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Single Case

Delayed Diagnosis of Vulvar Crohn's Disease in a Patient with No Gastrointestinal Symptoms

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Vulvar Crohn's disease · Tumor necrosis factor-α inhibitors · Absence of gastrointestinal symptoms · Infliximab

Abstract
Though Crohn's disease primarily affects the gastrointestinal tract, cutaneous Crohn's disease of the vulva can occur in the absence of gastrointestinal symptoms, complicating the diagnosis. Once clinicians suspect cutaneous Crohn's disease, antibiotics and traditional immunosuppressants comprise initial treatment. Unfortunately, sometimes these therapies are not effective, or they provide only short-lived symptomatic improvement. A few case reports have found tumor necrosis factor-α inhibitors to be helpful in such refractory cases. We describe a patient with long-standing, painful vulvar Crohn's lesions with no gastrointestinal manifestations of the disease. Her diagnosis was delayed for years, and initial therapy with antibiotics and steroids was unsuccessful. Finally, the patient experienced effective and long-lasting symptom improvement with infliximab (Remicade™).

Introduction

Cutaneous Crohn's disease of the vulva is a rare condition with a diverse pattern of presentation [1]. In patients without a prior documented history of Crohn's disease, the

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condition may not be considered for years [2]. Moreover, due to the rarity of cutaneous vulvar Crohn's disease, there are no well-established treatment strategies. Traditional first-line therapy consists of antibiotics and immunosuppressants [2, 3]. Tumor necrosis factor (TNF) inhibitors, have recently demonstrated effectiveness in the treatment of severe cases [2, 4–6]. The patient we describe suffered from painful vulvar lesions for years before she was diagnosed with cutaneous Crohn's disease. Of note, her vulvar lesions were the initial manifestation of Crohn's disease. Though prior attempts at treatment with antibiotics and steroids were ineffectual, infliximab provided substantial and lasting improvement in her symptoms.

Case Presentation

A 55-year-old female presented to the dermatology office with a chief complaint of extremely painful vulvar ulcers that had been present for several years, substantially decreasing her quality of life. She had required multiple hospital visits, but none resulted in a clear diagnosis. Previous treatment included antibiotic therapy, which was not effective, and oral steroid therapy that only alleviated her symptoms for a short time. On examination, the groin, vulva, and perianal region were diffusely erythematous, swollen, and weeping with some hyperkeratotic lesions present (Fig. 1). At that time, serologic testing for lymphogranuloma venereum, syphilis, and HIV were negative for current infection. Immunofluorescence staining was negative for spirochetes, herpes simplex virus, and varicella zoster virus. A biopsy was performed, revealing no microorganisms on special staining. Acute on chronic inflammation as well as non-necrotizing granulomas were present, consistent with possibly infectious granulomatous disease, or granulomatous vulvitis associated with Crohn's disease or sarcoidosis. A normal chest computed tomography suggested that sarcoidosis and tuberculosis were unlikely. Even though the patient had no history of gastrointestinal symptoms, the most likely diagnosis was cutaneous Crohn's disease. Infliximab infusions, over the course of several months, led to dramatic and sustained improvements in the patient's symptoms. She was referred to the appropriate specialists to have a colonoscopy and further evaluation for possible gastrointestinal involvement.

Discussion

Anogenital granulomatosis can have multiple etiologies. Underlying disease is detected in 38.4% of the patients, with the most common being Crohn's disease (33% of the cases) [7]. Crohn's disease is a systemic inflammatory condition, predominantly known for its effects on the gastrointestinal system. However, it has been estimated that cutaneous symptoms are present in 18–44% of the patients with Crohn's disease [8]. Vulvar Crohn's disease is a rare cutaneous manifestation, with only 124 cases reported in the literature [2]. The development of vulvar lesions can occur as a direct extension of intestinal involvement or as a noncontiguous complication in which there is no direct connection between the gastrointestinal tract and genitalia, as suspected in our patient [3]. It has been proposed that a T lymphocyte-mediated type IV reaction is responsible for the latter "metastatic" Crohn's disease [4]. Some suggest this reaction is to gut antigens that have traveled to the skin. Others hypothesize that antibodies sensitized to gut antigens may be subsequently cross-reacting with skin antigens [8].

The most common presentation of vulvar Crohn's disease is edema, but hypertrophic lesions can also occur, as in our patient. Furthermore, one study found concomitant perianal

lesions in 48% of the patients [1]. Additionally, although most cases of vulvar Crohn's disease cause minimal discomfort, this same study found vulvar pain in 34% of the patients, and pruritus in 9%, both significantly affecting the quality of life [1]. In long-standing disease, patients may develop "knife-cut" ulcers that are highly specific for cutaneous Crohn's disease [1, 3]. The multiple presentations of vulvar Crohn's disease lead to difficulty in the clinical recognition of the condition.

