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CASE BASED REVIEW

Kawasaki disease or polyarteritis nodosa: coronary involvement, a diagnostic conundrum

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Abstract

Polyarteritis nodosa (PAN) is a medium-vessel vasculitis presenting with cutaneous and multisystem involvement with considerable morbidity. The necrotizing vasculitis in PAN typically involves renal, celiac, and mesenteric vascular beds. Coronary artery involvement is a characteristic feature of Kawasaki disease, another medium-vessel vasculitis; however, it has been rarely reported with PAN. Here, we present 2 cases with PAN involving coronaries mimicking Kawasaki disease. A 3.5-year-old boy with classical features of Kawasaki disease with giant coronary aneurysm refractory to IVIg, methylprednisolone, infliximab presented with persistent rise in inflammatory markers and gastrointestinal bleeding. Digital subtraction angiography (DSA) revealed celiac artery branches stenosis and beading suggestive of PAN. Another 2-year-old girl presented with persistent fever, abdominal pain, and distension. She had hypertension, hepatomegaly, and splenomegaly on examination. Echocardiography revealed multiple coronary aneurysms and DSA revealed numerous renal artery aneurysms. Coronary aneurysm although is a rare presentation of childhood PAN, and can mimic Kawasaki disease. Although both are medium-vessel vasculitis differentiation between these two entities is pivotal, as there are differences in treatment modalities, duration of immunomodulatory therapy, and the outcome. This manuscript describes the salient differences which can help differentiate PAN masquerading as Kawasaki disease at initial presentation.

Keywords PAN · Coronary aneurysm · Cyclophosphamide · Kawasaki disease

Introduction

Polyarteritis nodosa (PAN) is a systemic vasculitis chiefly affecting medium vessels. Coronary involvement in childhood PAN has rarely been reported. Unlike Kawasaki disease, the predilection for coronary involvement is rare in PAN. However, at times the distinction between two vasculitides may be challenging, particularly at the onset, which has a bearing on the therapeutic plan and long-term outcome.

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Case report

Case 1 A three and half-year-old boy had a history of fever for 1 month, maculopapular rash over the trunk, periungual peeling, non-exudative conjunctivitis, and cheilitis. The child was diagnosed with Kawasaki disease and managed with oral steroids and low-dose aspirin for around a week with a transient resolution of symptoms. After 15 days, the child presented with chest pain, abdominal pain, fever, similar rash, and non-exudative conjunctivitis. The ECG was suggestive of inferior wall ischemia (Q wave in the lead 2, 3, and aVF). 2D echocardiography showed giant coronary aneurysms/dilations with the left main coronary artery (LMCA), left circumflex artery (LCx), and left anterior descending (LAD) measuring 7.1 mm (13 z score), 5.6 mm (11 z score), and 2.9 mm (2.5 z score), respectively, and right coronary artery (RCA) 2.7 mm (2.4 z score). The left ventricular ejection fraction (LVEF) was 45–50%. Inflammatory markers (CRP 187 mg/L and ESR 35 mmHg) were elevated. Kawasaki disease was diagnosed, and the child was treated with IVIg 2 g/kg, low-dose aspirin and low-molecular weight heparin (LMWH). The child continued to have fever and raised inflammatory markers (CRP 239 mg/L; ESR 48) with deteriorating cardiac function (EF 25–30%). The child was started on steroids, decongestive measures, and transiently required dobutamine support with the resolution of symptoms. He was discharged on oral steroids with tapering, oral enalapril, aspirin, and warfarin with a targeted INR of 2–3. After two months of asymptomatic period, the child presented with fever, blood in stools with persistently elevated inflammatory markers (CRP 170 mg/l and ESR 55), and echocardiogram showing increased coronary sizes (LMCA 15 z and LCx 12 z with dilated LAD 2.5 z and RCA 2.4 z). The child was treated with IV methylprednisolone 30 mg/kg in three pulses with symptom resolution. But the child had persistently elevated inflammatory markers with increasing coronary sizes, and hence a single dose of infliximab was also administered. Following this, a decline in CRP (CRP 2.3 mg/l) was observed, and he was discharged on tapering steroids, aspirin, warfarin, along with enalapril, and spironolactone. However, on tapering steroids, there was a resurgence in the levels of CRP. With GI bleed in the background with persistent increased coronary sizes and inflammatory markers, digital subtraction angiography (DSA) was performed, which showed stenosis and beading in branches of celiac arteries (Fig. 3a). Considering a long disease course of months with the elevation of inflammatory markers on weaning steroids and the characteristic DSA findings, the diagnosis was revised to PAN with the giant coronary aneurysm. The child was treated with cyclophosphamide pulse with a plan of six each monthly pulse followed by mycophenolate mofetil (MMF). The child has completed four cycles of cyclophosphamide and is doing well without recurrence of symptoms and normal inflammatory markers. Repeat echocardiography shows a decrease in the dimensions of the coronary arteries.

