

# Metastatic Crohn Disease Clinically Reminiscent of Erythema Nodosum on the Right Leg

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## PRACTICE POINTS

- Metastatic Crohn disease (MCD) may be an initial sign indicating the aggravation of intestinal Crohn disease (CD).
- Metastatic Crohn disease on the legs could be clinically reminiscent of erythema nodosum (EN).
- Physicians should be aware of the possibility of MCD when encountering EN-like lesions on the legs in a CD patient.

*Cutaneous manifestations are well-recognized complications of Crohn disease (CD) that can be divided into disease-specific and reactive conditions. One of the most common reactive conditions is erythema nodosum (EN), which presents as subcutaneous tender nodules most often on the legs. On the other hand, metastatic Crohn disease (MCD) is a rare cutaneous manifestation of CD defined as the presence of noncaseating granulomas that are not contiguous with the gastrointestinal (GI) tract. The clinical presentation of MCD is variable; however, lesions often are located on the legs and genital region. We report the case of a 21-year-old woman with a 6-year history of CD who presented with MCD clinically simulating EN.*

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Metastatic Crohn disease (MCD) is defined by the presence of cutaneous noncaseating granulomatous lesions that are noncontiguous with the gastrointestinal (GI) tract or fistulae.<sup>1</sup> The clinical presentation of MCD is so variable that its diagnosis requires a high index of suspicion.<sup>1,2</sup> In particular, the presence of erythematous tender nodules on the legs is easily mistaken for erythema nodosum (EN). Skin biopsy has an important role in confirming the diagnosis, as histopathological examination would reveal a noncaseating granuloma similar to those in the involved GI tract.<sup>2</sup> Herein, we report a case of MCD on the right leg that was clinically reminiscent of unilateral EN.

## Case Report

A 21-year-old woman presented to the dermatology department with 2 painful erythematous nodules on the lower right leg of 2 weeks' duration. She also reported abdominal pain, diarrhea, and bloody stool. She had been diagnosed with Crohn disease (CD) 6 years prior that had been well controlled with systemic low-dose steroids (5–15 mg/d), metronidazole (750 mg/d), and intermittent mesalamine and antidiarrheal drugs. However, she had not taken her medication for several weeks on her own authority. Subsequently, the patient developed skin lesions,

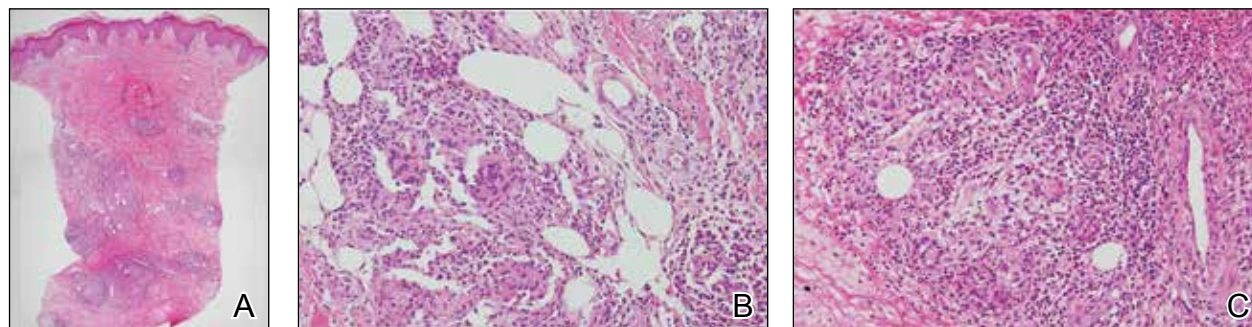
which were characterized by ill-defined erythematous nodules with tenderness on the right lower leg along with GI symptoms (Figure 1). Laboratory studies revealed anemia (hemoglobin, 9.9 g/dL [reference range, 12.0–16.0 g/dL]) and an elevated C-reactive protein level (4.3 mg/dL [reference range, 0–0.3 mg/dL]). Other routine laboratory findings were normal.

