurysm of left main coronary artery (z score +3.5) and left anterior descending coronary artery (z score +2.8) without intracoronary thrombus, luminal irregularity, or perivascular brightness [Figure 1]. The left circumflex and right coronary arteries were normal (z scores +1.5 and +1.1, respectively). Global cardiac function and cardiac dimensions were normal without evidence of regional wall motion abnormality.

With a diagnosis of atypical KD (clinical background, raised acute-phase reactants, and coronary involvement), IVIG at 2g/kg combined with aspirin (acetylsalicylic acid) at 50 mg/kg/day was started as per the AHA protocol. Pyrexia (38.3°C) persisted after 48 h of completion of IVIG infusion, but the family denied second course of IVIG. Fever subsided spontaneously 4 days later. He received high-dose aspirin up to 72 h of subsidence of fever and was subsequently monitored for another 2 days. With a consequent continuous afebrile period of 48 h, he got discharged on antiplatelet dose of aspirin (5 mg/kg/day once daily orally). Same management was continued in the outpatient department.

Two months later, he suffered another episode of self-limiting low-grade fever for 5 days without any localizing signs and was empirically treated as viral fever. Laboratory and echocardiography markers did not show any new finding.

During scheduled cardiology follow-up 12 weeks after the first episode, he was afebrile, active, and asymptomatic. Auscultation revealed a blowing early diastolic murmur in the aortic area without congestive cardiac failure.

Echocardiography revealed dilated left ventricle (LV) (LV internal diameter end diastole 30 mm, z score +2.32 and LV internal diameter end systole 19 mm, z score +2.02), LV ejection fraction 53% (Simpson’s method), no regional wall motion abnormalities, and persistence of coronary artery aneurysm. LV Tei index was 0.95 (indicative of cardiac dysfunction, most likely systolic). Aortic annulus (9 mm, z score +0.3) and ascending aorta (11 mm, z score −0.62) were not dilated. The unique finding noted here was prolapse of NCC of aortic valve, leading

![Figure 1: Parasternal short-axis echocardiogram at the level of semilunar valves with arrow pointing to the coronary artery aneurysm (CAA). RA: Right atrium, LA: Left atrium, RVOT: Right ventricular outflow tract, Ao: Aorta](image)

![Figure 2: (a) Apical five-chamber view demonstrating the new-onset moderate aortic regurgitation. (b) Parasternal long-axis view demonstrating the eccentric aortic regurgitation. (c) Two-dimensional parasternal long-axis view demonstrating the mechanism of aortic regurgitation with arrow pointing to prolapse of noncoronary cusp with defective coaptation. Ao: Aorta, LA: Left atrium, LV: Left ventricle, RV: Right ventricle](image)
to diastolic noncoaptation. The aortic valve was tricuspid having thin, nonbeaded, pliable cusps [Video 1]. No vegetation was found on transthoracic echocardiogram. Color flow mapping in the apical five-chamber, parasternal long- and short-axis views [Figure 2a-c and Videos 2, 3] showed moderate AR with two eccentric jets arising from NCC and right coronary cusp junction with cumulative vena contracta of 6 mm. Trivial MR was also noted. Both the new-onset valvulopathies were detected in this later echocardiogram, with AR being the dominant lesion. Pulmonary artery systolic pressure estimated from tricuspid regurgitant jet was 25 mmHg. The right ventricular function assessed by tricuspid annular plane systolic excursion and fractional area change was normal [Table 1].

In view of this unusual development of delayed-onset AR in KD, three differential diagnoses were considered, namely: (1) infective endocarditis, (2) ischemic heart disease, and (3) sequelae of KD. Other etiologies of pediatric AR such as trauma, connective tissue disorder, genetic syndromes, and structural heart defects were absent.

