



## A brief account of the pathology and pathogenesis of the cutaneous manifestations of Crohn's disease.

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### Abstract

Inflammatory Bowel Disease (IBD) is a lifelong condition, which may occur in patients of any age. Prior to confirming a diagnosis of IBD, clinicians may face unusual non gastrointestinal symptoms. The extra intestinal manifestations of Crohn's disease (CD) may develop prior to signs of gastrointestinal involvement. Many of these extraintestinal clinical signs overlap with those seen in patients with Ulcerative Colitis (UC) making the diagnosis of CD more difficult.

Aphthous ulceration of the buccal mucosa, lips or tongue for example should alert the clinician to consider the presence of intestinal involvement. Skin manifestations such as Erythema Nodosum, Pyoderma gangrenosum occur more commonly in CD than in UC. The aim of this article is to review the most frequent and important skin manifestations of CD including the primary cutaneous manifestations and those manifestations which are treatment related.

**Key words:** Crohn's disease, cutaneous manifestations, complications, skin features.

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### Methods

A literature search was undertaken using Medline, Pubmed, Dialog data star and a general Internet search under the following terms: Crohn's disease, skin features and cutaneous manifestations. Abstracts that provided information on skin manifestation and /or complications of crohn's disease were reviewed as well as some of the related full text articles. References from these articles were also reviewed. The review was divided to include the following subtopics.

1. Primary cutaneous manifestations
  - a) General skin disease
  - b) Perianal skin disease
11. Secondary cutaneous manifestations
  - a) Cutaneous surgical complications
  - b) Skin features related to enterocutaneous fistula
  - c) Pharmacologically induced cutaneous manifestations.

### Introduction

As early as 1929 Bargen<sup>2</sup> stated "any discussion of IBD would seem incomplete without reference to the lesions that occur in the skin". CD was first recognised as a distinct medical entity when it

was described by Crohn, Ginzburg and Oppenheimer in 1932<sup>3</sup>. The aetiology of CD remains unclear however a greater understanding of the pathogenesis has been developed. This

multi-factorial process is considered to involve a combination of infectious agents and environmental factors which activate an immune response in a genetically susceptible host. Skin manifestations which are much more common in CD than in UC occur in 14 to 44% of Patients 4, 5, 6 .In general Skin conditions in CD are believed to be the result of an imbalance between pro-inflammatory and anti-inflammatory

mediators 7.In some circumstances skin involvement may be caused by an extension of local necessary gastrointestinal disease which manifests with perineal and perianal fissuring or abscess formation.

In some cases distinctive dermatoses are present. An overview of the cutaneous manifestations is presented in figure one.

### Fig. 1

#### General Skin diseases

- Pyoderma gangrenosum
- Erythema Nodosum
- Necrotising Vasculitis
- Epidermolysis bullosa acquisita
- Finger clubbing
- Palmar erythema
- Pustular response to trauma
- Cutaneous metastatic disease
- Granuloma annulare/necrobiosis lipoidica like lesions
- Neutrophilic folliculitis/dermatoses
- Panniculitis
- psoriasis
- Lichenoid granulomatous inflammation
- Bullous pemphigoid
- Sweets syndrome
- Erythema multiforme
- Fournier gangrene

#### Perianal Skin Disease

- Perianal Destruction and Sepsis
- Fistula in ano
- Perianal Skin Tags
- Anal Squamous cell carcinoma

#### Skin features related to enterocutaneous fistula

#### Cutaneous surgical complications

- Peristomal complications
- Peristomal dermatitis
- Pyoderma gangrenosum

#### Drug cutaneous side effects

- Anti-Tumour Necrotic factor-alpha therapy (infliximab)
- Thalidomide
- Azathioprine

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## Primary Cutaneous Manifestations

### Pyoderma Gangrenosum (PG)

Pyoderma Gangrenosum is the most severe skin lesion associated with IBD 10. There are two common variants, the classic ulceration observed on the legs and a more superficial variant known as atypical PG which tends to occur on the hands. The frequency of PG in CD varies from 1.2 – 2.0% 4, 8 and 0.8 % in another study 14. According to the data of Levitt et al 8, 14 PG is associated with the acute phases of CD in 75% of the patients. Activity of the pyoderma frequently parallels the

activity of the intestinal disease and may herald the reactivation of previously quiescent Crohn's. Patients with PG may have involvement of other organ systems which can present as a sterile neutrophilic abscess in an unusual site. The earliest symptom caused by PG is pain at the site of the future lesion. The lesion progresses from a localised formation of a pustule to a "haematoma" like lesion which subsequently evolves into a fluctuant sterile abscess. The abscess spreads concentrically to rapidly undermine adjacent areas of healthy skin. Finally ulceration occurs

