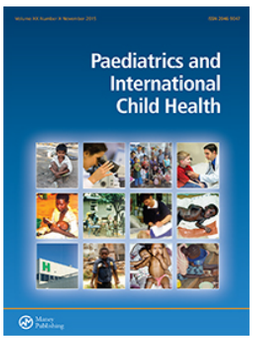

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Is coronary arteritis a feature in secondary haemophagocytic lymphohistiocytosis?

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is rare. Although Kawasaki disease (KD) has been reported as a precursor to HLH, coronary arteritis occurring at the onset of secondary HLH, not in association with KD, has not been reported. An 8-year-old girl presented with virus-induced secondary HLH associated with a giant aneurysm and ectasia of the coronary arteries which was detected incidentally at onset of the disease. She did not fulfill the criteria for diagnosis of KD. The coronary lesions improved after 6 months of treatment with dexamethasone and etoposide. Echocardiography early in the course of HLH is a useful tool to detect the unusual finding of coronary arteritis which may carry significant clinical sequelae.

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KEYWORDS
Coronary arteritis; haemophagocytic lymphohistiocytosis; coronary aneurysm

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare disorder which affects young children. The annual incidence is estimated to be 1/800,000, with 56% occurring in patients < 15 years [1]. HLH is characterised by excessive proliferation and activation of histiocytes with concurrent functional impairment of natural killer (NK) cells. Familial HLH usually presents in infancy whilst secondary sporadic forms usually affect those above 6 years of age [2] While the mortality rate of familial HLH in children is high (60%) with deaths largely attributed to progressive disease and invasive infections, the outcome of secondary HLH is variable [3].

Although no data are available to link HLH to coronary artery (CA) abnormalities, there are studies which describe Kawasaki disease (KD) as precursor to secondary HLH [4–6]. KD is a vasculitic syndrome involving medium-sized arteries with a predilection for CA disease, especially aneurysms. The cardinal features of KD include fever of at least 5 days duration and at least four of five clinical manifestations such as cervical lymphadenopathy, skin rash, changes in the extremities, mucosal erythema and non-purulent conjunctivitis. One study found that 24% of children with HLH presented initially as KD with significantly higher ferritin and aspartate transaminase (AST) levels compared with HLH of other aetiology [4]. A girl with secondary HLH is presented who did not fulfill the diagnostic criteria for KD, and was incidentally found to have a giant CA and ectasia of the coronary arteries at onset of the disease.

Case report

An 8-year-old girl with no significant past illnesses presented to a private hospital with left cervical lymphadenopathy and fever of 2 days duration. There was no history of coryza, ear pain or dental issues. She was treated with oral amoxicillin for the cervical lymphadenitis, but her condition deteriorated. On day 5 of the illness, she was referred to the University of Malaya Medical Center (UMMC) because of rapidly progressing lethargy and jaundice. There was no report of a rash, conjunctivitis, mucosal inflammation or changes in the extremities. On examination, the liver was enlarged 6 cm and the spleen 4 cm below the costal margin and there was ascites. The axillary temperature was 39.8°C. The heart rate was 126/min, blood pressure 92/47 mm Hg, respiratory rate 54/min, and capillary refill time 2 s. The results of respiratory and cardiovascular examination were unremarkable, apart from dyspnoea. There was no peripheral oedema. Because of worsening respiratory distress, she was intubated and commenced on intravenous (IV) noradrenaline owing to widened pulse pressure. IV imipenem and IV amikacin were also commenced.

Investigations

Blood gas analysis showed persistent metabolic acidosis with a pH of 7.28 (7.35–7.45), bicarbonate 13.6 mmol/L (21.0–28.0), base excess -14.1 mmol/L (-4.0 to + 2.0) and elevated lactate of 6.9 mmol/L (0.6–0.9).

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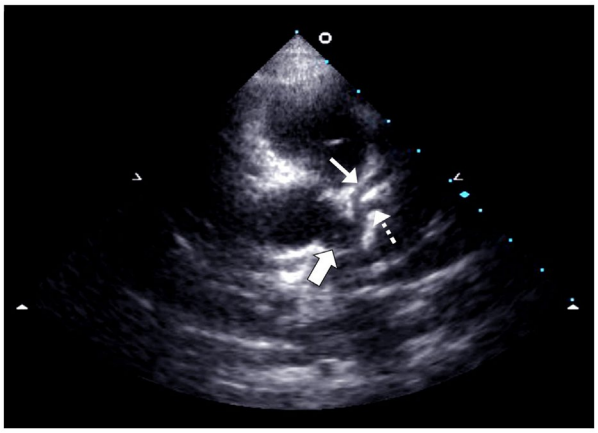

Figure 1. Day 7: Echocardiography demonstrating saccular aneurysm of left main coronary artery (bold arrow), ectatic left anterior descending coronary artery (thin arrow) and left circumflex coronary artery (dashed arrow).

