*Case Report*

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# PYODERMA GANGRENOSUM WITH NON-PSEUDOMONAL ECTHYMA GANGRENOSUM IN MYELODYSPLASTIC SYNDROME TREATED WITH ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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## Abstract

**Background**: Co-occurrence of pyoderma gangrenosum (PG) and ecthyma gangrenosum (EG) pose diagnostic and therapeutic challenges in immunocompromised patients.

**Case Report**: A 47-year-old Filipino woman with transfusion-dependent intermediate-risk myelodysplastic syndrome (MDS) was admitted to our institution for allogeneic hematopoietic stem cell transplantation (HSCT). During the preparation for allogeneic HSCT, she developed several erythematous ulcerated lesions on the lower extremities, which were initially managed as PG. Subsequent febrile episodes and worsening lesions with isolated *Escherichia coli* in blood and tissue cultures lead to the diagnosis of EG complicating PG. She was treated through targeted antibiotics, wound debridement, and proper wound care. After the resolution of the infection and upon starting low-dose immunosuppression followed by allogeneic HSCT, her left leg lesions showed progressive improvement. Six months after HSCT, lesions were completely resolved with complete epithelialization.

**Conclusion**: This case highlights the importance of accurate diagnosis and integrated management of complex conditions like PG and EG in immunocompromised patients. The successful resolution of lesions post-HSCT underscores the potential curative role of stem cell transplantation in managing MDS-associated PG.

**Key words** myelodysplastic syndrome, pyoderma gangrenosum, ecthyma gangrenosum, hematopoietic stem cell transplantation

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## Introduction

Pyoderma gangrenosum (PG) is an inflammatory, non-infectious ulcerative skin condition requiring immunosuppressive therapy[1-6]. Ecthyma gangrenosum (EG) is an infectious, ulcerative skin condition often associated with bacterial infection requiring antibiotics and surgical debridement[7,8]. Co-occurrence of PG and EG complicates diagnosis and management, especially in immunocompromised patients[9].

## Case Report

A 47-year-old Filipino woman presented with a 1-year history of easy fatigability in March 2020. Her comorbidities included Type 2 Diabetes Mellitus with good control, Hypertension stage 2, and past Hepatitis B infection. Initial workup showed pancytopenia with hemoglobin ranging from 40-60 g/L, white blood cells 2-3 $\times$ $10^9$/L, and platelets 10-30 $\times$ $10^9$/L. Bone marrow studies revealed hypocellular marrow with trilineage hematopoiesis without significant blasts. Fluorescence in situ hybridization (FISH) was negative for chromosomal abnormalities: 5q-, -5, 7q-, -7, 20q- and +8, suggesting at least a normal karyotype, despite the unavailability of karyotyping at that time. She was diagnosed with intermediate-risk myelodysplastic syndrome (MDS) (IPSS-R 3.3). After treatment with lenalinomide, azacitidine, decitabine, and eltrombopag in the past 2 years, she remained transfusion-dependent, lead-

