Neonatal medium-sized vessel vasculitis: A rare case report

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Vasculitis is a rare disorder during the neonatal period. We present a term male neonate of consanguineous parents and birthweight of 4 030 g who presented at 11 days of life with an evolving skin rash. There was no history of drug exposure in the neonate except for routine care. On day 7 of life, multiple erythematous plaques with necrotic or pustular centres appeared. There were no signs of mucosal involvement or sepsis and laboratory findings were normal. Skin biopsy revealed small and intermediate vessel vasculitis. At follow-up 2 weeks after discharge from the hospital, the skin lesions persisted, and at age 2 months, the patient presented with features of severe pneumonia and subsequently died. Vasculitis was reported as the cause of death on postmortem biopsy.

Keywords. neonate; vasculitis; cellulitis; acute oedema of infancy.

Inflammation of the skin and soft tissues is uncommon in healthy neonates, but when it occurs it should primarily be considered as being due to infective or inflammatory processes, most commonly cellulitis. Organisms commonly implicated in neonatal cellulitis include group B Streptococcus (GBS), Staphylococcus aureus, Gram-negative bacteria, anaerobic microorganisms and fungi. In primary neonatal cellulitis, the infection is acquired from the mother during the intrauterine period or during the passage from the vaginal canal, or postnatally from environmental sources. In secondary skin infections, haematogenous spread of microorganisms to the skin occurs during systemic infection, i.e. neonatal sepsis. Clinical symptoms of infection such as fever, poor feeding, lethargy, irritability, respiratory distress, vomiting and gastrointestinal problems, along with skin manifestations, support infection as a potential cause of disease. Drug reactions, although uncommon, may cause skin eruptions in the neonatal period.

Skin eruptions may be a symptom of systemic disorders other than infections, and may be prominent in patients with vasculitis disorders.

Vasculitis is defined as inflammation of the wall of blood vessels. Its aetiology is not fully understood but during pregnancy the immune system undergoes many changes to accommodate the fetus. Known causes of vasculitis include the following: infections (hepatitis B and Streptococcus spp.); other autoimmune diseases (lupus and scleroderma); and malignancies (leukaemia and lymphoma). The treatment of vasculitis in infants is not defined and recommendations are based on generalisations from large observational cohort studies in adults. The overall goal of treatment is control of vessel inflammation and prevention of irreversible vascular and organ damage. Corticosteroids are the first-line therapy; however, half of affected children need an additional immunosuppressant. Additionally, intravenous immunoglobulin (IVIG; 2 g/kg) and aspirin should be administered within 10 days of fever onset.

The classification and severity of disease are determined based on the size and site of involved vessels, underlying pathophysiology and the extent of vascular injury. Takayasu’s arteritis is an example of a large-vessel vasculitis in childhood, whereas Kawasaki disease and polyarteritis nodosa are examples of medium-vessel vasculitis disorders. Henoch-Schönlein purpura is a vasculitic process involving small vessels. The neonatal period is an uncommon time for the presentation of vasculitis and primary neonatal vasculitis is a particularly rare entity.

We report a rare case of neonatal vasculitis presenting with skin manifestations similar to infection-based cellulitis.

Case report

An 11-day-old term male neonate with a birthweight of 4 030 g was delivered by caesarean section from a healthy mother after a normal pregnancy (gravida 1, para 1 miscarriages 0). From the third trimester, the mother received levothyroxine (50 µg daily) to treat primary hypothyroidism. There was parental consanguinity, with no specific family history of vasculitis. There was no history of significant medical problems or drug exposure in the parents. There was no history of drug exposure in the neonate except vaccination with oral poliovirus vaccine, bacille Calmette-Guérin (BCG) and hepatitis B vaccine, and oral vitamin D drops for the first 5 days of life in accordance with routine care in Iran. He was circumcised on the fifth day of life with lidocaine as a local anaesthetic. The patient was breastfed. There were no concurrent symptoms of sepsis such as fever, irritability, poor feeding, lethargy, vomiting, diarrhoea, respiratory distress, or other problems in neonates.

After the appearance of skin lesions, the patient was admitted to a paediatric hospital in his hometown (Qom, Iran) for sepsis work-
up and antibiotic treatment. Owing to the lack of improvement, he was referred to our hospital.

From day 7 of life, a disseminated skin rash manifesting as large, targetoid erythematous patches was noted. There were purpuric plaques on the face, trunk, limbs and digits. The proximal, middle and distal phalanges of the middle fingers of both hands were involved. Fig. 1 illustrates the skin lesions. There were no concurrent symptoms of sepsis and no sign of mucosal involvement. The vital signs of the neonate were normal as follows: axillary temperature, 37.2°C; pulse rate, 110 bpm, respiratory rate, 38 bpm; oxygen saturation on room air, 95%. On further examination, he had a mild hydrocele.

