THE NORTHERN HOSPITAL

PYODERMA GANGRENOSUM

"Voltaire", in marble, 1781, Jean Antoine Houdon, Hermitage Museum St Petersburg.

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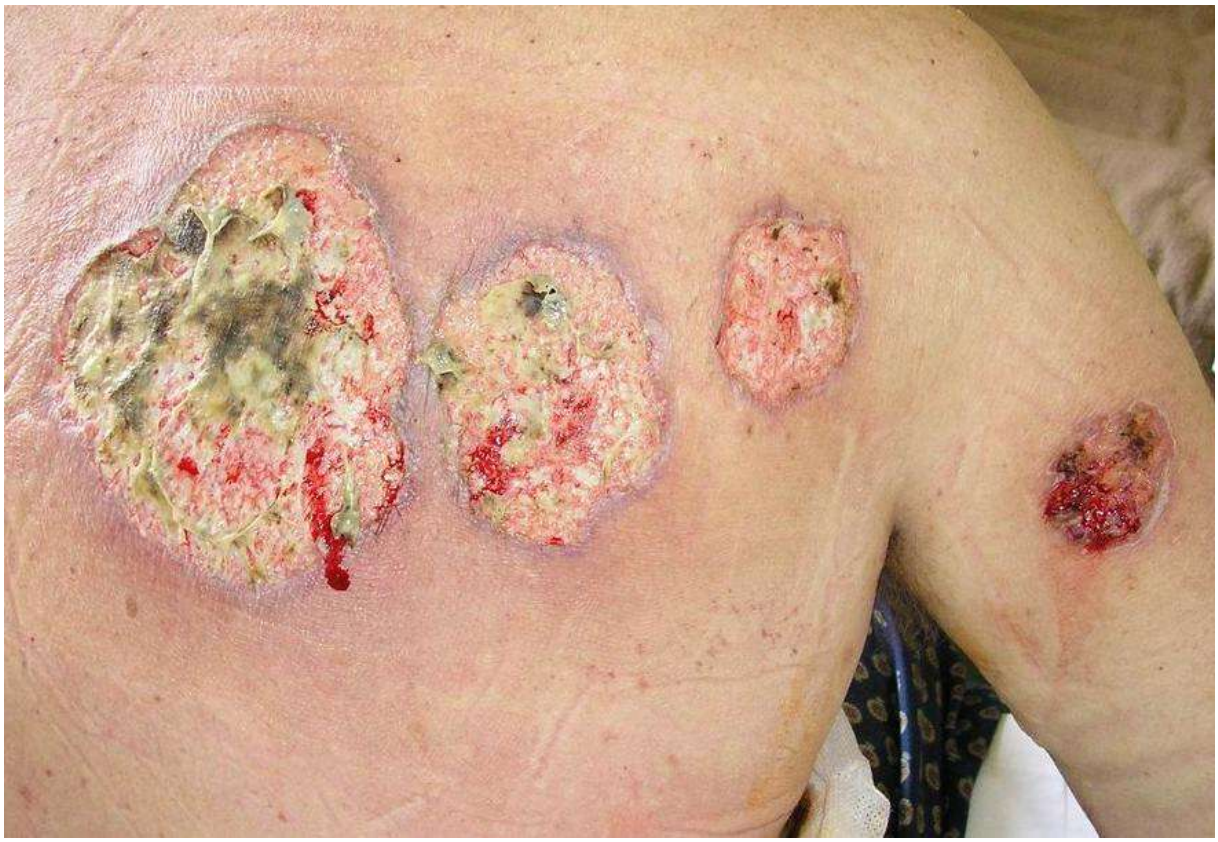
"This agglomeration which was called and which still calls itself the "Holy Roman Empire" is neither holy, nor Roman, nor an empire!" - François-Marie Arouet (Voltaire).

On Christmas day in the year 800 A.D, the Frankish Empire was at the very height of its powers. Ruled over by the greatest ever Frankish Monarch, Charles the Great, known to history as Charlemagne, the time appeared right to make some recognition of this fact and further - to have it recorded for posterity in the long annals of human history. And Charlemagne, never one to do things by half, had just the thing - he would assume the long lost mantle of Emperor of the West. The Western Roman Empire had fallen in 476 A.D, and while the East had survived, even prospered and then evolved, the territories of the ancient West had fallen into the very darkest depths of ignorance and chaos. Charlemagne, a brilliant soldier, though completely illiterate, sought to redress the long lost prestige of the West. He would become the reincarnate Roman Emperor of the West, the inheritor by right of conquest, of the legacy of Augustus. Thus it was that on Christmas day 800 A.D, the spiritual leader of Christendom, Pope Leo III, crowned Charlemagne "Emperor of the West". It so happened that just at this time, the Emperor of the East was a woman! - the Byzantine Empress Irene. For a brief moment, the thought crossed Charlemagne's mind that he should take Irene as his wife and by so doing restore the old Roman Empire in its entirety! Irene was tempted - but deep religious schism with the West, ensured that this dream would remain just that - another great "what if..." of history.