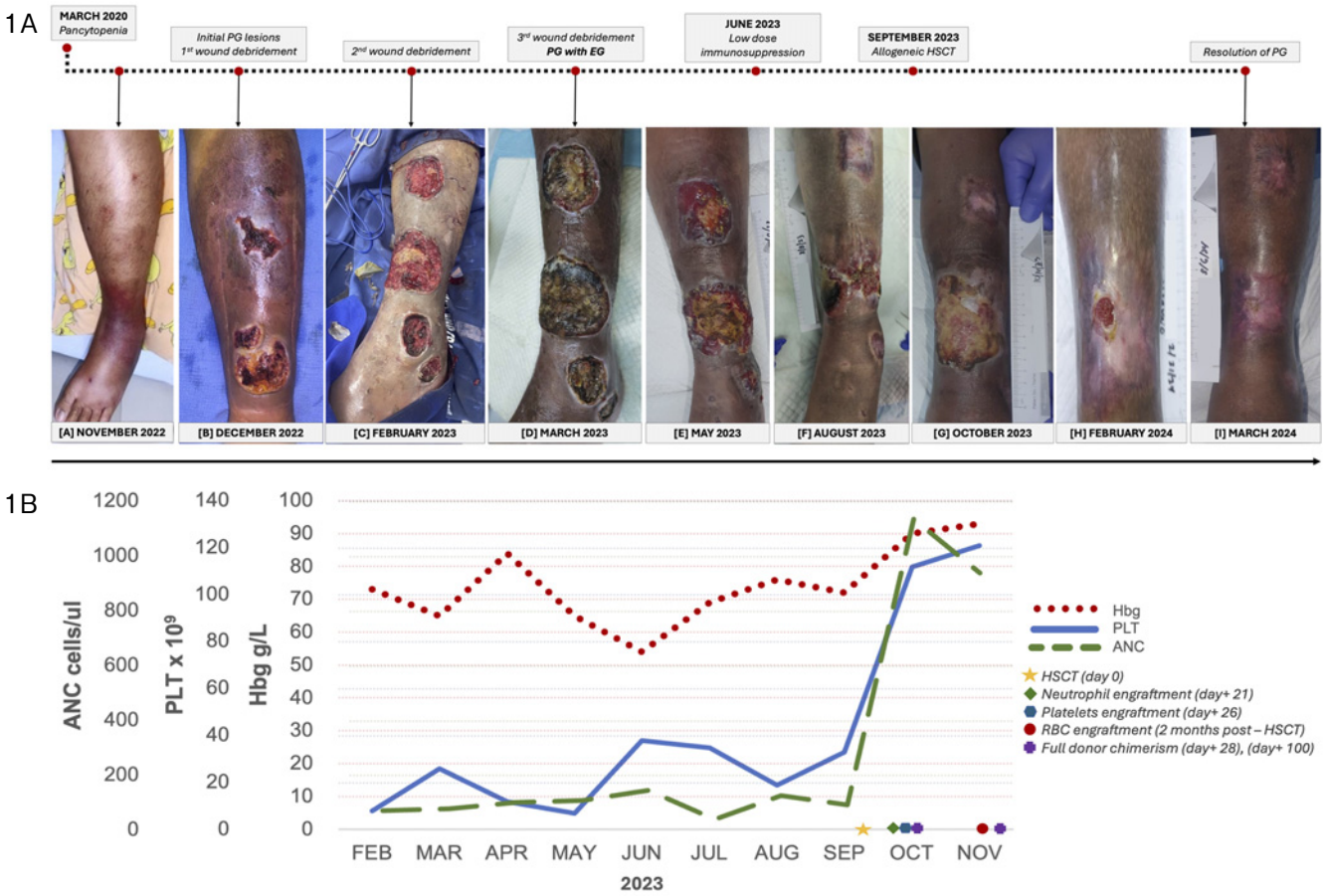


**Figure 1. Evolution of lesions and timeline of events (1A) paralleled to blood count trends pre and post HSCT (1B)**
1A. Evolution of left leg lesions and timeline of events
1B. Trends of Hemoglobin (Hbg), Platelets (PLT) and Absolute Neutrophil Count (ANC) pre and post HSCT in September 2023

ing to an Hematopoietic Stem Cell Transplantation (HSCT) recommendation.

Ten months pre-HSCT in November 2022, she developed left leg cellulitis (**Figure 1A[A]**), progressing to multiple ulcerated lesions approximately 3 × 4 cm (**Figure 1A[B]**). Upon wound debridement, biopsy showed pyogenic granuloma with *Escherichia coli* (*E. coli*) growth, treated with culture-guided cefixime for 7 days. Seven months pre-HSCT, she was admitted to our institution for pre-transplantation workups. She presented with progressively enlarging, painful, violaceous-erythematous, necrotic ulcers on her left leg and foot, with the largest approximately 5 × 4 cm. Baseline laboratory exams revealed pancytopenia, normal bleeding parameters, procalcitonin, and chemistries. Plain Magnetic Resonance Imaging (MRI) of her left leg revealed cutaneous to subcutaneous thickening without evidence of osteomyelitis. On repeat debridement (**Figure 1A[C]**), histopathology showed dermal inflammation with several inflammatory infiltrates (**Figure 2**). Tissue cultures and special stains, including blood cultures, were negative. Hence, PG was mainly considered.

