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## April 2022 Critical Care Case of the Month: Bullous Skin Lesions in the ICU

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**History of Present Illness:** A 29-year-old female with past medical history of mixed connective tissue disease [lupus predominant], prior pulmonary embolism complained of a 2-week history of nonproductive cough. The cough began after her son was diagnosed with respiratory syncytial virus (RSV). Symptoms progressively worsened and now she is admitted from the emergency department (ED) with generalized weakness and progressive shortness of breath. Earlier in the day at an outside hospital, she tested positive for RSV, negative for COVID-19 and had normal O<sub>2</sub> saturations and was discharged home. She has not received COVID-19 vaccine. Symptoms progressed, 911 called and in the ED, she was found to have temperature = 104°F, SpO<sub>2</sub> = 64% on room air, and fasting blood sugar in the 40s. She was lethargic with visible respiratory distress and unable to answer questions.

### Past Medical History:

- Mixed connective tissue disease [features of systemic lupus erythematosus, rheumatoid arthritis, polymyositis, scleroderma]
- Membranous lupus nephritis [class V]
- History of pulmonary embolus

- Posterior intracranial artery infarct with venous sinus thrombosis in February 2020
- Hypertension
- Recent septic shock due to pneumococcal bacteremia 2 months prior to admission
- Post-op C section

### Medications:

- Atovaquone 750 mg BID
- Eliquis 5 mg BID
- Fluconazole 150 mg Q 72h
- Hydroxychloroquine 200 mg daily
- Nifedipine 30 mg daily
- Pantoprazole 40 mg BID
- Prednisone 5 mg daily
- Vitamin D<sub>3</sub> 2000 IU daily
- Albuterol PRN SOB
- Ferrous sulfate 325 mg daily
- Losartan 25 mg daily

### Social History and Family History

- Married, nonsmoker, rare social ethanol use, no recreational drug use
- Father with hypertension, mother with autoimmune disease

### Physical Examination:

- T = 40°C, heart rate = 130 beats/min, respiratory rate = 28 breaths/min, BP = 100/61 mm Hg, SpO<sub>2</sub> = 95% on

100% nonrebreathing mask, BMI = 24

- General: Lethargic well-nourished young woman unable to answer questions, accessory respiratory muscle use
- HEENT: Dry mucosa, no scleral icterus, injected conjunctiva
- Pulmonary: No audible wheeze, crackles, rhonchi
- CV: Tachycardic, regular, no murmur
- Abd: Tender bilateral upper quadrants, nondistended, no HSM
- Neurological: Moving extremities but unable to follow commands, CN grossly intact
- Psychiatric: Unable to assess, mentation/mood normal earlier in day per her husband
- Extremities: Warm with mottled UE and LE digits, scattered areas of purpura



Figure 1. Photographs of extremities taken during day 4 at the time of dermatology consult.

With this patient's presentation, what is the ***most likely cause of the purpura?***

1. Angioinvasive fungal infection

2. Thrombotic related to cryoglobulinemia
3. Septic emboli
4. Thrombosis from disseminated intravascular coagulation (purpura fulminans)
5. Depositional vessel disease from calciphylaxis

**Correct!**

#### **4. Thrombosis from disseminated intravascular coagulation (purpura fulminans)**

The skin changes are best described as retiform purpura, see the photos above. Retiform purpura is a branching (reticular), nonblanching (purpuric) patch or plaque that can occur anywhere on the body or mucous membranes. They are typically accompanied by central necrosis and/or ulceration. It differs from livedo reticularis and livedo racemosa which have partial or intermittent reduction of blood flow and are rarely necrotic.

Initial Laboratory Evaluation

- Na 128, K 3.8, Cl 98, HCO 9, BUN 27, Cr 1.8, Glu 195 (post D50 given in ED)
- WBC 3.0, Hgb 9.7, hematocrit 34.3, Platelets  $65 \times 10^6/\text{mcL}$ . (new thrombocytopenia)
- PT 63, INR 5.4, PTT >150
- AST 273, ALT 120
- Venous blood gases (peripheral) 7.13 / 33
- Procalcitonin 74 ng/ml (normal <0.1 ng/ml), fibrinogen 44 g/L (normal 200-465), D-dimer >7650 (normal <0.5)
- Lactic acid 10.7 mm/L

What is the ***most likely underlying cause(s)*** of her skin lesions?

1. Discoid lupus
2. Cholesterol emboli
3. Sepsis syndrome

4. 1 and 3
5. All of the above

**Correct!**

### 3. Sepsis syndrome

There are many causes of retiform purpura and in this patient's presentation, she has several potential causes. The most likely is intravascular occlusion related to disseminated intravascular occlusion (DIC) and when presentation is widespread, it is called purpura fulminans. Another potential cause in this patient is a hypercoagulable state such as from catastrophic anti-phospholipid syndrome, antithrombin III deficiency, protein C/S deficiency, prothrombin III mutation, factor V Leiden or hyperhomocysteinemia.

Purpura from cryoglobulinemia due to hyperviscosity and blood vessel occlusion can occur as well as cryofibrinogenemia resulting from the precipitation of fibrin, fibrinogen also due to cold exposure. Both cryoglobulinemia and cryofibrinogenemia purpura tend to occur in acral or peripheral parts of the body.

