DOI: http://dx.doi.org/10.3315/jdcr.2016.1230

Journal of Dermatological Case Reports

Pyoderma gangrenosum with spleen involvement. Review of the literature and case report.

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Keywords:

bowel infarction, dapson, eye, ophthalmology, neutrophils, peritonitis, pyoderma gangrenosum, skin ulcers, spleen

Abstract

Background: Pyoderma gangrenosum is a rare, ulcerative, destructive, non-infectious dermatologic disease and it is one clinical entity within the spectrum of neutrophilic dermatoses. Visceral involvement, manifesting as sterile neutrophilic infiltrates in sites other than skin and, is infrequent. Splenic involvement is very rare.

Main observations: We present a case of a 58-year-old woman with pyoderma gangrenosum with spleen involvement and review all reports of similar cases. We have found nine reported cases, our case being the tenth.

Conclusion: Our review showed that spleen involvement in the course of pyoderma gangrenosum can occur at any age. It is slightly more frequent in men. An underlying or associated neutrophilic disorder is present in almost half of the patients. Skin manifestations were usually present before splenic involvement. In most cases the disese responds well to glucocorticosteroids. (*J Dermatol Case Rep*. 2016; 10(2): 26-31)

Introduction

Pyoderma gangrenosum (PG) is a rare, ulcerative, destructive, non-infectious dermatologic disease and it is one clinical entity within the spectrum of neutrophilic dermatoses (ND). The etiology is unknown, but more than 50% of PG cases are associated with an underlying systemic disease, such as inflammatory bowel disease, rheumatoid arthritis, hematological disorder or malignancy.[1] The diagnosis of PG is based on the clinical picture, in conjunction with compatible histology.[2] Cases of PG with visceral involvement, consisting of a sterile neutrophilic infiltrate in sites other than skin and/or mucous membranes, are very rare.

We present a case report of a patient with PG with spleen involvement and a review of the literature.

Case report

A 58-year-old woman was admitted to the Dermatology Department with a 6-month history of ulcerative skin lesions affecting the trunk, the limbs and the left upper eyelid. The first lesion appeared on the right breast, was misdiagnosed as an abscess and was treated by surgical incisions which lead to the extension of the lesion, despite antibiotic therapy. Later, new lesions developed. Physical examination revealed multiple, oval, ulcerative, tender lesions with well-circumscribed and raised edges, surrounded by a livid halo located on the trunk and limbs. The size of the lesions varied between 2-10 cm in diameter and the floor of the ulcerations was covered with red granulation tissue and purulent exudate. Also, multiple subcutaneous, tender, erythemato-violaceus nodules were present on the trunk and limbs, together with cribriform scars with many little burrows and indentations (Fig. 1). The left upper eyelid was red, swollen and tender and a purulent discharge and multiple ulcerations were present on the conjunctiva. Ophthalmologic examination revealed multiple scleral and conjunctival abscesses, corneal ulcerations and abundant purulent discharge. There was neither lymphadenopathy nor organomegaly. A presumptive clinical diagnosis of Pyoderma gangrenosum was made.

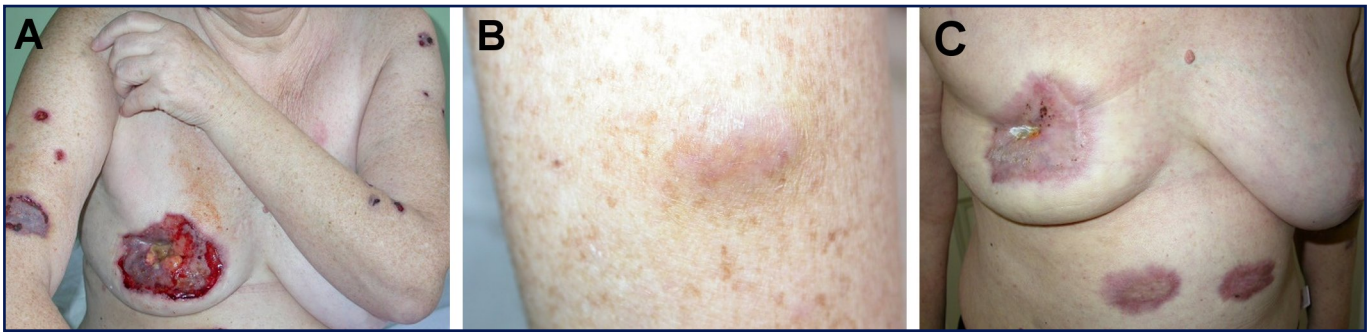

Figure 1

(A) Multiple, oval, ulcerative, tender lesions with well-circumscribed and raised edges, surrounded by a livid halo; the floor of the ulcerations is covered with red granulation tissue and purulent exudate; (B) Subcutaneous, tender, erythemato-violaceus nodule; (C) Multiple cribriform scars following the healing of the ulcerations.

