Eosinophilia and Ulcerative Colitis Associated with Eosinophilic Myocarditis

Katie Murphy, MBBCh
Oral Waldo, MD
Graham M. Lohrmann, MBBCh
Henry D. Tazelaar, MD
Clinton E. Jokerst, MD
Farouk Mookadam, MBBCh

Reactive eosinophilia is associated with inflammatory bowel disease, but its association with eosinophilic myocarditis is rare. We report a case of a 42-year-old man who presented with hypovolemic shock secondary to diarrhea and recently diagnosed non-ischemic cardiomyopathy (left ventricular ejection fraction, 0.29). Laboratory evaluation revealed marked peripheral eosinophilia. Cardiac magnetic resonance imaging showed evidence of subacute-to-chronic myocarditis, and endomyocardial biopsy results were consistent with eosinophilic myocarditis. Colonic biopsy specimens revealed ulcerative colitis and no eosinophils. Hematologic evaluation was negative for an alternative cause of eosinophilia. The patient was given corticosteroids; his diarrhea resolved, but there was no short-term improvement in his ejection fraction, so an implantable cardioverter-defibrillator was placed. Follow-up at one year showed that the patient's left ventricular ejection fraction had improved to 0.42. **(Tex Heart Inst J 2017;44(3):219-22)**

Eosinophils, granular cells that make up 1% to 3% of the total white blood cell count, primarily defend the body against parasitic organisms.[1] When activated by an immune stimulus, they release cytotoxic granules, causing tissue damage and inflammation.[1] Mild eosinophilia, characterized by an absolute eosinophil count of 500 to 1,500 cells/µL, is frequently associated with asthma and helminthic infection. Moderate and severe eosinophilia, characterized by absolute eosinophil counts of 1,500 to 5,000 cells/µL and >5,000 cells/µL, respectively, are rare and need comprehensive evaluation. Eosinophilia can affect many organs, and rapid, appropriate treatment is of paramount importance.[2]

Eosinophilia can have a primary (clonal) cause, such as eosinophilic leukemia; or a secondary (reactive) cause, such as atopy, a response to infection, a reaction to a drug, or an inflammatory disorder like Churg-Strauss syndrome. It can also be idiopathic.

Eosinophilic myocarditis (EM) is a rare disease that occurs when eosinophils infiltrate the myocardium. Sometimes, the eosinophils are confined to the perivascular and interstitial spaces, but they might also mix with myocytes, in which case they can be associated with myocyte damage and necrosis.[3]

Patients with eosinophilic myocarditis can present with arrhythmias or with heart failure. Echocardiograms will often reveal a left ventricular (LV) thrombus due to an inflamed and prothrombotic endocardial surface, and cardiac magnetic resonance might show evidence of myocarditis and of myocardial fibrosis. Endomyocardial biopsy, which reveals the presence of eosinophils, can provide a definitive diagnosis. Treatment is aimed at identifying and removing the offending agent and prescribing corticosteroids, which can improve symptoms and resolve organ dysfunction because of their immunosuppressive effects.[4]

The medical literature includes a few case reports of patients with inflammatory bowel disease (IBD) that led to eosinophilia, which in turn led to myocarditis.[5] Eosinophilia has also been described as a side effect of therapy with 5-aminosalicylic acid (mesalamine).[6] We report a case of EM associated with IBD and no other known cause.

Case Report

In December 2015, a 42-year-old man was referred to our institution for intractable diarrhea that had led to hypovolemic shock. He had a history of nonischemic cardio-

myopathy with subsequent development of a pericardial effusion that had necessitated a pericardial window. He also had worsening heart failure despite having received optimal medical therapy. The patient reported having intractable diarrhea of unknown cause for 2 years, along with a 40-lb weight loss. He had not sought treatment for his diarrhea.

At presentation, the patient was afebrile, had a blood pressure of 90/60 mmHg, and appeared cachectic. Cardiac examination revealed a laterally displaced point of maximal impulse. On auscultation, the patient's chest was clear. There was an increased tactile fremitus of the lower lobe of the right lung, and bowel sounds were hyperactive. No skin lesions were identified, and the patient reported no recent travel.

Laboratory results included a peripheral eosinophil count of 3.67×10^9/L (normal level, $<0.4 \times 10^9$/L) with a total white cell count of 10.1×10^9/L (normal range, 4.2–10.2×10^9/L), a creatinine level of 1.1 mg/dL (normal range, 0.8–1.3 mg/dL) and an N-terminal pro-brain natriuretic peptide level of 4,987 pg/mL (normal level, <167 pg/mL). A chest radiograph showed mild pulmonary interstitial edema and a small right pleural effusion. An electrocardiogram showed nonspecific anterior T-wave changes. A transthoracic echocardiogram revealed generalized LV hypokinesis, a small anterior pericardial effusion, and an LV ejection fraction of 0.29. No ventricular thrombus was seen (Fig. 1).

