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.

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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 leukocytoclasis 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.

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The authors report no conflict of interest.

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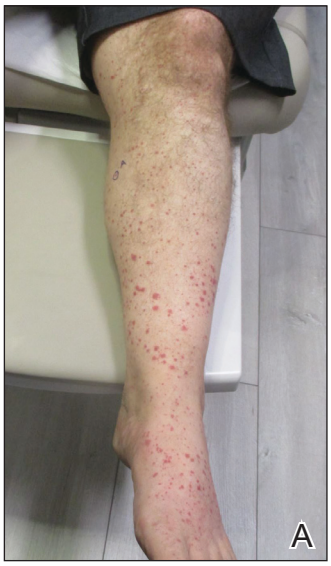

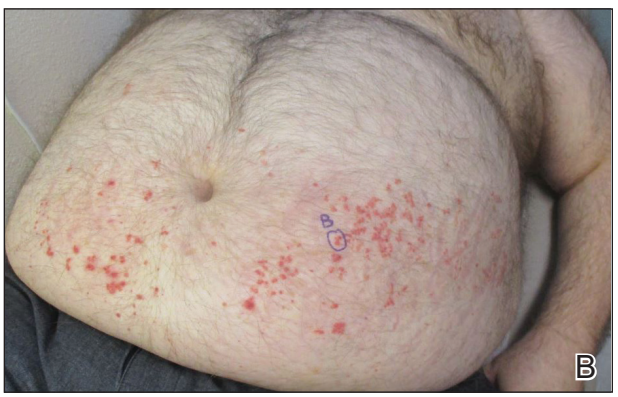

FIGURE 1. A and B, Numerous thin purpuric papules distributed on the left lower leg and abdomen, where the lesions were confined to weight-related striae.

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.

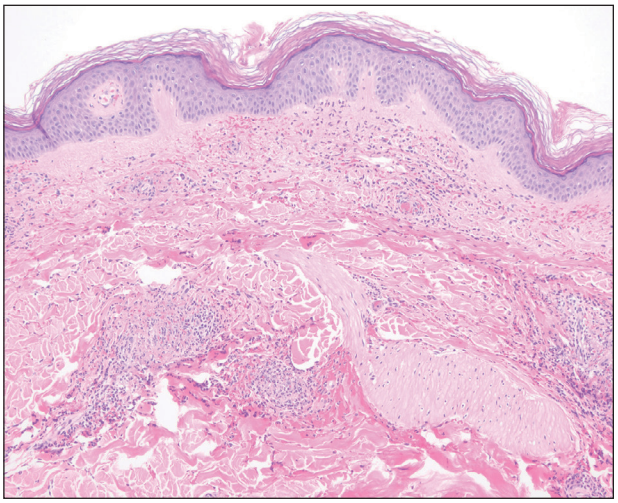

FIGURE 2. A biopsy from the left dorsal forearm showed superficial dermal perivascular extravasation of erythrocytes, neutrophils, eosinophils, and leukocytoclasis surrounding blood vessels associated with fibrin (H&E, original magnification ×10).

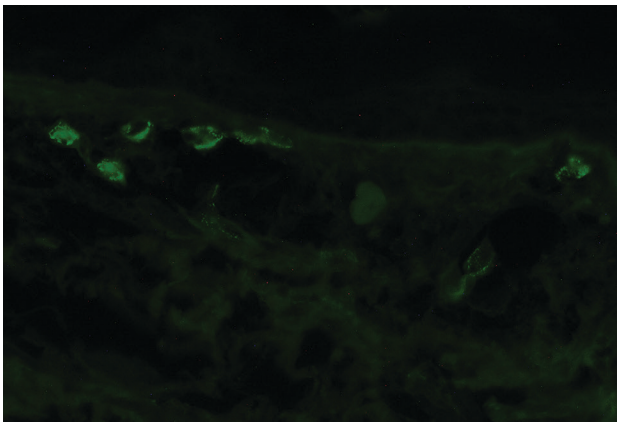

FIGURE 3. Direct immunofluorescence obtained from perilesional skin of the left forearm showed granular deposition of IgA, complement component 3, and fibrinogen in a superficial dermal vascular pattern (IgA, original magnification ×40).

