IgA Vasculitis in the Setting of Biologic Therapy for Psoriasis and Recurrent Cutaneous Methicillin-Resistant Staphylococcus aureus Colonization

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PRACTICE POINTS

- Biologic medications including adalimumab and more rarely secukinumab may be associated with leukocytoclastic vasculitis; a smaller subset of patients may experience IgA vasculitis.
- The IL-23 blocker ustekinumab may represent an ideal therapeutic agent when secukinumab-associated vasculitis is suspected. Because IL-23 is the main driver and sustainer of T_h17 cell differentiation, it may cease the main causative cytokine cascades “upstream.”

IgA vasculitis is a form of cutaneous small-vessel leukocytoclastic vasculitis (LCV) that has various triggers, including anti–tumor necrosis factor (TNF) α therapy. As the use of more targeted biologic therapies such as the IL-17 inhibitor secukinumab increases, so do reports of associated adverse events. Herein, we describe an uncommon case of IgA vasculitis in a man undergoing biologic therapy with adalimumab and secukinumab for psoriasis with recurrent cutaneous methicillin-resistant Staphylococcus aureus (MRSA) colonization. A review of the current literature also is provided.

Case Report

A 47-year-old man presented with a sudden-onset rash consisting of red bumps on the abdomen and legs that had been ongoing for several days. He had known psoriasis and psoriatic arthritis that had been well controlled with adalimumab for the last 18 months. He reported concurrent onset of nausea but denied fevers, chills, night sweats, unintentional weight loss, abdominal pain, and pruritus. He endorsed prior cutaneous infections of methicillin-resistant Staphylococcus aureus (MRSA). His medical history also included diabetes mellitus, hypertension, and obesity. His other medications included oral losartan-hydrochlorothiazide, amlodipine, naproxen, and atorvastatin.

Physical examination revealed numerous thin purpuric papules—some with adherent scale—distributed on the lower legs, extensor forearms, and abdomen. Abdominal lesions were confined to weight-related striae (Figure 1). The palms, soles, oral mucosa, and face were spared. Three punch biopsies were performed, including 1 for direct immunofluorescence (DIF), and the patient was instructed to apply clobetasol to the affected areas twice daily until further notice.

Pathology showed perivascular extravasation of erythrocytes, neutrophils, eosinophils, and leukocytoclasia surrounding blood vessels associated with fibrin (Figure 2). Direct immunofluorescence showed granular deposition of IgA, complement component 3, and fibrinogen in a superficial dermal vascular pattern (Figure 3). These results were consistent with IgA small-vessel vasculitis. One specimen was consistent with the patient’s known psoriasis.
Urinalysis revealed moderate hemoglobinuria, and urine microscopy showed 174 red blood cells per high-power field. Creatinine was high at 1.87 mg/dL (reference range, <1.34 mg/dL; patient’s baseline, 0.81 mg/dL) and glomerular filtration rate was low (42 mL/min, patient’s baseline, >60 mL/min [reference range, 90–120 mL/min]). Erythrocyte sedimentation rate (21 mm/h [reference range, 0–22 mm/h]) and C-reactive protein were elevated (2.2 mg/dL [reference range, 0.3–1.0 mg/dL]). Given his history of cutaneous MRSA infections, a bacterial culture swab was collected from the skin surface to check for colonization, which showed moderate growth of MRSA. Naproxen was discontinued over concern of worsening the patient’s renal status. The patient was instructed to rest at home with his legs elevated, wear compression socks when ambulatory, use chlorhexidine antiseptic daily as a body wash when showering, and apply mupirocin three times daily to the biopsy sites. He was referred to urology for his microhematuria, where cystoscopy revealed no abnormalities.

A month passed with no improvement of the patient’s cutaneous vasculitis, and his psoriatic arthritis worsened without his usual use of naproxen. He developed abdominal pain and loss of appetite. A prednisone taper was ordered starting at 40 mg/d (28.8 mg/kg), which provided relief of the skin and joint symptoms only until the course was completed 12 days later.

Five weeks after the initial presentation, the patient returned with a more severe eruption consisting of innumerable purpuric papules that coalesced in plaques on the abdomen, arms, and legs. He also had erythematous facial pustules and mild palmar petechiae (Figure 4). Three biopsies were performed, including 1 for DIF and 1 from a pustule on the forehead. Histology and DIF were again consistent with IgA small-vessel vasculitis. The forehead biopsy was compatible with steroid acne (attributed to recent prednisone use) and psoriasis.
Rheumatology was consulted, and adalimumab was discontinued 6 weeks after the initial presentation out of concern for drug-induced cutaneous vasculitis. Vasculitis work-up was unremarkable, including antineutrophil cytoplasmic antibodies, rheumatoid factor, cyclic citrullinated peptide, and serum protein electrophoresis. Oral dapsone was started at 100 mg/d, with the tentative plan of starting secukinumab if cutaneous symptoms improved. For 3 weeks, the patient’s cutaneous symptoms steadily improved.

