Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
A 57-Year-Old Man With COVID-19 Pneumonia Who Required Venovenous Extracorporeal Life Support With a Rapidly Escalating WBC Count

Joshua A. Krieger, MD; Jenna R. Wixon-Genack, MD; Samuel P. Mandell, MD; and James A. Town, MD

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 vaspressors 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.

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 SpO₂, 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).

AFFILIATIONS: From the Division of Pulmonary, Critical Care and Sleep Medicine (J. Krieger and J. Town) and the Department of Internal Medicine (J. Wixon-Genack), University of Washington; and the Department of Surgery (S. Mandell), Harborview Medical Center, Seattle, WA.

CORRESPONDENCE TO: Joshua A. Krieger, MD; email: jakrieger@gmail.com
Published by Elsevier Inc. under license from the American College of Chest Physicians.
DOI: https://doi.org/10.1016/j.chest.2021.04.003
**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               |
What is the diagnosis?

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.
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.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Other contributions: CHEST worked with the authors to ensure that the Journal policies on patient consent to report information were met.

Suggested Readings

Marinella MA. Extreme leukemoid reaction associated with retroperitoneal hemorrhage. Arch Intern Med. 1998;158(3):300-301.

Sakka V, Tsiodras S, Giamarellos-Bourboulis EJ, Giamarellou H. An update on the etiology and diagnostic evaluation of a leukemoid reaction. Eur J Intern Med. 2006;17(6):394-398.

Thachil J, Hill QA, eds. Haematology in Critical Care: A Practical Handbook. John Wiley & Sons Ltd; 2014.

Kaushansky K, ed. Williams Hematology. Ninth ed. McGraw-Hill; 2016.

Gao X, Bachan M, Khan Z, Siegel R. 509: fulminant clostridium difficile colitis associated with extreme leukemoid reaction. Crit Care Med. 2018;46(1):239.

Hoffman R, ed. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018.

Thomas J, Kostousov V, Teruya J. Bleeding and thrombotic complications in the use of extracorporeal membrane oxygenation. Semin Thromb Hemost. 2018;44(1):20-29.

Karakonstantis S, Koulouridi M, Pitsillos K, et al. A prospective study of hospitalized patients with leukemoid reaction; causes, prognosis and value of manual peripheral smear review. Rom J Intern Med. 2019;57(3):241-247.

Shekar K, Badulak J, Peek G, et al. Extracorporeal life support organization coronavirus disease 2019 interim guidelines: a consensus document from an international group of interdisciplinary extracorporeal membrane oxygenation providers. ASAIO J. 2020;66(7):707-721.

Wahidi MM, Shojaee S, Lamb CR, et al. The use of bronchoscopy during the coronavirus disease 2019 pandemic. Chest. 2020;158(3):1268-1281.