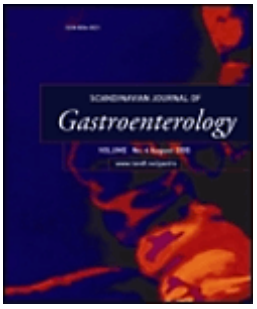

Managing metastatic Crohn's disease: A single centre experience, review of the current evidence and treatment algorithm

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Title: Managing metastatic Crohn's disease: A single centre experience, review of the current evidence and treatment algorithm

Authors: Beysens S, Wellens J[1,4], De Hertogh G[2], Van Laethem A[3], ~~Guedelha~~ Sabino J[1,4], Hillary T[3], Vermeire S [1,4]

1. KU Leuven Department of Chronic Diseases and Metabolism, Translational Research Center for Gastrointestinal Disorders (TARGID), Leuven, Belgium.
2. KU Leuven Department of Imaging & Pathology, Translational Cell and Tissue Research Unit, Leuven, Belgium.
3. Department of Dermatology, University Hospitals Leuven, Leuven, Belgium.
4. Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium.

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Corresponding author:

Séverine Vermeire, Herestraat 49, 3000 Leuven. severine.vermeire@uzleuven.be

ABSTRACT

Background ~~& aims~~: Crohn's disease (CD) is an inflammatory bowel disease (IBD) that, besides gastrointestinal symptoms, may encompass extra-intestinal symptoms, such as dermatological manifestations. Of those, metastatic Crohn's disease (MCD) is a rare extra-intestinal manifestation for which the management is ~~rather~~ uncertain.

Methods: We conducted a retrospective case series of patients with MCD seen at the University hospital Leuven, Belgium, combined with an overview of the recent literature. ~~An automatic search of the e~~Electronic medical records were searched~~as performed~~ from January 2003 till April 2022. For the literature search, Medline, Embase, Trip Database and The Cochrane Library were searched from inception to April 1st, 2022.

Results: A total of 11 patients ~~(whereof 7 women)~~ with MCD were retrieved. In all cases non-caseating granulomatous inflammation was found on skin biopsies. Two adults and one child were diagnosed with MCD prior to their diagnosis of CD. Seven patients were treated with steroids (intralesional, topical or systemic). Six patients needed a biological therapy ~~like infliximab or ustekinumab~~ to treat MCD. Surgical excision was performed in three patients. All patients reported a successful outcome ~~of their MCD~~ and most cases achieved remission. The literature search yielded 53 articles, including three reviews, three systematic reviews, 30 case reports and six case series. A treatment algorithm was generated based on literature and multidisciplinary discussion.

Conclusion: MCD remains a rare entity and diagnosis is often difficult. A multidisciplinary approach including skin biopsy is necessary to diagnose and treat MCD efficiently. Outcome is generally favorable, and lesions respond well to steroids and biologicals. We propose a treatment algorithm based on the available evidence and multidisciplinary discussion.

INTRODUCTION

Crohn's Disease (CD) is a multisystem ulcerative granulomatous inflammatory bowel disease (IBD) that may involve any part of the gastrointestinal tract, but most commonly the terminal ileum and the colon. Extra-intestinal manifestations of the skin are common, and can occur in up to 44% of the patients. (1) There are several types of skin manifestations. First, they can be caused by direct extension from the gastrointestinal tract, thereby affecting the perianal or peristomal region. Second, manifestations can be immune-related such as erythema nodosum. Third, skin lesions can be provoked by nutritional deficiencies like zinc deficiency. The last and least common category includes metastatic CD (MCD) which are dermal manifestations that are non-contagious to the gastrointestinal tract by definition. (2, 3) Although it was first described by Parks as early as the year 1965, until now, the precise prevalence and pathogenesis remains unclear.(4) Based on the rarity of the condition and thereby scarcity of large case series, MCD is often thought to be underdiagnosed or misclassified, and a standard therapy is non-existing. (5, 6) The lesions can have a heterogeneous clinical presentation and might be localized at different body sites. Besides a clinical suspicion, a biopsy of the skin lesions, showing non-caseating granulomatous inflammation is needed to confirm the diagnosis. (4, 7) In many patients, several treatments are tried but the therapeutic approach remains challenging and is often unsatisfactory. (3) Therefore, we aimed to review all patients who presented with MCD at our referral hospital, compare this to the latest evidence through a literature review and to propose an algorithm for clinical management of MCD.

METHODS

All patients diagnosed with MCD and treated at the University Hospital Leuven, Belgium from 1/1/2003 till 6/4/2022, were included. Patients with IBD and skin lesions were selected by means of an automated search of the electronic medical records of the hospital. When

available, clinical data on age, sex, CD duration, Montreal classification score, IBD therapy, clinical aspect of skin lesions, anatomopathological findings, treatment of MCD and outcome were extracted. Approval for the study was obtained via the Ethics Committee of Leuven (S53684).

