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REVIEW ARTICLE

Crohn's disease of the vulva

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Vulvar swelling

Abstract

Crohn's disease (CD) of the vulva is a rare, yet under recognized condition. Fistulae arising from the digestive tract account for the greater part of genital lesions in CD. However, cutaneous so-called metastatic lesions of the vulva have been reported in the literature. They are clinically challenging for gastroenterologists as well as for gynecologists, with numerous differential diagnoses, especially among venereal diseases, and require a multidisciplinary approach. The most frequently observed features of the disease are labial swelling, vulvar ulcers, and hypertrophic lesions. Biopsy samples for histological study are mandatory, in order to establish the diagnosis of vulvar CD. Treatment options include oral prolonged courses of metronidazole and systemic immunosuppressive therapy such as corticosteroids and azathioprine, with promising data published on the efficacy of infliximab. Surgery remains restricted to medical treatment failures or resection of unsightly lesions. Prospective studies or case series with long follow-up data are still missing to guide the treatment of this condition.

Contents

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1. Introduction

Extra intestinal manifestations of Crohn's disease (CD) could affect up to 35% of patients.[1] Among these, cutaneous lesions may be classified as follows: (i) peri-anal and peri-stomal lesions (the most frequent presentation); (ii) various skin lesions linked to CD: erythema nodosa, pyoderma gangrenosum, Sweet's syndrome, acrodermatitis enteropathica, epidermolysis bullosa acquisita; (iii) granulomatous cutaneous lesions separated from the affected gut by healthy tissue, so-called metastatic lesions. The latter form may affect the genitalia, but also the other parts of the skin.[2–4] Over 50% of patients with CD are women,[5] and gynecological involvement of CD, besides fistulas arising from the gastrointestinal tract, were already mentioned in the first reports of cutaneous CD in 1965.[6] However, in spite of major quality of life impairment for the patients, these lesions are often unrecognized and misdiagnosed. Vulvar CD is a rare condition, with 101 cases reported since 1965. In the present work, we aimed at describing clinical presentations, course and current therapeutic options in vulvar CD, outside fistulating CD.

2. Materials and methods

We performed a literature search without language barrier from 1965 to March 2013 through Pubmed using the MeSH terms "vulva" and "Crohn disease", then the following keywords: vulva and Crohn's disease, vulvitis and Crohn's disease, vulvovaginal Crohn's disease, genital Crohn's disease. Further research was done on the basis of the references and links of the articles found. Inclusion criteria was the presence of vulvar granulomatous lesions related to Crohn's disease; articles reporting on CD of the vagina, or on vulvar involvement in perineal fistulating CD were excluded. All articles were assessed by MB and VDP.

3. Results

Among the 290 articles retrieved, 66 relevant articles, reporting 101 patient's cases with non-fistulous vulvar CD, were selected and reviewed. Two cases of high-grade vulvar intraepithelial neoplasia were excluded from the study.[7] Intraepithelial neoplasia, although more frequent in patients under immunosuppressive therapy, are not specific from CD. 10 articles were excluded from the analysis because of insufficient data[8–17]: finally, 56 publications, reporting on 86 cases, were included in the study.[18–20]

3.1. Clinical presentations

Most vulvo-vaginal lesions in CD are linked to fistulas arising from the anus or the rectum. However, primary dermatologic inflammatory lesions may occur in the genital region in patients with CD and should be individualized, since they sometimes require a specific treatment. The majority of cases are associated with intestinal (69/86, 80%) or perianal (41/86, 48%) lesions. In these patients, luminal CD does not seem to exhibit specific features (the stricturing or penetrating behavior of the disease is rarely specified) and vulvar lesions may precede the diagnosis of the digestive CD in about 25% of cases.[21,22] This number includes patients with non-specific digestive symptoms, often unrecognized or neglected by non-gastroenterologists, and children, in which invasive endoscopic work-up is often avoided. In a study involving 50 women with CD, Graham et al. reported a 20% rate of vulvo-vaginal complaints, fistulas left apart. Eighty-one percent of these patients had an active colonic and perianal disease at the time of the study.[23] Thus, we may distinguish vulvar CD associated with active luminal and perianal disease (the most frequent form, reported in 48% of patients), vulvar CD with only luminal CD, without perianal involvement, and finally isolated granulomatous vulvitis without previously diagnosed digestive CD.[24] This latter presentation has brought some authors to separate "vulvitis granulomatosa" from CD,[9] however without consequences in patient management. Similar clinical and histological lesions have been reported in males on the penis and the scrotum,[25–27] suggesting a specific tropism of cutaneous CD for the genital region.

