



Metastatic Crohn's disease: an underestimated entity

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Summary

Cutaneous metastatic Crohn's disease (MCD) is a rare but challenging dermatologic manifestation of Crohn's disease. It is histologically defined as the presence of non-caseating granulomas at skin sites separated from and non-contiguous to the gastrointestinal tract. Cutaneous metastatic Crohn's disease should be distinguished from the much more frequent contiguous cutaneous manifestations of Crohn's disease that present at perianal or, less common, peristomal sites with direct extension from the intestine to the adjacent skin. Versatile clinical presentation and the fact that occurrence can predate the initial diagnosis of Crohn's disease may lead to misdiagnosis, delayed treatment and underreporting. As case numbers are small and randomized controlled studies on management are lacking, the therapeutic approach remains challenging and is often unsatisfactory. We here performed a systematic literature search identifying 264 published pediatric and adult cases of MCD and additionally report three of our own cases. Our review summarizes clinical characteristics, putative etiopathology, histologic findings, differential diagnoses and treatment options for MCD.

Introduction

Crohn's disease (CD) is a multisystem granulomatous inflammatory disease that may involve any part of the gastrointestinal tract from the oral cavity to the anus [1]. Associated extraintestinal manifestations at the skin are quite common with a reported prevalence of 22–75 % [2, 3]. Clinical presentations include granulomatous lesions by direct extension from the gastrointestinal tract affecting the perianal or peristomal region, genital or non-genital granulomatous lesions of metastatic Crohn's disease (MCD) non-contiguous to the gastrointestinal tract, immune-related (or reactive) lesions (such as pyoderma gangrenosum or erythema nodosum), and skin lesions from nutritional deficiencies [1]. Skin manifestations of MCD are rare; prevalence and incidence estimates are lacking owing to its variable clinical presentation, and the actual figures are likely to be higher [4].

MCD was first described by Parks et al. [5] in 1965. Histologically, non-caseating, sarcoid-like granulomas comprise abundant multinucleated Langhans giant cells as well as foreign body giant cells and can be found in the papillary (more commonly) and reticular dermis with occasional extension into the adipose tissue (Figure 1d, e) [4, 6]. Granulomas are surrounded by an inflammatory cell infiltrate consisting mainly of histiocytes, plasma cells, lymphocytes and,

sometimes, polymorphonuclear leukocytes. Perivascular (granulomatous perivascularitis) or perifollicular accentuation present frequent findings, whereas concomitant true vasculitis is only noted in exceptional cases. Rarely, necrobiosis has also been reported [7, 8].

The pathogenesis of MCD is still poorly understood. It is speculated that yet unknown (intestinal?) antigens circulate to the skin where they trigger a granulomatous response at the level of the dermis [1, 2, 6]. Other authors consider an underlying sensitization to gut antigens of possibly bacterial origin, which entails a putative cross-reaction with structurally similar skin antigens [1, 9]. Another postulated mechanism assumes a T-lymphocyte-mediated type IV hypersensitivity reaction to a yet unknown antigen in the skin leading to granuloma formation and vascular damage, which, due to the closeness of the inflammatory reaction to a vessel, results in either granulomatous perivascularitis or true vasculitis [2]. Further hypotheses claim multifactorial immune mechanisms, altered enzymes, genetic factors or bacterial Id-reactions to be causative [9, 10]. On the molecular level it is unclear whether the same pathogenic events play a role in MCD as reported in CD. Besides tumor necrosis factor (TNF) α an enhanced interleukin (IL)-23/Th17 axis seems to be of pathogenic relevance for CD [11] and elevated IL-23 expression can also be detected

