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Case Report

Isolated vulvo-vaginal Crohn's disease: case report of the rare entity

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ABSTRACT

The vulva is a rare site for extra-intestinal manifestation of Crohn's disease, and is usually a late feature of severe, fulminant, unrelenting disease. These islands of granulomatous tissue in the female genitalia are considered "metastatic" deposits as they are separated from the intestinal lesions by healthy tissue. Very rarely, Crohn's disease may manifest first in an extra-intestinal site, without any bowel lesions. In extremely rare cases, the genitalia is the site of isolated primary Crohn's disease and serves as a harbinger for bowel lesions.

Keywords: Crohn's disease, Vulva, Inflammatory bowel disease

INTRODUCTION

Crohn's disease and ulcerative colitis form two ends of the spectrum of inflammatory bowel disease. Crohn's disease is classically a relapsing and remitting inflammatory condition that can affect the entire length of the gastrointestinal tract, from the mouth to the anus. Abdominal pain and bowel disturbance are the classical features. About a third of the patients with Crohn's disease develop extra-intestinal manifestations, usually correlating to the duration and severity of the disease.[1] In rare cases, the extra-intestinal manifestations may be the presenting symptom, with underlying Crohn's disease in the gastrointestinal tract diagnosed serendipitously during evaluation. In a small subset of patients, Crohn's disease begins with extra-intestinal lesions prior to development of bowel lesions.[2] These conditions may be misdiagnosed due to being isolated and no features of gastrointestinal Crohn's disease present. Vulvar lesions occur in less than 2% of women with Crohn's disease, with majority of cases having gastrointestinal involvement preceding vulval symptoms, making isolated vulval Crohn's disease extremely rare.[3]

CASE REPORT

A 52 year old woman presented with discharging wounds over the groin for the last 1 ½ years with exacerbations since 2 weeks. The wounds were insidious in onset, first notice on the inner aspect of the right thigh 1 ½ years ago while bathing and slowly spread to the other side. There was initially no pain or discharge. She had sought treatment from a local non-allopathic practitioner, with no improvement in the wounds but as she was otherwise asymptomatic she ignored it. She then developed pain, itching, increased discharge and foul smell since the last 2 weeks and hence sought treatment again. Discharge was copious, liquid, yellowish in colour, non-blood stained and present throughout the day that it would soak her under garments prompting her to change her clothing multiple times a day. The embarrassment due to the smell also caused her anguish and caused her to not go to work. She had abstained from sexual intercourse since 1 1/2 years. No history of fever, weight loss, or cough with expectoration; and no history suggestive of sexually transmitted infections.

Patient had attained menopause 4 years back, prior to which there was no menstrual disturbance. Systemic examination was unrevealing, and head to toe examination showed mild conjunctival pallor and melasma over the face.

Local examination revealed generalized inflammatory features over the groin with erythema, erosions and ulcerations noted. Linear, sharply demarcated deep ulcers with "knife-cut" appearance were noted on both sides of the medial aspect of the thigh along the creases, as well as infra-vuval region of perineum (Figure 1). The perineum was coated with foul-smelling purulent exudate.

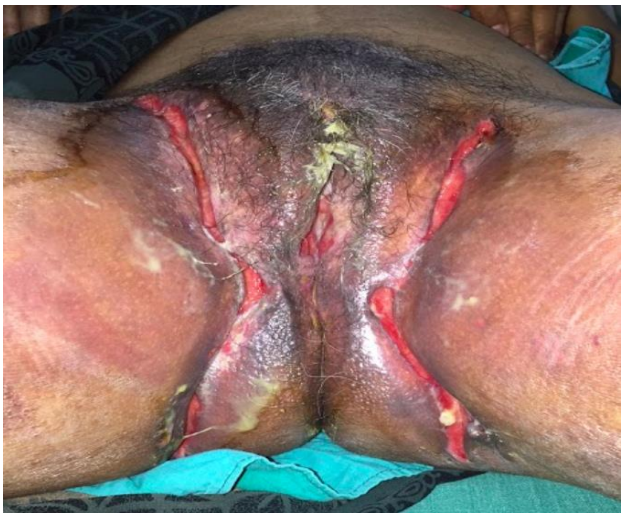

Figure 1: Knife-cut ulcers with purulent exudate.

