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

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INTRODUCTION

Cutaneous vasculitides include an extensive and diverse cluster of diseases affecting the tegumentary blood vessels; these 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).
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 (++++) (Fig. 1c). 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).](image)
of IgD has been poorly understood. In our case, we
immunologic response [16]. For many years, the role
IgM and IgD receptors, indicating a more complex
been shown that polyvalent antigens activate both
isotype B cell antigen receptors (BCRs). B cells express immunoglobulin M (IgM) and IgD-
(anti-topo I, 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
vasculitides. 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
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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