

Dermatological signs during inflammatory bowel diseases

C. FELICIANI, C. DE SIMONE, P. AMERIO

Department of Dermatology, Catholic University of the Sacred Heart, Rome (Italy)

Abstract. – Crohn disease (CD) and Ulcerative Colitis (UC) are characterized by ulcerative lesions of the bowel. Some patients show similar lesions of the skin or oral and/or perianal mucosa. Sometimes these lesions, or some other skin lesions are the first sign of bowel disease. Dermatologists could suspect an inflammatory bowel disease (IBD) during skin lesions such as pyoderma gangrenosum (PG) or erythema nodosum (EN). These entities are very well known by dermatologists and its role is to diagnose internal chronic disease associated to EN or PG. Depending on the associated disease the treatment may vary from steroids to anti TNF biologics.

Key Words:

Inflammatory bowel diseases, Crohn disease, Ulcerative Colitis, Skin lesions, Pyoderma gangrenosum, Erythema nodosum.

Introduction

Skin signs are sometimes useful to diagnose an indeterminate systemic disease. In a clinical course of inflammatory bowel disease (IBD) skin clinical signs may be ulcerative lesions of oral mucosa or the perianal area. Aspecific, but frequently associated to IBD, dermatological diseases are erythema nodosum and pyoderma gangrenosum. About 20-35% of IBD patients show extraintestinal signs. The most frequent organs involved are skin, eye and joint. Skin is involved as a “reactive” sign in 5 to 15% of IBD patients developing EN or PG. Rarely a “metastatic Crohn” has been described with multiple non-caseating granulomatous cutaneous lesions on non-contigal skin (mostly on the arms).

Pyoderma Gangrenosum

Pyoderma Gangrenosum (PG) is a rare, chronic, recurrent, ulcerative skin disease belonging to the neutrophilic dermatosis spectrum, which includes non-infectious inflammatory cutaneous diseases, characterized by prominent neutrophilic infiltration of the skin. PG typically starts with pustules which rapidly evolve to painful ulcers with undermined violaceous borders and surrounding erythema.

Due to the rarity of the disease accurate epidemiological data on PG are missing. The general incidence has been estimated to be between 3 and 10 per million per year.

Pathogenesis of PG is still unknown although it has been hypothesized for two decades that an abnormal immune response, to yet unidentified factor could be involved¹. Possible mechanisms that have been considered include an aberrant T-cell response (supported by the therapeutic success of cyclosporine), the increased tissue expression of interleukin-8 (IL-8), interleukin 16 (IL-16) tumor necrosis factor- α (TNF- α) (supported by the therapeutic success of TNF- α inhibitors), and a neutrophil dysfunction^{2,3}.

In 50-70% of cases PG is associated with an underlying systemic disease, most frequently inflammatory bowel diseases (IBD). Ulcerative colitis is found in 10-15% of cases. Another associated disease is Crohn’s regional enteritis with a frequency close to that of ulcerative colitis^{4,5}. Arthritis, monoclonal gammopathy, solid tumours and malignant haematological diseases (leukaemia, lymphoma, and myelodysplastic syndrome) have also been described in association⁶⁻¹⁰.

Probably triggering factors and pathogenetic mechanisms leading to neutrophilic infiltration of the skin are different depending on the under-

