

An extraordinary case of oral leukocytoclastic vasculitis demonstrating IgD deposition around dermal vessels and within mucosal keratinocytes

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ABSTRACT

Cutaneous vasculitides include a widespread and heterogeneous cluster of diseases affecting the blood vessels that are clinically characterized by polymorphic skin lesions, including palpable purpura, urticarial and/or necrotic-ulcerative lesions. Often, they can be manifestations of a systemic disease. Selected cases occur in the mouth. A 75-year-old female presented to her physician for the sudden appearance of blisters in her mouth, with severe orodynia and no history of other diseases or medication intake. A skin biopsy of the oral mucosa yielded a diagnosis of leukocytoclastic vasculitis. The direct immunofluorescence and immunohistochemistry stains demonstrated deposits of IgD, IgG, IgA, IgM, kappa, lambda, C1q, C3c, albumin and fibrinogen at the upper dermal neurovascular plexus. IgD also demonstrated positive nucleolar staining of the keratinocytes. Our case involves a rare presentation of oral cutaneous vasculitis with immune deposits of several immunoglobulins, complement, albumin and fibrinogen. Our case adds importance to studies of the IgD role in antigenic complex immune responses, especially in the mouth.

Key words: Leukocytoclastic vasculitis; IgD; Nucleolar autoantibodies

Abbreviations: Leukocytoclastic vasculitis (LV); Hematoxylin and eosin (H&E); Periodic acid–Schiff (PAS); Immunohistochemistry (IHC); Direct immunofluorescence (DIF); Fluorescein isothiocyanate (FITC); 4',6-diamidino-2-phenylindole (DAPI); *Ulex europaeus* agglutinin (ULEX).

INTRODUCTION

Cutaneous vasculitides include an extensive and diverse cluster of diseases affecting the tegumentary blood vessels; these are clinically manifested as polymorphic skin lesions, including palpable purpura, as well as urticarial and necrotic-ulcerative lesions. Sometimes extracutaneous involvement occurs [1]. Leukocytoclastic vasculitis (LV) was formerly known as hypersensitivity vasculitis. LV can have an acute form and a chronic presentation [2]. Cutaneous leukocytoclastic angiitis and urticarial vasculitis, which are the two most common variations of this disease cluster, are frequently idiopathic but may also

be triggered by diverse agents, including drugs and infections, or may be as part of systemic disorders, predominantly systemic lupus erythematosus (SLE) [1]. Vasculitic skin lesions can also occur during the chronic-relapsing course of systemic vasculitides, including Wegener's granulomatosis (WG). These vasculitides often share clinical and immunohistopathologic features [1,2]. The vasculitides are associated with blood vessel inflammation that can cause internal organ damage [1-3].

The American College of Rheumatology (ACR) recommends standards for cataloging the primary vasculitides, established via a compilation of clinical

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and immunological characteristics of multiple patients. The following are types of characterized vasculitis: Takayasu arteritis, polyarteritis nodosa (PAN), WG, giant cell arteritis, and Henoch–Schönlein purpura (currently known as IgA vasculitis) [3-11].

STATEMENT OF ETHICS

Our patient gave informed consent. Although Institutional Review Board (IRB) approval for a case report is not needed, the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule restricts how protected health information (individually identifiable health information) on any patient may be utilized. Compliance with patient privacy, institutional rules, and federal regulations were followed. No photos or illustrations that contain identifiable features are included in the case report, and the case(s) described in the report are not so unique or unusual that it might be possible for others to identify the patients.

CASE REPORT

A 75-year-old woman presented to her doctor for the presence of small blisters, erythematous areas, and purpuric patches in the oral mucosa with severe orodynia. Lesional oral skin biopsies for hematoxylin and eosin (H&E), for direct immunofluorescence (DIF) and for periodic acid–Schiff (PAS) stains were taken. The staining techniques were performed as previously described [11,12]. Additional systemic testing for an underlying disease was performed, including a complete blood count, and liver panel assays and kidney function testing; urinalysis was also performed. Other tests included an anti-streptococcal antibody titer, and HIV testing. Further testing for rheumatologic diseases included testing for systemic lupus erythematosus (SLE), Sjogren's syndrome, antinuclear antibodies (mostly via IgG), anti-ceruloplasmin antibodies and anti-rheumatoid factor. Additional testing included serum protein electrophoresis, serum complement levels, and testing for the presence of cryoglobulins. The test results were all non-contributory, and essentially ruled out any systemic involvement. For DIF, we classified our findings as previously documented [12-14]. IHC staining was performed utilizing a Leica Bond MAX IHC automatized platform (Buffalo Grove, Illinois, USA) and a Novolink™ detection with Compact Polymer™ technology. For red staining, the Bond Max platform autostainer utilized red detection DS9390, an alkaline phosphatase linker

and a fast-red chromogen. For brown staining, we used DS9800 as reported before [8-11]. We also ran negative and positive controls. We used anti-human monoclonal antibody to HLA-ABC antigen, clone W6/32, polyclonal rabbit anti-human IgD (code IR517), and C5b-9 (code M077), all from Dako (Carpinteria, California, USA).

