Pyoderma Gangrenosum: An Autoimmune Condition

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We hear it all the time, that we're lucky to be in a time where medical science is at the top its game of diagnosing and treating conditions, that once seemed impossible. However, for many patients with Pyoderma Gangrenosum (PG), it's a completely different story. Although this condition has been around for more than 100 years, there are still a lot of unknowns to be answered. PG, is a rare inflammatory, autoimmune condition that's causing many patients to become disabled. So, how do we take what we know to help us create a plan to treat, and maybe even give new life to patients with this disabling condition? Let's explore this condition at all levels.

PG first came into context when a French doctor by the name of Louis Brocq (**as seen in Figure 1**), in 1908 and again in 1916.

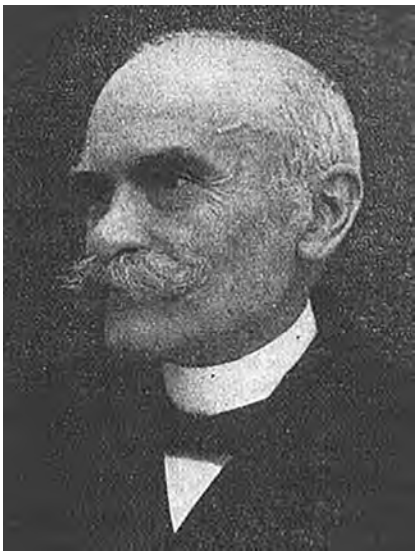


Figure 1 (Hobbs, Ortega, 2020).

"Brocq reported a series of patients with distinct ulcers of which he discerned three major components: (a) the ridge, (b) the external slope of the border; and (c) the internal slope of the border. He described the ridge as "featuring a regular, geometric, circular,

or elliptic pattern; the external slope as erythematous, infiltrated, and sometimes painful; and the internal slope as undermined, sharp as a cliff," and "dimpled by purulent cavities. Histopathology showed neutrophilic infiltration. Brocq chose the name *geometric phagedenism* to capture both the geometrical pattern of the ulcer and its rapidly extensive, necrotic nature (phageton [Greek], meaning consumption)" (Hobbs, Ortega, 2020).

Almost thirty years went by before PG would come to the forefront of medicine, in 1930, by an American physician named Louis Brunsting (**seen in Figure 2**). Brunsting, like Brocq, noticed the same detailings of PG. Unlike Brocq, Brunsting was seeing this as a common issue with patients that had Ulcerative Colitis; another autoimmune digestive disorder.

Figure 2 (Hobbs, Ortega, 2020).

In the last few decade PG has become a more common diagnoses for many patients. Although, opinions vary on if it's being over-diagnosed, or if trained doctors are able to spot it easier. Either way, there's still a lot of unknown information being researched. PG is a condition that is diagnosed base on exclusion. The problem with that is many procedures, medications, and surgeries can cause more damage to its patients. Known pathergy issues that can initiate and make pyoderma worse are, "minor trauma, surgical debridement, by a surgical procedure, namely breast surgery, cesarean section, or colostomy" (Gameiro, Pereira, Cardoso, Goncalo, 2015). It's also know to become inflamed when using TNF-factor medications, such as Humira and Remicade. Because this conditions is hard diagnosis, it's usually missed or missed treated by other medical specialties.

Why is PG consider an autoimmune condition? What effects does it have on the human body? To understand this, we really have to see what PG is, and how it attacks the immune system. Medically speaking, we have to first understand the definition, aka etiology, and the pathogenesis of PG. "Pyoderma Gangrenosum (PG) is a neutrophilic ulcerative dermatosis with a spectrum of clinical presentations and variable clinical course. PG is caused by genetic alterations of the immune system (both innate and adaptive), leading to inflammatory activation, cytokine production, and neutrophilic infiltration. Genetic mutations, neutrophil dysfunction, and abnormal inflammation contribute to the pathogenesis and clinical manifestations of PG"
(Kang, Alvai, 2021). Like many, we must also understand what this means in layman's terms. The best way to say it, is the body attacks itself.

The most common cell that effects PG patients, is neutrophils. “Neutrophils help your immune system fight infections and heal injuries. Neutrophils are the most common type of white blood cell in your body. An absolute neutrophil count identifies whether your body has enough neutrophils or if your count is above or below a healthy range” (Cleveland Clinic, n.d.). The article from Cleveland Clinic continues by saying, “Think of your immune system as the general of your body’s army that works to prevent bacteria and viruses from entering” (Cleveland Clinic, n.d.). Neutrophils are suppose to capture and protect invaders, but for patients with autoimmune conditions, such as pyoderma, it’s the opposite. These cells then attack what they’re suppose to be protecting. This means that people with PG are usually overflowed with neutrophil production in their body, allowing for these cells to attack healthy cells that they’re not suppose to go after in the your body. Because of this, it forces the body to eat at itself from the inside-out causing massive damage to ulcer’s eating at the victims skin.