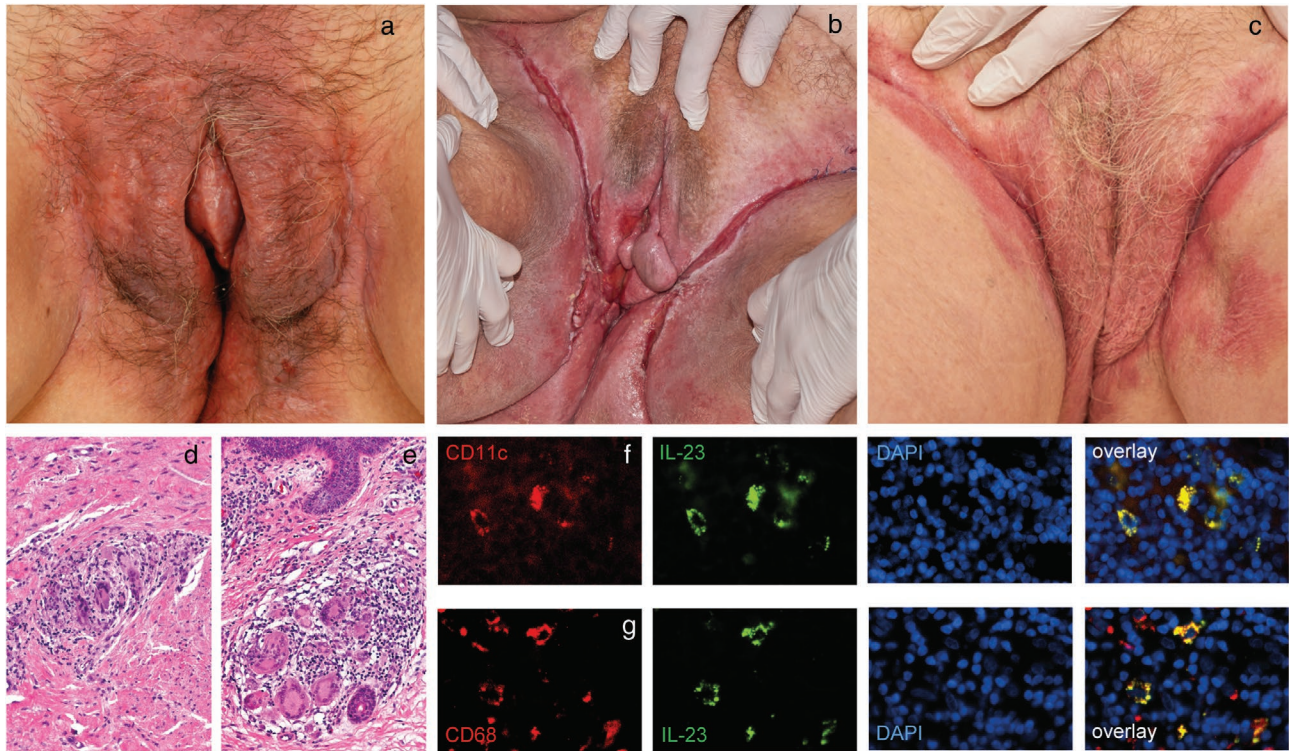


Figure 1 Clinical manifestation and histology of MCD. A 54-year-old woman presenting with erythematous swelling of the genitals that persisted for three years (a). A 64-year-old woman with a 19-year-history of well-demarcated, deep, linear, “knife-like” inguinal and vulvar ulcers with edematous and erythematous surrounding skin and up to 4 cm large pedunculated skin-colored nodules adhering to the left labium majus (b). A 76-year-old woman with linear, fissurated but more superficially localized inguinal ulcers and erythematous plaques on genitals and inguinal region. In all cases bacterial and fungal swabs were unremarkable (c). Histology of MCD: Deep spindle-shaped biopsies from the left groin of the patients pictured in b (d) and c (e). Histological presentation of sarcoid-like, non-caseating granulomas in the deep reticular (d) or superficial dermis (e). The latter are usually found in case of plaques (c). Periodic Acid-Schiff (PAS), Ziehl-Neelsen and Giemsa stainings were unremarkable with respect to detection of pathogens. Light polarization was unsuspecting for birefringent material. Immunofluorescence double-labeling of CD11c⁺ dendritic cells (f, red) or CD68⁺ macrophages/histiocytes (g, red) with interleukin-23 (IL-23, green). One representative immunolabelling of all three cases (a–c) is depicted. DAPI (blue) displays the nuclear counterstain. Note that granulomas themselves do not express IL-23 (data not shown) (f, g).

in CD11c⁺ dendritic cells as well as CD68⁺ macrophages/histiocytes in MCD (Figure 1f, g).

