SUCCESSFUL TREATMENT OF GANGRENE IN SYSTEMIC NECROTIZING VASCULITIS WITH ILOPROST

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SUMMARY

Systemic necrotizing vasculitis is uncommon in children and may be rarely associated with gangrene. We describe a 3-yr-old girl with parvovirus B19-induced necrotizing vasculitis whose digital gangrene was successfully treated with iloprost, a prostanoid analogue.

Key words: Parvovirus B19, Polyarteritis nodosa, Necrotizing Vasculitis, Iloprost.

CASE REPORT

AP, a 3-yr-old Caucasian girl, came to our attention in May 1996 for necrotic lesions of the fingers of both hands and vasculitic rash. Her illness started in February 1996 with rash on her cheeks, oedema of the upper lip, low-grade fever, arthralgias and anorexia. The rash involved both the upper and lower extremities, and lasted 2 weeks. On admission to a local hospital, physical examination showed arthritis of both ankles and the right wrist, and vasculitic rash involving the lower limbs and cheeks. All inflammatory parameters were elevated. Positive IgM antibodies, IgG antibodies and parvovirus B19 DNA in the serum documented infection with parvovirus B19. She was treated with prednisone (1 mg/kg/day) and aspirin (100 mg/kg/day) with no significant improvement. In April, she started having aches and pain in her hands and feet, and low-grade fever. She was readmitted to hospital and treated with IVIG (1 g/kg/day) which gave a mild decrease in symptoms and complete control of fever. A month later, her parents noted severe pain and discoloration of the fingers of both hands. She was referred to the Department of Paediatrics, University of Padua.

At the time of admission, she was irritable but not febrile. Physical examination showed livedo reticularis of both hands and feet. The third, fourth and fifth fingers of the right hand, and the second, third and fifth fingers of the left hand, were cold and bluish. Dry necrosis (gangrene) of the distal phalanges of the right second and left fourth fingers was present (Fig. 1). There were no ischaemic lesions in the feet or arthritis. Examination of other systems was normal.

Results of the laboratory tests were as follow: WBC $16.3 \times 10^9/l$ (71% segmented neutrophils, 23% band forms and 19% lymphocytes), Hgb 91 g/l, platelet count $678 \times 10^9/l$, ESR 102 mm/h, CRP 97 mg/l (normal value $<6$). Results of tests for cold agglutinins, antinuclear antibodies, pANCA and cANCA were negative. There was no evidence of hepatitis A, B or C viruses, or HIV. Serum complement fractions (C3, C4 and C3a), serum immunoglobulins and coagulation panel including protein S, protein C, Factor V Leiden, antiphospholipid antibodies and LAC were normal. The only significant finding was the elevation of vW factor VIII antigen as a result of the vasculitic process and, probably, secondary also to the steroid treatment. Echo Doppler and plethysmography of the upper and lower limbs were normal. Angiography of the distal upper limbs showed narrowing of the external and internal digital arteries of the second, third and fourth fingers of the right hand, and of...
the second, fourth and fifth fingers of the left hand. EMG, total body Te⁹⁹⁹ scintiscan and bone marrow examination were normal. Serology for parvovirus B19 was positive for IgG, low level for IgM and negative for B19 DNA. Skin biopsy of a nodular lesion showed a medium-size artery with transmural cell infiltrate, intimal proliferation and luminal occlusion consistent with polyarteritis nodosa (PAN) (Fig. 2).

Because of the rapid progression of gangrene of the fingers, the patient was started on i.v. iloprost 2 ng/kg/min for 6 h/day for 14 days. Treatment with prednisone was maintained at the same dose at 1 mg/kg/day. The ischaemic fingers regained their colour and temperature within 24 h. There was no progression of the necrotic lesions of the two fingers. There were no significant changes in blood pressure. The only side-effect related to treatment with iloprost was episodes of irritability at night-time. At the end of the treatment with iloprost, cyclophosphamide (2 mg/kg/day) and nicardipine (1 mg/kg/day) were added. Two weeks later, the patient recovered completely and the inflammatory indices normalized. Of course, the two necrotic phalanges were partially amputated (necrectomy) to avoid the risk of osteomyelitis. At the end of 6 months follow-up, the patient is symptom free.

