CASE REPORT

Fever without a source: evolution of a diagnosis from Kawasaki disease to acute myelogenous leukaemia

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SUMMARY

A previously healthy 11-month-old male patient presented with fever, abdominal pain and irritability. As part of an extensive evaluation for the cause of his fevers, an echocardiogram was performed and showed mildly dilated coronary arteries, leading to a diagnosis of incomplete Kawasaki disease (KD). He was treated with intravenous immunoglobulin (IVIG), defervesced and was discharged home. Two weeks later, he presented with anaemia initially attributed to haemolytic anaemia secondary to IVIG and received a red blood cell transfusion. However, his anaemia recurred 2 weeks later with leucocytosis, prompting a bone marrow aspirate 4 weeks after his diagnosis of KD. This demonstrated acute myelogenous leukaemia most consistent with acute megakaryocytic leukaemia. This case highlights the potentially subtle presentation of acute leukaemia and the need to keep an open mind and reconsider the initial diagnosis as new information comes to light in the care of an ill child.

BACKGROUND

Fever without a source is a frequent presentation in inpatient paediatrics and requires a thorough evaluation with a broad differential including oncologic, infectious and rheumatologic causes. As the most common cause of acquired heart disease in children in the developed world, Kawasaki disease (KD) needs to be considered in the differential of a child with a prolonged febrile course, especially in a child less than a year old who is at high risk for coronary artery aneurysms.^{1 2} In addition, as the most common cause of cancer in paediatric patients, leukaemia is often a consideration in the work-up of fever without a source in children. Acute myelogenous leukaemia (AML), accounting for a minority of leukaemia diagnoses, can present with non-specific symptoms, and patients may have a relatively unremarkable peripheral blood smear, requiring a bone marrow biopsy for definitive diagnosis. We report a case of an infant with fever without a source that was initially diagnosed as incomplete KD based on fever, normocytic anaemia, bandaemia, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), hyponatraemia, hypoalbuminaemia, increased alanine aminotransferase (ALT), pericardial effusion and dilated coronary arteries. However, ultimately the patient was found to have AML. While this presentation for AML is rare, a previous case report has described the development of Kawasaki-like disease in an

11-year-old patient receiving induction therapy for AML.³ This case illustrates an important lesson in the need to continue to reassess the primary diagnosis as new data become available and when the patient does not respond as expected.

CASE PRESENTATION

A previously healthy 11-month-old male patient presented to a tertiary paediatric centre with fever for 2 days, and abdominal pain and irritability for 3 days. He was initially seen at a community emergency department 1 day prior to admission where he was diagnosed with an ileus after having had a normal abdominal X-ray and abdominal ultrasound. He did not have vomiting, joint swelling, rash or blood in the stool. He had an unremarkable prior medical history and social history, and family history was only significant for environmental allergies in the father and paternal grandmother. There was no family history of KD, autoimmunity or cancer.

Upon presentation to the emergency department at the tertiary paediatric centre, he was febrile, tachycardic and pale with abdominal distension and tenderness. Laboratory evaluation was significant for mild leucocytosis and mild normocytic anaemia (table 1), a reticulocyte count of 0.9, low sodium 129 mmol/L, low chloride 95 mmol/L, low albumin 3.3 g/L, slightly elevated liver function tests, and significantly elevated CRP and ESR. Urine dipstick analysis was negative for nitrates, leukocytes, no blood and had 1+ protein. The initial working diagnosis was acute abdomen, with intussusception being high among the differential diagnoses. Abdominal X-ray, ultrasound and CT scan of the abdomen and pelvis were negative for intussusception or other abdominal pathology. There was no concern for meningitis, so a lumbar puncture was not performed. He received fluid resuscitation, was administered ceftriaxone due to concern for sepsis and admitted to the inpatient unit for further evaluation. During this initial evaluation, an elevated lactate dehydrogenase of 3253 µ/L, markedly elevated ferritin of 1992 ng/mL, and normal iron, iron saturation and total iron binding capacity were also noted.