In order to compare our findings to the available literature, we searched the databases Medline (PubMed), Embase, Trip Database and The Cochrane Library from inception to April 1st, 2022 using the following search terms “Metastatic Crohn”, “Metastatic Crohn’s disease” and [“Metastatic” AND “Crohn”]. We only included articles written in English that ~~focussed~~focused on MCD. Reviews, case reports and case series were selected. Letters to the editor or conference abstracts were included when detailed enough (e.a. anatomopathological findings, outcome). Three articles dealing with rare locations (e.a. scalp, ear) were excluded.

RESULTS

The electronic database search revealed a total of 11 patients with MCD, summarized in table 1. The systematic review resulted in 53 articles that were included using four different databases, whereof 3 reviews, 3 systematic reviews, 30 case reports and 6 case series (Table 2). The clinical implications of this review and the proposed algorithm is elaborated upon in the discussion.

Case 1

A 37-year-old woman with a longstanding history of CD presented with an erythematous indurated plaque on the left elbow with a small central crust. More distally a second similar lesion on the same arm was noted. At the age of 20, CD with ileocolonic involvement (Montreal score A2B1L3) was diagnosed and treated with methylprednisolone and budesonide. After a disease flare, her maintenance therpay was switched to azathioprine and later to infliximab which led to longstanding remission. A biopsy of the skin lesions showed a dermal lymphoplasmacytic infiltrate and non-caseating granulomas, confirming the diagnosis of MCD (Figure 1). Ileocolonoscopy showed complete mucosal healing. Given that these lesions occurred while treated with infliximab with therapeutic serum drug concentrations, her treatment was switched to ustekinumab, after which inflammation and induration

improved rapidly. Ustekinumab 90 mg eight-weekly subcutaneously is continued up until now with complete disappearance of the lesions.

Case 2

A 23-year-old woman presented with a skin lesion on the left gluteal region (Figure 2). At the age of 20, she was diagnosed with penetrating CD including ileocolonic involvement (A2B3L2). She underwent an ileoceacal resection followed by maintenance therapy with adalimumab. The MCD lesion consisted of a dried crust at the left intergluteal cleft with a subcutaneous nodule. A biopsy confirmed the diagnosis of MCD showing a chronic inflammatory infiltrate and non-caseating granulomas consisting of histocytes and multinuclear giant cells. Treatment consisted of surgical excision. Until now, the skin lesion has not reoccurred, and the patient is continued on adalimumab.

Case 3

A 22-year-old woman was diagnosed with ileocolonic CD (A2B1L3) and rapidly started on adalimumab. Four months later a vulvar erythematous swelling of the right major labium ~~majora~~ occurred (Figure 2). Imaging ruled out abscesses or fistulation from the gastrointestinal tract. A vulvar biopsy showed dermal non-caseating granulomas consisting of histiocytes and giant cells surrounded by a lymphoplasmacytic inflammation infiltrate (Figure 3). Intralesional steroids were administered, and adalimumab was switched to vedolizumab given concomitant active luminal disease. After four monthly steroid intralesional injections, clinical improvement was seen after which vedolizumab was continued in monotherapy.

Case 4

A 12-year-old boy with the diagnosis of structuring CD with ileocolonic and upper gastrointestinal tract involvement (A1B2L3+L4) presented six year earlier with a persistent swelling of his upper lip. A biopsy showed non-caseating granulomas in the subepithelial stroma surrounded by lymphoplasmacytic inflammation. The diagnosis of granulomatous cheilitis was made, and intralesional steroids were given. After one month the condition had

improved, though recurrent infiltrations were needed. Full remission was achieved five months after the diagnosis of CD when infliximab was started. In retrospect and after discussing this case with dermatologists and IBD specialists, this young patient was diagnosed with MCD prior to his IBD diagnosis.

Case 5

Two years and 7 months before the diagnosis of CD this patient presented with a diffuse soft swelling of the lower lip. On the inside of the lip several superficial ulcerations could be noticed. A biopsy showed stroma consisting of a lymfohistiocytic inflammation infiltrate with granulomas corresponding to granulomatous sialadenitis. Intralesional steroids were used with suboptimal response. Penetrating CD was eventually diagnosed at the age of 34 with colonic involvement (A2B3L2). The swelling of the lip lingered on, even when infliximab was started. More details regarding the outcome are not available. We assume remission has been achieved since no clinical contacts with dermatology were found in the electronic record.

Case 6

A 42-year-old woman, with CD of the colon and upper gastrointestinal tract since the age of 27 (A2B1L2+L4), presented with an erythematous plaque on her back. She received no maintenance treatment for CD at the time of the lesion. Skin biopsy revealed granulomatous dermatitis. Local steroids were used, followed by surgical excision. Three years later, similar lesions appeared on the left side of the thorax and on the right shoulder. Another biopsy showed again granulomatous inflammation possibly due to MCD. Topical corticosteroid creamme was started, which led to remission.

Case 7

A 46-year-old man known with colonic CD diagnosed ten years earlier (A2B1L2) complained of a penile lesion, indurated on the dorsal side combined with a punctiform pus draining wound and a chronic ulcer on the glans. Maintenance therapy for CD at that time consisted of sulfasalazine. Biopsy showed a well differentiated stratified squamous epithelium with granulomas accompanied by loose edematous stroma. Infections were ruled out. To treat this lesion, excision was sufficient.