PG’s clinical features includes extremely painful erythematous lesions or redness of the skin, which can quickly and progressively turn into blisters or necrotic ulcers. These ulcers can then have a rough edge of undermining with a violaceous (violet colored border). These lesions may gain speed and damage after the body has perceived minor trauma to itself, this term is called pathergy. PG is one of the most missed diagnosed conditions in today’s world. It is a condition that is given based on exclusion vs. through blood work, biopsy, or any other examination. Although, this condition tends to effect young/middle aged adults, it has been seen in pediatric patients as well. There are six types of Pyoderma noted to date, they are:

Classical PG: The most common form of PG presents as a rapidly progressive painful ulcer with a violaceous undermined edge. (**See Appendix A**)

Bullous PG: This form presents with rapidly evolving painful superficial vesicles and bull arising in waves, often coalescing together most commonly on the arms. Histologically this shares similarities with Sweet's Syndrome. A hematological malignancy should sought as these are identified in up to 70% cases. (**See Appendix B**)

Pustular PG: This form is most commonly seen in the context of flaring inflammatory bowel disease and presents with painful pustules on a background of erythema, often exterior surfaces. (**See Appendix C**)

Granulomatous Superficial PG: Otherwise known as vegetative PG, this subtype usually progresses more slowly and presents with verrucous and ulcerative lesions. These patients are less likely to have an underlying systemic condition and do not usually require systemic treatment. (**See Appendix D**)

Peristomal PG: This variant probably results from a pathogenic response to trauma from focal irritation or secondary to appliances on the skin and is most frequently seen in the context of stomas in patients with inflammatory bowel disease. (**See Appendix E**)

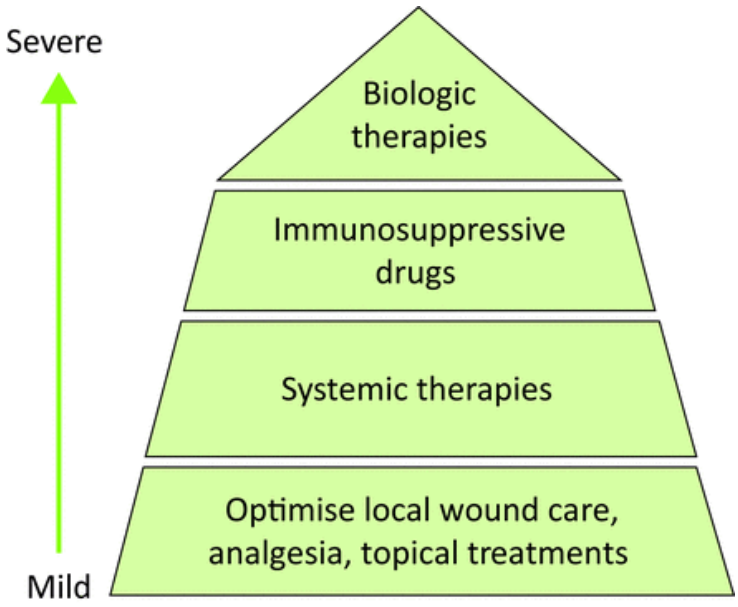
Malignant PG: This is important but rare clinical variant that presents with destructive ulcerations affecting the upper torso, head, and neck. Lesions do not display at the violaceous edge seen in classical PG and the condition is not associated with systemic disease (**See Appendix F**)

(Deriude, George, Rustin, 2019).

As stated under these different types of PG, we see that it's commonly a condition with comorbidity. Truthfully, about half of all diagnosed cases have a systemic conditions. Comorbidity means that there's more than one condition that can be involved. Like many PG patients, I suffer from a comorbidity of Crohn's Disease, a common autoimmune condition that involves the digestive tract, eye, skin, genitals and mouth. Due this underlining condition, it increase the rapid rate and aggressiveness of my PG. And like many patients, I suffer from multiple forms of PG.

The history of treatments of PG is not impressive, to say the least. However, Dr. Brocq felt the best place to start for treating or even getting rid of the ulcerations and neurotic tissues by surgical excision. It was the most recognized treatment until the 1960s. "By 1960, Ulcerative Colitis (UC) , was generally thought to occur through autoimmune mechanisms, and an estimated 30% to 40% of PG was associated with UC. The strategy up until this point was to administer antibiotics and treat the associated disorder (before proceeding with surgical excision) given the lack of knowledge regarding PG-specific mechanisms" (Hobbs, Ortega, 2020). Also, Hobbs and Ortega continues, they state that, "The first randomized controlled trial (RCT) for corticosteroids as a treatment for UC was published in 1955, 1 year prior to Wright and Greco's report of PG treat with corticosteroids" (Hobbs, Ortega, 2020). They soon realized that treating PG with corticosteroids and azathioprine, "was a novel idea in that they did not appear to be associated with an underlying comorbidity" (Hobbs, Ortega, 2020). With this new found knowledge, they started treating PG patients with immunosuppressive drugs. It was around 20 years later that they soon realized using things like oral and topical tacrolimus was also a helpful treatment. Since the

mid-1980s, other forms of medications were coming forward as being helping treat PG every decade. It was in the early twenty-first century that anti-TNF medications like Humira and Remicade were also a good place for dermatologist to start.