The median age at diagnosis was 34 (6–70) years, and vulvar CD affected children in 18 (21%) cases.[7,22,24,28–38]

Vulvar CD is typically asymptomatic, and the diagnosis will be brought up in front of vulvar ulcers or hypertrophic lesions discovered by clinical examination. However, complaints such as vulvar pain (29/86, 34%) or pruritus (8/86, 9%) are reported, as well as vulvar discharge or dyspareunia,[39] and also urinary symptoms such as dysuria.[40,41]

On physical examination, four main types of vulvar lesions may be observed:

- Vulvar swelling or edema: might affect both labia minora and majora or the vaginal wall, and is typically inflammatory and asymmetrical (Fig. 1). Swelling is reported in 67% (58/86) of cases of vulvar CD.
- Ulceration: might be totally asymptomatic or tender, unique or multiple, aphtoid and superficial or deep with an indurated base. Linear "knife-like" ulcerations, with

possible extension to the groins, are characteristic of genital CD (Figs. 2,3,4). Vulvar ulcerations were present in 40% (34/86) of the patients.

- Hypertrophic lesions: either extensive with the infiltration of a whole labia (Fig. 5) or localized and exophytic, then presenting as pseudo-marisca or pseudo-condyloma acuminata (Fig. 3). 24% (21/86) of reported vulvar CD exhibited hypertrophic lesions. In these cases, the main complaint is the aesthetically unpleasant appearance rather than functional symptoms, since these isolated hypertrophic lesions are not inflammatory. The pathogenesis of these spectacular lesions might imply impaired lymphatic drainage resulting from chronic inflammation linked to CD and recurrent cellulitis, resulting in lymphatic vessel destruction or obstruction, as shown by localized lymphangiectasia on pathological examination.[42–44]
- Chronic suppuration (Fig. 6): Physicians should not overlook the differential diagnoses of bartholinitis (in case of a single lesion) and of hidradenitis suppurativa when multiple recurring lesions with keloid scars — also involving the groins, the armpits, and the retroauricular folds — are found (Fig. 2). The presence of a vulvar abscess in a patient with CD requires a pelvic MRI, in order to diagnose a possible entero-cutaneous fistula. Abscesses were reported in 17% (15/86) cases of vulvar CD.

