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CHEST

A 57-Year-Old Man With COVID-19 Pneumonia Who Required Venovenous Extracorporeal Life Support With a Rapidly Escalating WBC Count

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CASE PRESENTATION: A 57-year-old man who had been intubated and placed on venovenous extracorporeal membrane oxygenation for hypoxemic respiratory failure due to COVID-19 pneumonia was transferred to our facility. He underwent anticoagulation with IV heparin titrated to an anti-Factor Xa goal of 0.1 to 0.3 international unit/mL. Over extracorporeal membrane oxygenation days 13 to 17, his WBC count rose from 17,500 to 47,000 cells/μL. He simultaneously experienced the development of fluid-refractory shock that required multiple vasopressors and received stress-dose hydrocortisone when his WBC was 30,000 cells/μL. He remained afebrile and was started on broad-spectrum antimicrobials that included antifungal and anthelminthic therapy. CHEST 2021; 160(2):e189-e193

Physical Examination Findings

The following vital signs were recorded: temperature, 36.4°C; heart rate, 146 beats per minute; BP, 106/62 mm Hg; respiratory rate, 10 breaths per minute, and SpO_2, 91%. He had been sedated and was immobile and unresponsive. There were moderate thin white secretions in his chest with minimal breath sounds; he was receiving a tidal volume of 100 mL on pressure control ventilation. His abdomen was soft and benign. His skin and extremities were cool with no edema or rashes; the 31Fr right internal jugular dual lumen catheter site was clean.

The following are the extracorporeal life support circuit values: flow, 4.67 L/min with a speed of 3,550 rpm for 24 hours; sweep gas flow, 7 L/min, up from 5 L/min.

Diagnostic Studies

His WBC count rose as described earlier (Fig 1). The WBC differential was 68% neutrophils, 9% lymphocytes, 12% monocytes, 2% eosinophils, 1% basophils, 8% immature granulocytes, and 6% nucleated RBCs. A peripheral smear revealed toxic granulations, Dohle bodies, increased bands, and nucleated RBCs.

Clostridioides difficile stool test was negative. Multiple blood and urine cultures and BAL for bacteria and fungus were negative. His anti-Xa level was undetectably low.

Relevant laboratory values are noted in Table 1. His WBC count and hemoglobin trend with key events indexed are shown in Figure 1.

We obtained a CT scan of his abdomen and pelvis with IV contrast (Fig 2).

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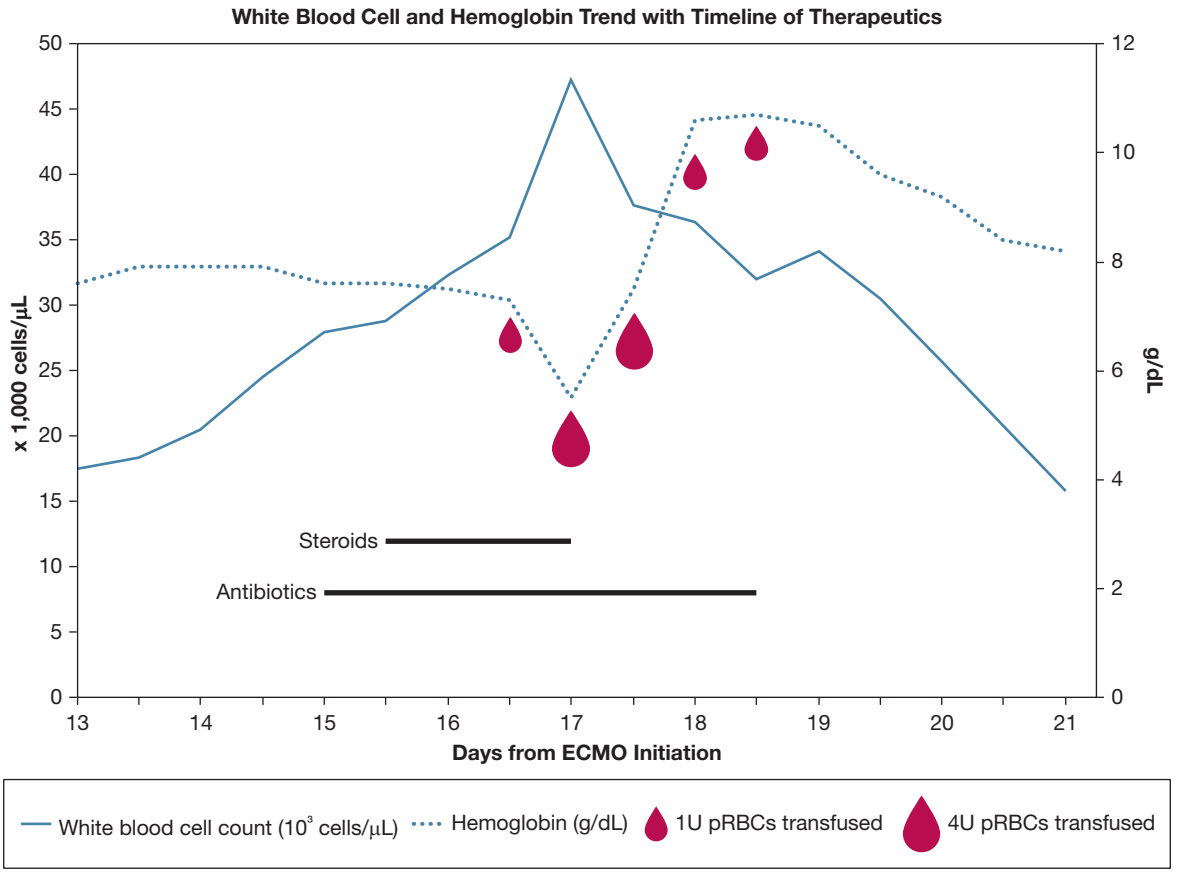

