Received: 7 May 2018 | Revised: 14 May 2018 | Accepted: 16 May 2018

DOI: 10.1002/ccr3.1631

CASE REPORT

WILEY Clinical Case Reports Open Access

Blistering eruptions with tissue eosinophilia in a child with IgA vasculitis

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Key Clinical Message

We present a child with bullous IgA vasculitis. Because skin biopsy showed epidermal vesicles with neutrophil infiltration and leukocytoclastic vasculitis in all layers of the dermis, with IgA deposits and tissue eosinophilia, extensive dermal infiltration of neutrophils may have led to both blistering eruptions and tissue eosinophilia in our patient.

KEYWORDS

bullous disorders, drug, eosinophil, infection, purpura, vasculitis

1 | INTRODUCTION

IgA vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is the most common childhood vasculitis that predominantly affects small vessels, and is characterized by purpura, abdominal pain, arthritis and renal involvement.[1] Although the exact etiology of IgAV remains unknown, environmental factors, including infectious agents, drugs and vaccinations, have been implicated as possible triggers of IgAV. The main cutaneous finding of IgAV is palpable purpura. Skin biopsy shows leukocytoclastic vasculitis (LCV) of the small vessels in the upper layer of the dermis with IgA and C3 deposition in the affected vessel walls.[1]

As with other skin manifestations of IgAV, blistering eruptions sometimes develop in adult patients, but they are rare in children.[2] Here, we describe a child with IgAV who developed blistering eruptions with tissue eosinophilia.

2 | CASE REPORT

A 5-year-old girl presented to us with vesicular purpura, abdominal pain, and tarry stool. She had been suffering from erythematous papules for 2 months and consulted the local dermatology clinic 5 days before admission to our hospital. She was suspected to have folliculitis, and treatment with oral cefdinir was initiated. She developed vesicular purpura and abdominal pain 1 day after initiation of cefdinir treatment. Because these symptoms and signs worsened and tarry stool developed, she was referred to our hospital. She had never been prescribed cefdinir before, although she had taken cefditoren pivoxil four times before without any adverse events. She had a history of bronchial asthma attacks from 2 years of age. Her maternal uncle had a past history of IgAV.

Physical examination revealed vesicular purpura with surrounding erythematous induration (Figures 1 and 2) on the arms, legs, left cheek and left ear, and abdominal pain and tenderness in the periumbilical area. Her blood pressure, pulse rate, and temperature were normal.

Laboratory studies revealed normal values for the following: complete blood cell count, platelet count, activated partial thromboplastin time, prothrombin time, electrolytes, liver enzymes, blood urea nitrogen, creatinine, urinalysis, antistreptolysin O, IgG, IgA, IgM, C3, C4, and CH50. Tests for hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, myeloperoxidase-antineutrophil cytoplasmic antibodies (ANCA), and proteinase 3-ANCA were negative. Her serum eosinophil count was 153/μL (2%, normal range 0.5%-6.6%). Her C-reactive protein level (1.20 mg/dL,

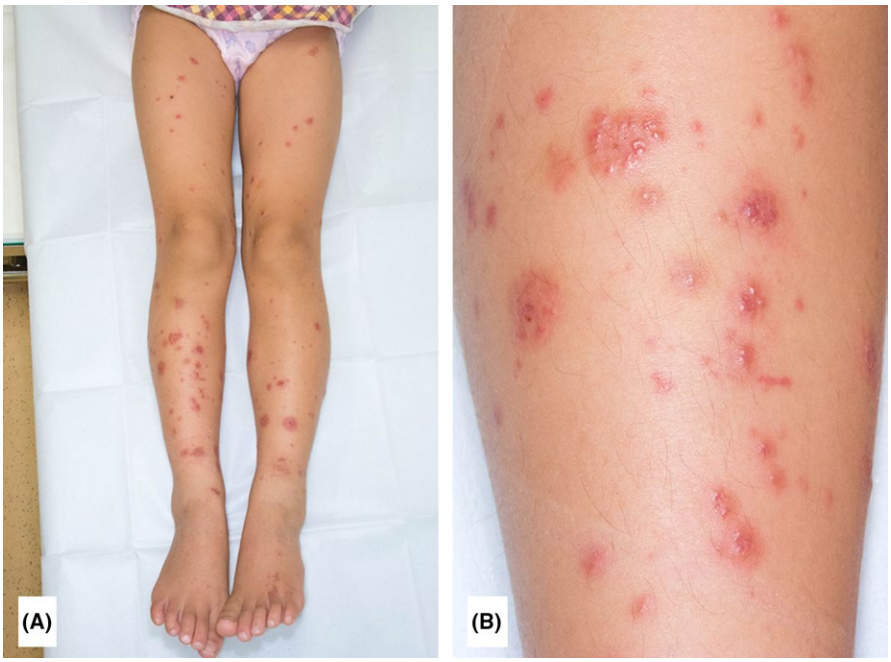

FIGURE 1 A, Vesicular purpura with surrounding erythematous induration on the legs. B, Close-up of lesions on the right leg

