Case 1.1

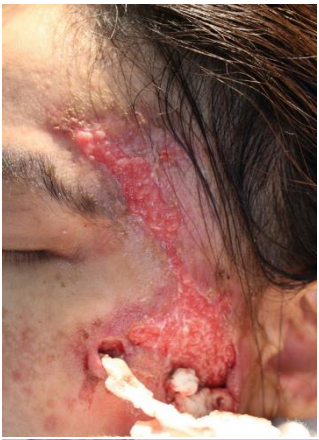
A 38-year-old Thai female from Saraburi

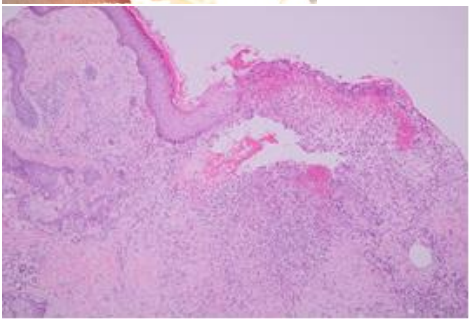
Chief complaint: Chronic ulcer on left side of face for 1 month

Presentillness:
1 month previously, the patient developed pustule on left of her cheek with low grade fever, then the pustule rapidly progressed to a widening, painful ulcer on left side of face. No weight loss, no lymphadenopathy. She came to see the primary physician who gave her oral antibiotic and surgical debridement. The ulcer was still rapidly expanded.

Past history:
Diagnosis of hypothyroidism for 1 year and receiving treatment with levothyroxin 0.15 mg/day

Skin examination:
A large sharply demarcated ulcer with undermined violaceous border with granulation tissue in the central area on left side of face





Histopathology: (S15-10246, face)

- Superficial ulcer with granulation tissue
- Inflammatory cell infiltrate composed of mainly lymphocytes and neutrophils
- Marked fibrosis in the adjacent dermis

Diagnosis: Pyoderma gangrenosum

Investigation:

Laboratory tests

CBC: WBC 7,510/cumm (N 68%, L 24%, Mo 5%, Eo 3%), Hct 33.7%, Platelets 476,000/cumm
ESR: 60 sec
BUN: 11mg/dL, Cr: 0.7mg/dL
Hemoculture for aerobe: No growth
Pus gram stain, AFB, mAFB: No organism
Pus culture for aerobe, fungus, TB: No growth
Tissue imprint for gram stain, GMS, AFB, mAFB: No organism
Tissue culture for aerobe, TB, fungus: No growth
Tissue for TB direct detection: Negative

Treatment:

- Dexamethasone 5 mg IV q 6 hr for 5 day
- Prednisolone(1MKD) 60 mg/day
- Cyclosporin A(100) once a day
- Colchicine(0.6) once a day
- Vitamin D(20,000 IU) once a week
- $CaCo_3$(1250) once a day
- Dressing wound q 2-3 day with normal saline and intrasite gel, urgotul SSD

Case 1.2

A 45-year-old Thai male from Bangkok

Chief complaint: Ulcer and abscesses at right arm for 3 days

Present illness:

2 months previously, the patient developed ulcer on right 4th finger. The first treatment from his gastroenterologist was oral Clindamycin 600 mg thrice a day. His ulcer was not healed.

1 month ago, he developed fever with right upper quadrant abdominal pain. His ulcer was rapidly enlarged. He was admitted to the hospital and was investigated. The ultrasonograpy of abdomen revealed three hepatic abscesses. He was treated by imipenem intravenous for 2 weeks without any improvement.

3 days ago, he developed painful erythematous linear-shape patch with pustules ontop along of arteriovenous bridge graft (AVBG) site on right arm. He also had high grade fever and arthralgia.

1 day, his right arm becomes more swollen with very red and painful.

Past history:

History of Dicloxacillin induced agranulocytosis 5 years ago.

Underlying disease: ESRD, hypertension, Pauci-immune crescentic glomerulonephritis with rapid progressive glomerulonephritis 6 years ago. Liver mass on right lobe liver S/P liver biopsy. The histology shown chronic inflammation with fibrosis, possible part of fibrotic wall. He had history of recurrent infection AVBG site.

4 months ago, he was admitted to the hospital due to fever with anemia. He was diagnosed as AIHA and still had low grade fever.

