Annals of Gastroenterology (2023) **36,** 466-476

Cutaneous Crohn's disease after proctocolectomy for medically refractory colonic Crohn's disease: a case series and review of the literature

Sandra Naffouj[a], Gabriel E. Marrero-Rivera[b], Johan Nordenstam[c], Kyle T. Amber[d,e], Itishree Trivedi[a]

University of Illinois Chicago, IL; University of Florida at Gainesville, Gainesville, FL; Rush University Medical Center, Chicago, IL, USA

Abstract

Background Cutaneous Crohn's disease (CCD), also known as metastatic Crohn's disease (CD), is one of the rarest and most challenging cutaneous manifestations of CD. It is characterized by non-caseating granulomatous inflammation of the skin at sites that are non-contiguous with the gastrointestinal (GI) tract. Diagnosis of CCD needs a high clinical suspicion since morphological presentation varies widely and lacks an apparent correlation to the activity of the luminal CD. The onset of CCD in patients without active GI CD is a particularly understudied phenomenon.

Methods We present a case series of a unique patient group who developed CCD while in remission from a luminal CD perspective, mainly after a proctocolectomy for Crohn's colitis. We also provide a literature review and summary of case reports of CCD after proctocolectomy.

Results Our 4 adult patients diagnosed with CCD after proctocolectomy presented herein, were successfully treated with high-dose corticosteroids, followed by biologic therapy. Furthermore, a comprehensive review of CCD is provided regarding its pathogenesis, clinical presentation, differential diagnosis, and the evidence behind the available treatments.

Conclusions CCD should be considered in any CD patient presenting with skin lesions regardless of their disease activity status and history of proctocolectomy. The treatment remains challenging; biologics remain the cornerstone and a multidisciplinary approach is recommended. Larger randomized clinical trials are essential to determine the optimal treatment protocol and to improve outcomes.

Keywords Cutaneous Crohn's disease, metastatic Crohn's disease, dermatologic manifestations, proctocolectomy, inflammatory bowel disease

Ann Gastroenterol 2023; 36 (4): 466-476

[a]Division of Gastroenterology and Hepatology, Department of Medicine, University of Illinois Chicago, IL (Sandra Naffouj, Itishree Trivedi); [b]Department of Medicine, University of Illinois Chicago, IL (Gabriel E. Marrero-Rivera); [c]Division of Colorectal Surgery, University of Florida at Gainesville, Gainesville, FL (Johan Nordenstam); [d]Department of Dermatology, Rush University Medical Center, Chicago, IL (Kyle T. Amber); [e]Department of Internal Medicine, Rush University Medical Center, Chicago, IL (Kyle T. Amber), USA

Conflict of Interest: None

Correspondence to: Sandra Naffouj, MD, Gastroenterology and Hepatology Fellow, PGY-5, University of Illinois Chicago, 840 South Wood Street, MC 716, Chicago, IL 60612, USA,
e-mail: snaffo2@uic.edu

Received 23 January 2023; accepted 10 April 2023;
published online 30 May 2023

DOI: https://doi.org/10.20524/aog.2023.0811

Introduction

Cutaneous Crohn's disease (CCD) is a rare form of extraintestinal Crohn's disease (CD) consisting of granulomatous lesions that are non-contiguous with the gastrointestinal (GI) tract (i.e., separated from it by normal skin) [1]. CCD is considered a different entity than other cutaneous manifestations of CD, like those involving the skin at sites contiguous with the GI tract, such as perianal, peristomal, and peri-fistular inflammation, also characterized by granuloma formation [2]. In CCD, lesions have similar pathological findings to the ones found in the GI tract and contiguous skin lesions of CD patients, in addition to the presence of multinucleated giant cells, as well as a diffuse infiltrative pattern and a lack of acute inflammatory cells [3]. Clinically, CCD tends to have variable skin morphologies, including plaques, nodules, abscesses, and fistulas [4]. Rare but pathognomonic findings include "knife-life" fissuring and deep linear ulcers [5]. Although these lesions can manifest anywhere,

they have a strong predilection for the moist environments of skin folds, including sub-mammary and abdominal creases as well as the perianal and inguinal regions [6]. It is noteworthy that the severity of these cutaneous lesions does not correlate with the severity of the luminal disease [6].

The onset of CCD in patients without active bowel disease, such as after proctocolectomy in colonic CD, is a particularly understudied phenomenon. It also carries significant challenges in terms of management, not only from a medical standpoint, but also breaking the news to patients that they may need to continue biologics after surgery. Less than 30 case reports in the literature have presented the onset of CCD post-subtotal or proctocolectomy in adults, and little has been studied about the association between this skin manifestation and the role of surgical intervention in their etiology. Herein, we report a case series of 4 patients with absent luminal CD who developed CCD, with a focus on the development of post-surgical CCD, and review the literature on this topic to find common characteristics that can predict CCD onset after proctocolectomy and the best-described management.

Patients and methods

This case series included 4 adult patients with CCD following proctocolectomy between January 2014 and December 2021 at our tertiary referral center. Baseline characteristics are demonstrated in Table 1A.

This study design was approved by the Institutional Review Board (IRB) at our hospital; given the observational and de-identified nature of the data, the requirement for a signed informed consent form was waived.

Literature review of CCD post-proctocolectomy

A comprehensive literature review was conducted by searching the PubMed and Embase databases from inception to December 2021 to identify all publications regarding CCD. The initial query identified 5,481 articles. Titles were revised, and those that discussed "cutaneous Crohn's disease," "metastatic Crohn's disease," and "cutaneous granulomatous skin lesions" were included. After verifying duplicate articles, the literature accounted for 410 studies. Of those, 29 were included based on the following inclusion criteria: 1) adult patients >18 years old; 2) biopsy-proven CCD; and 3) history of subtotal colectomy or total proctocolectomy. Table 1B demonstrates patients' characteristics, skin areas affected, treatment prior to presentation with CCD (if any), and treatment after presentation that led to clinical response.

Case 1

A 49-year-old African American female with severe ileocolonic CD complicated by fistulizing perianal disease and perianal hidradenitis suppurativa (HS) who had a disease course refractory to medical therapy with infliximab (IFX) and azathioprine (AZA) and eventually underwent total proctocolectomy 4 years after her diagnosis. She remained in clinical remission while off medical therapy. She presented 6 years later with new "knife-cut" linear ulcerations in the groin area consistent with CCD, as demonstrated in Fig. 1A. The diagnosis was confirmed by pathology, which showed cutaneous ulceration with diffuse acute on chronic inflammation associated with loose granulomas involving the dermis and subcutaneous tissue, consistent with CCD. She was treated with a prolonged steroid tapering for 2 months and restarted on IFX every 8 weeks with significant improvement and stable condition at her 7-year follow up from therapy re-initiation (Fig. 1B). Her GI luminal disease remained quiescent on subsequent endoscopic and radiographic examinations. Few of the pathology slides are demonstrated in Fig. 1C-F.