Case 2 A two-year-old girl presented with fever and abdominal pain for three months. The child had received multiple antibiotics for a presumed infection without any response. Echocardiography done as a part of the workup for persistent fever revealed multiple coronary artery aneurysms following which a diagnosis of Kawasaki disease was offered, and she received intravenous immunoglobulin (IVIG). However, because of persistent fever, she was referred to our center. Physical examination revealed pallor, stage I hypertension and hepato-splenomegaly (liver span of 9 cm with spleen palpable 3 cm below left costal margin). The rest of the systemic examination was unremarkable.

Investigations revealed anemia (Hemoglobin of 7 gm/dl), neutrophilic leukocytosis (total leucocyte count of TLC 26,000/mm^3 with neutrophil 80%), thrombocytosis (platelet count 6.6 lakh/mm^3) and raised inflammatory markers (CRP 30 mg/dl and ESR 40 mm 1st hour). The echocardiography revealed multiple coronary aneurysms (Figs. 1, 2).

In view of persistent fever, abdominal pain, and hypertension, the possibility of polyarteritis nodosa was considered, which was supported by DSA, which revealed multiple aneurysms in bilateral renal arteries (Fig. 3b). Contrast-enhanced computed tomography (CT) of the abdomen revealed multiple vasculitic infarcts involving bilateral kidneys and spleen.

She was managed with three doses of methylprednisolone 30 mg/kg/day followed by oral steroids and monthly intravenous cyclophosphamide at 500 mg/m^2 planned for

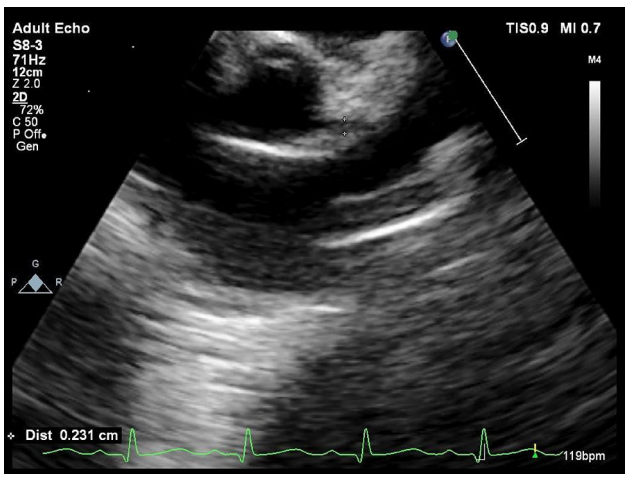

Fig. 1 ECHO showing dilatation of left anterior descending artery. RCA: 4 mm (+7.5 Z score) LMCA: 3.2 mm (+2.9 Z score) LAD: 2.9 mm (+5.2 Z score) EF: 60%

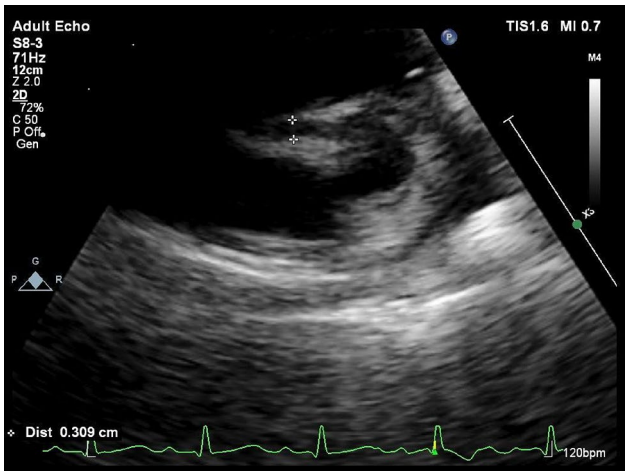

Fig. 2 ECHO showing dilatation of right coronary artery. RCA: 4 mm (+7.5 Z score) LMCA: 3.2 mm (+2.9 Z score) LAD: 2.9 mm (+5.2 Z score) EF: 60%

six months. Hypertension was managed with amlodipine and enalapril. The child has completed six cycles of cyclophosphamide and is doing well with no recurrence of symptoms. Currently, child is on oral MMF. Steroids were tapered and stopped. Repeat echocardiography shows a decrease in the dimensions of the coronary arteries.

