ACG CASE REPORTS JOURNAL

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Leukocytoclastic Vasculitis-Associated Myocarditis as an Extraintestinal Manifestation of Crohn's Disease

Roney Shibu, MD[1], and Waled Mohsen, MBBS, FRACP[2]

[1]*Royal Brisbane & Women's Hospital, Brisbane, Australia*
[2]*Department of Digestive Diseases, Gold Coast University Hospital, Gold Coast, Australia*

ABSTRACT

Cardiac extraintestinal manifestations (EIMs) of Crohn's disease (CD) are uncommon. They include pericarditis, myocarditis, and arrhythmias; however, distinguishing these from alternative causes including medication-related adverse effects is often challenging. Leukocytoclastic vasculitis is another uncommon EIM of CD that may present with systemic involvement. We present a rare case of myocarditis associated with leukocytoclastic vasculitis occurring as EIMs of CD. The myocarditis proved refractory to standard therapy and biologics targeting underlying gut inflammation. She developed an inflammatory cardiomyopathy and symptoms consistent with heart failure with preserved ejection fraction. Anakinra was tried, but despite the initial response, it should be used cautiously in patients with CD.

KEYWORDS: Myocarditis; Leukocytoclastic vasculitis; Crohn's disease

INTRODUCTION

Myocarditis is a possibly fatal extraintestinal manifestation (EIM) of Crohn's disease (CD) requiring prompt diagnosis and management.[1] Leukocytoclastic vasculitis (LCV) refers to small vessel vasculitis predominantly affecting postcapillary venules, histologically characterized by neutrophilic inflammation, fibrinoid necrosis, and nuclear debris.[2] These are rare EIMs of CD that may manifest during periods of disease activity or remission.[3] Although extracutaneous manifestations are less common in LCV, we present a rare case of myocarditis associated with LCV occurring as EIMs of CD and discuss the role of Anakinra in managing refractory myocarditis in the context of underlying CD.[4]

CASE REPORT

A 45-year-old woman on methotrexate and certolizumab for rheumatoid arthritis and ileal CD with past ileocecal resection 25 years ago presented with bowel-associated dermatosis-arthritis syndrome during a CD flare. Bowel-associated dermatosis-arthritis syndrome responded poorly to steroids and ustekinumab, which was commenced after ceasing certolizumab, and postsurgical CD worsened (Rutgeerts score i3) despite 9 months of ustekinumab therapy, culminating in terminal ileum stricturing with severe obstructive symptoms requiring another resection.

Days after resection, a nontender, nonulcerated, maculopapular rash developed over the abdomen, spreading to the chest, neck, and arms. Ileal CD was in clinical and biochemical remission. Biopsy demonstrated an acute small vessel vasculitis with predominantly neutrophilic perivascular infiltrate and some leukocytoclasia, most consistent with LCV (Figure 1). Atypical features of LCV included lower limb sparing and Koebnerization, the eruption of identical cutaneous lesions secondary to trauma. estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio were normal. Antinuclear antibodies were low-positive. Other immunological screening, including perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), cytoplasmic anti-neutrophilic cytoplasmic antibodies (cANCA), C3, C4, Extractable nuclear antigen (ENA), rheumatoid factor, Anti-cyclic citrinullated peptide antibodies (anti-CCP), and Human leukocyte antigen (HLA)-B27, was negative. Tumour necrosis factor alpha (TNF-α) inhibitor-induced LCV was considered. However, certolizumab was ceased 9 months ago, and although TNF-α inhibitor-induced LCV may rarely present after years, this was less likely as subsequent LCV exacerbations occurred during CD flares.[5] Infectious etiologies were

ACG Case Rep J 2024;11:e01371. doi:10.14309/crj.0000000000001371. Published online: June 3, 2024

Correspondence: Roney Shibu, MD (Roney.shibu@health.qld.gov.au).