Case 2

A 21-year-old Hispanic man with severe Crohn's colitis complicated by fistulizing perianal disease who had a rapidly progressive course due to toxic megacolon and required an emergent total colectomy with Hartmann pouch and diverting ileostomy in the same year of diagnosis. Despite IFX and AZA therapy, he developed severe skin lesions manifested as new "knife-cut" linear ulcerations with draining pustules involving the gluteal cleft, perianal area, perineum, genitalia, and groin areas, consistent with CCD, 5 years after his surgery, as demonstrated in Fig. 1G. Lesions initially responded to high-dose steroid therapy with an extended taper, however, they relapsed despite dose escalation of IFX and continuing AZA. He eventually underwent a complete proctectomy for ongoing, severe proctitis. One year later, he developed recurrent painful gluteal cleft and inguinal skin lesions while having quiescent GI disease. Ustekinumab was started with improvement in these cutaneous lesions as demonstrated in Fig. 1H.

Case 3

A 35-year-old African American female with stenotic and fistulizing colonic and upper GI Crohn's disease, diagnosed at age 23, that was complicated by perianal disease and rectovaginal fistulas who underwent diverting loop ileostomy 5 years after her diagnosis. Luminal CD worsened despite multiple biologics, including IFX, adalimumab (ADA) and certolizumab pegol (CZP), with progressive left sided colonic strictures. She eventually underwent a total proctocolectomy. Two months postoperatively, she developed new "knife-cut" linear ulcerations involving the inguinal area, perineum, and gluteal cleft consistent with CCD, as demonstrated in Fig. 1I. She was started on high-dose oral prednisone and IFX, without significant improvement. She has also failed multiple lines of therapy, including doxycycline, dapsone, cyclosporine, topical tacrolimus, topical metronidazole, intralesional triamcinolone,

Table 1 (A) Characteristics of patients presenting with CCD after proctocolectomy

Patient	Age	Sex	Race	Montreal Classification	IBD prior to procto-colectomy	Duration between surgery and CCD	Areas affected	Treatment prior to CCD onset	CCD therapies	Follow up from CCD onset
#1	49	F	AA	A2 L3 B3p	4 years	6 years	Inguinal, perianal, gluteal	IFX+AZA	IFX	7 years
#2	26	M	Hispanic	A2 L2 B3p	Same year	5years	Inguinal, gluteal, genitals	IFX+AZA	Ustekinumab	3 years
#3	35	F	AA	A2 L2 B3p	5 years	7 years	Inguinal, perineum genitals, perianal	IFX, ADA, CZP	Doxycycline, Dapsone, CyA, ADA, IVIG-IFX and hyperbaric O_2 therapy +/- surgery	3 years
#4	37	F	AA	A2 L2 B3p	Same year	4 years	Gluteal, groin	IFX+AZA	IFX dose escalation	2 years

Table 1 (B) Summary of CCD cases after proctocolectomy reported in the literature

Study, year [ref.]	# N	Age	Sex	Colectomy prior to CCD	Biopsy proven	Time between Colectomy and CCD diagnosis	Areas affected	Tx before CCD	Tx after CCD	Response
Bohdanowicz *et al*, 2019 [5]	1	53	F	Yes	Yes	36 years	Vulva	None	N/A	N/A
Guest *et al*, 2000 [6]	1	55	F	Yes	Yes	N/A	Inguinal, perineal, sub-mammary	N/A	Topical steroids, antibiotics, surgery	No
Abdat *et al*, 2016 [7]	1	62	F	Yes	Yes	6 months	Vulva	IFX	ustekinumab	Yes
Al-Chalabi *et al*, 2018 [8]	1	49	F	Yes	Yes	3 years	Vulva	N/A	ADA, steroids	Yes
Argyriou *et al*, 2018 [9]	1	26	M	Yes	Yes	1 year	Inguinal	IFX, vedolizumab	ustekinumab	Yes
Ballester *et al*, 2021 [10]	1	49	F	Yes	Yes	9 years	Leg	IFX, AZA, steroids	ustekinumab	Yes
Bardazzi *et al*, 1995 [11]	1	20	F	Yes	Yes	6 years	Vulva	N/A	CyA	Yes
Biancone *et al*, 2002 [12]	1	35	F	Yes	Yes	2 years	Forehead	N/A	Steroids, AZA, 6MP	Yes
Bloget *et al*, 1996 [13]	1	23	M	Yes	Yes	3 years	Penile	N/A	CyA	Yes
Cockburn *et al*, 1980 [14]	1	32	M	Yes	Yes	4 years	Penile, scrotum	N/A	Steroids, surgery	Yes
Daunton *et al*, 2015 [15]	1	25	F	Yes	Yes	7 years	Groin, sub-mammary	N/A	ADA	Yes

(*Contd...*)

Table 1 (B) *(Continued)*

Study, year [ref.]	# N	Age	Sex	Colectomy prior to CCD	Biopsy proven	Time between Colectomy and CCD diagnosis	Areas affected	Tx before CCD	Tx after CCD	Response
Dave *et al*, 2004699 [16]	1	44	F	Yes	Yes	30 years	Vulva	N/A	Anti-mycobacterial tx	Yes
Foreman *et al*, 2016 [17]	1	64	M	Yes	Yes	30 years	Penile, scrotum	None	Metronidazole	Yes
Goh *et al*,1998 [18]	1	35	M	Yes	Yes	N/A	Penile	None	Topical steroids	Yes
Goyal *et al*, 2006 [19]	1	46	F	Yes	Yes	5 years	Nipple	None	Surgery	Yes
Graham *et al*, 2006 [20]	1	30	F	Yes	Yes	10 years	Facial (chin, malar)	IFX	IFX dose increase, cipro, topical steroids	Yes
Guglielmetti *et al*, 2018 [21]	1	82	F	Yes	Yes	20 years	Groin, genitals, gluteal cleft	N/A	Dapsone	Yes
Ilangovan *et al*, 2008 [22]	1	50	F	Yes	Yes	15 years	Vulva (polyp)	N/A	Surgery	Yes
Kim *et al*, 1992 [23]	1	16	F	Yes	Yes	5 months	Vulva	N/A	Steroids, metronidazole	Yes
Konrad *et al*, 2002 [24]	1	34	F	Yes	Yes	9 years	Abdomen, sub-mammary	N/A	IFX +MTX	Yes
Lavery *et al*, 1985 [25]	1	31	F	Yes	Yes	12 years	Vulva	N/A	Topical tetracycline	Yes
Leu *et al*, 2009 [26]	1	43	F	Yes	Yes	27 years	Vulva, perineal	Antibiotics, steroids	Antibiotics, steroids, 6-MP	yes
Moyes *et al*, 2007 [27]	1	39	M	Yes	Yes	24 years	Perineum	N/A	Surgical debridement	Yes
Patel *et al*, 2012 [28]	1	37	F	Yes	Yes	N/A	Leg	ADA	MTX SQ	Yes
Rispo *et al*, 2004 [29]	1	37	F	Yes	Yes	18 years	Perineal, gluteal	None	IFX	Yes
Shields *et al*, 2020 [30]	1	31	F	Yes	Yes	N/A	Vulva	None	Antibiotics, topical tacrolimus	Yes
Stoleru *et al*, 2020 [31]	1	24	F	Yes	Yes	3 years	Vulva	None	Ustekinumab	Yes
Tweedie *et al*, 1984 [32]	1	65	M	Yes	Yes	6 months	Forearm, leg, thigh, abdomen	N/A	Steroids	Yes
Vint *et al*, 2012 [33]	1	24	M	Yes	Yes	12 years	Genitals	N/A	Intralesional steroid injections	Yes