Current medication: folic acid(5) 1x1pc, FBC 1x3 pc, metoprolol(100)1x2 pc, doxazocin(4)2x1 pc, diltiazem (30) 3x3 pc, calcitriol (0.25) 1x1pc, amlodipine (10)1x1 pc, hydralazine (25) 2x4 pc, CaCO3 (1250) 1x3 pc, sodamint 2x3 pc, erythropoietin 4000 U SC twice a week

Physical examination:

V/S: T 38.3°C, PR 98/min, RR 20/min, BP 140/80 mmHg

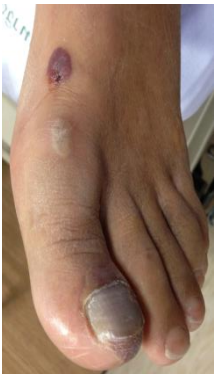
HEENT: moderately pale conjunctivae, no jaundice, injected and swollen left conjunctiva with purulent discharge, no regional lymphadenopathy

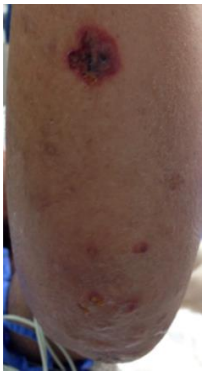
Abdomen: soft not tender, liver just palpable at 1cm below RCM, not tender, liver span=14 cm, spleen is palpable, 4 cm below LCM, no ascites

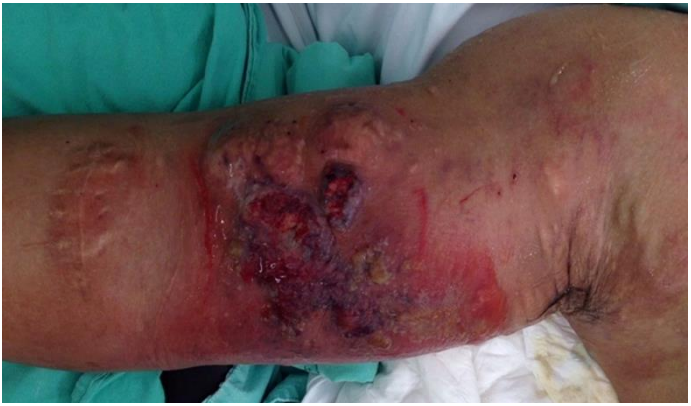
Extremities: no edema

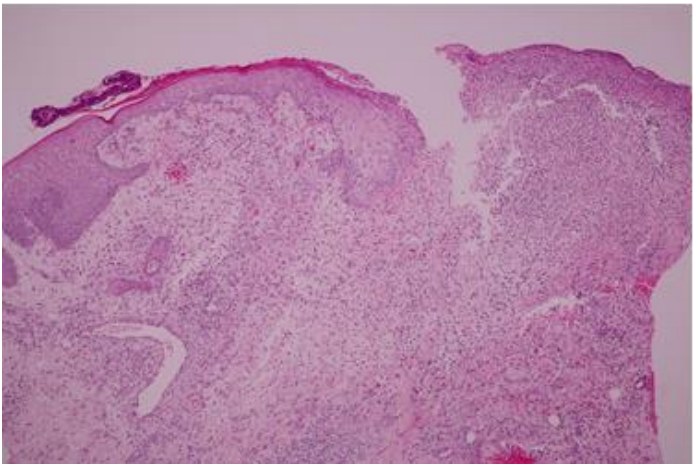
Skin examination:

Purplish painful ulcer with hemorrhagic crusted on right swollen arm. Few discrete pustules and hemorrhagic bleb on right elbow and feet.









Histopathology: (S14-26425, right arm)

- Dense diffuse inflammatory cell infiltrate of neutrophils, extravasated red blood cells, basophilic debris in the deep dermis.
- Fibrosis around the inflammatory foci.

