CASE REPORT

# *LPIN2* gene mutation in a patient with overlapping neutrophilic disease (pyoderma gangrenosum and aseptic abscess syndrome)

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Neutrophilic disease encompasses a spectrum of conditions characterized by neutrophilic aseptic inflammation in the skin and internal organs. The prototype of this group is pyoderma gangrenosum (PG); however, the existence of transitional and overlap forms is always a consideration when facing patients with autoinflammation.[1] We report on a patient with overlapping neutrophilic disease with a novel mutation in a gene involved in autoinflammation.

*Abbreviation used:*
PG: pyoderma gangrenosum

## CASE REPORT

A previously healthy 44-year-old Italian man had an elective circumcision because of chronic phimosis of the penis presented with nonhealing ulcer of the glans (Fig 1, upper left panel) and ulcers of the lower abdomen (Fig 2, upper left panel). Biopsy of the penis found a diffuse neutrophilic infiltrate (Fig 1, upper right panel). Concomitantly, the patient had draining abscesses on the arms and torso (Fig 2, upper right panel). A skin biopsy of one of these abscesses found diffuse dermal and subcutaneous neutrophilic infiltrate. Microbiologic tissue cultures for bacteria, fungi, and mycobacteria were all negative. He also complained of intermittent subjective fever and mild shortness of breath. Computed tomography of the chest (Fig 2, lower left panel) showed the presence of cavitations, but tubercolin skin test and QuantiFERON gold (Qiagen, Germantown, MD) were both negative. The patient was referred to our institution for further evaluation. Because previous infection workup was negative, a diagnosis of PG associated with aseptic abscess syndrome was made. The negativity of circulating antineutrophil cytoplasmic antibodies made the diagnosis of granulomatosis with polyangiitis unlikely. Upper and lower endoscopy did not show evidence of colitis. Other conditions presenting with skin ulcers were ruled out by the absence of monoclonal components, lupus anticoagulant, anti−$\beta$2-glycoprotein I antibodies and antistreptolysin antibodies. Because PG and aseptic abscess syndrome are included within the group of autoinflammatory diseases, most commonly defective autoinflammatory genes were tested using Ion AmpliSeq Designer (Thermo Fisher, Waltham, MA), which found a nonsynonymous variant of *LPIN2* gene (region V140I rs7510224451).

Because of the aggressive clinical presentation of this patient, infliximab was started (5 mg/kg on weeks 0, 2, and 6) in combination with systemic corticosteroids. Despite this approach, penile lesions continued to rapidly progress. Pulmonary cavitations were also recalcitrant. Therefore, therapy was

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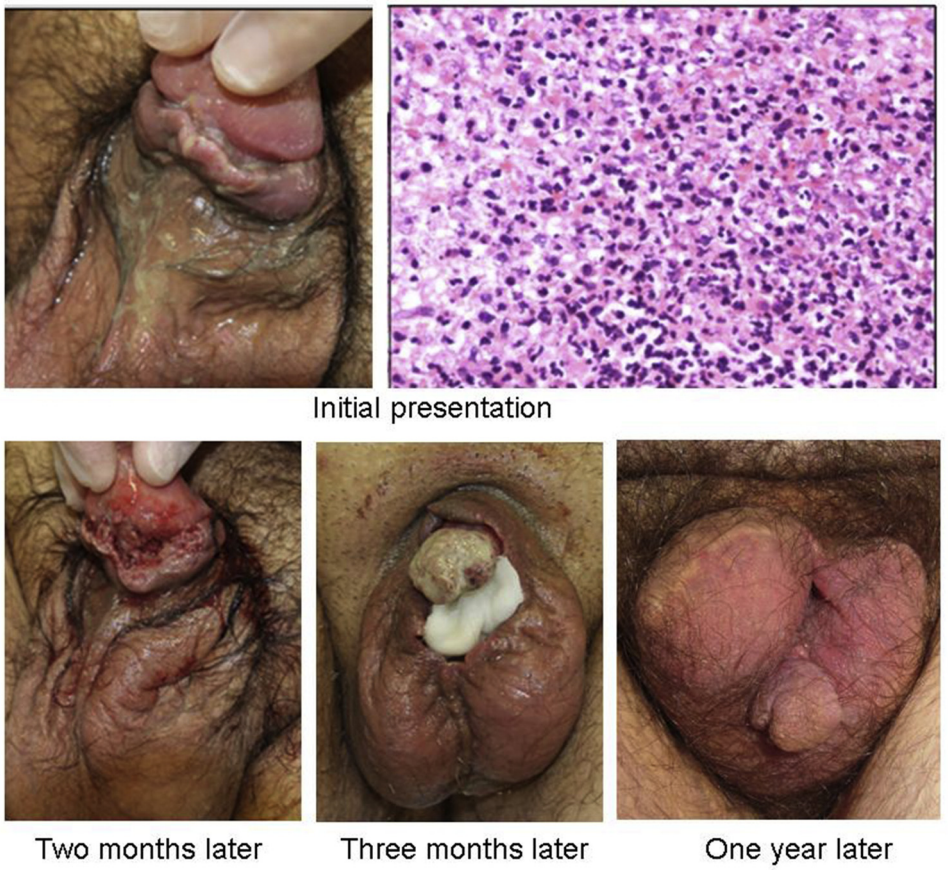


