

# Metastatic vulvar Crohn's disease preceding intestinal manifestations: a case report and short review

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## Abstract

Crohn's disease (CD) is a multi-systemic chronic granulomatous inflammatory disease with a constellation of extraintestinal manifestations affecting various organs, including the skin. Metastatic CD (MCD), defined as granulomatous lesions of the skin occurring at sites separate from the gastrointestinal (GI) tract in patients affected with CD, is the least common cutaneous manifestation, and it is occasionally the primary manifestation of the disease. It may precede any symptoms from the GI tract by months or even years, and it often remains undiagnosed. We present the case of a 42-year-old woman with a rare cutaneous manifestation of MCD involving the external genitalia. The cutaneous lesions of the mons pubis and vulva preceded GI manifestations of CD by 2 years. The patient was treated with azathioprine, oral steroids, and antibiotics. Reduction of the cutaneous nodules, discharge, and erythema was achieved, accompanied by relief of GI symptoms. Response to treatment was maintained during a follow-up of 6 months. In MCD, involvement of the external genitalia is exceedingly rare, with few documented cases in the literature. The integration of clinical information, microscopic findings, and exclusion of other cutaneous granulomatous processes is necessary in order to accurately diagnose this rare dermatologic entity and provide an opportunity for successful therapeutic intervention.

**Keywords:** metastatic Crohn's disease, inflammatory bowel disease, noncaseating granuloma, cutaneous manifestations of Crohn's disease

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## Introduction

The entity known as metastatic Crohn's disease (MCD) was first described by Parks et al. in 1965 (1) and refers to the presence of sterile, non-caseating granulomatous skin lesions at sites non-contiguous with the gastrointestinal (GI) tract in patients with Crohn's disease (CD) (2–3).

MCD is the least common dermatologic manifestation of CD, with as few as 100 cases reported in the literature since 1965 (2, 4). The most common site of cutaneous involvement in CD is the perineal area. Involvement of the external genitalia is exceedingly rare, with few documented cases in the literature. MCD may precede, develop concurrently with, or follow any symptoms from the GI tract by months or even years, and it often remains undiagnosed (5–6).

We present a rare case report of a 42-year-old female patient diagnosed with MCD of the external genitalia preceding the GI manifestations by 2 years, and we discuss the various manifestations and treatment options.

## Case report

A 42-year-old HIV-negative Caucasian woman presented to our department with a 2-year history of progressively increasing painful bilateral edema and erythema in the vulvar area with spontaneous periodic bloody or purulent discharge. During the previous 2 months, she also complained of mild localized left lower quadrant abdominal pain accompanied by frequent bowel movements and mucus in the stool. There was no fever or vaginal discharge.

Past medical history included papillary thyroid gland carcinoma 1 year earlier, which was successfully treated with surgery. The

patient had been receiving 137 µg of thyroxine daily since then. Her family medical history was unremarkable.

Physical examination revealed hardness in the vulva and the presence of small abscesses and cauliflower, genital wart-like lesions in the absence of concurrent inguinal lymphadenopathy.

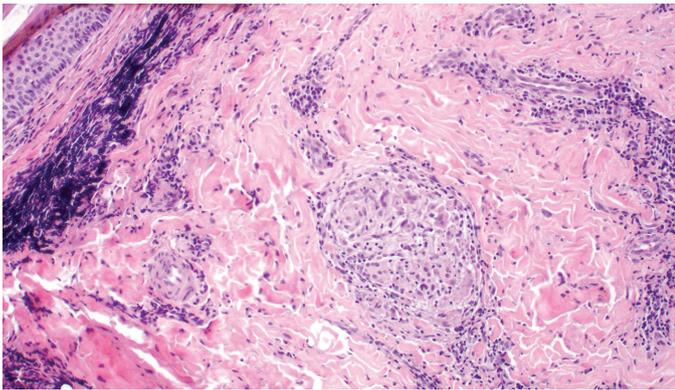
The clinical differential diagnosis of the vulvar cutaneous lesions included MCD, granulomatous diseases (sarcoidosis, tuberculosis, or other mycobacterial infection), sexually transmitted diseases such as lymphogranuloma venereum or granuloma inguinale, deep fungal infection, actinomycosis, chronic primary or secondary lymphedema, hidradenitis suppurativa, and foreign body reaction.

Two skin biopsies from the mons pubis and labia majora were obtained. Histopathological examination (Fig. 1) revealed the presence of multiple cutaneous noncaseating granulomas and multinucleated giant cells in the pubic area that were noncontiguous with the GI tract as well as a sufficient number of dilated lymphatic vessels, suggestive of lymphedema in the labia majora and labia minora of the vulva.