producing a purulent necrotic centre. PG is more commonly seen on the lower extremities e.g. dorsum of feet and hands and the lower trunk. Unusual locations include face, breast, buttock and even the oral mucosa 10. The primary histological process is non specific and parafollicular in location with polymorphonuclear infiltration and oedema in the epidermis associated with interstitial and peri-vascular infiltration with lymphocytes, mononuclear cells and plasma cells in the dermis<sup>14</sup>. As the area of PG matures there is necrosis of both the superficial dermis and epidermis resulting in an ulcer. The ulcer base typically shows a mixed inflammatory cell infiltrate. The histological appearance of PG could be confused with severe folliculitis, hidradenitis suppurativa and metastatic crohn's disease as none of the features are pathognomonic. The most cogent reason for histological diagnosis is the exclusion of a vasculitic process as the subsequent treatment is different. The prognosis of PG is generally good, however recurrences may occur and residual scarring is common. Treatment of pyoderma is directed at the underlying disease.

### **Erythema nodosum (EN)**

Erythema nodosum (EN) is more commonly seen in CD than in UC 4, 8, 9. It has been reported in up to 15% of patients with granulomatous colitis 4. Women are more frequently affected 8. Episodes of EN can occur at any time from the onset of the first attack of colitis to a maximum of 16 years later with a mean time of presentation of 5 years 10. Patches of EN are typically found on the lateral aspect of the tibia, although it has also been described on the calf, ankle and arm 8 10. The lesions are usually tender bright red nodules which are round tipped or oval shaped. Their presence often correlates with but can precede an active state of inflammation in the bowel 11. Histologically there is an acute inflammatory reaction within the connective tissue of the lower dermis and subcuticular layer. Panniculitis with infiltration of the connective tissue by leucocytes and lymphocytes is often present 8, 12. Oedema with extravasation of erythrocytes and numerous leucocytes and histiocytes can be detected. At a later stage tissue collagen swells, fragments and exhibits fibrinoid degeneration. Often the venous walls are oedematous and are invaded by inflammatory cells, but changes of leukocytoclastic or Lymphocytic vasculitis are not seen 10.

Boulay et al 13 described a skin lesion in association with Crohn's disease which resembled Erythema induratum but was histologically similar to erythema nodosum. Histologically these specimens showed poorly defined areas of necrobiosis of collagen in the lower dermis with an

inflammatory infiltrate composed of lymphoid cells, histiocytes and epithelioid cells. As the diagnosis of erythema induratum is often based on its clinical appearance the histological features of necrobiotic collagen with surrounding epithelioid and giant cells may be missed as routine biopsies are not performed. The authors suggested the term "nodular necrobiosis" for this extra intestinal manifestation of CD and felt that the characteristic feature of necrobiotic collagen is a central feature of this lesion. The presence of these lesions may be easily missed without a biopsy as the histology is of diagnostic importance. The pathogenesis of these necrobiotic lesions are not known.

### **Cutaneous metastatic disease**

Cutaneous Granuloma formation or granulomatous dermatitis occurring remote from the site of gastrointestinal involvement of Crohn's lesions has been termed Metastatic cutaneous disease 9.

This recently recognised unusual feature of Crohn's disease presumably represents an extension of the same disease process present in the GIT and perianal tissues at an ectopic site 12. Most metastatic disease is ulcerated as described by Mountain 12 and anatomical sites include vulva, penis or scrotum and the trunk. The lesions resemble superficial ulcerations, crusted papules, nodules or ulcerating and non ulcerating plaques 9. Cutaneous metastatic disease can be viewed as a great imitator both clinically and histologically. These cases have been initially misdiagnosed as factitial dermatitis, intertrigo, severe acne, hidradenitis suppurativa, chronic cellulitis. Fortunately metastatic CD does not seem to appear in the absence of gastrointestinal CD 12. Cutaneous biopsies have revealed dermal or subcutaneous non caseating granulomas with epithelioid histiocytes and multinucleated giant cells. Treatment has varied from curettage, oral zinc to intralesional and systemic corticosteroids, dapsone, sulphasalazine 9.

### **Neutrophilic folliculitis /dermatoses**

Magro et al 15 described 20 cases of skin biopsies which demonstrated neutrophilic or suppurative granulomatous folliculitis. Although these raised the diagnostic consideration of bacterial folliculitis patients frequently expressed systemic complaints such as arthritis, fever and malaise and special stains for micro organisms were negative. The authors suggested that this could be a clue to underlying systemic disease and/or an extra cutaneous infection. All biopsies showed a neutrophilic or suppurative and granulomatous folliculitis with variable follicular epithelial necrosis accompanied by perifollicular vasculopathy.