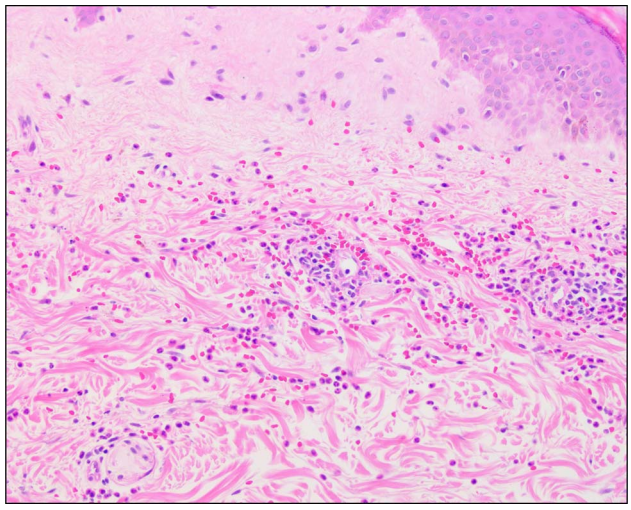

Figure 1. Perivascular neutrophils, leukocytoclastic debris, and red blood cell extravasation indictive of leukocytoclastic vasculitis (magnification 200×).

excluded. Negative congo red and crystal violet stains excluded amyloidosis. A Positron emission tomography / Computed tomography (PET/CT), evaluating for malignant transformation of her monoclonal gammopathy of undetermined significance, and a malignancy screen including tumor markers were negative. As simultaneous oral Crohn's and arthritis occurred with LCV, a 4-week tapering course of 25 mg prednisolone was commenced. Although LCV improved, complete resolution was not achieved.

Three months later, she presented with acute dysphagia, odynophagia, and sharp, nonpleuritic chest pain radiating interscapularly that was relieved on leaning forward. She was febrile and had a 2-month history of dyspnea and lethargy. Food bolus and infective causes were excluded. ECG revealed no ischemic changes, but troponin was 22 ng/L (Reference range (RR) <10 ng/L) and on repeat testing, was 28 ng/L. Ileal CD was in remission (Rutgeerts score i0); however, she experienced severe EIMs, including LCV and oral Crohn's, and thus, a 4-week tapering course of 25 mg prednisolone was commenced. However, due to poor response and quality of life, infliximab was commenced. Cardiac Magnetic resonance imaging (MRI) at 1 month revealed late gadolinium enhancement in the basal inferoseptal and inferior segments in a mid-wall distribution consistent with myocarditis (Figure 2). Common infectious and noninfectious causes of myocarditis were excluded. Ejection fraction (EF) was preserved at 58%.

Although arthritis, cutaneous LCV, and oral Crohn's responded to infliximab, she experienced 6 myocarditis flares over the subsequent 6 months, which culminated in new paroxysmal nocturnal dyspnea, orthopnea, and reduced exercise tolerance. Troponin remained 11 ng/L (RR <10 ng/L), and Brain natriuretic peptide (BNP) was 69 ng/L (RR <100). Four-month follow-up cardiac MRI showed EF of 53% and near transmural infarction of the basal to mid-inferolateral segments of the left ventricle with ongoing inflammation. Computed tomography coronary angiography (CTCA) excluded epicardial coronary artery disease. Together, this was consistent with heart failure with preserved ejection fraction (HFpEF) secondary to an inflammatory cardiomyopathy. Spironolactone, bisoprolol, and frusemide were commenced. Owing to concerns infliximab was worsening cardiac function, it was paused, and prednisolone 25 mg was started. However, she experienced 2 severe myocarditis flares within 3 weeks of ceasing infliximab, associated with troponins of 37 ng/L (RR <34 ng/L) and newly elevated BNP of 595 ng/L (RR <100 ng/L). Sixty milligram prednisolone was commenced with good symptom improvement. Cardiac function failed to improve after the 1-month infliximab break, excluding HFpEF precipitated by a TNF-α inhibitor. Thus, infliximab was restarted while weaning prednisolone. However, at 1-month reevaluation, her heart failure worsened with symptoms consistent with New York Heart Association (NYHA) Class III. Thus, Anakinra was commenced after ceasing infliximab.

