Case Reports in Gastroenterology

Case Rep Gastroenterol 2023;17:143–147
DOI: 10.1159/000529045
Received: February 28, 2022
Accepted: December 29, 2022
Published online: March 1, 2023

Single Case

Leukocytoclastic Vasculitis Associated with Adalimumab Therapy for Crohn's Disease

Lankai Cathy Xu[a] Sirisha Grandhe[b] Joseph G. Marsano[b]

[a]Department of Internal Medicine, University of California-Davis, Sacramento, CA, USA;
[b]Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of California-Davis, Sacramento, CA, USA

Keywords
Adalimumab · Crohn's disease · Leukocytoclastic vasculitis · Case report

Abstract
Leukocytoclastic vasculitis (LCV) is rarely associated with anti-tumor necrosis factor [TNF] α therapy. We report a 22-year-old man with new onset of a pustular rash on his bilateral upper and lower extremities while on adalimumab therapy for Crohn's disease. Skin biopsy of the affected area showed perivascular extravasation of erythrocytes, neutrophils, eosinophils and vascular damage surrounding blood vessels associated with fibrin, consistent with LCV. Patient was treated with topical steroids and subsequently transitioned to ustekinumab therapy with follow-up colonoscopy showing minimal active disease. Our report highlights the association of a unique dermatologic autoimmune manifestation with TNF-targeted therapy in a patient with Crohn's disease.

Introduction

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract that can cause lesions anywhere from the mouth to the anus. The pathogenesis of inflammation in Crohn's disease involves increased production of cytokines and signaling proteins including interleukin-12, tumor necrosis factor (TNF), and interferon γ [1]. The dysregulation of pro-inflammatory and anti-inflammatory processes contributes to tissue injury along with other potential genetic and environmental factors [2]. TNF is an important component of the

Correspondence to:
Lankai Cathy Xu, lcxu@ucdavis.edu

Case Rep Gastroenterol 2023;17:143–147
DOI: 10.1159/000529045

immune system and is chronically elevated in patients with Crohn's disease [1]; therefore, the advent of anti-TNF α therapy has greatly transformed the course of inflammatory bowel disease. Currently, treatment involving suppression of TNF function has been shown effective for treating refractory Crohn's disease [3]. However, anti-TNF therapies have been associated with adverse skin manifestations including palmoplantar psoriasis, a chronic inflammatory plaque-type skin disease affecting the palms and soles, nonmelanoma skin cancers, and rarely cutaneous vasculitis, caused by inflammation of small blood vessels [4]. Herein, we report a unique case of adalimumab-induced leukocytoclastic vasculitis (LCV).

Case Presentation

A 22-year-old man with a history of gout and sacroiliitis initially presented to the ED with worsening right lower quadrant abdominal pain for 2-week duration. CT scan demonstrated right-sided colitis and sacroiliitis. A subsequent outpatient colonoscopy showed moderate inflammation with scattered ulcerations in the ascending colon, scattered erythema with aphthous ulcerations in the descending and transverse colon, sparing of the sigmoid colon and rectum. A total of 4 sessile polyps (ranging from 5 to 12 mm in size) were found and removed as well. Pathology was notable for chronic active colitis with crypt abscesses in the proximal colon with normal colonic mucosa in the distal colon and rectum, overall consistent with a diagnosis of Crohn's colitis. Three polyps were characterized as hyperplastic polyps, though one polyp in the sigmoid colon was a tubular adenoma with low-grade dysplasia. Patient was initiated on 6-mercaptopurine monotherapy; however, this was soon discontinued given nausea and abdominal pain after 2 weeks of usage. He was then transitioned to adalimumab 40 mg every 2 weeks and achieved clinical remission within the next 3 months. A colonoscopy with chromoendoscopy was performed about 8 months later and was notable for a normal terminal ileum, nodular cecal base with minimal inflammation, and otherwise normal colon and rectum. Biopsies did not show dysplasia, and patient was advised to repeat colonoscopy in 1 year for colon cancer surveillance. He resumed adalimumab and clinically felt well with none to minimal gastrointestinal symptoms.