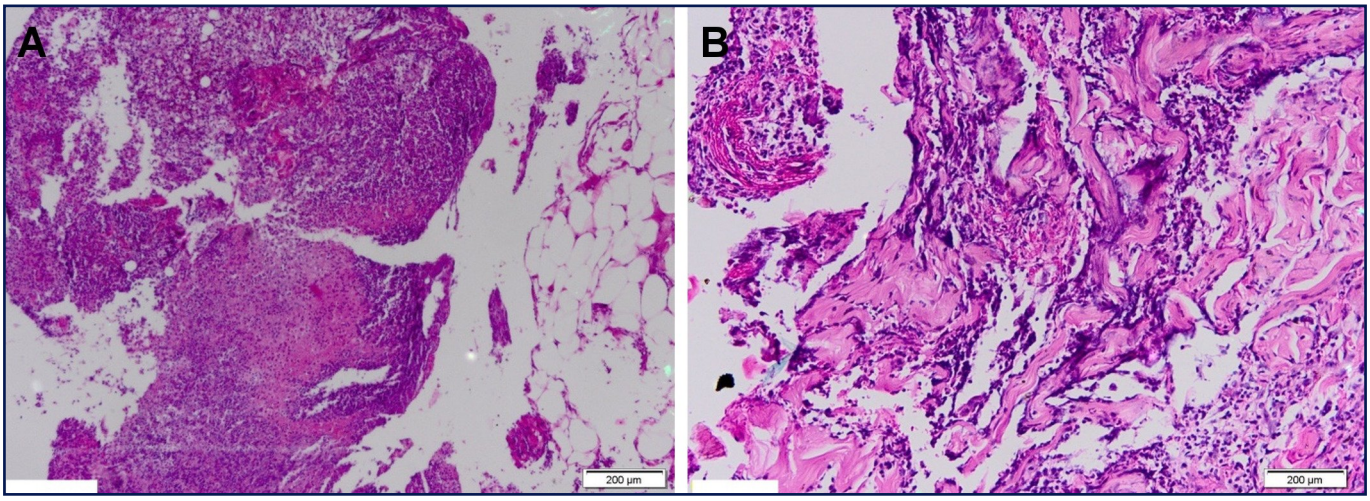

Figure 2

Histopathological exam showing a dense, neutrophilic infiltrate extending through the dermis and the subcutaneous fat (haematoxylin and eosin staining; original magnification (A) x4, (B) x10).

A laboratory work-up revealed the following abnormal values: erythrocyte sedimentation rate 88 mm/h, erythrocytes 3.54x106/mm^3 (normal 4.2-5.4), hemoglobin 8.5 g/dL (normal 12-16), platelet count 881x109/L (normal 150-400x109), C-reactive protein 12.5 mg/dL (normal <0.1), glucose 156 mg/dL (normal 65-110). The serum proteinogram revealed decreased levels of albumins and elevated levels of α1-, α2- and β- globulins. All the other blood test results were within normal range.

A skin biopsy from the edge of one lesion showed a dense, neutrophilic infiltrate extending through the dermis to the subcutaneous fat (Fig. 2). Cultures for aerobic and anaerobic bacteria, fungi and mycobacteria obtained from skin samples were negative.

Chest X-ray did not disclose any abnormality. Abdominal echography and abdominal computed tomographic scan revealed a 5.5/6/6 cm abscess in the peripancreatic space; multiple small, splenic abscesses and thrombosis of the splenic vein (Fig. 3).

The possibility of an underlying haematological disease was considered, due to abnormalities in the blood count cell (thrombocytosis and anaemia). A peripheral blood smear showed microcytic erythrocytes and thrombocytosis, without dysplasia of the cells. The changes were interpreted by the hematologist as reactive to chronic inflammation, so the bone marrow biopsy was not felt to be indicated.

Based on the clinical and paraclinical findings a diagnosis of pyoderma gangrenosum, with systemic involvement, reactive thrombocytosis and splenic vein thrombosis was made and treatment with dexamethasone 8 mg/day and enoxaparin 80 mg/day was started. Subsequently, dapsone was added to the therapy in an increasing dose from 50 to 150 mg/day, Dexamethasone was switched to prednisone 45 mg/day and enoxaparin was reduced to 40 mg/day. The skin lesions healed, leaving cribriform scars, the ocular inflammation plummeted, and the laboratory work-up showed the normalization of the abnormal values and further imaging showed the disappearance of the abdominal abscesses. Prednisone was slowly tapered to 10 mg/day and dapsone and Enoxaparin were maintained at the mentioned dose.