CD, Crohn's disease; CCD, cutaneous CD; AZA, azathioprine; 6-MP, 6 mercaptopurine; CyA, cyclosporine; IFX, infliximab; ADA, adalimumab; CZP, certolizumab; MTX, methotrexate; IVIG, intravenous immunoglobulins; N/A, not available

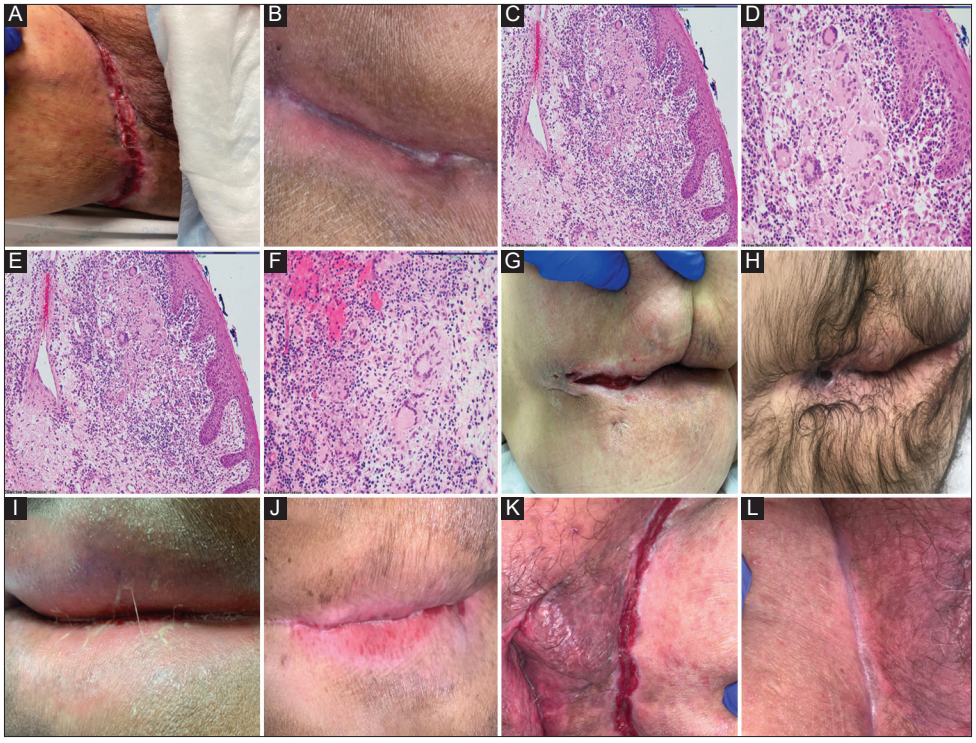

Figure 1 (A, B) Patient 1: pre- and post-treatment of ulcerated, linear "knife-like" lesion in the right groin consistent with cutaneous Crohn's disease (C, D, E, F) patient 1 pathology images: cutaneous ulceration with diffuse marked acute and chronic inflammation associated with loose granulomas, involving dermis and subcutaneous tissue consistent with cutaneous Crohn's disease. (G, H) Patient 2: pre- and post-treatment of ulcerated, linear "knife-like" lesion in the gluteal cleft consistent with cutaneous Crohn's disease. (I, J) Patient 3: pre- and post-treatment of erythematous fissured plaque with purulence in the gluteal cleft consistent with cutaneous Crohn's disease. (K, L) Patient 4: pre- and post-treatment of a groin wound in cutaneous Crohn's disease

ustekinumab, and intravenous immunoglobulins (IVIG). GI disease remained quiescent with recalcitrant CCD. Persistent perineal sinus syndrome was raised as a possible diagnosis as well. She was re-trialed on high dose IFX and hyperbaric oxygen therapy with some improvement (Fig. 1J).

Case 4

A 37-year-old African American female with severe fistulizing Crohn's ileocolitis, diagnosed at the age of 31, complicated by perianal involvement, rectovaginal fistula, and concurrent severe HS, underwent a diverting loop ileostomy at the time of diagnosis. Her post-operative course was complicated by non-healing HS despite being on weekly ADA. She eventually underwent abdominal perineal resection (APR) and end sigmoid colostomy. She was started on IFX and AZA post-operatively for severe ileocolitis. Two years later, she underwent takedown of loop ileostomy. She had marked clinical and endoscopic improvement on subsequent colonoscopies while on IFX therapy. She presented with new "knife-cut" linear ulceration in the gluteal cleft and wounds in the groin area consistent with CCD (Fig. 1K). She was treated with a prolonged course of steroids in addition to dose escalation of IFX to every 4 weeks due to subtherapeutic level and eventual complete healing at the 2-year follow-up visit (Fig. 1L).

We identified 29 cases of CCD after proctocolectomy reported in the literature [5-33]. Characteristics of the patients are demonstrated in Table 1B. The majority of cases were noted in the perineal and gluteal regions. Different treatment modalities were tried, including oral and topical steroids, antibiotics, and biologics, specifically IFX and ustekinumab.

CD, Crohn's disease; CCD, cutaneous CD; AZA, azathioprine; 6-MP, 6 mercaptopurine; CyA, cyclosporine; IFX, infliximab; ADA, adalimumab; CZP, certolizumab; MTX, methotrexate; IVIG, intravenous immunoglobulins; N/A, not available

Discussion

Cutaneous manifestations are reported in 22-44% of CD patients [34,35]. Cutaneous manifestations of CD are generally divided into 4 groups [36]: 1) cutaneous lesions as a direct extension of bowel disease such as oral, perianal, or peristomal skin lesions [37,38]; 2) reactive inflammatory dermatoses that do not share the same histopathological findings as CD but have a strong association with it, such as pyoderma gangrenosum (PG) and erythema nodosum (EN) [39]; 3) drug-related skin reactions [40]; and finally, 4) metastatic CD characterized by skin lesions that are noncontiguous with the GI tract and have similar sterile granulomatous inflammation

histologically [39,41]. However, the term "metastatic" CD can be a misnomer since CD is not a malignancy, and these cutaneous lesions can occur before the onset of the GI disease or develop without any luminal involvement. Therefore, the term noncontiguous CCD would be more precise [5]. CCD is considered the rarest form of the skin manifestations of CD [42]. We present a case series and literature review of a unique subgroup of patients who had CCD onset in the setting of absent luminal CD, particularly after complete proctocolectomy or, theoretically, after removing the nidus of the inflammation.