## Cutaneous polyarteritis Nodosa

Cutaneous polyarteritis nodosa was first described by Dyer et al 16 as an extra intestinal manifestation of CD. Kahn et al 17 described a granulomatous panarteritis of two muscular arteries in a young woman who developed recurrent erythematous tender palpable cords and nodules in both upper and lower limbs. Evidence of a granulomatous transmural colitis without vasculitis was obtained from the same patient on examination of the colonic specimen. The relationship between cutaneous polyarteritis nodosa and systemic polyarteritis nodosa is debatable.

Some authorities consider the former to be polyarteritis with only cutaneous manifestations 18, 19 while others believe it is merely one stage of a diffuse systemic disease 20, 4. The authors recommend that biopsy of cutaneous nodules is performed as the association of cutaneous polyarteritis and CD may be more common than previously realised.

## Leucocytoclastic Vasculitis

Cutaneous vasculitis is the least common of the different dermatologic manifestations associated with CD. Review of the literature shows that very few cases have been reported. These patients present with a palpable purpura on their lower extremities 21. Histologically leucocytoclastic vasculitis usually involves post capillary venules with neutrophilic infiltration, necrosis of the walls of vessels as well as fibrin deposition. It is accepted now that leucocytoclastic vasculitis is associated with circulating immune complexes.

Other skin manifestations have been described although they are not as commonly encountered as those already described. Erythema multiforme is seen less commonly in patients with CD

however it may be seen coincidentally with Erythema Nodosum 11. Stephen et al 22 reported an isolated case of erythema multiforme and Crohn's disease. This case documented both pathological lesions in the absence of disease of the small intestine and previous drug therapy. Aphthous ulceration and stomatitis also occurs with Crohn's disease 11. Scherbaum et al 23 reported a case of Henoch schonlein purpura in association with terminal ileitis which was indistinguishable from Crohn's disease. Chalvardjian et al 24 reported the association of Crohn's ileocolitis with an unusual cutaneous manifestation. They described a cutaneous lesion which was characterised by granulomatous rather than leucocytoclastic vasculitis which mainly affected the venules of the superficial dermis. They also commented that cutaneous vasculitis may be more prevalent in CD than the literature indicated and recommended that histological examination of unusual skin lesions, coupled with immunologic assessment on such patients in an endeavour to confirm this observation. Burgdorf et al 25 described a case of granulomatous perivascularitis which reflected a combination of granulomatous inflammation and vasculitis characterised by fibrinoid necrosis and localisation of histiocytes and lymphocytes in the adventitial wall. Rappaport et al 26 reported a case of Sweet's syndrome in association with Crohn's disease. Although both genders are equally affected 90% of the reported cases who suffered from both Sweet's syndrome and CD were females 27. The appearance of Sweet's syndrome usually follows the onset of Crohn's disease but may precede the intestinal symptoms by several years. Sweet's syndrome is characterized by tender raised erythematous plaques or nodules occasionally with vesicles, pustules or bullae. Histologically an interstitial mixed infiltrate with numerous neutrophils and scattered eosinophils with subepidermal edema is characteristic.

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## Peri-anal Skin Disease:

Peri-anal disease is the presenting manifestation of CD in approximately 10% of patients 28. This may be due to active disease in the rectum or anus although occasionally simple perianal sepsis or excoriation is caused by Crohn's colitis producing increased stool frequency.

### Perianal abscesses

Over 50% of patients with perianal CD will develop abscesses 29, 30. Abscesses in these patients may be multiple and complex. Some authorities believe that Crohn's abscesses have

identical aetiologies to abscesses found in the general population i.e. infection in the intersphincteric anal glands. Others believe that the abscesses are resultant from deep cavitating ulcers that penetrate the anorectal wall. Surgical management of these abscesses depends upon careful evaluation under anaesthesia; simple abscesses can be incised and drained. Attempts to lay open fistulous tracts detected at this stage is inadvisable due to the risk of sphincter damage 31.

## **Anal Fistulae**

Anorectal fistulas in CD can be simple or complex depending on their origin. Complex fistulae may result from active rectal or proximal colonic lesions which form deep cavitating ulceration; the resultant abscess formation produces tissue destruction and colo-cutaneous fistulation. Large cavities and aggressive disease can result in the "watering can" perineum. Fistulae are classified according to their relationship with the sphincters e.g.: intersphincteric, trans-sphincteric, supralelevator, extrasphincteric, and Submucosal. Some surgeons advocate simple observation with the expectation that these fistulae will heal spontaneously 32, 33. Most colorectal surgeons follow more conventional approach using fistulotomy in low or intersphincteric fistula, non-cutting seton in trans-sphincteric fistula, mucosal advancement flap when sphincters are involved and the mucosa is intact 34. High peri-anal fistulas are often very difficult to eradicate with local measures and Proctectomy is often required. Recently perianal disease in combination with rectal involvement has been treated using infliximab with some success.