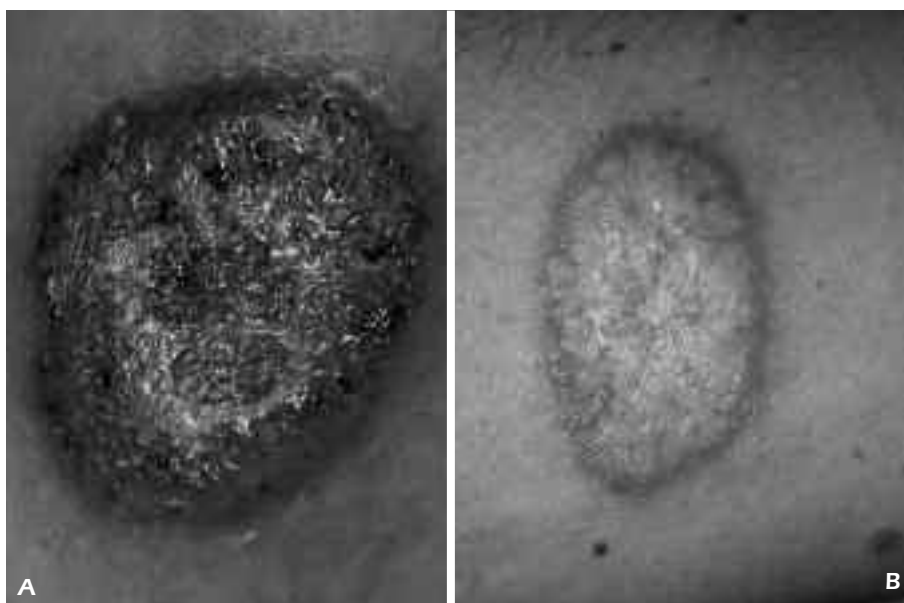


Figure 1. Classical pyoderma gangrenosum lesion in a patient with IBD before **(A)** and after **(B)** therapy.

lying systemic disease. It has been suggested that in PG associated with IBD (Crohn disease, ulcerative colitis) cross reacting antigen(s) in the bowel and in the skin could be responsible for secondary cutaneous lesions⁴.

The pathergy phenomenon, frequently observed in this patients, consists in the induction of a typical PG lesion at site of a minor skin trauma, insect bite or surgical procedure¹¹. Based on these observation it has been suggested that PG represents a hyper-reactive response to inflammatory, neoplastic or traumatic processes in susceptible persons¹².

The histopathology is nonspecific and changes with the stage of lesion and clinical variant of the disease. The initial lesions show a deep dense neutrophilic infiltrate in the dermis; in about 40% of cases, leukocytoclastic vasculitis can be found. PG with granulomatous inflammation has also been described¹³.

PG can be induced by drugs such as propylthiouracil, pegfilgrastim (a granulocyte-stimulating factor), and gefinib (an inhibitor of epidermal growth factor receptor)¹⁴.

Clinical Presentation

PG has been classified into four major types on the basis of clinical and histological features: ulcerative, pustular, bullous and vegetative. Each

of these variants is frequently associated with a different underlying disease, management and prognosis, although different subtypes can coexist or appear in subsequent time in the same patient¹⁵.

Classical or Ulcerative PG

The initial lesions starts from an inflammatory pustule with rapid growth or nodule that rapidly breaks down and undergoes necrosis. Typical lesions consist of very painful, large ulcers with a purulent base and indeterminate violaceous borders that enlarge peripherally. Ulcers arise most frequently on the lower extremities or the trunk, though they can occur anywhere including unusual body sites such head, neck region, genitalia^{11,16}. The pathological process affects primarily the dermis, being the epidermal necrosis a secondary event. While early lesions show fibrinoid necrosis of the vessel wall and a mixed lympho-neutrophilic perivascular infiltration, fully developed lesions show abscess formation and epithelial necrosis. Ulcerative PG is frequently associated with underlying diseases such as rheumatoid arthritis or seronegative arthritis (>30% of cases), IBD (>30% of cases) monoclonal gammopathy (10%) malignancy, including haematological and solid tumors (<10%)¹⁰. In 25% of patients ulcerative PG is induced by a precipitating event, including surgical procedures¹¹.