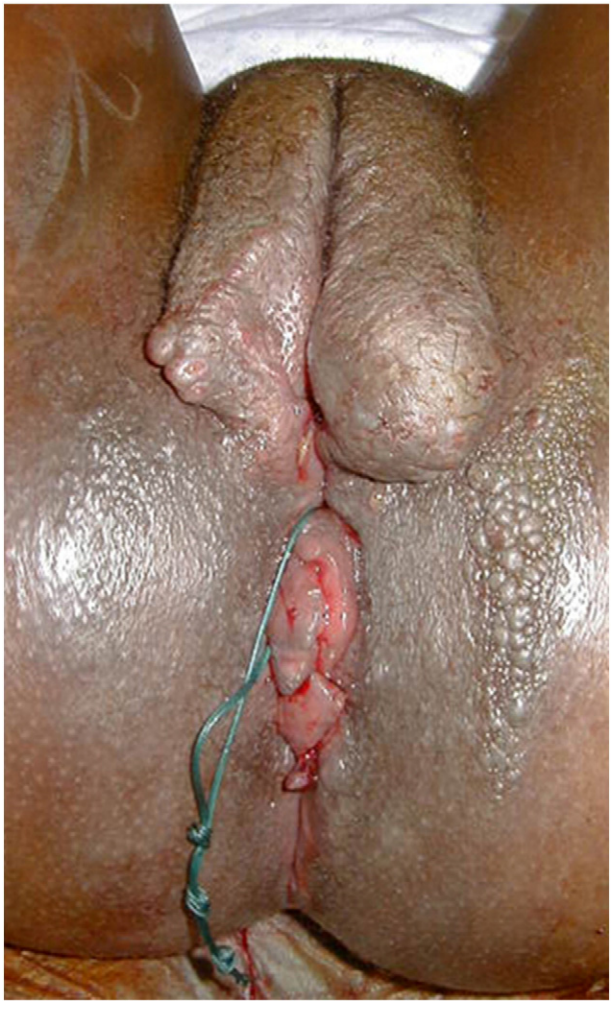

Figure 1 Asymmetric labial swelling, associated with exophytic hypertrophic lesions (on the right), and with active perianal disease, drained with a seton.

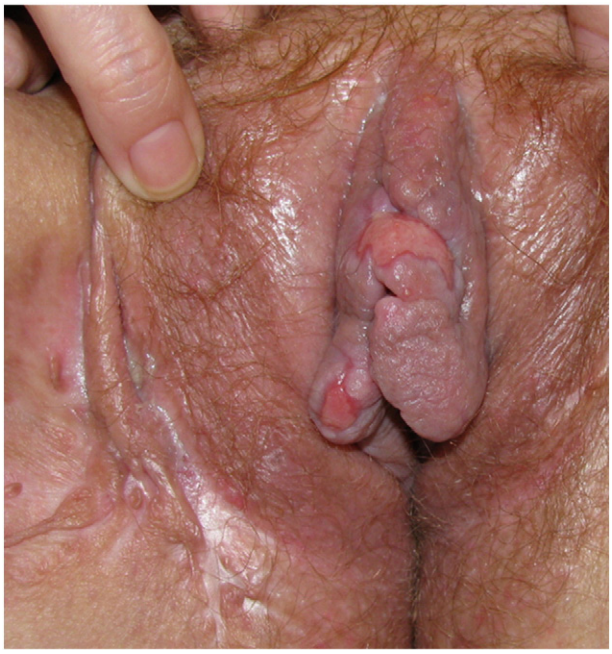

Figure 2 Superficial ulcers of the labia minora. Of note are the scars attesting of previous incision/drainage of skin abscesses, on the right thigh.

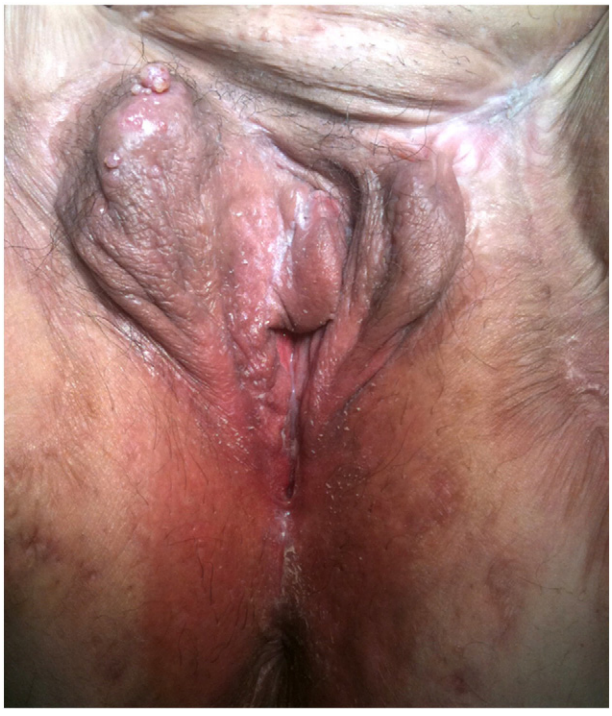

Figure 3 Ulcers of both right labia majora and minora, with exophytic lesions of the right labia majora.