Unfortunately, 4 months later, the disease became active again, and the patient was readmitted with new skin lesions, diffuse and severe abdominal pain and malaise. A laboratory work-up revealed elevated erythrocyte sedimentation rate

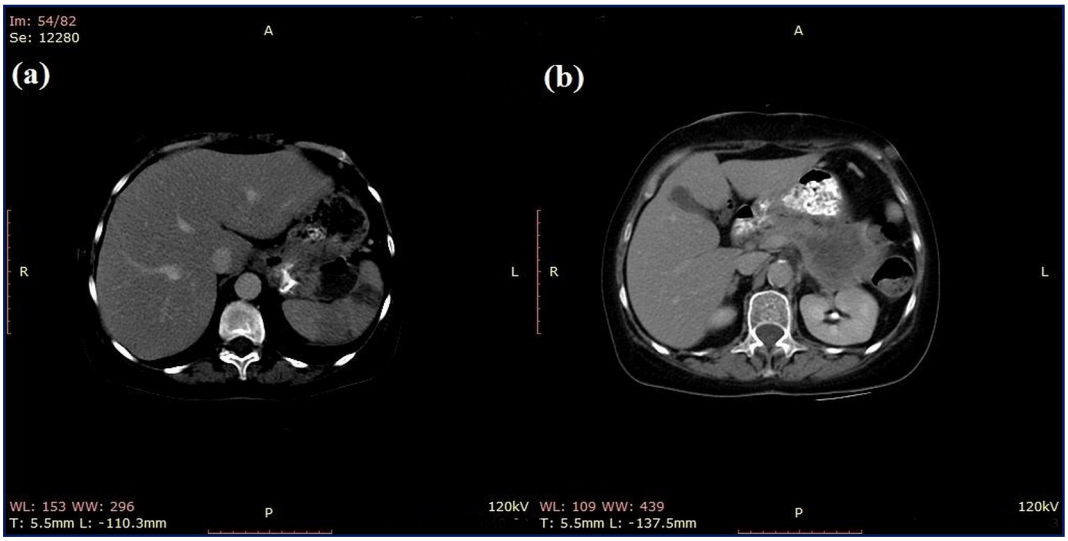

Figure 3
MRI – Computed tomography image showing multiple small, splenic abscesses and an abscess in the peripancreatic space.

and C-reactive protein, thrombocytosis, anemia, leukocytosis, hypoproteinemia and hypoalbuminemia. The abdominal pain became more pronounced, a surgical consult diagnosed a bowel infarction with peritonitis and the patient was surgically treated by partial resection of the small bowel. Four days after surgery an anastomotic dehiscence occurred and the patient was treated by right hemi-colectomy. The anastomotic dehiscence occurred again seven days later, the patient developed generalized peritonitis and died despite surgical and antibiotic treatment.

Discussion

We performed a search on PubMed with the terms "pyoderma gangrenosum", "spleen" and "splenic" and restricted the papers to those published in English or French. We selected all case reports of PG associated with aseptic splenic involvement. Aditional articles were identified using the reference lists of the identified papers. We have found nine reported cases[3-11]; the clinical information of the cases including ours is summarized in Table 1.

Epidemiology

Epidemiological data regarding PG is based mostly on case reports and cohort studies. Visceral involvement with sterile neutrophilic infiltrates in sites other than the skin is rare in PG, and splenic involvement is rarer. We found only 9 cases reported in the literature, our case being the tenth. Recent studies suggested that the disease affects predominantly middle aged women but may occur at any age.[12] The female-to-male ratio has been estimated to 1.44, 1.21 and 3.12.[13,14] In discordance with this we found that 6 out of 10 cases with splenic involvement were men. Regarding age, our findings are consistent with those reported by the literature, the mean age being 45.1 but age ranged between 8 and 82 years, supporting the idea that PG can affect any age.

Table 1. Summary of 10 patients with splenic manifestations of pyoderma gangrenosum regarding epidemiology, clinical picture, treatment, and prognosis.