Pustular PG

First described by O'Loughlin and Perry¹⁷, pustular PG is characterized by multiple sterile pustules (0.5-2 cm in diameter) with a surrounding erythematous halo arising on the trunk and extensor aspect of the limbs, often symmetrical and associated with systemic symptoms (fever and arthralgias). Histopathology reveals a dermal neutrophilic infiltrate and subcorneal neutrophilic micropustule. There are a strong association with IBD: the eruption frequently coincides with an exacerbation of bowel disease and often subsides after controlling the bowel symptoms¹⁸. A vesiculopustular follicular variant has been described in the patients with hepatobiliary diseases (hepatitis, primary biliary cirrhosis)¹⁹. Involvement of oral mucous by multiple pustules, often seen in association with IBD, has been defined as pyostomatitis vegetans and probably represents the oral pustular PG²⁰.

Bullous PG

Described by Perry and Winkelmann²¹ in 1972, bullous PG is characterized by grouped vesicles (mostly on the dorsal surface of the hands, the extensor aspects of the arms, or on the head) that rapidly spread and coalesce to form large bullae, showing a central necrosis and a peripheral halo of erythema. Histology reveals a subepidermal bulla, a dermal neutrophilic infiltrate and, at a later stage, epidermal necrosis. The bullous PG is frequently associated with haematological, often malignant, diseases (leukaemia, polycythemia rubra vera) and the patient with this clinical variant should be carefully examined.

Vegetative PG

Vegetative PG, described by Wilson-Jones and Winkelmann²², is characterized by a solitary, erythematous ulcerated plaque, and lacks the violaceous border which is characteristic of the classical variant. An underlying disease is associated only in a minority of cases (<20%). Histopathological features include histiocytes within the neutrophilic infiltrate, tissue eosinophilia and granuloma formation. Based on these findings this variant has also been defined as superficial granulomatous pyoderma. Prognosis of vegetative PG is usually good and response to treatment satisfying²³.

Management

PG can be associated with extracutaneous manifestations such as the involvement of upper airway mucosa, eye, genital mucosa, sterile pulmonary neutrophilic infiltrates or spleen infiltrates, neutrophilic myositis and sterile cortical osteolysis (adjacent to PG ulcers)²⁴.

Diagnosis of PG relies on clinical examination that evaluates type, number, size and site of skin lesion and symptoms of associated disease. Although histopathology is not diagnostic, a skin biopsy is necessary to rule out other disease mimicking PG. Weening et al¹² have identified six disease categories (vascular occlusive or venous disease, vasculitis, cancer, infection, exogenous tissue injuries, drug reaction) that mimic PG and should be excluded in a diagnostic setting.

A detailed history and physical examination are essential in order to identify any underlying disorder. Laboratory investigation such gastrointestinal study, bone marrow examination, chest X-ray and CT scan should be dictated by the suspect of an associated systemic disease.

The topical treatment provides local conditions that enables wound healing. Secondary infection must be avoided and, if present, adequately treated. Occlusive dressing is contraindicated in lesions with heavy or purulent exudates.

Several topical agents can be used for treatment of PG and can be sufficient alone to control some variants (vegetative). Among local treatments, high potency steroids, topical calcineurin inhibitors (tacrolimus, pimecrolimus), human platelet-derived growth factor, intralesional injection of cyclosporine are included. However, in the majority of cases the association of both local and systemic therapy is necessary.

The systemic treatment supported by clinical evidence of efficacy include corticosteroid, cyclosporine dapsone, sulfasalazine and other steroid sparing agents (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, tacrolimus). Corticosteroids, like prednisolone, 1 to 2 mg/kg/day, are widely used for the initial therapy. Pulse therapy with suprapharmacological doses of corticosteroids (1 g of methylprednisolone) may be helpful to rapidly control the refractory cases²⁵.

Cyclosporin is considered an effective treatment for widespread PG and is often prescribed in combination with the steroids. In many cases, steroids can be completely replaced by cy-

cyclosporin. Doses of 3-5 mg cyclosporin A per kg/day show efficacy in PG. Dapsone (up to 200 mg daily) is useful in milder cases of PG. Dapsone inhibits the neutrophil migration and production of reactive oxygen species and exerts a variety of other anti-inflammatory activities. Thalidomide shows immunomodulatory activity such as suppression of Tumour Necrosis Factor alpha (TNF- α), basic fibroblast growth factor and neutrophil chemotaxis. It was used in combination with steroids.