The pathogenesis of CCD is still poorly understood. One proposed mechanism is the passage of an intestinal antigen to the skin triggering a subsequent granulomatous response at the level of the dermis [43-45]. Another suggested mechanism is antibody sensitization to gut antigens, possibly bacterial antigens, which then cross-react with analogous skin antigens [3,43]. Other authors suggested a T-lymphocyte mediated type IV hypersensitivity reaction to an unknown antigen in the skin leading to granuloma formation and potentially vascular damage resulting in secondary vasculitis [43]. Other hypotheses suggest that a multifactorial mechanism, including genetic factors, uninhibited immune reaction, altered enzymes, and bacterial reactions contribute to the pathogenesis of CCD [46]. It has been reported that elevated interleukin (IL)-23 expression was detected in dendritic cells as well as macrophages in CCD, suggesting that an intensified IL23/TH17 axis in addition to tumor necrosis factor (TNF)-α may play a vital role in the pathogenesis of CCD, similar to CD (47).

CCD has been identified in all age groups [44]. Some studies report that CCD affects men and women equally [46,48], whereas other reports in the literature suggest that women are more commonly affected compared to men [3]. Based on our observation in these case series, there was no correlation between the severity of these skin lesions and the activity of the luminal disease, and onset after a mean of 5 years from proctocolectomy. The clinical manifestations vary widely morphologically [49]. A strong predilection to moist environments in intertriginous areas has been documented [6]. When CCD affects such sites, it presents with an ulcerated "knife-like" fissuring and cuts, as shown in Fig. 1A, 1G, 1I, and 1K. Lesions on the extremities and face usually present with erythematous violaceus nodules or plaques that can be painful [46,48]. Generally, the most common areas affected are the genitals, legs, and face, as proven by a variety of case reports listed in Table 1B. Other less common areas reported in the literature include the breast, ear, and umbilicus [19,50,51].

Histological features of CCD are similar to those of the GI tract [52]. The dominant feature is an inflammatory infiltration with sterile non-caseating sarcoid-like granulomas with ample number of multinucleated giant cells (Langerhans giant cells) and plasma cells in the dermis and occasionally can extend into the subcutaneous tissue with a lack of acute inflammatory neutrophilic cells [3,35,46,48,52]. These granulomas can surround small and medium vessels and cause secondary vasculitis pattern [53-55]. This inflammatory perivascular reaction is attributed to the fact that CCD is related to circulating antigens into the dermis or perhaps due to immune complexes deposition within the skin layers [56]. Other less prevalent findings include collagen degeneration in the dermis called "necrobiosis" [55,57,58], eosinophilic infiltration with overlying epidermal ulceration, and lichenoid dermatitis [3].

CCD has been referred to as a great imitator both clinically and histologically [44]. As such, obtaining an accurate history, physical exam, considering other differential diagnosis, and most importantly performing a skin biopsy become very important. The differential diagnosis of CCD consists of any granulomatous inflammation that may involve the skin as demonstrated in Table 2. Histopathological findings are essential in differentiating these entities. For all granulomatous lesions, appropriate staining and cultures should be performed to rule out infectious etiologies.

One important distinction to make is differentiating HS from CCD as they can present in an overlap fashion and share common anatomical locations, specifically the anogenital region [59]. As both conditions can show similar histopathology with chronic inflammation and the presence of granulomas, clinical distinction is most critical. HS is fundamentally a disease of the hair follicle. Thus, while scarring can lead to sinus tract formation and ulceration, this is generally a sequela of chronic follicular inflammation beginning as an abscess. While pyoderma-like ulcerations can occur in areas of HS mimicking CCD, these generally develop over time and in association with a follicular unit. In CCD, this characteristic "knife-cut" fissures are an initial presentation and not anatomically tied to a hair follicle. In severe cases with overlap disease, it can be impossible to distinguish each lesion as there is likely shared pathophysiology between the entities. In our cases, clear knife-cut fissures were not associated with the hair follicle and were consistent with CCD rather than HS [60]. Another condition that poses a diagnosis dilemma is persistent perineal sinus syndrome after proctocolectomy for CD with possible overlap with CCD, as presented in case #3.

CCD carries significant morbidity and can have a negative impact on patients' quality of life [6]. Although there is some evidence regarding the spontaneous resolution of these skin lesions, they are most likely to persist or even progress [56,63]. There is no consensus guideline regarding the best treatment approach for CCD [6,46]. Due to a lack of prospective studies and clinical trials in this domain, most evidence behind the available treatments is based on case reports and case series. A multidisciplinary approach to management, with close coordination between dermatology, gastroenterology, and colorectal surgery, is key to CCD management. Systemic steroids, such as high-dose oral prednisone or prednisolone, remain the cornerstone therapy to induce remission in the acute phase with a favorable clinical response [46,49,52,63]. Additionally, topical steroids such as betamethasone cream have been reported to result in the resolution of mild lesions [64]. Successful use of intralesional steroids has been reported as well [65]. Adding metronidazole to steroids in some cases has resulted in mixed outcomes [61,66]. In general, antibiotics such as oral ciprofloxacin or cephalosporines have been advocated for preventing infections and abscess formation but have no proven benefit [6,66]. A noteworthy efficacious therapy is topical tacrolimus 0.1% ointment, especially in

Table 2 Differential diagnosis and their key differences from cutaneous Crohn's disease [1,3,61,62]

Granulomatous disorders	Key clinical differences
Cutaneous sarcoidosis	Clinical context, systemic manifestations of sarcoid Wide variety of skin presentations (usually asymptomatic plaques) Non-caseating granulomas similar to CCD
Lymphogranuloma venereum	Painless genital ulcer, test for *Chlamydia trachomatis*
Granuloma inguinale	Painless genital ulcer, test for *Klebsiella granulomatis*
Mycobacterial infections	Culture and amplification of *Mycobacterium tuberculosis* DNA by polymerase chain reaction (PCR) in skin biopsies Caseating granulomas on pathology
Syphilis	Symmetric papular eruption involving the trunk, extremities, palms and soles. Test for venereal disease research laboratory and rapid plasma reagin
Necrobiosis lipoidica	Association with diabetes mellitus Necrobiosis of collagen, lymphocyte and plasma cells infiltration
Non-granulomatous disorders	**Key differences**
Hidradenitis suppurativa	Clinical more than pathological distinction, a disease of the hair follicle
Pyoderma gangrenosum	Neutrophilic infiltrate on biopsy, pathery, rapidly ulcerating skin lesions
Impetigo	Bullous bullae vs non bullous plaques, pustules, or vesicles
Erythema nodosum	Tender nodules/plaques on the bilateral shins
Erythema multiforme	Multiple small target-like lesions, association with medications or infections
Schistosomiasis	Pruritic rash – Swimmer's itch
Erysipelas	Skin erythema, edema, and warmth from bacterial infections
Foreign body reaction	Refractile material with polariscopic exam, foreign body giant cells
Leukocytoclastic vasculitis	Fibrinoid necrosis and inflammation of damaged vessels
Anti-tumor necrosis factor-associated skin lesions	Variety of manifestations (psoriatic-like and lupus-like lesions, injection site reactions)
Sweet syndrome	Non-vasculitic neutrophilic skin inflammation associated with fever and underlying hematologic or visceral malignancy, inflammatory disease or preceded by an infection

perineal involvement [67]. Previously, Cyclosporine A was used with success in more severe CCD cases [11,13]. However, given its side effects profile and the availability of biologics, it has fallen out of favor. Immunomodulators like AZA, mercaptopurine (6-MP), and MTX have shown some promise when used as adjunct therapies to biologics. Konrad *et al* reported a case of recalcitrant CCD of the abdominal wall and bilateral sub-mammary folds that failed IFX therapy alone and only improved with the addition of MTX 15 mg weekly while continuing maintenance IFX [24]. Another non-traditional therapy is IVIG, used as a trial in case #3, which has been suggested in several reports to induce remission in fistulizing steroid-refractory CD but has not been studied in CCD [68].

