

A novel *NFκB1* mutation linking pyoderma gangrenosum and common variable immunodeficiency



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Key words: dermatoses; genetics; immunodeficiency; inflammatory; neutrophilic; pyoderma gangrenosum; ulcers.

INTRODUCTION

Pyoderma gangrenosum (PG) is a sterile neutrophilic dermatosis manifesting as painful inflammatory plaques and ulcers, frequently associated with inflammatory bowel disease, rheumatoid arthritis, myelodysplastic syndrome, and acute myeloid leukemia.¹ We present a case of a young woman with a novel mutation in *NFκB1* who experienced common variable immunodeficiency (CVID) and severe recurrent PG episodes.

CASE REPORT

A 24-year-old woman with CVID treated with intravenous immunoglobulin presented with fever, leukocytosis, and painful dehiscence of incision sites following laparoscopic cholecystectomy. Across her abdomen were 5 deep ulcers with violaceous undermined borders (Fig 1). Histopathology revealed dense neutrophilic infiltrates, and cultures for bacteria, fungi, and acid-fast bacilli were negative, altogether consistent with a diagnosis of PG. Treatment with prednisone 1 mg/kg/day resulted in clinical improvement, but after 1 week, the patient developed posterior reversible encephalopathy syndrome. Prednisone was discontinued, and infliximab 5 mg/kg every 8 weeks was started, leading to resolution of lesions by the fourth infusion. Given her presentation of severe PG at a young age with coexisting immunodeficiency, exome sequencing was completed, which revealed a likely pathogenic

Abbreviations used:

CVID: common variable immunodeficiency
 NF-κB: Nuclear-factor kappa B
 PG: pyoderma gangrenosum

variant in *NFκB1* (C.A2415G, p.Q805Q), which she shared with her unaffected father.

Years later, she was in a motor vehicle accident resulting in a left scaphoid fracture, and she developed a 30-cm undermined ulcer on the lower abdomen with purulent drainage (Fig 1). Biopsy again showed PG. Prednisone 50 mg (0.5 mg/kg), infliximab 500 mg (5 mg/kg), and 0.05% clobetasol resulted in abdominal ulcer resolution; however, infliximab treatment was complicated by debilitating arthralgias.

The patient's third episode of PG occurred after surgical repair of her scaphoid fracture. She developed fever, pain, and a purulent ulcer at the site of the surgical wound consistent with PG (Fig 2). Biopsy was deferred in the setting of PG history and pathergy risk. She was managed with a brief course of cyclosporine (5 mg/kg) twice a day with lower-dose prednisone 0.2 mg/kg/day, resulting in full healing of the surgical site.

DISCUSSION

The pathophysiology of PG is poorly understood, but increasing evidence supports the role of genetics

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;18:61-3.
 2352-5126

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<https://doi.org/10.1016/j.jidcr.2021.10.015>



Fig 1. Initial presentation of first and second PG episodes. Left: In the first pyoderma gangrenosum episode, the patient presented with 5 purulent ovaloid ulcers with pink-red margins and ragged undermined borders. Right: In her second pyoderma gangrenosum episode, she presented with a pink-red plaque containing a left-sided irregular 8 × 3-cm ulcer with purulent drainage.



Fig 2. Third pyoderma gangrenosum episode. Left: The patient presented with an evolving lesion with focal edema and pink-red margins at the surgical site with purulent debris. Right: Healing of the pyoderma gangrenosum lesion after initiation of cyclosporine and low-dose prednisone.

in PG pathogenesis. Most commonly associated with *PSTPIP1*, *MTHFR*, and *JAK2* mutations, PG typically presents in middle-aged women and rarely co-occurs with immunodeficiency.¹⁻⁴

We describe a young woman in her early 20s with CVID and PG linked to a novel, heterozygous *NFκB1* variant. *NFκB1* in the nuclear-factor kappa B (NF-κB) pathway encodes the p105 protein, which is processed to generate the p50 transcription factor that then activates the NF-κB cascade central to immune function.⁵ *NFκB1* mutations are known to cause CVID,

primarily through a loss of function of the p50 subunit.³ Studies demonstrate that the absence of a properly functioning NF-κB protein disrupts the expression of the cytidine deaminase gene, resulting in defective class-switch recombination.³ Furthermore, *NFκB1* deficiency can lead to defective B and T cells, generating hypogammaglobulinemia.⁵

Emerging evidence suggests that *NFκB1* mutations exhibit a more diverse phenotypic profile than previously thought, including autoinflammatory episodes such as aphthae, febrile attacks, and

small-vessel vasculitis.^{3,5,6} Recently, there have been increasing reports of concurrent CVID and PG linked to *NFκB1* mutations. To our knowledge, there are 3 such cases in the literature.⁶ All 3 patients were middle-aged or elderly at PG onset; 2 individuals developed PG that resolved with intravenous immunoglobulin, while the other developed PG of unclear severity that did not respond to etanercept.^{6,7}

Several studies have elucidated the relevance of NF-κB signaling in PG development. For instance, wild type NF-κB protein regulates the nucleotide-binding leucine-rich repeat (NLR) family pyrin domain containing 3 (NLRP3) inflammasome, and a loss of regulation results in hyperactivation of this inflammasome, the mechanism underlying many autoinflammatory diseases.⁵ Some *NFκB1* mutations deplete both p50 and p105, resulting in excessive Interleukin 1 beta secretion, inflammasome activation, and extreme pathergy-like responses (familial autoinflammatory necrotizing fasciitis) to minor trauma.^{5,8} Additionally, *NFκB1*-deficient mice demonstrate enhanced neutrophil recruitment, which may also drive the hyperinflammation seen in PG.^{9,10}

Our case is unique because this is the first reported patient with a novel *NFκB1* mutation who developed severe, recurrent PG episodes with coexisting immunodeficiency at a young age. In contrast to prior reports, our *NFκB1* variant is located 2 base pairs 5' to the end of exon 21, with *in silico* analysis predicting complete obliteration of normal splicing.⁵ Unidentified modifier genes and environmental exposures may explain the variable penetrance and expressivity, as the father remains unaffected without CVID, recurrent and chronic infections or PG. We were unable to perform maternal sequencing. Our case expands the phenotypic landscape of *NFκB1* mutations to include severe,

recurrent PG at a young age and further supports the association between NF-κB pathway dysregulation and CVID and PG pathogenesis.

We would like to thank the Yale Center for Mendelian Genomics for their assistance in genetic analysis.

Conflicts of interest

None disclosed.

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