Case 8

A 38-year-old man developed multiple oral ulcers and a swollen lip. At the age of 15, a diagnosis of stricturing ileal CD (A2B2L1) was made and treated with adalimumab and multiple stricturoplasties. Biopsies of the lip and buccal mucosa revealed lymphocytes and some necrotic keratocytes accompanied by non-caseating granulomas with multinucleated giant cells and epithelioid histiocytes. Adalimumab was switched to ustekinumab in combination with systemic corticosteroids given the severity of the lesions, which led to fast response. Although the buccal lesions might be a manifestation of oral CD, the manifestations of the lip were judged to be related to MCD by the dermatologist and IBD specialist. MCD remission was maintained after ~~starting~~ etanercept was associated by the rheumatologist, because of concomitant arthralgias as a second extra-intestinal manifestation of CD.

Case 9

This female patient, known with ileocolonic CD (A1B1L3) since the age of 14, treated with infliximab, presented 11 years later with a swollen upper lip (Figure 2). A biopsy showed a linear superficial infiltrate of lymphocytes and in the dept infiltrates of plasma cells and aggregates of multinucleated giant cells, consistent with MCD (Figure 3). Infliximab was switched to adalimumab without success. In addition, a psoriasiform eczema probably secondary to infliximab use, was diagnosed. Different therapeutic options like dapsone, intralesional steroids and azathioprine were inefficient. After starting thalidomide and metronidazole a good response was seen. Given the Tumor Necrosis Factor (TNF)-induced skin lesions, infliximab was switched to ustekinumab. When switched from intravenous to subcutaneous injections, the swollen lip deteriorated.

Case 10

A 33-year-old women presented with a firm and red nodule on the left labium major. Biopsy showed non-caseating granulomas in the superficial and deeper derma with no signs of vasculitis or ulceration. An initial diagnosis of Behçet's disease was made. At that time there were no gastrointestinal symptoms, although diffuse ulcers in the colon were noted on colonoscopy, which were attributed to Behçet's disease as well.

Fucidin creamème and colchicine twice daily was prescribed. Six years later the patient developed frequent diarrhea with mucus and blood, consistent with CD (A2B1L2) on

colonoscopy with perianal involvement for which ~~and~~ infliximab was started. In retrospect, the vulvar swelling was most probably ~~was~~ an early diagnosis of MCD, that preceded~~ing~~ the diagnosis of CD. Infliximab led to complete remission.

Case 11

A 43-year-old female patient diagnosed with colonic CD (A3B2L2) and treated with azathioprine, presented at the age of 51 and 54 with a swelling of her upper lip (Figure 2). Biopsy revealed superficial and deeper granulomatous inflammation and some granulomas with possible compression of vascular lumina (Figure 3). Following the first episode of MCD, infliximab was added to azathioprine with success. The second episode was treated with topical potent steroids, after which the swelling decreased. Infliximab had to be stopped due to a Campylobacter sepsis and a diagnosis of breast cancer. Her disease remains in remission thus far without maintenance therapy.

DISCUSSION

MCD is a rare entity which can affect adults and children. There is no gender discrepancy, although some authors describe a female predominance. (8, 9) In 70% of the adult cases, MCD appears after the diagnosis of CD at an average age of 29-39 years old (10). However, in children about half of the cases of MCD appear at the same time as intestinal CD. MCD can also precede the diagnosis of CD, from 9 months to 14 years before any gastrointestinal manifestations. (3, 11~~10~~) In our case series, a female predominance was observed as 7 out of 11 identified patients were female, with an average age of diagnosis of 35 years. Two adult patients and one child were diagnosed with MCD prior to CD.

Most of the patients had CD with colonic involvement, which is in line with available literature. (12, 13~~1~~). Four patients had colonic involvement only, while the others had extensive disease including ileal, perianal or upper-gastrointestinal tract involvement. We did not see a

correlation between the underlying disease activity of CD and the appearance of skin lesions in the available literature. (~~12, 13~~14, 15) In our patients with CD, 6 patients were in remission and 1 patient had active luminal disease.

Until this day, the etiology of MCD is not well-understood. However, different theories suggest a process involving the immune system and possibly other factors such as genetic predispositions, environmental exposures and epithelial barrier dysfunction. Subsequently, a granulomatous reaction and inflammatory cascade arise because of the formation of immune complexes secondary to unknown antigens originating from the gastrointestinal tract or elsewhere. (1, 3, 5, 7, ~~14, 15~~16, 17)

MCD presents mostly as an erythematous plaque that may enlarge, become nodular, then ulcerate and ultimately exude pus, but not necessarily in this order (~~ref~~18). It may present as a solitary or as multiple lesions. (3, 5) In our series, most lesions were solitary. The cutaneous lesions can be categorized by localization. First, non-genital MCD refers to lesions on trunk or extremities, on which red-brown papules, nodules or erythematous plaques are seen more frequently. (3) Second, genital MCD is usually described as edema with or without erythema and knife-cut ulcers in the genital region. (9) The majority of the MCDs in our cases series were located on the lips (5/11) followed by the genital region (3/11) and non-genital group (3/11). Most lesions included a swelling, but also erythematous plaques, ulcers or indurated regions were seen. We can conclude that edema is more likely when mucosa is involved (lips, labia majora).