Nine weeks after initial presentation to dermatology (3 weeks after discontinuing adalimumab) the patient self-administered his first dose of secukinumab at home. Several hours later, he reported sudden reappearance of vasculitis. He denied diarrhea, abdominal pain, bowel movement urgency, fevers, fatigue, and unintentional weight loss. Antistreptolysin O and hepatitis A antibodies were negative. He was instructed to hold secukinumab indefinitely.

Four weeks after his only secukinumab injection, the patient reported another episode of acute worsening cutaneous symptoms. A 4-week prednisone taper starting at 40 mg/d was ordered. Computed tomography of the chest, abdomen, and pelvis to rule out internal malignancy was unremarkable. Around this time, the patient reported major emotional distress related to an unexpected death in his family, which added to a gradual increase in his stress level related to the COVID-19 pandemic.

Three weeks later, dapsone was increased to 100 mg twice daily on account of the patient’s adiposity and lack of cutaneous improvement on the lower dose. Subsequently, the vasculitis rapidly improved for 2 weeks. The patient then reported symptoms of headache, dizziness, and chills. He was tested for COVID-19 and was negative. Six weeks after increasing the dapsone dose (5 months after initial presentation), the skin was normalizing, showing only faintly hyperpigmented macules confined to areas of resolved vasculitis (forearms, abdomen, legs).

The patient had been on dapsone 100 mg twice daily for 3 months when he was started on ustekinumab (90 mg at weeks 0 and 4, with planned doses every 12 weeks) for psoriatic arthritis in hopes of withdrawing dapsone. His cutaneous symptoms have remained well controlled on this regimen for 18 months. Lowering of dapsone below 100 mg daily has resulted in recurrent mild vasculitis symptoms; he now maintains the once-daily dosing without negative side effects.

**Comment**

IgA vasculitis is a form of cutaneous small-vessel leukocytoclastic vasculitis (LCV) characterized by episodes of palpable purpura on the extensor surfaces of the arms and legs that may be associated with arthritis, abdominal pain, and/or hematuria. Although vasculitis is a known potential adverse effect of anti–tumor necrosis factor (TNF) α therapy, cases of adalimumab-induced IgA vasculitis are uncommon. As use of more targeted therapies for psoriasis and psoriatic arthritis, such as the IL-17 inhibitor secukinumab, increases so do reports of associated adverse events. Of 6 previously reported cases of secukinumab-associated vasculitis, at least 4 were IgA vasculitis (Table). Another case described one patient with rheumatoid arthritis undergoing secukinumab treatment who experienced necrotizing glomerulonephritis; however, the authors concluded secukinumab likely was not causative in that case, as serologies and urinalyses suggested gradual onset of the process prior to initiating the medication.7

The exact pathogenesis of IgA vasculitis is unclear, but a prevailing theory involves the dysregulation of IgA synthesis and metabolism. Other than increased serum levels of transforming growth factor β, which is a major stimulating factor for IgA production, it also has been hypothesized that the presence of aberrantly hypoglycosylated IgA exposes an autoepitope for recognition by other pathogenic IgG and IgA, leading to the formation of large immune complexes that can readily deposit in postcapillary venules. The deposition of IgA immune complexes in postcapillary venules and the subsequent activation of the complement system causes...
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IgA vasculitis is a rare disorder characterized by inflammation of small vessels, often involving the skin, causing painful nodules and ulcerations. In this case report, we describe a patient with IgA vasculitis that developed after starting secukinumab, a medication used to treat psoriasis.

**Pathogenesis:**
- The TH17 cytokine network is implicated in the pathogenesis of IgA vasculitis. TH17 cells are a subset of T helper cells that produce proinflammatory cytokines, including IL-17, which can recruit neutrophils and monocytes to sites of inflammation.
- Secukinumab is a monoclonal antibody that inhibits IL-17, leading to a reduction in TH17 cell numbers and downstream proinflammatory cytokines.
- The re-emergence of the condition after restarting secukinumab suggests a potential role for TH17 cells in the maintenance of IgA vasculitis.

