Cutaneous Crohn disease without gastrointestinal involvement in a 9-year-old boy

Jason F Wang[1] BA, Laura E Melnick[1] MD, Lauren A Penn[2] MD, Nooshin K Brinster[1] MD, Vikash S Oza[1]MD

Affiliations: [1]The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York, USA, [2]Westmed Medical Group, Purchase, New York, USA

Corresponding Author: Vikash S. Oza MD, 240 East 38th Street, 11th Floor, New York, NY 10016, Email: Vikash.Oza@nyumc.org

Abstract

Cutaneous Crohn disease (CCD) is a rare dermatologic manifestation of Crohn disease and is defined as noncaseating, granulomatous skin lesions noncontiguous with the gastrointestinal tract. It most commonly affects the skin of the legs, although genital CCD is the most common presentation in children. Diagnosis of CCD is made by a combination of clinical and histopathological findings. Therapeutic options include topical, intralesional, and systemic corticosteroids as well as topical and systemic immunosuppressants and immunomodulators. Surgical excision may be considered for refractory cases. We report CCD in a 9-year old boy with penile swelling, granulomatous cheilitis-like lesions, and perianal plaques.

Keywords: cutaneous Crohn disease, metastatic Crohn disease, inflammatory bowel disease

Introduction

Cutaneous lesions in Crohn disease (CD) are broadly divided into three categories: contiguous lesions, discontinuous or metastatic lesions, and lesions that are indirectly related but nonspecific for CD. Cutaneous Crohn disease (CCD), also known as metastatic Crohn disease (MCD), falls into the second category and is defined as noncaseating, granulomatous lesions noncontiguous with the gastrointestinal tract. The diagnosis of CCD is based on both clinical and histopathological evaluation. Treatment data for CCD is limited owing to its rarity.

Case Synopsis

A 9-year-old boy with a history of prematurity (born at 27 weeks) presented for evaluation of persistent swelling of the lips and penis of two-years duration.

Two years prior to presentation, the patient developed intermittent swelling of the upper and lower lip, which gradually became persistent. He denied itching or pain of his lips. Treatments prior to presentation included a short course of prednisone, which led to temporary improvement in the swelling. In addition to lip swelling, he also had thickened upper gums. A biopsy performed by an oral surgeon showed a chronic inflammatory reaction.

During these preceding two years, the patient also reported persistent swelling of the penile shaft. He denied urogenital symptoms, including dysuria. He was evaluated by urologists and allergists and had been on multiple courses of antibiotics without clinical improvement. Radiographic imaging of the area was unrevealing.

Of note, the patient's family history was notable for Hashimoto thyroiditis in his father and paternal aunt but negative for inflammatory bowel disease. A colonoscopy obtained for lower abdominal pain seven months prior to his presentation showed nonspecific, mild-to-moderate, chronic colitis.

On the face, there was mild swelling of the perioral area and uniform swelling of the upper and lower lips without nodularity, warmth, erythema, or exudate (**Figure 1**). On oropharyngeal exam, there was upper right gingival overgrowth (**Figure 1**). In the