The clinical characteristics of MCD strongly vary depending on the affected site [1, 12]. While basically every part of the skin may be involved lesions may be solitary or multiple. They are usually asymptomatic but sometimes tender on palpation [2]. Non-genital lesions present as erythematous, violaceous or brownish papules, plaques or nodules as well as fissures and/or ulcers. Genital lesions show swelling and/or even induration of the genitalia (Figure 1a) [2, 13]. Moreover, vegetating papillomatous nodules mimicking condylomata and lesions resembling skin tags have been described [4, 13]. In some cases, skin tags may evolve to pedunculated nodules (Figure 1). Intertriginous manifestations of MCD commonly ulcerate as a result of friction and moisture. They may present

fissurated and rhagadiform (Figure 1b, c) as is also observed in oral CD.

In 2008, Palamaras et al. published a review on 156 patients (including 40 children) suffering from MCD [2]. Since additional MCD cases have been reported in the meantime, we performed a systematic literature search on published cases of MCD to provide a comprehensive up-to-date overview.

Methods and Results

Using the PubMed data bank (search strategy: metastatic Crohn's disease, cutaneous Crohn's disease, non-genital granulomatosis, vulvitis granulomatosa, granulomatous vulvitis, penile Crohn's disease) and considering the literature

Table 1 Overview on published cases of MCD.

#	Reference	Number of pat., age, sex	Diagnosis of intestinal CD	Location of lesions	Treatment	Outcome (skin lesions)
1	van de Scheur MR et al., J Eur Acad Dermatol Venereol 17: 184–9 (2003)	1, 10 yr, m	a	genital, ano-perineal	TCS, MN, MTX, CsA, SCS, TNF α -I	each n.e. each p.i.
2	Günther AR et al., Am J Obstet Gynecol 191: 1719–20 (2004)	1, n.a., f	p (6 yr)	genital genital	MTX surgery+SSZ	cl. cl.
3	Hoque SR et al., Clin Exp Dermatol 30: 727–8 (2005)	1, 10 yr, m	c	genital, upper lip	SCS MN+SSZ	p.i. p.i.
4	Bhaduri S et al., Int J STD AIDS 16: 512–4 (2005)	1, 23 yr, f	a	genital	SCS+AZA	p.i.
5	Makhija S et al., Can J Gastroenterol 21: 835–7 (2007)	1, 48 yr, f	p (3 yr)	genital	TCS+MN SCS+AZA TNF α -I+AZA	n.e. n.e. cl.
6	Palamaras I et al., JEADV 22: 1033–3 (2008)	Total 156 116 adults (18–78 yr, mean 38.5), 43 m/73 f 40 children (5–17 yr, mean 11.1), 21 m/19 f	Adults: a 2 (1.7 %), p 81 (69.8 %), c 22 (19 %), s 7 (6 %), n.a. 4 Children: a 3 (7.5 %), p 8 (20 %), c 19 (47.5 %), s 9 (22.5 %), n.a. 1	Adults: genital 68 (59 %), non-genital 48 (41 %) Children: genital 34 (85 %), non-genital 6 (15 %)	n.a.	n.a.
7	Emanuel PO et al., J Cutan Pathol 35: 457–61 (2008)	12 (19–66 yr, mean 36), 8 m/4 f	11 p, 1 s	5 genital, 5 perineal, 1 inguinal, 1 gluteal	n.a.	n.a.
8	Keiler S et al., Pediatr Dermatol 26: 604–9 (2009)	1, 13 yr, f	c	genital	SCS+AZA AZA+5-ASA	n.a. p.i.
9	Fernandes MD et al., An Bras Dermatol 84: 651–4 (2009)	1, 40 yr, f	c	breast, gluteal, abdomen, leg	5-ASA+SCS	n.e.

Continued

Table 1 Continued.