His abdominal symptoms and irritability improved, but he continued to be febrile. Ceftriaxone was stopped after 48 hours of negative urine and blood cultures. To evaluate his persistent fevers, further work-up was pursued and demonstrated continued leucocytosis and mild anaemia (table 1), a complete metabolic panel which demonstrated normalisation of the ALT and AST, and normal gamma-glutamyl transpeptidase,

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Table 1 Laboratory results

Laboratory results	Admission	One day after presentation	Two weeks after presentation: diagnosis of IVIG-associated haemolytic anaemia	Four weeks after presentation: diagnosis of AML
White blood cell count ($10^9/L$)	16.3	20.3	11.1	25.3
Haemoglobin (g/L)	89	91	61	69
Haematocrit (%)	27.7	28.2	19.2	20.9
MCV (fL)	85.9	86	86.1	84
Platelets ($10^9/L$)	190	203	289	116
Differential				
Neutrophils (%)	41	38	22	17
Bands (%)	23	23	11	21
Lymphocytes (%)	26	31	47	48
Atypical lymphocyte (%)	0	1	0	0
Monocytes (%)	10	7	14	7
Eosinophil (%)	0	0	3	2
Basophil (%)	0	0	0	1
Metamyelocyte (%)	0	0	3	1
Myelocyte (%)	0	0	0	3
Absolute neutrophil count (μL)	10 432	12 383	3663	9614
CRP (mg/L)	27.4	18.7	4.7	
ESR (mm/hour)	128			
ALT (U/L)	62	32	44	37
AST (U/L)	62	27	22	20

ALT, alanine aminotransferase; AML, acute myelogenous leukaemia; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; MCV, mean corpuscular volume.

and a decrease in the CRP. Peripheral smear demonstrated normocytic anaemia, leucocytosis with bandaemia and absolute neutrophilia. Stool occult blood test, *Clostridium difficile* toxin assay, stool culture, rapid influenza, viral respiratory panel and serum Quantiferon were all negative. Chest X-ray was normal. An echocardiogram of adequate diagnostic quality demonstrated borderline dilation of the right coronary artery (RCA 2.2 mm, Z score 2.15) and left main coronary artery (LMCA 2.4 mm, Z score 2.1 mm) without evidence of aneurysm or valvular involvement and a small pericardial effusion. He was diagnosed with incomplete KD given the clinical history of prolonged fevers for 8 days, laboratory findings of leucocytosis with bandaemia, normocytic anaemia, elevated CRP and ESR, hyponatraemia, and elevated ALT, and echocardiographic findings of borderline-dilated coronary arteries. He was treated with IVIG and his fevers resolved the next day, further supporting the diagnosis. He was discharged the following day.

After discharge, he started to return to baseline activity and had two fevers at home that quickly resolved. He was seen by his primary care physician 10 days after discharge and was noted to be anaemic with haemoglobin of 61 g/L. He was then readmitted to the hospital, and laboratory evaluation was significant for normocytic anaemia (table 1), reticulocyte count of 4.2 and a positive direct Coombs (IgG positive, C3 negative). Peripheral blood smear review demonstrated normocytic anaemia, relative eosinophilia, leucoerythroblastic reaction, scattered elliptocytes, dacryocytes, helmet cells and schistocytes. The working diagnosis at the time was haemolytic anaemia as a side effect of IVIG. A repeat echocardiogram of adequate diagnostic quality during that admission showed resolution of the pericardial effusion and decrease in internal diameters of the LMCA and RCA. He was transfused packed red blood cells and discharged with haemoglobin of 9.2 g/L.

Two weeks later, he was again seen by his primary care doctor for follow-up of anaemia. He had an unremarkable physical examination, but his haemoglobin had fallen again to 66 g/L. He was admitted and laboratory results were significant for leucocytosis with immature cells, normocytic anaemia, slightly decreased platelets (table 1) and a negative direct Coombs. His persistent anaemia with increasing immature myeloid elements prompted evaluation with bone marrow aspiration and biopsy, which demonstrated AML most consistent with acute megakaryocytic leukaemia (AMKL) and severe trilineage haematopoietic hypoplasia. Flow cytometry was consistent with AMKL with 82% blasts by flow cytometry. Cytogenetics found a tetraploid clone (92,XXYY[5]/46,XY[15]) in 25% of cells. Molecular testing was negative for t(9;11), t(6;11), Inv16, t(8;21), t(15;17), NPM1 mutations, CEPBA mutations and for Flt3 ITD.

Another echocardiogram of adequate diagnostic quality done after the diagnosis of AML did not demonstrate coronary artery dilation.