Diagnosis:

- **Pyoderma gangrenosum**
- **SLE (ANA 1: 1280, AIHA, polyarthritis, History of GN)**
- **ESRD, HT**

Investigation:

Laboratory tests

CBC: Hb 7.2 gm%, Hct 22.6%, MCV 71.5 ,
WBC 9900/cumm (N78%, L13%, M7%, Eo2%),
platelets 196,000/cumm
ESR 99 mm/hr (1-10 mm/hr), CRP 215.49 mg/L
LFT: AST 12 IU/L, ALT 13 IU/L, ALP 119 IU/L , GGT 51 IU/L, TP 79.6 mg/L, Alb 25.9 mg/L, TB 0.7 mg/dL, DB 0.3 mg/dL, Chol 129 mg/dL
ANA > 1:1,280 (homogeneous pattern),
RF 12.2 IU/ml (<15),
P-ANCA positive 25.11 RU/ml (negative < 20),
C-ANCA negative 10.4 RU/ml (negative < 20),
Anti Cardiolipin IgG < 2 GPL (negative < 12),
Beta2 Glycoprotein1 IgG 2.3 U/ml (0-20),
Anti HIV negative,
HBsAg: negative, Anti-HBs: positive, Anti-HBc: positive,
Anti-HCV: negative
Serum VDRL: non-reactive
Hemoculture culture for aerobe: no growth
Pus from abscess at right arm, right elbow and left eye ; gram stain: no organism, culture for aerobe: no growth
Tissue from right arm; gram stain: numerous PMN, no organism AFB stain: no acid fast bacilli seen, modified AFB stain: no modified acid fast bacilli seen, GMS stain: no fungus seen,
Tissue culture for aerobe: no growth
Tissue from right arm; PCR for mycobacterial: negative, PCR for 16s RNA: negative, PCR for 18s RNA: negative

Imaging

Ultrasound of upper right extremities: Patent AVF at the right arm, soft tissue edema suggestive of cellulitis, myositis and fasciitis extending from proximal right arm to distal right forearm

CT upper abdomen: Hepatosplenomegaly with perfusion abnormality of liver parenchyma and portal hypertension with splenic varices. Subcapsular hypodense lesion at hepatic segment IV, V, VII, and VIII 2.1x1.3 cm in size. Heterogeneous hypodense lesion 2.6 cm at inferior portion of the spleen.

Treatment:

- Prednisolone 1 mg/kg/day
- Mycophenolate mofetil(250) 3x2 oral pc
- Dressing with normal saline

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Discussion:

Pyoderma gangrenosum (PG) is neutrophilic dermatoses (NDs) which first description by Brocq and Simon in 1908. PG is a rare inflammatory skin disease with a chronic relapsing course, commonly associated with severe pain that often regresses with cribriform mutilating scars.[1] Epidemiological data are variable among different populations. The incidence of, PG has been estimated as 3–10 per million population per year. In most cases, the disease manifests between the second and fifth decade of life. About 4 % of the affected patients are children, without a clear gender predilection.[2]

The pathogenesis of pyoderma gangrenosum (PG) is multifactorial and involves neutrophilic dysfunction, inflammatory mediators, and genetic predisposition. The role of neutrophils has been suggested by the histology of PG, the pathergy phenomenon, and association with other neutrophilic conditions It is unclear if primary neutrophil dysfunction is responsible for the pathology of PG or if neutrophils are the effector cells of an aberrant immune system. The role of T cells and cytokines, such as IL-8 and IL-1b are currently investigated. Genetics have been proven to play a role in described PG-associated syndromes and autoinflammatory predisposition such as inflammatory bowel disease, PAPA syndrome, PAPASH syndrome.[3]

Clinical manifestations: A PG lesion typically starts as a tender nodule, plaque, or sterile pustule that

enlarges and erodes, over a course of days, into a sharply marginated ulcer with undermined, violaceous borders and a surrounding zone of erythema, pain is a characteristic feature. The skin and subcutis become necrotic, creating a friable wound bed often with a hemorrhagic or purulent exudate, sometimes extending as deep as muscle. Cribiform or 'sieve-like' atrophic scars often form as the lesions heal. Lesions typically are multiple and occur at areas of trauma in 25–50% of cases, a process known as pathergy. PG lesions in adults most frequently affect the lower extremities; any anatomic site can be affected. In children (approximately 4% of cases), PG typically involves the lower extremities, buttocks, and perineal region, as well as the head and neck. PG may also involve extracutaneous sites such as the eye (scleritis and orbital inflammation), the lungs (aseptic pulmonary nodules), the spleen, and the musculoskeletal system in the form of sterile pyoarthrosis and neutrophilic myositis.

