Kawasaki Disease Masquerading as Hepatitis: A Diagnostic Challenge for Pediatricians

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Introduction

Kawasaki disease (KD) is a systemic vasculitis affecting medium size arteries.¹ It is often included in the differential diagnosis when a young child presents with persistent fever. Diagnosis can be challenging as there are no specific diagnostic tests. Persistent fever for ≥5 days with 4 of the 5 clinical criteria (bilateral bulbar nonexudative conjunctivitis, oral mucosal changes, diffuse rash, changes in extremity, and cervical lymphadenopathy [size > 1.5 cm]) and exclusion of other causes is required for diagnosis.² However, the clinical criteria for typical KD may not be fulfilled at presentation and signs may evolve over time. The involvement of coronary arteries and subsequent risk of development of coronary aneurysm, ischemic heart disease, and sudden death in individuals with inadequate or delayed treatment creates a sense of diagnostic urgency.³⁻⁵ Here we report cases that will help illustrate the difficulties encountered in the diagnosis and management of children presenting as jaundice with fever.

Case 1

A 5-year-old previously healthy male presented with 2 days of fever up to 39°C, multiple episodes of nonbilious emesis, and right upper quadrant abdominal pain that had worsened progressively. At admission, he was febrile, tachycardic, mildly dehydrated, with scleral icterus, and had no bulbar conjunctivitis, lymphadenopathy, oral mucosal changes, extremity edema, rash, cardiac murmur, respiratory distress, or hepatosplenomegaly. Initial investigations revealed a normal hemoglobin concentration (127 g/L), mild leukocytosis (11.8 × 10⁹/L), normal platelet count (258 × 10⁹/L), low serum sodium concentration (133 mmol/L), elevated serum total bilirubin (88.9 µmol/L; normal = 5–21 µmol/L), direct bilirubin (71.8 µmol/L; normal = 0–6.8 µmol/L), mild elevation of serum aspartate aminotransferase (AST; 1.25 µkat/L; normal = 0.17-0.84 µkat/L), alanine aminotransferase (ALT; 3.31 µkat/L; normal = 0.17-0.84 µkat/L), γ-glutamyl transpeptidase (GGT; 2.49 µkat/L; normal = 0-1.25 µkat/L), and normal serum albumin concentration (36 g/L; normal = 35-50 g/L). Coagulation profile was normal.

The patient was initially presumptively managed as a case of viral hepatitis with fluids and anti-emetics. Serological markers for hepatitis A, B, and C, herpes simplex virus (HSV) type 1 and type 2, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and parvovirus B19 were negative. Nasopharyngeal secretions for common respiratory viruses (“Respiratory screen” for Adenovirus, influenza A and B, parainfluenza A and B, respiratory syncytial virus, and human metapneumovirus by direct fluorescence antibody test) and enterovirus RNA PCR were negative. Stool adenovirus antigen test was negative. Mycoplasma pneumoniae IgG was elevated (1.14; normal index = <0.9) but IgM level was normal suggesting that the patient did not have an acute mycoplasma infection. Serum streptolysin O antibody (ASO) titer and urine Streptococcal antigen test were normal. Urine analysis was significant for the presence of urobilinogen but did not show red blood cells, leukocytes, casts, or hemoglobin. Aerobic and anaerobic blood cultures and urine cultures remained negative for more than 72 hours.

Over the next 4 days, fevers up to 39.6°C persisted requiring frequent antipyretic administration. The child also developed bilateral nonexudative conjunctivitis and inguinal rash with pealing. Suspecting KD, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were followed serially, which showed progressive increase. ESR increased from 25 to 85 mm/h and CRP increased from 280.9 to 373.3 nmol/L (normal = 0.76-28.5 nmol/L). Anti-nuclear antibody, smooth muscle antibody, and serum creatine kinase levels were normal.

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A diagnosis of incomplete KD was made in consultation with KD experts. Diagnostic criteria leading toward KD included persistence of high fever for greater than 5 days, presence of 3 of the 5 clinical criteria—bilateral bulbar nonexudative conjunctivitis, oral mucosal changes, and polymorphous rash. Supportive tests included elevated ESR and CRP, mild liver dysfunction, as well as an exclusion of alternative etiologies. Echocardiogram demonstrated normal cardiac function and ruled out coronary artery lesions (CAL). Treatment with high-dose aspirin and intravenous immunoglobulin (IVIG) infusion was initiated on day 8 of illness, but the patient developed high fever with chills and rigors, prompting IVIG discontinuation. IVIG retreatment after 24 hours with antihistamine and steroid premedication was well tolerated. Patient became febrile in 24 hours and liver functions normalized within 48 hours. Follow-up echocardiogram at 1 month after discharge was normal.

