SKIN

BRIEF ARTICLE

Etanercept-Induced IgA Vasculitis: A Case Report

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ABSTRACT

Introduction: IgA vasculitis is a subtype of leukocytoclastic vasculitis. Approximately 90% of cases of IgA vasculitis are seen in the pediatric population. Causes of IgA vasculitis may be idiopathic or may be secondary to infections or medications. Etanercept has been rarely associated with IgA vasculitis.
Case presentation: A 59-year-old female presented with a 2-year history of red bumps on the bilateral lower extremities. She noted that after etanercept administration she would get new lesions and the existing lesions would be more red and painful. Examination showed red-to-violaceous purpuric papules on the bilateral lower extremities and a few purpuric papules on the arm and abdomen. A biopsy of the lesion showed leukocytoclastic vasculitis. Direct immunofluorescence showed granular deposition of IgA and C3 within small vessels, consistent with IgA vasculitis.
Conclusion: IgA vasculitis is a serious illness that may be associated with systemic organ involvement. It can lead to chronic renal insufficiency and require dialysis. Identifying an underlying etiology may allow treatment that resolves this condition. We identified a patient whose disease was exacerbated by etanercept therapy and was “80%” better 4 weeks after stopping etanercept. She had complete resolution of remaining lesions within 2 weeks of starting colchicine therapy. She remained symptom-free at 11 months after discontinuation of etanercept therapy. As biologic therapy use becomes increasingly prevalent, associated adverse events are expected to similarly become more frequent. When a cause can be identified, a patient like our patient can be cured.

INTRODUCTION

Etanercept is a tumor necrosis factor (TNF) receptor fusion protein acting as a soluble TNF receptor.[1-3] FDA-approved indications for etanercept include rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.[3] Commonly reported side effects of the medication include injection site reactions, headaches, and diarrhea.[4] More rare and severe adverse effects include infections, exacerbating congestive heart failure, and hematological abnormalities.[4] With the increased use of TNF inhibitor therapies rare immunologic adverse events have been reported.[1,2,5]

Leukocytoclastic vasculitis (LCV) is a form of small vessel vasculitis.[1] IgA vasculitis is a distinct form of LCV with IgA-dominant immune deposition in the vessel walls.[6-8] IgA vasculitis presents with the classic tetrad of

palpable purpura, arthritis, abdominal and renal involvement.[1,6,7]

IgA vasculitis in adults is rare and is often idiopathic.[7] In adults, IgA vasculitis may be more severe than in children with a higher risk of progression to chronic renal failure.[5,6] In this case study we report a case of IgA vasculitis due to Etanercept.

CASE REPORT

A 57-year-old female with a history of RA, on etanercept and methotrexate, presented with a 2-year history of a skin eruption on the legs. She complained of developing red pruritic bumps that would subsequently become painful and ulcerate on her legs. Her rash would predictably flare, becoming more painful, redder, and more numerous, with her etanercept injections. She denied any fevers, abdominal pain, chest pain, leg swelling, shortness of breath, blood in urine or stool, or new or worsening joint pains.

Examination showed scattered palpable purpuric papules in various stages of evolution on the bilateral lower extremities (**Figure 1**). She had a few purpuric papules on the arms and abdomen. She had no synovitis, tenosynovitis, or conjunctivitis. Her complete blood count and complete metabolic were within normal limits. Her urinalysis was negative for RBC casts or proteinuria. She had an elevated ESR (28 mm/hr, URN 20 mm/hr) and CRP (0.58 mg/dL, URN 0.3 mg/dL).