Now we can look at see how a doctor would start a patient with various treatments. Although, PG is a hard condition to diagnose, at times even misdiagnosed, but once you are diagnosed the conversation with your doctors turns into trying to figure out what treatments may be useful to treat the different ulcerations that a patient may have. As seen in the figure up top, which gives us a general idea where a doctor may start a patient to treat their type(s) of PG. You always need to keep in mind that each case of PG differs from patient to patient. We can see that the first go to for many doctors is wound care. This includes topical ointments, and packing materials, which can include: gauze, aqua cell, calcium alginate, and other forms of packing materials. Systemic therapies can consist of steroids (prednisone, solu-medrol injections). As well as antibiotics. Then you head into areas of immunosuppresive drugs such as, Remicade, Humira, Skyrizi, and Methotrexate—which is used in treating some cancer patients. The recently new forms of treatments is using biological therapies. This includes things like, epicord (human umbilical cord), epifix (placental tissue), stravix (also placental tissue). Even though biologicals are new

to being used, they have seen remarkable healing from them. I was blessed to have Oregon Health & Science University to pay under charity, to get hyperbaric oxygen therapy (HBOT). It took both OHSU and UCLA, to fight for me to get this treatment. We saw healing but were able to realize that my condition being an autoimmune disorder, that HBOT can help with healing but would never cure me of my condition. As advancements in medical science pushes to new boundaries, we may even start to see treatments designed specifically for PG.

There's one aspect in the medical field that many patients don't get an opportunity to observe, and that's how doctors and researchers come together to form clinical studies. Dr. Alex Ortega, of OHSU dermatology department, has set up a research group by the name of u**PG**rade. He's one of only a handful of dermatologist in the United States, that have focused their research in PG. I have a very difficult PG case, and because of my extreme desire and interest in doing more, I've been allowed to join in during his medical conferences. To go behind the scenes and see leading doctors and researchers around the world come together to discuss the parameters of how to start a study into PG, was a true honor and privilege. During the conference that occurred on November 3rd & 4th of 2022, many research hospitals around the United States came to present their findings both of doctors who treat PG patients, and PG patients themselves. It was noted that many of the same concerns that doctors have, patients, have as well. The top six issues that were of concern for both doctors and patients was, pain, quality of life, physical symptoms, mortality, mental health, and physical signs of PG (as

Rank	Domain	Mean
1.	PAIN	2.99
2.	QUALITY OF LIFE	3.10
3.	PHYSICAL SYMPTOMS	3.90
4.	MORTALITY	4.80
5.	MENTAL HEALTH	6.20
6.	PHYSICAL SIGNS	6.64

seen in **Figure 4**). I later asked Dr. Ortega, “What is the mortality rate of people with Pyoderma?” In an email to me, he told me, that “someone like you who has a comorbidity condition of Crohn’s Disease and Pyoderma, your mortality rate is 3 times higher, than someone with just Pyoderma” (Ortega, 2022). Like it was stated above, many PG patients suffer from comorbidity, specifically digestive disorders like Crohn’s and Ulcerative Colitis, making the underline condition part to the complications to PG.

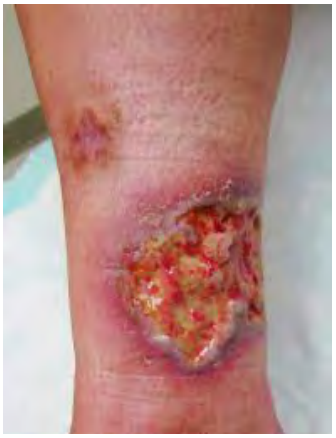
One big topic that was discussed in depth, was if the location of the PG should have a point value. Interestingly enough, many of the doctors were against a point scale, however, as patients, we all agreed that location does make a difference when treating PG. For many of the doctors, thought that a patient could have a very large ulceration on their forearm, and get two points because of its location vs. someone who may have a much smaller ulceration on their head and get a score of four. As patients, we recognize that care for an arm wound would probably be easier and probably less painful, vs. a wound on the head that could be more painful, and even head into a dangerous direction, such as into the eye. The respect and courtesy everyone on the panel had for one another, was a truly wonderful to witness. The ironic occurrence that happened to me listening to everyone talk, was to have a new understanding about how dangerous my condition really is. It will be a life long battle that I will have to deal with, along with many other PG patients. Due to the ulcerations and neurotic tissue that occurs with PG, can actually kill a patient. What seems so simple, is really not simple at all. PG is truly a complicated condition that leaves many of us disabled by its effects on our bodies. Many symptoms that are disabling to its patients are, the associated pain, which during the u**PG**rade conference stated that, “the pain is as bad as cancer pain”