The histopathologic findings of MCD are similar to those seen in CD apart from the anatomic location of the lesions who by definition occur at sites discontinuous from the gastrointestinal tract. (~~14~~16) For all cases of MCD non-caseating granulomatous inflammation located in the superficial papillary and deep reticular dermis was described. Langerhans multinucleated giant cells are involved as well as epithelioid histiocytes, eosinophils, lymphocytes and occasional plasma cells. (4,7) Remarkably, neutrophils are not a typical feature of MCD in contrast to the presence of acute inflammatory cells as seen in intestinal CD. (~~14~~16)

The diagnosis of MCD remains difficult, as illustrated by one of our patients who was labelled as Behçet's disease and treated ineffectively. Therefore, a multidisciplinary approach by dermatologists, pathologists and gastroenterologists, combining clinical aspects together with skin biopsy is necessary. Patients should be referred to a gastroenterologist when there is high suspicion for MCD or when the biopsy indicates MCD, for a general comprehensive examination including complete blood count, iron levels, erythrocyte sedimentation rate, albumin, CRP and faecal calprotectin and if recommended a colonoscopy. (5) The differential diagnosis consists of granulomatous and non-granulomatous lesions of the skin, illustrated below (Table 3). (6, 8, ~~14~~16)

Because of its rare incidence, adequately powered clinical trials in MCD are nearly impossible to achieve. Therefore, there is no consensus on a standard therapy for MCD. Although some authors report a spontaneous resolution of the lesions, the majority of lesions will persist and often need multiple treatments before remission can be achieved. (~~15, 16~~17, 19~~,~~) Glucocorticoids are one of the primary treatment options for MCD, since effectively remission can be achieved. Topical steroids are used for mild, localized or single MCD lesions, whereas systemic steroids for more extensive or recalcitrant MCD. Steroids reduce inflammatory cytokines like TNF and deplete lymphocytes and macrophages. (8, ~~17~~20) When glucocorticoids alone are insufficient, oral metronidazole for four months can be considered, due to its antimicrobial properties and its capacity to suppress granuloma formation. (8) In anogenital MCD oral antibiotics seem more promising and are recommended as a first option. (9) In most of our patients, steroids were used as first-line therapy (intralesional (N=3), 2 local (N=2), oral (N=1)). For some patients, monotherapy was sufficient with immediate improvement and no recurrence. However, in several other patients, multiple treatments were necessary to achieve remission.

TNF inhibitors such as adalimumab or infliximab have shown efficacy in the treatment of CD as well as MCD, because of inducing apoptosis of target immune cells and blocking TNF activation. In our cohort, biological agents were used when traditional therapy failed, but also as first-line therapy in some cases. Two patients, already on infliximab or adalimumab for their CD when the MCD developed, needed a switch to ustekinumab with adequate response. Given the positive results of anti-p40 antibodies in chronic inflammatory skin disorders,

ustekinumab and the more novel anti-p19 IL23 monoclonal antibodies may be a valid treatment option in patients not responding to anti-TNF therapy. (~~18, 19~~21, 22) The gut-selective anti-alfa-4-bèta-7-integrine, vedolizumab seems less promising to treat MCD but strong evidence to support this claim is lacking. (~~20~~23) Topical tacrolimus and cyclosporine, azathioprine and methotrexate have also shown promising results in literature as well as thalidomide, dapsone and hyperbaric oxygen. (~~15, 21, 22~~17, 24, 25) If monotherapy fails to control the skin lesions, various combinations of these agents could be considered. (~~23~~26) Lastly, surgical treatment may result in clearance of MCD, although there is a significant risk of poor wound healing and recurrence of MCD. (~~15, 23, 24~~17, 26, 27) In our cohort three cases underwent surgical excision, of which two were successful. Of note, surgery of the gastrointestinal tract has not shown to be effective regarding the disease activity of MCD. (~~25~~28)

Based on our retrospective study and review of the literature, we propose the following algorithm for managing MCD (Figure 4).