Cardiac magnetic resonance images revealed patchy, inflammatory myopericardial areas with delayed gadolinium enhancement in the mid-to-distal interventricular septum, as well as focal hypokinesis and wall-thinning. These findings suggested some remodeling in the most severely affected myocardium and indicated subacute-to-chronic myocarditis (Fig. 2). An endomyocardial biopsy specimen contained eosinophilic infiltrates and showed signs of myocyte destruction and early fibrosis; these findings were consistent

Fig. 1 Transthoracic echocardiogram shows generalized left ventricular hypokinesis, a small anterior pericardial effusion, and no left ventricular thrombus.
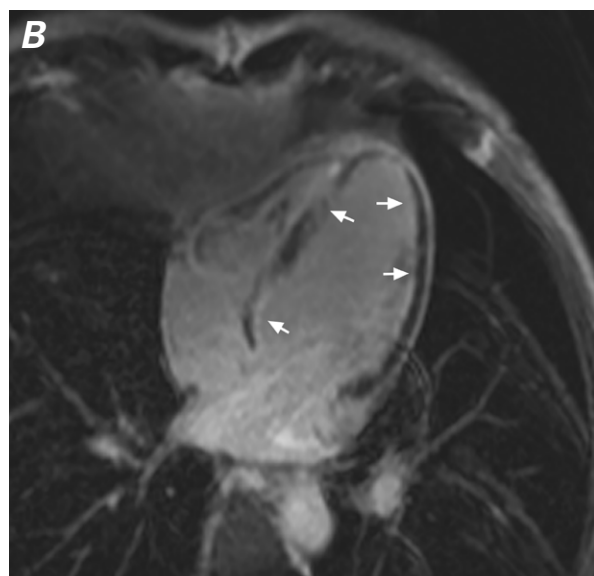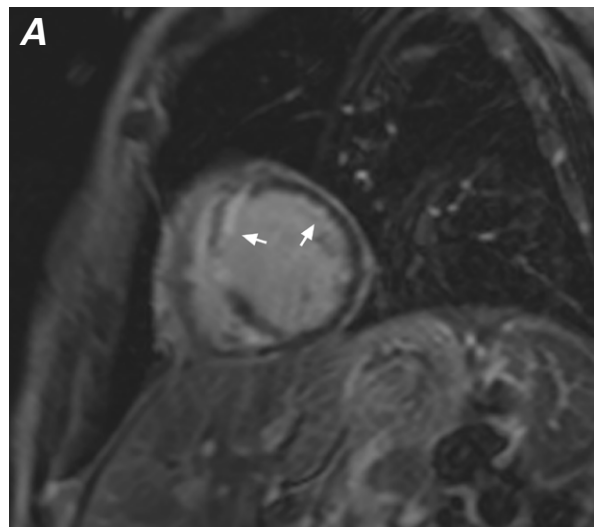

Fig. 2 Delayed postcontrast cardiac magnetic resonance images in **A**) short-axis and **B**) long-axis views reveal subtle widespread subendocardial enhancement (arrows) that extends into the mesocardial aspect of the interventricular septum, no associated thrombus, and diffuse smooth pericardial enhancement related to the patient's recent pericardial window operation.

with EM. No parasitic organisms were identified (Fig. 3).

We performed a comprehensive evaluation to determine the cause of the patient's eosinophilia. A detailed history revealed no medications that could cause eosinophilia. Autoimmune, infectious, and neoplastic causes were excluded based on the results of cultures, serology tests, and a bone marrow biopsy. No eosinophils were seen in the colon. Colonic biopsy specimens revealed chronic active ulceration and colitis. The diagnosis was ulcerative colitis with reactive eosinophilia resulting in EM.
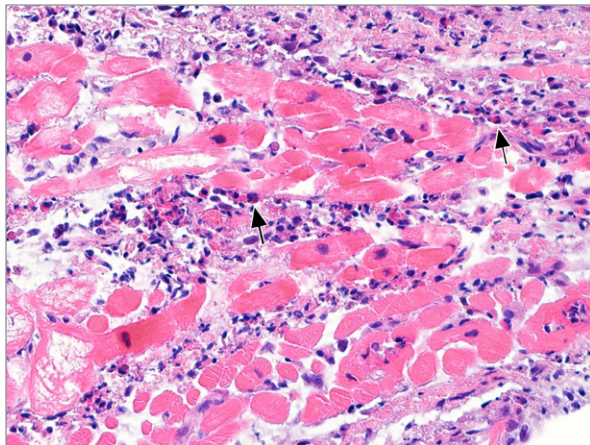
Fig. 3 *Photomicrograph of an endomyocardial biopsy specimen shows diffuse interstitial inflammatory cell infiltrate, including mononuclear cells and numerous eosinophils (arrows); myocyte destruction; and early fibrosis (H & E, orig. ×200). The findings are consistent with eosinophilic myocarditis.*