The role of biologics in CCD appears promising based on the available evidence showing significant efficacy in severe cases. One caveat is recognizing paradoxical skin reactions related to TNF-α inhibitors, including anti-TNF-α-induced psoriasis, which are a separate category of cutaneous Crohn's manifestations [69]. Additionally, patients may present with CCD while being on a TNF-α inhibitor and in complete remission of their luminal disease [70]. Therefore, high clinical suspicion is needed to make the diagnosis in such cases. There is one prospective study performed by Bhoyol *et al*, which included 31 women with a median age of 40 who had vulvar CD and were followed prospectively [71]. Eighty percent had active GI disease at the time of presentation. Topical therapies were effective in mild cases. Whereas TNF-α inhibitors were the most effective second-line therapy achieving complete clinical remission in 53% of patients. Since IFX was the first anti-TNF-α to be approved for IBD management, data supporting its use in CCD goes back 2 decades. IFX has shown encouraging results from several case reports in refractory CCD achieving clinical remission [72-74]. A case of diffuse and extensive CCD refractory to steroids, antibiotics, immunomodulators, and repeated surgical debridement reported by Miller *et al*, achieved rapid subjective and objective improvement with IFX 400 mg infusions used over 7 weeks [66]. Additionally, Yoong *et al* report one of the longest follow-up periods regarding CCD remission over 4.5 years on IFX [75]. This case series (cases #1 and #4) supports these results. Another TNF-α blocker, ADA, has shown efficacy in inducing and maintaining remission in CCD. Clinical remission has been reported by using ADA 40 mg injection biweekly in new-onset CCD concomitant with GI symptoms with rapid response achieving

clinical remission within 6 weeks [76,77]. Additionally, Lazaro *et al* report a case of clinical remission of CCD after ADA dose escalation in a patient previously maintained on ADA for luminal GI disease [78]. Less data is available on CZP, a pegylated TNF-α blocker, with one case reporting complete resolution of CCD involving the lower extremities in a patient with known perianal CD and previous reaction to IFX [79]. All these encouraging results highlight the importance of future larger studies regarding the role of TNF-α inhibitors in CCD.

Ustekinumab, a monoclonal antibody against IL-12 and IL-23, is rising as a promising safe and effective treatment for CCD refractory to TNF-α blockers. Recent data showed that ustekinumab resulted in full clinical remission of severe recalcitrant CCD involving the vulva, perineum, gluteal, and facial regions within 7-28 months [7,10,31,80,81]. One case report suggests the use of 390 mg IV for 2 doses followed by the standard 90 mg injection every 8 weeks [80]. Our #2 case also corroborates those findings. Additionally, a meta-analysis including 22 studies showed that ustekinumab is a safe and effective treatment for all cutaneous manifestations of CD, including CCD [82]. However, comparative studies are lacking regarding the efficacy of its use compared to other biologics.

Although vedolizumab, a monoclonal antibody against α4β7-integrin, could have some efficacy in controlling extraintestinal manifestations in IBD [83], its role in CCD is unclear and perhaps less favorable. A multi-center case series study supported by the European Crohn's and Colitis Organization (ECCO) assessed the role of vedolizumab vs. ustekinumab in the management of cutaneous manifestations of CD [84]. It included 28 patients, of which ten had CCD. Five achieved clinical remission on ustekinumab after 1-2 doses over a median follow up of 5 months. In contrast, only one patient improved on vedolizumab, suggesting that ustekinumab may be more useful in treating skin lesions in CD.

The role of surgery and hyperbaric oxygen therapy lack further evidence but have been shown to be effective in several case reports. Similar to luminal CD, surgical evaluation and input remain important in managing severe refractory CCD [14,27]. Williams *et al* report a case series of 6 patients with severe perineal CCD, who failed multiple lines of medical therapies, and underwent surgical management and debridement of their wounds. Five of them had a good clinical response and adequate cosmetic outcomes [85]. Moreover, the use of hyperbaric oxygen in addition to metronidazole has shown a dramatic improvement in severe perineal CCD within 3 months of treatment initiation in a case report by Brady *et al* [86]. In case #3, hyperbaric oxygen seemed to be beneficial when used in addition to biologics.

The association between colonic surgeries and CCD has not been studied and based on our observation, CCD can occur post-proctocolectomy and have variable disease course. A retrospective study by Roth *et al* evaluated the impact of

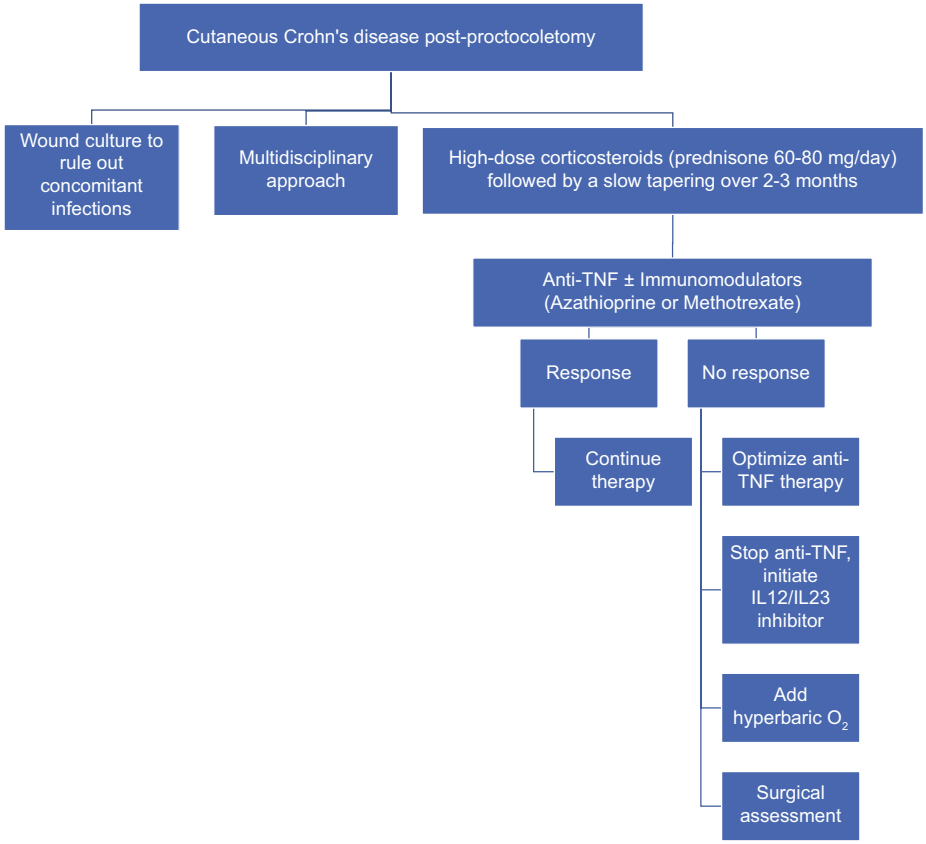

Figure 2 Suggested algorithm for approach and management of cutaneous Crohn's disease post-proctocolectomy
TNF, tumor necrosis factor; IL, interleukin

colectomy on the extraintestinal manifestations of IBD and showed that almost half of the patients continue to have symptoms after surgery, and about 13% developed *de novo* manifestations after colectomy [87]. Although this study did not focus on cutaneous manifestations or CCD after colonic surgery per se, it supports our observation that resecting the initial nidus of the disease by performing proctocolectomy or APR may not prevent the occurrence of cutaneous disease.