#	Reference	Number of pat., age, sex	Diagnosis of intestinal CD	Location of lesions	Treatment	Outcome (skin lesions)
10	Leu S et al., Dig Dis Sci 54: 1565–71 (2009) ²	1, 43 yr, f	p (27 yr)	genital, perianal	SCS+CIP+MN 6-MP	p.i. p.i.
		1, 52 yr, f	a	genital, inguinal, gluteal, abdomen infra-mammary	n.a.	n.a.
11	Lane V A, et al., J Pediatr Urol 6: 270–3 (2010)	1, 5 yr, m	p (6 mth)	genital	TAC+MN	n.a.
12	Lestre S et al., Eur J Dermatol 20: 504–5 (2010)	1, 21 yr, f	p (2 yr)	perianal, gluteal	TNF α -I	p.i.
13	Corbett SL et al., Pediatrics 125: e1518–22 (2010)	1, 8 yr, f	c	genital	5-ASA MN	p.i. n.e.
14	Mun JH et al., J Dermatol 38: 303–7 (2011)	1, 10 yr, f	c	genital	SCS+MN	p.i.
15	Foo WC et al., Am J Dermatopathol 33: 588–93 (2011)	5 ² (8, 26, 28, 43, 43 yr), 5f	CD in all cases, but time of diagnosis n.a.	1 genital 1 genital 1 genital 1 inguinal 1 genital	SCS+MN 5-ASA TCS SCS+MN+Am/CI n.a.	n.a.
16	Madhani NA et al., Indian J Dermatol Venereol Leprol 77: 342–4 (2011)	1, 37 yr, f	a	genital	SCS MN discontinued AZA	p.i. cl w p.i.
17	Khaled A et al., Indian J Dermatol 56: 101–3 (2011)	1, 46 yr, f	a	genital, inguinal, gluteal	MN	p.i.
18	Reinders MG et al., J Am Acad Dermatol 65: 449–50 (2011)	1, 13 yr, m	c	genital	oral budesonide	p.i.
19	Ghosh D et al., J Low GenitTract Dis 15: 322–4 (2011)	1, 64 yr, f	a	genital	FCX+TCS+TOT+TNY	p.i.
20	Zabetian S et al., Pediatr Dermatol 29: 765–6 (2012)	1, 11 yr, m	c	genital	TNF α -I	p.i.
21	Weimberg AE et al., Urology 80: 1132–4 (2012)	1, 17 yr, m	c	genital	SCS TNF α -I	p.i. n.a.
22	Asakura M et al., JCD SA Vol. 2 No. 2: 60–1 (2012)	1, 13 yr, f	c	genital, ano-perineal	TNF α -I	p.i.

#	Reference	Number of pat., age, sex	Diagnosis of intestinal CD	Location of lesions	Treatment	Outcome (skin lesions)
23	Gordon KD et al., Int J STD AIDS 24: 149–51 (2013)	1, 21 yr, m	c	genital	Cotrim SCS AZA+TNF α -I MMF	n.e. p.i. n.e. n.a.
24	Weitz N et al., Pediatr Dermatol 30: e278–80 (2013)	1, 9 yr, f	p (6 mth) ^a	genital, ano-perineal	SCS+TNF α -I+FLU+ CIP+MN	w
25	Lee Y et al., J Crohns Colitis 7: e146–9 (2013)	1, 15 yr, m	p (2 years)	genital	TNF α -I	cl
26	Salvaggio HL et al., JAMA Dermatol 150: 1083–7 (2014)	1, mid-40, f	p (30 years) ^a	genital, perianal, inguinal, axillary	SCS+AZA+NAB TNF α -I+SCS+surgery	p.i. p.i.
27	Mirheydar HS et al., Urology 83: 1165–9 (2014)	1, 6 yr, m	c	genital	SCS	n.e.
28	Lang N et al., J Dtsch Dermatol Ges 13: 571–4 (2015)	1, 35 yr, m 1, 55 yr, m	p p (6 mth)	elbow arms and legs	TCS SCS TCS AZA SCS TNF α -I	w cl n.e. p.i. p.i. cl
29	Laftah Z, J Crohns Colitis 9: 318–25 (2015)	13 ² (ages n.a.), f	n.a.	genital	TCS, SCS, MN, ERY, AZA, MTX, 5-ASA, TNF α -I, surgery ^s	p.i. ^s
30	Barrick BJ, Pediatr Dermatol 33: 172–7 (2016)	5 ^s (7, 8, 12, 16, 16 yr), 5m	1 p, 2 c, 2 a	5 genital	TCS TAC TNF α -I TNF α -I+AZA CIP AZA+5-ASA SCS+AH SCS+5-ASA	1 p.i., 1 n.e. 1 n.e., 1 n.a. 2 p.i., 1 n.e. 1 p.i. 1 p.i. 1 n.a. 1 n.e. 1 w
31	Sabbadini C et al., J Dtsch Dermatol Ges 14: 431–4 (2016)	1, 10 yr, m	p (5 yr)	genital	TNF α -I	p.i.
32	Aberumand B et al., Biomed Res Int. 2017: 8192150 (2017)	1, 20 yr, f	p	cutaneous upper lip	TAC	p.i.

