Case report

Cytomegalovirus-related necrotising vasculitis mimicking Henoch-Schönlein syndrome

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ABSTRACT

Viral vasculitides have been previously reported in the literature, the role of infections in their pathogenesis ranging from direct cause to trigger event. Here we report the case of a 3-year-old immunocompetent girl who developed a systemic vasculitis leading to ileal perforation, mimicking a full blown picture of Henoch-Schönlein purpura. High dosage steroid treatment was started, with good response. The anatomopathological examination of the resected gastrointestinal tract showed features of necrotising vasculitis and cytomegalovirus (CMV)-related inclusion bodies in the endothelial cells, with direct correlation to vascular damage. The causative role of viral infection was revealed by the presence of CMV DNA in patient's blood and positive IgG titer against the virus. Steroid therapy was then tapered: the patient achieved clinical remission, which still persists after a six-months follow-up. Our report suggests that CMV vasculitis is probably more frequent than previously thought, even in immunocompetent patients, with a protean clinical presentation, mimicking other types of vasculitides.

Introduction

Vasculitis are a heterogeneous group of inflammatory diseases occurring in childhood as well as in adulthood, whose main feature is blood vessel wall immunomediated inflammation which causes blood flow alteration and damage of the perfused tissues. The disease may be limited to skin or other organs, or may have multisystemic features (1, 2). A multifactorial aetiology (idiopathic, post-infectious, drug related) is commonly accepted. Although the pathogenesis still remain poorly understood, three possible mechanisms are usually implicated in vascular damage: immune complexes (ICs) deposition, antineutrophilic cytoplasmic antibodies (ANCAs)-related humoral response and T cell-mediated mechanisms (3). Clinically, signs and symptoms are highly variable depending on the size of the involved vessel: hence, they range from systemic symptoms (*e.g.* fever and malaise) to more organ-specific manifestations. The diagnosis can therefore be difficult and histological findings may represent an useful diagnostic tool. Therapeutic approach is aimed to inflammation remission with glucocorticoids and immunosuppressive agents, as aetiology-based therapy is usually unachievable (1, 2). The relationship between infection and vasculitis is still a highly debated topic: even if a causative role has been documented only for few pathogens (*e.g.* some bacterial and fungal aortitis), several others have been considered trigger factors for different types of vasculitis.

Case report

A 3-year-old caucasian girl was admitted to the local Paediatric Unit because of cutaneous vasculitis, characterised by purpuric skin lesions mainly restricted to lower limbs and bottocks, oedema of the extremities, acute arthritis at ankles and knees; urine analysis showed microscopic haematuria. Her parents reported an upper respiratory tract infection one week before admission. Given the following haemorragic evolution of cutaneous lesions, a diagnosis of Henoch-Schönlein (HSP) was made. A few days after the disease onset, severe abdominal pain occurred: the ultrasound (US) scan showed small bowel intussusception which required surgical manual reduction. The girl was then referred to our hospital. At admission her general conditions were poor and she complained of diffuse mild abdominal

pain; moreover systemic hypertension (150/100 mm/Hg), nephritic range proteinuria (0.9 g/24h), microscopic haematuria (231 RBC/HPF) and low albumin level (2.1 g/dL) were observed. Renal biopsy was not performed due to patient's critical conditions; moreover renal function was within normal range. The ongoing enteral nutrition was stopped and a parenteral feeding schedule was started in association with iv steroid therapy (methylprednisolone 1 mg/kg/day). Nonetheless, five days later, her clinical conditions suddenly worsened with high fever spikes and severe abdominal pain: abdominal x-ray showed signs of gastrointestinal perforation, requiring surgical resection of 20 cm of perforated ileum, associated with corticosteroid therapy increase up to 2 mg/kg/day. Histological findings were consistent with necrotising vasculitis associated with granulomatous features, involving small and medium vessels (Fig. 1). Furthermore typical "owl eye" nuclear inclusions were found; the immunohistochemical (IHC) staining conformed them to be CMV-related inclusion bodies (Fig. 2). Blood test showed positive anti-CMV IgG titer (114 U/mL, negative values <14 U/mL) whereas anti-CMV IgM were absent. The polimerase chain reaction (PCR)-based assay for CMV DNA on blood sample was positive (8,300 copies/mL), confirming CMV infection. Serological investigations were negative or within normal range for anti-nuclear antibody (ANA), anti-extractable nuclear antigen (ENA), ANCA, anti-dsDNA, anti-cardiolipin and anti-β2 glycoprotein I, C3 and C4 complement fraction decrease and cryoglobulins. Althought no recurrent infections were referred, patient's immune response was studied resulting within normal range: notably, we found normal white blood cell differential count, immunoglobulin (Ig) level and lymphocyte subset determination. Finally we performed direct immunofluorescence (DIF) examination on skin biopsy which showed granular shaped-IgM deposition at dermo-epidermal junction, without any IgA deposition.
During the next four weeks we tapered methylprednisolone dosage down to 0.75 mg/kg/day, without relapses of the symptoms. The child was finally discharged with the diagnosis of CMV associated-systemic vasculitis; steroids were subsequently progressively tapered and discontinued. We re-evaluated the patient 3 and 6 months later. Her clinical conditions were good, blood tests were all within normal range and C-reactive protein (CRP) was negative; serology showed a decrease in IgG titer against CMV and PRC-based assay for CMV was negative in all the measurements.