The mouth lesions are shown in Fig. 1a. The microscopic examination of the H&E stains revealed an inflammatory process involving capillaries and small blood vessels of the dermis. Fibrinoid deposits were identified within the blood vessels walls. Leukocytoclasia, swelling of endothelial cells, occlusion of blood vessels, accumulation of fibrin and fibrinoid degeneration were all observed (Fig. 1b). Some red blood cells were seen outside the vessel walls, situated in the dermal interstitial tissue. The diagnosis of leukocytoclastic vasculitis (LV) was rendered based upon the histologic changes. The PAS stain demonstrated positivity (+++) in the same pattern of deposits as the polyclonal auto-antibody response. The DIF displayed positive staining around the upper dermal vessels with IgG (+++), IgA (++), IgM (++), IgD (+++), IgE (+), kappa (++), lambda (++), C1q (++), C3c (++), albumin (++) and fibrinogen (++++). Of interest, nucleolar staining in epidermal keratinocytes was seen with the anti-IgD antibody (Fig. 1d). In addition, the mucosal stratum

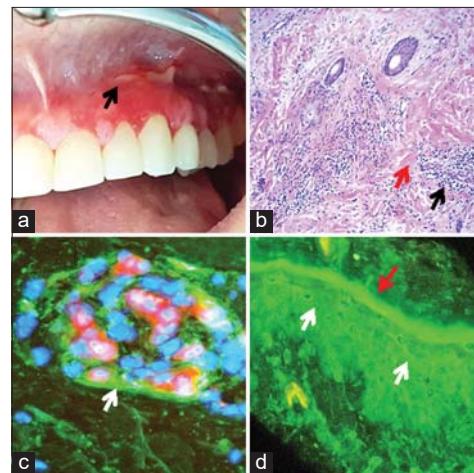


Figure 1: (a) Small blisters, erythematous areas and purpuric patches on the oral mucosa (black arrow) (b) H&E staining demonstrating affected dermal vessels, surrounded by a strong lymphohistiocytic inflammatory infiltrate (black arrow) and fibrinoid deposits (red arrow) (100X). (c) DIF positive staining on dermal blood vessels with FITC conjugated fibrinogen (++++) (green staining, white arrow) (400X). The vessels were also positive for ULEX (red staining). The nuclei of the cells were counterstained with DAPI (blue staining). (d) DIF using FITC conjugated anti-human IgD, positive in the mucosal corneal layer (yellow staining; red arrow) as well as nucleolar staining on the keratinocytes (punctate yellow staining; white arrows) (400X).

corneum demonstrated thick linear staining with the same antibody (++). The purely nucleolar staining may be seen in selected patients with systemic sclerosis. Our patient was evaluated for systemic sclerosis and this disease was excluded by negative studies, specifically with the anti-RNA polymerase I, anti-U3 ribonucleoprotein antibody, anti-topoisomerase 1, anti-centromere, and anti-RNA polymerase III, PM-Scl (anti-topo 1, Ribosomal P), and polymyositis/dermatomyositis (PM/DM) (PM-Scl, anti-RNAP III).

DISCUSSION

Vasculitis may be categorized based on the size of the affected vessels, specifically small, medium, or large vessel [1]. Alternatively, classification may reflect the etiology: idiopathic or linked with an underlying pathology/disease. Confirming the diagnosis of a vasculitis ideally requires characteristic mucosal/cutaneous lesions, an appropriate clinical history, the histologic and immune pathologic patterns, [12] pertinent laboratory data and possible extracutaneous manifestations due to the complexity of these disorders [1]. Leukocytoclastic vasculitis was previously also called anaphylactoid purpura [15] and has been considered an immune complex disorder (Gell Coombs Type III) [2]. The histologic findings are of paramount importance in reaching the diagnosis of vasculitis, and it is imperative to consider the timing of the biopsies for H&E, PAS [12] and DIF and IHC staining. DIF is highly recommended in cases of suspected leukocytoclastic vasculitis. Routinely, most laboratories test DIF antibodies against IgM, IgG, complement C3, albumin and fibrinogen in cases of suspected vasculitis. Because of our extended experience with DIF testing, we tested for all the immunoglobulins (including IgD and IgE), complement factors C1q, C3c and C4, plus albumin and fibrinogen. We had noticed that most vasculitis and autoimmune blistering diseases, as well as rheumatologic diseases affecting the skin and oral mucosa demonstrate some reactivity via IgD (publication in preparation). In the current case, we utilized our routine panel of autoantibodies and markers. Thus, we tested for the presence of IgD and noted positive findings. It is known that mature B cells express immunoglobulin M (IgM) and IgD-isotype B cell antigen receptors (BCRs). It has further been shown that polyvalent antigens activate both IgM and IgD receptors, indicating a more complex immunologic response [16]. For many years, the role of IgD has been poorly understood. In our case, we

note that many autoantibodies were positive including IgM and IgD; their role *vis-a-vis* BCRs not only establishes a novel concept for immune regulation, but also might open new opportunities for improving vaccination approaches. These approaches could be aimed at protection from autoimmune disorders or pathogens in light of the B cell antigen receptors. In this rare case of oral leukocytoclastic vasculitis, the presence of IgD antibodies deposits is quite intriguing. Some authors have speculated that in renal vasculitis an IgD response may be formed to a variety of illnesses, including autoimmune disorders. Again, in our experience the role of autoantibodies against IgD are important in the context of current reports in the medical literature [17,18]. Moreover, these authors state that glomerular deposits of IgD suggest that immunoglobulins of this class may be present in association with some immunologically induced systemic processes [17].

We conclude that in our case of oral leukocytoclastic vasculitis with polyclonal autoantibody deposition, the response of IgD antibodies is uncommon. Indeed, oral manifestations of a leukocytoclastic vasculitis are infrequent, although a few cases have been described [2]. Thus, we document a combination of rare leukocytoclastic vasculitis oral mucosal involvement with a rare LV autoantibody deposition.

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