Recently, the positive effect of anti TNF- α treatment in PG has been reported. The efficacy of infliximab, a chimeric anti TNF- α antibody, has been reported in patients with PG refractory to systemic corticosteroid and cyclosporine therapy²⁶. In many instances, specifically in Crohn disease, infliximab helps both PG and the underlying disease. Usually 5 mg/kg body weight are infused at weeks 0, 2 and 6, and every 8 week thereafter. Therapeutic efficacy on PG has also been seen with other TNF- α antagonists: i.e. adalimumab (a fully human anti TNF- α antibody) and etanercept (a fusion protein bearing a fragment of TNF- α p75 receptor)²⁷. The benefit of TNF- α antagonists outweighs the risk of their use, especially when administered to patients with PG that not responded to standard therapies. An appropriate caution before treatment with TNF- α antagonists is screening for latent tuber-

culosis, and patients with a history of active tuberculosis or who may have recently been in contact with the disease should most likely not receive the drug. While administering anti TNF- α agents, the patients should be monitored for infections and the therapy should be discontinued if the symptoms develop.

Long term prognosis of PG is unpredictable since the disease often shows a chronic and relapsing course that makes difficult decision on the treatment duration. Relapses occur even in patients who respond to drug therapy. Mortality rate of PG to 30% has been reported in some series¹⁶. The prognosis is poor for the patients with associated haematological malignancies. PG, and the associated underlying diseases tend to have an independent course, with the exception of the pustular and bullous variants when associated respectively with IBD or haematological malignancies. The PG-ulcers associated with arthritis seem to have a poorer prognosis than others²⁸. PG involvement of the hands shows a higher percentage of lymphoproliferative than chronic IBD²⁹.

Erythema Nodosum

The most frequent clinical picture of panniculitis is erythema nodosum (EN).



Figure 2. (A) Bilateral multiple lesions in a patients with idiopathic erythema nodosum and (B) single lesion on the leg of a patients with concomitant streptococcal infection therapy.

Table I. Triggers for a reactive “erythema nodosum”.

Infections	Drugs	Cancer	Others
<i>Bacteria</i> <ul style="list-style-type: none"> • Streptococcus • Pseudomonas • M. Tuberculosis • Propionibacterium • Treponema • Meningococcus • Chlamidia 	<i>Antibiotics</i> <ul style="list-style-type: none"> • Amoxicillin • Ampicillin • Levofloxacin • Minocyclin • Ofloxacin • Erythromycin • Penicillin • Piperacillin • Streptomycin • Sulfonamides 	<ul style="list-style-type: none"> • Carcinomas (colon, uterine, hepatic, lung, pancreatic, kidney, gastric) • Hodgkin’s disease • Leukaemia • Sarcoma 	<ul style="list-style-type: none"> • Behçet Syndrome • Coeliac disease • IBD • Autoimmune connective diseases • Arthritis (Still, Reiter, spondylitis, rheumatoid)
<i>Virus</i> <ul style="list-style-type: none"> • Hepatitis • HIV • Measles • Herpes family • Parvovirus 	<i>NSAIDs (Not steroidal drugs)</i> <ul style="list-style-type: none"> • Ibuprofen • Diclofenac • Naproxen • Acetaminophen 		
<i>Fungal</i> <ul style="list-style-type: none"> • Dermatophytes • Deep fungal infections 	<i>Others</i> <ul style="list-style-type: none"> • Phenitoin • Amiodarone • GMCSF • Anti leukotriene • Oral contraceptives/estrogens • Isotretinoin • Azathioprine • Iodides 		
<i>Protozoa</i> <ul style="list-style-type: none"> • Ameba • Giardia • Toxoplasma • Trichomonas 			