Haemoglobin was 9.4 g/dL (11.5–14.5)], total leucocyte count 3.2 × 10^9/L (4.5–12.0), neutrophils 2.18 × 10^9/L (3.0–5.8), lymphocytes 0.64 × 10^9/L (1.5–3.0), monocytes 0.1 × 10^9/L (0.28–0.50) and platelet count 9 × 10^9/L (150–400). Erythrocyte sedimentation rate, which was sampled twice, was 2 mm/hr (0–20). Serum bilirubin was 101 µmol/L (<17) with 95% conjugated, alanine transaminase (ALT) 259 U/L (5–45), aspartate transaminase (AST) 680 U/L (15–50) and C-reactive protein 185 mg/L (0.5–10.0). Serum ferritin was 5236 µg/L (10–60), fibrinogen 1.07 g/L (2.0–5.0) and triglyceride 6 mmol/L (0.32–1.46). Blood urea was 5.9 mmol/L (1.8–6.4) and serum creatinine 38 µmol/L (19.4–52.2). Although serology for the Epstein–Barr virus (EBV) was persistently negative, PCR was positive for EBV DNA with 2.9 million copies/ml per blood sample. Dengue, herpes simplex, measles, *Mycoplasma pneumoniae*, scrub typhus and leptospiral serology was unremarkable. Urinalysis was negative for leucocytes, nitrites and leucocyte esterase, but protein was 1 + and Hb 1 + . Urine culture was negative. HLH was diagnosed in view of the clinical signs of lymphadenopathy and hepatosplenomegaly, supported by the laboratory findings of pancytopenia, hyperferritinaemia, hypofibrinogenaemia, hypertriglyceridaemia and raised liver enzymes.

Because of her unstable haemodynamic status requiring inotropic support, echocardiography was performed on day 7 of admission which demonstrated a large saccular aneurysm of the left main coronary artery (LMCA) measuring 8.0 mm, an ectatic left anterior descending coronary artery (LAD) of 2.8 mm, left circumflex coronary artery (LCX) of 3.0 mm and a right coronary artery (RCA) of 3.3 mm (Figure 1). She was commenced on two courses of intravenous immunoglobulin of 2 g/kg each. Despite this, her condition worsened with recalcitrant fever.

Histopathological examination of a bone marrow sample demonstrated significant infiltration of histiocytes and the presence of EBV-encoded small RNAs. Immunophenotyping showed abundant numbers of activated CD38+ and CD8+ lymphocytes which supported EBV-induced secondary HLH. Targeted therapy for HLH with daily IV dexamethasone 10 mg/m^2/day and twice-weekly IV etoposide 150 mg/m^2 was commenced.

On day 11 of her illness, the patient developed a florid and generalised erythematous, non-blanchable, purpuric rash on the trunk and limbs. Skin biopsy was not performed. After 5 days of HLH therapy (dexamethasone and etoposide) she became afebrile, the rash began to subside and she was weaned off mechanical ventilation. The only clinical features of fever and lymphadenopathy were insufficient to make a diagnosis of KD. She

