ILLUSTRATIVE CASE

Weighing Evidence and Art: A Challenging Case of Early-Onset Atypical Kawasaki Disease

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CASE

A 3-month-old previously healthy boy first presented to the emergency department (ED) with a 2-day history of diarrhea, severe dehydration, and fussiness with apneic spells. He also had developed a maculopapular rash on his extremities and trunk that had almost completely resolved on presentation to the ED and had conjunctival erythema with discharge. Several children at home had "pink eye" the same week the infant became ill. From the ED, he was admitted to the PICU, where he was intubated. Although his initial laboratories were unremarkable (white blood cell [WBC] count 11.0 k/uL, 39% neutrophils, platelets 342 k/uL), he also underwent an extensive septic workup (including blood cultures, urine culture, cerebrospinal fluid analysis and culture, herpes simplex virus and enterovirus cultures, respiratory viral panel by polymerase chain reaction, respiratory culture, and influenza A/B direct antigen detection tests) along with empirical treatment with antibiotics for a total of 5 days. These laboratory and imaging studies (serial chest x-rays, head computed tomography scan) were not clinically significant. He defervesced for a 48 hours, but still experienced low-grade fever (Tmax 38.3°C) and intermittent episodes of irritability. After 8 days of hospitalization, he was discharged from the hospital after apparent resolution of most of his symptoms. At his follow-up outpatient pediatric visit 4 days after discharge, 12 days since the onset of his illness, he was afebrile and clinically quiet.

Question *Is there objective evidence that this patient had Kawasaki disease (KD) on initial visit?*

Discussion

Tomisaku Kawasaki described the criteria for diagnosing KD in 1967.[1] The criteria require presence of fever for duration of ≥5 days along with 4 of the 5 following physical findings without an alternative explanation:

- Bilateral bulbar conjunctival injection
- Oral mucus membrane findings, strawberry tongue, fissured lips
- Erythema of palms and soles, edema of hands and feet or periungual desquamation
- Polymorphous rash
- Cervical lymphadenopathy

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Typical laboratory findings of this entity include presence of elevated inflammatory markers (erythrocyte sedimentation rate, C-reactive protein [CRP]), leukocytosis, and WBC count with left shift, reactive thrombocytosis, sterile pyuria, hyponatremia, and at least 1 abnormal liver function test.

Atypical or incomplete KD is an entity where the patient appears clinically similar to a case of classic KD but lacks the number of physical features to meet the diagnostic criteria. These children are known to be at a greater risk for cardiac sequelae. The American Heart Association in 2004 developed an algorithm[2] that indicates use of an echocardiogram to supplement the laboratory tests among children in whom atypical KD is suspected. The treatment indication for atypical KD includes elevated erythrocyte sedimentation rate or CRP and ≥3 abnormal laboratory findings or a single abnormal finding on echocardiogram.

Patients with KD are usually diagnosed during the acute period of disease presentation when characteristic clinical features meet the diagnostic criteria.[3] However, the diagnosis of KD may be challenging when its presentation is atypical, especially in young infants.[4,5] Retrospective studies have shown that males with early-onset (<1 year of age) KD