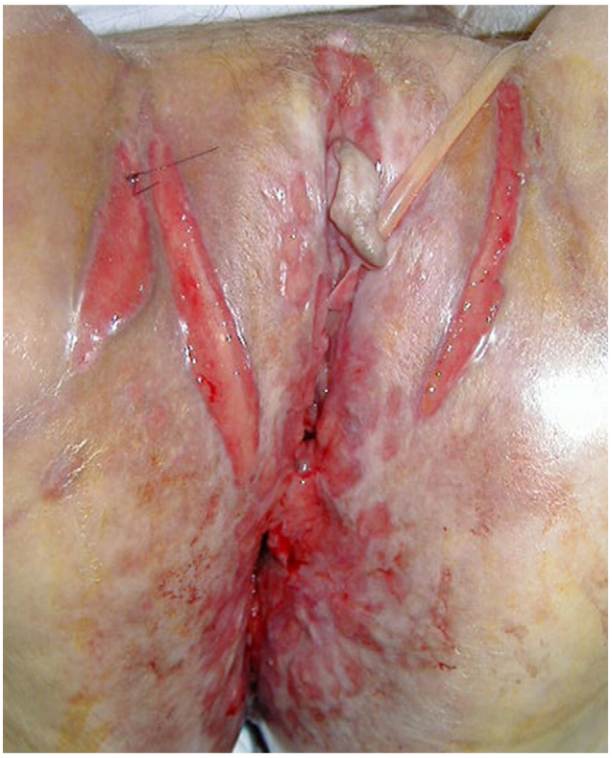

Figure 4 Round and linear "knife-like" perianal and vulvar ulcerations.

The most frequent clinical presentation of vulvar CD is an indolent unilateral labial swelling, associated with chronic vulvar ulceration. Perianal lesions were reported in 41 (48%)

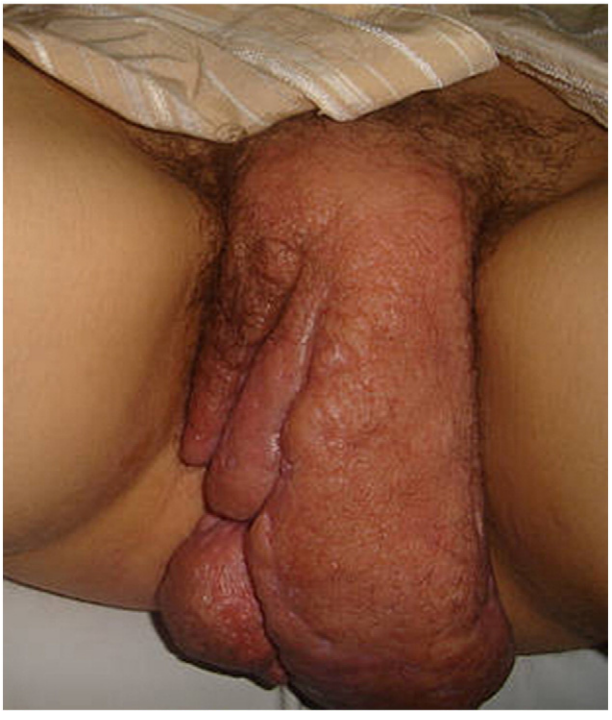

Figure 5 Major hypertrophy of the labia majora.