**Clinical Course:**
- The patient's vasculitis resolved after discontinuing secukinumab and initiating prednisone and colchicine. This highlights the importance of considering TH17 cell metabolism in the management of IgA vasculitis.
- Given the established safety of IL-23 inhibitors and that ustekinumab has been suggested by other authors as an alternative treatment, it may be worth considering 

**Conclusion:**
- Multifactorial processes likely contribute to the etiology of IgA vasculitis, and treatment strategies should be individualized.
- Secukinumab may induce or exacerbate IgA vasculitis, and clinicians should be aware of this potential complication.

**References:**
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<td>Reverte et al(^1) (2019)</td>
<td>43/M</td>
<td>Psoriasis</td>
<td>PUVA, cyclosporine A, acitretin, adalimumab, etanercept</td>
<td>3 mo after starting secukinumab</td>
<td>Petechial purpura on the legs, ascending progression</td>
<td>DIF negative, diagnosis of IgA vasculitis based on EULAR criteria</td>
<td>Abdominal pain, joint pain in wrists and MCPs, acute pancolitis with bleeding suffusions</td>
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<td>Chelli et al(^2) (2020)</td>
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<td>Necrotic purpura of the legs</td>
<td>DIF negative; diagnosis of IgA vasculitis probable based on EULAR criteria</td>
<td>Fever, diarrhea, colitis, and terminal ileitis; elevated CRP, positive ANA</td>
<td>Prednisone + colchicine (both &gt;6 mo), then prednisone replaced with MTX; no recurrence after 2 mo</td>
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<td>da Silva Cendon Duran and Santiago(^3) (2020)</td>
<td>39/F</td>
<td>Reactive arthritis, history of IgA vasculitis on infliximab, HLA-B27</td>
<td>NSAIDs, prednisone, sulfasalazine, MTX, infliximab, azathioine</td>
<td>5 y of infliximab: IgA vasculitis, short break in symptoms (unspecified time), then relapse; started secukinumab; improved for 2 mo, then IgA vasculitis relapsed</td>
<td>Painful, ulcerating, purpuric papules on the lower legs and feet</td>
<td>DIF positive</td>
<td>Peripheral arthritis, positive c-ANCA</td>
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<td>No systemic involvement</td>
<td>Topical steroids, withdrawal of secukinumab; regression of purpuric lesions</td>
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<td>Psoriasis, psoriatic arthritis, HLA-B27</td>
<td>Sulfasalazine, MTX, infliximab, golimumab</td>
<td>18 mo after starting secukinumab</td>
<td>Palpable purpura on the legs, psoriasis on entire body</td>
<td>DIF not performed; serum IgA: 5.7 g/L (reference range, 0.7–4.0 g/L)</td>
<td>Elevated CRP, leukocyturia, proteinuria, erythrocyturia</td>
<td>MTX + methylprednisolone; resolution and follow-up time not specified</td>
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\(^a\) Histology in all cases was consistent with LCV.
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<td>8 mo after starting</td>
<td>Painful erosions and ulcers on the buttocks; palpable purpura of the axillae and popliteal fossae</td>
<td>DIF not performed; serum IgA: 8.13 g/L (reference range, 0.7–4.0 g/L)</td>
<td>Fever</td>
<td>Prednisone (×1 mo) + cyclosporine; resolved in 3 mo, no recurrence after 7 mo</td>
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<td>Current case</td>
<td>47/M</td>
<td>Psoriasis, psoriatic arthritis</td>
<td>Apremilast, adalimumab</td>
<td>18 mo of adalimumab: IgA vasculitis; same-day recurrence after starting seukinumab</td>
<td>Purpuric papules on abdomen, arms, and legs; palmar petechiae; DIF positive</td>
<td>Nausea, abdominal pain, peripheral arthritis, hemoglobinuria, low GFR, high ESR and CRP</td>
<td>Prednisone + dapsone, then ustekinumab; no recurrence after 9 wk</td>
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Abbreviations: ANA, antineutrophil cytoplasmic antibodies; c-ANCA, c-antineutrophil cytoplasmic antibodies; CRP, C-reactive protein; DIF, direct immunofluorescence; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; F, female; GFR, glomerular filtration rate; HS, hidradenitis suppurativa; LCV, leukocytoclastic vasculitis; M, male; MOPs, metacarpophalangeal joints; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PUVA, psoralen plus UVA.

*Histology in all cases was consistent with LCV.
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represent an ideal treatment option for patients in whom adalimumab- or secukinumab-associated vasculitis is suspected. Further research is needed given the complex interplay of so many variables and the increasingly common reports of adverse cutaneous events associated with these drugs.1-6,10

REFERENCES