A CHALLENGING CASE OF PYODERMA GANGRENOSUM
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Introduction:
Pyoderma gangrenosum (PG) is an uncommon, ulcerative disease characterized by neutrophilic infiltrates on histology. 1 Brunning et al first described PG as a purulent skin infection caused by microorganisms such as Streplococcus and Staphylococcus. Today, although the pathogenesis remains largely unknown, it is widely accepted that PG does not have an infectious etiology. 2 PG typically affects women during the second to fifth decades of life and is seen in only 3-10 patients per million per year. 3 Fifty percent of cases have an associated disease or condition which may emerge either before, during, or after PG is evident on the skin. The most common associations with PG are inflammatory bowel disease (Crohn’s disease, ulcerative colitis), arthritis (seronegative arthritis, rheumatoid arthritis), or lymphoproliferative diseases (acute and chronic myelogenous leukemia, myelodysplasia, monoclonal gammopathy). 1, 3 Classically, PG appears as a rapidly enlarging, painful ulceration with irregular, undermined borders however, variants such as vesiculobullous, pustular, superficial granulomatous, and pyostomatitis vegetans exist. 1, 3

Case Report:
A 63 year old Caucasian female presented to her primary care physician for evaluation of two new onset erythematous cutaneous plaques located on the bilateral dorsal hands. The lesions began as erythematous crusty papules, which progressed to nodules and plaques. An oral antibiotic was prescribed for a suspected infectious etiology and she was referred to wound care for further management. The wound care physician recommended a shave biopsy of one of the lesions. The pathology was read as a squamous cell carcinoma and she was referred to dermatology for a Mohs micrographic surgery. The surgery was performed on both areas and the defects were repaired with skin grafts. The patient returned for follow up visits because the skin grafts were not healing as expected. The lesions became erythematous, edematous, pustular and very painful. She completed multiple courses of oral antibiotics without improvement and was then admitted to the hospital for intravenous antibiotics. During her hospitalization, the diagnosis of pyoderma gangrenosum was suspected and she was started on oral prednisone. The lesions on her hands were noted to have rapid improvement, however, the patient did not receive a confirmed diagnosis of pyoderma gangrenosum.

After being discharged, the patient continued to take prednisone and her condition was stable. She sought a second opinion at a tertiary medical center, where the diagnosis of pyoderma gangrenosum was confirmed. She was advised to follow up with a local dermatologist and primary care physician for further evaluation and management.

The patient was subsequently referred to a rheumatologist, where she was started on azathioprine 100 mg daily and prednisone 40 mg daily. She was worked up for underlying malignancies and inflammatory bowel disease. The results of this were unremarkable. The patient discontinued the azathioprine after two months of therapy due to side effects, but continued the prednisone. After six months of taking oral prednisone for control of her disease, the patient was advised to discontinue the medication without a taper. She became ill, experiencing anorexia, confusion and flaring of the lesions on her hands. She was started on lorazepam 0.5 mg twice daily for symptom control. She was then referred to psychiatry for evaluation of suspected lorazepam abuse.

The patient followed up with a different local dermatologist where the diagnosis of vesiculobullous pyoderma gangrenosum was made. She is currently maintained on azathioprine 50 mg daily and prednisone 5 mg daily without clinical activity of PG.

Discussion
Pyoderma gangrenosum is a rare, neutrophilic dermatosis with an incidence of 3-10 cases per million each year. It is predominately seen in women who are in their second to fifth decade of life. 3 Although PG can be idiopathic, a recent review found the most common PG association is inflammatory bowel disease (65.2%), followed by arthritis (16.1%), and lastly, hematologic disorders such as paraproteinemia and malignancies. 4 The classic form of PG is ulcerative, but variants exist such as bullous, pustular, and vegetative exist.

Trauma, or pathergy, evoke further lesional neutrophil recruitment and therefore, potentiate PG. Tokalchajv et al found that 90% of patients with post-operative PG were initially treated with antibiotics and 73% of patients with PG underwent at least one surgical debridement. 5 Mislagnosis post-operatively is a risk secondary to PG initially being diagnosed as necrotizing fasciitis, which leads to further morbidity and increases the length of time before an accurate diagnosis is elucidated. 6

The patient presented in this case report was initially diagnosed with squamous cell carcinoma (SCC) secondary to a biopsy showing pseudoepitheliomatous hyperplasia (PEH), which is a benign histological finding characterized by epithelial proliferation into the dermis. PEH can be seen secondary to trauma, ulceration, infection, and/or neoplasms of the skin and is often misdiagnosed as SCC. 6, 7 However, PEH is differentiated from SCC by two main findings: the absence of nuclear atypia and mitoses, and positive immunohistochemical nuclear staining for Ki67 and p53 in the basal epithelial layer only (versus positive staining throughout the full-thickness of the epithelium in SCC). 8

PG is a diagnosis of exclusion and there are no pathognomonic histological findings, although skin biopsy should be performed to rule out other potential differentials. Differential diagnoses to exclude include: bacterial, parasitic or deep fungal infections, spitz nevus, melanoma, pigmented spindle cell nevus, sym pathetic ganglioneuroma, pyogenic vegetans, lichen sclerosus in the setting of severe scratching, granular cell tumors, necrotzing fasciitis, vasculitis, and other neutrophilic dermatoses. 9 Su et al developed a list of criteria to diagnose PG including two major criteria of a rapidly progressive ulcer with irregular, undermined borders and exclusion of other ulcerative etiologies. 10 Other minor criteria include: history of pathergy, associated systemic disease, histopathologic findings of dermal neutrophilia ± lymphocytic vasculitis, and rapid response to systemic steroid treatment. 10, 11

Unlike one surgically nature and various underlying diseases, there is no gold standard treatment of PG. One treatment approach is wound management with moisture-retentive dressings showing superiority over drying dressings in promoting collagen and vascular growth and facilitating natural debridement. 12 Topical calcineurin inhibitors and corticosteroids have had success in individual cases and smaller case studies, but unfortunately, there is limited evidence at a large case study level. 13 Pathergy is often used to quickly induce remission in patients with the classic variant of PG however, in some patients more time in need-spar for a response and therefore, steroid-sparing systemic agents are utilized such as: cyclosporine, methotrexate, and thalidomide. 13 Biologic, particularly TNF-α blocking agents, have more recently been studied for their role in the treatment of PG. However, infliximab is the only biologic proven in a randomized, double-blind study to show efficacy over placebo (46% vs. 6%). 14

Conclusion
Pyoderma gangrenosum is a challenging diagnosis to make due to limited knowledge regarding pathophysiology and histology, and its varying clinical presentation. Unfortunately, this uncertainty ultimately often leads to misdiagnosis and mismanagement causing significant morbidity and grief for patients.