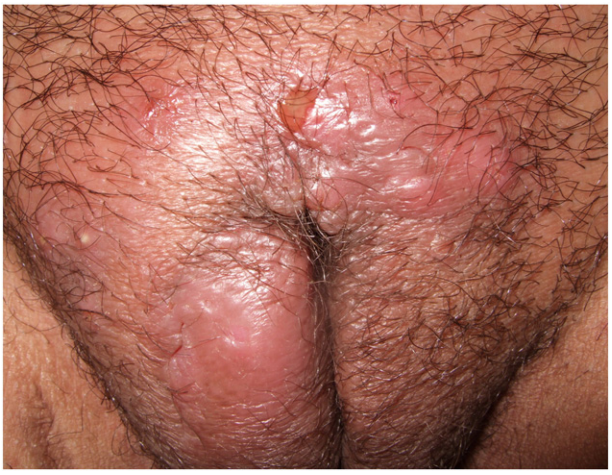

Figure 6 Abscesses of the right labia majora and the mons pubis, with yellowish discharge.

patients and other cutaneous lesions in 10 (12%) patients. In experience, among 8 patients referred for active perianal CD, 75% (6/8) had vulvar ulcerations (asymptomatic in 5 cases out of 6), and chronic suppuration, labial swelling, or asymptomatic (although sometimes dramatic) labial hypertrophy were observed in 38% (3/8), respectively. Symptoms and clinical presentations of vulvar CD are summarized in Table 1.

3.2. Diagnostic work-up

Since clinical lesions are non-specific and are frequently mistaken for infectious or traumatic vulvitis, diagnostic biopsy for histological analysis is mandatory. The presence of subacute or chronic inflammatory infiltrate, epidermal ulceration, together with noncaseating tuberculoid granulomas strongly supports the diagnosis (Fig. 7). Of note is the case of hypertrophic lesions, which have various histopathologic features. They show dilated lymphatics with varying degree of fibrosis, and varying degree of inflammation (Fig. 8). At the end of the histopathological spectrum of these hypertrophic lesions, the features are close to lymphangioma circumscriptum, with reticular dermis containing multiple dilated lymphatic vessels.[44]

Differential diagnoses are numerous, and presented in Table 2. Recent unprotected sexual intercourse, HIV seropositivity, and extragenital symptoms should be asked for. Initial clinical assessment should include a complete

Table 1 Main clinical presentations of vulvar Crohn's disease.

Clinical finding	Patient's complaint
Asymmetrical labial swelling (possibly affecting either labia minora or majora)	Pruritus, tenderness
Aphtoid or linear "knife-like" vulvar ulceration	Vulvar pain, discharge, pruritus, dyspareunia. May be asymptomatic.
Hypertrophic exophytic lesions	Aesthetic complaint
Vulvar abscess	Vulvar pain and discharge

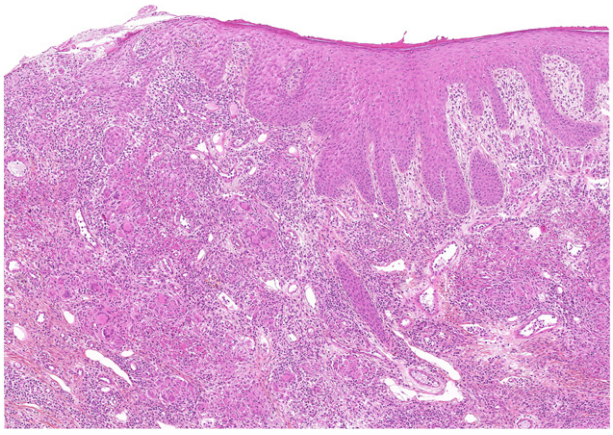

Figure 7 Vulvar Crohn's disease histopathology: epidermal ulceration and subacute inflammatory infiltrate of the dermis with non-caseating tuberculoid granulomas (HES staining, ×50 magnification).

gynecologic examination, in order to search for vaginal lesions, and perform a cervicovaginal pap smear, since these patients are likely to receive immunosuppressive medications in the course of their disease. The great clinical similarity of vulvar CD with Behcet's disease has been reported by some authors, and the exact diagnosis of young patients with oral and genital ulcers and colitis may be difficult to obtain. In both cases reported however, anti-TNFα antibodies showed dramatic efficacy.[45,46]