Figure 1 – *WBC count and hemoglobin trend with timeline of therapeutics. ECMO = extracorporeal membrane oxygenation; pRBC = packed RBC.*

TABLE 1] Notable Laboratory Values

Variable	Day 13	Day 17
Haptoglobin	Undetectable	Undetectable
Thrombin time (heparin removed), 16-25 s	…	25
D-dimer, μg/mL	…	8.12
Fibrinogen, mg/dL	485	323
Aspartate aminotransferase, units/L	81	209
Alanine aminotransferase, units/L	35	103
Bilirubin, total, mg/dL	0.9	3.2
Bilirubin, indirect, mg/dL	0.4	1.1
Plasma free hemoglobin, (normal, 0-5; days 12 and 17), mg/dL	41	8

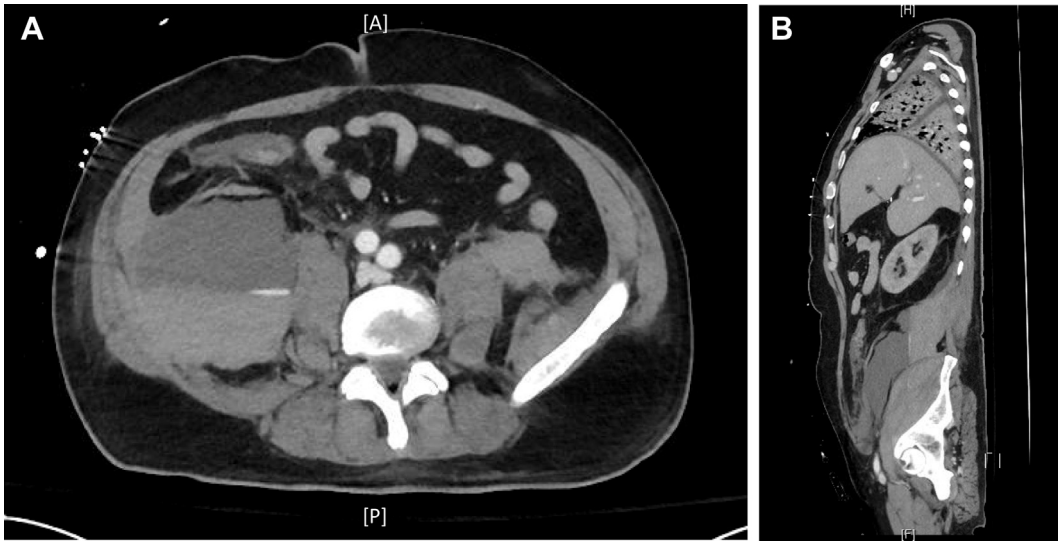

Figure 2 – *CT images of the patient's abdomen. A, Axial cut at the superior portion of the iliac wings; B, sagittal cut. A = anterior; F = foot; H = head; P = posterior.*

What is the diagnosis?