Histopathologically, a skin biopsy from the right ankle showed vague, ill-defined, noncaseating granulomas scattered in the deep dermis and lobules of the subcutis (Figure 2). The granulomas were composed of epithelioid cells and Langerhans-type giant cells. Lymphocytes and neutrophils also were present, but eosinophils were absent. Immunohistochemical

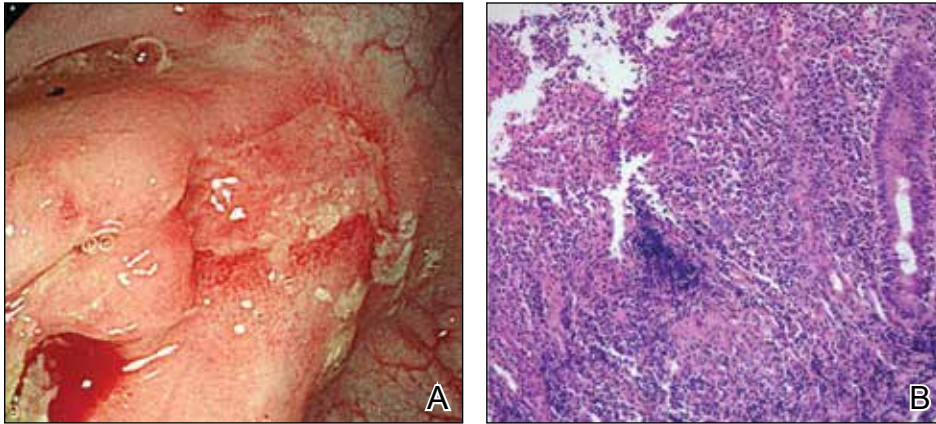
staining revealed that the infiltrating cells were mostly CD4<sup>+</sup> helper/inducer T cells intermixed with CD8<sup>+</sup> suppressor/cytotoxic T cells. The CD4:CD8 ratio was approximately 2:1. Counts of CD20<sup>+</sup> B cells were low. Epithelioid cells and giant cells were positive for CD68.

A colonoscopy was performed to evaluate the aggravation of CD. Multiple longitudinal ulcers were observed in the ileocecal valve area and from the transverse colon to the sigmoid colon (Figure 3A). Histopathologic findings from the colon showed mucosal ulceration and noncaseating granulomas with heavy infiltration of lymphocytes and plasma cells (Figure 3B). Staining for infectious microorganisms (eg, Ziehl-Neelsen, periodic acid–Schiff, Gram)

**Figure 1.** Erythematous nodules on the right lower leg and the lateral aspect of the right ankle (A and B). Arrow indicates biopsy site (B).



**Figure 2.** Skin biopsy from the right ankle showed scattered, ill-defined, noncaseating granulomas in the mid to deep dermis and lobules of the subcutis. The interlobular septum was thickened and hyalinized (A)(H&E, original magnification  $\times 20$ ). The skin biopsy showed granulomas composed of epithelioid cells and multinucleated giant cells in the deep dermis and in the lobules of the subcutis (B)(H&E, original magnification  $\times 200$ ). Histopathologic features such as small vessel vasculitis characterized by a fibrin deposit in the small blood vessels and swelling of the endothelial cells as well as granulomatous perivasculitis with perivascular infiltration of the epithelioid cells were present (C)(H&E, original magnification  $\times 200$ ).



**Figure 3.** Colonoscopic findings showed multiple longitudinal ulcers in the transverse colon to the sigmoid colon (A). Histopathologic findings from the colon showed infiltration of numerous inflammatory and multinucleated giant cells and mucosal ulceration (B) (H&E, original magnification  $\times 200$ ).

was negative. A polymerase chain reaction performed on sections cut from the paraffin block of the skin biopsy was negative for *Mycobacterium tuberculosis* DNA.

Based on the clinical and histopathologic findings, the patient was diagnosed with MCD that was clinically reminiscent of unilateral EN. Four weeks after the initiation of therapy with systemic corticosteroids (25 mg/d), oral metronidazole (750 mg/d), and mesalamine (1200 mg/d) for CD, the skin lesions were completely resolved and the patient's GI symptoms improved simultaneously.

### Comment

Crohn disease is a chronic inflammatory granulomatous disease of the GI tract that often is associated with reactive cutaneous lesions including EN, pyoderma gangrenosum, necrotizing vasculitis, and epidermolysis bullosa acquisita. Of these, EN is the most common to appear in CD patients and has been reported to occur in 1% to 15% of patients.<sup>3-5</sup> In particular, skin lesions on the leg presenting as tender erythematous nodules and patches are often diagnosed as EN, which is relatively common. In our case, we initially suspected EN due to the rare presentation of MCD and lack of specific clinical features; however, the skin biopsy revealed noncaseating granulomas in the mid to deep dermis and subcutis consistent with MCD.