Patient No.	Age	Sex	Distribution	Onset	Diagnosis	Duration from onset to diagnosis	Treatment	Outcome	Underlying disorder	Other neutrophilic dermatosss	Ref.
1	39	female	Skin, spleen, lymph node	Lymph node, spleen		6 years	Dapsone 100 mg/day Corticosteroid therapy 1.5 mg/kg/day	No reccurence	IgA paraproteinemia	Sneddon Wilkinson	Dallot *et al.*
2	73	male	Liver, spleen, skin	Liver, spleen, bones	Ultrasound, bacterial culture from spleen aspirate, bone scintigraphy, skin biopsy	40 days	Prednisone 1 mg/kg/day Cyclosporin 4 mg/kg/day	No reccurence	Chronic myelomonocytic leukaemia	No	Vadillo *et al.*

3	28	female	Eye, skin, liver, spleen	Eye (nodular scleritis, left orbital inflamation)	Skin biopsy, abdominal and chest CT, brain and orbit CT and MRI	1 year	Prednisone 60 mg/day Cyclosporin 300 mg/day	No reccurence	NA	No	Miserocchi E *et al.*
4	46	male	Skin, spleen	Skin	Skin biopsy, abdominal US, CT	NA	Prednisone 1 mg/kg/day Cyclosporine 5 mg/kg/day	No reccurence	IgA gammopathy	No	Mijuskovic *et al.*
5	27	male	Skin, spleen, psoas muscle	Skin	Skin biopsy, abdominal US, CT, bacterial culture from spleen aspirate, muscle magnetic resonance	NA	Unresponsive to Prednisone, MTX, Cyclosporine, Mycophenolate mofetil, dapsone, Etanercept 3x25 mg/week Responsive to Infliximab 5 mg/kg, Adalimumab 40 mg/week	No follow-up	NA	No	Hubbard *et al.*
6	68	male	Skin, spleen	Skin	Skin and spleen biopsy, abdominal CT scan	NA	Prednisone	No reccurence	Multiple myeloma	No	Brahimi *et al.*
7	82	male	Skin, spleen	Skin	Skin biopsy, torax and abdominal CT scan, spleen biopsy	10 days	Prednisone 1 mg/kg/day	No reccurence	NA	Sneddon Wilkinson	Audemard *et al.*
8	8	male	Skin, spleen, lungs	Skin	Skin biopsy, MRI of head, thorax, abdomen	2 weeks	Prednisone 30 mg/day Cyclosporin 5 mg/kg/day Infliximab iv 5 mg/kg Adalimumab 40 mg every 2 weeks	Skin and splenic reccurences before Adalimumab	NA	No	Allen *et al.*
9	22	female	Skin, spleen, kidney	Skin	Skin biopsy, skin culture, abdominal US and MRI, culture from spleen aspirate, renal biopsy, culture from renal aspirate	4 months	Corticosteroid, Cyclosporine Sulfasalazine	Reccurence upon tapering	NA	No	De Carvalho
10	58	female	Skin, spleen, eye, peripancreatic space	Skin	Skin biopsy, skin culture, abdominal US, CT	6 months	Dexamethasone 8 mg/day, Prednisone 0.5 mg/kg/day Dapsone 150 mg/day	Skin and eye reccurence; Death	NA	No	Present case

Etiology

The exact etiology of PG is not known, but approximately 50% of cases are associated with an underlying systemic disease.[15] This proves to be true in case of PG with splenic involvement too, in 4 of the cases an underlying disorder being present. IgA gammopathy was present in two cases, while chronic myelomonocytic leukemia and multiple myeloma has been diagnosed in single cases. In two cases PG was associated with other neutrophilic dermatoses, namely with Sneddon-Wilkinson disease.

Clinical picture

PG may vary in clinical presentation and course. The typical skin lesion starts as a sterile pustule that rapidly enlarges due to tissue necrosis; painful ulcers then develop, with undermined violaceous borders and purulent cover. The lesions can affect any part of the body, but are seen most often on the lower part of the legs. Although extracutaneous manifestations are unusual in PG, visceral complications can occur, the lung being the most frequently involved.[15] The chronology is variable: visceral involvement can appear before, simultaneously or after cutaneous manifestations develop.[2] When visceral involvement appears before the typical skin lesions, the diagnosis may be delayed.