Clinical Presentation

EN is characterized by the appearance on the legs of erythematous round/oval nodular lesions³⁰. These lesions are painful mostly after pressure, nodules range from 1 to 10 cm in diameter. Their colour evolve from red to brownish or bluish depending on the time of appearance. For unknown reasons the lower legs are the most frequent areas affected. An HLA predisposition has been supported by several Authors³¹. Nodules are usually multiple bilateral and self-healing within one month. Patients are usually young females which sometimes suffer from arthralgia, fever and malaise. EN could be idiopathic but usually is a reactive process to a huge variety of triggers ranging from infections, drugs, neoplastic disorders and systemic diseases. On Table I a list of possible triggers is shown. One third of EN are classified as idiopathic, but this large number of cases is probably due to the fact that it is not possible to perform tests in all patients for all kind of the causative agents. Several decades ago tubercu-

losis was a frequent cause of EN, actually the most frequent trigger of EN are the streptococcal infections, whilst an increasing cause of EN is the sarcoidosis. The association between bilateral hilar adenopathy and sarcoidosis is named Löfgren’s syndrome³². On the other hand, a bilateral hilar adenopathy could be also present during lymphoma and several other infections. In patients with EN and recurrent aphthosis a Behçet syndrome should be evaluated. Another possible association is with the Sweet syndrome which share also a common trigger mechanism³³.

EN could be a reactive response to a wide variety of triggers probably due to immune complex deposits. Probably a delayed hypersensitivity is the basal mechanism of this response³⁴.

Management

Patients afflicted at the legs by tender nodular lesions painful at pressure should be evaluated for EN. Since the possible triggers are in a large

Table II. Questions for clinical history in patients with erythema nodosum.

<p>When the lesions started?</p> <p>Do you or did you have any symptom in the last 1-2 months (fever, malaise, cough, gastrointestinal symptoms)?</p> <p>Do you have sore throat now ? and in the last month?</p> <p>Do you get any drug ?</p> <p>Did you loose weight in the last six months?</p> <p>Did you travel in a foreign country in the last year?</p>

Table III. Laboratory analysis steps in patients with erythema nodosum.

1 st step	2 nd step	3 rd step
<ul style="list-style-type: none"> • Blood count • ESR • ASO titer • Urine analysis 	<ul style="list-style-type: none"> • Chest X ray • ACE (angiotensin converting enzyme) • Intratuberculin test • Hepatitis B and C test • Skin histology (septal panniculitis without vasculitis) 	<ul style="list-style-type: none"> • Other rare causative agents? • Including parasite infections or neoplastic diseases

number, the most important clinical evaluation is the patient health history³⁵. A complete history should be taken from the last 1-3 months in particular infections and aspecific symptoms such as malaise, fever, diarrhoea. On Table II a summary of questions to the patients is shown. Depending on the answers to these questions a laboratory investigation should follow. On Table III a step list of laboratory investigations is illustrated. Initial investigations include ASO titer, ESR, urine analysis and a complete blood count. Further investigations include intratuberculin test, chest X ray³⁶. Often leukocytosis and increased ESR are present but these data are unspecific for any causative agent. In the case that all investigations are negatives a less frequent causative agent should be considered taking in mind the list shown in Table I.

Treatment is usually symptomatic but when it is possible the treatment of the causative agent should be performed. Non steroidal antiinflammatory drugs (NSAID) such as aspirin, naproxen or nimesulide are often helpful. Systemic steroids are also useful to manage the acute phase of EN Other drugs are potassium jodide (400-800 mg/day, taking in consideration thyroid function, pregnancy, allergies of the patients). Colchicines

and hydroxychloroquine are also useful in some patients. Finally in several patients with resistant and recurrent EN anti TNF therapy could be considered³⁷.

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