Six months pre-HSCT, she had a fever (Tmax 38.8℃) with the progression of necrotic areas of left leg lesions (**Figure 1A[D]**). Blood and tissue cultures upon repeat debridement grew *E. coli.* She was managed as EG, complicating PG, and culture-guided aztreonam was added to ceftazidime and completed for 14 days. After the resolution of the infection, wound debridement was stopped as lesions increased to 5.5 × 5.9 cm. Thereafter, left leg lesions remained stable (**Figure 1A[E]**).

Three months pre-HSCT, low-dose immunosuppression with oral tacrolimus (target trough level 3-5 ng/mL, titrated to approximately 0.03mg/kg) and mycophenolate mofetil (titrated to approximately 5mg/kg) were started for PG. Prophylactic acyclovir, levofloxacin, itraconazole, and entecavir were also started. One-month pre-HSCT, she underwent low-dose desensitization with therapeutic plasma exchange (TPE) and intravenous (IV) immunoglobulin (Ig) due to high ABO titer and high levels of non-donor specific anti-human leukocyte antigen (HLA) antibodies. After two months of immunosuppression, left leg lesions improved (**Figure 1A [F]**). The patient (O+, cytomegalovius (CMV) IgG+) subsequently underwent matched related peripheral

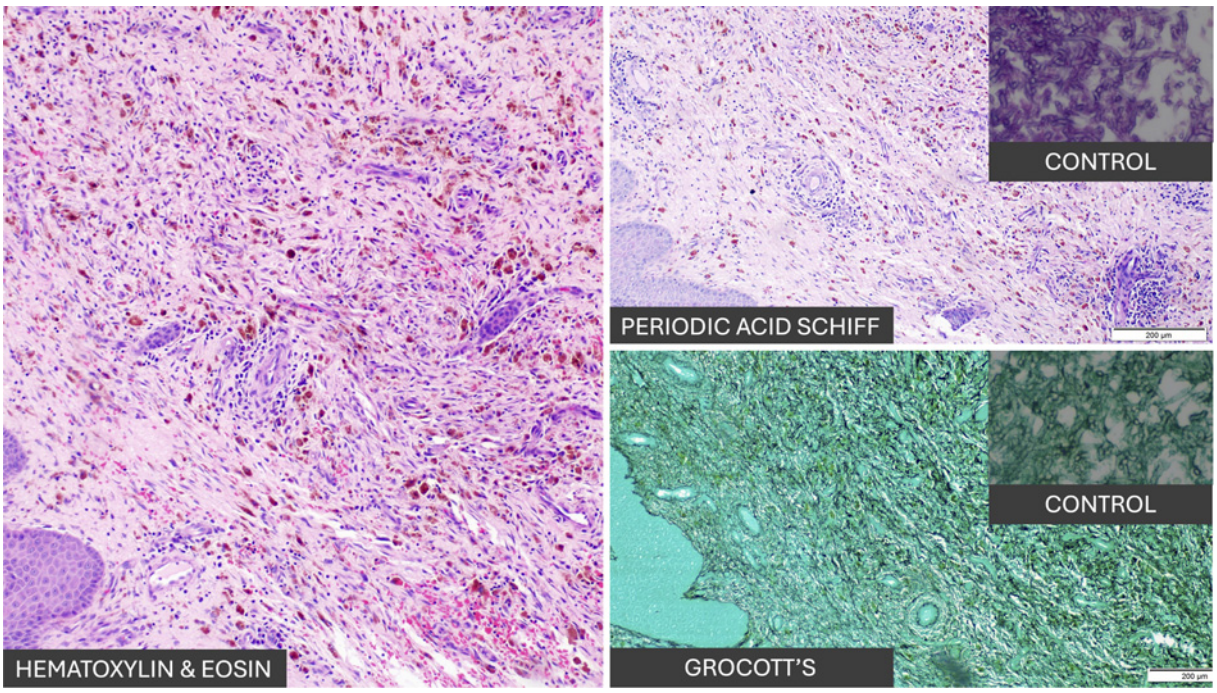


**Figure 2. Histopathology of left leg wound tissue**
Histologic sections show areas of hemorrhage and necrosis with several inflammatory infiltrates of plasma cells, lymphocytes, pigment-laden macrophages, and neutrophils are seen. No organisms and fungal elements are seen on special stain (PAS and Grocott's Special Stain).

blood stem cell transplantation with her brother as donor (B+, CMV IgG-) (11/12 HLA-matched with a single antigen mismatch at the HLA-A locus and completely mismatched at HLA-DPB1 locus), after reduced-intensity conditioning with fludarabine (25mg/$m^2$/day) from day-8 to day-4, busulfan (3.2mg/kg/day) from day-4 to day-3, cyclophosphamide (25mg/kg/day) from day-2 to day-1. She received post-transplant cyclophosphamide (PTCy)(40mg/kg) on day+3 and day+4, followed by tacrolimus (0.015mg/kg) from day+5 onwards and mycophenolate mofetil (MMF)(15mg/kg) from day+5 to day+35 as graft versus host disease (GVHD) prophylaxis. Post-HSCT complications include febrile neutropenia and transient left leg myositis. Septic work up was unremarkable; empiric cefepime and amikacin were completed for 14 days, and micafungin was shifted back to itraconazole upon lysis of fever on day+13 post-HSCT. Left leg myositis resolved after 7 days of vancomycin. Neutrophils engrafted on day+21 and platelets on day+26. Pre-emptive CMV Polymerase chain reaction (PCR) done every week post-HSCT was negative up to the time of discharge on day+37 post-HSCT. Following discharge post-HSCT, the patient underwent outpatient monitoring twice weekly for about a month, then at least weekly until day 100, including blood counts, blood chemistry, and wound care. Weekly CMV PCR testing continued until day 100, with pre-emptive Valganciclovir initiated for CMV PCR levels > 500 + 1,000 copies/mL. Monitoring was based on CMV mismatch, mismatched related HSCT, and PTCy. Red cell engraftment occurred 2 months post-HSCT, with the conversion of the patient's blood type from O Rh+ to B Rh+, similar to her donor's. The delay was attributed to an ABO mismatch. There was full donor chimerism on day+28 and day+100 based on short tandem repeat (STR) analysis and FISH XY analysis (female to male) (**Figure 1B**). PG lesions continued improving with blood count recovery (**Figure 1A[G], [H]**). Six months post-HSCT, PG lesions resolved (**Figure 1A[I]**). At the time of reporting, 12 months post-HSCT, there was no recurrence of her PG lesions, and MDS remained in remission.

## Discussion

PG has unclear pathogenesis involving immune complex-mediated neutrophil hyperactivity[1,2]. It is linked to underlying systemic diseases and myeloid malignancies such as myeloproliferative neoplasms or MDS (～12.5%)[1,2]. It is potentially fatal, with mortality rates reaching up to 30%[3]. It typically starts as a red nodule or a hemorrhagic pustule, which quickly transforms into a necrotic and painful ulcers with undermined border and induration. Diagnosis is clinical, while histopathology showing dermal neutrophilic and mixed lymphocytic infiltrates helps exclude other conditions[4,5]. Treatment includes immunosuppressive agents[4-6].