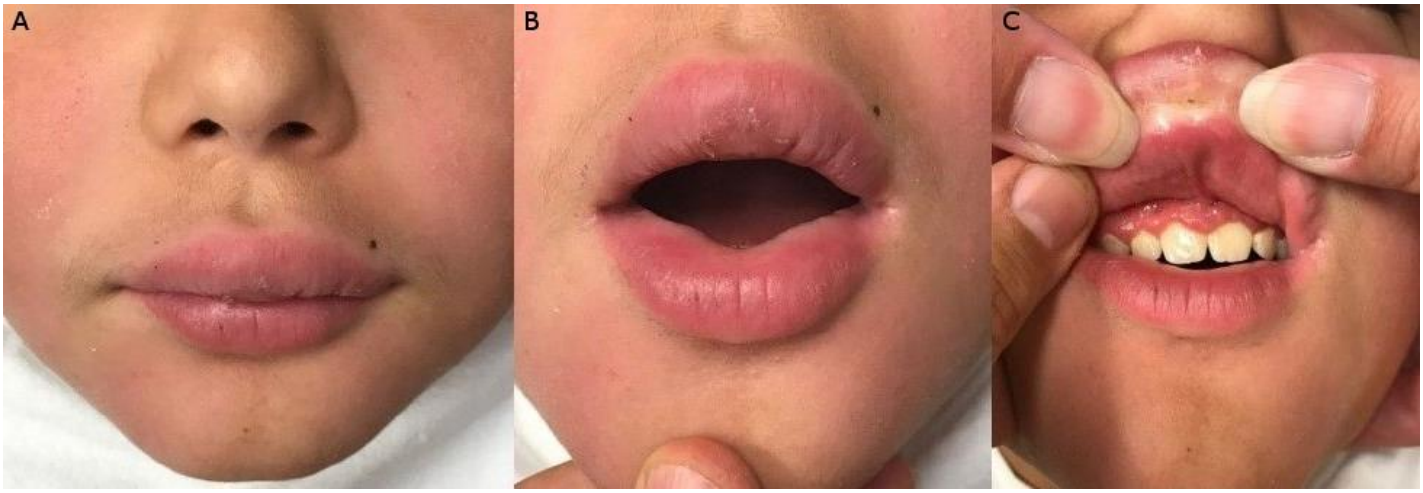

Figure 1. *A), B) Uniform swelling of the upper and lower lips. C) Upper right gingival overgrowth.*

anogenital region, there was lymphedema-like swelling of the penile shaft, with a normal-appearing glans without erythema or erosions (**Figure 2**). On the perianal buttocks, there were asymmetric, erythematous, indurated plaques (**Figure 3**).

Gastroenterology studies obtained prior to evaluation by dermatology included an elevated stool calprotectin, which subsequently normalized without intervention. A stool culture and stool studies for giardia, ova, parasite, and Shiga toxin were negative. Immunological studies prior to presentation revealed normal C4 and C1 inhibitor protein levels but an elevated total complement activity level. A total immunoglobulin E level was within normal limits. The erythrocyte sedimentation rate was within normal limits. Tests for antinuclear antibody and rheumatoid factor were negative. A Lyme enzyme immunoassay study was negative.

Two lesional punch biopsies, one of the inner buttock and one of the upper lip mucosa were performed. The punch biopsy from the inner buttock revealed pan-dermal granulomatous inflammation associated with lymphocytic inflammation extending into the superficial subcutaneous fat (**Figure 4**). The epidermis was slightly acanthotic and mildly spongiotic. The punch biopsy from the mucosal lip was remarkable for small, focal granulomata in the dermis (**Figure 5**). Special stains for microorganisms, performed on both biopsies, including PAS-D for fungus, AFB and Fite for mycobacteria, and Gram for bacteria, were negative.