It has been established that positive margins increase the risk of anastomotic recurrence after ileocecal resection for CD [88]. When proctectomy is performed in the setting of anorectal CD, the distal margin is frequently positive; the anal disease is often contiguous with the perianal tissues. In these cases, the perianal tissue is left in place and can potentially cause wound healing problems. Whether non-contiguous CD can be triggered from this tissue remains unclear.

Recent publications have suggested that the meso-colon and, possibly, the mesorectum, rather than the luminal intestinal tissue layers are driving the CD process [89,90]. Many surgeons perform a dissection between the mesorectum and the rectal wall when performing a proctectomy. This is done to minimize the post-surgical "dead space" in the pelvis and to decrease intestinal complications caused by bowel positioning and attaching itself deep in the pelvis. One recent retrospective review concluded that patients suffered a greater risk of perineal wound complications when the mesorectum was left in place [91]. There are ongoing trials comparing mesorectum sparing approaches to total meso-rectal excision techniques for proctectomy in CD patients. At this time, it is unknown whether mesorectum that has been left in the pelvis after proctectomy for CD could be a contributor to the development of CCD.

In summary, CCD is a rare condition that requires a complex treatment approach. Based on this case series, our group of patients developed CCD strictly in the perineal and gluteal regions after an average of 5 years post-proctocolectomy. Our suggested approach, demonstrated in Fig. 2, is to initiate a high-dose steroid course with a slow taper over 2-3 months, if there is no contraindication and after evaluation for possible superimposed infections, followed by an anti-TNF inhibitor (IFX was used in this case series) in combination with an immunomodulator. If there is no significant response despite therapy optimization, we suggest changing to ustekinumab and adding hyperbaric O_2 therapy for severe refractory wounds. Additionally, an early multi-disciplinary approach between Gastroenterology, Dermatology, Plastic Surgery, and Colorectal surgery is essential to achieve the best possible clinical outcome in these challenging cases.

Acknowledgment

The authors acknowledge the patients and their families, and the healthcare professionals at the affiliation center

Summary Box

What is already known:

- Cutaneous Crohn's disease (CCD) is the rarest cutaneous manifestation of Crohn's disease (CD)
- Diagnosing CCD is challenging as it can mimic a variety of other cutaneous pathologies
- CCD onset in the absence of active luminal gastrointestinal disease is an understudied phenomenon, and little has been studied about the role of surgical intervention, such as proctocolectomy, on the onset of CCD
- Treatment is challenging, and there is no consensus guideline regarding the best approach in management given its rare occurrence and lack of clinical trials

What the new findings are:

- We describe a unique subgroup of patients who developed CCD after undergoing proctocolectomy for medically refractory colonic CD
- We provide a comprehensive literature review on similar case reports of CCD after proctocolectomy to improve our understanding of this rare phenomenon
- Based on our case series, the suggested approach for CCD is to start with an extended course of high-dose corticosteroids once the diagnosis is confirmed by pathology, followed by an anti-tumor necrosis factor +/- an immunomodulator
- Interleukin (IL)-12/IL-23 inhibitors are effective and should be considered

References

1. Siroy A, Wasman J. Metastatic Crohn disease: a rare cutaneous entity. *Arch Pathol Lab Med* 2012;**136**:329-332.
2. Kafity AA, Pellegrini AE, Fromkes JJ. Metastatic Crohn's disease. A rare cutaneous manifestation. *J Clin Gastroenterol* 1993;**17**:300-303.
3. Emanuel PO, Phelps RG. Metastatic Crohn's disease: a histopathologic study of 12 cases. *J Cutan Pathol* 2008;**35**:457-461.
4. Greuter T, Navarini A, Vavricka SR. Skin manifestations of inflammatory bowel disease. *Clin Rev Allergy Immunol* 2017;**53**:413-427.
5. Bohdanowicz M, Ghazarian D, Rosen CF. Cutaneous Crohn's disease of the vulva after a total colectomy and without gastrointestinal manifestations: a case report. *SAGE Open Med Case Rep* 2019;**7**:2050313X19868390.
6. Guest GD, Fink RL. Metastatic Crohn's disease: case report of an unusual variant and review of the literature. *Dis Colon Rectum* 2000;**43**:1764-1766.
7. Abdat R, Markova A, Farraye FA, Lichtman MK. Ustekinumab for treatment of cutaneous Crohn's disease. *Dermatol Online J* 2016;**22**.
8. Al-Chalabi A TS, Lay R, Nawras A. Young Investigator: Metastatic

