

# Metastatic Vulvovaginal Crohn Disease in the Setting of Well-Controlled Intestinal Disease

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## PRACTICE POINTS

- Metastatic Crohn disease involves skin noncontiguous with the gastrointestinal tract and may involve any portion of the cutis.
- Vulvoperineal Crohn disease should be considered in the differential diagnosis of chronic vulvar pain, swelling, and pruritus, especially in cases resistant to standard therapies and regardless of whether or not gastrointestinal tract symptoms are present.
- Skin biopsy usually confirms the diagnosis by revealing noncaseating granulomas in the dermis.

The cutaneous manifestations of Crohn disease (CD) are varied and include pyoderma gangrenosum, erythema nodosum, and metastatic CD (MCD). The latter is defined as the occurrence of granulomatous lesions at a skin site distant from the gastrointestinal tract. Metastatic CD involving the vulva and perineum is rare and thus often is difficult to diagnose. It may precede, coincide with, or develop after the initial diagnosis of intestinal disease. A variety of clinical presentations have been described, including widespread nonspecific pain and swelling, erythematous papules and plaques, and nonhealing ulcers. The diagnosis often is delayed because of a low index of suspicion brought about by the rarity of the disease and its diverse and confusing manifestations. A skin biopsy usually confirms the diagnosis by revealing noncaseating granulomas in the dermis. Multiple oral and parenteral therapies are available, with surgical intervention reserved for resistant cases. We present a case of vulvovaginal MCD in the setting of well-controlled intestinal disease.

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The cutaneous manifestations of Crohn disease (CD) are varied, including pyoderma gangrenosum, erythema nodosum, and metastatic CD (MCD). First

described by Parks et al,<sup>1</sup> MCD is defined as the occurrence of granulomatous lesions at a skin site distant from the gastrointestinal tract.<sup>1-20</sup> Metastatic CD presents a diagnostic challenge because it is a rare component in the spectrum of inflammatory bowel disease complications, and many physicians are unaware of its existence. It may precede, coincide with, or develop after the diagnosis of intestinal disease.<sup>2-5</sup> Vulvoperineal involvement is particularly problematic because a multitude of other, more likely disease processes are considered first. Typically it is initially diagnosed as a presumed infection prompting reflexive treatment with antivirals, antifungals, and antibiotics. Patients may experience symptoms for years prior to correct diagnosis and institution of proper therapy. A variety of clinical presentations have been described, including nonspecific pain and swelling, erythematous papules and plaques, and nonhealing ulcers. Skin biopsy characteristically confirms the diagnosis and reveals dermal noncaseating granulomas. Multiple oral and parenteral therapies are available, with surgical intervention reserved for resistant cases. We present a case of vulvovaginal MCD in the setting of well-controlled intestinal disease. We also provide a review of the literature regarding genital CD and emphasize the need to keep MCD in the differential of vulvoperineal pathology.

## Case Report

A 29-year-old woman was referred to the dermatology clinic with vulvar pain, swelling, and pruritus of 14 months' duration. Her medical history was remarkable for CD following a colectomy with colostomy. Prior therapies included methotrexate with infliximab for 5 years followed by a 2-year regimen with adalimumab, which induced remission of the intestinal disease.

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The patient previously had taken a variety of topical and oral antimicrobials based on treatment from a primary care physician because fungal, bacterial, and viral infections initially were suspected; however, the vulvar disease persisted, and drug-induced immunosuppression was considered to be an underlying factor. Thus, adalimumab was discontinued. Despite elimination of the biologic, the vulvar disease progressed, which prompted referral to the dermatology clinic.

Physical examination revealed diffuse vulvar edema with overlying erythema and scale (Figure 1A). Upon closer inspection, scattered violaceous papules atop a backdrop of lichenification were evident, imparting a cobblestone appearance (Figure 1B). Additionally, a fissure was present on the gluteal cleft. Biopsy from the left labia majora demonstrated well-formed granulomas within a fibrotic reticular dermis (Figures 2A and 2B). The granulomas consisted of both mononucleated and multinucleated histiocytes, rimmed peripherally by lymphocytes and plasma cells (Figure 2C). Periodic acid–Schiff–diastase and acid-fast bacilli stains as well as polarizing microscopy were negative.

Given the patient's history, a diagnosis of vulvoperineal MCD was rendered. The patient was started on oral metronidazole 250 mg 3 times daily with topical fluocinonide and tacrolimus. She responded well to this

treatment regimen and was referred back to the gastroenterologist for management of the intestinal disease.

### Comment

Crohn disease is an idiopathic chronic inflammatory condition that primarily affects the gastrointestinal tract, anywhere from the mouth to the anus. It is characterized by transmural inflammation and fissures that can extend beyond the muscularis propria.<sup>4,6</sup> Extraintestinal manifestations are common.<sup>3</sup>

Cutaneous CD often presents as perianal, perifistular, or peristomal inflammation or ulceration.<sup>7</sup> Other skin manifestations include pyoderma gangrenosum, erythema nodosum, erythema multiforme, epidermolysis bullosa acquisita, and palmar erythema.<sup>7</sup> Metastatic CD involves skin noncontiguous with the gastrointestinal tract<sup>1-20</sup> and may involve any portion of the cutis. Although rare, MCD is the typical etiology underlying vulvar CD.<sup>8</sup>

Approximately 20% of MCD patients have cutaneous lesions without a history of gastrointestinal disease. More than half of cases in adults and approximately two-thirds in children involve the genitalia. Although more common in adults, vulvar involvement has been reported in children as young as 6 years of age.<sup>2</sup> Diagnosis is especially challenging when bowel symptoms are absent;



**FIGURE 1.** Metastatic vulvovaginal Crohn disease with diffuse vulvar edema with overlying erythema and scale (A). A closer view showed violaceous papules in a background of lichenification, edema, and erythema, imparting a cobblestone appearance (B).

