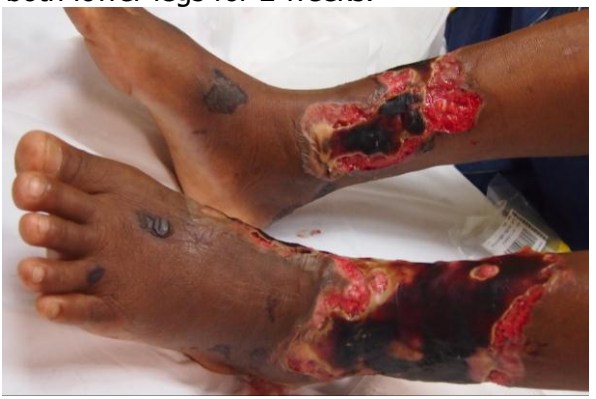
Case 6

A 38-year-old Thai woman from Bureerum.

Chief complaint: Painful ulceration with surrounding retiform purpura on both lower legs for 2 weeks.



Present illness: The patient developed off and on painful purpuras started from the right ear, tip of nose then progressed to both upper and lower extremities since November 2011. The lesions presented as painful purpuric plaques, some of which formed retiform patterns, evolving to skin necrosis, and hemorrhagic bullae. She was treated at a local hospital with topical wound care and analgesic drugs without complete recovery.

2 weeks PTA, the purpuras on both legs progressed to large painful foul smell ulcers. She also felt fatique and had low grade fever. She also lost 5 kilograms in 4 weeks. She denied history of photosensitivity, oral ulcer, cold intolerance, arthritis or other systemic symptoms.

Past history: She has 2 healthy children, with no history of previous abortion.

Family history: No family history of coagulopathy.

Medication: No history of any substance abuse or drugs.

Skin examination: Multiple discrete purpuric plaques with irregular retiform borders on tip of nose, ears, both upper and lower extremities (Figure.)

Necrotic ulcers with debris and hemorrhagic crusts on both lower

legs. Skin necrosis and hemorrhagic bullae also seen on both dorsum of feet.

Physical Examination:

VS: BT 37.7 ^{0} c (axillary), BP 110/70 mmHg, HR 80/min, PR 80/min RR 12/min

HEENT: Mild pale, no icteric sclera, no oral ulcer

Heart: Normal S1 and S2, no murmur

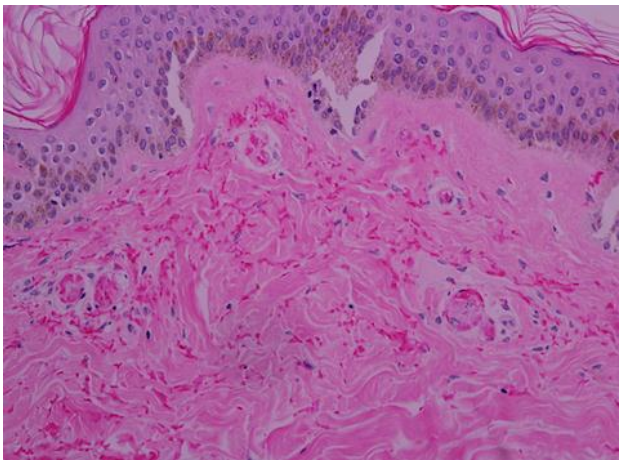
Lung: Normal breath sound

Abdomen: Soft, no hepatosplenomegaly

Neurological exam: Intact

Histopathology: (S13-02243)

There are numerous extravasated erythrocytes as well as the thrombi within lumens of small blood vessels in superficial and deep dermis, some of which associated with perivascular infiltrate with neutrophils, eosinophils and some nuclear dusts throughout the dermis.



PAS, GMS, Fite, and Brown Brenn staining failed to demonstrate any organisms.