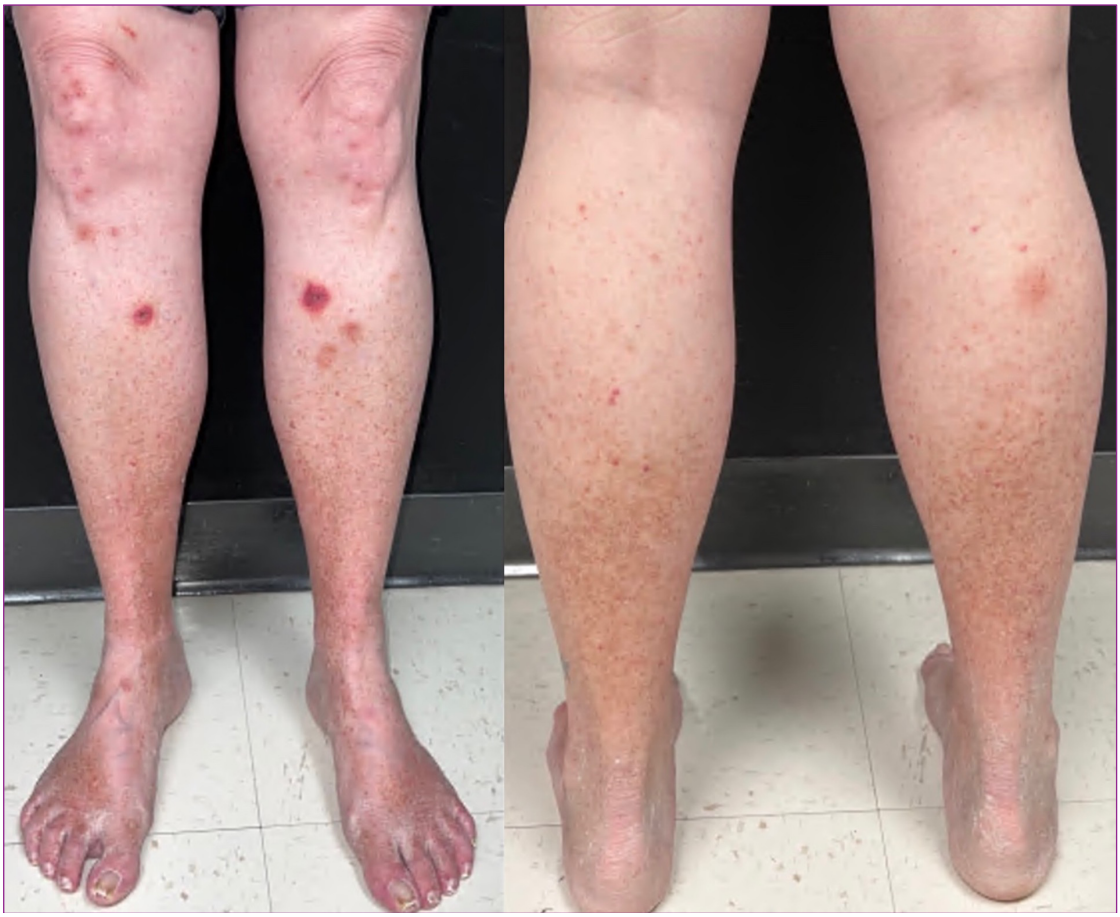

Figure 1. Scattered palpable purpura on the bilateral lower extremities with hyperpigmented tan-brown macules coalescing into patches from prior inflammatory lesions.

Punch biopsies were performed. The H&E showed a perivascular mixed infiltrate within and around the walls of vessels with fibrin deposition within the vessel walls (**Figure 2**). Direct immunofluorescence showed granular deposition of IgA and C3 within small caliber vessels which was consistent with IgA vasculitis (**Figure 3**).

Her etanercept was discontinued. Within 4 weeks of discontinuing the etanercept, she reported that she did not get any new lesions and had “80%” improvement. She was then started on colchicine with complete resolution of her remaining lesions within 2 weeks. After the complete resolution of the lesions, the patient discontinued her colchicine. Her RA therapy was changed to abatacept. 11 months following discontinuation of etanercept the patient remained clear without any new lesions.

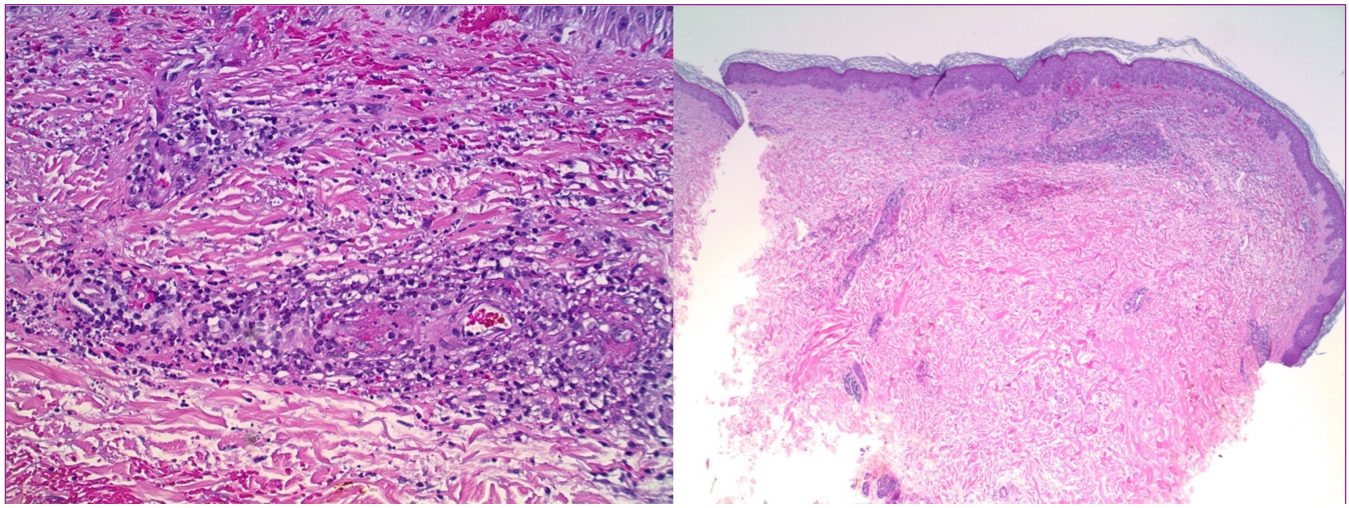

Figure 2. (A) and (B) Perivascular mixed inflammatory infiltrate with neutrophils, lymphocytes, histiocytes, and scattered eosinophils present around as well as within vessel walls. Fibrin deposition within the walls of vessels as well as extravasated red blood cells.