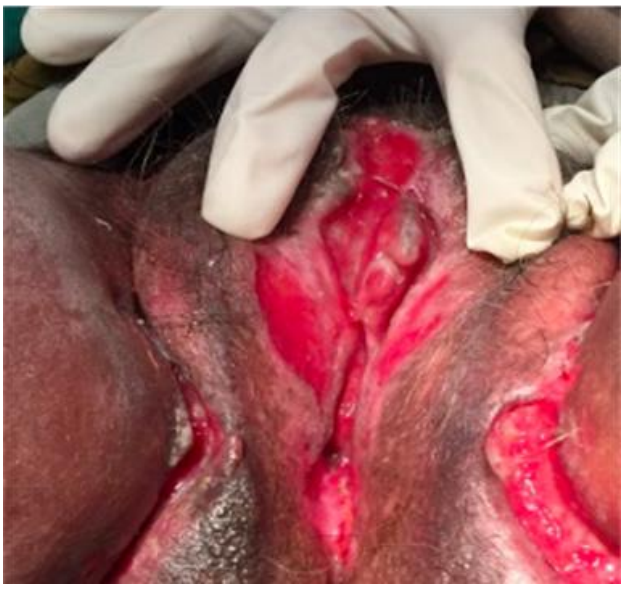

Figure 2: Vulvo-vaginal lesions.

The vestibule was hyperemic and labia edematous such that vulval anatomy was distorted. Separation of vulval folds revealed multiple aphthous-type as well as knife-cut ulcers (Figure 2).

The coating of exudate could be easily wiped-off, revealing bright red-coloured healthy looking granulation covering the ulcers. The margins were sloping and indurated signaling chronicity, and examination did not cause any pain or discomfort to the patient.

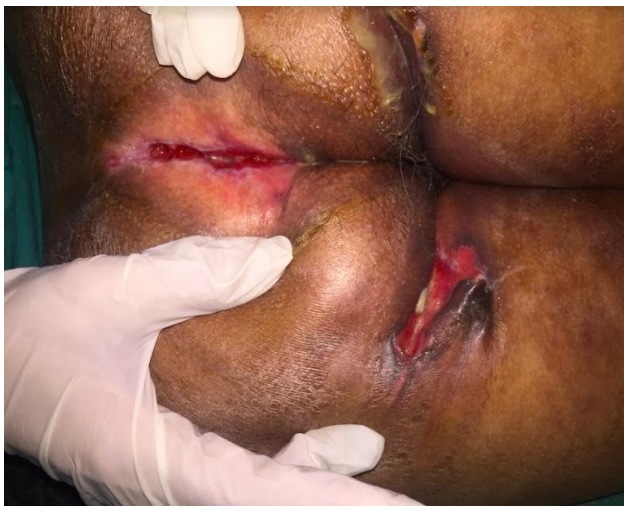

Figure 3: Natal cleft and perianal region.

Posteriorly around the perianal region a sharp, relatively superficial linear ulcer was noted of about 5-6 cm in length within the natal cleft, terminating 2-3 cm before the anal orifice (Figure 3).

Multiple, small, soft-to-firm, non-tender, discrete lymph nodes were noted in bilateral inguinal regions, involving both horizontal and transverse groups of superficial inguinal lymph nodes.

Investigations revealed increased urine pus cells, relative neutrophilila in the blood with otherwise normal hemogram, and other routine investigations were normal. Sexually transmitted infection (STI) screen was non-reactive. Urine culture revealed mixed flora, and culture from a swab of the exudate grew *Pseudomonas aeruginosa* and *Enterococcus species* with limited drug sensitivity.

Biopsy taken showed chronic granulomatous inflammatory change with epithelioid cells and Langhan's-type multinucleated giant cells (Figure 4). Acid-fast bacilli (AFB) were not demonstrated and nucleic-acid amplification test (NAAT) was negative.

Patient was started on intravenous injections of Piperacillin + Tazobactam in view of sensitivity pattern demonstrated from the swab for 5 days, along with Metronidazole (initially intra-venous, then changed to the oral route) as well as systemic steroids. Sitz bath was advised multiple times a day, and importance of local hygiene emphasized.

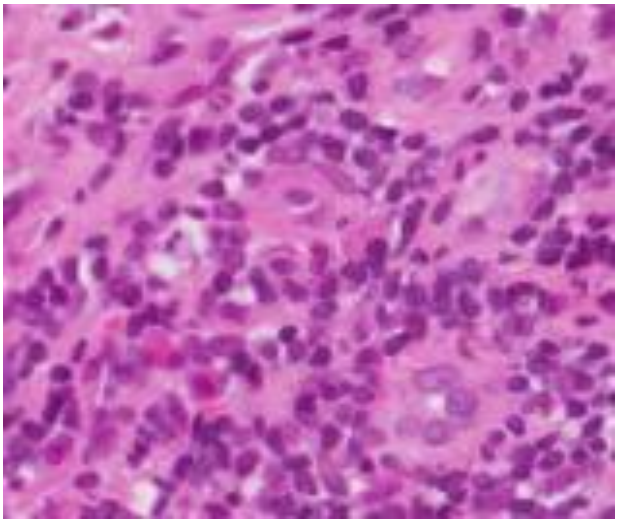

Figure 4: Histopathology.