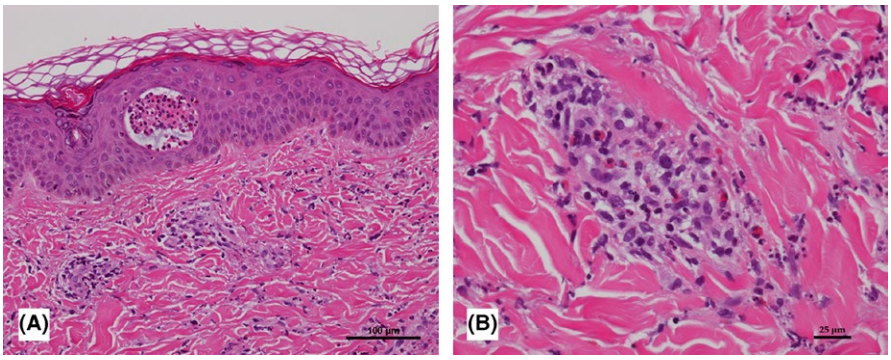

FIGURE 2 A, Hematoxylin and eosin staining of a skin biopsy specimen of a vesicular lesion shows an epidermal vesicle with neutrophil infiltration. B, Leukocytoclastic vasculitis of the small vessels with perivascular eosinophil infiltration

normal <0.31 mg/dL) and erythrocyte sedimentation rate (21 mm/1 h, normal <10 mm/1 h) were slightly increased, while her factor XIII activity was decreased (74%, normal >90%).

Skin punch biopsy of a fresh vesicular purpuric lesion showed epidermal vesicles with neutrophil infiltration (Figure 2A), and LCV of the small vessels with perivascular eosinophil infiltration in all the layers of the dermis (Figure 2B). The tissue eosinophilia ratio (the mean eosinophil score/the mean inflammatory density score), which was reported in a study by Bahrami et al,[3] was 5.80, indicating prominent tissue eosinophilia. Direct immunofluorescence studies revealed granular IgA (Figure 3A) and C3 (Figure 3B) staining of the vessel walls.

The patient was diagnosed with vesicular IgAV with prominent tissue eosinophilia. She discontinued oral cefdinir treatment and underwent intravenous prednisolone (2 mg/kg/d for 7 days, 1 mg/kg/d for 3 days and 0.5 mg/kg/d for 2 days), which promptly improved her abdominal pain and tarry stool, and her skin lesions completely disappeared 2 weeks later. Thereafter, she has experienced two episodes of nonvesicular purpura on the arms and legs 1 day following acute otitis media with oral cefditoren pivoxil treatment, and 2 days after upper respiratory tract infection without any drug usage, both of which subsided within 2 weeks without any medications. Urinalysis still remained normal 6 months after the onset of the illness on the latest outpatient examination.

3 | DISCUSSION

Our patient developed IgAV with blistering eruptions, while skin biopsy showed LCV of the small vessels in all the layers of the dermis with prominent tissue eosinophilia. Gration and Osakwe recently reported a case of a child with bullous IgAV whose skin biopsy showed pandermal LCV with tissue eosinophilia, histological findings similar to those of our patient.[4] Because LCV usually presents only in the superficial

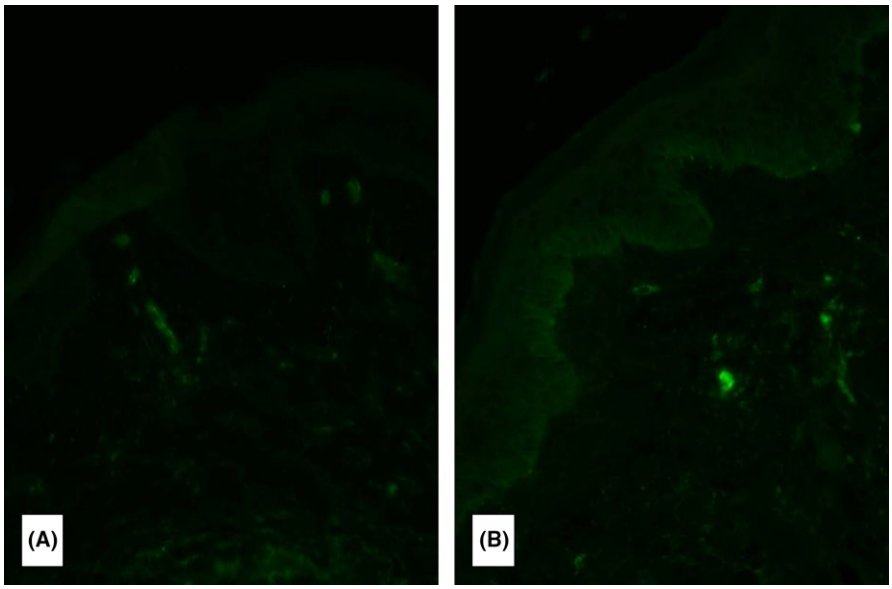

FIGURE 3 Direct immunofluorescence of a skin biopsy shows granular IgA (A) and C3 (B) staining of the vessel walls

layer of the dermis in IgAV, activated neutrophils infiltrated the skin more extensively in our patient and in the patient of Gration and Osakwe.

