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Case Report

Cutaneous Manifestations of Smoldering Inflammatory Bowel Disease: A Report of 2 Cases

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Abstract

Extra-intestinal manifestations are encountered in 6%-47% of patients with inflammatory bowel disease. Musculoskeletal and dermatologic systems are the most frequently affected sites. Some extra-intestinal manifestations arise before the disease flares; therefore, early awareness of these symptoms has great importance in inflammatory bowel disease management. In this article, we describe 2 cases with inflammatory bowel disease exhibiting 2 different skin manifestations, namely, Sweet's syndrome and erythema nodosum, and related issues in the diagnosis and management of extra-intestinal manifestations.

Keywords: Dermatology, cutaneous manifestations of inflammatory bowel disease, extra-int estinal manifestations, inflammatory bowel disease

INTRODUCTION

Inflammatory bowel disease (IBD), referred to as Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, relapsing, immune-mediated inflammation of the gastrointestinal tract. Previous studies from Turkey have demonstrated the incidence of IBD as 2.2/100 000 and 2.09/100 000 for CD and 4.4/100 000 and 4.87/100 000 for UC with a significant male predominance.[1,2] Besides the most common signs and symptoms related to intestinal inflammation, extra-intestinal features including musculoskeletal, gastrointestinal, pulmonary, cardiac, ocular, and dermatologic findings can be associated with IBD. Extra-intestinal manifestations (EIMs) with a prevalence ranging from 6% to 47% are generally parallel with disease activity, whereas some develop independently prior to the onset of IBD symptoms.[3,4] Skin lesions are one of the most common complications of IBD and are divided into 4 different forms composed of specific lesions, reactive lesions, skin manifestations secondary to malnutrition or malabsorption, and those secondary to treatment. Erythema nodosum (EN), which is the most common cutaneous manifestation, frequently occurs in patients with CD and is characterized by painful tender, red nodules most often over the shins. Sweet's syndrome (SS), a rare skin disorder associated with IBD, is characterized by high-grade fever and painful erythematous papulonodular lesions usually affecting the face, neck, and upper limbs.[5]

Herein, we describe 2 cases; one patient with both CD and SS and the other patient diagnosed with both UC and EN.

CASE 1

A 65-year-old woman, a retired bank employee, was admitted to our clinic with a 5-day history of rectal bleeding and constipation. She had a history of ulcerative pancolitis diagnosed 7 years ago. During this period, she had used 5-ASA (aminosalicylic acid) treatment (mesalamine or salazopyrin), but she stopped the treatment when she had no symptoms for the last 3 years. Physical examination revealed no abnormalities, except for active internal hemorrhoids. The patient underwent colonoscopy which disclosed rectal and cecal aphthous ulcers compatible with IBD. Biopsies obtained from the rectal and colonic lesions disclosed intense mucosal eosinophilia, multifocal crypt abscesses with moderately active transmucosal colitis, and findings consistent with UC. A combination treatment of mesalamine enema and oral mesalamine 3 g/day was initiated.

During her follow-up, 1.5 months after active illness, she developed arthralgia and multiple erythematous papules and plaques over her upper and lower extremities. The lesions were painful and showed a pseudo vesicular appearance (Figure 1). Skin biopsy showed neutrophilic dermatosis. Response to systemic steroid therapy was excellent. All the lesions healed with post-inflammatory pigmentation. After 3 years, the patient consulted once again with the abrupt onset of erythematous targetoid skin lesions on her arms (Figure 2). A new skin biopsy revealed a dense neutrophilic infiltrate of the upper and mid-dermis, leucocytoclasia, extravasated erythrocytes, and plump endothelial cells compatible with diffuse

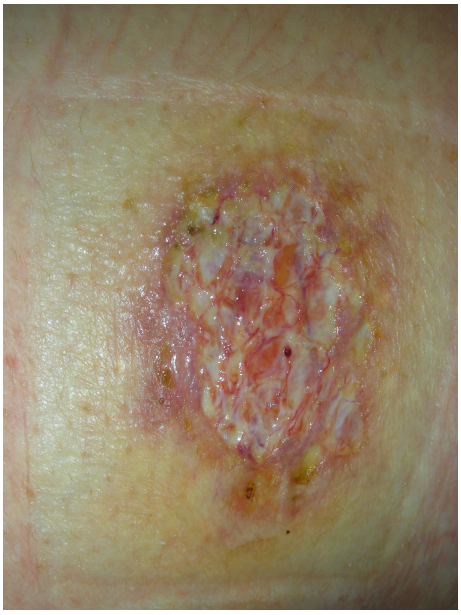

Figure 1. Well demarcated erythematous and edematous lesions with pseudo vesicular appearance on the extensor surface of the leg.