Search strategy

We searched PubMed/Medline and Google scholar for articles with key words "Kawasaki versus Polyarteritis Nodosa", "Coronary involvement Polyarteritis Nodosa/ PAN", "Coronary involvement rheumatological diseases in children" the articles were carefully reviewed by first authors. We excluded articles in language other than English, irrelevant articles, and duplicates. Relevant articles to the topic of our discussion are included in literature review.

Discussion

These cases illustrate a rare clinical manifestation of childhood PAN in the form of coronary aneurysm, which is more frequently associated with Kawasaki disease (KD), leading to a diagnostic and therapeutic dilemma. Although both PAN and Kawasaki are medium-vessel vasculitis, usually with distinct clinical presentation, rarely can PAN have KD-like features as in our case 1.

Kawasaki disease, predominating in the toddler age group, presents with mucocutaneous rash and fever of acute onset along with or without coronary aneurysm [1, 2]. In contrast, the spectrum of organ involvement in PAN is wider, with a chronic course predominantly affecting school-age children and more widespread multisystem involvement in the form of hypertension, neuropathy, purpura or gangrene of skin, retinal vasculitis, aneurysm, and infarct in various sites like liver, spleen, gastrointestinal tract, and kidney [3–5].

The presence of coronary aneurysm is an atypical finding in PAN which, though rare, has been described in the literature. Histopathology performed post-mortem in adults with polyarteritis nodosa has demonstrated evidence of cardiac involvement with coronary arteritis found in 18/36 cases of necrotizing vasculitis on autopsy [6]. However, only a few reports of childhood PAN with coronary involvement exist. Our case 2 had a chronic course with fever and abdominal

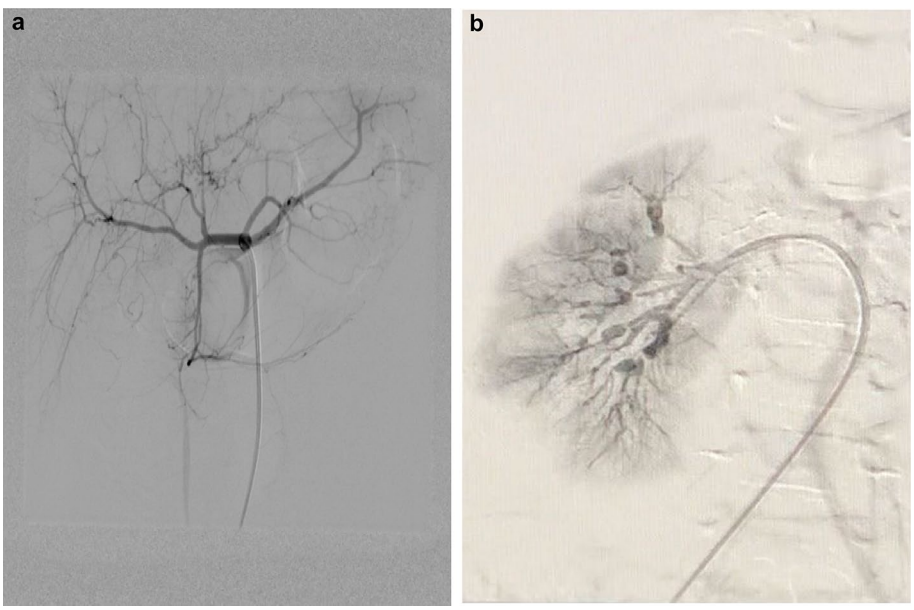

Fig. 3 **a** DSA showing stenosis and beading in celiac trunk branches; **b** DSA image showing aneurysm in the segmental renal arteries

pain for three months with hepato-splenomegaly, hypertension, and showed wedge-shaped infarcts in the kidney and spleen. The child met the EULAR/PRINTO/PRES 2010 classification criteria of childhood PAN established by [7]. Bowyer and coworkers presented two such cases in 1994 where the children had aneurysms in the coronary as well as in hepatic or renal vessels [8]. Munro and coworkers recently described a 3-month-old boy who had bloody diarrhea, fever, vomiting, a very high C-reactive protein, leukocytosis, and thrombocytosis [9], in whom, on autopsy, a generalized pan arteritis was revealed, including the coronary, renal, and mesenteric arteries, consistent with diagnosis of PAN. Canares and coworkers presented a case of a 16-year-old girl with PAN and coronary aneurysm who was successfully treated with pulse cyclophosphamide therapy [10]. Yamazaki-nakashimada and coworkers [11] reported a 3-year-old child with coronary involvement and rash. The child was initially suspected of having atypical Kawasaki and was refractory to IVIG. Child had finally improved with pulse methylprednisolone after diagnosis was revised to be childhood PAN due to multiple intra-abdominal visceral vascular involvement. Table 1 summarizes the reported cases of PAN with coronary involvement, including ours.