All hematological, biochemical, and immunological investigations, including tumor markers, angiotensin converting enzyme (ACE), VDRL, and viral markers, were either negative or within the normal range, with the exception of a small increase in CRP at 3.0 mg/dl (normal reference value: ≤ 0.5 mg/dl). The Mantoux test was negative.

Direct gram staining and cultures of the rectum, vagina, and cervix, as well as skin lesions of the vulva, were negative for fungi, protozoa, and bacteria, including *Haemophilus ducreyi*, *Klebsiella granulomatis*, *Chlamydia trachomatis*, *Mycobacterium tuberculosis*, and atypical mycobacteria.

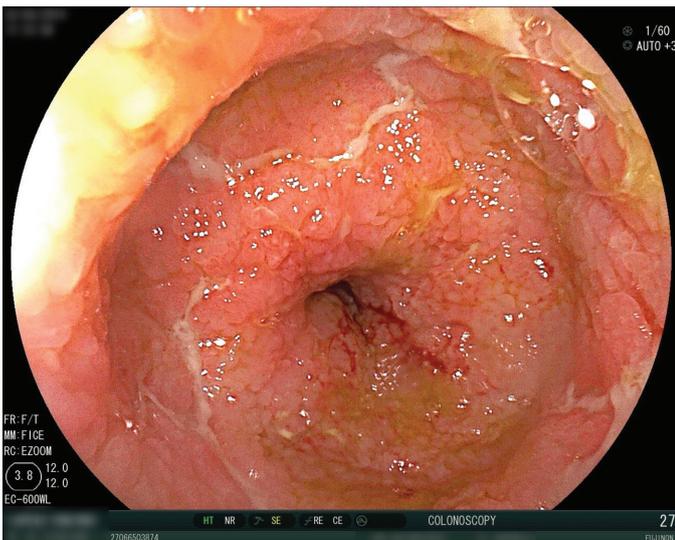
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**Figure 1** | Hematoxylin and eosin (H&E) section of the vulvar biopsy demonstrating aspects of chronic inflammation with the presence of a noncaseating granuloma and multinucleated giant cells in the dermis ( $\times 100$ ).

Chest X-ray examination revealed no pathological findings. Ultrasonography and magnetic resonance imaging (MRI) scan of the abdomen and pelvic organs revealed inflammation of the skin and subcutaneous fat in the inferior anterior abdominal wall with extension to the external genital organs as well as multiple swollen regional and perirectal lymph nodes. Colonoscopy (Fig. 2) and biopsies taken from the intestinal mucosa were consistent with CD.

On the basis of the clinical, laboratory, and endoscopic data, and the exclusion of other granulomatous and infectious diseases, the diagnosis of “metastatic” vulvar CD was established.



**Figure 2** | Conventional colonoscopy of the patient with an estimated Simple Endoscopic Score for CD (SES-CD) value of 4. Typical endoscopic features of CD are present, including mucosal inflammation, nodularity, and deep linear ulcerations with discrete margins in the terminal ileum and ileocecal valve.

The patient was initially started on oral antibiotics (ciprofloxacin 500 mg b.i.d. and metronidazole 500 mg t.i.d.) for 2.5 months and oral methylprednisolone (32 mg/day) with tapering to the maintenance dosage of 6 mg/day over a period of 6 months. She reported complete relief of GI symptoms along with substantial clinical improvement of the cutaneous edema and erythema. However, the patient developed moderate Cushing's syndrome and suffered from periodic recurrences of the nodules. Azathioprine was used as an “add-on” therapy to oral steroid treatment at a dosage of 150 mg/day and the maintenance methylprednisolone dose was gradually reduced to 2 mg daily. After 6 months of treatment with azathioprine along with oral steroids, both intestinal and cutaneous CD remain in remission, with noticeable reduction of the nodules and discharge (Fig. 3), but only minimal morphological improvement of the labial lymphedema.



**Figure 3** | Vulvar lesions before (left) and 1 year after treatment initiation (right).

## Discussion

First described by Crohn et al. (7), CD is a chronic granulomatous inflammatory bowel disorder characterized by subacute or chronic necrotizing inflammation of the terminal ileum that may also affect any region of the GI tract from the mouth to the anus (3). At the same time, a constellation of extraintestinal manifestations affecting various organs may occur, including ocular findings, musculoskeletal pathology, and mucocutaneous manifestations (8).

A multitude of associated cutaneous manifestations have been described, which may significantly contribute to the morbidity and impairment of the overall quality of life of the affected patients (9). It is estimated that 18 to 44% of patients with CD have some form of cutaneous manifestation (10).