There are currently five widely recognized subtypes of PG, classic (ulcerative), bullous, pustular, vegetative, and peristomal(Table.1).

Table.1 Subtypes of pyoderma gangrenosum

Type	Clinical presentation and morphology	Notable features on histopathology	Typical location	Associated systemic disease
Ulcerative 'classic'	A single or a few small pustules without an inflammatory halo that rapidly ulcerate with inflamed, violaceous, undermined borders. Painful and often associated with systemic illness	Subcorneal collections of neutrophils; endothelial cell swelling; fibrin deposition in dermal vessel walls with thrombosis	Ulcers in sites of minor trauma are common. Most frequently on lower extremities	IBD; seronegative arthritis; RA; sacroiliitis; monoclonal gammopathy; malignancy
Vegetative	Usually a single superficial ulcer with rapid response to treatment. May form sinus tracts. Less aggressive than classic PG. Responds well to topical treatment	Pseudoepitheliomatous hyperplasia, dermal neutrophilic abscesses, sinus tracts, palisading granulomatous reaction	Typically on trunk, lacks the violaceous undermined border or pustular base seen in ulcerative PG	No systemic diseases
Bullous	Rapidly spreading, painful superficial bullae with inflamed blue-gray borders that break down to form ulcers. Less destructive than ulcerative type	Subepidermal bullae with intra-epidermal and dermal neutrophilic infiltrate	Affects face, upper more than lower extremities	Myeloproliferative disorders (most common): leukemia, myelodysplasia. Also IBD
Pustular	Rare, painful pustular lesion(s), often symmetric, with erythematous halo	Subcorneal pustules with perifollicular neutrophilic infiltrate, dense dermal neutrophilic infiltrates, subepidermal edema	Legs and upper trunk	IBD (most common); less common: jejunoileal bypass; PCV; hepatobiliary disease
Peristomal	Painful erythematous to violaceous papules that erode into ulcers with violaceous, undermined borders	Neutrophillic collections with granulation tissue and a mixed dermal inflammatory infiltrate	Occurs near stoma sites	IBD; enteric malignancies; monoclonal gammopathy; connective tissue disease

IBD = inflammatory bowel disease; **PCV** = polycythemia vera; **PG** = pyoderma gangrenosum; **RA** = rheumatoid arthritis.

Ulcerative or classical pyoderma gangrenosum is the most commonly presentation. Patients with pyoderma gangrenosum can also have systemic symptoms. In addition to fever, these include malaise, arthralgia, and myalgia.

Associated Conditions: PG is associated with underlying systemic diseases in approximately 50% of patients, the remainder of cases are considered idiopathic. Inflammatory bowel disease (IBD), arthritis,

and hematologic disorders are the most common disease associations. Although in most cases PG was diagnosed after the associated disease, it may also precede or be the presenting sign of an underlying disease. The courses of the two diseases are sometimes, but not necessarily, parallel.[4,5,6]

The diagnosis PG remains a clinical diagnosis; it lacks specific serologic or histologic markers. PG is also a diagnosis of exclusion it is crucial to rule out other etiologies of ulcers, especially infectious causes. The minimum evaluation should include a complete history, physical examination, and skin biopsies.

Investigations: Skin biopsies are essential both for histologic examination with routine hematoxylin and eosin and special stains for infectious organisms, as well as for culture of bacteria, viruses, fungi, and atypical mycobacteria. Direct immunofluorescence studies may be helpful to exclude autoimmune skin disease or vasculitis (though findings are neither sensitive nor specific for PG). Direct immunofluorescence studies show IgM, C3, and fibrin deposits in blood vessels of the papillary and reticular dermis in a majority of PG biopsy specimens. Routine laboratory tests such as complete blood count with differential, electrolytes, urinalysis, and liver function tests may be helpful as an initial screen for hematologic disorders, liver or kidney dysfunction related to a variety of possible associated conditions, and hepatitis. Additional studies are helpful in excluding systemic disorders: anti-nuclear antibody, coagulopathy panel including antiphospholipid antibody test,

cryoglobulins, rheumatoid factor, and circulating antineutrophil cytoplasmic antibodies. Further work-up for associated conditions may include chest x-ray (for infections or systemic vasculitis), fecal occult blood test and sigmoidoscopy or colonoscopy for IBD, and evaluation for hematologic disease (serum protein electrophoresis, urine spot protein or urine protein electrophoresis, immunofixation electrophoresis, peripheral smear, and bone marrow biopsy), especially in cases of bullous PG. Infectious causes should be excluded including HIV, hepatitis serologies, and rapid plasma reagin, if risk factors exist.[7]