Granulomatous cheilitis (GC) is a persistent swelling and inflammation of the lips and is a manifestation of orofacial granulomatosis (OFG). OFG is a clinical entity describing facial and oral swelling in the setting of non-caseating granulomatous inflammation and in the absence of systemic disease such as Crohn's disease and sarcoidosis. Other proposed causes of OFG include dietary allergens such as benzoates and cinnamon (~~28~~29,30). It should be noted that discussion remains

~~Of note, there is discussion~~ whether granulomatous cheilitis ~~(GC)~~ on the lips should be classified as MCD, since this condition is often, but not always associated with ~~may present without~~ CD. ~~Because~~ However, since GC corresponds with the definition of MCD from a histopathological point of view, these patients were included in this case series. In addition, the approach and treatment of GC is similar to other MCD locations with intralesional steroids as the proposed first-line therapy. (~~26-29~~29, 31-33)

In conclusion, MCD is a rare dermatological cutaneous manifestation, usually secondary to underlying CD, although it may precede the diagnosis of CD. The skin lesions may be

heterogeneous in their clinical presentation and affected anatomical region. A biopsy showing a non-caseating granulomatous inflammation is necessary to confirm the diagnosis. Since RCTs are lacking and available evidence is scarce, a multidisciplinary approach including gastroenterologists, pathologists and dermatologists is necessary to prevent misdiagnosis and to treat patients effectively. Topical and intralesional steroids are often first line options although excellent results have been reported with biological agents.

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Figures

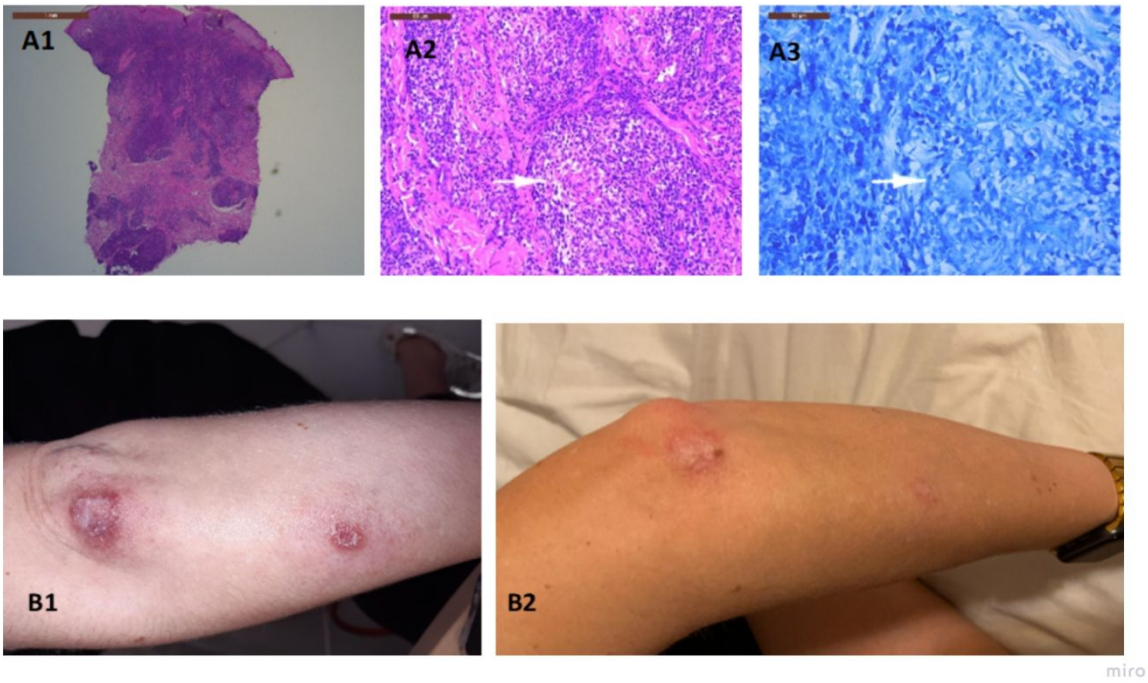

Figure 1: (A) Histopathological findings. 1/ overall haematoxylin and eosin stain; 2/ arrow: fuzzy defined non-caseating granuloma; 3/ arrow: multinuclear giant cell. (B) Clinical characteristics. 1/ initial presentation of the skin lesions on the left elbow. 2/ improvement of redness, inflammation and induration after first infusion of ustekinumab.