Depending on the pathogenetic mechanism, the cutaneous manifestations of CD may be subdivided into four categories, including specific and reactive cutaneous manifestations, cutaneous disorders with a strong association with CD, and secondary cutaneous manifestations due to nutritional deficiencies or adverse reactions of the treatment (3, 6, 9, 11).

MCD is an uncommon specific cutaneous manifestation, with vulvar involvement in particular being exceedingly rare. MCD is defined as granulomatous lesions of the skin occurring at sites separate from the GI tract in patients affected with CD. It most commonly affects adult females with already established intestinal CD (6, 12).

No clear correlation between the presence of MCD and the activity of the intestinal disorder or its response to treatment severity has been established (2). In fact, although the majority of MCD cases present after at least 6 months of initiation of GI symptoms, skin lesions may also present during—and in rare cases prior to—the onset of inflammatory bowel disease (2, 13).

MCD is known as a great mimicker and is often misdiagnosed (6, 14). Lesions vary in morphology (6, 10) and may present as cutaneous ulcerations, plaques with or without ulceration, papules, or nodules (15). According to Barret et al., four main types of vulvar lesions may be observed, including vulvar swelling or edema, ulceration, hypertrophic lesions presenting as pseudo-condylomata acuminata, and chronic suppuration (16). A detailed history and thorough physical examination may help narrow the differential; however, the confirmation of the clinical diagnosis is based on the histological findings, which are identical to those of CD (17). The hallmark histopathologic features include an inflammatory infiltrate located primarily in the superficial papillary and deep reticular dermis with occasional extension into the subcutis (3) consisting of discrete, non-caseating granulomas with Langerhans-type

giant cells (10, 18), epithelioid histiocytes, lymphocytes, and occasional plasma cells (3, 6, 19).

In our case, the diagnosis of metastatic vulvar CD was supported by the GI manifestations, chronicity of the lesions, histological findings, and exclusion of other granulomatous and infectious disease.

The evolution of MCD can be unpredictable and sometimes refractory to medical treatment, although cases with spontaneous healing have also been reported (20). An established standard therapy for MCD remains underwhelming due to the lack of randomized control studies and definite guidelines (6, 20–21). In the literature, the initial management of MCD is medical, including topical antibiotics and topical, oral, or intralesional steroids (3), oral antibiotics (most commonly ciprofloxacin and metronidazole) (16, 22), sulfasalazine, and immunosuppressive agents such as azathioprine and cyclosporine (2, 16, 21–22). The introduction of anti-tumor necrosis factor (TNF) agents during the past two decades also marked an important milestone in the management of CD. Nevertheless, despite the significant response and remission rates achieved with anti-TNF therapy, the utility of these agents has been hampered by primary and secondary nonresponse in a significant proportion of patients (23). Ustekinumab is a laboratory-manufactured IgG<sub>1</sub>K monoclonal antibody representing an interesting new therapeutic option for the treatment of patients with CD that are refractory or intolerant to either conventional treatments or anti-TNF agents. It targets the p40 subunit shared by two proinflammatory cytokines, IL-12 and IL-23, thereby preventing their interaction with the receptor and blocking subsequent signaling (24–26). Vedolizumab is also a monoclonal IgG-1 anti-

body, with activity as an  $\alpha 4\beta 7$  integrin heterodimer antagonist. Via selective inhibition of the interaction between  $\alpha 4\beta 7$  integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1), vedolizumab inhibits the leukocyte binding to endothelial surface and its extravasation into inflamed GI parenchymal tissue. Both of these new therapeutic options appear to be associated with rapid and sustained clinical effect, paralleled by a favorable safety profile, dampening of the inflammatory cascade, and lack of immunogenicity (26–27). The recovery of skin lesions in MCD is variable and does not parallel that of intestinal lesions. When medical management fails, surgical excision may be considered in patients with either severe symptoms or disfigurement that interferes with the patient's social and private life (16, 28).

In our patient, treatment of vulvar CD with oral antibiotics and corticosteroids led to an initial clinical improvement, which was soon followed by clinical deterioration. Because she was not considered a suitable candidate for anti-TNF therapy due to her recent papillary thyroid carcinoma, treatment with azathioprine was chosen instead, with significant improvement.

## Conclusions

Patients with CD often develop dermatologic sequelae, with MCD being a rare but serious process. Awareness that such involvement may precede GI symptoms is important because vulvar manifestations of CD may be a cause of high morbidity if not promptly recognized. As such, particularly in the case of unusual sites of predilection, such as the vulva, a high index of suspicion is required for proper diagnosis and treatment.

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