DISCUSSION

Infection-related vasculitis, resembling PAN, has been described in adults, but rarely in children [1]. β-Haemolytic Streptococcus can be the aetiologic agent of the cutaneous form of PAN both in adults [6] and children [7]. Of the 12 children with vasculitis in association with streptococcal infection reported by David et al. [7], 10 followed a benign course and two were systemically unwell and had visceral microaneurysms. There were isolated case reports of vasculitis in association with infectious mononucleosis [8], cytomegalovirus infection [9] and HIV [10]. In these cases, the inflammatory process affects essentially small vessels and the histological picture does not resemble PAN.

The patient described in this report had typical features of necrotizing vasculitis and evidence of parvovirus B19 infection, documented by both serology (specific IgM and IgG) and serum DNA. Even in the absence of internal organ involvement, the clinical picture satisfied four out of the 10 ACR 1990 criteria for the diagnosis of PAN [11].

Two other cases of systemic vasculitic syndrome with clinical features of PAN have been described recently in children in association with parvovirus B19 infection [2]. As in our patient, none presented internal organ involvement but, different from our patient, none presented gangrene. Previously, the association parvovirus B19 infection–PAN has been described in adults in two case reports [3, 4]. One patient presented purpuric lesions with necrosis at the lower limbs that healed without any treatment in 1 month [3]. The other case did not present any necrosis, just vasculitic rash [4]. Peripheral gangrene due to necrotizing vasculitis is a very rare condition in children [7, 12, 13]. Boren and Everett [12] described a case of necrotizing vasculitis in a 3-day-old baby girl born to a mother who had developed cutaneous PAN in the second month of pregnancy. In this case, no laboratory evidence of immunological abnormalities had been demonstrated, biopsy specimens were normal and the patient improved without any treatment. Among the 12 patients with PAN associated with streptococcal infection described by David et al. [7], only one presented gangrene of a terminal digit but, unlike our patient, he responded to steroid therapy. In the series of 10 children with cutaneous PAN reported by Kumar et al. [13], eight had peripheral gangrene in both upper and lower limbs leading to autoamputation in seven of them. In all these patients, there was a delay in the diagnosis and the treatment did not prevent further progress of gangrene [13]. Treatment of severe necrotizing vasculitis associated with connective tissue diseases can be difficult. Steroids and cytotoxic agents, such as cyclophosphamide and azathioprine, represent the treatment of choice [5, 14]. The toxicity of these drugs is considerable because of the dose used and the duration of therapy. Intravenous immunoglobulins seem to be effective in particular conditions [15].

Iloprost, an analogue of epoprostenol (PGI₂), mimics the pharmacodynamic properties of prostacyclin, namely inhibition of platelet aggregation and vasodilatation [16]. Some anti-inflammatory properties have also been reported [17]. It has been used successfully, in adults, for the treatment of critical leg ischaemia [18], thromboangiitis obliterans [19], severe Raynaud’s phenomenon [20] and ischaemic ulcers secondary to systemic sclerosis [21]. Iloprost has also been used in the treatment of vasculitic leg ulcers in connective tissue disease [22]. In a series of eight patients, six with rheumatoid arthritis and two with overlap connective tissue diseases, complete ulcer healing was achieved in four patients within 6 weeks. A substantial improvement occurred in the other four patients [22].

Our patient presented necrotizing vasculitis with gangrene 2 months after the onset of vasculitis. Unlike the report of Finkel et al. [2], our patient did not respond to repeated treatments with i.v. gamma globulin and oral prednisone. The evidence of gangrene in
two fingers and ischaemic lesions in six more fingers led us to try a more aggressive treatment by using i.v. iloprost. This treatment stopped the progression of gangrene and provided a rapid improvement of blood flow in all the ischaemic fingers within 24 h. The only side-effects related to treatment were brief, self-limiting episodes of irritability at night-time. Headache and flushing, reported commonly in adults [23], were not seen in our patient.

Intravenous iloprost has to be considered in children with severe necrotizing vasculitis, in conjunction with other immunosuppressive treatment, when first-line drugs, such as steroids and/or IVIG, are ineffective or in the presence of progressive gangrene. To our knowledge, this is the first successful application of this treatment in a child with necrotizing vasculitis.

Acknowledgements
The authors acknowledge the precious and thoughtful comments of Barbara M. Ansell, Stoke Poges, Bucks., and Balu H. Athreya, Department of Pediatrics, Thomas Jefferson University, Philadelphia, USA.

References