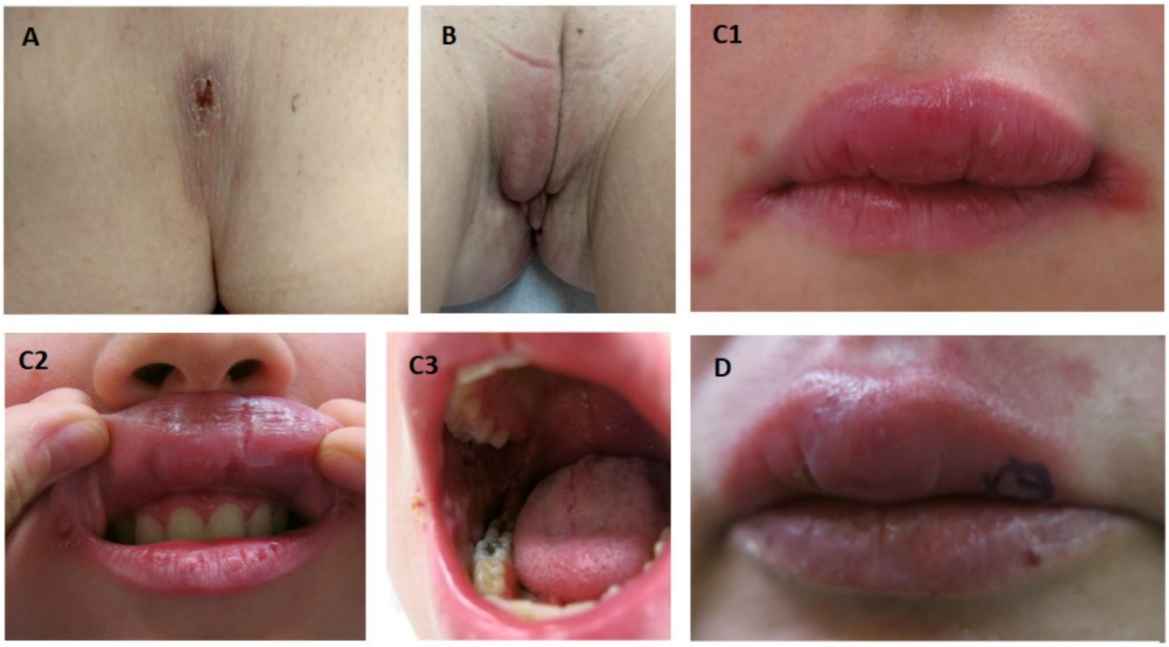

Figure 2: Clinical characteristics of some cases. (A) case 2: initial presentation of the left gluteal region (B) case 3: initial presentation of vulvar erythematous swelling of right labium major (C) case 9: 1 and 2/ initial presentation of granulomatous cheilitis upper lip; 3/ initial presentation of oral ulcers (D) case 11: swelling upper lip.

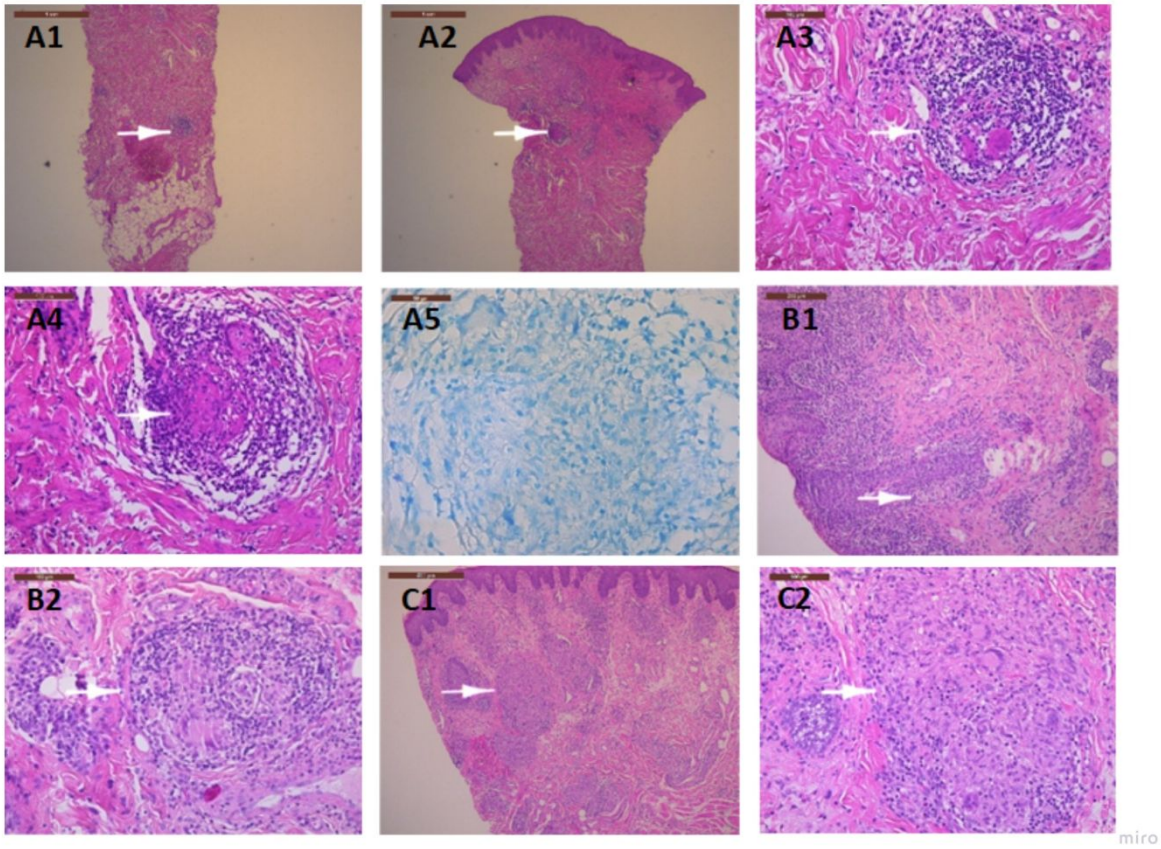

Figure 3: Histopathological findings of some cases, arrows pointed to non-caseating granulomas.
(A) Case 3: 1/ haematoxylin and eosin stain (HE) x25, superficial dermis; 2/ HE x25, deep dermis; 3/ HE x200, superficial dermis; 4/ HE x200, deep dermis; 5/ negative Ziehl stain
(B) Case 9: 1/ HE x100, subepidermal; 2/ HE x200, deep dermis
(C) Case 11: 1/ HE x50, multiple granulomas; 2/ HE x200, granuloma in detail.