Figure 5: Post antibiotic therapy.

By 5th day of IV antibiotics, discharge had completely ceased and wounds appeared healthier with minimal signs of contraction (Figure 5).

The ulcers continued to improve albeit at a slow pace, with 50% healing observed by 4 weeks.

DISCUSSION

Crohn's disease is a multi-systemic condition, with primarily lesions in the gastrointestinal tract, and extra-intestinal manifestations that complicate the disease. These extra-intestinal manifestations may either be immune-mediated (including ocular, oral and joint pathologies) or are a direct exhibition of the disease (such as cutaneous involvement) in an eccentric location; and are reported in as high as 35% of patients with gastrointestinal Crohn's disease.[1]

The cutaneous manifestations too may be immunological such as *erythema nodosum* and *pyoderma gangrenosum;* or may be a primary disease feature such as the ano-genital manifestations. In majority of the patients, the gastrointestinal manifestations develop years before the extra-intestinal manifestations, but in a small subset, the latter may infact be the harbinger of the disease.[1,2] Ano-genital manifestations are seen in about 22% of these patients. Of this subset, less than one-fifth develop ano-genital features before gastrointestinal symptoms (the emphasis of the rarity was not clear, and that each percentage mentioned is a take away from the previously established cohort and not the overall number so have changed the wording a little).

Ano-genital Crohn's disease can occur by contiguous spread from the gastrointestinal tract presenting with fistulas, or as granulomatous skin changes via non-contiguous ("metastatic") spread, making the primary disease difficult to identify.[2]

Perianal disease is the most common gynecologic manifestations of Crohn's, and vulvar involvement is a marker for fulminant, often unrelenting disease. The first case of vulval Crohn's disease was reported in 1965 by Parks et al.[4] Since then, only about 100 cases have been reported.[2] With regard to cutaneous disease, Crohn's may present as perianal and peri-stomal lesions; immunological mediated skin conditions including Sweet's syndrome and *epidermolysis bullosa acquisita*; or as granulomatous "metastatic" lesions from the gut.[2]

Thus, vulval Crohn's may be associated with other cutaneous or non-cutaneous extensions of the primary disease process or be *isolated granulomatous vulvitis* without accompanying or previously diagnosed Crohn's disease in the gut.[2] Therefore, dermatological inflammatory vulvo-vaginal lesions may not be due to fistulisation. Granulomatous lesions of a similar nature have also been reported involving the male genitalia.[5] The isolated and non-indicative nature of this condition thus makes the primary etiology difficult to identify. Non-fistulous Crohn's disease is thus often misdiagnosed. Diagnosis may even be delayed for years when gastrointestinal symptoms are absent.[1]

Presentation of vulvo-vaginal Crohn's disease

Mean age of presentation is around 34 years; in our case, patient's symptoms developed at 50 years of age.[1] The patient may present with a visible skin lesion, or due to pain, pruritus, dysuria or dyspareunia.[6]

Pathologically, the vulvar lesions may be edematous, ulcerative, hypertrophic or due to chronic suppuration, with vulvar abscess noted in 17% of patients with vulvo-vaginal Crohn's disease.[1]

Vulvar Crohn's disease most commonly (48%) presents as unilateral labial swelling with chronic ulceration and co-existing perianal disease.[2] The edema is typically inflammatory and asymmetrical; sometimes with severe

lymphangiectasia.[1] The lymphedema occasional produces a "peau d'orange" appearance.[7]

The ulceration in Crohn's disease has varying character, ranging from superficial aphthoid ulcers, to deep trench-like ulcers with extensions. The cutaneous granulomatous reactions resulting in ulceration usually occur in the flexures; specifically, the the inter-labial folds and at the lateral edge of the hair-bearing labia majora. They may be asymptomatic or tender, and usually always have an indurated base. Linear "knife-like" ulcerations, often with extension to the groins, are characteristic of genital Crohn's disease.[2]

Similar lesions have been reported in herpetic infections in immunocompromised patients and with cutaneous tuberculosis. The previously established tell-tale sign of herpetic infection, Grossman's geometric glossitis (manifested as extremely tender dorsal tongue fissures in a striking cross-hatched, or branched geometric pattern) is the other unique virus-associated lesion in immunocompromised individuals.[8,9]

Hypertrophic lesions develop secondary to impaired lymphatic drainage and chronic inflammation, and histopathologically mimic *lymphangioma circum-scriptum*.[1]

The hypertrophic lesions may be localized and exophytic or extensive with the infiltration of a whole labia, the former presenting as pseudo-marisca or pseudo-condyloma acuminata.[2] Presentation in this subset of patients is due to aesthetically unpleasant appearance.[2]