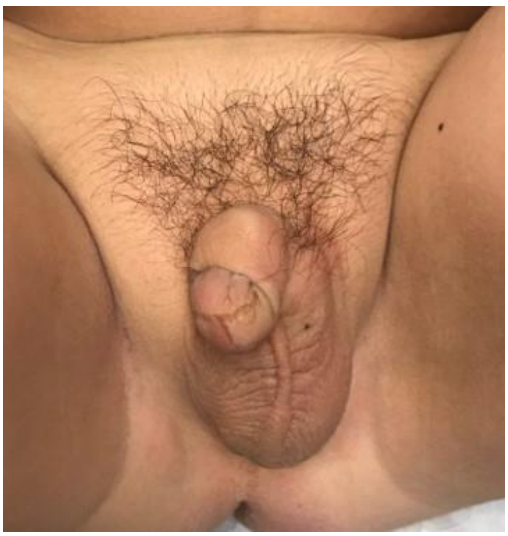

Figure 2. *Lymphedema-like swelling of the penile shaft.*

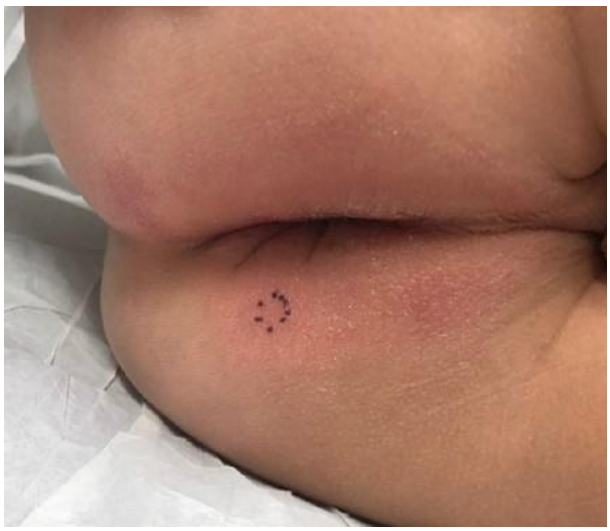

Figure 3. *Asymmetric, erythematous, indurated plaques on bilateral perianal buttock.*

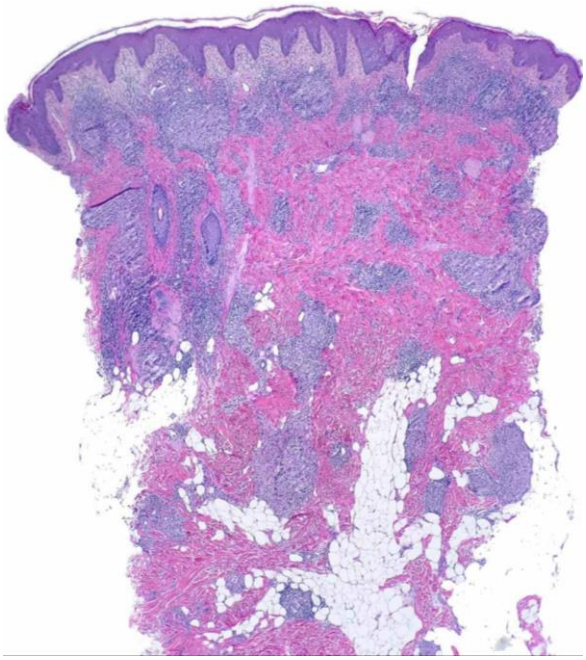

Figure 4. *Pan-dermal granulomatous inflammation associated with lymphocytic inflammation, inner buttock. H&E, 4×.*