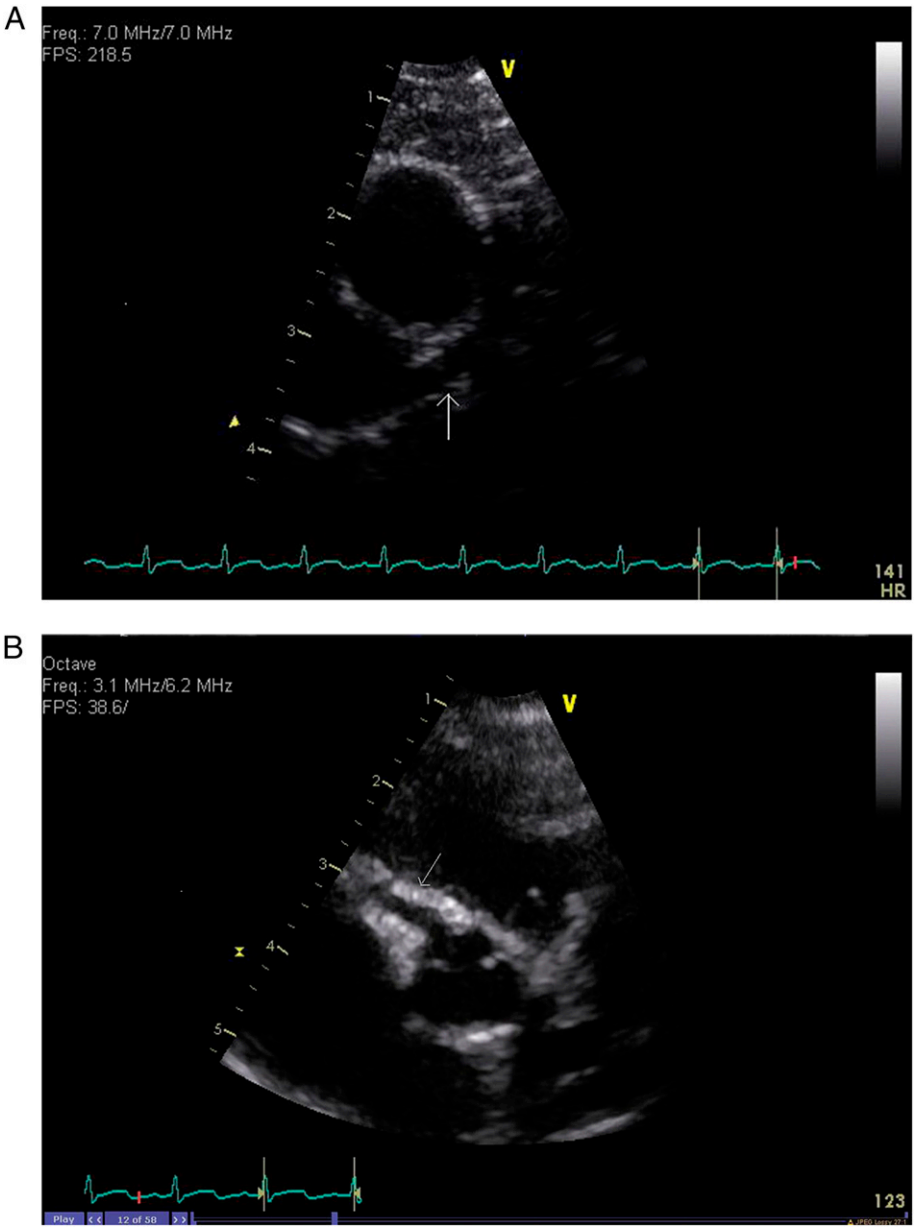

FIGURE 1 A, Fusiform aneurysm of the left anterior descending artery with maximal diameter of 2.8 mm with a length of 5 mm. B, Saccular aneurysm of right coronary artery, which is 2.8 mm with a length of 3.5 mm.

are at higher risk of disease-related morbidity.[6,7] Prompt recognition of KD and early initiation of treatment is paramount to prevent coronary artery aneurysm formation.

Our patient did not meet the criteria for either typical or atypical KD during this admission because all his laboratory tests remained within normal limits. Therefore, KD was not suspected, and an echocardiogram was not indicated per established guidelines.

Case Continuation

However, 2 days after his follow-up pediatric visit and 14 days since the onset of his illness, symptoms of his prodromal illness recurred which included fussiness and sleeping more than usual followed by low-grade intermittent fevers. His symptoms progressed over the next day to include increased irritability, increased stool output, and high-grade fevers to 39.8°C (103.7°F) not responding to antipyretics, so the patient was readmitted to the hospital 7 days after being discharged from his initial hospital stay, which equated to 16 days since his initial symptom onset. On readmission, he had leukocytosis (WBC 16.5 k/uL, 56% neutrophils), thrombocytosis (849 k/uL), transaminitis (aspartate transaminase 179 U/L), and hyponatremia (Na 131 mmol/L). A complete abdominal ultrasound (not done on before admission) was obtained that was negative for any significant abnormality. Given the clinical presentation with protracted fever and the diagnostic tests results, KD was suspected. His calculated Kobayashi risk score was 7 (high-risk patient score is $\geq$5). An echocardiogram revealed multiple saccular (largest 2.8 $\times$ 3.5 mm) and fusiform coronary aneurysms (Fig 1), supporting the diagnosis of incomplete KD.

Questions

From a diagnostic standpoint, what else can we learn from this case? What treatment options were available for our patient?

Discussion

Only a minority of KD cases, <3% in a regional study, present under age 90 days.[8] Infants younger than 1 year of age frequently show atypical forms of the disease, and a high index of suspicion of KD must be maintained in cases of protracted fever. Early diagnosis and treatment of these infants poses a special challenge because they are the least likely to present with signs and symptoms meeting strict American Heart Association diagnostic criteria of persistent fever and at least 4 of the 5 characteristic features. This may result in the delayed initiation of appropriate therapy and may be the reason for the increased frequency of coronary artery abnormalities observed in this age group.[7] It is important to mention that our patient's disjointed presentation, separated by 2 hospital visits, could have represented 2 unrelated febrile processes.