**Fig 1.** PG of the penis. Upper panels show clinical picture at presentation (left) and histology showing a dense neutrophilic infiltrate (right). Lower panels show different stages throughout the course of the disease and healing of large penile ulcer.

switched to intravenous methylprednisolone (1 mg/kg/d for 10 days) noticing improvement of the skin and pulmonary manifestations (Fig 2, lower right panel). Unfortunately, the penis was already widely damaged (Fig 1, lower panels). Subsequently, systemic steroids were switched to oral form with complete resolution after 3 months of treatment.

## DISCUSSION

The clinical presentation of this patient was challenging, as the main findings were polymorphic skin lesions in combination with pulmonary abnormalities complicated with initial lack of response to standard of therapy. The most likely entity to include all these clinical features would be PG associated with aseptic abscess syndrome. This diagnosis is different from PG with pulmonary involvement, as the presence of deep abscesses favored the latter association. Aseptic abscess syndrome is an autoinflammatory disease with fever, abdominal pain, and deep abscesses with predilection for the spleen. Skin lesions are present in 20% of the cases and are mainly cutaneous abscesses and neutrophilic dermatoses.[2] It is genetically characterized in association with genetic modifications in NOD2/CARD15 and CD2BP1/PSTPIP1.[3,4]

Our patient had a neutrophilic disease with polymorphic cutaneous involvement (classic PG, mucosal PG, cutaneous abscesses) and pulmonary involvement (cavitations) in association with *LPIN2* nonsense variant. Interestingly, *LPIN2* homozygous mutations have been linked to another autoinflammatory syndrome with familial cases of chronic osteomyelitis (Majeed syndrome),[5] and this gene seems to be also playing a role in SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis).[6] *LPIN2* encodes lipin2, which is involved in inflammation modulating apoptosis of polymorphonuclear cells. Interleukin-1 blockade is efficacious in the treatment of Majeed syndrome, supporting the hypothesis of *LPIN2* mutations being associated with increased inflammasome activity and interleukin-1 release.[7]

This was a unique case of ulcerative and mucosal PG associated with aseptic abscesses compromising skin and lungs. Our findings are different from those

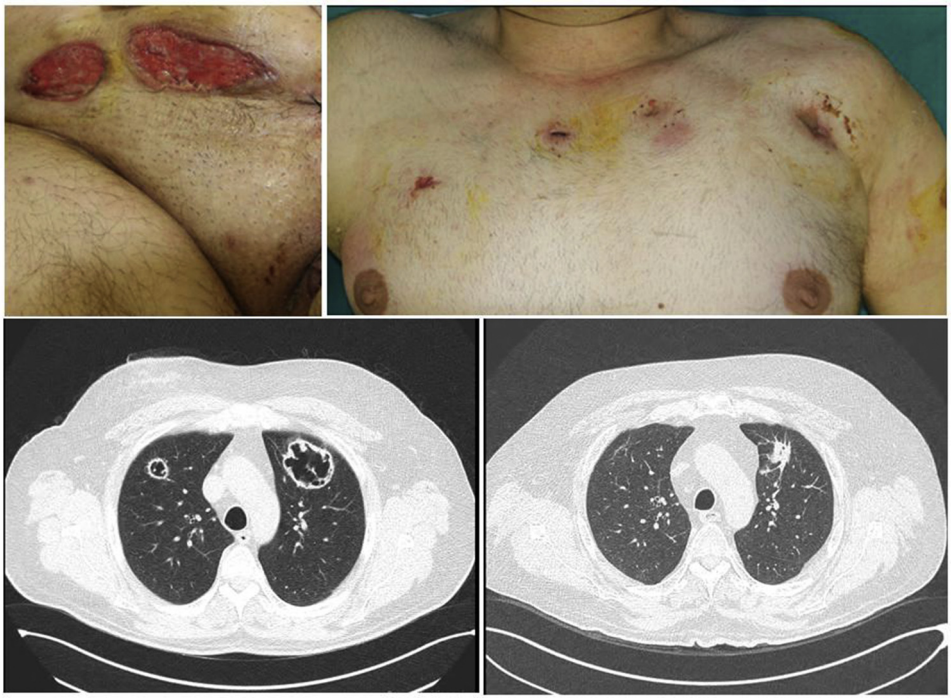

**Fig 2.** Upper panels show ulcerative PG of the lower abdomen (left) and aseptic abscesses of the torso and arms (right). Lower panels show evident cavitations on CT scan of the chest at presentation (left) and their resolution after treatment with systemic immunosuppression (right).

of the previous reports, as a simultaneous assessment of 10 classic autoinflammatory genes was carried out. This variation of *LPIN2* may play a role in the pathogenesis of overlapping clinical manifestations of neutrophilic diseases.

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