REVIEW

Metastatic Crohn's disease: A review and approach to therapy

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Metastatic Crohn's disease (CD) is a rare cutaneous manifestation of CD that was first described nearly 50 years ago. Many subsequent reports have defined its most common clinical and histopathologic features. The pathogenesis underlying metastatic CD is unknown but various hypotheses exist. An established standard therapy is lacking. Owing to its rarity and nonspecific clinical presentation along with the diversity of inflammatory skin disorders that often complicate CD, the diagnosis of metastatic CD may be overlooked. This report highlights the salient features of this disorder to facilitate recognition and management of this rare dermatosis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.04.002.)

Key words: cutaneous Crohn's disease; cutaneous manifestations of Crohn's disease; gastrointestinal disease; granulomatous inflammation; inflammatory bowel disease; metastatic Crohn's disease.

Crohn's disease (CD) is an idiopathic inflammatory disorder of the gastrointestinal (GI) tract that is frequently associated with skin and mucous membrane lesions. Metastatic CD (MCD), also known as cutaneous CD, is a rare manifestation of CD defined by granulomatous lesions infiltrating the skin that are discontinuous from the affected GI tract.[1,2] The pathophysiologic processes underlying CD are presumably responsible for lesions of MCD as the disorders share similar pathologic features.

The descriptor "metastatic" was ascribed to cutaneous lesions of CD after a peculiar case reported by Parks et al[3] of a 70-year-old woman with CD who developed persistent skin ulcers and inflammatory plaques that occurred contiguous with and remote from her diseased bowel. Microscopic examination of these lesions demonstrated a granulomatous pattern resembling her primary GI lesions, which convinced the authors that the remote lesions had metastasized from affected segments of bowel by an unknown mechanism. Subsequent reported cases have validated MCD as a distinct disease nosologically and have also supported that these initial observations are often reproducible among affected individuals as skin findings are usually characterized by cutaneous ulceration and nonspecific inflammatory lesions.[4,5] What follows is a review of the literature describing MCD that emphasizes its clinical and pathologic features and summarizes successfully used therapies.

Abbreviations used:

CD:	Crohn's disease
GI:	gastrointestinal
MCD:	metastatic Crohn's disease
TNF:	tumor necrosis factor

CUTANEOUS MANIFESTATIONS OF CD

Skin lesions commonly complicate CD with reported prevalence rates as high as 44%.[6-8] The current classification of skin disorders occurring in CD is organized according to the presumed pathologic mechanism. Mucocutaneous lesions are categorized as: CD-specific (involving the skin by a mechanism identical to that occurring in the GI tract); reactive (arising by distinct pathogenetic mechanisms); or associated (noted to occur without a well-defined mechanism) (Table I).[9,10] CD-specific lesions account for the majority of lesions observed. Of these, the best recognized are perianal and peristomal fissures and fistulae and oral disease.

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The former may develop in up to a third of patients. CD-specific lesions characteristically demonstrate granulomatous inflammation by histopathologic examination, a process that can be indistinguishable from affected GI segments. MCD is an exceptional CD-specific lesion as it rarely occurs.

Reactive lesions are well known to complicate the course of CD. Among these, erythema nodosum and oral aphthae are most common, whereas pyoderma gangrenosum, epidermolysis bullosa acquisita, erythema multiforme, and cutaneous vasculitis, although classically reported in cases of CD, are far less common (Table I).[11-16] These lesions are distinguishable from CD-specific lesions histopathologically, and their development may relate to cross-antigenicity between the skin and GI tract.

CAPSULE SUMMARY

- Metastatic Crohn's disease is a rare dermatosis with a nonspecific clinical presentation.
- Diagnosis should be suspected in any patient with Crohn's disease with persistent skin lesions and can be confirmed by histopathologic examination.
- This review summarizes the most common features of metastatic Crohn's disease to enhance recognition and discusses anecdotal therapies.

Associated skin disorders co-occur with notable frequency in CD but the mechanism of their onset is poorly understood. When compared with CD-specific lesions, the incidence of these disorders is relatively low. Those most often reported are palmoplantar pustulosis, vitiligo, palmar erythema, and hidradenitis suppurativa.[17-20] Isolated case reports of erythema annulare centrifugum,[21] linear IgA bullous dermatosis,[22] cutaneous Rosai-Dorfman disease,[23] polyarteritis nodosa,[24] pustular folliculitis,[25] and lichen planus have also been documented in association with CD.[26] Rarely, acrodermatitis enteropathica may develop as a consequence of nutritional deficiency particularly if malnutrition is long-standing.[2] Apart from intrinsic disease, CD-directed therapies can also result in skin lesions, an outcome with an increasing frequency that is likely attributable to the increased use of systemic therapies (Table I).[27-29]

Despite the apparent plethora of skin disorders that may arise during the course of CD, CD-specific lesions are the most frequently encountered with the exception of MCD, and although constituting a very small portion of these lesions, MCD nonetheless remains critical to recognize as it represents a disease-specific mucocutaneous lesion that may precede the diagnosis of GI disease.

PATHOGENESIS OF MCD

A precise understanding of the pathogenesis underlying CD is lacking. The current paradigm suggests that CD is less a disease restricted to the GI tract and more a multisystem inflammatory disorder with the potential to affect multiple organs including the skin.[30] CD likely develops from a complex interplay between genetic predisposition, environmental exposure, epithelial barrier dysfunction, and abnormal immune responses to pathogenic and commensal bacteria although the exact sequence of events that produces clinical disease in susceptible hosts is unknown.[31]

The pathogenesis behind MCD is less clear. Early investigators proposed that a circulating antigen is deposited in the skin eliciting a T-helper cell type 1 (Th1)-mediated delayed hypersensitivity reaction responsible for the development of skin lesions.[1,2,32] This hypothesis has not been confirmed experimentally; in fact, hematogenous deposition of an unknown antigen into the skin, possibly of bacterial origin, has been contended by Crowson et al,[6] who demonstrated a pathogenic role for bacteria in GI but not cutaneous lesions. The often reliable finding of perivascular granuloma formation has suggested that the primary pathogenic event is a vasculitis-mediated injury, a process described as granulomatous perivasculitis.[33-36] Circulating immune complexes have been detected in the sera of patients with CD, which also credits this idea.[37,38] Without validation and additional insight into the pathogenesis of CD, the pathomechanisms responsible for MCD will remain speculative owing to its rarity.

EPIDEMIOLOGY

Accurate prevalence and incidence estimates of MCD are lacking. The actual incidence is likely underestimated owing to its varied clinical presentation, which can lead to misdiagnosis and underreporting.[39,40] Case reports have included patients from every age group. Young adults in particular appear to be predisposed, which likely reflects the age distribution of CD, although MCD is less common in children than in adults.[15] There is no established gender discrepancy, but some authors report a slight female predominance.

CLINICAL FEATURES

MCD is rare.[41] In most instances MCD arises during the course of well-established GI disease,