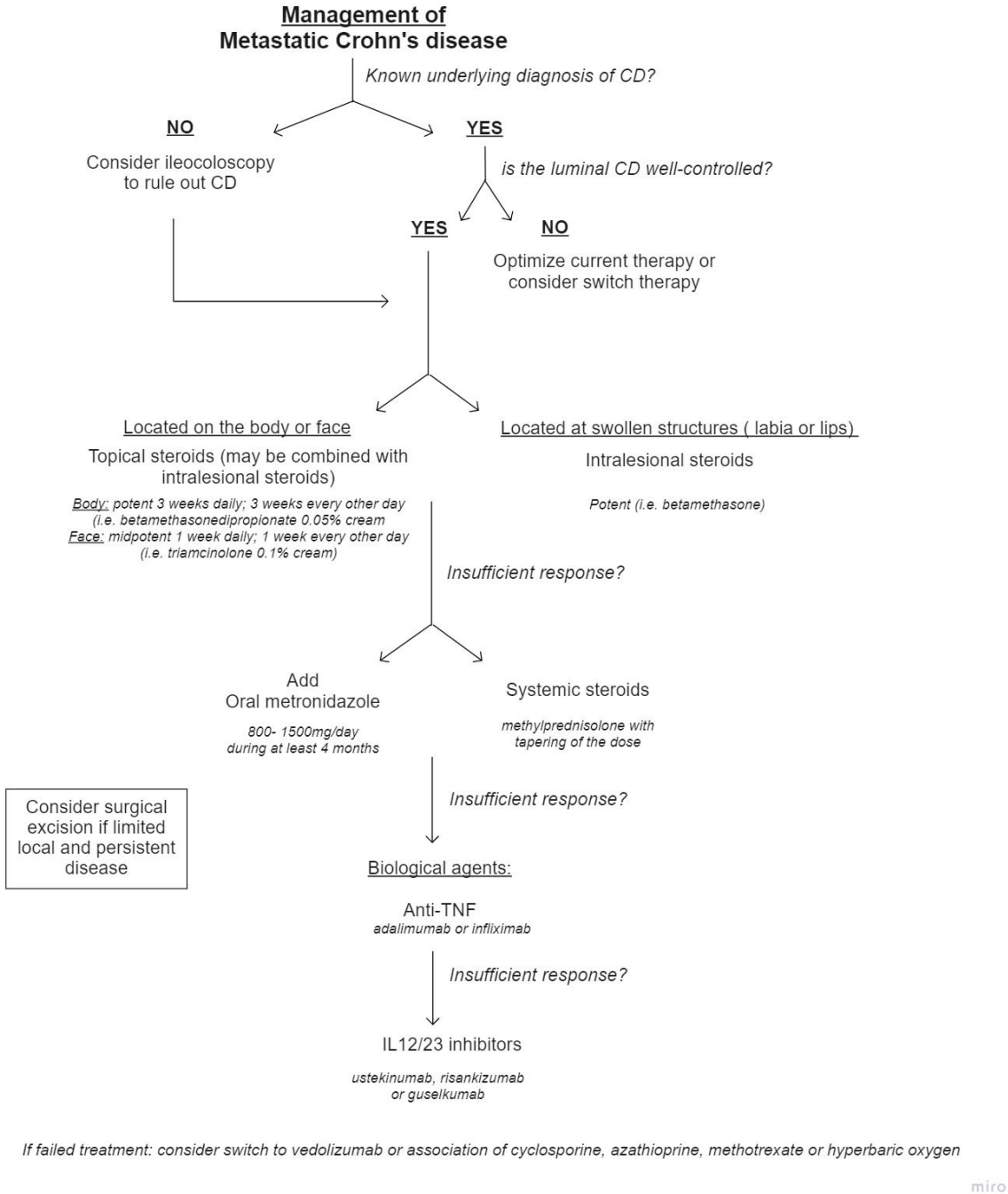

Figure 4: A therapeutic algorithm for managing metastatic Crohn's disease based on (limited) evidence, and expert opinion after multidisciplinary discussion.~~MCD~~