Diagnosis: Leukemoid reaction caused by acute blood loss anemia due to retroperitoneal hemorrhage

Discussion

A leukemoid reaction, sometimes defined as a WBC count exceeding 25,000 cells/μL, is a marked reaction to a neutrophilic stimulus; as such, the peripheral blood smear is characterized by mature cells with a neutrophilia with reactive changes present within the neutrophils. Leukemoid reactions are nonmalignant. They are due to physiologic stressors that cause the release of endogenous catecholamines, glucocorticoids, and inflammatory cytokines, leading to demargination of circulating neutrophils as well as increased bone marrow release of immature granulocytes and nucleated red cells.

A peripheral smear should be reviewed for malignancy as the cause of marked leukocytosis. Chronic myelogenous leukemia, the most common hematologic malignancy with a marked leukocytosis, is characterized by increased myelocytes and basophils. An acute leukemia may have blasts on WBC count differential, and the smear may demonstrate hypogranular neutrophils. Patients with hematologic malignancies may have even more extreme leukemoid reactions when critically ill (eg, >50-100,000 cells/μL). If leukemia remains on the differential, a hematologist should be consulted, and blood should be sent for immunophenotyping.

Once malignancy has been excluded, including paraneoplastic syndromes, the differential diagnosis of a leukemoid reaction includes severe bacterial infections (particularly *Clostridioides difficile*), TB, severe hemorrhage, exposure to medications, or toxins (eg, glucocorticoids, ethylene glycol). Dohle bodies and toxic granulation seen on a smear are not helpful in distinguishing infection from other causes. A leukemoid reaction secondary to hemorrhage arises from a stressed bone marrow releasing immature cells into the circulation. Leukemoid reactions generally resolve with treatment of the driving condition.

Distinguishing the cause of a leukemoid reaction in a patient on ECMO can be difficult. Fever to suggest infection or drug reaction can be masked by temperature regulation through the extracorporeal circuit. Patients with ARDS typically have abnormal chest radiographs, poor lung compliance, and minimal cough so that incipient pneumonia may require invasive testing to diagnose. Retroperitoneal hemorrhages or intraabdominal infections require cross-sectional imaging for diagnosis, and the risks of transporting a patient with an unstable condition must be weighed against the value of the diagnostic information. The logistics of patient transport and invasive diagnostic testing with patients who are critically ill with COVID-19 are significantly more burdensome, given the necessity for rigorous adherence to protocols for personal protection equipment and environmental cleaning.

Clinical Course

The patient experienced a retroperitoneal hemorrhage while receiving IV heparin to prevent circuit thrombosis while being supported by venovenous ECMO for hypoxemic respiratory failure. His hemorrhage was characterized by worsening shock over several days with a leukemoid reaction without evidence of infection or improvement on broad spectrum antibiotics. After discovery of his hemorrhage on CT scan, we resuscitated him with 4 units of packed RBCs, 3 units of fresh frozen plasma, and 1 unit of platelets. His WBC count improved to 31,500 cells/μL over the subsequent day and fell to 15,000 cells/μL 3 days later with all anti-infectives discontinued. He was still under physiologic stress, but we identified no infectious source or other cause of his leukemoid reaction. He remained on venovenous ECMO without improvement in lung function, and his family chose to withdraw life-sustaining treatments on ECMO day 23, after which he died.

Clinical Pearls

1. *The differential diagnosis of a leukemoid reaction includes severe infection, severe hemorrhage with acute anemia, and exposure to glucocorticoids or certain toxins. A peripheral blood smear should be obtained to exclude malignant causes.*
2. *Retroperitoneal hemorrhage in a patient on ECMO is difficult to detect. Patients experience multifactorial coagulopathy and acquired anemia due to frequent laboratory draws, critical illness, and hemolysis due to the ECMO circuit. Laboratory markers will frequently reflect hemolysis, but other sources of blood loss should be sought. Clinicians must be finely attuned to clinical changes and have a high index of suspicion for impending catastrophe.*

3. *Clinical changes in patients on ECMO are nonspecific; thus, cross-sectional imaging should be considered early. The decision to obtain additional imaging requires assessment of the risk/benefit ratio of transporting critically ill patients and preparing for logistical challenges.*

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Suggested Readings

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