Biological minimal testing should include vaginal smear, to search for *Herpes simplex* virus 1 and 2, *Chlamydia trachomatis*, *Neisseiria gonorrhoeae*, *Treponema pallidum* infection, and the following blood tests: complete blood cell count, C-reactive protein, HIV 1 and 2 and TPHA-VDRL serologies, angiotensin-converting-enzyme level, and tuberculosis screening with intradermal tuberculin reaction or Quantiferon® and a chest X-ray.

The role of morphological investigation is minor; however, in case of abscess or fistulated lesions, ano-rectal endoscopic ultrasound and/or pelvic MRI are advised, in order to rule out a digestive fistula.[3]

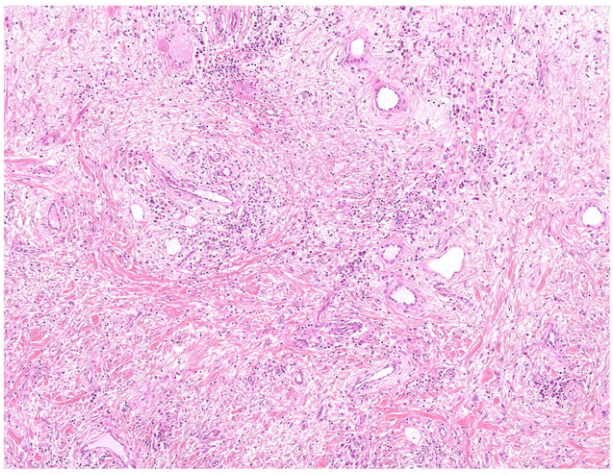

Figure 8 Vulvar Crohn's disease histopathology: in a hypertrophic lesion, fibrosis, edema, and dilatation of lymphatics and of capillary vessels (HES staining, ×200 magnification).

Table 2 Differential diagnoses of vulvar Crohn's disease.

Differential diagnoses	Suggestive features
Infectious	
Infectious vulvo-vaginitis: fungal (*C. albicans*), bacterial (*G. vaginalis*), parasital (*T. vaginalis*)	Vaginal discharge, positive vaginal smear results
Other bacterial vulvitis: venereal lymphogranulomatosis, actinomycosis, donovanosis, tuberculosis, leprosy	Suggestive patient history (unprotected sexual intercourse), vaginal discharge, positive vaginal smear results or suggestive histology
Syphilitic chancre	Solitary painless ulceration
Herpetic vulvitis (HSV-2)	Polycyclic painful ulcerations ++
Ulcus vulvae acutum	Painful vulvar ulceration and viral upper aerodigestive tract infection
Condyloma acuminata (HPV)	Exophytic painless lesions
Hidradenitis suppurativa	Nodular abscessed multiple lesions
Bartholinitis	Painful tumefaction of the labia majora
Inflammatory	
Behçet's disease	Bipolar aphtoid multiple ulcerations, arthralgia
Sarcoidosis	Non caseating granuloma on biopsy sample
Other	
Pyoderma gangrenosum	Unique ulceration with undertermined bluish borders
Eczema	Vesiculous pruriginous lesion
Epidermoid carcinoma of the vulva	Solitary chronic ulceration
Foreign-body reaction	Foreign-body granuloma on biopsy
Vulvar edema from another cause: post-radiotherapy, neoplastic lymphatic vessel obstruction, anasarca	Suggestive patient history