Blistering eruptions are rare in childhood IgAV, reported in only 1.5% of all patients.[2] However, they do not seem to have prognostic value, because they almost always spontaneously subside within 4 weeks.[2] The precise pathogenic mechanisms for the development of blistering eruptions in IgAV remain unclear; pressure or trauma, a pre-existing bullous condition, immunological dysregulation, and metalloproteinase (MMP)-9 and leukocyte elastase have been suggested as causes or triggers for this condition.[5] Kobayashi et al[6] reported that MMP-9 gelatinolytic activity was observed in the blister fluid of a patient with bullous IgAV, suggesting that MMP-9 derived from neutrophils might play an important role in blister formation. In this case, extensive infiltration of the skin by activated neutrophils may contribute to the development of blister formation in IgAV by MMP-9 secretion.

Tissue eosinophilia is rare in childhood IgAV,[7] and it is not mentioned in most textbooks or review articles regarding childhood IgAV.[1, 8] In contrast, Poterucha et al[9] reported that 35 of 68 (51%) adult patients with IgAV had tissue eosinophilia, and patients with tissue eosinophilia were less likely to have renal involvement. This study included 1 patient with drug-induced IgAV and 11 patients with IgAV induced by infection and antibiotic use. Based on these findings, the authors suggested that tissue eosinophilia might be a marker of drug-induced IgAV in this study population. In addition, Bataille et al[10] reported a case of an adult patient with vancomycin-induced IgAV whose skin biopsies showed LCV with tissue eosinophilia

Drug-induced vasculitis is the most common, accounting for about 20% of all cutaneous vasculitis.[11] Bahrami et al[3] reported that the mean tissue eosinophilia ratio was significantly higher in the drug-induced LCV group (5.20) than in the nondrug-induced LCV group (1.05) and proposed that a high degree of tissue eosinophilia in skin biopsies of purpuric lesions was a reliable indicator of drug-induced cutaneous small vessel vasculitis. Our patient had a high mean eosinophil ratio (5.80) in her skin biopsy, therefore, drugs may have led to IgAV in our patients. However, because the time that elapsed between the onset of vasculitis and drug use was very short for the first and second attacks of IgAV, despite no previous history of adverse events with these drugs, and because the third relapse occurred after only upper respiratory tract infection without any drug use, it cannot be concluded that drug use is as a cause of IgAV in our patient.

Heineke et al[12] recently proposed a multi-hit hypothesis to explain the systemic symptoms of IgAV and IgAV nephritis. In this hypothesis, IgA1 antibodies are generated against endothelial cells (antiendothelial cell antibodies [AECA]) by infectious pathogens, possibly influenced by genetics or molecular mimicry; IgA1 AECA bind to vascular endothelial cells; endothelial cells produce IL-8, inducing neutrophil migration; IgA1 complexes activate neutrophils via the IgA Fc receptor FcαRI; and finally, IgA-activated neutrophils release leukotriene B4 (LTB4), thereby attracting and activating other neutrophils in a positive feedback loop. LTB4 attracts and activates not only neutrophils, but also eosinophils, via a high-affinity receptor for LTB4, BLT1.[13] Furthermore, blood and urinary LTB4 levels were higher in children with IgAV than those in healthy controls in the active phase.[14] Based on these findings, tissue eosinophilia may also develop in nondrug-induced IgAV due to LTB4 secreted by neutrophils which are activated by infections.

In summary, we report a case of a child with IgAV who developed blistering eruptions. Extensive infiltration

of the skin by neutrophils which may be activated by infections or drug allergic reaction may have led to both blistering eruptions and tissue eosinophilia in our patient with IgAV.

CONFLICT OF INTEREST

There is no conflict of interest of all authors.

AUTHORSHIP

TW and ST: helped draft the manuscript and then revised the manuscript and gave final approval for the manuscript to be published and take full responsibility for the content of the paper.

CONSENT FOR PUBLICATION

Consents for publication were obtained from all authors.

INFORMED CONSENT

An informed consent for publication was obtained from patient's mother.

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How to cite this article: Watanabe T, Tsukano S. Blistering eruptions with tissue eosinophilia in a child with IgA vasculitis. *Clin Case Rep*. 2018;6:1422–1425. https://doi.org/10.1002/ccr3.1631