TREATMENT

The patient was treated with intensive chemotherapy for AML and attained morphologic remission with positive minimal residual disease studies of 1.6% after two cycles of induction chemotherapy. He continued on therapy but he remained positive for a significant detectable minimal residual level of AML of 2.2% despite a total of four courses of intensive chemotherapy. At that time he had no matched related donor, but his mother was expecting to deliver a full sibling soon thereafter. As patients who enter haematopoietic stem cell transplant (HSCT) with positive minimal residual disease have high risks of relapse, he was removed off the initial protocol and received alternative therapy with vorinostat and decitabine based on two large studies in adults showing better response rates than either agent

used alone.^{4 5} He remained positive for AML with 5% blasts after one cycle of vorinostat and decitabine. His recently born baby sister was found to be a human leucocyte antigen (HLA) match for transplant, but his disease status had worsened, so further chemotherapy was pursued to get his disease back into a state of remission. After a subsequent course of clofarabine and cytarabine, he continued to have persistent disease with 17% blasts. After a course of chemotherapy with fludarabine, cytarabine and gemtuzumab, his disease control improved dramatically with a minimal residual disease test of 0.19%.

OUTCOME AND FOLLOW-UP

He underwent a matched related HSCT with stem cells from his sister's umbilical cord blood. His conditioning regimen for his bone marrow transplant included fludarabine and busulfan and his treatment course was complicated by veno-occlusive disease of the liver. Approximately 70 days after the bone marrow transplant, he was found to have 1.3% AML blasts in his bone marrow.

Despite receiving many potentially cardiotoxic medications during chemotherapy, his heart function remained normal, and the triad of symptoms at presentation of fever, irritability and abdominal pain has not recurred.

DISCUSSION

Fever is a very common presenting symptom in paediatrics. Most febrile illnesses in paediatrics are viral in aetiology and quickly self-resolve. At other times, a bacterial source is identified and appropriate therapy is administered with expected resolution. If fevers persist, it is important to distinguish between the common benign causes of childhood febrile illness and the more dangerous causes of fever.

KD is an important diagnosis to consider when evaluating children with a febrile illness without a source. The diagnostic criteria for KD include fever for at least 5 days and four of the following five criteria: bilateral conjunctival injection, changes of the mucous membranes (cracked lips, strawberry tongue, erythema), polymorphous rash, changes of the extremities (oedema, erythema, desquamation) and cervical lymphadenopathy.² Coronary artery aneurysms can develop in up to 25% of patients without treatment, and prompt diagnosis and treatment reduces the risk of developing an aneurysm to 5%.⁶ Incomplete KD can be diagnosed using supplementary laboratory data and echocardiography in the absence of classic clinical criteria.²

Oncologic causes should also be considered in the evaluation of fever without a source though they more commonly present with suggestive physical examination findings (ie, splenomegaly, diffuse lymphadenopathy, pallor or bruising) or laboratory findings suggestive of malignancy. Although acute leukaemia is the most common childhood cancer, AML only accounts for 18% of leukaemia diagnoses and is much less common than acute lymphoblastic leukaemia (ALL).⁷ There are approximately 500 new cases of AML diagnosed every year in the USA.⁸ AML is a haematopoietic cancer arising from the precursor cells of the myeloid line. AML is further differentiated into subtypes according to the WHO classification system based on morphology, cytochemistry, immunophenotype, genetics and clinical features.⁹ AML and ALL commonly present with fever, fatigue, night sweats, easy bruising or bleeding, bone or joint pain, and lymphadenopathy. A peripheral smear will classically demonstrate myeloblasts, and complete blood count may show anaemia, thrombocytopenia, leucopaenia or leucocytosis with

blasts. Definitive diagnosis is made with bone marrow biopsy demonstrating bone marrow infiltration and myeloid leukaemic cells.

This was a challenging case as the patient initially presented with concerns of abdominal pain, irritability and fever, with his evaluation broadening to fever without a source when his fevers persisted without development of new symptoms. He was then treated for possible incomplete KD when an echocardiogram demonstrated borderline dilated coronary arteries and small pericardial effusion on the eighth day of illness in the absence of an alternative diagnosis. The first subsequent episode of anaemia was attributed to a well-described side effect of IVIG. Although IVIG-associated haemolytic anaemia is rare, it tends to occur after receiving high doses of IVIG, such as in patients treated for KD.^{10 11} Despite having two peripheral smear reviews without evidence of leukaemic blasts, it was his persistent anaemia and the development of increasing number of immature myeloid elements in the peripheral smear that prompted the bone marrow biopsy which ultimately demonstrated AML. While there are case reports of patients with associations between malignancies and KD, these cases are not common and the temporal association between the two phenomena in some of these cases can be very distant.^{12–14} While it may be tempting to search for an immunologic causative association between KD and the development of malignancies, this would be a hypothesis without strong evidence at this point in time.