Continued

Table 1 Continued.

#	Reference	Number of pat., age, sex	Diagnosis of intestinal CD	Location of lesions	Treatment	Outcome (skin lesions)
33	Alexakis C et al., J Crohns Colitis 11: 454–9 (2017)	12 ² (ages n.a.), 12m	n.a.	genital	OA ⁵ SCS AZA TNF α -I surgery	p.i. 76 % p.i. 72 % p.i. or cl 60 % p.i. 50 % mostly p.i.
34	Dederichs F et al., J Crohns Colitis 12(2): 197–203 (2018)	28 ² (ages n.a., mean 32.5 yr), 5 m/23 f	18 p, 10 s	genital	OA ⁵ SCS 5-ASA AZA/6-MP/MTX TNF α -I	p.i. 10/13, n.e. 3/13 p.i. 12/15, n.e. 3/15 p.i. 1/3, n.e. 2/3 p.i. 9/14, n.e. 5/14 p.i. 18/26, n.e. 8/26
35	Motamed F et al., Clin Case Rep 6: 2396–8 (2018)	1, 11 yr, m	a	genital	AZA	p.i.
36	Ahmad A et al., JAAD Case Rep 6: 552–4 (2020)	1, 53 yr, f	a	genital	HCQ+SCS	p.i.
37	El-Enany G et al., Clin Exp Dermatol 45: 1080–3 (2020)	1, 31 yr, f	a	genital, gluteal, postauricular fold	SCS	cl.
38	This study	1, 64 yr, f (Figure 1b)	a	genital, inguinal, perianal	TA+TCS TNF α -I	n.e. cl.
		1, 76 yr, f (Figure 1c)	a	genital inguinal	TA+TCS	p.i.
Total		1, 54 yr, f (Figure 1a)	a	genital, gluteal	TA+TCS, OA TNF α -I	n.e. cl.
		Adults (18–78 yr) 152 ⁶ , mean age 38.5 yr 54 m (36 %) /98 f (64 %) s 8 (5.6 %) n.a. 8	a 12 (8.3 %) p 99 (68.8 %) c 25 (17.4 %) s 8 (5.6 %) n.a. 8	genital, gluteal	TNF α -I (43 cases)	cl. 11.5 %, p.i. 62.8 %, n.e. 23.3 %, w 2.3 %
		Children (5–17 yr) 61 ⁶ , mean age 11 yr, 36 m (59 %) /25 f (41 %) s 9 (15.3 %) n.a. 2	a 7 (11.9 %) p 13 (22 %) c 30 (50.8 %) s 9 (15.3 %) n.a. 2	genital, gluteal	SCS (35 cases)	cl. 5.7 %, p.i. 68.6 %, n.e. 20.0 %, w 5.7 %

#	Reference	Number of pat., age, sex	Diagnosis of intestinal CD	Location of lesions	Treatment	Outcome (skin lesions)
					AZA (10 cases)	cl. 10 %, p.i. 70 %, n.e. 20 %
					TCS (10 cases)	p.i. 30 %, n.e. 60 %, w 10 %
					MN (9 cases)	cl. 11.1 %, p.i. 44.4 %, n.e. 33.3 %, w 11.1 %
					SSZ/5-ASA (8 cases)	cl. 12.5 %, p.i. 37.5 %, n.e. 37.5 %, w 12.5 %
					TAC (3 cases)	2 p.i., 1 n.e.
					MTX (2 cases)	1 cl., 1 n.e.
					6-MP (1 case)	1 p.i.
					CsA (1 case) (others see above)	1 p.i.

