DOI: https://doi.org/10.3126/njdvl.v21i2.56528

# Pyoderma Gangrenosum with Neurofibromatosis: Understanding a Possible Relationship and Identifying Risk with Immunosuppressants

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## Abstract

Association of pyoderma gangrenosum with neurofibromatosis is extremely rare; only one case has been reported so far. We present one such patient, who also developed bone marrow suppression after treatment with Azathioprine, and reported an acute onset of Telogen Effluvium. The rare association of these two seemingly unrelated conditions and the need to be vigilant about the possibility of myelosuppression with azathioprine presenting as sudden onset, severe alopecia is highlighted.

**Key words:** Azathioprine, Neurofibromatosis, Pyoderma Gangrenosum, Telogen Effluvium

## Introduction:

Neurofibromatosis is a neuro-cutaneous disorder with multi-system involvement. Pyoderma Gangrenosum is an ulcerative disease classified under neutrophilic disorders. Though idiopathic most often, it can be associated with other collagen vascular diseases like Rheumatoid arthritis and malignancies like leukemias and lymphomas. Association of these two seemingly contrasting and unrelated conditions is extremely rare, with only one report in literature so far.[1] Our patient was one such, who also developed bone marrow suppression after treatment with Azathioprine. He presented with an acute onset of Telogen Effluvium after two weeks of starting treatment. The probable pathway leading to the rare association is being discussed, and the need to be vigilant about the possibility of myelosuppression with Azathioprine in these patients is highlighted.

## Case report:

A 44-year-old male patient presented with multiple non-healing ulcers over his right leg for 1 month. Three months before the presentation patient had developed two blisters which broke down to form ulcers over his right leg. There was no history of trauma. In view of a past history of venous ulcers, in the other leg that had healed after split skin grafting (SSG) and perforator ligation, the same procedure was attempted on the right leg a month ago. Seven days after discharge, the patient noticed blisters which burst to reveal ulcers at the margins of the SSG and perforator ligation sites which progressively increased in size to 5 x 5 cm. The surgeons debrided the ulcers and put him on Amikacin, Amoxycillin + Clavulanate. However, since there was no improvement, a dermatology consultation was sought. There was no history of gastrointestinal complaints, joint pains, weight loss, decreased appetite, recurrent infections or bleeding manifestations. There was a history of painless swelling on the skin since the age of 15 which had not been evaluated. On further probing there was no history of consanguinity or no similar history in the family.

On examination, there were three ulcers of approximately 3x3 cm around the graft site on the posterior aspect of the right leg and one ulcer of size 5x5 cm on the medial aspect of the right leg. The ulcers were oval in shape with well-defined, undermined,

**Funding:** None
**Conflict of Interest:** None

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**Date of Submission:** 25th June 2023
**Date of Acceptance:** 30th August 2023
**Date of Publication:** 1st October 2023

**How to cite this article**

Noronha M, Aithal V. Pyoderma Gangrenosum with Neurofibromatosis: Understanding a possible relationship and identifying risk with immunosuppressants. NJDVL 2023;21(2): 35-38. https://doi.org/10.3126/njdvl.v21i2.56528

violaceous borders with surrounding erythema. The base of the ulcers were covered with red exuberant granulation tissue and pus. These ulcers were distinctively suggestive of Pyoderma Gangrenosum (Fig 1).

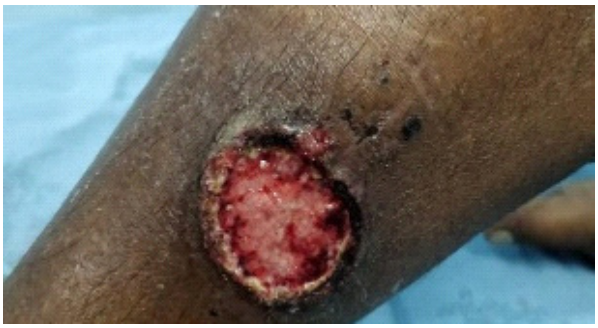

**Fig.1** Pyoderma Gangrenosum ulcer over medial aspect of right leg

Insignificant regional lymphadenopathy was noted. Pathergy test with an insulin syringe and normal saline was done, it showed a 2x2 mm skin-coloured papule at injection site.

Multiple soft to firm subcutaneous swellings suggestive of neurofibromatosis were noted (Fig 2).