For decades the standard initial treatment of KD has remained intravenous immune globulin (IVIG) and acetyl-salicylic acid (aspirin).[2] Several studies have examined the efficacy of high-dose pulse methylprednisolone therapy in patients with KD, but results have been inconclusive.[9–11] The Kobayashi risk score, developed to predict IVIG unresponsiveness, includes 7 variables with parts and cutoff values for each variable as follows: 2 points each for sodium 133 mmol/L or less, 4 or fewer days of illness before initial treatment, aspartate transaminase $\geq$100 IU/L, percentage of white cells representing neutrophils at least 80%; and 1 point for platelet count 30.0 $\times$ 10^4 or less, CRP at least 10 mg/dL, and age $\leq$12 months. KD patients are considered high risk when their risk score is points or more. Results of the recent meta-analysis of 9 clinical studies by Chen et al support administration of steroids to patients at the greatest risk of IVIG nonresponse and coronary artery aneurysm.[12] Similarly the results of the randomized clinical RAISE trial show that a subgroup of KD patients, identified as high risk of developing coronary artery aneurysm, had improved coronary artery outcomes when daily oral steroids for 3 weeks were used concomitantly with IVIG compared with IVIG alone.[13] The RAISE trial was limited to patients older than 6 months of age and to those without history of coronary artery aneurysm. However, limited data exist on what is appropriate treatment of the youngest KD patients (<6 months), especially in those such as ours whose coronary aneurysms have already been identified by ECHO during the subacute period of disease when coronary lesions are known to progress.

Only a few cases of treatment with infliximab have been reported in KD patients less than 6 months of age, one a 1 month old,[14] the other a 7 week old.[15] To add to this data a recent large double blinded randomized placebo-controlled trial assessing the effect of addition of infliximab to standard therapy for KD (IVIG plus Aspirin) showed that it did not significantly reduce the rate of treatment resistance.[16] The treatment group receiving infliximab however was found to have shorter febrile duration, greater mean decrease in CRP and decrease in Z score of LAD (not significant by 5 weeks post treatment). No significant adverse events were noted in either group.

Case Continuation

Conscious of the limited window of time available to effectively treat our patient, set in a point in time during the subacute stage of active KD, we took a proactive approach patterning treatment after the intervention studied in the RAISE trial with a tapering prednisone course (2 mg/kg/day weaned by 0.5 mg/kg/dose weekly) in addition to the standard regimen of IVIG and ASA.

Question *Is there evidence available for improved efficacy of supplemental steroid use versus traditional treatment of atypical KD in high-risk patients?*

Discussion

Safe and efficacious use of a tapering oral glucocorticoid course as an adjunct therapy to IVIG and ASA is demonstrated in our case, an infant < 6 months of age who presented in the subacute phase of KD with multiple coronary aneurysms. The age of disease onset, male gender, and known presence of coronary aneurysm classified the patient as high risk for worsening coronary artery morbidity pushing us to use aggressive therapy in our high risk patient. Certainly, we cannot conclude that our patient's resolution of coronary aneurysms was due to having received daily steroids. However, we feel it is important to share this case

and discussion with the broader medical community. We are not aware of prior cases in the literature describing the efficacy of steroids in quickening the resolution of or improving the short-term outcome of existing coronary artery aneurysms. Certainly, the use of steroids in such a young patient should be done cautiously, with respect given to the child's risk for infection or worsening of concomitant infection with KD presentation, in addition to the potential for development of other known adverse effects such as avascular necrosis.

The RAISE trial is one of the largest multicenter cohorts of pediatric KD cases in recent history to be randomized and prospectively treated in a blinded trial. The addition of corticosteroids to IVIG was studied as a primary treatment in patients deemed high risk for IVIG unresponsiveness as per the scoring system validated by Kobayashi et al.[17] Results showed a preventive effect from steroids on the development in coronary artery aneurysmal lesions in high-risk patients, as well as less need for additional immune-suppressant medications, in the group treated with IVIG plus prednisolone ($n = 125$) compared with the group treated solely with IVIG immune modulation ($n = 123$). Also, there were no significant differences in serious adverse events between the 2 groups.

