Inflammatory process, with initial suspicion of aortic root abscess. Urgent cardiac surgery was performed which involved mitral valve repair, aortic root homograft replacement and reimplantation of the left coronary artery. There was no frank pus around the aortic root. Blood cultures were sterile, the CRP was 27 mg/l (reference range <20 mg/l) and the ESR 35 mm/h (reference range <10 mm/h). Extensive infectious workup including syphilis serology and tuberculosis was negative. Histology of the aortic root revealed an inflammatory reaction with plasma cell infiltration affecting the adventitia (Fig. 1A). The mitral valve leaflet demonstrated fragmented elastic laminae, fibroblast proliferation, increased vascularity and neovascularization with small blood vessels and mixed eosinophilic and plasma cell infiltrate. There was no histological evidence of acute bacterial endocarditis. Magnetic resonance angiography (MRA) and cardiac MRI confirmed the presence of large-vessel vasculitis affecting much of the aortic arch and its major branches, with arterial wall thickening and gadolinium uptake, luminal irregularity and patchy fusiform dilatation extending to the iliac bifurcation (Fig. 1B), confirming the diagnosis of Takayasu arteritis (TA). She was treated with daily oral prednisolone (2 mg/kg per day; with planned taper to 0.2 mg/kg over 4–6 months pending response), weekly s.c. MTX (15 mg/m² per week) and 5 mg/kg per day of aspirin as antiplatelet therapy. She made an excellent clinical recovery following her cardiac surgery and had prompt and complete normalization of her acute phase reactants. Three months later, she attended a routine outpatient appointment and was clinically in remission, with normal ESR and CRP. Two days later, however, she had an out-of-hospital cardiac arrest, requiring cardiopulmonary resuscitation for 30 min. She was transferred back to the cardiac intensive care unit, with recurrent episodes of unstable angina (severe pain and ST depression associated with bradycardia and apnoea). Emergency cardiac catheterization revealed severe stenosis of the reimplanted left coronary artery. Infliximab (6 mg/kg, at weeks 0, 2, 6 and four weekly thereafter) was added to her immunosuppressive therapy, and she received continuous i.v. unfractionated heparin, later converted to clopidogrel. One month after her cardiac arrest, she underwent successful left internal mammary artery bypass graft for stenotic left coronary artery disease. Again she made an excellent and rapid recovery. Five months later, however, she re-presented with transient ischaemic attacks with intermittent weakness affecting her right leg related to an occluded left carotid artery, which was not amenable to angioplasty or stenting. Warfarin was then added in place of clopidogrel, aiming for a therapeutic international normalized ratio of 2–3. MRA 22 months from initial presentation revealed a slender left common carotid and left subclavian artery, but no discrete focal narrowing. There was tapering of the infrarenal abdominal aorta and some stenosis of the superior mesenteric artery, although there were no areas of late gadolinium enhancement, and the aortic wall thickening had resolved. Twenty-four months from her initial presentation, she has been successfully weaned off

References


daily prednisolone and is maintained on weekly s.c. MTX, adalimumab 24 mg/m² every 2 weeks, warfarin and aspirin. She remains asymptomatic, although her development is still not yet back to the expected level for her age.