He commenced intravenous antibiotic therapy with vancomycin and gentamycin to cover common skin infections, i.e. infection with Staphylococcus spp., group B Streptococcus spp. and Gram-negative bacteria. Antibiotics were administered after culture results were obtained. The white blood cell count (WBC) was 9.7 x 10^9/L, with 34% polymorphonuclear cells and 56% lymphocytes. The neonate's haemoglobin level was 14 g/dL, and platelets were 301 000/µL. C-reactive protein (CRP), blood urea nitrogen (BUN) and creatinine levels were normal, and blood, skin lesion, cerebrospinal fluid (CSF) and urine cultures were negative for bacteria.

Owing to the lack of improvement of the skin lesions despite antibiotic administration, and after consultation with a dermatologist, a differential diagnosis of acute haemorrhagic oedema of infancy or erythema multiforme was considered, and a skin biopsy was done. Histology confirmed the presence of small and medium-sized vessel vasculitis (Fig. 2). The histological findings were notable in terms of the dense perivascular inflammation in the dermis and subcutaneous tissue, small vessel damage with swelling of endothelial cells, fibrinoid necrosis of vessel wall, leukocytoclasis and intraluminal thrombus were observed (arrow). Perivascular inflammation consists of neutrophils, lymphocytes and a few eosinophils (H&E; 40×). (C) A medium-sized subcutaneous vessel (arrow) also revealed dense perivascular infiltration of neutrophils and lymphocytes and leukocytoclasis (H&E; 40×).

At subsequent follow-up, the skin lesions persisted. In the autumn of 2019, early in the influenza season, the patient died with fulminant respiratory disease (rapidly progressing over 4 - 5 hours) that was non-responsive to medical intervention. He was 2 months old at the time of death. No aetiological agent was identified in the terminal disease episode. A postmortem examination revealed vasculitis as the cause of death.

**Discussion**

This case was notable for the early onset of idiopathic histologically confirmed vasculitis involving small- and medium-sized blood vessels, and a rapidly fatal course. Vasculitis is an unusual disorder in the neonatal period. Transplacental passage of maternal protein may lead to a transient vasculitis in infants born to mothers with underlying disorders such as Behçet disease, Sjögren's syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease, or microscopic polyarteritis.[12-15]

Although Kawasaki disease is a relatively common form of vasculitis in children, it is rarely reported in neonates.[16] Infantile Henoch-Schönlein purpura, or acute haemorrhagic oedema of infancy (AHEI), is a self-limiting cutaneous vasculitis of small vessels without any systemic involvement that occasionally presents at birth.[12]

AHEI manifests with fever, oedema and large palpable purpuric skin lesions that resemble those seen in Henoch-Schönlein purpura. Conservative management is the most commonly adopted approach in
treatment of AHEI. The skin manifestations of our patient were similar to those observed in AHEI; however, fever and oedema were not significant. The persistence of the skin manifestations and outcome of our patient do not support a diagnosis of AHEI. In a report by Roy et al., an 8-month-old male infant presented with skin eruptions which developed following a mild respiratory illness for which amoxicillin-clavulanate and paracetamol were prescribed. The rash consisted of multiple plaques and oval-to-rounded ecchymotic patches varying in diameter from 2 to 5 cm, involving the arms, hands, face, gluteal area, feet and legs. No histological assessment was done in the diagnostic work-up of the case. Topical application of calamine lotion resulted in resolution of the skin rash.

Allergic reactions to drug administration often involve the skin.[27] In view of the low prevalence of allergy in the neonatal period,[16] and the negative history of drug exposure in our patient, this diagnosis would have been highly unlikely. Malignancies, including lymphoma and other lymphoproliferative syndromes, may result in secondary vasculitis and in cases of persistent vasculitis,[14] malignancy should be considered. Altammar and Lang[15] reported a case of Kawasaki disease in a 15-day-old male who presented with irritability, a rash and poor feeding. Fever (39.6°C), tachypnoea, tachycardia, extreme irritability and a generalised maculopapular rash were noted on physical examination. Bilateral non-purulent conjunctivitis, bilateral non-pitting oedema, palmar erythema, erythema of the feet and arthritis were present on day 6 of hospitalisation. The complete blood count, CRP, and erythrocyte sedimentation rate (ESR) were normal at baseline, but thrombocytosis was detected on day 9 of hospitalisation. Symptoms of the disease resolved subsequent to intravenous immunoglobulin administration. Coronary artery aneurysms were not detected in the echocardiography.[20]

Krapf et al.[24] reported a neonate with fatal myocardial infarction owing to vasculitis of the coronary arteries. Pathological involvement of the coronary arteries is indistinguishable from mucocutaneous lymph node syndrome and/or infantile periarteritis nodosa. The epidemiology and etiology of these rare conditions remain to be clarified.[21]

In a case report by Simonetti et al.,[22] a term neonate with asephagoeal atresia requiring surgery on day 2 of life developed respiratory distress, empyema, thrombocytopenia, severe proteinuria, and haematuria with red cell casts on urinalysis, a rise in creatinine at long-term follow-up (12 months old) the patient was well.[22]

Also, we conclude that the parents need to be investigated for an autoimmune disease.

Declaration. Written informed consent was obtained from the parents of the patient to publish this information and the images of the neonate.

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