While PG is a non-infectious skin condition, EG is a

rare skin condition from severe infection commonly caused by *Pseudomonas aeruginosa* (*P. aeruginosa*), and rarely, also by other gram-negative bacteria such as *E. coli* as seen in our case, including gram-positive and viral pathogens[7]. It also starts as hemorrhagic pustules, progressing into ulcerations and eschars with an erythematous halo. Diagnosis is clinical, relying on the appearance of the lesions, biopsies, tissue, and blood cultures. Treatment includes administration of culture-guided antibiotics and, if necessary, surgical debridement to remove necrotic tissue. Bacteremia and delayed diagnosis can lead to poorer prognosis. Non-pseudomonal EG caused by *E. coli* is rare and was previously reported in only 10 literatures prior to our case[8]. Since both PG and EG present with gangrenous lesions featuring black eschar, their co-occurrence can complicate diagnosis and treatment.

Our patient had PG, but subsequent febrile episodes, *E. coli* bacteremia, and worsening of lesions led to a revised diagnosis of EG, complicating PG along its course. A sudden appearance or progression of a necrotic eschar in a healing PG ulcer should raise suspicion for EG or other gangrenous infections, necessitating a repeat skin biopsy and cultures[9]. Surgical debridement was done cautiously because while it is beneficial to EG, it is controversial to PG since it might trigger pathergy that can lead to poor outcomes[3,5,9]. In the interim, left leg lesions remained stable until low-dose immunosuppression was started 3 months prior to HSCT for PG, upon ensuring that there were no signs of infection. Consequently, there was a significant improvement and eventual resolution of the left leg lesions 6 months post-HSCT, which further strengthened the diagnosis of PG complicated by EG along the patient's course.

The choice of reduced intensity conditioning (RIC) with fludarabine-busulfan-cyclophosphamide in this case was influenced by the need to minimize further immunosuppression due to a recent active infection (*E. coli)* before transplant to reduce transplant-related complications. Myeloablative doses may severely impair wound healing[10]. RIC offers less severe immunosuppression compared to myeloablative conditioning, lower risk of organ toxicity, potentially better infection control during the transplant period, and allows for some host immunity to remain during the early post-transplant period[11,12].

While PTCy was originally established for haploidentical transplantation, its application in our case could be justified by multiple immunological risk factors: the presence of a single HLA mismatch, major ABO incompatibility, high levels of non-donor specific anti-HLA antibodies, and the use of peripheral blood stem cells as the graft source, which contains higher T cell doses compared to bone marrow. These factors collectively increase the risk of GVHD. Additionally, given the patient's complex pre-transplant conditions, including PG and EG, the selective timing of PTCy's immunosuppression might offer advantages in balancing GVHD prevention while allowing immune recovery[13].

Early consideration of HSCT is crucial in PG cases associated with MDS. While immunosuppressive drugs may provide temporary control, allogeneic HSCT remains the only curative treatment for MDS[4]. Previous studies have demonstrated successful treatment of PG associated with MDS using HSCT[4,14], highlighting its role in resolving complex inflammatory conditions linked to hematologic disorders. To the best of our knowledge, this is the first documented case of non-Pseudomonal EG caused by *E. coli* complicating PG in an MDS patient. The patient was successfully treated with culture-guided intravenous antibiotics and subsequent allogeneic HSCT. This unique, infectious complication underscores the significance of individualized therapeutic strategies, integrating targeted anti-infective treatments with definitive HSCT to address both systemic disease and associated inflammatory conditions. Our conjecture is that the immune-regulatory effects of HSCT, combined with hematologic recovery, played a critical role in the resolution of PG in this patient.

## Conclusion

Successful resolution of PG complicated by EG following wound care, culture-guided therapy, immunosuppression, and subsequent allogeneic HSCT underscores the importance of accurate diagnosis and integrated treatment. This case demonstrates HSCT's potential curative impact in managing complex inflammatory skin conditions associated with hematologic disorders, providing valuable insights for similar future cases.

## Informed Consent

Informed consent was obtained from the patient.

## Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

## Author Contributions

The paper was authored by CFVT, LBB, and MCOR, with surgical contributions from ACP. All authors participated in patient management and approved the final manuscript for publication.

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