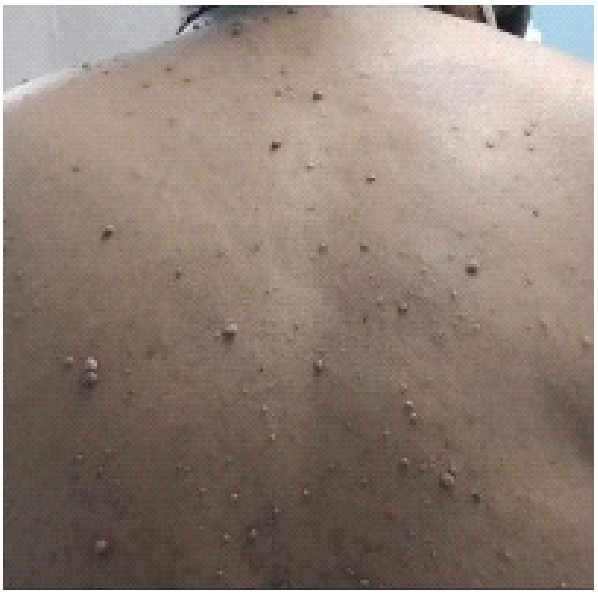

**Fig.2.** Multiple pedunculated Neurofibroma over upper and lower back

Patient had axillary freckling (Crowe's sign), Lisch nodules and palmoplantar freckling. Neurological and audiological examination was normal. There was no evidence of optic glioma or bony dysplasia. Other systems including skeletal (sphenoid,long bones and vertebra), renal and cardiac were within normal limits. Clinically, there was no evidence of internal malignancy. The patient's total count and other blood investigations including biochemical profile were within normal limits. Serology for Hepatitis B and C and HIV-1 and 2 were negative. The wound swab initially grew Enterobacter *cloacae* which resolved on treatment with intravenous Ciprofloxacin 400mg twice daily and Clindamycin 600mg thrice daily for seven days. Repeat cultures were negative.He also received Colchicine 0.5mg twice daily.

An incison biopsy of the ulcer edge showed ulceration covered by granulation tissue and fibropurulent exudate. Marked mixed inflammatory infiltrate with neutrophilic micro abscess formation and ill-formed macrophage clusters were noted (Fig 3).

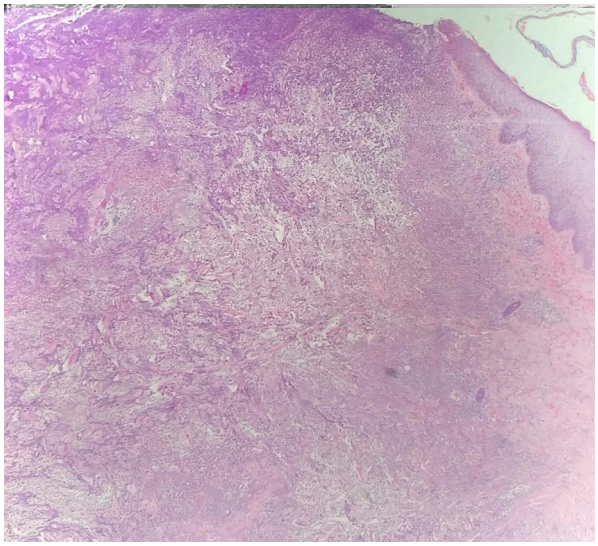

**Fig 3.** Histopathology of the ulcer edge(H&E section) at 40 X magnification

Our patient hence fulfilled Maverakis criteria for Pyoderma Gangrenosum (Table 1) and National Institutes of Health (NIH) criteria for neurofibromatosis type 1 (Table 2).

| Table 1: Pyoderma Gangrenosum- Maverakis criteria[2] in our patient | |
|---|---|
| Major criteria | |
| Biopsy from the ulcer edge showing neutrophilic infiltrate | Present |
| **Minor criteria** | |
| Exclusion of infection | Present |
| Positive pathergy | Present |
| History of inflammatory bowel disease or inflammatory arthritis | Absent |
| History of papule, pustule, or vesicle ulcerating within 4 days of appearing | Present |
| Peripheral erythema, undermining border, and tenderness at ulceration site | Present |
| Multiple ulcerations, at least 1 on anterior lower leg | Present |
| Cribriform or "wrinkled paper" scar(s) at healed ulcer sites | Present |
| Decreased ulcer size within 1 month of initiating immunosuppressive medication(s). | Present |

**Table 1.** Pyoderma Gangrenosum- Maverakis criteria

| Table 2: Neurofibromatosis Type 1- National Institutes of Health(NIH) criteria[3] in our patient | |
|---|---|
| 6 or more café-au-lait macules (>0.5 cm in children or >1.5 cm in adults) | Absent |
| 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibromas | Present |
| Axillary or groin freckling | Present |
| Optic pathway glioma | Absent |
| 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination) | Present |
| Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis) | Absent |
| First degree relative with NF1 | Absent |

**Table 2: Neurofibromatosis Type 1- National Institutes of Health (NIH) Criteria**

Patient was given Injection Dexamethasone 4mg three times daily, along with Azathioprine 50 mg twice daily. After three weeks, ulcers seemed to be healing well (Fig 4).