Crohn's disease of the vulva: a diagnostic challenge. *Am J Gastroenterol* 2018;**113**:S7.
9. Argyriou K, Khan M, Samuel S. Multiple unusual ulcerated skin lesions in a Crohn's disease patient. *Gastroenterology* 2018;**155**:e17-e18.
10. Ballester Sanchez R, Sanchis Sanchez C, Rodrigo Nicolas B, Valcuende Cavero F. Metastatic Crohn disease treated with ustekinumab. *Actas Dermosifiliogr (Engl Ed)* 2021;**112**:182-183.
11. Bardazzi F, Neri I, Tosti A, Guidetti MS. Cutaneous Crohn's disease responsive to cyclosporin A. *J Eur Acad Dermatol Venereol* 1995;**5** Suppl: S87.
12. Biancone L, Geboes K, Spagnoli LG, et al. Metastatic Crohn's disease of the forehead. *Inflamm Bowel Dis* 2002;**8**:101-105.
13. Bloget F, Bisiau S, Delaporte E, Mazeman E, Cortot A, Gosselin B. Metastatic Crohn's disease of the penis. *Ann Pathol* 1996;**16**:296-298.
14. Cockburn AG, Krolikowski J, Balogh K, Roth RA. Crohn disease of penile and scrotal skin. *Urology* 1980;**15**:596-598.
15. Daunton A, Langman G, Goulding JM. A cutaneous presentation of a common condition. *BMJ* 2015;**351**:h6711.
16. Dave A WJ, Shea C, Rubin D. Metastatic Crohn's Disease of the vulva and perineum treated with Anti-mycobacterial Therapy. *Inflamm Bowel Dis* 2009;**15**(Suppl_2):S5.
17. Foreman B FG, Tinsley A, Williams E. Granulomatous lymphangitis of the genitals: a rare variant of cutaneous Crohn's disease. *Inflamm Bowel Dis* 2016;**22**(Suppl_1):S11.
18. Goh M, Tekchandani AH, Wojno KJ, Faerber GJ. Metastatic Crohn's disease involving penile skin. *J Urol* 1998;**159**:506-507.
19. Goyal A, Mansel RE, Young HL, Douglas-Jones A. Metastatic cutaneous Crohn's disease of the nipple: report of a case. *Dis Colon Rectum* 2006;**49**:132-134.
20. Graham DB, Jager DL, Borum ML. Metastatic Crohn's disease of the face. *Dig Dis Sci* 2006;**51**:2062-2063.
21. Guglielmetti A, Gompertz M, Jahr C, Silva T, Gonzalez S. Remission of refractory metastatic Crohn's disease achieved with dapsone. *Int J Dermatol* 2018;**57**:467-469.
22. Ilangovan KR, Yeo R. Unusual presentation of metastatic Crohn's disease. *Eur J Obstet Gynecol Reprod Biol* 2008;**137**:259.
23. Kim NI, Eom JY, Sim WY, Haw CR. Crohn's disease of the vulva. *J Am Acad Dermatol* 1992;**27**:764-765.
24. Konrad A, Seibold F. Response of cutaneous Crohn's disease to infliximab and methotrexate. *Dig Liver Dis* 2003;**35**:351-356.
25. Lavery HA, Pinkerton JH, Sloan J. Crohn's disease of the vulva--two further cases. *Br J Dermatol* 1985;**113**:359-363.
26. Leu S, Sun PK, Collyer J, et al. Clinical spectrum of vulva metastatic Crohn's disease. *Dig Dis Sci* 2009;**54**:1565-1571.
27. Moyes LH, Glen P, Pickford IR. Perineal metastatic Crohn's disease: a case report and review of the literature. *Ann R Coll Surg Engl* 2007;**89**:W1-W3.
28. Patel AV, Jones DM, Hill JC, MacDermott RP. Development of metastatic Crohn's disease of the skin while on anti-TNF biologics. *Inflamm Bowel Dis* 2012;**18**:1188-1190.
29. Rispo A, Lembo G, Insabato L, Cozzolino A, Pesce G, Castiglione F. Successful treatment of therapy-resistant metastatic Crohn's disease with infliximab. *Br J Dermatol* 2004;**150**:1045-1046.
30. Shields BE, Richardson C, Arkin L, Kornik R. Vulvar Crohn disease: Diagnostic challenges and approach to therapy. *Int J Womens Dermatol* 2020;**6**:390-394.
31. Stoleru G, Robbins G, Papadimitriou JC, Wong U. Rapid resolution of vulvar Crohn's disease with ustekinumab. *ACG Case Rep J* 2020;**7**:e00452.
32. Tweedie JH, McCann BG. Metastatic Crohn's disease of thigh and forearm. Gut 1984;**25**:213-214.
33. Vint R, Husain E, Hussain F, McClinton S, Ormerod A. Metastatic Crohn's disease of the penis: two cases. *Int Urol Nephrol* 2012;**44**:45-49.
34. Levine N, Bangert J. Cutaneous granulomatosis in Crohn's disease. *Arch Dermatol* 1982;**118**:1006-1009.
35. McCallum DI, Kinmont PD. Dermatological manifestations of crohn's disease. *Br J Dermatol* 1968;**80**:1-8.
36. Antonelli E, Bassotti G, Tramontana M, et al. Dermatological manifestations in inflammatory bowel diseases. *J Clin Med* 2021;**10**:364.
37. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol* 2005;**11**:7227-7236.
38. Gomollon F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn›s disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3-25.
39. Marzano AV, Borghi A, Stadnicki A, Crosti C, Cugno M. Cutaneous manifestations in patients with inflammatory bowel diseases: pathophysiology, clinical features, and therapy. *Inflamm Bowel Dis* 2014;**20**:213-227.
40. Hindryckx P, Novak G, Costanzo A, Danese S. Disease-related and drug-induced skin manifestations in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2017;**11**:203-214.
41. Ungureanu L, Cosgarea R, Alexandru Badea M, Florentina Vasilovici xA, Cosgarea I, Corina Senila S. Cutaneous manifestations in inflammatory bowel disease (Review). *Exp Ther Med* 2020;**20**:31-37.
42. Chatterjee D, Bhattacharjee R, Khullar G, et al. Metastatic Crohn disease: a clinicohistological appraisal from a tertiary care center in India. *Am J Dermatopathol* 2020;**42**:506-512.
43. Palamaras I, El-Jabbour J, Pietropaolo N, et al. Metastatic Crohn's disease: a review. *J Eur Acad Dermatol Venereol* 2008;**22**:1033-1043.
44. Bender-Heine A, Grantham JT, Zaslau S, Jansen R. Metastatic Crohn disease: a review of dermatologic manifestations and treatment. *Cutis* 2017;**99**:E33-E40.
45. Aberumand B, Howard J, Howard J. Metastatic Crohn's disease: an approach to an uncommon but important cutaneous disorder. *Biomed Res Int* 2017;**2017**:8192150.
46. Hackzell-Bradley M, Hedblad MA, Stephansson EA. Metastatic Crohn's disease. Report of 3 cases with special reference to histopathologic findings. *Arch Dermatol* 1996;**132**:928-932.
47. Ickrath F, Stoevesandt J, Schulmeyer L, Glatzel C, Goebeler M, Kerstan A. Metastatic Crohn's disease: an underestimated entity. *J Dtsch Dermatol* Ges 2021;**19**:973-982.
48. Buckley C, Bayoumi AH, Sarkany I. Metastatic Crohn's disease. *Clin Exp Dermatol* 1990;**15**:131-133.
49. Chen W, Blume-Peytavi U, Goerdt S, Orfanos CE. Metastatic Crohn's disease of the face. *J Am Acad Dermatol* 1996;**35**:986-988.
50. Chuah JH, Kim DS, Allen C, Hollis L. Metastatic Crohn's disease of the ear. *Int J Otolaryngol* 2009;**2009**:871567.
51. Phillips RK, Glazer G. Metastatic Crohn's disease of the umbilicus. *Br Med J (Clin Res Ed)* 1981;**283**:887.
52. Shum DT, Guenther L. Metastatic Crohn's disease. Case report and review of the literature. *Arch Dermatol* 1990;**126**:645-648.
53. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* 1976;**55**:401-412.
54. Slater DN, Waller PC, Reilly G. Cutaneous granulomatous vasculitis: presenting feature of Crohn's disease. *J R Soc Med* 1985;**78**:589-590.
55. Perret CM, Bahmer FA. Extensive necrobiosis in metastatic Crohn's disease. *Dermatologica* 1987;**175**:208-212.
56. Burgdorf W, Orkin M. Granulomatous perivasculitis in Crohn's disease. *Arch Dermatol* 1981;**117**:674-675.
57. Du Boulay C, Whorwell PJ. 'Nodular necrobiosis': a new cutaneous manifestation of Crohn's disease? *Gut* 1982;**23**:712-715.
58. Peltz S, Vestey JP, Ferguson A, Hunter JA, McLaren K. Disseminated metastatic cutaneous Crohn's disease. *Clin Exp Dermatol* 1993;**18**:55-59.
59. Giudici F, Maggi L, Santi R, et al. Perianal Crohn's disease and