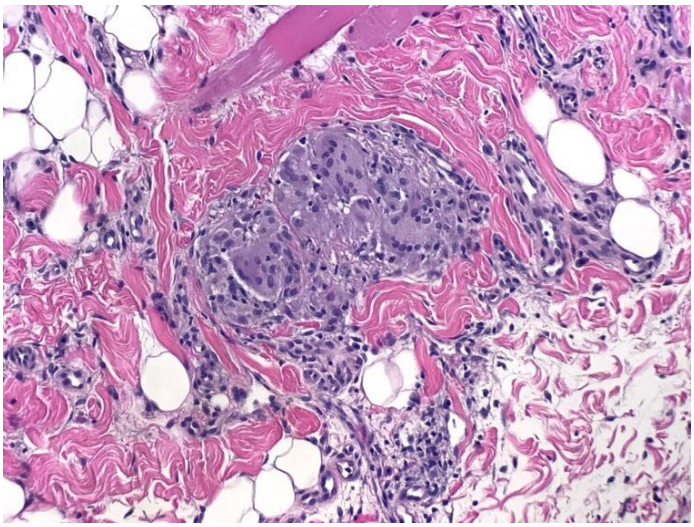

Figure 5. *Granulomatous inflammation, lip. H&E, 20×.*

The differential diagnosis in this patient with persistent lip and genital swelling includes allergic contact dermatitis, hereditary angioedema, and sarcoidosis; however, the persistent nature of the disease and multiple sites of granulomatous inflammation histopathologically inconsistent with sarcoidosis led to a diagnosis of CCD. He was initially treated with clobetasol ointment and tacrolimus 0.03% ointment twice daily to the lips, penis, and perianal area with slight improvement only to the penis. Two months later, 250mg of daily oral azithromycin was added to the treatment regimen, and the only topical therapy continued was clobetasol ointment to the penis to reduce swelling. The patient has been on this regimen for seven months with some improvement to the lips and perianal area but persistent penile swelling. A repeat colonoscopy after presentation to dermatology was without evidence of CD. The patient will likely be started on a systemic immunosuppressant (likely adalimumab) in the near future given the multifocal extent of cutaneous disease.

Case Discussion

Crohn disease is an idiopathic, chronic inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal mucosa and can have extraintestinal manifestations [1]. There are three broad classifications of cutaneous lesions in CD: contiguous lesions, such as perianal and peristomal fissures and fistulas; discontinuous or metastatic lesions, such as CCD, also known as MCD; and lesions indirectly related but not specific for CD, such as oral aphthae, erythema nodosum, pyoderma gangrenosum, epidermolysis bullosa acquisita, erythema multiforme, and cutaneous vasculitis. CCD is rare in adults and even rarer in children [1, 2]. It is defined as noncaseating, granulomatous skin lesions noncontiguous with the gastrointestinal tract [3, 4].

The clinical presentation of CCD is variable and may be classified as either genital or extragenital [1]. Genital manifestations are more common in children and include ulceration, fissures, edema, and erythema [1, 5]. Extragenital manifestations are most commonly found on the legs and include ulceration, pustules, and erythematous plaques and papules [1, 3, 6]. In addition, granulomatous cheilitis can occur in isolation or as part of Melkersson-Rosenthal syndrome, which can be associated with CD [7]. In one systematic review, 51.4% of patients with orofacial granulomatosis progressed to intestinal CD [8]. Cutaneous Crohn disease is more common in patients with colonic than ileal disease [1, 9]. In children, genital CCD tends to precede intestinal manifestations of CD [2, 10]. Thus, it is important to consider a diagnosis of CCD in unexplained genital swelling in a child, as progression to intestinal CD can lead to weight loss and growth failure [5].

The pathophysiology of CCD is presumed to be similar to that of CD due to their shared pathologic features, although the pathogenesis of both conditions remains unclear [1]. *TRAF3IP2* gene variants have been identified as risk factors for cutaneous manifestations of CD but so far have only been studied in relation to erythema nodosum and pyoderma gangrenosum [11]. Other hypotheses for the pathogenesis of CCD include vasculitis-mediated injury and T-helper cell type 1-mediated delayed hypersensitivity reactions [1].

Diagnosis of CCD is based on clinical and histological findings after excluding other causes of granulomatous dermatitis, such as sarcoidosis, foreign body granulomas, and mycobacterial and fungal infections [1, 6]. A full diagnostic workup includes biopsies with periodic acid-Schiff and acid-fast bacillus stains and polarizing microscopy, a tuberculin skin test, tissue cultures, and a chest x-ray [1]. On histopathologic examination, CCD is characterized by noncaseating granulomatous inflammation of the reticular and papillary dermis, occasionally extending into underlying subcutaneous fat [1, 12]. The inflammatory cell infiltrate may contain epithelioid and multinucleated histiocytes, plasma cells, lymphocytes, and eosinophils [1, 12]. The histopathologic findings of CCD are very similar to gastrointestinal CD with subtle differences: in CCD, the inflammatory infiltrate is more diffuse, neutrophils are rarely found, and giant cells are often present [13].