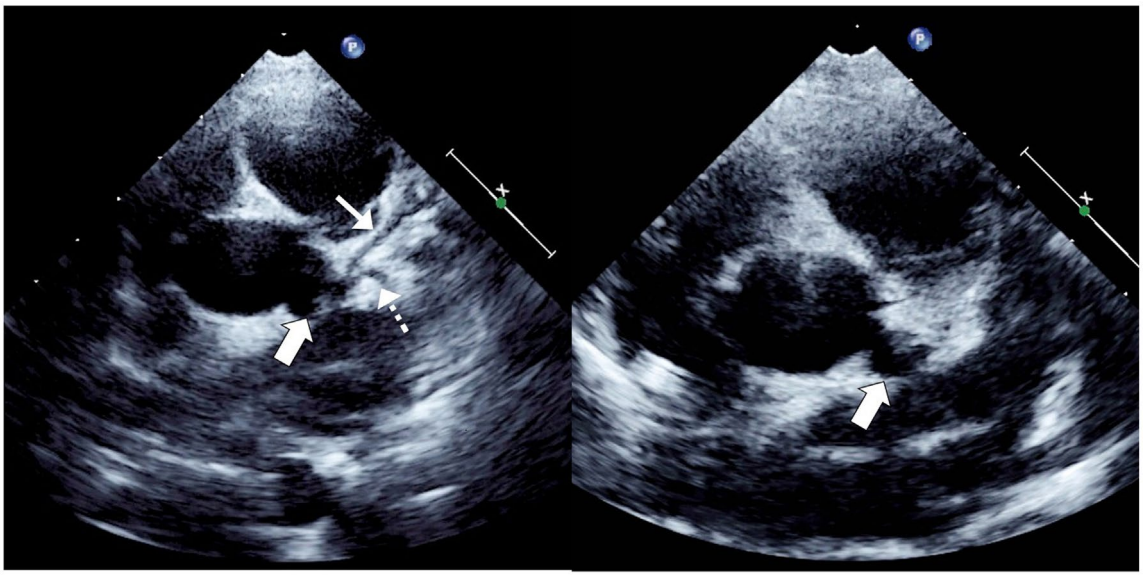

Figure 2. 3 months (left) and 9 months (right): Echocardiography showing improved dimensions of the coronary arteries. Left main coronary artery (bold arrow), left anterior descending coronary artery (thin arrow), and left circumflex coronary artery (dashed arrow).

was discharged after 3 weeks with improved full blood counts. Owing to persistently deranged liver transaminases, thromboprophylaxis was not commenced.

Thereafter, she was managed as an outpatient with 2-weekly pulsed oral dexamethasone 10 mg/m^2/day for 3 days and 2-weekly IV etoposide 150 mg/m^2. Repeat echocardiography 3 months after onset of the disease showed improvement of CA dimensions. Although the LMCA remained aneurysmal with a diameter of 7.0 mm, LAD, LCX and RCA regressed to 2.2, 2.0 and 2.5 mm, respectively (Figure 2). When liver function returned to normal limits, aspirin was commenced. At 9 months after onset of the disease, the LMCA had decreased to a diameter of 3.3 mm, although appearing tortuous and irregular (Figure 2). The diameter of the LAD was 1.7 mm, of the LCX was 1.4 mm and of the RCA was 1.7 mm. On electrocardiography, there was no electrical evidence of myocardial ischaemia. She was well and asymptomatic of her coronary artery disorder 9 months after admission.

Discussion

Although there are case studies demonstrating KD as a precursor to HLH with most developing after prolonged or recurrent courses of KD [4–6], coronary arteritis occurring in HLH not associated with KD has not been documented. One report described a 7-week-old infant who presented with fever, conjunctivitis, rash and splenomegaly with supportive laboratory results of anaemia and thrombocytopenia, and haemophagocytosis on histopathological examination of the bone marrow. HLH was diagnosed and he was treated with dexamethasone, etoposide and cyclosporin. He responded well but unfortunately died 1 month later. Post-mortem examination demonstrated inflammatory panarteritis, intimal fibrosis and fibrinoid necrosis in the CA with resultant myocardial infarction. Retrospective analysis of the clinical presentation demonstrated overlapping features of HLH and KD, prompting a revision of the diagnosis to possible 'atypical' KD [7]. Apart from fever and cervical lymphadenopathy, our patient had no clinical features resembling Kawasaki disease.

The coronary arteritis in this patient is intriguing as it occurred at the initiation of HLH. As far as we are aware, CA lesions presenting as a primary manifestation of non KD-related secondary HLH has not been reported. Inflammation of small vessels in the brain has been reported previously in HLH patients [8]; however, there is no substantial evidence to correlate HLH with any specific vasculitides. The Histiocyte Society's HLH-2004 treatment protocol mentions a heterogeneous aetiology of HLH which includes rheumatoid disorders but there is no elaboration on known entities [9].

HLH in this patient was triggered by an acute EBV infection. One study described CA lesions in individuals with EBV infections, but no clear mechanisms of disease were identified [10]. A more recent Japanese study found CA lesions in nine of 15 children with chronic active EBV infection [11]. However, there was insufficient evidence to associate CA lesions with acute primary EBV infections, as in this case.

Detection of CA lesions in HLH is unusual, probably because echocardiography is not a routine investigation included in the work-up of this disease. This case report seeks to examine whether it is worthwhile to undertake screening echocardiography in HLH patients at the outset. Although HLH is very rare and concomitant coronary arteritis can be a very remote occurrence, the morbidity caused by missed CA lesions can be significant. CA lesions can be clinically silent and demonstrate no electrical changes on electrocardiography. The cost-effectiveness of screening echocardiography is uncertain, hence audits are necessary to evaluate this.

The patient showed improvement of CA lesions as she recovered from HLH. This suggests a possible pathophysiological interconnection between the disease and development of coronary arteritis. Since the outcome of coronary arteritis demonstrates intervention-related effects, echocardiography performed at an early stage and before treatment of the HLH would be useful for the detection of lesions in the most florid states. Progression of the coronary arteritis can subsequently be assessed by echocardiographic surveillance at regular intervals.

Disclosure statement

No potential conflict of interest was reported by the authors.

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