3.3. Clinical course and treatment options

The evolution of vulvar CD is unpredictable, with cases reported of spontaneous healing,[47] and lesions refractory to medical therapy, requiring major surgery such as partial or total vulvectomy.[40,48–50] Only one case triggered by a vaginal delivery with episiotomy has been reported, while other authors do not report local injury as a causative factor.[51] In children however, CD has been stressed as a differential diagnosis of traumatic lesions from sexual abuse.[30] First-line therapy usually consists in antibiotics, but second and third-line medical treatments are needed in 32% and 5%, respectively. Most

case reports do not mention follow-up data: hence, reliable recurrence rates are not available in the literature. In the largest case series, including 11 patients with vulvar CD and a median follow-up of 80 months, 1 out of the 5 patients with medical management experienced recurrence, and no recurrence was observed after surgical resection of hypertrophic lesions in the other patients.[7] Therapeutic data have low levels of evidence, given the lack of prospective studies. The treatment mainly relies on medical therapy, with minimal resort to surgery.

Since corticosteroids (CS) are the cornerstone of the treatment of CD, and the vast majority of the patients also had luminal CD, the use of systemic CS is widely reported. Among the 28 patients who received systemic CS alone, the vulvar lesions healed in 3[7,34,52] out of 4 patients.[39] All other patients received combined treatments: combination of CS with metronidazole was effective in all 8 cases[7,28,33,34,53,54]; combination with azathioprine was effective in 5 cases[3,6,37,55,56] and insufficient to obtain control of the vulvar disease in 7 cases.[40,57–61] The other patients received triple therapies (CS, metronidazole and azathioprine),[3,51,62] or combined therapies with 5-aminosalicylates[31,35,63] without efficacy. Local administrations or injections[54,64] of corticosteroids have not been followed by satisfying results[6,7,22,29,32,34,35,53,60,62,65] except in one case.[41]

Oral metronidazole, at doses ranging from 10 to 20 mg/kg/day appears to be the second major therapy of vulvar CD, with 19 cases reporting its efficacy, alone[3,29,38,42,57,63,65–70] or in combination with oral corticosteroids[7,28,33,34,54], sulfasalazine,[49] or other antibiotics.[71] Metronidazole has initially been proposed in the treatment of vulvar CD, as in perianal CD, before the development of anti-TNFα therapies.[72] The effects of metronidazole are anti-infectious, but also immunomodulatory and anti-inflammatory. Metronidazole remains an interesting treatment option, given its low cost and a favorable risk/benefit ratio, as compared to immunosuppressive or immunomodulatory treatments, or to surgery (Fig. 9). The treatment should be maintained several months, and clinical improvement is generally observed around the sixth week of treatment.[57] The administration of other antibiotics did not result in satisfying clinical outcome.[22,30,31,34,48,53,57,60,66]

The use of oral 5-aminosalicylates (mesalamine or sulfasalazine) was reported in 11 cases.[7,22,29,31,35,41,49,53,63,68] The treatment alone was effective in 3 cases[7,22,49] and in the three other patients with good clinical results, mesalamine was associated with major treatments such as oral corticosteroids and immunosupressives.[31,35,53]

As in luminal CD, the use of anti-TNFα treatment is growing in vulvar CD. To date, six cases have been reported, all of which implied infliximab, either alone[58,61,64] or combined with azathioprine[57,59] or methotrexate,[62] with clinical remission in five cases out of six. All patients had received prior treatments with antibiotics, CS, or immunosuppressives, and significant clinical improvements were recorded after the first infusion.[62]

Only one publication reports the use of ciclosporin, after failure of a CS, azathioprine, and metronidazole treatment regimen, without significant benefit.[62] The use of rescue treatments of metastatic CD, such as thalidomide, mycophenolate mofetil, or hyperbaric oxygen therapy has not been reported in vulvar CD.