Both PAN and Kawasaki disease can present with a febrile illness, and it is challenging to differentiate between the two entities, particularly in the absence of typical dermatological features. Such a presentation may pose a diagnostic and therapeutic dilemma as the treatment option differs. Kawasaki disease presents more acutely with predominant affection to coronary vasculature, while PAN presents as a more insidious disease with multisystem involvement, vascular ulcer, and aneurysms in the celiac, mesenteric axis, and renal arteries (Supplementary Fig. 4) [12, 13]. Delineating the two conditions is essential to optimize the therapeutic strategy; IVIG is the first treatment option for Kawasaki disease. While prolonged immunosuppression withcyclophosphamide/MMF with steroids in this type of disease presentation having features of both diseases as indicated in PAN [10, 14]. Table 2 summarizes the key clinical and laboratory differences which can help to manage such challenging cases.

Kawasaki disease is an overt immunological reaction to superantigens mediated by T cells leading to infiltrates and inflammatory cascade. In contrast, in PAN, there is a pre-existing genetic predisposition or parainfectious activation of CD 8 + T cells with macrophages leading to the destruction of the vessel wall [15, 16].

In both cases, initial immunomodulation was as per the recent guidelines for the management of Kawasaki disease. However, the initial management with IVIG might have been insufficient for the underlying PAN, and the unchecked inflammation might have resulted in giant coronary aneurysms in both cases. This proves the value of the early diagnosis of PAN, even in cases of the coronary aneurysm,

Table 2 Comparing features of PAN and Kawasaki disease

	Kawasaki disease	Polyarteritis nodosa
Age	< 5 years usually	> 5 years
Fever	Acute onset	Insidious onset
Coronary involvement	Common	Rare
Skin manifestations	Maculopapular rash/edema/periungual peeling	Purpura, livedo reticularis, gangrene
Multisystem involvement	Rare	Common
· GI involvement	Rare	Common
· Renal involvement	Rare	Frequent
· Hypertension	Rare	Frequent
· ANCA positivity	Rare	Occasional
Disease course	Short (weeks)	Chronic
Therapy	Short (weeks)	Long (years)

Table 1 Reported cases of PAN with coronary involvement including our case

Author	Age/gender	Presentation	Coronary involvement	Other organs involved
Therese L Canares et al. (Paediatric rheumatology online journal)	16 Y/F	Fever and Arthritis	Yes (2 giant coronary aneurysms)	uveitis
Yamazaki-Nakashimada et al. (Seminars in arthritis and rheumatism)	3Y/F	Fever, pain abdomen, hypertension, neuropathy	Yes (Dilated right coronary artery 3.5 mm)	Intestinal perforation, pancreatitis
Bowyer et al. (The journal of rheumatology)	3Y/F	Fever, hypertension, seizure	Yes	Renal and hepatic aneurysms
Bowyer et al. (The journal of rheumatology)	15Y/F	Fever, rash, strawberry tongue	Yes	Renal aneurysm and Liver infarct
Munro et al. (Journal of paediatrics and child health)	3 M/M	Fever, hematochezia	Yes	Renal infarct and mesenteric vasculitis
Index case	2 Y/ F	Fever, abdominal distension	Yes	Renal infarct

without being biased towards a diagnosis of Kawasaki disease as coronary aneurysm is not a sine qua non for Kawasaki disease, particularly in cases with an unusually long course and persistently raised inflammatory markers like the index cases.

Conclusion

Coronary aneurysm, although a rare presentation of childhood PAN, can be a sole presenting feature and can mimic Kawasaki disease. However, prolonged course and persistently raised inflammatory markers can guide subsequent investigations like DSA for confirmatory diagnosis of PAN in such cases.

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Author contributions SPM, SD: literature review and wrote initial draft. LP, MJ, PN, SG: reviewed the draft. NB: concept, design, and review of the draft. All authors approved the final version of the draft. All authors take full responsibility for the integrity, accuracy, and all aspects of the work.

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Declarations

Conflict of interest No conflict of interest among the authors.

Informed consent Informed consent was obtained from the patients' parents.

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