Case nr.	Gender	Age at MCD	Location of MCD	Clinical appearance	Biopsy results	Age and location at diagnosis of CD	Treatment of CD	Treatment of MCD	Response or Remission
1	F	37	Elbow (left)	Erythematous indurated plaque, in the centre a small crust + distally a similar lesion	Dermal lymphoplasmacytic infiltrate + fuzzy defined non-caseating granulomas	Ileocolonic CD (20y)	Methylprednisolone + budesonide ->> azathioprine ->> infliximab	Switch: infliximab -> ustekinumab + topical therapy	Yes
2	F	23	Gluteal region, intergluteal cleft (left)	Dried crust + underneath a subcutaneous mobile nodule	Scarring region + chronic inflammatory infiltrate + little non-caseating granulomas (histocytes & multinuclear giant cells)	Penetrating colonic CD (20y)	Adalimumab	Surgical excision	Yes
3	F	22	Labium major (right)	Vulvar erythematous swelling + thickening of the perianal region (+ anal tag)	Dermal non-caseating granulomas (histiocytes + giant cells) surrounded by lymphoplasmacytic inflammation infiltrate	Ileocolonic CD (22y)	Adalimumab ->> vedolizumab	Intralesional steroids (vulvar and anal) (in total 5 injections)	Yes
4	M	*6*	Upper lip	Persistent swelling	Non-caseating granulomas in the subepithelial stroma surround by lymphoplasmacytic inflammation = granulomatous cheilitis	Stricturing ileocolonic + upper gastrointestinal CD (12y)	Infliximab	Intralesional steroids ->> infliximab (azathioprine or other molecules not effective)	Yes
5	M	*31*	Lower lip	Soft swelling + superficial ulcerations	Lymfohistiocytic inflammation infiltrate with granulomas = granulomatous sialadenitis	Penetrating colonic CD (34y)	*Infliximab*	Intralesional steroids ->> Infliximab	No

Case nr.	Gender	Age at MCD	Location of MCD	Clinical appearance	Biopsy results	Age and location at diagnosis of CD	Treatment of CD	Treatment of MCD	Response or Remission
6	F	42	1. Back 2. Thorax side (left) + shoulder (right)	Erythematous plaque	1. Granulomatous dermatitis 2. Granulomatous inflammation	Colonic + upper gastrointestinal CD (27y)	None	1. Local steroids + excision 2. Local corticoid creme	Not available
7	M	46	Penis: dorsal side	Indurated + a punctiform wound + pus + chronic ulcer on the glans	Well differentiated stratified squamous epithelium within the surroundings granulomas + loose oedematous stroma	Colonic CD (36y)	Salazopyrine	Excision	Yes
8	M	38	Mouth and lips	Multiple oral ulcers + swollen lips	Showed stratified squamous epithelium infiltrated by & necrotic keratocytes + non-caseating granulomas (multinucleated giant cells and epithelioid histiocytes) = granulomatous cheilitis	Stricturing ileal CD (15y)	Adalimumab ->> ustekinumab	Oral corticosteroids	Yes
9	F	25	Upper lip	Swollen lips + oral ulcer	Superficially a linear infiltrate of lymphocytes + in dept infiltrates of plasma cells and aggregates of multinucleated giant cells	Ileocolonic CD (14y)	Infliximab	Adalimumab + intralesional steroids (inefficient) ->> thalidomide + flagyl (hormonal disbalance) ->> ustekinumab	Yes
10	F	*33*	Labium major (left)	Hard region + redness (2 weeks earlier)	Normal stratified squamous epithelium + non-caseating granulomas in the superficial and deeper derma	Fistulated left colonic CD + perianal involvement (39y)	*Infliximab*	Fucidin + colchicine ->> infliximab	Yes
11	F	51 (&53)	Upper lip	Swelling	Superficial and deeper granulomatous inflammation + some granulomas: compression on the lumen of vascular structures	Colonic CD (43y)	Azathioprine	1. Azathioprine + infliximab 2. Local steroids + Fucidin ->> immunomodulators had to be stopped	Yes

Table 1: Summary of MCD cases (UZ Leuven) [italic: MCD predates the diagnosis of CD]

Medline (PubMed)	Embase	Trip Database	The Cochrane Library
"Metastatic Crohn": 181 results (filter last 5 years - 35 results and filter systematic review - 5 results) "Metastatic" AND "IBD": 50 results ↓	"Metastatic Crohn's disease": 80 results ↓	"Metastatic Crohn's disease": 23 results ↓	"Metastatic Crohn's disease": 1 results "Metastatic" AND "Crohn disease": 9 results ↓
21 articles included	**25** articles included	**7** articles included	**0** articles included

Table 2: Search strategy and results

Differential Diagnosis	
Granulomatous	*Non-granulomatous*
Cutaneous sarcoidosis*	Hidradenitis suppurativa or intertrigo**
Tuberculosis	Cellulitis***
Mycobacterial disease	Granulomatosis with polyangiitis***
Actinomycosis	Eczematous dermatitis***
Lymphogranuloma venereum	Pyoderma gangrenosum***
Foreign body reaction	Acne
	Erysipelas
	Behçet's disease
	Herpes simplex
	Erythema nodosum****
	Hepatitis B/C
	HIV

Table 3: Differential diagnosis divided in granulomatous and non-granulomatous diseases

* granulomas with a minimal lymphocytic infiltrate (<-> MCD: prominent lymphoplasmacytic infiltrate and possible epidermal ulceration) (14)

** folliculitis with keratin plugging and abscess formation

*** neutrophilic abscesses and pseudoepitheliomatous hyperplasia

**** mixed inflammatory infiltrate including neutrophils in the acute phase