The pathologic findings are not specific and vary depending on the timing and the site of the biopsy. Neutrophilic infiltration into dermis is the histological hallmark of PG. Early in the disease, a biopsy taken from the advancing erythematous border will usually show a dermal perivascular lymphocytic infiltrate with endothelial cell swelling. Later in the course of the disease, biopsy from an area of ulceration will show a neutrophilic dermatosis characterized by a dense polymorphonuclear leukocyte infiltrate, and biopsy from the margin of the ulcer will show not only perivascular lymphocytes but also thrombosis of vessels with extravasated erythrocytes.

There is no gold standard of treatment or published algorithm for choice of therapy for pyoderma gangrenosum. Choice of therapy will depend on multiple factors including size and depth of the lesion, the rapidity of lesion growth and appearance of new lesions,

the associated disease (eg, inflammatory bowel disease, arthritis), and general medical status of the patient. The therapy of PG usually is systemic but may include topical drugs as well (Table.2). Classic ulcerative PG is often treated initially with high-dose corticosteroids (prednisone 1-2 mg/kg/d), because of the rapidity of response. However, because some ulcers may require months to years to fully resolve and/or are unresponsive to corticosteroids, other immunomodulators have been used. The next most commonly used agent, cyclosporine, can help act as a corticosteroid-sparing therapy. However, cyclosporine has its own side effect profile that includes renal toxicity with prolonged use. Azathioprine is administrated in combination with corticosteroids, with the aim being a gradual tapering off the corticosteroids. Azathioprine alone is not effective in PG. Dapsone is a second-line drug used in daily doses of 200 mg in patients with normal glucose-6-phosphate dehydrogenase levels. Clofazimine stimulates phagocytosis and possesses an additional, direct antibacterial effect. The dosage varies between 300–400 mg daily. Thalidomide has a blocking effect on TNF-a. It also blocks chemotaxis of neutrophils in the acute phase of the disease. Monotherapy and a combined therapy with corticosteroids is possible. Mycophenolate mofetil doses of 2 g daily, also appears to be a good alternative to azathioprine with comparatively low side effects. The selective calcineurin inhibitor tacrolimus has been used in PG at a daily dosage of 0.1 mg/kg body weight. The serum level of the drug should be between 4 and 6 ng/L. Colchicine is another therapeutic option but

common gastrointestinal adverse effects limit its use in maintenance therapy. Cyclophosphamide pulse therapy followed by either azathioprine or methotrexate is an effective treatment option in steroid-refractory Crohn's disease. TNF-a inhibitors may be considered third-line treatments in steroid refractory cases with the need of systemic treatment.[8,9,10]

In summary, we present two different cases of pyoderma gangrenosum. Case 1.1 the patient presented with chronic ulcer on left side of the face. She is no known underlying disease except hypothyroidism. She received the treatment with intravenous dexamethasone 20 mg/day for 5 day then switch to prednisolone 1 mg/kg/day, and cyclosporine A 3 mg/kg/day for 4 months.The local wound care with normal saline, intrasite gel and urgotul SSD were administraed. The cicatrisation and epithelization from the edges of ulcer was almost completed. We precribed colchicine 0.6 mg/day for maintenance therapy, now the ulcer was completely healed.

Case 1.2 the patient present with chronic ulcer on right upper arm. He is known case ESRD, hypertension. After extensive investigated, he was diagnoses as system lupus erythematosus by ANA positive 1:1280, history of AIHA, polyarthritis, glomerulonepritis. He has started treatment with intravenous dexamethasone 15 mg/day for 6 week then switch to prednisolone 1 mg/kg/day, and increase cyclosporine A dose 3 mg/kg/day. He developed cyclosporine induced hypertension and hypertensive

crisis. The cyclosporine was discontinued and mycophenolate mofetil 1,500 mg/day was administrated for 2 months in addition with local wound care. The upper arm ulcer was re-epithelized.

References:

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