Presence of a vulvar abscess in a patient with diagnosed or suspected Crohn's disease warrants for a pelvic MRI, or ano-rectal endoscopic ultrasound to rule out enterocutaneous fistula.[2]

Diagnosis

Histological analysis of biopsy specimens is the most reliable diagnosis, showing chronic inflammatory infiltrates, multinucleated giant cells, non-caseating granulomas (which are seen in 83-89% of patients), epidermal spongiosis and acanthosis.[1] Negative Ziehl–Nielson stains and culture helps rule out a tubercular etiology.[9]

Differential diagnosis includes genital ulcers which may be infections (including STIs and non-sexually acquired genital ulcer (NSAGU)) or non-infectious (aphthous ulcers, Behcet's disease, malignancy); vulvo-vaginitis due to candida, bacterial vaginosis and other bacterial infections such as actinomycosis, donovanosis, tuberculosis and venereal lymphogranulomatosis, suppuration in the form of Bartholinitis or hidradenitis suppurativa; inflammatory conditions such as sarcoidosis; cutaneous conditions including pyoderma gangrenosum, epidermoid carcinoma of vulva and vesiculous pruriginous eczema; or vulval edema due to other causes such as malignancy, post-radiotherapy status or anasarca.[2,7]

Isolated granulomatous vulvitis may also occur in Melkersson-Rosenthal syndrome (triad of granulomatous cheilitis, facial nerve paralysis and fissured tongue).

Testing therefore involves full sexually transmitted disease work-up including serology, vaginal smears, tuberculosis screening with Quantiferon® and chest X-ray and histopathological evaluation.

Table 1: Treatment modalities for vulvo-vaginal Crohn's disease.

Treatment modality	Options available	Results
Topical therapy	Corticosteroids	Sustained improvement lacking.
	Tacrolimus	
Oral therapy	Antibiotics (most commonly metronidazole and erythromycin)	Sustained improvement seen when oral steroids are used along with antibiotics and immunosuppressants.
	Immunosuppressive agents (Including azathioprine, methotrexate, mesalazine, thalidomide and ciclosporin)	
	Monoclonal antibodies (infliximab - anti-TNFα)[11]	
Intralesional therapy	Local steroid injection and infiltration (Triamcinalone)	Results mostly unsatisfactory [11]
Miscellaneous unconventional therapies	Laser (CO_2 laser)	Useful for vulval lymphangiectasia
Surgery	Hyperbaric oxygen therapy (HBOT)	Reduction of pro-inflammatory cytokines may promote healing
	Excisions, debulking, reconstructive surgery	Surgery is reserved for exceptional refractory cases because of poor healing and relapse, making results mutilating.
	Incision & drainage procedures, debridement	Debridement or drainage of abscesses is probably the only definitive indication for surgery.

Treatment

The progress of vulvar Crohn's disease is unpredictable. The disease is frequently fulminant and refractory to medical therapy, and sustained improvement with any single modality of therapy is rarely seen. Topical steroids in combination with antibiotics and immunosuppressants are often used as first-line therapy.[1,2]

Metronidazole (owing to its antibacterial, immunomodulatory and anti-inflammatory properties) was used as the first-line therapy of choice before the advent of anti-tumor necrosis factor alpha (anti-TNFα) therapy, with improvement seen around 6 weeks after starting treatment.[1] In combination with steroids and immunosuppressants, success rate is satisfactory.[10] The recommended dose of metronidazole is 20 mg/kg/day for at least 12 to 36 months, however bilateral pedal paresthesia is a complication reported with long-term use.[10]

Antibiotics and immunosuppressive therapy can make patients susceptible to fungal infections, which may require concomitant management. Secondary bacterial infections are common, especially when enteric fistulas are present, and broad-spectrum or gram-negative plus anaerobic cover would be the ideal empirical antibiotics of choice when suppuration is present.

Anti-TNFα (infliximab) has shown good results when combined with azathioprine or methotrexate, but its use is advocated only after unsuccessful trial of other therapies.[11]

Psychosocial functioning is often impaired in patients with chronic debilitating diseases, and issues relating to sexuality, perineal disease and fistulas require specific addressing and counselling.[12] Multidisciplinary approach to management should be advocated.

The various treatment modalities are summarized in Table 1.[1,2]

CONCLUSION

Isolated Crohn's disease of the vulva is extremely rare and a challenging entity to manage, since it may be unaccompanied by gastrointestinal symptoms, and clinical presentation is highly varied – making diagnosis difficult, and often delayed. The "knife-cut" ulcers seen are nearly pathognomonic of the condition, and a high index of suspicion is required for timely diagnosis.

Various modalities of treatment are available, but none without known recurrences or side-effects. Due to poor healing, recurrences and fistulisation, medical management is preferred, which surgery being reserved for exceptional cases.

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