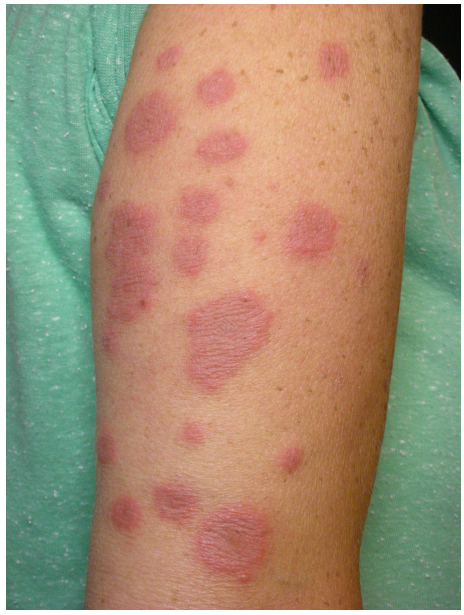

Figure 2. Erythematous targetoid skin lesions that occurred suddenly on the arm.

neutrophilic dermatosis. A diagnosis of SS was made by the presence of 2 major and 2 minor criteria.[6] Meanwhile, multiple new lesions appeared on the legs and thighs. Following systemic steroid therapy, the patient was free of lesions with the exception of an ulcerated plaque on the right thigh after 3 months (Figure 3). Low-dose methylprednisolone 32 mg/day and intralesional steroid injections provided cure. She also experienced a flare-up of her IBD symptoms at the same time with skin lesions.

During her follow-up visits within the succeeding 3 years, she had several colitis flares that required short courses of methylprednisolone. Given her need for frequent corticosteroids over the previous years, she was started on adalimumab injections. However, as her symptoms persisted and she failed to improve under this treatment, the patient underwent a total proctocolectomy with an ileal pouch–anal anastomosis. The pathology of resected colon confirmed ulcerative pancolitis. Three years after the operation, the patient is well, apart from a mild pouchitis, which improved with high-dose probiotic (VSL # 3) treatment.

CASE 2

A 39-year-old woman presented with rectal pain for the last 2 weeks. Initial laboratory tests revealed nothing abnormal, except for an elevated C-reactive protein level of 1.67 mg/dL (normal < 0.5 mg/dL). Physical examination revealed an anal fissure. Pelvic Magnetic Resonance Imaging (MR) disclosed an 8-mm-sized abscess at 12 o'clock position with surrounding induration. After medical treatment with antibiotics and drainage of the abscess, her complaints improved.

Two years later, exacerbation of intestinal symptoms occurred with rectal and abdominal pain. Increased fecal calprotectin levels (1395 mg/kg, N < 50 mg/kg) were detected. Infectious etiology has been ruled out through an extensive laboratory work-up. Colonoscopy revealed round ulcers with a diameter of 3-8 mm and white exudates in the terminal ileum and the ascending colon. The patient was diagnosed with ileo-colonic CD and was started on mesalazine

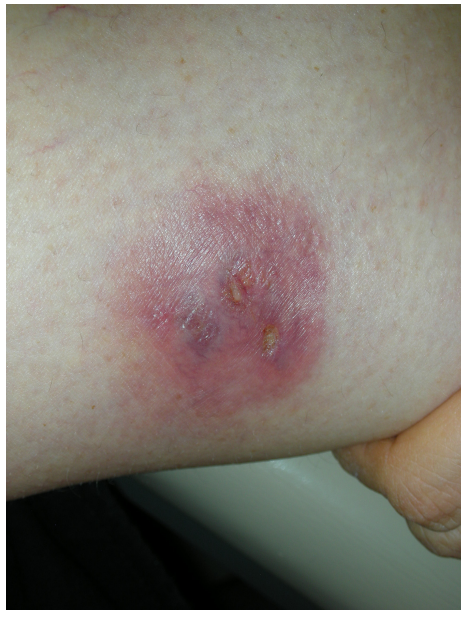

Figure 3. Persisting ulcerated plaque on the right thigh despite systemic steroid therapy.

MAIN POINTS

- Cutaneous manifestations of inflammatory bowel disease (IBD) may range from mild skin lesions to severe forms.
- The presence of IBD-related skin manifestations should alert the clinician to screen the patient for an associated silent IBD.
- A specific skin manifestation could be a harbinger of IBD flare and should be carefully evaluated.
- Early diagnosis and management of extra-intestinal manifestations can help to control the activity of IBD.

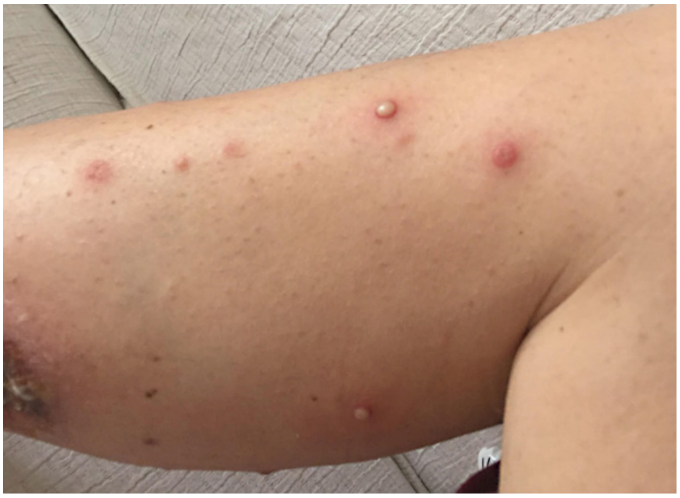

Figure 4. Erythematous papular lesions on the lower extremities.