hidradenitis suppurativa: a possible common immunological scenario. *Clin Mol Allergy* 2015;**13**:12.
60. Napolitano M, Megna M, Timoshchuk EA, et al. Hidradenitis suppurativa: from pathogenesis to diagnosis and treatment. *Clin Cosmet Investig Dermatol* 2017;**10**:105-115.
61. Duhra P, Paul CJ. Metastatic Crohn's disease responding to metronidazole. *Br J Dermatol* 1988;**119**:87-91.
62. Lebwohl M, Fleischmajer R, Janowitz H, Present D, Prioleau PG. Metastatic Crohn's disease. *J Am Acad Dermatol* 1984;**10**:33-38.
63. Tatnall FM, Dodd HJ, Sarkany I. Crohn's disease with metastatic cutaneous involvement and granulomatous cheilitis. *J R Soc Med* 1987;**80**:49-51.
64. Farhi D, Duriez P, Aractingi S, Cosnes J, Khosrotehrani K. Misleading pustular plaques of the lower limbs during Crohn's disease: two case reports. *J Med Case Rep* 2007;**1**:109.
65. Alegre VA, Pujol C, Calatayud A, Martinez A, Fortea JN, Aliaga A. Cutaneous Crohn's disease: treatment with intralesional steroids. *Int J Dermatol* 1989;**28**:552-554.
66. Miller AM, Elliott PR, Fink R, Connell W. Rapid response of severe refractory metastatic Crohn's disease to infliximab. *J Gastroenterol Hepatol* 2001;**16**:940-942.
67. Rice SA, Woo PN, El-Omar E, Keenan RA, Ormerod AD. Topical tacrolimus 0.1% ointment for treatment of cutaneous Crohn's Disease. *BMC Res Notes* 2013;**6**:19.
68. Rogosnitzky M, Danks R, Holt D. Intravenous immunoglobulin for the treatment of Crohn's disease. *Autoimmun Rev* 2012;**12**:275-280.
69. Farkas K, Nagy F, Kovacs L, Wittmann T, Molnar T. Anti-tumor necrosis factor-alpha induced systemic lupus erythematosus in a patient with metastatic Crohn's disease--what is the role of anti-TNF antibody? *J Crohns Colitis* 2013;**7**:e143-e145.
70. Campos S, Coutinho I, Cardoso JC, Portela F. Metastatic Crohn's disease despite infliximab therapy. *An Bras Dermatol* 2017;**92**(5 Suppl 1):104-106.
71. Bhoyrul B, Lyon C. Crohn's disease of the vulva: A prospective study. *J Gastroenterol Hepatol* 2018;**33**:1969-1974.
72. Geyer AS, Anhalt GJ, Nousari HC. Effectiveness of infliximab in the treatment of refractory perineal cutaneous Crohn disease. *Arch Dermatol* 2000;**136**:459-460.
73. Makhija S, Trotter M, Wagner E, Coderre S, Panaccione R. Refractory Crohn's disease of the vulva treated with infliximab: a case report. *Can J Gastroenterol* 2007;**21**:835-837.
74. van Dullemen HM, de Jong E, Slors F, Tytgat GN, van Deventer SJ. Treatment of therapy-resistant perineal metastatic Crohn's disease after proctectomy using anti-tumor necrosis factor chimeric monoclonal antibody, cA2: report of two cases. *Dis Colon Rectum* 1998;**41**:98-102.
75. Yoong C, Schofield C, Rodins K, Faulkner C. Cutaneous Crohn's disease treated with infliximab and 4 years of follow up. *Australas J Dermatol* 2014;**55**:e40-e43.
76. Cury DB, Moss AC, Elias G, Nakao A. Adalimumab for cutaneous metastatic Crohn's disease. *Inflamm Bowel Dis* 2010;**16**:723-724.
77. Miller FA, Jones CR, Clarke LE, Lin Z, Adams DR, Koltun WA. Successful use of adalimumab in treating cutaneous metastatic Crohn's disease: report of a case. *Inflamm Bowel Dis* 2009;**15**:1611-1612.
78. Lazaro Saez M, Hernandez Martinez A, Bendezu Garcia RA, et al. Metastatic Crohn's disease. Response to adalimumab dose intensification. *Gastroenterol Hepatol* 2012;**35**:321-325.
79. Kiuru M, Camp B, Adhami K, Jacob V, Magro C, Wildman H. Treatment of metastatic cutaneous Crohn disease with certolizumab. *Dermatol Online J* 2015;**21**.
80. Zullow SML, Michael K, MD; Larson, Allison MD; Stier, Elizabeth A. MD; Farraye, Francis A MD, MSc, FACG. Case Series: Ustekinumab Use in Metastatic Cutaneous Crohn's Disease. *Am J Gastroenterol* 2017;**112**(pS1102).
81. Martins Figueiredo L, Oliveira AM, Martins A. Metastatic cutaneous Crohn's disease of the face-a case successfully treated with ustekinumab. *J Crohns Colitis* 2020;**14**:874-875.
82. Wu J, Smogorzewski J. Ustekinumab for the treatment of paradoxical skin reactions and cutaneous manifestations of inflammatory bowel diseases. *Dermatol Ther* 2021;**34**:e14883.
83. Hanzel J, Ma C, Casteele NV, Khanna R, Jairath V, Feagan BG. Vedolizumab and extraintestinal manifestations in inflammatory bowel disease. *Drugs* 2021;**81**:333-347.
84. Phillips FM, Verstockt B, Sebastian S, et al. Inflammatory cutaneous lesions in inflammatory bowel disease treated with vedolizumab or ustekinumab: An ECCO CONFER multicentre case series. *J Crohns Colitis* 2020;**14**:1488-1493.
85. Williams N, Scott NA, Watson JS, Irving MH. Surgical management of perineal and metastatic cutaneous Crohn's disease. *Br J Surg* 1993;**80**:1596-1568.
86. Brady CE, 3rd, Cooley BJ, Davis JC. Healing of severe perineal and cutaneous Crohn's disease with hyperbaric oxygen. *Gastroenterology* 1989;**97**:756-760.
87. Roth R, Vavricka S, Scharl M, et al. The impact of colectomy on the course of extraintestinal manifestations in Swiss inflammatory bowel disease cohort study patients. *United European Gastroenterol J* 2021;**9**:773-780.
88. Ryan JM, Rogers AC, O'Toole A, Burke JP. Meta-analysis of histological margin positivity in the prediction of recurrence after Crohn's resection. *Dis Colon Rectum* 2019;**62**:882-892.
89. Kono T, Ashida T, Ebisawa Y, et al. A new antimesenteric functional end-to-end handsewn anastomosis: surgical prevention of anastomotic recurrence in Crohn's disease. *Dis Colon Rectum* 2011;**54**:586-592.
90. Coffey CJ, Kiernan MG, Sahebally SM, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis* 2018;**12**:1139-1150.
91. de Groof EJ, van der Meer JHM, Tanis PJ, et al. Persistent mesorectal inflammatory activity is associated with complications after proctectomy in Crohn's disease. *J Crohns Colitis* 2019;**13**:285-293.