About 8 months later, the patient endorsed a new rapidly progressive pustular and painful rash on his bilateral upper and lower extremities (shown in Fig. 1). He was referred to dermatology due to concern for a drug-induced pustular psoriasis. Skin biopsy of the affected area was obtained, which demonstrated perivascular extravasation of erythrocytes, neutrophils, eosinophils, and leukocytosis surrounding blood vessels associated with fibrin (shown in Fig. 2). This was consistent with the diagnoses of LCV and palmoplantar pustular psoriasis. The patient was treated with topical clobetasol 0.05% and doxycycline 100 mg daily for 3 months with drastic improvement of the rash (shown in Fig. 3). Given the rare association between adalimumab and LCV, he was switched from adalimumab to ustekinumab. After 5 months of ustekinumab therapy, a follow-up colonoscopy with chromoendoscopy showed minimally active disease with simple endoscopic score for Crohn's disease (SES-CD) score of 4. To date, he remains on ustekinumab with minimal gastrointestinal symptoms and without adverse effects or recurrence of rash.

Discussion and Conclusions

Adalimumab is an anti-TNF agent frequently used to treat moderate to severe Crohn's disease [1]. Rarely, it has been associated with LCV, a small vessel vasculitis that typically presents as painful purpuric papules in the upper and lower extremities [5–7]. LCV is a histological diagnosis and classically demonstrates perivascular and vascular leukocytic

Case Rep Gastroenterol 2023;17:143–147
DOI: 10.1159/000529045

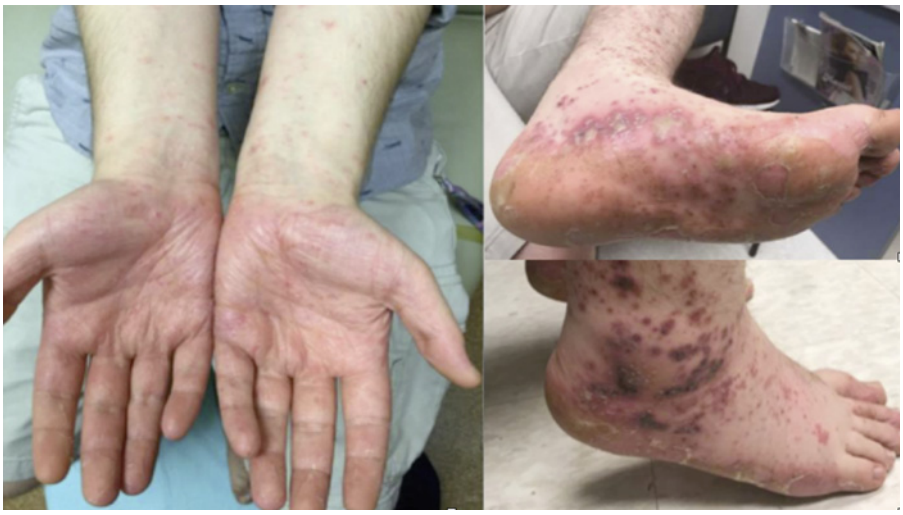

Fig. 1. Initial presentation of pustular rash on hands and lower extremities approximately 1 year after initiating adalimumab.

infiltrates along with fibrinoid necrosis [8]. The exact pathophysiology of anti-TNF-induced LCV is unknown; however, one thought is that the TNF alpha antagonist induces apoptosis, which results in aggregation of nucleosomal antigens causing overproduction of autoantibodies, thus eliciting an autoimmune response and lower extremity rash [9].

An analysis of 233 case reports of autoimmune diseases secondary to TNF-targeted therapy found that the use of anti-TNF agents has been associated with an increasing number of cases of autoimmune diseases [10]. The more common autoimmune diseases include cutaneous vasculitis, lupus-like syndrome, systemic lupus erythematosus, palmoplantar psoriasis, and interstitial lung disease [11].