Metastatic Crohn disease is a rare disease entity and is characterized by the presence of noncaseating granulomas of the skin at sites separated from the GI tract by normal tissue.<sup>1</sup> Although its pathogenesis is unclear, it has been suggested that immune complexes deposited in the skin could be responsible for the granulomatous reactions.<sup>4</sup> A T lymphocyte-mediated type IV hypersensitivity reaction

also could be responsible.<sup>6,7</sup> Because antimicrobial therapy can be curative for infection-related MCD, special histologic stains and/or tissue cultures can help to exclude an infectious etiology.<sup>8</sup>

Clinical presentations of MCD vary greatly, with observations such as single or multiple erythematous swellings, papules, plaques, nodules, abscesses, and ulcers.<sup>1,2</sup> The relationship between these clinical presentations and the intestinal activity of CD still is unknown; in some cases, however, the metastatic granulomatous lesions and the bowel disease show comparable severity.<sup>2,9,10</sup> In a review of the literature, MCD was generally reported to present in the genital area in children. In adults, lesions most frequently present in the genital area, followed by ulcers on the arms and legs.<sup>1,2</sup> These variations in clinical features and location resemble benign or infectious disease and can lead to delays in diagnosis.

Histopathologically, MCD lesions usually are ill-defined noncaseating granulomas with numerous multinucleated giant cells and lymphomononuclear cells located mostly in the dermis and occasionally extending into the subcutis. The cutaneous granulomata are similar to those present in the affected GI tract. Lymphocytes and plasma cells also are commonly present and eosinophils can be prominent.<sup>1,2,11</sup> In some cases of MCD, granulomatous vasculitis of small- to medium-sized vessels can be found and is associated with dermal and subcutaneous granulomatous inflammation.<sup>8,11,12</sup> Misago and Narisawa<sup>13</sup> suggested that granulomatous vasculitis and panniculitis associated with CD is considered to be a rare subtype of MCD. Few cases of MCD presenting as granulomatous panniculitis have been described in the literature.<sup>14-16</sup> Our patient presented with lesions that clinically resembled EN; however, the biopsy was more consistent with MCD. The

## Distinguishing Features of MCD Versus EN<sup>1,2,11-16</sup>

### MCD (Current Case)

### EN

#### Clinical Features

Acute onset; tender, painful, erythematous, warm nodules; unilateral involvement; GI symptoms including abdominal pain, diarrhea, bloody stool

Acute onset; tender, painful, erythematous, warm nodules and plaques; bilateral involvement; fever, fatigue, malaise, arthralgia, and headaches are common; abdominal pain, vomiting, diarrhea, and cough are less frequent; tonsillitis, pharyngitis, and upper respiratory tract infection may precede EN

#### Histopathological Features

Discrete, noncaseating, epithelioid granulomas surrounding lymphocytes present in the deep dermis and subcutaneous layer; mainly lobular panniculitis; granulomatous vasculitis (small-sized vessel)

Early lesion of acute EN: minimal perivascular lymphocytic infiltrate in the dermis (often), septal panniculitis with lymphohistiocytic infiltration (occasional eosinophils and neutrophils), Miescher radial nodule, lacelike pattern of inflammatory cells infiltration into the periphery of the fat lobules, necrosis of the vessel walls is rare; later lesion of acute EN: septal widening often with fibrosis and with inflammation at the edge of the septa and involving the periphery of the fat lobules, neutrophils usually are absent, granulomas formed by macrophage with multinucleated giant cells in the septa

Abbreviations: MCD, metastatic Crohn disease; EN, erythema nodosum; GI, gastrointestinal.

Table summarizes the distinguishing clinical and histopathological features of MCD in our case and classic EN.

Although some authors believe that MCD is not related to CD activity, others assert that MCD lesions may parallel GI activity.<sup>1,2</sup> Our patient was treated with systemic corticosteroids, oral metronidazole, and mesalamine to control the GI symptoms associated with CD. Four weeks after treatment, the GI symptoms and skin lesions improved simultaneously without any additional dermatologic treatment. We believe that MCD has the potential to serve as an early marker of the recurrence of CD and can help with the early diagnosis of CD aggravation, though an association between MCD and CD activity has not been confirmed.

### Conclusion

We reported a case of MCD that was clinically reminiscent of unilateral EN and associated with GI disease activity. Physicians should be aware of the possibility of skin manifestations in CD,

especially when erythematous nodular lesions are present on the leg.

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