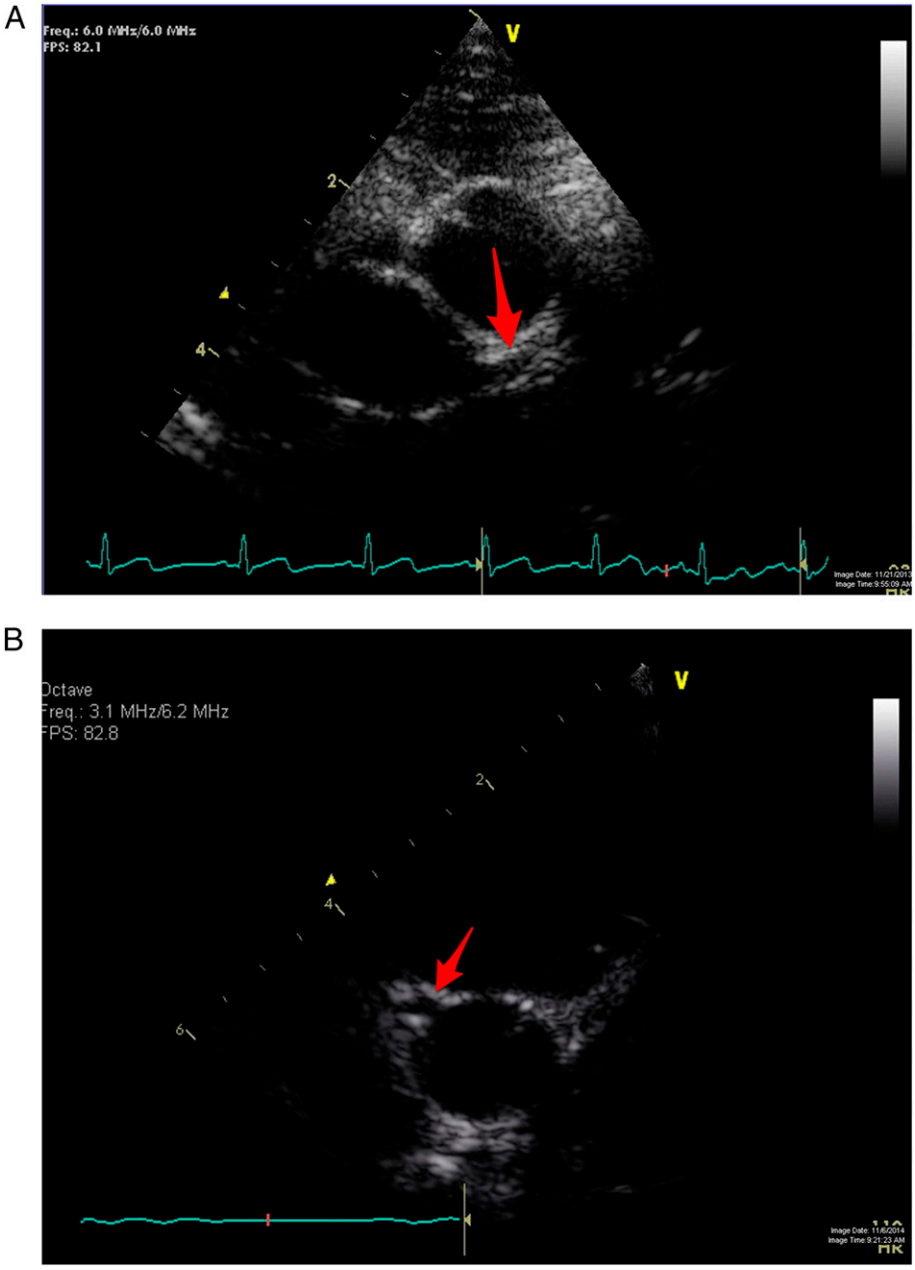

FIGURE 2 A, Normalization of the left coronary artery at 6-month interval. B, Normalziation of right coronary artery) at 6-month interval.

Although our patient's age, timing of presentation, and presence of coronary lesions differed from the cohort studied in the RAISE trial, we used knowledge from the reported positive results of the trial to help base our unique treatment decision. The Kobayashi risk score was developed to predict IVIG unresponsiveness. Our patient's Kobayashi risk score was 7, putting him at increased risk of treatment failure and coronary artery abnormality with IVIG alone (vs treatment with IVIG plus prednisolone).[18] There is some concern that KD in Japan may behave differently from the disease in non-Japanese populations, highlighted in the failure of the Kobayashi score to accurately predict nonresponse to IVIG in the United States.[17] Due to previously reported differences in incidences of coronary artery aneurysmal rates among US and Japanese populations arising from use of disparate scores, Ogata et al has recently suggested use of *z* scores as the standardized calculation of coronary artery internal diameter, allowing for a more uniform comparison of cases worldwide.[19]

Case Resolution

During readmission, the patient remained clinically stable on the regular nursing floor, and at no point did his care require escalation. Patient was discharged from the hospital in stable condition after 8 days of inpatient treatment. No adverse events occurred as a result of the therapeutic intervention. Follow-up echocardiograms performed 2, 6, and 30 weeks after treatment induction have shown complete resolution of coronary artery aneurysms (Fig 2).