Our review showed that skin manifestations of PG were present before splenic involvement in 7 out of 10 cases. Only 3 patients with splenic changes before appearance of skin lesions have been described.[3,4,5] The splenic lesions can be asymptomatic or present with fever, abdominal pain and splenomegaly. From the 10 reviewed cases, 3, including the reported case, were completely asymptomatic,[6,8] one presented only with splenomegaly without symptoms,[9] one presented fever and splenomegaly,[3] one fever and malaise,[10] 3 patients presented fever with abdominal pain[4,5,7] and one presented fever, abdominal pain and splenomegaly.[11] Our patient had cutaneous manifestations before the diagnosis of splenic involvement was made and splenic lesions were asymptomatic. The presence of splenic abscesses was an incidental finding on the abdominal US which was prescribed in order to rule out an underlying disorder, and was confirmed by abdominal CT scan. Besides the splenic abscesses our patient presented a large abscess in the peripancreatic space. The clinical presence of the pre-existing skin lesions confirmed to be PG by skin biopsy combined with the rapid response to steroids and Dapsone lead to the diagnosis of aseptic abscesses inside of PG.

Investigations

In the reviewed cases imaging techniques and skin biopsy were used for the diagnosis in all patients, spleen culture was performed in 3 of the cases, while spleen biopsy was used in 3 cases.

Abdominal echography and abdominal CT scan showed in all of the cases multiple abscesses in the spleen. Fine needle aspiration, performed in 3 cases[4,7,11] revealed purulent fluid, but cultures for aerobic and anaerobic bacteria, fungi and mycobacteria were negative. Histopathologic assessment was performed in 3 cases,[3,8,9] but the findings were not specific, the main finding being predominant neutrophil infiltration, similar to those observed in skin biopsy specimens. The histopathologic assessment helps, however, in the differential diagnosis with other diseases as tumors, infections, and vasculitis.

Treatment

The treatment of PG is usually based on immunosuppression.[16] Although no randomized controlled trials have been performed, systemic corticosteroids have been the mainstay of treatment and typically, a rapid response is observed within days to weeks. In combination with steroids or in resistant cases, other immunosuppressant agents may be used, such as cyclosporine A, azathioprine, methotrexate, or mycofenolatemofetil. Dapsone can also be used in the treatment of PG and help reduce exposure to corticosteroids. Cyclophosphamide is used in severe, non-responsive cases and intravenous immunoglobulins may be an option for flares, especially in pregnant women.[17] Biological agents such as infliximab have shown promising results, a rapid and significant improvement of cutaneous PG being described in one randomized, double blinded, placebo-controlled trial.[16]

Three of the reviewed cases of PG with splenic involvement responded well to corticosteroids alone;[3,8,9] in other three cases corticosteroids associated with cyclosporine led to a good response;[4,5,6] in one case sulfasalazine was added to corticosteroids and cyclosporine.[11] Two of the reviewed cases were nonresponsive to corticosteroids and other suppressive agents.[7,10] Infliximab was tried, with good response in one of the cases;[7] unfortunately the patient developed an allergic reaction to the product, precluding further infusions; subcutaneous Etanercept was of no benefit over a 3-week period and hence Adalimumab was commenced with great improvement. The second patient receiving Infliximab developed new lesions during the treatment so Adalimumab was tried with good results.[10]

Our case showed good improvement to corticosteroids associated with dapsone. The skin lesions healed, leaving cribriform scars, the ocular inflammation plummeted, and the laboratory work-up showed the normalization of the abnormal values and imaging showed the disappearance of the abdominal abscesses. Unfortunately, the disease became active 4 months after tapering of the doses, and the outcome was unfavorable due to the development of bowel infarction of unknown etiology.

Conclusions

PG is a rare neutrophilic disease that primarily affects the skin. Cases of PG with visceral involvement, consisting of a sterile neutrophilic infiltrate in sites other than skin and/or mucous membranes, are rare. Spleen involvement is a very

rare condition and only nine cases were described previously in the literature, our case being the tenth. Our review showed that spleen involvement in PG can occur at any age and seems to be more frequent in men. An underlying disorder can be present, as well as the association with other neutrophilic diseases. Regarding clinical picture, skin manifestations were usually present before splenic involvement, and the last one can be asymptomatic or present with fever, abdominal pain and splenomegaly. The diagnosis of spleen manifestations is usually made in the presence of typical cutaneous findings, by imaging techniques; rarely, especially in the absence of skin lesions, spleen cultures or spleen biopsy are used. Spleen manifestation is, however, a diagnostic challenge and ruling out other conditions, such as malignancies, infections or vasculitis is mandatory. Most of the cases associated with spleen involvement respond well to steroids associated or not with other supressive agents. Biological agents, such as infliximab or adalimumab may be considered in non-responsive cases.

Acknowledgement — this work was partially supported by the Iuliu Haţieganu University of Medicine and Pharmacy Internal Grant No. 4945/8/08.03.2016.

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