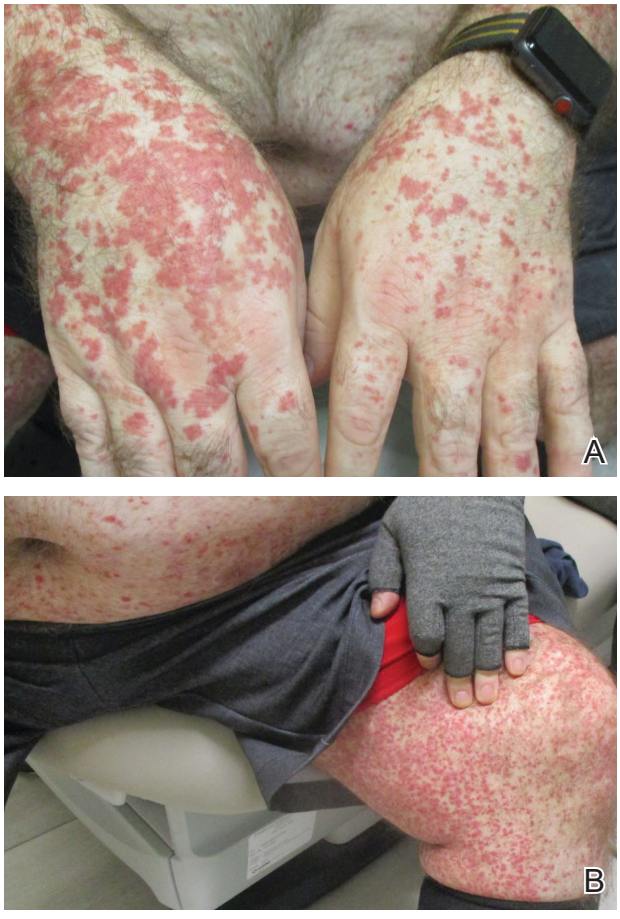

FIGURE 4. A and B, Numerous purpuric thin papules coalescing in plaques on the dorsal hands and left medial thigh.

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).[1-6] 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

direct damage to the endothelial cells of vessel walls. This complement activation is evidenced by vascular complement component 3 deposition on DIF (a nonspecific feature of LCV). Chemotaxis of neutrophils ensues, followed by their firm adherence and transendothelial migration (mediated by monocyte chemoattractant protein 1 [MCP-1]). Neutrophil degranulation releases reactive oxygen species and cytokines, which in turn recruit additional leukocytes to the area of inflammation, subsequently undergoing degeneration (leukocytoclasis). Microvascular permeability also is enhanced by MCP-1, allowing exudation of serum, erythrocytes, and fibrin. In the setting of elevated circulating TNF and IL-1, endothelium is stimulated to activate the intrinsic and extrinsic coagulation pathways. This decreases endothelial fibrinolytic activity, leading to thrombosis. The high venous pressure and low fibrinolytic activity in the lower legs explains why vasculitic lesions often are confined to or begin in this distribution.[1,8-10]

There also are noteworthy roles for cytokines in LCV. Circulating transforming growth factor β and IL-6—which are necessary for development of T helper 17 (T_H17) cells and production of IL-17—are higher in patients with LCV compared to controls. Peripheral blood monocytes in patients with LCV demonstrate higher production of IL-17. Once T_H17 cells develop, their survival and phenotype are maintained by IL-23 (considered the master regulator of T_H17 differentiation). IL-17 is a potent chemoattractant of IL-8 (CXCL8) and MCP-1, both of which promote neutrophil-mediated perivascular inflammation. The IL-23 and IL-17 pathways implicated in the pathogenesis of psoriasis also cause neutrophil activation and upregulate transcription of proinflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α), which overlap with those implicated in LCV. Autoimmune disease generally entails some positive feedback loop of progressively severe self-recognition and tissue destruction by the immune system. These shared cytokinetic processes may explain how the internal environment of psoriasis could perpetuate IgA vasculitis.[1,2,8,10-12]