CONCLUSIONS

We present a case of a high-risk young patient (<6 months of age) with subacute KD who was successfully treated with a tapering course of systemic steroids along with a concomitant standard treatment protocol. Learning points to be taken from this case include the following:

- The clinician's index of suspicion needs to remain heightened to make the diagnosis of early-onset KD, which not uncommonly presents with incomplete diagnostic features.
- Despite the lack of evidence-based guidance from the literature, important informed treatment decisions need to be made for KD patients diagnosed late in the subacute period who have documented coronary artery aneurysms.
- Steroids may be an effective and safe therapeutic tool to supplement conventional treatment in the high-risk infant population with atypical KD if used judiciously.

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REFERENCES

1. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet*. 2004;364(9433):533–544
2. Newburger JW, Takahashi M, Gerber MA, et al; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Diagnosis, treatment and long-term management of Kawasaki disease: A statement for health professionals from the committee on rheumatic fever, endocarditis and Kawasaki disease, council on cardiovascular disease in the young, american heart association. *Pediatrics*. 2004;114(6):1708–1733
3. Yim D, Curtis N, Cheung M, Burgner D. Update on Kawasaki disease: epidemiology, aetiology and pathogenesis. *J Paediatr Child Health*. 2013;49(9):704–708
4. Falcini F, Ozen S, Magni-Manzoni S, et al. Discrimination between incomplete and atypical Kawasaki syndrome versus other febrile diseases in childhood: results from an international registry-based study. *Clin Exp Rheumatol*. 2012; 30(5):799–804
5. Dodi I, Raggi V, Verna M, et al. Atipical Kawasaki disease with coronary aneurysm in infant. *Ital J Pediatr*. 2011; 37(1):19
6. Song D, Yeo Y, Ha K, et al. Risk factors for Kawasaki disease–associated coronary abnormalities differ depending on age. *Eur J Pediatr*. 2009;168(11): 1315–1321
7. Pannaraj PS, Turner CL, Bastian JF, Burns JC. Failure to diagnose Kawasaki disease at the extremes of the pediatric age range. *Pediatr Infect Dis J*. 2004; 23(8):789–791
8. Bhatt M, Anil SR, Sivakumar K, Kumar K. Neonatal Kawasaki disease. *Indian J Pediatr*. 2004;71(4):353–354
9. Wooditch AC, Aronoff SC. Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: a meta-analysis of 862 children. *Pediatrics*. 2005;116(4):989–995
10. Newburger JW, Sleeper LA, McCrindle BW, et al; Pediatric Heart Network Investigators. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med*. 2007;356(7):663–675
11. Burns JC. Revisiting steroids in the primary treatment of acute Kawasaki disease. *J Pediatr*. 2006;149(3):291–292
12. Chen S, Dong Y, Yin Y, Krucoff MW. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. *Heart*. 2013; 99(2):76–82
13. Kobayashi T, Saji T, Otani T, et al; RAISE study group investigators. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. 2012;379(9826):1613–1620
14. Oishi T, Fujieda M, Shiraishi T, et al. Infliximab treatment for refractory Kawasaki disease with coronary artery aneurysm. *Circ J*. 2008;72(5): 850–852
15. O'connor MJ, Saulsbury FT. Incomplete and atypical Kawasaki disease in a young infant: severe, recalcitrant disease responsive to infliximab. *Clin Pediatr (Phila)*. 2007;46(4):345–348

16. Tremoulet AH, Jain S, Jaggi P, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet*. 2014;383(9930):1731–1738

17. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113(22):2606–2612

18. Kobayashi T, Inoue Y, Otani T, et al. Risk stratification in the decision to include prednisolone with intravenous immunoglobulin in primary therapy of Kawasaki disease. *Pediatr Infect Dis J*. 2009;28(6):498–502

19. Ogata S, Tremoulet AH, Sato Y, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. *Int J Cardiol*. 2013;168(4):3825–3828

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