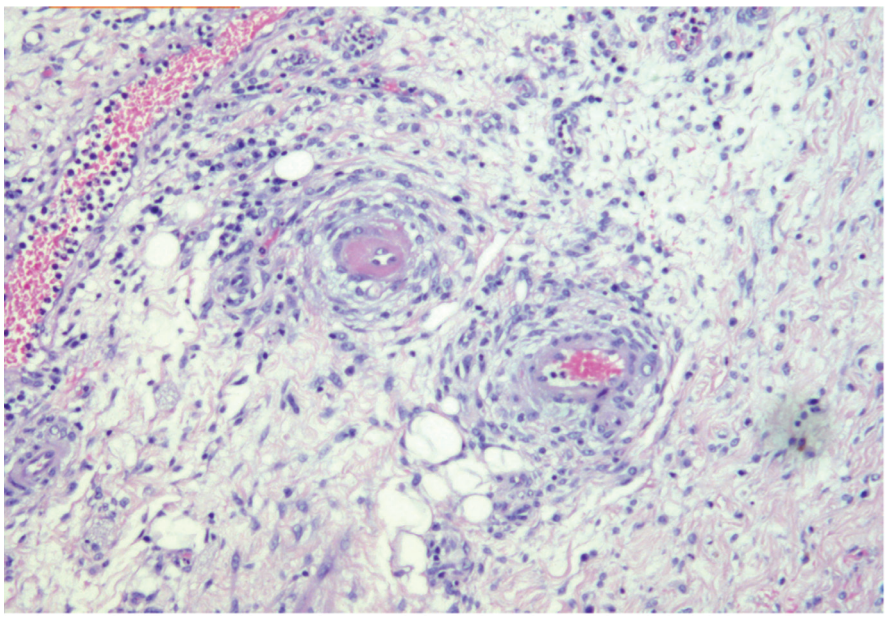

Fig. 1. 10X zoom picture showing fibrinoid necrosis of ileal vessels with initial granulomatous organisation around them.

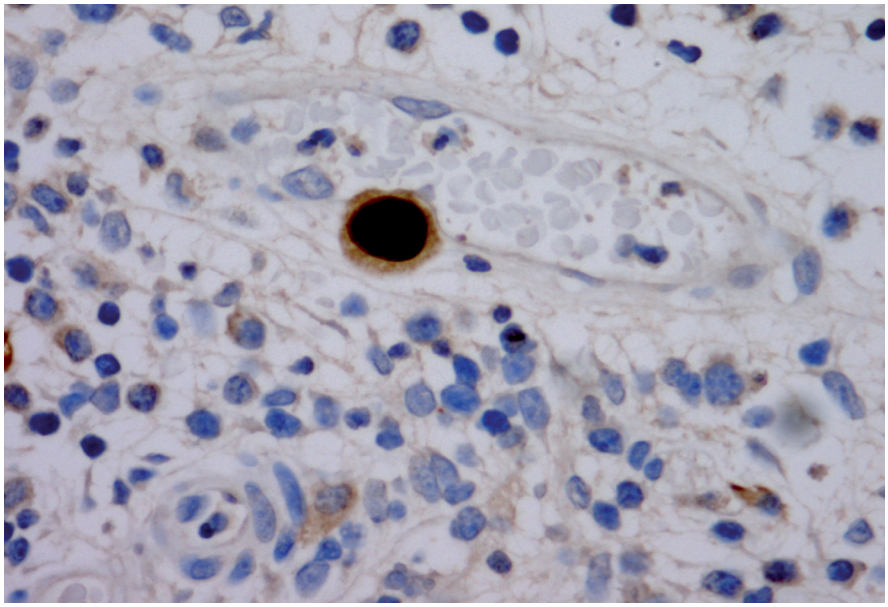

Fig. 2. 40X zoom picture showing CMV-related "owl eye" nuclear inclusion involving ileal endothelial cell, positive to immunohistochemical staining.