The mechanisms underlying vasculitis associated with adalimumab are unclear, but hypotheses involve direct toxicity on vessels, capillary deposition of anti-TNF/TNF immune complexes, or an inflammatory process resulting in autoantibodies. Similar hypotheses are posited for secukinumab-associated vasculitis, including deposition of secukinumab–IL-17 complexes. Anti–TNF-α medications may increase T_H17 cell numbers, leading to increased production of IL-22 and a resultant immunologic microenvironment conducive to vasculitis. All 6 published cases of secukinumab-associated vasculitis that we found had received prior treatment with a TNF-α blocker, but only 1 had occurrence of vasculitis during that treatment.[1-6,10]

In the 6 cases we reviewed, the time from starting secukinumab to onset of vasculitis ranged from 1 to 18 months. Our patient's same-day re-emergence of vasculitis after his first secukinumab dose was so acute that we were skeptical of secukinumab as a potential trigger; this may simply have been coincident to the natural waxing and waning of the vasculitis (although onset of IgA vasculitis within 1 day of starting anti–TNF-α therapy has been reported).[1-6,13]

Specific associations of IgA vasculitis are many and can include bacterial organisms such as *Helicobacter pylori*, streptococci, and staphylococci. Although internal mucous membrane infections are considered more linked because of the surveillance role of IgA predominantly in mucosal tissues, it is possible that our patient with cutaneous MRSA harbored the same within the nasal mucosa. Our patient also received multiple vaccinations outside our department throughout his clinical course (2 hepatitis B and 1 pneumococcal conjugate), which are known potential triggers for vasculitis. Psychological stress is a known trigger for psoriasis, and given the cytokinetic relationship of psoriasis to vasculitis described previously, it may have indirectly contributed to vasculitis in our case. The anxiety associated with being immunosuppressed during the COVID-19 pandemic and bereavement of losing a family member may have contributed to the refractory nature of our patient's condition. Renal involvement is relatively common in adults with IgA vasculitis and so should be ruled out, as should occult internal malignancy.[8,10,14]

It is unclear which of the above factors was causative in our case, but a multifactorial process is likely. Treatment of monoclonal antibody–associated vasculitis entails investigating for triggers and systemic involvement, removing the most likely culprit, quelling the vasculitis acutely, avoiding known potential exacerbators, and introducing an alternative long-term immunomodulant. In all 6 reported similar cases, discontinuation of secukinumab and initiation of prednisone or colchicine led to resolution.[1-6] Dapsone also is acceptable for acute control of IgA vasculitis, although this medication is highly lipid soluble and penetrates well into various tissues.[15] Thus, lower doses may prove ineffective for obese patients, as was demonstrated in our case. Given the known potential of vaccinations, infections, and other factors (eg, alcohol, penicillin) to trigger IgA vasculitis, these should be avoided.[10]

Blockade of IL-23 with ustekinumab has been suggested by other authors encountering secukinumab-associated vasculitis, as IL-23 is the main driver and sustainer of T_H17 cell differentiation.[8] Although 6 previously reported cases of secukinumab-associated vasculitis achieved resolution without long-term recurrence, none did so using an IL-23 inhibitor (nor had any of the described patients received IL-23 inhibitors previously).[1-6] Given the established safety of IL-23 inhibitors and that they theoretically are well suited for this unique circumstance (by ceasing the main causative cytokine cascades "upstream") and were efficacious in quickly resolving our patient's vasculitis, we suggest that ustekinumab may

Reported Cases of IgA Vasculitis Associated With Secukinumab[a]