(3 × 800 mg) and budesonide (3 × 3 mg) treatment which led to the improvement of her symptoms.

At her follow-up visits, she developed a painful, swollen subcutaneous nodular lesion of 3 cm diameter on the extensor surface of her leg, which was clinically suggestive of EN. There was no history of Behcet's disease or sarcoidosis. When new nodules and arthralgia started to appear, a biopsy carried out from the nodule demonstrated interstitial dermatitis and neutrophilic septal panniculitis, consistent with the acute stage of EN.

While her IBD was under remission, joint pain and erythematous, tender, and well-demarcated pretibial nodular lesions recurred on the extensor surface of her both legs (Figure 4). Histopathology of the skin biopsy revealed an abscess formation within the subcutaneous adipose tissue with surrounding vessel proliferation suggesting infectious dermatitis and panniculitis. Treatment with prednisolone resulted in the improvement of skin lesions and arthritis.

During the follow-up, the patient got pregnant and delivered a healthy baby at term. She did not use any medication during her pregnancy. Two years after the delivery, she was diagnosed with breast cancer for which she received both chemo-radiotherapy.

During her follow-up colonoscopies, hyperemic mucosa and ulcerative lesions both in sigmoid and transverse colon were detected. Histopathologic examination of the specimen disclosed moderately active colitis, goblet cell depletion in crypts with apoptotic crypt abscesses, which were more compatible with a diagnosis of CD. As the patient was steroid-dependent and also had breast cancer history, vedolizumab therapy was initiated when she was in complete remission from breast cancer. This treatment had no effect on bowel and skin lesions. Since she was tumor-free for years, vedolizumab was switched to infliximab infusions at a dose of 400 mg once every 8 weeks in consultation with oncologists. At the second infusion, the bowel symptoms improved, and the skin lesions disappeared completely. The patient is well and continues her anti-TNF treatment .

DISCUSSION

Extra-intestinal manifestations associated with IBD include musculoskeletal, gastrointestinal, pulmonary, cardiac, ocular, and dermatologic disorders. Extra-intestinal manifestations are relatively common throughout the IBD course and pose considerable morbidity and mortality. Although the relationship between IBD and associated EIM is not well understood, they have some pathogenic mechanisms in common.

Cutaneous manifestations are one of the most frequent EIMs in patients with IBD and occur in up to 15% of IBD patients.[7] They can range from mild skin lesions such as aphthous ulcers and EN to more severe forms such as SS and pyoderma gangrenosum. The most common conditions include EN, pyoderma gangrenosum, SS, and oral aphthous lesions. Sweet's syndrome and pyoderma gangrenosum are neutrophilic dermatoses characterized by dense neutrophilic infiltration of the affected tissue. For the diagnosis of SS major and minor, criteria are defined. Accordingly, diagnostic criteria are met by abrupt onset of erythematous painful nodules, a predominantly neutrophilic infiltration (major criteria), association of inflammatory bowel disease, and excellent response to systemic steroid treatment (minor criteria). Sweet's syndrome generally correlates with intestinal-IBD activity but may precede the diagnosis as well. On the second SS attack of our patient, systemic steroids could control the disease within 5 months. Since this is a reactive skin condition, underlying disease activity was a concern in this patient.

Early diagnosis and management of EIMs can help early control of a flare in IBD patients. The treatment of neutrophilic dermatoses usually requires 4-6 weeks of glucocorticoid therapy. Drugs that have been successfully implemented as glucocorticoid-sparing agents include dapsone, azathioprine, tacrolimus, and methotrexate.[8] Tumor necrosis factor (TNF)-alpha inhibitors have been shown to be helpful in refractory disease.[8] While the efficacy of anti-TNF drugs has been well-demonstrated, the role of other biologics, such as vedolizumab, remains unclear. In our case, vedolizumab was not beneficial for clinical improvement in IBD. Prospective long-term studies are needed to confirm the effect of vedolizumab and other biologics on the management of EIMs. Recently, ustekinumab provided higher clinical benefit in this group of patients.[9]

As cutaneous manifestations may occur before the diagnosis of IBD, the presence of IBD-related skin lesions must alert the physician to screen the patient for an underlying silent IBD. In fact, these manifestations can present after years in advanced IBD, as well as simultaneously or later.[10] In a great majority of patients with EN and to a lesser extent, with pyoderma gangrenosum, the cutaneous features are closely related to flare-ups of the IBD.[11]

A detailed physical examination plays an important role in the diagnosis and management of these patients. Specific skin manifestations, such as EN or SS, as was the case in our patients, could be a harbinger of an IBD flare and should be carefully evaluated by a multidisciplinary team for the early diagnosis and treatment of underlying IBD.

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