After Charlemagne's death in 814 A.D there was a bewildering kaleidoscopic array of divisions and mergers of kingdoms that largely reflected Carolingian reproduction and mortality, but by the late Ninth century the definitive divisions of the old Frankish kingdom had occurred leaving essentially what would become the successor kingdoms of France, Italy and Germany. In the year 962 AD the title of Emperor was revived by the German Monarch Otto I. He renewed Charlemagne's claim over the inheritance of the old Empire of the Roman West. Amidst much pomp and ceremony the "Holy Roman Empire" was proclaimed. "Holy" in keeping with the extreme religious fervor of the age, as well as keeping in well with the Papacy, "Roman" due its perceived inheritance, and "Empire" for its perceived unified glory to come. Yet the Holy Roman Empire was and remained so, a pure chimera. Its territories remained hopelessly fragmented and disunified. Great sections of it were ruled independently of the supposed "emperor". The emperor became merely an elected representative of literally hundreds of smaller sub-units, principalities, duchies, counties, Free Imperial Cities, and other domains of confusing and uncertain status, who spent their entire existence in conflict with both each other and the supposed central authority. By the early Nineteenth century the "empire" had become a completely dysfunctional fossilized relic of the past. In 1806 Napoleon Bonaparte finally put an end to the pantomime of the Holy Roman Empire, by defeating its disunified armies and forcing its last Emperor, Francis II, to abdicate. In its last years the brilliant Voltaire best summed up the long and tortuous history of the Holy Roman Empire, with his famous observation, "This agglomeration which was called and which still calls itself the Holy Roman Empire is neither holy, nor Roman, nor an empire".

When we discover a case of the enigmatic "pyoderma gangrenosum" we recall the famous words of Voltaire when he spoke of the degenerate Holy Roman Empire - the term is an utter and complete misnomer - this degenerate condition is neither infectious ("Pyoderma") nor is it a gangrene, ("gangrenosum")!

PYODERMA GANGRENOSUM



The horrible lesions of the enigmatic, Pyoderma Gangrenosum.

Introduction

Pyoderma gangrenosum (PG) is an *uncommon* painful destructive skin condition, which presents as progressive deep ulcerations or superficial bullous erosions.

The name pyoderma gangrenosum is an historical misnomer. The condition is not an infection (pyoderma), nor does it cause gangrene.

Its aetiology is uncertain, but is currently classified amoung the diseases of autoimmunity.

It frequently causes significant morbidity because of **delays in diagnosis** and so consequent delays in instituting effective treatments.

Often the diagnosis is not considered until there is no response to anti-infective or surgical treatments.

The most appropriate referral is to **dermatology.**

It is predominantly treated with immunosuppressive agents.

Its prognosis is variable and unpredictable.

Epidemiology

All ages may be affected by Pyoderma gangrenosum, however it predominantly occurs in adults during the fourth and fifth decades of life.

Children account for only 3-4% of the total number of cases.

Pathology

The aetiology remains uncertain, but it is best thought of as an **autoimmune** process that is characterised by a **sterile neutrophilic infiltrate**. It is presumed that cytokine release attracts neutrophils and that there is an abnormal neutrophil chemotaxis response.

Pyoderma gangrenosum is thus classified as a **neutrophilic dermatosis**. Other neutrophilic dermatoses, include, Behcet's disease and Sweet syndrome.

Neutrophilic dermatoses often arise at the **site of injury** such as a needle prick, biopsy or insect bite. This abnormal reaction to injury is known as **Koebner phenomenon**, **pathergy** or **isomorphic response.**

The fact that 25% of cases of PG show pathergy (where the condition appears at the site of skin trauma), suggests an abnormal inflammatory response to wound healing.

Causes

1. Primary or Idiopathic (50% of cases):

    - But often at the site of some precipitating physical injury.

2. Secondary causes (50% of cases):

    Many cases are seen in association with an underlying systemic disease.

    Associations with autoimmune diseases include:

    - Inflammatory bowel diseases (Ulcerative colitis and Crohn's disease)
    - Rheumatoid arthritis
    - Chronic active hepatitis.
    - Wegener's granulomatosis

    Associations with haematological malignancies include:

    - Myeloid blood dyscrasias
    - Monoclonal gammopathies.

Clinical Features

Pyoderma gangrenosum is largely a diagnosis of exclusion because no specific criteria have been determined to confirm its diagnosis.

Characteristic clinical features of Pyoderma gangrenosum include:

1. Pain:

    - Pain is often severe and seemingly **out of proportion** to the physical findings.

2. Constitutional symptoms:

    - Non-specific constitutional symptoms such as arthralgias and malaise are also often present.

3. Morphology:

    The clinical presentation may be confusingly variable, with the following forms being described:

    - Ulcerative (also known as the "typical" form).