After 1 month of Anakinra and azathioprine therapy, there was marked clinical and echocardiographic improvement including reversal of some preexisting regional wall motion abnormalities. However, at 2 months, there was clinical, biochemical, and echocardiographic deterioration of HFpEF. Repeat cardiac MRI showed rapid development of findings consistent with cardiac amyloidosis and renal biopsy confirmed Light chain (AL) amyloidosis secondary to progression of monoclonal gammopathy

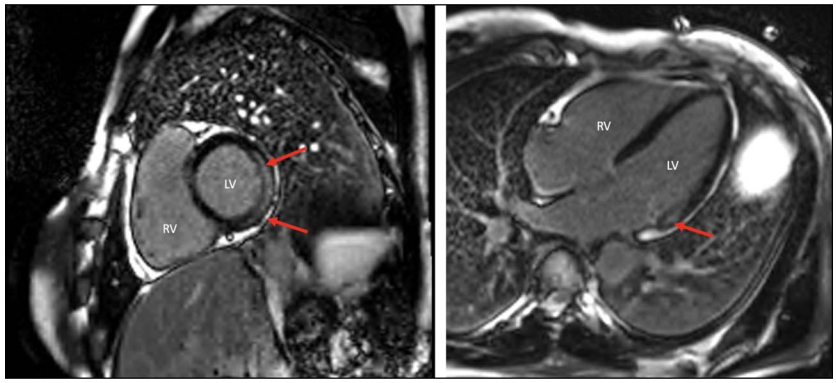

Figure 2. Broad mid-wall-delayed gadolinium enhancement involving the basal lateral and inferolateral regions.

of undetermined significance to plasma cell myeloma. As available evidence-suggested myocarditis was likely an EIM of CD, this may represent a superimposed process, which may explain the initial response to Anakinra and subsequent treatment failure.

DISCUSSION

LCV is a rare reactive cutaneous EIM that may occur independently of CD activity, classically manifesting as palpable purpura of the lower extremities. It is proposed to be a hypersensitivity vasculitis secondary to immune complex deposition in small vessels, which could represent an extension of the intestinal immune response in patients with CD.[6] A recent review showed 14 cases of LCV in patients with CD; however, only 5 were EIMs, and the remaining were medication-induced.[3] Notably, unlike the cases described, our patient had sparing of the lower limbs and koebnerization.

Koebnerization is a rare phenomenon in LCV characterized by development of an existing dermatosis secondary to trauma on previously unaffected skin.[7] Unlike our case, most reported cases of Koebner phenomenon in LCV were secondary to Henoch-Schonlein purpura or medications.[8] One of the proposed mechanisms of koebnerization is immunoglobulin aggregation at sites of inflammation.[7] Thus, it is often associated with pruritic conditions where scratching stimulates local inflammation. This may explain its low incidence in LCV, a nonpruritic disease. In our patient, localized skin irritation, possibly from dry skin, triggered scratching.

Secondary causes of LCV include medications, infections, malignancy, and immunological disease. TNF-α inhibitor-related LCV is generally responsive to discontinuation of therapy, although some require adjuvant steroids.[9] However, our patient's lack of response and the temporal association of LCV and CD exacerbations suggested an alternative cause. There are case reports of ustekinumab causing LCV; however, it was discontinued before onset of the rash.[10,11]

Cardiac involvement in LCV is rare and associated with increased morbidity and mortality.[12] To our knowledge, this is only the second case of LCV-associated myocarditis and first as an EIM of CD.[13] Subendocardial Late gadolinium enhancement (LGE) on cardiac MRI, classically suggestive of ischemia, is rare in myocarditis and portends a poor prognosis.[14,15] Dysregulated interleukin (IL)-1-mediated inflammation is central to the pathogenesis of myocarditis, regardless of etiology.[16] Emerging evidence shows that Anakinra, an IL-1 receptor antagonist, could effectively treat fulminant myocarditis irrespective of etiology, with most striking benefits seen in myocarditis-associated acute heart failure.[17,18] This combined effect on tissue inflammation and contractility may explain the initial clinical and radiographic improvement in our patient. However, the safety and effectiveness of Anakinra in CD requires further study. Although IL-1β levels are raised during active CD and positively correlate with severity of mucosal inflammation, several case reports demonstrate worsening of CD after Anakinra therapy and possible Anakinra-induced CD.[19-21] Therefore, these patients require timely disease activity monitoring.

DISCLOSURES

Author contributions: W. Mohsen devised the project, identified key discussion points and R. Shibu drafted the manuscript. All authors critically revised the manuscript, approved the final version for submission, and agreed to be accountable for all aspects of the work. R. Shibu is the article guarantor.