Endocarditis was excluded by absence of fever, toxemia, vegetation, negative blood cultures, and inflammatory markers (ESR, CRP, and procalcitonin). Transesophageal echocardiography was avoided due to excellent transthoracic echo windows and small size of the child. Cardiac enzyme panel (CPK, CPK-MB, and high-sensitivity troponin I) was normal excluding myocardial ischemia. Electrocardiogram showed normal sinus rhythm without ST-T wave changes. Resting wall motion abnormalities were absent while aortic root was normal. Family denied consent for computed tomography (CT) coronary angiogram.

The only remaining possibility was delayed sequelae of KD. At this stage, all the inflammatory parameters were normal except high platelet counts (832,000/cumm). Anti-streptolysin O was normal. Serum B-natriuretic peptide was mildly elevated (725 vs. 123 pg/ml at 1st presentation). The child was started on oral frusemide due to elevated brain natriuretic peptide and LV Tei index, enalapril, and dual antiplatelet drugs (aspirin and clopidogrel). Concurrently, intravenous infliximab (5 mg/kg) infusion was given over 2 h. Frusemide was stopped after a week.

A multidisciplinary team postulated that new-onset moderate AR was due to subclinical inflammation, and medical management with dual antiplatelets and enalapril was continued in the OPD with close cardiology follow-up. Aortic valve surgery was not considered due to asymptomatic clinical status, good response to medical management, small size of aortic root, and underlying indolent inflammation.

Follow-up (2 years to date) reveals status quo. The growth, development, physical activity, and asymptomatic status mirror normal pediatric population.

**DISCUSSION**

The eponymous mucocutaneous lymph node syndrome was discovered in 1961 by Dr. Kawasaki. Western data record it as the most common acquired pediatric heart disease. From three published case reports before 1990, a tenfold increase was documented in India in 2017.

So far, the focus of cardiac evaluation in Kawasaki survivors was coronary arteries. Our case illustrates significant delayed-onset aortic valvulopathy with silent external clinical features. KD histopathology demonstrates three linked pathological stages. These consecutive histopathological stages seen in autopsy specimens are 1. acute phase (duration first two weeks) marked by pancarditis and epicardial coronary involvement, 2. subacute phase (duration >2 weeks from onset, continuing for months to years, 3. final phase characterized by luminal myofibroblastic proliferation. Acute and chronic MR is common in KD as mentioned before.

However, AR due to leaflet prolapse with normal aortic root is rarely reported. Myocardial ischemia was excluded to the best of our ability. CT coronary angiogram is definitely superior to echocardiography, but parental consent was lacking. Unlike rheumatic AR, commissural fusion, thickening, and calcification of leaflets were absent in echo. We postulate that this may be due to very early diagnosis of valvulitis and needs to be specially looked for in chronic follow-up. The NCC prolapse distorted the valve structure and produced eccentric regurgitant jets. Thus, we zeroed down on ongoing valvulitis as the culprit destructing aortic valve. The child also responded well to escalated immunomodulatory treatment and antiplatelets.

Literature review documented similar case reports from Japan. Fukunaga et al. in 1996 reported two infants with KD who developed severe AR 18 months and 36 days after the initial episode. Both eventually underwent valve replacement with histopathology demonstrating

| Table 1: Longitudinal echocardiographic evaluation of reported case |
| --- |
| **Longitudinal Echo parameters** | At presentation | After 8 weeks | After 12 weeks |
| LV FS (%) | 33 | 31 | 27 |
| LV MPI (Tissue Doppler) | 0.34 | 0.4 | 0.95 |
| MR | Nil | Nil | Trivial |
| AR | Nil | Nil | Moderate |
| RWMA | Absent | Absent | Absent |
| Aortic root | Normal | Normal | Normal |

MR: Mitral regurgitation, AR: Aortic regurgitation, LV: Left ventricle, FS: Fractional shortening, MPI: Myocardial performance index, RWMA: Regional wall motion abnormality
CONCLUSIONS

KD is still a cryptic disease and often involves beyond the coronaries. As infants are unable to communicate, the onus of diagnosing progression of disease lies primarily with echocardiographer. Delayed valvular involvement is also a red flag demanding prompt action. To the best of our knowledge, such unique presentation is reported for the first time from India.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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