Laboratory investigation:

CBC: **Hct 30%, Hb 10 mg/dL, WBC 2,940/mm^3** (N 48% L46% M 5% E 1%), Platelet 337,000/mm^3

Direct and indirect Coomb's test: Negative

Liver function test: Within normal limits
BUN: 0.54 mg/dL, Cr: 0.9 mg/dL
Partial thromboplastin time: 23.9 sec (22.0- 33.0)
Prothrombin time: 13.5 sec (10.5-13.5)
Thrombin time: 10.6 sec (10.0-13.0)
Lupus anticoagulant: Positive
Cryoglobulin: Weakly positive (cryocrit <1%)
Anticardiolipin antibody: Negative
β2 glycoprotein antibody: Negative
Protein C, protein S level: Normal
ANA: 1:80 (fine speckled pattern), Anti-dsDNA: Negative
C3c: 1070 ug/mL C4: 178 ug/mL CH50: 75%
Anti-HIV: Negative, HBsAg, Anti-HBs, Anti HCV: Negative
Hemoculture: No growth after 3 days
Wound pus culture: Numerous *Proteus mirabilis* and *Aeromonas hydrophila*
Urinalysis: Protein negative, WBC negative, RBC negative

Diagnosis: Antiphospholipid antibody syndrome secondary from probable systemic lupus erythematosus with secondary bacterial wound infection

Treatment: Anticoagulant (Enoxaparin 0.4 ml SC qd for 8 days then warfarin 7.5mg per week to achieve INR ranging from 2 to 3) Hydroxychloroquine (200) 1 tab oral qd.
Surgical wound debridement and systemic antibiotics (Ciprofloxacin 400mg IV q 12 h for 7 days then switch to oral Ciprofloxatin (500) 1 tab oral twice a day for 7 days).

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Discussion

Antiphospholipid antibody syndrome (APS) is a prothrombotic disorder that affects both the venous and arterial circulations [1,2], characterized by recurrent thrombosis and/or

pregnancy morbidity in the presence of autoantibodies against phospholipid-binding plasma proteins which may occur alone (primary), or in association with any other autoimmune diseases for example, systemic lupus erythematosus (secondary). APS has a strong female predominance (82% women, 18% men) with the mean age of 42 ± 14 years.[2]

There are multiple mechanisms for antiphospholipid antibody-mediated thrombosis; increased oxidative stress[4], impaired function of endothelial nitric oxide synthase[5], activation of receptors by anti-β2GPI antibodies[6], increased expression and activation of tissue factor[7], increased in free thiol form of factor XI[8], disruption of the annexin A5 shield[9], antibody-mediated activation of complement C3 and C5[10], increased expression of TLR7 and TLR8 and sensitization to TLR7 and TLR8 agonists.[11]

Clinical manifestations represent mainly a direct or indirect expression of venous or arterial thrombosis and/or pregnancy morbidity. The common cutaneous findings in patients with APS are livedo reticularis, 24%; leg ulcers, 5.5%; digital gangrene, 3.3%; cutaneous necrosis, 2.1%; and splinter hemorrhages, 0.7%[2] Deep vein thrombosis/pulmonary embolus and CNS disease are the most common extracutaneous manifestations. Catastrophic APS is defined as a rapidly progressive thromboembolic disease involving simultaneously three or more organs, organ systems, or tissues leading to corresponding functional defects.[3]

The diagnosis of APS should be seriously considered in cases of thrombosis, cerebral vascular accidents in individuals younger than 55 years of age, or pregnancy morbidity in the presence of livedo reticularis or thrombocytopenia. The presence of at least one clinical and one laboratory criterion ensures the diagnosis of APS as the table 1.

Histologic features of early lesions typically reveal non-inflammatory thrombosis of small dermal vessels; later lesions may show inflammation following necrosis or with wound healing.

Table 1: Criteria for the antiphospholipid syndrome[1]

Clinical criteria
1. **Vascular thrombosis** • One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. • Thrombosis must be confirmed by objective validated criteria • For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity **(a)** One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, **or** (**b)** One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, **or** **(c)** Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria
1. Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma, present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA

APS patients should be placed on warfarin for life aiming to achieve an international normalized ratio (INR) ranging from 2 to 3, alone or in combination with 80 mg of aspirin daily.[15] In patients with recurrent thrombotic events despite appropriate anticoagulation, Intravenous immunoglobulin 400mg/kg qd for 5 days, antiCD20 monoclonal antibody 375 mg/m^2 per week for 4 weeks may be of benefit.[13] In lupus patients with this syndrome, antimalarial therapy may be helpful in treating the atrophie blanche-type lesions and may be protective against arterial or venous thrombosis.[12] Pregnancy morbidity is prevented by a combination of heparin with aspirin 80 mg daily. Intravenous immunoglobulin 400mg/kg qd for 5 days may also prevent abortions, while glucocorticoids are ineffective.[14]

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