Acknowledgments: We acknowledge Richard Slaughter of Excellence in Cardiovascular MRI for the cardiac MRI images.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received November 19, 2023; Accepted April 22, 2024

REFERENCES

1. Bunu D, Timofte C, Ciocoiu M, et al. Cardiovascular manifestations of inflammatory bowel disease: Pathogenesis, diagnosis, and preventive strategies. *Gastroenterol Res Pract.* 2019;2019:3012509.
2. Russell JP, Gibson LE. Primary cutaneous small vessel vasculitis: Approach to diagnosis and treatment. *Int J Dermatol.* 2006;45(1):3–13.
3. Buck M, Dumic I, McDermott W, et al. Leukocytoclastic vasculitis as a rare dermatologic manifestation of Crohn's disease mimicking cellulitis: A case report. *BMC Gastroenterol.* 2020;20(1):240.
4. Hung JT, Yang YH, Hsiao CH, et al. Leukocytoclastic vasculitis with severe cardiac involvement in an infant: A case report. *Clin Rheumatol.* 2008;27(7):945–7.
5. Wu A, Brown D, Wong U. A rare case of leukocytoclastic vasculitis associated with infliximab. *Gastro Hep Adv.* 2023;2(3):322–4.
6. Hedin CRH, Vavricka SR, Stagg AJ, et al. The pathogenesis of extraintestinal manifestations: Implications for IBD research, diagnosis, and therapy. *J Crohns Colitis.* 2019;13(5):541–54.
7. Weiss G, Shemer A, Trau H. The koebner phenomenon: Review of the literature. *J Eur Acad Dermatol Venereol.* 2002;16(3):241–8.
8. Kassam F, Nurmohamed S, Haber RM. Koebner phenomenon in leukocytoclastic vasculitis: A case report and an updated review of the literature. *SAGE Open Med Case Rep.* 2019;7:2050313X19850353.
9. Sokumbi O, Wetter DA, Makol A, Warrington KJ. Vasculitis associated with tumor necrosis factor-α inhibitors. *Mayo Clin Proc.* 2012;87(8):739–45.
10. Chugh R, Proctor DD, Little A, et al. Cutaneous vasculitis after ustekinumab induction in Crohn's disease. *Inflamm Bowel Dis.* 2020;27(3):e30–e31.
11. Costa-Moreira P, Lopes S, Santos AL, et al. Leukocytoclastic vasculitis related to ustekinumab in a Crohn's disease patient: First case report and literature review. *J Crohns Colitis* 2019;14(2):274–6.
12. Miloslavsky E, Unizony S. The heart in vasculitis. *Rheum Dis Clin North Am.* 2014;40(1):11–26.
13. Khanji MY, Sekhri N. Leukocytoclastic vasculitis associated myocarditis: Differentiating inflammatory from inherited heart muscle disease. *Eur Heart J.* 2021;42(18):1812.
14. Belin RJ, Ghasemiesfe A, Carr J, Miller FH, Parada C, Akhter N. Crohn's colitis-induced myocarditis. *J Cardiol Cases.* 2016;14(1):4–7.
15. Li JH, Xu XQ, Zhu YJ, et al. Subendocardial involvement as an underrecognized cardiac MRI phenotype in myocarditis. *Radiology.* 2022;302(1):61–9.
16. Cavalli G, Colafrancesco S, Emmi G, et al. Interleukin 1α: A comprehensive review on the role of IL-1α in the pathogenesis and treatment of autoimmune and inflammatory diseases. *Autoimmun Rev.* 2021;20(3):102763.

17. Cavalli G, Dinarello CA. Anakinra therapy for non-cancer inflammatory diseases. *Front Pharmacol.* 2018;9:1157.
18. Van Tassell BW, Arena R, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with Anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot Study). *Am J Cardiol.* 2014;113(2):321–7.
19. Dosh RH, Jordan-Mahy N, Sammon C, Le Maitre C. Interleukin 1 is a key driver of inflammatory bowel disease-demonstration in a murine IL-1Ra knockout model. *Oncotarget.* 2019;10(37):3559–75.
20. Carter JD, Valeriano J, Vasey FB. Crohn disease worsened by Anakinra administration. *J Clin Rheumatol.* 2003;9(4):276–7.
21. Hashmi S, Lehne R, Hoff RT, Ehrenpreis ED. S0748. *De novo* inflammatory bowel disease in patients on IL-1 inhibitor therapy for rheumatologic diseases. *Am J Gastroenterol.* 2020;115(1):S378.