Case 27
A 62-year-old Thai female from Bangkok
Chief complaint: An erythematous rash on the face and a painful purpuric rash on the lower extremities for 1 week

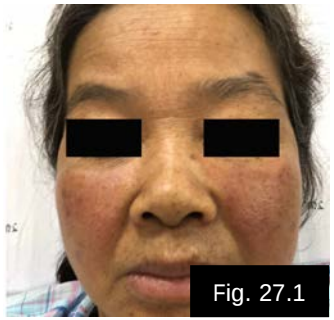
Fig. 27.1

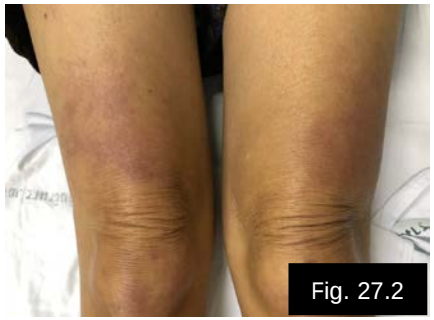
Fig. 27.2

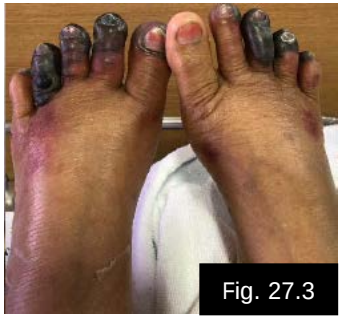
Fig. 27.3

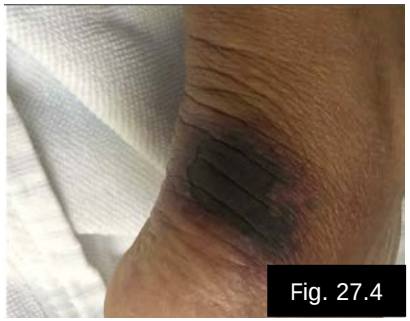
Fig. 27.4

Present illness:
This is a known case of paroxysmal nocturnal hemoglobinuria (PNH) presenting with bicytopenia comfirmed by flow cytometry. The disease was stable for 9 months with cyclophosphamide 50 mg/day, prednisolone 15 mg/day, blood transfusion every 3 weeks and desferiprone 3000 mg/day.

Patient presented with a 1-week history of erythematous patches on the face (Fig27.1) and a 2-day history of purpuric patches on both thighs, right ankle and both feet (Fig27.2, 27.3, 27.4). She also had a fever, cough and dyspnea. She denied history of dark urine.

Past history:
Paroxysmal nocturnal hemoglobinuria (PNH), Iron overload
No history of thrombosis

Physical examination:
General appearance: A Thai female, looked-well
HEENT: moderately pale conjunctivae, no anicteric sclerae,
Heart: Normal S1S2, no murmur
Lung: Normal breath sounds, no adventitious sound
Abdomen: Soft, not tender, liver 2 FB BRCM, liver span 11 cm, no splenomegaly
Lymph nodes: not palpable
Extremities: no pitting edema
NS: no facial palsy, motor power grade V all extremities

Dermatological examination (Fig 27.1, 27.2, 27.3, 27.4):
- Erythematous edematous patches on both cheeks
- Multiple reticulated partially blanchable erythematous to purplish patches on both lower extremities
- Dry gangrene on left 2^{nd}- 4^{th} toes and right 3^{rd} - 5^{th} toes
- Ill-defined purplish patch with central necrosis on the right ankle

Histopathology: (S18-030369, Right ankle) (Fig 27.5):
- Numerous thrombi occlusion in the vascular lumen within the dermis admixed with some neutrophils, lymphocytes and numerous extravasated erythrocytes (Fig 27.5)
- Special stains (AFB, Fite, Brown & Brenn, GMS, PAS): Failed to demonstrate organisms
- Pythium IHC: negative
- Direct immunofluorescent (DIF): non-specific finding
- Tissue C/S for aerobe, TB, fungus: negative
- Tissue PCR for TB, 16s, 18s: negative

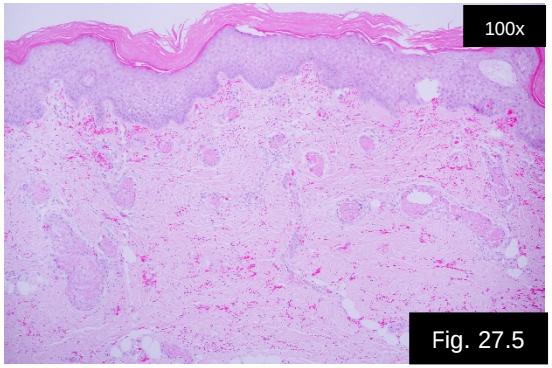

Fig. 27.5

Laboratory investigations:

- **CBC: Hb 7.5 g/dL, Hct 22.8%,** Plt 152,000 /mm^3, **WBC 1,900 /mm^3 (N 88%, L 10%, M 2%)**
- PT/INR: 12.7/1.07, APTT: 20.3 (wnl)
- Reticulocyte: 0.4
- **LDH: 384 U/L (125-220 U/L), Ferritin: 3707**
- LFT: AST/ALT: 41/34 U/L
- BUN/Cr: 10/0.58 mg/dl
- ANA: negative
- Cryoglobulin: negative
- Lupus anticoagulant, Beta 2 glycoprotein IgG, Anticardiolipin IgG: negative
- P and c -ANCA: negative
- Serum galactomannan: negative
- **CT Whole aorta and bilateral femoral artery:** No aortic aneurysm, dissection, aortic wall thickening, mild atherosclerosis with scattered calcified and soft plaque of aorta and its branches with mild stenosis of origin of bilateral internal iliac artery, no evidence of deep vein thrombosis and arterial occlusions both legs

Diagnosis: Thrombotic vasculopathy from PNH

Treatment:

- Enoxaparin 0.6 ml sc every 12 hours then bridging to warfarin
- Prednisolone 15 mg/day
- G-CSF 300 mcq/day, blood component

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Discussion:

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare bone marrow failure disorder, characterized by the triad of pancytopenia, hemolytic anemia, and thromboembolism in various organs.[1] The annual incidence is 1-1.5 cases per million individuals worldwide. The disease occurs more frequently in eastern countries than in western countries.[2]

PNH is caused by a somatic mutation in PIG-A (phosphatidyl inositol glycan class A) in hematopoietic stem cell, resulting in the disruption of glycosylphosphatidylinositol (GPI) biosynthesis and followed by a deficiency of all GPI-anchored proteins (eg. CD55, CD59) which leads to dysregulated complement activation that accounts for hemolysis.[1]

Thromboembolism is the most common cause of morbidity and mortality in patients with PNH which cause up to 40-67% of deaths.[3] Thromboembolism in PNH may occur at any site especially in uncommon sites such as hepatic, mesenteric, cerebral and cutaneous veins.[4] Asian patients have a higher risk of arterial thrombosis than western patients.[5]

The mechanism of thromboembolism is complex. Previous studies hypothesized that platelet activation, complement-mediated hemolysis, impaired nitric oxide bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are responsible for the increased thrombotic risks.[3]

PNH-associated cutaneous lesions are extremely rare. A variety of cutaneous manifestations have been reported, including localized or wide spread petechiae, hemorrhagic bullae, ear or leg ulcers, non-inflammatory retiform purpura and purpura fulminans.[5,6,7,8,9] Skin biopsy can help to exclude other causes of purpura. Histopathology shows hemorrhagic necrosis of the epidermis and dermis, dense perivascular and interstitial cell infiltrate of neutrophils admixed with mononuclear cells, thrombosis and necrosis of dermal blood vessels.

The diagnosis of PNH is confirmed with peripheral blood flow cytometry by detecting the absence or severe deficiency of GPI-anchor proteins on > 2 lineages using the reagent fluorescent aerolysin (FLAER).[5]

Anticoagulation and corticosteorid therapy are the treatment of choice in cutaneous lesions.[5] In severe PNH, Eculizumab which works as a complement blockade through the anti-C5 monoclonal antibody, is highly effective in stopping intravascular hemolysis, eliminating and decreasing red blood cell transfusion and also reducing the risk of thrombosis.[3] Allogenic stem cell transplantation is an option for patients with severe aplastic anemia or those who do not respond to eculizumab therapy.[5,10]

Our patients received oral prednisolone 15 mg/day, enoxaparin 0.6 ml sc every 12 hr, GCSF 300 mcg/day and blood transfusion and showed clinical improvement within 2 months.

In conclusion, PNH should be suspected in patients with a thrombosis in unusual sites including intraabdominal, cerebral and dermal veins as well as those who are young or have accompanying symptoms and signs such as intrahemolysis anemia and pancytopenia.[3] Life-threatening conditions such as hepatic failure, alteration of consciousness, bowel ischemia can occur, so early diagnosis and effective treatment are of critical importance. Treatment consists of anticoagulants and eculizumab.

References:

1. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood 2014;124:2804e11.
2. Hill A, DeZern AE, Brodsky RA et al. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017;3:17028.
3. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;20;121:4985-96;
4. Zhao H, Shattil S. Cutaneous thrombosis in PNH. Blood. 2013;7;122:3249.
5. Fu-Nien Hsieh, Tsai-Yun Chen, Julia Yu-Yun Lee. Severe cutaneous thrombosis with hemorrhagic necrosis in a patient with paroxysmal nocturnal hemoglobinuria: A case report and review of literature, Dermatologica Sinica; 2017; 35, 138-141
6. May C, O'Rourke K, Jackson K, Francis L, Kennedy GA. Purpura fulminans in a patient with paroxysmal nocturnal haemoglobinuria. Intern Med J. 2013;43:102
7. Watt SG, Winhoven S, Hay CR et al. Purpura fulminans in paroxysmal nocturnal haemoglobinuria. Br J Haematol.2007;137:271
8. Rompoti N, Hillen U, Rösch A et al. Purpura fulminans related to paroxysmal nocturnal haemoglobinuria. Eur J Dermatol. 2016;26:397-8.
9. Rietschel RL, Lewis CW, Simmons RA et al. Skin lesions in paroxysmal nocturnal hemoglobinuria. Arch Dermatol. 1978;114:560-3.
10. Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. *Ther Adv Hematol*. 2017;8:119–126.