In patients without intestinal involvement, CCD can be difficult to differentiate from sarcoidosis. However, compared to sarcoidosis, there are more foreign body and Langhans-ype giant cells [12]. In addition, in CCD, necrobiosis is often present, and the inflammatory infiltrate often surrounds dermal vessels, a phenomenon known as granulomatous perivasculitis [1, 12]. An ulcerated epidermis, an eosinophil-rich infiltrate, and marked dermal edema can also be present in CCD but are not characteristic of sarcoidosis [13].

Cutaneous Crohn disease should be treated with a multidisciplinary approach, with a goal of suppressing cutaneous manifestations as well as screening or managing any underlying gastrointestinal disease [14]. Cutaneous Crohn disease may coexist with either active or quiescent gastrointestinal disease and can respond to the same treatments as CD [14]. Patients either with or without intestinal involvement should be continuously monitored by a gastroenterologist, as intestinal CD can manifest months to years after CCD is diagnosed [1]. Our patient is following up with a gastroenterologist every six months for fecal calprotectin monitoring and a review of systems. Owing to its rarity, CCD literature on treatment is mostly anecdotal; however, a review article in the *Journal of the American Academy of Dermatology* has proposed a treatment algorithm for CCD. For single lesions, recommended first-line therapy can be topical super-potent corticosteroids or intralesional corticosteroids, with the addition of oral metronidazole as second-line therapy and systemic corticosteroids as third-line therapy [1, 15, 16]. In corticosteroid-sensitive areas, topical calcineurin inhibitors are recommended, with systemic corticosteroids as second-line therapy [1, 17, 18]. For CCD presenting as multiple lesions, systemic corticosteroids are recommended as first-line therapy [1, 19].

For patients unresponsive to systemic corticosteroids either with or without gastrointestinal involvement, other systemic drugs, such as azathioprine, cyclosporine, or methotrexate should be added to the treatment regimen, and several reports have highlighted the success of tumor necrosis factor (TNF) inhibitors [1, 15, 20-22]. In treatment-refractory patients, thalidomide, hyperbaric oxygen, or surgical excision and debridement of skin lesions may be considered [1, 23, 24, 25]. Interestingly, resection of gastrointestinal involvement does not improve CCD [1, 26].

Conclusion

Cutaneous Crohn disease, also known as MCD, is defined as noncaseating, granulomatous lesions noncontiguous with the gastrointestinal tract. Skin findings, both genital and extragenital, can predate the development of Crohn disease and do not correlate with activity or severity of intestinal disease. It is important to add CCD to the differential

diagnosis when evaluating a child with unexplained genital swelling given CCD's nonspecific and varied clinical presentations. Treatment goals for CCD are to suppress the cutaneous manifestations and to screen and manage the underlying intestinal disease. Treatment recommendations for CCD exist; however, there is no consensus given its rarity.