Surgical management was reported in 20 patients. In 13 cases, the surgical procedure, either vulvectomy,[50] laser vaporization,[73] or excision of the lesions[7,24,43,74–76] was conducted before any medical treatment, and a vulvar adenocarcinoma was found in one of these patients. In two cases, surgical drainage of vulvar abscesses was performed before further medical management.[35,64] In the five other cases, vulvar lesions were resected because they were considered to be refractory to medical management.[2,40,48,49,60] Three of the four cases of

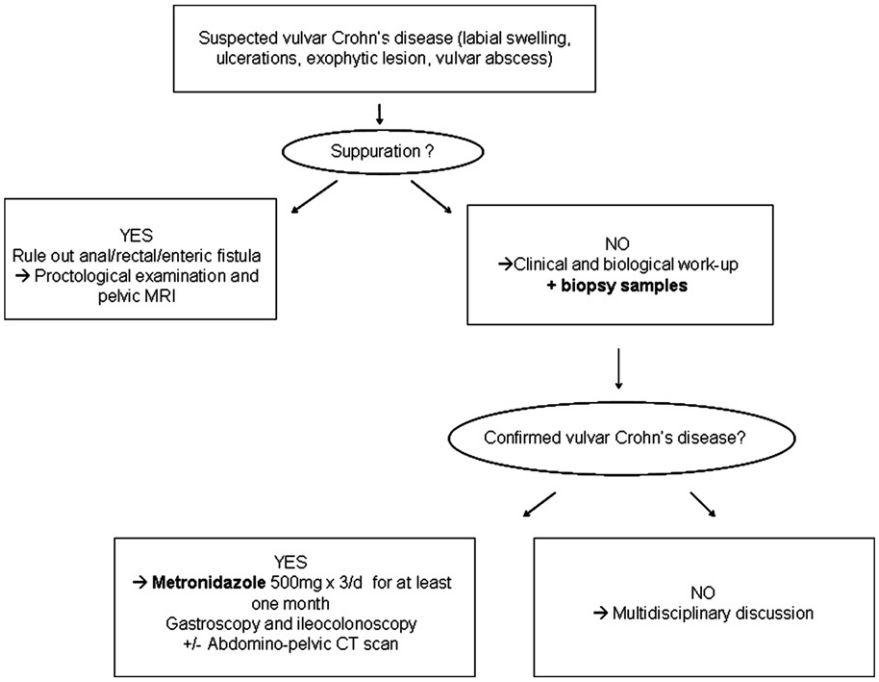

Figure 9 Decision algorithm in suspected vulvar Crohn's disease.

major surgery, i.e. vulvectomy or hemivulvectomy, were performed in this setting.[40,48,49] Of note is the fact that hypertrophic lesions were found in 12 patients out of 20 (60%) who underwent surgery. Various post-operative treatments were administered in 3 cases.[49,60,75] In only eight cases out of 20 (40%),[35,40,48–50,75,76] the surgical resection of the vulvar lesions allowed for complete disease control with complete wound healing. Hence, we consider that surgical treatment should remain minimal. Since patients with CD have impaired wound healing and surgical procedures might become mutilating, surgery should be limited to three clinical situations: (i) failure of medical treatment with major impairment of the patient's quality of life; (ii) debridement or drainage of vulvar abscesses; (iii) resection of hypertrophic unsightly lesions. No data have been reported on reconstructive vulvar surgery in this clinical setting. This question seems of major importance, once inflammation is controlled, in these young patients desirous of a sexual activity.

4. Conclusion

If fistulous gynecological lesions of CD are well known, specific "metastatic" vulvar lesions are a clinical challenge for gastroenterologists. They are unfrequent, difficult to diagnose, and the symptoms as well as the clinical lesions are non-specific. Therefore, a multidisciplinary approach, involving gastroenterologists, proctologists, gynecologists, pathologists, and dermatologists, of women with CD and vulvar complaints or lesions is required. Treatment currently relies on prolonged courses of oral metronidazole and surgical excision of refractory lesions. However, anti-TNFα treatments have shown promising results.

Conflict of interest statement

None

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MBt collected data and drafted the manuscript. VdP conceived and designed the study. MBa collected data, contributed to the drafting of the manuscript, and revised the paper. HS revised the paper for major intellectual content. NL analyzed the data. PM revised the paper for major intellectual content. All authors approved the final version of this manuscript.

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