    Various "atypical" forms can include:

    - Pustular
    - Bullous
    - Vegetative

4. Site:

    - Pyoderma gangrenosum may affect any part of the skin, but the **lower legs** are the most common site
    - One distinctive and at times difficult to manage variant is **peristomal PG**, again thought to result from the pathergic effect of skin trauma or inflammation in this area.

      It is often mistaken for a wound infection or irritation from the appliance.

5. Progression:

    - Onset is abrupt
    - The ulcer is rapidly progressive.

- Even with appropriate treatment PG lesions can take many months to fully heal.
- Healed lesions will often leave scarring.
- In some patients, **new ulcers** may form at sites of skin trauma.

6. The failure of conventional investigations and treatments:

   This will often be the first indication that the lesions could be pyoderma gangrenosum.

   Typically the following may be seen:

   - Negative results of bacterial cultures
   - Failure to respond to antibiotics
   - Worsening after surgical debridement

Differential diagnoses:

There are many, but as the most common site of Pyoderma gangrenosum is the legs, the principle differential diagnoses will relate to the causes of leg ulcerations.

These can include:

1. Vascular ulcers:
   - Arterial ulcers/ Venous ulcers
2. Infection:
   - In particular **Mycobacterium Ulcerans** and **anthrax.**
3. Malignant lesions.
4. Neuropathic ulcers
5. Pressure ulcers
6. Envenomation reactions:
   - Necrotising arachnodism, (rare).
7. Other autoimmune lesions:
   - Pemphigus/ pemphigoid.
8. Ulcerating STDs:

- Vulvar or penile pyoderma gangrenosum, must be differentiated from sexually transmitted *ulcerating* diseases.

Investigations

There is no *specific* test for pyoderma gangrenosum.

1. FBE
    - For underlying haematological malignancies
2. CRP
3. U&Es/ glucose
4. LFTs

Wound swabs for M&C

The lesion is not infective (unless there is secondary infection).

Lack of an identifiable causative organism helps point the way toward a diagnosis of pyoderma gangrenosum.

Tissue cultures of the ulcer/erosion for bacteria, fungi, atypical mycobacteria, and viruses are needed to help exclude infective causes of the lesions.

Biopsy

Skin biopsy can be useful even though there is no diagnostic histological feature to definitively confirm the diagnosis.

The histopathological examination can **help exclude other diagnoses**, such as **malignancy** or **infection,** (such as Mycobacterium Ulcerans) while at the same time showing features that an experienced histopathologist can identify as *suggestive* of a diagnosis of PG.

There is massive (though non-specific) neutrophilic infiltration.

Pathergy testing:

A pathergy test is usually positive (i.e a skin prick test causing a papule, pustule or ulcer).

Further investigations:

Further specialised investigations may be directed toward the known underlying systemic disease associations, e.g colonoscopy to exclude IBD.

Management

1. Analgesia, as required:

    - Pain can be severe and may require opioids.

2. General wound dressing care:

    - Silver sulfadiazine dressings or hydrocolloids

3. Debridement:

    - Any clearly necrotic tissue should be *gently* debrided.

    - Treatment however is **non-surgical**. The necrotic tissue should be gently removed and wide surgical debridement should be *avoided* because it may result in *enlargement* of the ulcer.

      In some patients, grafting has resulted in the development of pyoderma gangrenosum at the harvest site!

4. Protection from skin trauma:

    - In some patients significant pathergy is seen and so it is important for these patient to protect themselves from any skin injuries.

5. Antibiotics, (for secondary bacterial infection):

    - Often conventional antibiotics have been given prior to making the correct diagnosis. These may be continued if bacteria are cultured in the wound (i.e there is **secondary bacterial infection**) or there is surrounding secondary cellulitis, but they are **not** helpful for pyoderma gangrenosum itself.

6. Steroid therapy:

    This can take the form of

    - Potent topical steroid creams

    - Intralesional steroid injections

    - Oral prednisolone therapy.

7. Anti-inflammatory antibiotic agents:

    Oral antibiotics that have significant anti-inflammatory actions may be used. They are effective no because of anti-microbial activity, but rather from their anti-inflammatory activity.

Agents that have been used include:

- Dapsone
- Minocycline.

8. Immunosuppressive therapy:

More severe disease will require immunosuppressive therapy

The following agents have been used:

- Tacrolimus ointment is an immune modulating drug that inhibits calcineurin.
- Ciclosporin.
- Methotrexate.
- Cyclophosphamide
- Mycophenolate mofetil
- Infliximab

Intravenous immunoglobulins and plasmapheresis have also been used.

Disposition:

Referral should be made to **Dermatology**, where the diagnosis is often first considered!.

Severe cases will require protracted use of steroids and immunosuppressives and this treatment is best undertaken under the care of a specialist Dermatologist.

Rheumatology referral may also be appropriate, if there is an underlying Rheumatological disorder.

References

1. Alan J Cooper, Pyoderma gangrenosum - a frequently misdiagnosed skin condition. MJA 199 (6) 16 September 2013.

2. Pyoderma gangrenosum in DermNet NZ, Website:

    - dermnetnz.org/

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