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CASE REPORT

A Rare Case of Leukocytoclastic Vasculitis Associated With Infliximab

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Infliximab is a chimeric monoclonal antibody to tumor necrosis factor-α used commonly in several autoimmune conditions including Crohn's disease. We present a case of a 33-year-old man with inflammatory ileocolonic Crohn's disease who developed biopsy-proven leukocytoclastic vasculitis (LCV) exacerbated by a rechallenged dose of infliximab after years of tolerating the drug. To our knowledge, this is the first reported case of infliximab-associated LCV that occurred years after initiation of the drug. This case highlights that LCV can be a potential adverse reaction of infliximab, and health-care providers should consider a change in therapy.

Introduction

Infliximab (IFX), a chimeric monoclonal antibody to tumor necrosis factor-α (TNF-α), is a biologic used to treat several autoimmune diseases including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. IFX is commonly used as first-line therapy in Crohn's disease (CD) and ulcerative colitis. It has also been shown to be safe and effective through pregnancy and breastfeeding.[1] Adverse events previously reported with IFX include infection, melanoma skin cancer, lymphoma, psoriasiform or eczematous lesions, and lupus-like reaction.[2] In general, IFX is well tolerated in short-term and long-term follow-up.[2,3]

Hypersensitivity vasculitis (HV) is a small-vessel vasculitis typically associated with a drug or infection but can also be idiopathic. Leukocytoclastic vasculitis (LCV) is the histologic diagnosis of HV, as the term "leukocytoclasis" refers to neutrophil degeneration due to immune complex deposition in the dermal capillaries and venules resulting in vessel damage, cellular infiltrates, and cytokine release.[4,5] HV typically presents as palpable nonpruritic purpura over the bilateral lower extremities and buttocks. Systemic symptoms associated with HV include low-grade fevers, malaise, myalgias, and arthralgias. A multiorgan disease is associated with a more severe disease course.

Here, we present a unique and rare case of a young man with CD who developed IFX-associated HV with biopsy-proven LCV after 13 years of stability on the drug.

Case

A 33-year-old man on IFX with inflammatory ileocolonic CD with perianal involvement presented with arthralgias, petechiae, and purpura. Three months prior, he attended an outdoor wedding after which he noticed small, painless, nonpruritic petechiae over his bilateral legs (Figure 1). He had not taken any new medications and was otherwise in his usual state of health. Over the next 2 weeks, the petechiae progressed to palpable purpura extending to his bilateral thighs. He also developed malaise and severe arthralgia of his bilateral hips, knees, and Achilles tendons. He went to an urgent care clinic where he was diagnosed with a chigger rash and tendonitis and was prescribed a low-dose methylprednisolone pack with minimal alleviation of the arthralgias or purpura. Several days later, he received his scheduled IFX infusion after which his arthralgias worsened, and he developed new petechiae over his bilateral elbow.

He was evaluated by a dermatologist who performed shave biopsies of the lesions, with histologic findings consistent with LCV (Figure 2). A rheumatologic workup revealed a positive speckled antinuclear antibody pattern with a 1:80 titer as well as negative anti-double-stranded DNA, anti-Smith, anti-Sjogren's-syndrome-related antigen A and B, anti-topoisomerase I (Scl70), antiribonucleoprotein, anti-IFX, and anti-Lyme antibodies. Erythrocyte sedimentation rate, C-reactive protein, C3, and C4 levels were within normal limits.

Given the biopsy-proven LCV and worsened arthralgias and purpura immediately after his routine IFX infusion, he was diagnosed with IFX-induced LCV. After holding IFX, his symptoms improved within 2 weeks. The patient was later switched to risankizumab, an anti-interleukin-23 monoclonal antibody for treatment of his CD, without recurrence of LCV.

Discussion

Previous studies found that anti-TNF-α agents, such as IFX, have induced autoimmune diseases including vasculitis,

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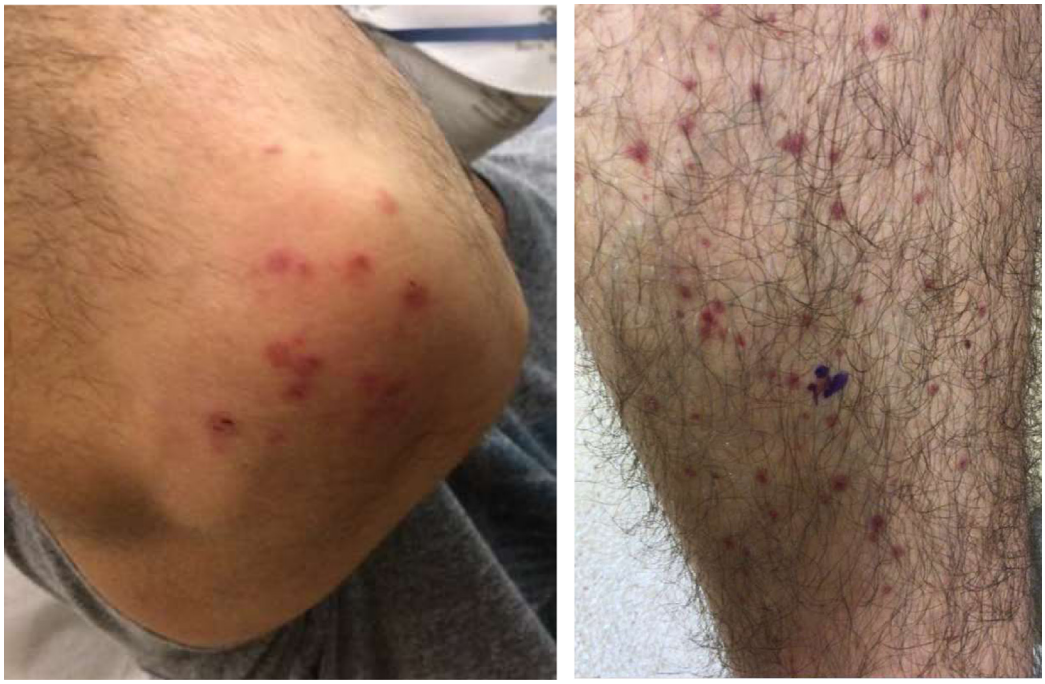