The annual incidence of biopsy-proven LCV is approximately 45 per million individuals [12]. Drugs cause 10% of cases of LCV, with TNF alpha antagonists representing a small percentage of these cases [13]. The exacerbation of psoriasis by TNF alpha inhibitors has been more widely reported. Of the autoimmune diseases, inflammatory bowel disease was the least common, and plaque psoriasis and palmoplantar pustulosis were the most common psoriasis subtypes [12]. Unlike other medications, LCV induced by biological agents may have a prolonged latency period [14]. The onset of drug-induced cutaneous vasculitis is typically 1–3 weeks after drug initiation; however, latency period can be extended with the use of biological agents [12]. This was demonstrated in our case where the patient presented with LCV a year after initiating therapy. It has been hypothesized that the use of repeated biological agents and higher cumulative dose therapy can compound the development of autoantibodies such as antinuclear antibodies, anti-dsDNA, and anti-cardiolipid antibodies [15], which further increase the risk of developing an autoimmune phenomena. Most cases of palmoplantar psoriasis can be managed conservatively without a need for discontinuing the TNF alpha inhibitor. Depending upon severity, the recommended treatments include topical corticosteroids, vitamin D analogs, phototherapy, and systemic therapies such as methotrexate and cyclosporine [16]. Treatment of LCV is primarily supportive with discontinuation of culprit anti-TNF alpha agent. Though subsequent use of alternative agents may be possible, the decision to switch to a different agent from the offending agent should be approached with caution [13]. In our case, the patient was quickly transitioned from adalimumab to ustekinumab after the development of LCV. However, it should be noted that recent reports are highlighting the association between LCV and the use of ustekinumab as well [14].

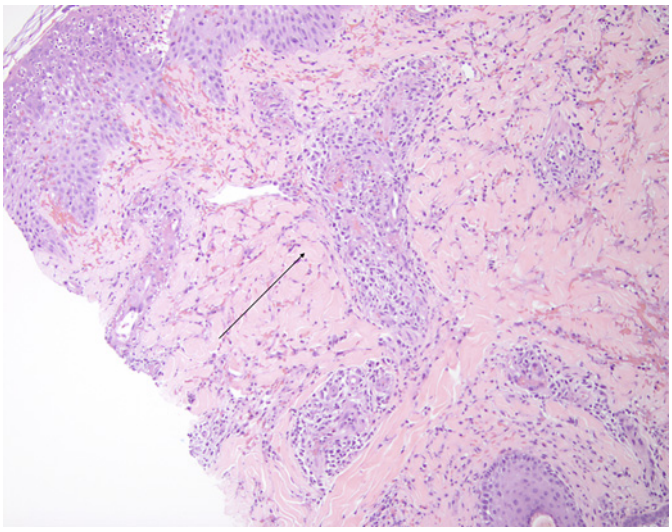

Fig. 2. Pathology of skin biopsy sections shows perivascular extravasation of erythrocytes, neutrophils, eosinophils as well as leukocytoclasis (vascular damage) surrounding blood vessels associated with fibrin. These findings are consistent with LCV. H&E stain, ×10 magnification.

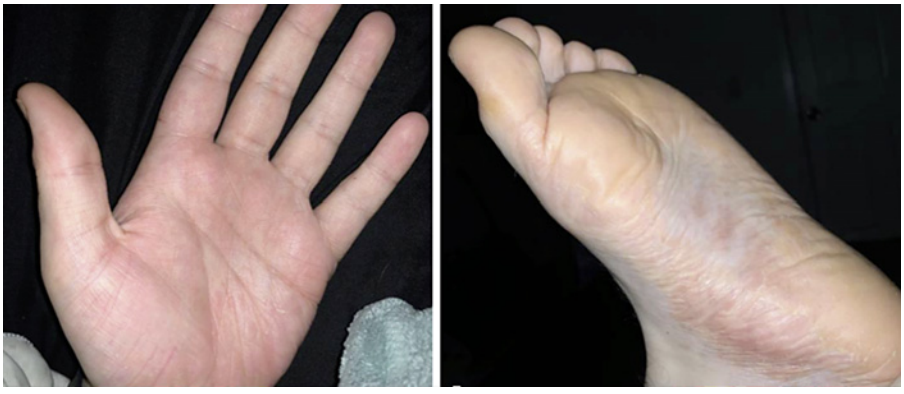

Fig. 3. Improvement in LCV 3 months after cessation of adalimumab and treatment with doxycycline and topical clobetasol.