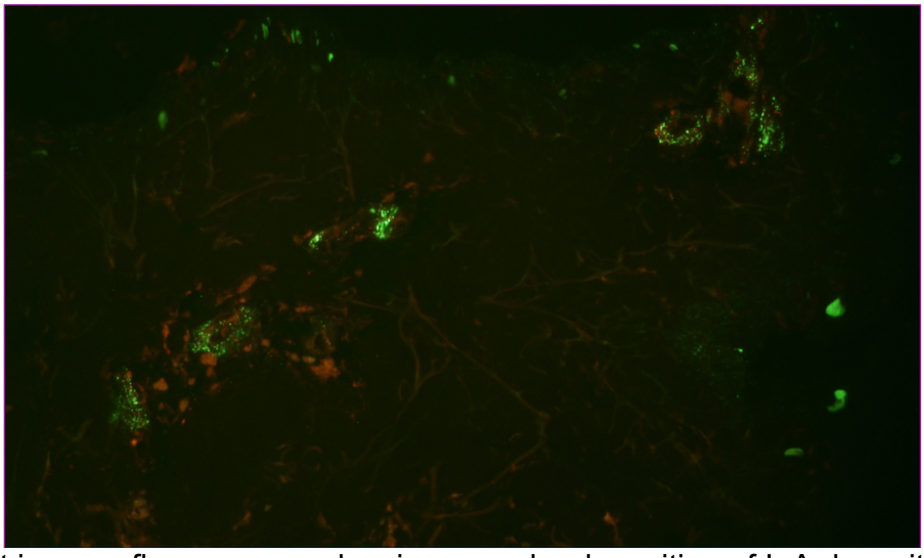

Figure 3. Direct immunofluorescence showing granular deposition of IgA deposition within small vessels.

DISCUSSION

The first reported case of etanercept-induced IgA vasculitis was in a patient being treated for psoriasis.[4] Other cases include axial spondylarthritis, psoriasis, and RA.[4,9,10] A systemic literature review identified 18 cases of etanercept-induced vasculitis.[5] Among these cases only 5 cases of IgA vasculitis were reported.[5] A retrospective study of the BIOGEAS registry investigating nearly 13,000 autoimmune cases in patients exposed to biologic therapy identified 291 cases of vasculitis.[11] The majority (n=232, 80%) of these patients had RA or JIA.[11]

A drug causality study investigated the causes of IgA vasculitis in a combined data set that included the French pharmacovigilance database and the WHO global individual case safety report database.[8] The results of their study showed that the most common etiology were vaccines (24%), and antibiotics (21%), followed by TNF-alpha inhibitors (8%).[8] Of note, in this study adalimumab and infliximab were reported to cause IgA vasculitis while etanercept was not reported.[8]

As is seen in this case, in patients who have drug-induced vasculitis, cessation of inciting medication may lead to the resolution of symptoms.[5,8] Additionally, those with drug-induced vasculitis are more likely to have skin-limited disease.[8] However renal involvement may be present in up to 1/3 of cases.[8]

While TNF-alpha inhibitors may incite LCV, not all patients who have the inciting medication discontinued have complete resolution of their vasculitis.[1,12] One study using the FDA adverse events reporting system noted that 62.8% (22/35) had complete or marked improvement in lesions after discontinuation of TNF-alpha inhibitor therapy.[1] 8.6% (3/35) of these patients were on etanercept and had skin lesions that persisted despite discontinuation of therapy.[1] Rechallenging these patients with a TNF-alpha inhibitor may cause recurrence of their vasculitis.[1,5] There were 6 patients with documented recurrence with rechallenge and 3 patients that had a negative rechallenge.[1] A systemic analysis using the Preferred reporting items for systematic reviews and metanalysis investigated vasculitis induced by biologics including TNF-alpha inhibitors, secukinumab, rituximab, abatacept, ustekinumab, and tocilizumab.[5] 23 patients were rechallenged with a different biologic.[5] 4 of these patients had recurrence of the vasculitis.[5] 10 patients were challenged with the same biologic.[5] 7 of these patients had a recurrence of the vasculitis.[5] 6 patients were maintained on therapy with 1 having worsening of the vasculitis and 5 with improvement in their vasculitis.[5]

CONCLUSION

LCV can be due to medications, illnesses or may be idiopathic.[7] When a cause is identified, patients like in this case can be cured.[1,5] This case presents a rare adverse event of IgA vasculitis induced by etanercept that resolved with withdrawal of the inciting medication. While more common in pediatric patients after an upper respiratory infection, when IgA vasculitis is seen in adults, it often has a more severe disease course.[5,6] TNF-alpha inhibitors are a rare cause of LCV.[1,5,8,10,12-14] Rarely, Etanercept has been associated with IgA vasculitis. 5 cases of etanercept-induced IgA vasculitis were noted based on systemic review.[5] A PubMed search for “IgA vasculitis” “Etanercept” and “Henoch-Schoenlein purpura” showed 5 case reports in the English language. As biologic therapies become increasingly prevalent,

associated adverse events are expected to similarly become more common. These adverse events must be recognized for optimal management.

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