The patient was given corticosteroids for his ulcerative colitis. Four days later, he was diagnosed with pulmonary emboli and was given an anticoagulant. He received guideline-directed heart failure therapy while being treated with corticosteroids and anticoagulants. The patient's diarrhea subsided, his eosinophil count returned to normal, and he continued heart failure therapy. At 3-month follow-up evaluation, there was no improvement in cardiac function, so an implantable cardioverter-defibrillator was placed. The patient's most recent transthoracic echocardiogram, obtained in December 2016, showed that his LV ejection fraction had improved to 0.42 and that his eosinophil count had normalized. The treatment plan was to transition him to steroid-sparing maintenance therapy for ulcerative colitis and to continue heart failure therapy.

Discussion

Eosinophil-mediated cardiac dysfunction occurs in 3 stages.[7] The first stage is an acute necrotic stage, during which eosinophils infiltrate the endocardium. Patients might experience ventricular dysfunction or arrhythmia, but they are frequently asymptomatic. If an angiogram is obtained during the first phase, patients might be diagnosed with nonischemic cardiomyopathy. The second phase is characterized by the formation of thrombus along the damaged endocardium. The third phase is marked by progression of the disease, which leads to fibrotic changes and restrictive cardiomyopathy. A full-fledged manifestation of the disease can lead to Loeffler endocarditis, which is characterized by endomyocardial fibrosis, apical LV obliteration, and restrictive heart failure.[4-7]

The nature of the association between IBD and cardiovascular disease is a topic of debate. Some investiga-

tors have reported a higher incidence of ischemic heart disease in patients with IBD.[8-14] This correlation was thought to be caused by chronic inflammation; however, there is evidence that the relationship might be more complex, and diagnosis of ischemic heart disease often predates that of IBD. Investigators in some large studies have failed to prove an association between IBD and cardiovascular disease.[10] In a large Danish cohort study, IBD was associated with increased risk of hospitalization for heart failure, particularly during periods of active disease.[15] The authors of this study did not, however, suggest a mechanism for the heart failure.

Just as IBD is rarely associated with cases of myocarditis, including EM, it is also infrequently associated with other cardiovascular diseases, including cardiomyopathies, pericarditis, noninfectious (Loeffler) endocarditis, heart block, aortic insufficiency, and aortitis, and with the treatments for these diseases.[16-19] The mechanisms of these associations are unclear. For example, although 5-aminosalicylic acid can be used to treat ulcerative colitis, it can also cause eosinophilia, pericarditis, and myocarditis.[20-24] Of note, our patient had never taken this medication because his ulcerative colitis was newly diagnosed.

Koneru and colleagues[5] have described a case of Loeffler endocarditis in a patient with ulcerative colitis and reactive eosinophilia. The case was complicated by an LV thrombus and a cerebral infarction. The patient's LV function returned to normal after treatment of the underlying IBD with a colectomy, steroids, and anticoagulants.

Myocarditis associated with IBD has been reported with and without eosinophilia.[25] There are also reports of an association between IBD and lymphocytic myocarditis.[26] This suggests multiple pathologic mechanisms for myocarditis. The treatment of EM is focused on the management of IBD, often with corticosteroid therapy along with guideline-directed heart failure therapy. Definitive pathologic diagnosis does not change the management protocol for these patients[25-27]; accordingly, only a small percentage of patients with nonischemic cardiomyopathy undergo endomyocardial biopsy to identify the cause of the disease. Whenever nonischemic cardiomyopathy presents itself in a patient with ulcerative colitis, with or without eosinophilia, one should consider performing an endomyocardial biopsy so that EM can be identified or ruled out. Prompt diagnosis and treatment can lead to the resolution of cardiac dysfunction. Early recognition and treatment can also prevent the development of fibrosis and progression of disease.

References

1. Kariyawasam HH, Robinson DS. The eosinophil: the cell and its weapons, the cytokines, its locations. Semin Respir Crit Care Med 2006;27(2):117-27.

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2. Gotlib J. World Health Organization-defined eosinophilic disorders: 2015 update on diagnosis, risk stratification, and management. Am J Hematol 2015;90(11):1077-89.

3. Seidman MA, McManus BM. Myocarditis. In: Buja LM, Butany J, editors. Cardiovascular pathology. London: Academic Press; 2016. p. 341-63.

4. Li H, Dai Z, Wang B, Huang W. A case report of eosinophilic myocarditis and a review of the relevant literature. BMC Cardiovasc Disord 2015;15:15.