Abbr.: #, number; a, absent; c, concomitant; CD, Crohn's disease; cl, clearance; f, female; m, male; mth, month(s); n.a., not available; n.e., no effect; p, prior; pap/nod/pl, papules/nodules/plaques; pat., patient(s); p.i., partial improvement; s, subsequent; w, worsening; wk, week(s); yr, year(s)
 Medications: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AH, antihistamines; Am/Cl, amoxicillin clavulanate; AZA, azathioprine; CIP, ciprofloxacin; Cotrim, cotrimoxazole; CsA, ciclosporin A; ERY, erythromycin; FCX, flucloxacillin; FLU, fluconazole; HCO, hydroxychloroquine; MMF, mycophenolate mofetil; MN, metronidazole; nabumetone, NAB; OA, oral antibiotics; SSZ, sulfasalazine; SCS, systemic corticosteroid; TA, topical antiseptics; TAC, topical tacrolimus; TCS, topical corticosteroid; TNF α -I, tumor necrosis factor- α -inhibitors (infliximab, adalimumab); TNY, topical nystatin; TOT, topical oxytetracycline.

¹For more details see original article.
²Only cases with evidence of granulomas in the biopsy specimen included.
³2 yr earlier histologic diagnosis of oro-facial granulomatosis.
⁴Crohn's-like granulomatous colitis as part of the Hermansky-Pudlak Syndrome.
⁵Clear allocations of the given treatments and response rates n.a.
⁶Division in groups children/adults n.a. in 54 cases.
 *Not divided into monotherapy or combination therapy, for more details see text respectively original article.

published in English or German language until December 4, 2020 we identified 264 cases of histology-proven MCD and added another three from our clinic. In 213 of 267 cases the patient's age was specified, allowing identification of 152 adult cases ranging from 18 to 78 years with a mean age at disease onset of 38.5 years and, consistent with former reviews on MCD, a female predominance of 64 %. There were 61 documented pediatric cases, ranging from 5 to 17 years with a mean presentation at 11 years and a slight predominance of male cases at 59 %, which differs to previously published articles that refer to equal incidences of both sexes in children. Whereas genital lesions are by far the most common presentation of MCD in children (90.2 % genital versus 16.4 % non-genital), genital manifestations in adults are only slightly more common than extragenital presentations (59.9 % versus 52.6 %). With regard to the frequency of lesions in pediatric cases, genital swelling is seen in 82 %, followed by non-genital papules/nodules/plaques (8.2 %), genital ulcers (4.9 %), genital nodules/plaques (4.9 %), non-genital swelling (4.9 %) and non-genital ulcers (3.3 %). In adults, the most common lesions are genital fissures/ulcers (37 %) followed by genital swelling (35 %), non-genital papules/nodules/plaques (28.6 %), non-genital fissures/ulcers (25 %), genital papules/nodules/plaques (2.1 %) and non-genital swelling (0.7 %) (Table 2).

In adults, MCD postdates the initial diagnosis of CD in 68.8 % of cases. However, it may also occur simultaneously (17.4 %) or precede the onset of gastrointestinal symptoms (5.6 %). Diagnosis of CD is absent in 8.3 % of cases. In children, MCD appears at the same time as CD in half of the cases

(50.8 %) while CD is diagnosed prior to manifestation of MCD in 22 % and afterwards in 15.3 % and is absent in 11.9 % of the published cases (Table 1). According to Palamaras et al., the time span of subsequent onset of CD after diagnosis of MCD is two months to four years in adults as compared to nine months to 14 years in children. MCD manifestations appear to persist longer in adults (mean 21.3 months, range 1 day to 15 years) than in children (mean 6.4 months, range 7 days to 4 years) [2]. In cases of granulomatosis without or with a yet-to-be diagnosed, associated CD, some authors favor the terms “(ano)-genital granulomatosis” or “vulvitis granulomatosa” instead of MCD.

In CD the small intestine, especially the terminal ileum is the most commonly affected portion of the gastrointestinal tract [1]. Interestingly, the frequency of accompanying contiguous lesions and non-contiguous MCD is higher in the setting of colonic involvement of CD as compared with ileal involvement alone [2]. Concomitant occurrence of MCD and contiguous CD (mainly perianal) is seen more often in females (61 %) than in males (39 %) and also children (62.5 %) appear to be frequently affected [2]. MCD is generally unrelated to the activity of bowel disease and surgical removal of the affected bowel in severe cases of CD does not necessarily improve MCD or prevent its development [2, 6].