References

1. Kurtzman DJ, Jones T, Lian F, Peng LS. Metastatic Crohn's disease: a review and approach to therapy. *J Am Acad Dermatol*. 2014;71(4):804-13. [PMID: 24888520].
2. Ploysangam T, Heubi JE, Eisen D, Balistreri WF, Lucky AW. Cutaneous Crohn's disease in children. *J Am Acad Dermatol*. 1997;36(5 Pt 1):697-704. [PMID: 9146530].
3. Lebwohl M, Fleischmajer R, Janowitz H, Present D, Prioleau PG. Metastatic Crohn's disease. *J Am Acad Dermatol*. 1984;10(1):33-8. [PMID: 6693597].
4. Mountain JC. Cutaneous ulceration in Crohn's disease. *Gut*. 1970;11(1):18-26. [PMID: 5435264].
5. Vaid RM, Cohen BA. Cutaneous Crohn's disease in the pediatric population. *Pediatr Dermatol*. 2010;27(3):279-81. [PMID: 20609145].
6. Billings JK, Ellis CN, Milgraum SS. Cutaneous granuloma formations in Crohn's disease. *JAMA*. 1986;255(19):2661. [PMID: 3701982].
7. Ratzinger G, Sepp N, Vogetseder W, Tilg H. Cheilitis granulomatosa and Melkersson-Rosenthal syndrome: evaluation of gastrointestinal involvement and therapeutic regimens in a series of 14 patients. *Journal of the European Academy of Dermatology and Venereology: JEADV*. 2007;21(8):1065-70. [PMID: 17714126].
8. Lazzerini M, Bramuzzo M, Ventura A. Association between orofacial granulomatosis and Crohn's disease in children: systematic review. *World J Gastroenterol*. 2014;20(23):7497-504. [PMID: 24966621].
9. 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(5):401-12. [PMID: 957999].
10. Barrick BJ, Tollefson MM, Schoch JJ, McEvoy MT, Hand JL, Wieland CN, Davis DM. Penile and Scrotal Swelling: An Underrecognized Presentation of Crohn's Disease. *Pediatr Dermatol*. 2016;33(2):172-7. [PMID: 26764123].
11. Ciccacci C, Biancone L, Di Fusco D, Ranieri M, Condino G, Giardina E, Onali S, Lepre T, Pallone F, Novelli G, Borgiani P. TRAF3IP2 gene is associated with cutaneous extraintestinal manifestations in inflammatory bowel disease. *J Crohns Colitis*. 2013;7(1):44-52. [PMID: 22445837].
12. 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(8):928-32. [PMID: 8712843].
13. Emanuel PO, Phelps RG. Metastatic Crohn's disease: a histopathologic study of 12 cases. *J Cutan Pathol*. 2008;35(5):457-61. [PMID: 18261113].
14. Daunton A, Langman G, Goulding JM. A cutaneous presentation of a common condition. *BMJ*. 2015;351:h6711. [PMID: 26681202].
15. Slaney G, Muller S, Clay J, Sumathipala AH, Hillenbrand P, Thompson H. Crohn's disease involving the penis. *Gut*. 1986;27(3):329-33. [PMID: 3699553].
16. 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(8):552-4. [PMID: 2583899].
17. 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. [PMID: 23331739].
18. Sanchez L, Cabanillas M, Alvarez JC, Echarri A. Topical tacrolimus for recurrent penile Crohn's disease. *JCrohns Colitis*. 2014;8(10):1145-6. [PMID: 24815787].
19. Atherton DJ, Massam M, Wells RS, Harries JT, Pincott JR. Genital Crohn's disease in a 6-year-old boy. *Br Med J*. 1978;1(6112):552. [PMID: 630216].
20. Carranza DC, Young L. Successful treatment of metastatic Crohn's disease with cyclosporine. *J Drugs Dermatol*. 2008;7(8):789-91. [PMID: 18720698].
21. Bajaj V, Sripathy TK, Ralph S. Penile ulceration: a rare manifestation of cutaneous crohn's successfully treated with subcutaneous methotrexate. *J Eur Acad Dermatol Venereol*. 2016;30(10):e87-e8. [PMID: 26373246].
22. Geyer AS, Anhalt GJ, Nousari HC. Effectiveness of infliximab in the treatment of refractory perineal cutaneous Crohn disease. *Arch Dermatol*. 2000;136(4):459-60. [PMID: 10768643].
23. Kolivras A, De Maubeuge J, Andre J, Song M. Thalidomide in refractory vulvar ulcerations associated with Crohn's disease. *Dermatology*. 2003;206(4):381-3. [PMID: 12771492].
24. Brady CE, 3rd, Cooley BJ, Davis JC. Healing of severe perineal and cutaneous Crohn's disease with hyperbaric oxygen. *Gastroenterology*. 1989;97(3):756-60. [PMID: 2753335].
25. Hogan N, Byrnes V, Hussey A, Joyce M. Surgical management of gluteal metastatic cutaneous Crohn's disease. *J Crohns Colitis*. 2012;6(5):617-20. [PMID: 22398091].
26. Cockburn AG, Krolikowski J, Balogh K, Roth RA. Crohn disease of penile and scrotal skin. *Urology*. 1980;15(6):596-8. [PMID: 7394990].