5. Koneru S, Koshy G, Sharp C, Khalafallah AA. Hypereosinophilic syndrome associated with ulcerative colitis presenting with recurrent Loeffler's endocarditis and left ventricular thrombus treated successfully with immune suppressive therapy and anticoagulation. BMJ Case Rep 2013;2013.

6. Usta Y, Ozen H, Gurakan F, Uslu N, Saltik-Temizel IN, Demir H, Yuce A. Hypereosinophilia due to mesalazine treatment. J Clin Gastroenterol 2009;43(4):382.

7. Parrillo JE, Borer JS, Henry WL, Wolff SM, Fauci AS. The cardiovascular manifestations of the hypereosinophilic syndrome. Prospective study of 26 patients, with review of the literature. Am J Med 1979;67(4):572-82.

8. Close H, Mason JM, Wilson DW, Hungin AP, Jones R, Rubin G. Risk of ischaemic heart disease in patients with inflammatory bowel disease: cohort study using the general practice research database. PLoS One 2015;10(10):e0139745.

9. Osterman MT, Yang YX, Brensinger C, Forde KA, Lichtenstein GR, Lewis JD. No increased risk of myocardial infarction among patients with ulcerative colitis or Crohn's disease. Clin Gastroenterol Hepatol 2011;9(10):875-80.

10. Rungoe C, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. Gut 2013;62(5):689-94.

11. Singh S, Kullo IJ, Pardi DS, Loftus EV Jr. Epidemiology, risk factors and management of cardiovascular diseases in IBD. Nat Rev Gastroenterol Hepatol 2015;12(1):26-35.

12. Theocharidou E, Gossios TD, Karagiannis A. Are patients with inflammatory bowel diseases at increased risk for cardiovascular disease? Clin Gastroenterol Hepatol 2014;12(12):2134-5.

13. Lee T, Singal AG, Sussman J, Waljee AK. At the "heart" of inflammatory bowel diseases. Gastroenterology 2013;145(6):1486-8.

14. Yarur AJ, Deshpande AR, Pechman DM, Tamariz L, Abreu MT, Sussman DA. Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. Am J Gastroenterol 2011;106(4):741-7.

15. Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Lamberts M, Khalid U, et al. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. Circ Heart Fail 2014;7(5):717-22.

16. Blum A, Shalabi R, Brofman T, Shajrawi I. Cardiac manifestations of ulcerative colitis. Isr Med Assoc J 2009;11(12):764-5.

17. Bragagni G, Brogna R, Franceschetti P, Zoli G. Cardiac involvement in Crohn's disease: echocardiographic study. J Gastroenterol Hepatol 2007;22(1):18-22.

18. Virovic Jukic L, Duvnjak M, Barsic N, Lerotic I, Tomasic V, Pavic T. Pericarditis in exacerbation of ulcerative colitis. Acta Gastroenterol Belg 2006;69(4):390-2.

19. Stasinopoulou P, Kaziani A, Mantzaris G, Roussos A, Skoutelis A. Parallel manifestation of Crohn's disease and acute pericarditis: a report of two cases. Int J Colorectal Dis 2007;22(9):1123-5.

20. Galvao Braga C, Martins J, Arantes C, Ramos V, Vieira C, Salgado A, et al. Mesalamine-induced myocarditis following diagnosis of Crohn's disease: a case report. Rev Port Cardiol 2013;32(9):717-20.

21. Liu Y, Ye J, Zhu J, Chen W, Sun Y. Myocarditis due to mesalamine treatment in a patient with Crohn's disease in China. Turk J Gastroenterol 2012;23(3):304-6.

22. Stelts S, Taylor MH, Nappi J, Van Bakel AB. Mesalamine-associated hypersensitivity myocarditis in ulcerative colitis. Ann Pharmacother 2008;42(6):904-5.

23. Kiyomatsu H, Kawai K, Tanaka T, Tanaka J, Kiyomatsu T, Nozawa H, et al. Mesalazine-induced pleuropericarditis in a patient with Crohn's disease. Intern Med 2015;54(13):1605-8.

24. Sabatini T, Filippini A, Nicosia F, Preti S, Bertoli M. Recurrence of myocarditis after mesalazine treatment for ulcerative colitis: a case report. Inflamm Bowel Dis 2013;19(3):E46-8.

25. Gruenhagen B, Alraies MC, Vakil KP, March SK. Ulcerative colitis-induced myocarditis. BMJ Case Rep 2014;2014.

26. Varnavas VC, Reinsch N, Perrey M, Nensa F, Schlosser T, Baba HA, et al. Recurrent lymphocytic myocarditis in a young male with ulcerative colitis. Eur J Med Res 2014;19:11.

27. Nishtar SS, Rajendran R, Mathur A, Khattak S. Fulminant myocarditis: a rare but life-threatening association of Crohn's disease. Emerg Med J 2008;25(5):314-5.