Differential diagnosis

Differential diagnoses to be considered are numerous owing to the polymorphic clinical features of MCD. With regard to

Table 2 Typical clinical findings in pediatric and adult MCD.

Children		Adults	
Genital lesions predominate (~90 % of cases¹):		Genital manifestations (in up to 60 % of cases²):	
<i>type of skin lesions</i>	%	<i>type of skin lesions</i>	%
swelling	82.0	fissures/ulcers	37.0
nodules/plaques	4.9	swelling	35.0
ulcers	4.9	papules/nodules/plaques	2.1
Non-genital skin lesions (in up to 16 % of cases¹):		Non-genital skin lesions (~53 % of cases²):	
papules/nodules/plaques	8.2	papules/nodules/plaques	28.6
swelling	4.9	fissures/ulcers	25.0
ulcers	3.3	swelling	0.7
Special features			
rarely ulcers in the intertriginous area		intertriginous ulcers tend to display a fissured, rhagadiform-like appearance	
rarely skin tags/nodules on the genitals		skin tags/nodules on the genitals possible	
¹ 61/61 patients; ² 142/152 patients, data extracted from publications as shown in Table 1.			

the site of involvement intertriginous lesions may resemble hidradenitis suppurativa or intertrigo, lesions on the limbs should be distinguished from cellulitis, pyoderma gangrenosum, granulomatosis with polyangiitis or eczematous dermatitis. In case of facial involvement, acne, erysipelas and sarcoidosis are to be considered. Genital lesions may mimic Behçet's disease or sexually transmitted infections such as syphilis, lymphogranuloma venereum and (chronic) herpes simplex. Histopathological differential diagnoses comprise sarcoidosis, mycobacterial and deep fungal infections as well as granulomatous reactions to foreign bodies [4]. In case of not otherwise explainable plaques/ulcers/oedema especially in the genital/inguinal area a detailed history and physical examination as well as deep and, ideally, multiple lesional biopsies are essential to exclude other etiologies and verify the diagnosis of MCD. Other helpful investigations include serologic testing (*Treponema pallidum* particle agglutination assay, hepatitis B and C, and human immunodeficiency virus), chest radiograph, interferon- γ release assay for *Mycobacterium tuberculosis* or, if inconclusive, tuberculin skin test [1]. In case of suspected MCD gastroenterological workup including colonoscopy is mandatory.

Therapy

Metastatic Crohn's disease is a rather uncommon dermatologic entity and randomized controlled studies addressing its therapeutic management are lacking. Despite incidents of spontaneous resolution, the cutaneous lesions are often persistent and cause significant morbidity [6]. Existing literature comprises case reports and small case series describing a variety of agents and modalities applied and reported as successful, but no single therapy has shown reliable effects as interindividual responses are highly variable [4]. We classified treatment outcomes of published cases applying the categories "clearance", "partial improvement", "no effect" or "worsening" (Table 1). Notably, comparatively good results with partial improvement in 64.3 % to 70.6 % were obtained with the TNF α inhibitors infliximab and adalimumab, azathioprine and systemic corticosteroids (both in monotherapy and in combination with each other). Partial improvement was also achieved in 44.4 % of patients treated with metronidazole alone or in combination with systemic corticosteroids, in 37.5 % of patients with sulfasalazine/5-aminosalicylic acid alone or in combination with systemic corticosteroids, surgery or metronidazole and in 30 % of patients with topical corticosteroids (amongst others in combination with oral antibiotics). However, with respect to the relatively low number of cases and the heterogeneity of reported findings, the significance of these data is limited. Further agents with only sporadic use in MCD (in-

ter alia topical tacrolimus, methotrexate, 6-mercapto-purine and ciclosporin A) are listed in Table 1. With regard to the demonstration of IL-23-expressing dendritic cells and macrophages/histiocytes (Figure 1f, g) one may speculate that anti-IL-23 antibodies may be of benefit in treatment of MCD.

Conclusions

In summary, owing to its relative rarity, a better knowledge of MCD is essential to avoid a diagnostic delay. The complex therapeutic management requires interdisciplinary cooperation, especially in case of coexisting MCD and CD.

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Conflict of interest

None.

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