Reference (year)	Patient age, y/ sex	Known disease(s)	Prior treatments	Time of onset of vasculitis	Cutaneous signs	Presence of IgA	Systemic involvement	Treatment and follow-up
Reverte et al[1] (2019)	43/M	Psoriasis	PUVA, cyclosporine A, acitretin, adalimumab, etanercept	3 mo after starting secukinumab	Petechial purpura on the legs, ascending progression	DIF negative, diagnosis of IgA vasculitis based on EULAR criteria	Abdominal pain, joint pain in wrists and MCPs, acute pancolitis with bleeding suffusions	Colchicine (×3 mo) + etanercept; follow-up time not specified
Chelli et al[2] (2020)	54/F	Palmoplantar pustular psoriasis, psoriatic arthritis	MTX, then MTX + adalimumab	1 mo after starting secukinumab for psoriasis and pustular purpura; developed LCV 1 mo after treatment discontinuation	Necrotic purpura of the legs	DIF negative; diagnosis of IgA vasculitis probable based on EULAR criteria	Fever, diarrhea, colitis, and terminal ileitis; elevated CRP, positive ANA	Prednisone + colchicine (both >6 mo), then prednisone replaced with MTX; no recurrence after 2 mo
da Silva Cendon Duran and Santiago[3] (2020)	39/F	Reactive arthritis, history of of IgA vasculitis on infliximab, HLA-B27	NSAIDs, prednisone, sulfasalazine, MTX, infliximab, azathioprine	5 y of infliximab: IgA vasculitis, short break in symptoms (unspecified time), then relapse; started secukinumab: improved for 2 mo, then IgA vasculitis relapsed	Painful, ulcerating, purpuric papules on the lower legs and feet	DIF positive	Peripheral arthritis, positive c-ANCA	Prednisone, then etanercept; no recurrence after 3 y
Bostan et al[4] (2021)	56/M	HS	Adalimumab	9 mo of adalimumab, switched to secukinumab with LCV onset during second month	Violaceous/dark red pustular lesions and palpable purpura on bilateral lower legs	DIF negative	No systemic involvement	Topical steroids, withdrawal of secukinumab; regression of purpuric lesions
Perkovic et al[5] (2021)	39/F	Psoriasis, psoriatic arthritis, HLA-B27	Sulfasalazine, MTX, infliximab, golimumab	18 mo after starting secukinumab	Palpable purpura on the legs, psoriasis on entire body	DIF not performed; serum IgA: 5.7g/L (reference range, 0.7–4.0 g/L)	Elevated CRP, leukocyturia, proteinuria, erythrocyturia	MTX + methylprednisolone; resolution and follow-up time not specified

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TABLE (continued)

Reference (year)	Patient age, y/ sex	Known disease(s)	Prior treatments	Time of onset of vasculitis	Cutaneous signs	Presence of IgA	Systemic involvement	Treatment and follow-up
Villani et al[6] (2021)	28/F	Psoriatic arthritis	MTX, adalimumab	8 mo after starting secukinumab	Painful erosions and ulcers on the buttocks; palpable purpura of the axillae and popliteal fossae	DIF not performed; serum IgA: 8.13 g/L (reference range, 0.7–4.0 g/L)	Fever	Prednisone (×1 mo) + cyclosporine; resolved in 3 mo, no recurrence after 7 mo
Current case	47/M	Psoriasis, psoriatic arthritis	Apremilast, adalimumab	18 mo of adalimumab: IgA vasculitis; same-day recurrence after starting secukinumab	Purpuric papules on abdomen, arms, and legs; palmar petechiae	DIF positive	Nausea, abdominal pain, peripheral arthritis, hemoglobinuria, low GFR, high ESR and CRP	Prednisone + dapsone, then ustekinumab; no recurrence after 9 wk

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; MCPs, metacarpophalangeal joints; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PUVA, psoralen plus UVA.

[a]Histology in all cases was consistent with LCV.

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]

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