Discussion

We report the case of a 3-year-old girl who developed a CMV-related necrotising vasculitis leading to acute life-threatening gastrointestinal complication and mimicking a full blown picture of HSP.
Virus-associated vasculitis has been previously reported in literature; notably CMV-related vasculitis shows particular association with immunocompromised patients (4) and ANCA-associated subsets of vasculitides (3, 5).

The pathogenetic mechanisms relating CMV infection to systemic vascular damage still remain poorly understood, especially in immunocompetent hosts. A direct endothelial CMV infection, with subsequent lytic cycle and vessel damage, has been widely reported (6), as well as immunomediated vascular injury through CMV-related induction of autoimmunity (molecular mimicry) (7). It is noteworthy that both endothelial cells and circulant monocytes have been described as preferential target for primary CMV infection and latency, probably due to common CD34+ progenitor in which CMV infection is established (8). Moreover the use of steroids and other immunosuppressive drugs, especially in patient affected by ANCA-associated vasculitis, may allow CMV reactivation and facilitate viral escape strategies from host's immunologic system. Common treatment of CMV vasculitis usually consists of antiviral drugs (ganciclovir) and discontinuation of immunosuppressive therapy (4).

In the immunocompetent paediatric patient we reported, CMV infection/reactivation triggered a systemic vasculitis strickly mimicking HSP, both in cutaneous and systemic manifestations. However histologic features of the resected ileus showed a widespread necrotising vasculitis associated with granulomatous features, involving small and medium vessels (Fig. 1). Moreover the absence of leukocytoclastic features and IgA deposition on skin biopsy, in addition to diffuse medium vessels involvement, were not consistent with the HSP diagnosis. In our patient, the relevant role of CMV in the pathogenesis of the disease was documented by 1) positive serology test and direct PCR-based assay, 2) documented viral invasion of perfored ilieum with "owl eye" inclusion bodies on histological examination, confirmed as CMV related by IHC staining (Fig. 2); 3) negativisation of CMV-DNA assay and decrease in IgG antibodies titer three months after the flare-up phase. Moreover, histological examination showed a direct positive correlation between CMV nuclear inclusions and vascular damage.

Thought it is difficult to establish whether this is a primitive disease or a steroid induced-reactivation of a previous latent infection, the serological status of the child suggests it could be the latter. As a result, we confirmed the diagnosis of CMV associated-systemic vaculitis. In this case ganciclovir was not used: viral aetiology was discovered only after histological examination of the resected ileum, when clinical conditions were considerably improved; so we decide only to start steroid tapering. Furthermore, there is no consensus or international guidelines on viral vasculitis treatment, expecially in paediatric population.

Although murine CMV infection is one of the most widely used models of vasculitis, CMV associated vasculitis is rarely observed in humans and mainly occurs in immunocompromised patients. The main target organs are represented by the gastrointestinal (GI) tract and the central nervous system (CNS); haematological disorders are also frequent (9). Notably the GI tract seems to be a preferential target, both in immunocompetent and immunodeficient patients (10-12). Although multicentric surveys have been showed that life-threatening complications of CMV infection in immunocompentent adult hosts are not uncommon, there are no studies equally comprehensive for the paediatric population (9). Moreover few reports describe CMV associated-vasculitis; most of them were negative for direct search of viral DNA (13) and pathognomonic histological findings (14), both present in our patient.

In conclusion, our case report underlies the importance to include CMV-related vasculitis in the diagnostic work-up of paediatric vasculitis, even in immunocompetent children. This form of vasculitis is probably underdiagnosed, due to aspecific clinical presentation, mimicking other types of vasculitis (HSP in our case). We underline the pivotal role of histological examination, which ruled out the previous clinical diagnosis of HSP, demonstrating the causative role of CMV infection in the pathogenesis of the disease.

Key message

CMV vasculitis is probably more frequent than previously thought with a protean clinical presentation.

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