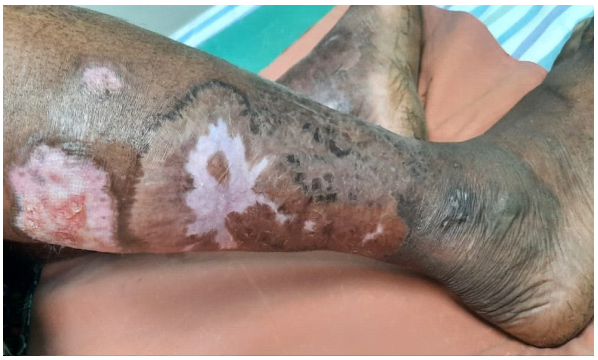

**Fig 4.** Almost completely healed ulcers in 3 weeks

He however complained of sudden onset diffuse hair loss (Fig 5).

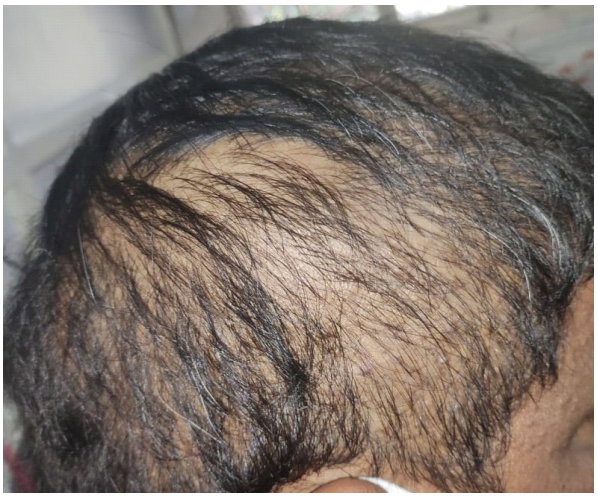

**Fig 5.** Sudden onset alopecia following Azathioprine

Trichogram showed almost 50% of the hairs to be in telogen phase. This prompted us to consider this as an early marker of myelotoxicity. Investigations showed a significant drop in total leucocyte and platelet counts. Hence, Azathioprine was immediately stopped. Patient refused admission and further investigations, citing financial constraints. He did not come for follow-up subsequently.

## Discussion:

Pyoderma Gangrenosum is a neutrophilic dermatosis, often associated with other conditions like Rheumatoid arthritis, Ulcerative colitis, malignancies like acute Myelocytic Leukemia. There is only one case report of Pyoderma Gangrenosum in association with Neurofibromatosis reported so far.[1] Both Pyoderma Gangrenosum and Neurofibromatosis can be associated with an underlying malignancy.[4,5] While looking at the possible aetiology, JAK pathway appears to be common in the pathogenesis of both Pyoderma Gangrenosum and Neurofibromatosis. A mutation affecting Janus kinase (JAK) 2, a non-receptor tyrosine kinase involved in signalling via several cytokines, including the granulocyte monocyte colony-stimulating factor (GMCSF) receptor family, has been reported in Pyoderma Gangrenosum.[6] Neurofibromin 1 (encoded by the NF1 gene) downregulates RAS activation. Neurofibromatosis type 1 has a loss of function mutation in NF1 and has a 200 to 500-fold increased risk of juvenile Myelomonocytic leukaemia. Leukaemia cells from patients with juvenile Myelomonocytic leukaemia display hypersensitivity to certain cytokines, such as granulocyte-macrophage colony-stimulating factor. The granulocyte-macrophage colony-stimulating factor receptor utilizes pre-associated JAK2 to initiate signals after ligand binding. JAK2 subsequently activates STAT5, among other downstream effectors. Although STAT5 is thought to mediate growth factor signalling in myeloid leukaemia, the contribution of STAT5 to the development of hyperactive RAS-initiated myeloproliferative disease has not been well described.[7]

Diffuse non patterned alopecia is considered to be a hallmark indicator of myelosuppression. There is mutation in the TPMT and NUDT 15 genes, which affect the metabolism of purine analogues like Azathioprine.[8] Our patient showed Telogen effluvium, which on investigation revealed leukopenia and anaemia. Even though TPMT genes did not show any mutation, we could not perform NUDT 15 gene analysis, since it was not available. Whether this was the cause of myelosuppression after Azathioprine, in the background of Neurofibromatosis, needs to be further explored.

**Conclusion:**

Apparently unrelated dermatoses such as Neurofibromatosis and Pyoderma Gangrenosum can co-exist and share a common pathway related to JAK2 and GMCSF. Such patients should be followed up regularly for malignancy. Such patients could be prone to other gene mutations, and could develop serious adverse effects of metabolism of chemotherapeutic drugs.

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