The case demonstrates the importance of keeping a broad differential especially when the presentation is atypical or the course of the disease does not progress as expected. In medicine, there is increasing awareness about cognitive biases, such as anchoring and premature closure.^{15 16} Anchoring occurs when a physician makes an insufficient assessment based on the over-emphasising of an initial (anchor) value. Due to the 'anchor diagnosis,' other alternative diagnoses are not fully considered, and subsequent information is selectively chosen to confirm the initial bias. This results in premature closure, which is when one stops considering new diagnoses or explanations before the data are fully mature or available. This case helps illustrate the importance of avoiding anchoring and premature closure in the evaluation of patients, and the need to continuously re-evaluate the previously established diagnoses, especially when a patient does not respond as anticipated.

Learning points

- ▶ Acute myelogenous leukaemia is a leukaemia arising from the myeloid line, and it can present without significant cytopenias.
- ▶ There needs to be a high index of suspicion for oncologic aetiologies for children presenting with fevers and haematological abnormalities despite the absence of blasts on peripheral smear.
- ▶ Frequent re-evaluation of diagnoses is important, especially when the presentation or clinical course is atypical. It is important to avoid anchor diagnosis, the development of an insufficient diagnosis based on overemphasising the importance of one or more findings, and premature closure, the tendency to stop considering alternative diagnoses when an initial diagnosis is presumptively established.

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REFERENCES

- 1 Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. *J Epidemiol* 2012;22:79–85.
- 2 Newburger JW, Takahashi M, Gerber MA, et al. 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. *Circulation* 2004;110:2747–71.
- 3 Akita H, Matsuoka S, Takahashi Y, et al. Kawasaki-like disease in early course of acute monocytic leukaemia. *Eur J Pediatr* 1992;151:177–8.
- 4 Kirschbaum M, Gojo I, Goldberg SL, et al. A phase 1 clinical trial of vorinostat in combination with decitabine in patients with acute myeloid leukaemia or myelodysplastic syndrome. *Br J Haematol* 2014;167:185–93.
- 5 How J, Minden MD, Brian L, et al. A phase I trial of two sequence-specific schedules of decitabine and vorinostat in patients with acute myeloid leukemia. *Leuk Lymphoma* 2015;56:2793–802.
- 6 Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341–7.
- 7 Puumala SE, Ross JA, Aplenc R, et al. Epidemiology of childhood acute myeloid leukemia. *Pediatr Blood Cancer* 2013;60:728–33.
- 8 Children's Oncology Group (Internet). Acute Myeloid Leukemia. <https://childrensoncologygroup.org/index.php/acute-myeloid-leukemia> (cited 1 Aug 2016).
- 9 Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009;114:937–51.
- 10 Berg R, Shebl A, Kimber MC, et al. Hemolytic events associated with intravenous immune globulin therapy: a qualitative analysis of 263 cases reported to four manufacturers between 2003 and 2012. *Transfusion* 2015;55(Suppl 2):S36–S46.
- 11 Berard R, Whittemore B, Scuccimarri R. Hemolytic anemia following intravenous immunoglobulin therapy in patients treated for Kawasaki disease: a report of 4 cases. *Pediatr Rheumatol Online J* 2012;10:10.
- 12 Akita H, Matsuoka S, Takahashi Y, et al. Kawasaki-like disease in early course of acute monocytic leukaemia. *Eur J Pediatr* 1992;151:177–8.
- 13 Suzuki H, Takeuchi T, Minami T, et al. Neoplasms in three patients following Kawasaki disease. *Pediatr Int* 2005;47:217–9.
- 14 Murray JC, Bomgaars LR, Carcamo B, et al. Lymphoid malignancies following Kawasaki disease. *Am J Hematol* 1995;50:299–300.
- 15 Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science* 1974;185:1124–31.
- 16 Graber ML, Franklin N, Gordon R. Diagnostic error in internal medicine. *Arch Intern Med* 2005;165:1493–9.

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