TA is a non-specific large-vessel vasculitis of unknown origin, with possible genetic contribution [1]. To the best of our knowledge, this is the first report of an acute cardiac presentation of TA in an infant. TA is exceedingly rare in pre-school children, and cardiac involvement is under-recognized in paediatric patients although it is described (rarely) in infantile TA [2–5]. Coronary arteritis resulting in stenoses and aneurysms, cardiac valvular lesions and ventricular aneurysm are among the various cardiac manifestations reported in children with TA [6]. Prior to our case, the youngest patient reported with primary involvement of aortic and mitral valves in TA was 3 years old [7]. Early diagnosis of large-vessel vasculitis and institution of immunosuppressive therapy is essential to avoid complications resulting from stenotic disease. It is likely that delayed diagnosis (often several years [8]) in the paediatric population contributes to the high frequency (80%) of patients who require surgery for stenotic/occlusive lesions [9]. Granulomas are a major feature of the histopathology; however, this may not be the case in children in the early phase of the disease where mononuclear infiltration of the adventitia with perivascular cuffing of the vasa vasorum occurs early [10]. Thus, in the early phase of the disease, histopathological findings may only reveal rather bland lymphocytic inflammation with some neovascularization as in our case. Once considered, the diagnosis of TA can be confirmed by angiography; MRA is advocated as it avoids radiation, provides adequate lumenography for large arteries and detects arterial intramural inflammatory changes including increased wall thickness and late gadolinium enhancement that may be used to monitor disease activity/progression. In conclusion, we wish to raise awareness of the occurrence of TA in infancy and emphasize that cardiac involvement can be feature of large-vessel vasculitis in children and adults.

**Rheumatology key message**

- TA can occur in very young children, who may present with acute cardiac valve involvement.
Distal lower extremity swelling as a prominent phenotype of NOD2-associated autoinflammatory disease

Sirs, We previously reported an autoinflammatory disease associated with nucleotide-binding oligomerization domain containing protein 2 (NOD2) gene mutations, designated as NOD2-associated autoinflammatory disease (NAID) [1, 2]. Herein we report the presence of distal lower extremity (ankle and foot) swelling as a prominent phenotype of this disease. Five patients were recruited as they met diagnostic criteria for NAID [2] and had a clinical commonality: distal lower extremity swelling/pain. The consent of the patients was obtained and the study was approved by the Institutional Review Board of the Cleveland Clinic.

Patient 1, a 64-year-old white woman, presented with intermittent fever with maximum temperature of 39.4°C and each episode typically lasted 2 days followed by abdominal erythematous patches. These symptoms had recurred every 4 weeks during the previous 5 years, with each episode lasting for several days. A skin biopsy showed dermatitis. There was also intermittent polyarthralgia, with notable left ankle and foot swelling; US examination excluded deep vein thrombosis (Fig. 1A); radiographic examination was unremarkable. Oesophagogastroduodenoscopy (EGD) and colonoscopy with biopsy were performed for heartburn, but the results were unremarkable.

Patient 2, a 47-year-old white woman, had intermittent erythematous patches and plaques on the face and neck. They had recurred every 6 weeks for the past 3 years, and each episode lasted for 5–7 days. A skin biopsy showed spongiotic dermatitis. She also had intermittent polyarthralgia, particularly unilateral ankle and foot swelling, on both physical and radiographic examination. A workup for mild diarrhoea, including EGD, colonoscopy and CT enterography, was unremarkable.

Patient 3, a 49-year-old white woman, presented with intermittent erythematous rash on her extremities over the past 6 years. She also had intermittent polyarthralgia, with notable ankle and foot swelling with unremarkable radiograph, and each episode of the articular presentation lasted for a few hours to 3 days. Besides low-grade fever, she also had intermittent moderate left upper quadrant pain, which prompted a workup including chest radiograph, EGD and CT scan of the abdomen and pelvis. The results were normal as were her serum lipase and amylase levels.

Patient 4, a 29-year-old white man, presented with multiple episodes of bloody stools and abdominal pain of 1 month duration. His father had been diagnosed with colitis but did not have any known NOD2 mutations. A colonoscopic examination with biopsy showed non-specific pancolitis with normal terminal ileum and the absence of granulomas. The patient reported left lower chest pain, and a chest radiograph and CT revealed left lower lobe infiltrate with a small pleural effusion, which resolved with several days of high-dose prednisone. He also had right foot/ankle redness and swelling (Fig. 1B) and transient freckle-like rash on the extremity. A skin biopsy showed leucocytoclastic vasculitis (LCV).

Patient 5, a 52-year-old white woman, reported high fever of 3 years’ duration; it recurred every 10 days, and each episode lasted for several hours. She also had intermittent polyarthralgia with notable ankle swelling and pain...