A portable chest x-ray was taken post intubation in the ICU (Figure 2).



Figure 2. Portable chest x-ray taken after intubation in the ICU.

This patient had bacteremia twice with *Streptococcus pneumoniae* within two months. **What statements are correct?**

1. Historically, invasive *Streptococcus pneumoniae* is of high incidence in persons with HIV.
2. Purpura fulminans may occur with *S. pneumoniae* in splenectomized individuals.
3. CRP binds to the C-polysaccharide of *S. pneumoniae* and kills the bacterium.
4. *S. pneumoniae* bacteremia is often seen in patients with multiple myeloma.
5. All the above

**Correct!**

### 1. All of the above

Infection can cause retiform purpura particularly meningococemia which is a common cause of DIC. Her blood cultures showed 2 of 2 bottles cultured Gram positive cocci in pairs and chains.

Septic vasculitis presents with retiform purpura with meningococemia, pseudomonal or streptococcal septicemia, gonococemia, and rickettsial infections. Purpura fulminans has a high mortality and high long-term morbidity. Gangrene in the acral areas is common and can require amputation of multiple digits after the patient stabilizes often late in the hospital course. Upon presentation, dermatology, rheumatology, nephrology and infectious disease physicians were consulted and the consensus was that the extensive skin lesions were from severe DIC or purpura fulminans. Several additional tests should have been performed to further evaluate this patient with recurrent pneumococcal bacteremia including determining whether she has a spleen; measuring her antibody levels and doing an HIV test as well. Patients with lupus can sometimes autoinfarct their spleen essentially creating a splenectomized patient.

Important questions arise given her history and presentation including the differential diagnosis from a rheumatologic standpoint, and does she need high dose steroids for disease flare, does she need urgent plasma exchange in the setting of life-threatening clinical condition with underlying SLE, and/or does she need IVIG related to ITP from lupus or cutaneous lupus?

Based on the initial presentation, what is the patient's *most likely rheumatological diagnosis*?

1. Lupus flare (cutaneous lupus, lupus nephritis, diffuse alveolar hemorrhage, pneumonitis)
2. Catastrophic antiphospholipid syndrome (CAPS)
3. Hemophagocytic lymphohistiocytosis (HLH) also called macrophage activation syndrome (MAS)?
4. Vasculitis (vasculitis secondary to lupus)
5. None of the above

**Correct!**

**5. None of the above**

Discoid lupus causes round, coin-shaped lesions (sores). The sores most commonly develop on the scalp and face, but they may show up on other parts of your body. Discoid lesions typically do not hurt or itch. They may be scaly, thick or red. When the lesions go away, they may leave scars or skin discoloration.

Not known initially on admission the patient's double stranded DNA (DsDNA) levels which correlate with lupus disease flare were trending down even on this admission-321 on 10/6, 40 on 12/17, 18 on 12/20. C3 was slightly lower than previous value but sepsis itself can cause C3 to be lower. C4 level is similar to past levels. The main point regarding active lupus is to check DsDNA, C3 and C4 levels in order to trend values and help determine diagnosis.

Leukopenia often correlates with disease activity in lupus. Leukocytosis in lupus patients is worrisome for infection. Direct antiglobulin (Coombs) test was negative and severe thrombocytopenia is uncommon in lupus. Our patient's labs are more suggestive of DIC.

Catastrophic antiphospholipid syndrome (CAPS) consists of widespread thrombotic disease with multiorgan failure. Classification criteria is 3 or more organs involved simultaneously accompanied by small vessel thrombosis in a patient with antiphospholipid antibodies. Testing involves IgG and IgM antibodies to cardiolipin, beta2-glycoprotein I and lupus anticoagulant (LA).

In this patient, there was no clear evidence of thrombosis, and aPL antibodies were negative in the past. The history of PE, left PICA territory infarct with venous thrombosis of left sigmoid sinus did make CAPS a strong possibility however.

Hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) is an aggressive and life-threatening syndrome of excessive immune activation and can occur with rheumatologic disorders. The term macrophage activation syndrome (MAS) is used when HLH develops in a rheumatologic condition. In addition, HLH may develop any time during the course of a rheumatologic disorder. HLH presents with fever, skin rash/purpura, bicytopenia, splenomegaly, elevated liver function tests, hypertriglyceridemia, elevated ferritin, evidence of hemophagocytosis, NK cell activity, and elevated sCD25. In this patient's presentation, the leukocytosis goes against HLH/MAS, ferritin was 1403 (less than 3000), and slightly elevated sCD25 likely represent bacterial or viral infections.

If suspecting purpura fulminans, what lab tests should you order?

1. DIC panel
2. Protein C
3. Protein S

4. Peripheral smear
5. All of the above

**Correct!**  
**All of the above**

In addition to the above laboratories, would also recommend adding LDH, haptoglobin, reticulocyte count, and HIT panel. This patient has acute purpura fulminans likely secondary to Streptococcus pneumococcal bacteremia with evidence of low Protein C (18%), Protein S (11%) and Antithrombin levels (20%). It is recommended to treat with supportive care using FFP transfusions, not plasmapheresis as it is not antibody mediated. Daily Protein C levels were followed in addition to routine labs. In addition, Protein C concentrate may also be required.

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