## **Fournier's Gangrene**

Fournier's gangrene is a form of necrotising fasciitis resulting from a source of anorectal or urological sepsis. The patient often presents with signs of systemic sepsis, marked cellulitis and rapid tissue necrosis arising from the perineum and extending anteriorly towards the scrotum and penis. The infective process is usually due to a synergistic infection producing thrombosis of

subcutaneous blood vessels resulting in necrosis of the overlying skin. Originally described as idiopathic gangrene of the genitalia, Fournier's gangrene has an identifiable cause in approximately 95% of cases. Fournier's gangrene occurs more commonly in diabetics. Fistulating CD with complicated perianal abscess formation is recognised as a risk factor for the development of this aggressive condition 35. The mainstay of treatment involves active resuscitation, wide spectrum intravenous antibiotics and radical surgical debridement of the necrotic tissue.

## **Perianal skin tags**

These are secondary lesions caused by repeated episodes of inflammation and attempts at healing. Approximately 25% resolve spontaneously, particularly after remission of the underlying bowel disease. These tags should not be removed because this may result in a chronic non healing wounds, chronic ulceration, or perianal sepsis.

## **Anal Carcinoma**

Squamous-cell carcinomas can develop as a result of metaplasia in areas of chronic ulceration. Although these carcinomas have been reported in patients with long standing CD the risk of developing this malignancy is not increased in Crohn's sufferers 36, 37. The presence of chronic inflammation may result in a delay in the diagnosis, so biopsy of any non healing perineal ulcers or fissures is imperative 34. Beck et al 38 reported a case of perianal Bowen's disease in a young woman who had Crohn's disease.

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# **11. SECONDARY CUTANEOUS MANIFESTATIONS**

## **Cutaneous Surgical Complications (Peristomal complications)**

### **Skin features related to enterocutaneous fistula**

Skin excoriation develops rapidly after the formation of the fistula due to the high concentration of digestive enzymes present in the chyme. Protection of the peristomal skin with correctly fitted appliances can reduce the development of this complication. Entero-and colocutaneous fistulae usually occur from a site of active disease. Surgical management with bowel resection, including the fistula, is the preferred method of treatment 39.

### **Parastomal dermatitis**

Parastomal skin irritation is caused either by technical problems with the construction of the stoma or poor stoma bag application. Meticulous planning prior to surgery regarding the placement of the stoma by the surgeon and the enterostomal therapist is essential. Occasionally parastomal skin ulceration may be an extraintestinal manifestation of CD. Hellman and Lago studied 362 patients with ostomies and concluded that skin disorders were a major problem occurring in 79% of ileostomy and 37% of colostomy patients. Skin manifestations were caused by primary irritant dermatitis, *Candida albicans* or bacterial



infections 40. Very rarely squamous cell carcinoma at the stoma site has been seen.

### Pharmacologically induced cutaneous side effects

CD is a lifelong condition characterised by a relapsing and remitting course. Therapeutic agents are added in a stepwise manner in response to the severity of the condition. In the early stages of the disease the mainstay of treatment is with corticosteroids and mesalazine. In steroid-dependent or steroid-refractory CD, immunomodulatory drugs such as azathioprine, mercaptopurine or intra muscular injections of methotrexate are added.

Infliximab is an anti tumor necrosis factor alpha (TNF-alpha) monoclonal antibody which is indicated in patients with disease refractory to conventional therapy. Anti TNF-alpha production inhibitors e.g. thalidomide and TNF-binding neutralizing fusion proteins e.g. etanercept have recently been added to the therapeutic armamentarium. The incidence of cutaneous side effects complicating treatment of CD with corticosteroids and mesalazine appears low. There are few accounts in the literature of skin eruptions caused as a side effect of azathioprine

or mercaptopurine 41. Infliximab is a new treatment for CD and the side effect profile is not fully established. The initial side effects of Infliximab are due to its immunological properties in the form of transfusion reactions, serum sickness syndrome etc. Serum sickness syndrome is an immune complex mediated phenomenon resulting in the development of cutaneous eruptions, fever, arthritis and lymphadenopathy<sup>42</sup>. Psoriatic type skin reactions have occurred in Crohn's patients receiving infliximab for the treatment of enterocutaneous fistulae<sup>43</sup>. Infliximab is a recognised treatment of many common skin disorders<sup>44, 45</sup>. Infliximab can be used to treat the cutaneous side effects of CD such as metastatic Crohn's and hidradenitis suppurativa<sup>46,47</sup>. The frequent development of cutaneous side effects has been reported in patients taking Thalidomide for the treatment of multiple myeloma, these include nonspecific dermatitis, exfoliative erythroderma, erythema multiforme<sup>48, 49</sup>. There are no accounts of the development of skin reactions caused by thalidomide being a major concern in the treatment of CD but the actual incidence of cutaneous reactions remains to be established as thalidomide is not as yet a commonly prescribed medication for the treatment of CD.

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