**FIGURE 2.** A punch biopsy from the left labia majora revealed epidermal acanthosis with spongiotic vesicles. Within a fibrotic dermis, there were perivascular and interstitial lymphocytic and granulomatous infiltrates (A and B)(H&E, original magnifications  $\times 20$  and  $\times 100$ ). A high-power view demonstrated a well-formed granuloma composed of mononucleated and multinucleated histiocytes surrounded by lymphocytes and plasma cells (C)(H&E, original magnification  $\times 200$ ). Reference bars indicate 100  $\mu\text{m}$ .

those patients should be evaluated and followed for subsequent intestinal involvement.<sup>6</sup>

Clinically, symptoms may include general discomfort, pain, pruritus, and dyspareunia. Psychosocial and sexual dysfunction are prevalent and also should be addressed.<sup>9</sup> Depending on the stage of the disease, physical examination may reveal erythema, edema, papules, pustules, nodules, condylomatous lesions, abscesses, fissures, fistulas, ulceration, acrochordons, and scarring.<sup>2-6,10,11</sup>

A host of infections (ie, mycobacterial, actinomycosis, deep fungal, sexually transmitted, schistosomiasis), inflammatory conditions (ie, sarcoid, hidradenitis suppurativa), foreign body reactions, Melkersson-Rosenthal syndrome, and sexual abuse should be included in the differential diagnosis.<sup>2,6,10-12</sup> Once infection, sarcoid, and foreign body reaction have been ruled out, noncaseating granulomas in skin are highly suggestive of CD.<sup>7</sup>

Histopathologic findings of MCD reveal myriad morphological reaction patterns,<sup>5,13</sup> including high-grade dysplasia and carcinoma of the vulva; therefore, it may be imprudent to withhold diagnosis based on the absence of the historically pathognomonic noncaseating granulomas.<sup>5</sup>

The etiopathogenesis of MCD remains an enigma. Dermatopathologic examinations consistently reveal a vascular injury syndrome,<sup>13</sup> implicating a possible circulatory system contribution via deposition of immune complexes or antigens in skin.<sup>7</sup> Bacterial infection has been implicated in the intestinal manifestations of CD; however, failure to detect microbial ribosomal RNA in MCD biopsies refutes theories of hematogenous spread of microbes.<sup>13</sup> Another plausible explanation is that antibodies are formed to conserved microbial epitopes following loss of tolerance to gut flora, which results in an excessive immunologic response at distinct sites in susceptible individuals.<sup>13</sup> A T-lymphocyte-mediated type IV hypersensitivity reaction also has been proposed via cross-reactivity of lymphocytes, with skin antigens precipitating extraintestinal granuloma formation and vascular injury.<sup>3</sup> Clearly, further investigation is needed.

Magnetic resonance imaging can identify the extent and anatomy of intestinal and pelvic disease and can assist in the diagnosis of vulvar CD.<sup>10,11,14</sup> For these reasons, some experts propose that imaging should be instituted prior to therapy,<sup>12,15,16</sup> especially when direct extension is suspected.<sup>17</sup>

Treatment is challenging and often involves collaboration among several specialties.<sup>12</sup> Many treatment options exist because therapeutic responses vary and genital MCD is frequently recalcitrant to therapy.<sup>4</sup> Medical therapy includes antibiotics such as metronidazole, corticosteroids (ie, topical, intralesional, systemic), and immune modulators (eg, azathioprine, 6-mercaptopurine, cyclosporine, methotrexate, mycophenolate mofetil, tumor necrosis factor  $\alpha$  inhibitors).<sup>2,3,6,10,16,18</sup> Thalidomide has been used for refractory cases.<sup>19</sup> These treatments can be used alone or in combination. Patients should be monitored for side effects and informed that many treatment regimens may be required before a sustained response is achieved.<sup>4,16,18</sup> Surgery is reserved for the most resistant cases. Extensive

radical excision of the involved area is the best approach, as limited local excision often is followed by recurrence.<sup>20</sup>

## Conclusion

Our case highlights that vulvar CD can develop in the setting of well-controlled intestinal disease. Vulvoperineal CD should be considered in the differential diagnosis of chronic vulvar pain, swelling, and pruritus, especially in cases resistant to standard therapies and regardless of whether or not gastrointestinal tract symptoms are present. Physicians must be cognizant that vulvar signs and symptoms may precede, coincide with, or follow the diagnosis of intestinal CD. Increased awareness of this entity may facilitate its early recognition and prompt more timely treatment among women with vulvar disease caused by MCD.

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