Anti-TNF therapies have transformed the way we treat and manage inflammatory disease, but it is important to be mindful of drug-induced adverse events. Dermatologic manifestations while on anti-TNF therapy can occur and it is prudent to include LCV as part of the differential, as it can impact evaluation and management of the underlying disease course. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529045).

Statement of Ethics

This study protocol was reviewed and the need for approval was waived by UC Davis Institutional Review Board Administration, Davis, CA (IRB ID 1879395-1). A written informed consent was obtained from the participant to report individual patient data and for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Funding sources are not applicable to this case report.

Author Contributions

LCX: writing, analysis, and research of case report; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published. SG: contribution to analysis of case report; drafting the work or revising it critically for important intellectual content, and final approval of the version to be published. JGM: drafting the work or revising it critically for important intellectual content and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232–9.
2 Mannon PJ. Environmental triggers, genetic background, and Crohn's disease. Gastroenterology. 2011;140(1):363–5.
3 Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Dis Mon. 2018;64(2):20–57.
4 Mocci G, Marzo M, Papa A, Armuzzi A, Guidi L. Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. J Crohns Colitis. 2013;7(10):769–79.
5 Amarante CF, Acedo LMS, Rabay FMd O, Campos Bd ES, Lira MLd A, Mandelbaum SH. Drug-induced lupus with leukocytoclastic vasculitis: a rare expression associated with adalimumab. Bras Dermatol. 2015;90(3 Suppl 1):121–4.
6 Bernardes C, Carvalho D, Saiote J, Ramos J. Leukocytoclastic vasculitis complicating adalimumab therapy for Crohn's disease: report of three cases. Gastroenterol Hepatol. 2018;41(7):442–3.
7 Cury DB, de Souza AWS, Vianna GA, Odashiro D, Farias A, Moss AC. Cutaneous vasculitis in a patient with crohn's disease treated with adalimumab. Inflamm Bowel Dis. 2017;23(1):E1–2.
8 Hussain N, Mustafa U, Davis J, Thakkar S, Ali AM, Mirrakhimov AE, et al. Indomethacin-related leukocytoclastic vasculitis: a case report and review of literature. Case Rep Dermatol. 2013;5(1):33–7.
9 De Bandt M. Anti-TNF-alpha-induced lupus. Arthritis Res Ther. 2019;21(1):235.
10 Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine. 2007;86(4):242–51.
11 Ramos-Casals M, Brito-Zerón P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol. 2008;22(5):847–61.
12 Baigrie D, Bansal P, Goyal A, Crane JS. Leukocytoclastic vasculitis. StatPearls. Treasure island (FL): StatPearls Publishing; August 11. p. 2020.
13 Sokumbi O, Wetter DA, Makol A, Warrington KJ. Vasculitis associated with tumor necrosis factor-α inhibitors. Mayo Clin Proc. 2012;87(8):739–45.
14 Costa-Moreira P, Lopes S, Santos AL, Pedrosa AF, Andrade P, Portugal R, et al. Leukocytoclastic vasculitis related to ustekinumab in a crohn's disease patient: first case report and literature review. J Crohns Colitis. 2020;14(2):274–6.
15 Ziolkowska M, Maslinski W. Laboratory changes on anti-tumor necrosis factor treatment in rheumatoid arthritis. Curr Opin Rheumatol. 2003;15(3):267–73.
16 Li SJ, Perez-Chada LM, Merola JF. TNF inhibitor-induced psoriasis: proposed algorithm for treatment and management. J Psoriasis Psoriatic Arthritis. 2019;4(2):70–80.