Further complicating the diagnosis, studies show that 20–36% of the patients with vulvar Crohn's disease will not exhibit any gastrointestinal symptoms, and vulvar Crohn's disease will be the first manifestation of their underlying disease [3]. Not surprisingly, a preceding diagnosis of gastrointestinal disease increases the likelihood of a prompt diagnosis of cutaneous Crohn's disease [2]. Therefore, a high index of suspicion is necessary for the timely diagnosis of vulvar disease, especially in patients with no prior documented history of Crohn's disease.

Differential diagnoses for vulvar lesions are numerous, including infectious causes such as tuberculosis, lymphogranuloma venereum, syphilitic chancre, and herpetic lesions [1, 3, 9]. It is also important to consider noninfectious possibilities, such as pyoderma gangrenosum and sarcoidosis [1, 3, 9]. Serologic testing and immunochemical staining can rule out venereal disease. Tuberculosis screening with intradermal tuberculin reaction or the QuantiFERON™-TB Gold test with a chest radiograph can evaluate for tuberculosis [1]. Obtaining tissue biopsy of a lesion is a wise step after this initial workup, as special staining for microorganisms can further rule out infection. In addition, the presence of subacute or chronic inflammatory infiltrate with noncaseating granulomas supports the diagnosis of cutaneous Crohn's disease [1, 3, 9]. A chest radiograph can rule out the other common cause of noncaseating granulomas, sarcoidosis. If cutaneous Crohn's disease is suspected, providers should arrange a gastroscopy and ileocolonoscopy with or without an abdominopelvic computed tomography scan to search for gastrointestinal Crohn's lesions [1]. If no evidence of Crohn's disease is found at that time, the disease can simply be labeled as anogenital granulomatosis. Treatment is similar regardless of the diagnosis as cutaneous Crohn's disease or anogenital granulomatosis of unknown origin [10].

Studies show that the natural course of vulvar Crohn's disease is unpredictable. Though some cases resolve spontaneously, the clear majority are persistent [4, 11]. Further, earlier treatment is more effective, before the tissue has undergone reorganization secondary to long-standing edema [11]. Because it is relatively rare, there are no randomized trials suggesting a particular treatment for vulvar Crohn's disease [8]. Further, the presently reported prospective studies and case series do not provide long-term follow-up data. Therefore, the literature presents no reliable recurrence rates following treatment [1]. Oral antibiotics, particularly metronidazole, have frequently been used as first line therapy [3]. Unfortunately, as with our patient, antibiotics are not always effective. Even if antibiotics are successful, rapid recurrence typically occurs when they are stopped [8, 12]. Oral steroids are also frequently utilized in vulvar Crohn's disease. Unfortunately, perineal Crohn's disease has been shown to be poorly controlled with steroids [8]. Many patients, like ours, experience initial improvement, but their symptoms eventually return. Other immunosuppressants such as cyclosporine, azathioprine, and 6-mercaptopurine are also treatment options, as they have shown some effectiveness [11]. In the event of moderate-to-severe refractory Crohn's disease, TNF-α inhibitors are the new treatment of choice [2, 4–6, 8]. Infliximab has been effective in cases that did not respond to other immunosuppressants including oral prednisolone, azathioprine, and cyclosporine [8]. Other biologics, adalimumab and certolizumab, have also shown effectiveness in resolving cutaneous Crohn's disease [5, 6]. Multilayer compression therapy is also an option,

as it has shown effectiveness in decreasing vulvar edema of various causes [13]. Surgical intervention may be required for vulvar Crohn's disease refractory to all medical therapies, such as in fixed edema [9]. Of note, localized surgical excision frequently results in localized recurrence and suboptimal wound healing, so radical vulvectomy is typically required in these difficult cases [9].

Conclusion

We report this case to demonstrate the importance of a high index of suspicion for cutaneous Crohn's disease in a patient with unexplained vulvar lesions, even in the absence of gastrointestinal symptoms. Furthermore, we highlight the therapeutic benefit provided by anti-TNF therapy in refractory cases.

Statement of Ethics

Patient consent for publication has been obtained.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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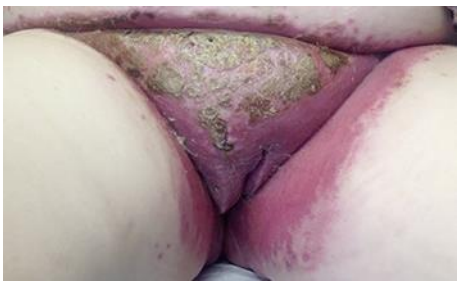

Fig. 1. Extensive erythema, edema, and hyperkeratotic lesions of the vulva were present on the patient's initial presentation to the dermatologist, prior to diagnosis with cutaneous Crohn's disease of the vulva. Antibiotics and steroids had been utilized previously but were not effective in providing long-lasting relief of symptoms. Therapy with infliximab had not been tried at the time this image was taken.