Case 2

A 4-year-old previously healthy female presented with jaundice, noted on the date of admission. The child had begun with fevers up to 38.9°C, 3 days prior to admission, along with abdominal pain and itchy rash on the arms and legs. She had been taking Augmentin oral suspension for 2 days as prescribed by her pediatrician. Rapid streptococcal antigen in the office had been negative. On admission, the patient was febrile and tachycardic. Physical examination findings included scleral icterus and maculopapular rash on the arms, legs, and trunk. She had no bulbar conjunctivitis, lymphadenopathy, oral mucosal changes, extremity edema, cardiac murmur, respiratory distress, or hepatosplenomegaly. Initial investigations revealed a low hemoglobin concentration (108 g/L), leukocytosis (14.6 ×10^9/L), normal platelet count (251 ×10^9/L), elevation of serum total bilirubin (87.2 µmol/L), direct bilirubin (51.3 µmol/L), along with mild AST (0.9 µkat/L), ALT (1.35 µkat/L), and GGT (1.29 µkat/L) elevation, and a low serum albumin concentration (31 g/L). Coagulation profile was normal. ESR and CRP were both elevated at 37 mm/h and 956.2 nmol/L, respectively.

Similar to case 1, this patient was also initially diagnosed as likely viral hepatitis. Management plan consisted of intravenous fluids and consultation with gastroenterologist. Infectious workup included serological markers for hepatitis A, B and C, HSV type 1 and type 2, CMV, EBV, HIV 1 and 2, parvovirus B19, nasopharyngeal secretions for “Respiratory Screen” and enterovirus RNA PCR, stool adenovirus antigen, and serum ASO titer. All tests were negative and/or within the normal range. Urine analysis was significant only for the presence of bilirubin and urobilinogen. Aerobic blood, throat, and urine cultures were all negative. Noninfectious workup including serum thyrotropin and free thyroxine concentrations, autoimmune hepatitis panel and celiac disease panel were negative and/or normal.

On hospital day 3, the patient was noted to have red, cracked lips, a red tongue, and pealing skin in the groin and on the hands. She also continued with fevers up to 39.4°C. Repeat investigations showed worsening of liver functions. KD expert was consulted, and IVIG and high-dose aspirin regimen were started. The patient responded poorly. Leukocytosis worsened (27.2 × 10^9/L), hemoglobin decreased (82 g/L), and thrombocytosis increased further (634 × 10^9/L). The patient developed coagulopathy, with an elevated prothrombin time (31.4 seconds; normal = 11-15), international normalized ratio (3.15), and activated partial thromboplastin time (56.9 seconds; normal = 25-34), which responded to oral vitamin K. Liver enzymes and bilirubin continued to rise. Recurrence of high fever up to 39.5°C on hospital day 8 (day 11 of illness) prompted repeat IVIG treatment. This resulted in resolution of fever and rash, as well as complete normalization of liver function tests. The patient’s hemoglobin continued a slow decline to a low of 62 g/L, 3 days after the second dose of IVIG, prompting a packed red blood cell transfusion. Pretransfusion investigations revealed an elevation of reticulocyte count (0.05 proportion of red blood cells; normal = 0.005-0.015) and haptoglobin (3030 mg/L; normal = 260-1850), and normal serum lactate dehydrogenase concentration (3.26 µkat/L; normal = 1.7-3.4), suggestive of extravascular hemolysis. Similar case of hemolytic anemia following IVIG treatment of KD has been reported in a case series by Berard et al.5 In this case series, hemolytic anemia was seen in patients after the second dose of IVIG as was seen in our patient.

Discussion

The cases presented here highlight the need for high degree of suspicion in order to accurately diagnose KD; especially in children presenting with nonclassical symptoms (Table 1).

Both children were admitted for suspected viral hepatitis, but signs of KD evolved over the course of hospitalization. Gastrointestinal symptoms, which were the presenting complaints, are not included in the diagnostic criteria of KD. In the absence of close monitoring, these symptoms may be misleading. KD has been found to be the second most frequent cause of febrile cholestatic
jaundice in children, after viral infections. Although gastrointestinal involvement is not part of the KD diagnostic criteria, it is important to remember that the presence of such abnormalities does not exclude a diagnosis of KD.

Diagnosis of KD with unusual presentations, including incomplete KD, remains a challenge. Incomplete KD has been shown to be an independent predictor of delayed treatment in a multicenter study. Extensive investigation may be needed to exclude other etiological conditions. Expert consultation and review of published guidelines is often needed to establish the diagnosis. Frequently, the pediatrician “races against time” to ensure timely management, since CAL development has been associated with delay of treatment of 10 days or more after the onset of clinical symptoms. At the same time, indiscriminate use of IVIG should be avoided without confirmation of diagnosis since IVIG therapy is associated with multiple side effects. These may range from minor side effects like allergic itching that is responsive to premedication with antihistamines, to serious side effects like anaphylaxis, hemolytic anemia, and aseptic meningitis.

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