Figure 1. Purpura over elbow (left image) and leg (right image) at the time of shave biopsy.

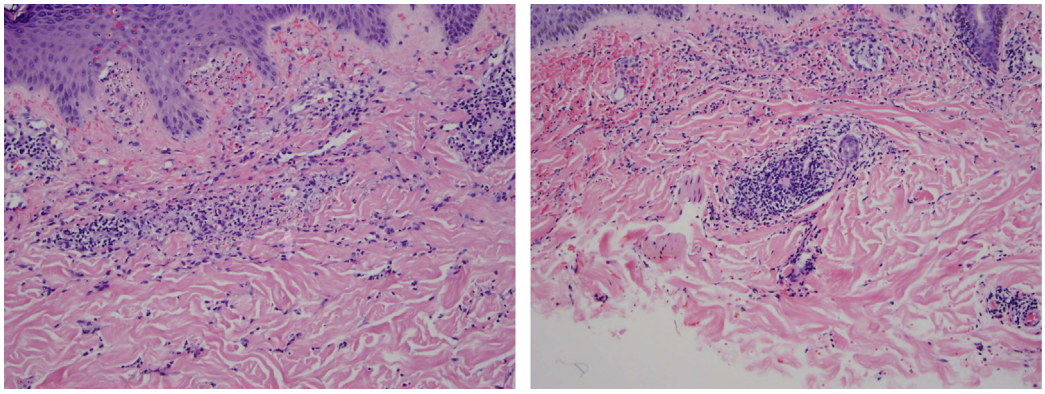

Figure 2. Hematoxylin and eosin stain shave biopsies from elbow (left image) and leg (right image) showing endothelial swelling and fibrin deposition within the small vessels, perivascular lymphocytic infiltrate with neutrophils and nuclear dust, and extravasated erythrocytes consistent with leukocytoclastic vasculitis.

systemic lupus erythematosus, or a lupus-like disease and some interstitial lung diseases. A systematic review of 233 cases of anti-TNF-α–induced autoimmune diseases between January 1990 and December 2006 found 113 total cases of vasculitis, of which 47 were secondary to IFX.[6] Cases of IFX-induced LCV related to CD remain rare.[7–11] Of these reported cases, the timing of skin manifestations occurred between 1 week to 10 months following IFX initiation. Curiously, our patient had tolerated IFX for 13 years prior to his diagnosis, making this an interesting case to report.

Our differential diagnosis for the etiology of LCV included medication, infection, and CD itself. Other than IFX infusions every 8 weeks, our patient was only taking a daily multivitamin, which has not been associated with LCV. Our diagnosis of IFX-induced LCV was further supported by the fact that his arthralgias and rash worsened after IFX infusion and improved once the drug was held. Infection was less likely given he had otherwise been in his usual state of health without any known sick contacts or recent illness. Finally, while there are case reports of LCV as an extra-intestinal manifestation of CD, these were in the setting of acute flares, whereas our patient had been in clinical remission for many years.[12–14]

The pathophysiology behind anti-TNF-α agents and LCV is unclear. One potential mechanism is by a type III hypersensitivity reaction secondary to the precipitation of anti-TNF-α immune complexes in the walls of small vessels, triggering local activation of the complement pathway.[7,15] Another potential explanation is through cytokine imbalance due to TNF-α suppression by inducing either a shift

from a T helper cell 1 to a T helper cell 2 pattern [15] or a locally sustained production of interferon-α.[16]

When determining next steps after the diagnosis is made, clinicians have 3 options: rechallenge IFX, try another anti-TNF-α agent, or switch to a different class of biologics. In considering continuing the same drug, most reported cases found that patients had reappearance or worsening of symptoms upon rechallenge.[6,17]

One case reported dose reduction of IFX reduced the severity and extent of the purpura.[9] Trying another anti-TNF-α agent such as adalimumab can be considered if treatment options are limited; this has been done in some cases without recurrence of vasculitis.[11] Still, it is important to note that there have been cases of adalimumab-induced LCV.[18–20] In addition, there was a case report of a patient whose LCV improved after discontinuing IFX but recurred when they began etanercept, another anti-TNF-α agent.[17] Most cases in the literature reported success switching drug classes entirely to avoid the risk of relapse.[6,8,11]

In conclusion, we present a patient with CD who developed HV with biopsy-proven LCV induced by IFX. Our case is the first occurrence of LCV to manifest years after tolerating IFX. This case highlights the point that IFX-induced LCV does not always occur shortly after drug initiation. Clinicians should have a high index of suspicion for LCV in patients on IFX for CD who develop an unexplained petechial or purpuric rash.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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