(u**PG**rade, 2022). Other challenges including, infection, systemic and reoccurring ulcerations, amputation, drainage, and smell. But as long as doctors fight along side their patients, a true healing and better quality of life is possible.

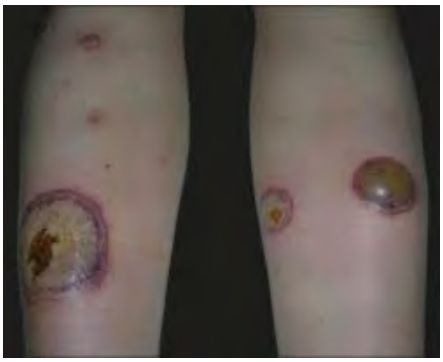
If we take a moment to really understand what it means to be a victim of an autoimmune condition, and possible more than one, gives us a moment to recognize that many people around the world suffer in silence. Although, Pyoderma can mostly be hidden behind the clothes we wear, it doesn't diminish the fact that PG is actually disabling to its patient's daily lives. So, what does the advancement medical science truly mean to the patients suffering from this disabling disease? The truth is, it gives us hope. Hope for more answers, hope for more treatments, and hope for a less disabling life. All of this is wrapped up in the advantage of medical science being where it is today, tomorrow, and years to come. To make pyoderma no longer a condition of disabilities but a condition of unlimited abilities.

Appendix

A) Classic Pyoderma

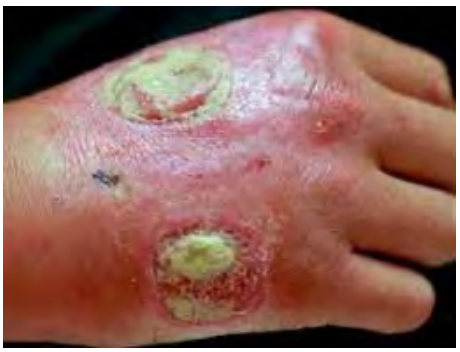


B) Bullous Pyoderma Gangrenosum



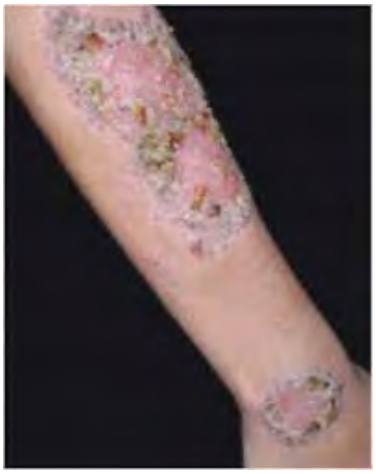
C) Pustular Pyoderma Gangrenosum

(Gameiro, Pereira, Cardoso, Goncalo, 2015)



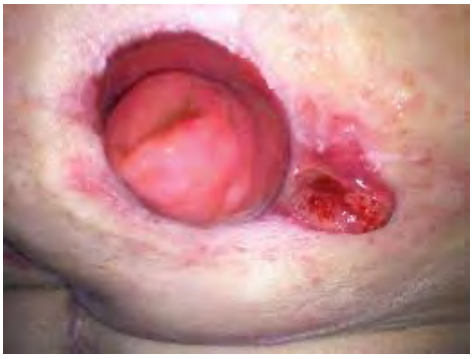
D) Granulomatous Pyoderma Gangrenosum

(Benedetti, 2022).



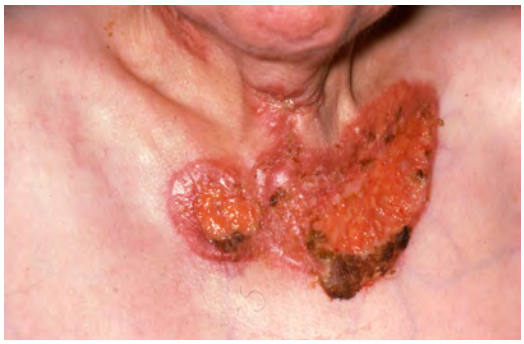
E) Peristomal Pyoderma Gangrenosum

(Guda, Rosen, 2022).



F) Malignant Pyoderma Gangrensoum

(Wallach, 2019).



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