Atypical Peripheral Smear Findings in a Patient With Fever and Cough During Spring of 2020

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CASE HISTORY

A 72-year-old man and former smoker with hypertension, obesity, and topical-steroid controlled psoriasis presented in mid April 2020 with a 2-week history of fevers, productive cough, body aches, and worsening dyspnea. His temperature was 98°F; weight, 107 kg; respiratory rate, 25 breaths per minute; and room air pulse oxygen saturation, 85%. Rhonchi were appreciated at both lung bases on physical examination. A portable chest x-ray revealed bilateral airspace opacities, right greater than left, with peribronchial cuffing, worrisome for pneumonia (Fig. 1). Due to worsening hypoxemia, the patient was intubated and placed on mechanical ventilation. The D-Dimer was 5346 ng/mL; ferritin, 525 ng/mL; C-reactive protein, 240 mg/L; and procalcitonin, 0.17 ng/mL. The white blood cell count was 9400/mm³, and the lymphocyte count was 600/mm³. The peripheral smear was reviewed, and four slides are being shown (Fig. 2).

WHAT IS THE DIAGNOSIS

Coronavirus disease-2019 (COVID-19) pneumonia with virocytes on peripheral smear.

Since the first reported cases in December 2019, infection with severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic.¹ The COVID-19—the illness caused by SARS-CoV-2—has overwhelmed health care systems globally, including the ones in Suffolk county, Long Island, NY. A nasopharyngeal swab was collected in our patient, and it was positive by rapid polymerase chain reaction (Xpert® Xpress; Cepheid, Sunnyvale, CA) for COVID-19. Hydroxychloroquine and azithromycin were started for COVID-19 treatment. The peripheral blood smear revealed 5% atypical lymphocytes (Fig. 2A). Other atypical lymphocytes, or "virocytes," were also seen. Figures 2B and C show large granular lymphocytes with azurophilic granules (arrow heads), and Figure 2D, a monocytoid cell with budding (asterisk) of the peripheral membrane.

Atypical or reactive lymphocytes can be seen in the peripheral smear by light microscopy. They are nonmalignant white blood cells of lymphoid origin and are observed in various conditions that include viral infections (e.g., infectious mononucleosis, respiratory syncytial virus, dengue hemorrhagic fever), nonviral

Medical Center, Northport, 79 Middleville Rd, Northport, NY 11768. E-mail: george.psevdos@va.gov. The authors have no funding or conflicts of interest to disclose. infections (e.g., Q fever, tuberculosis), reactions to drugs (e.g., Dilantin, phenothiazine), autoimmune (e.g., lupus) and idiopathic disorders (e.g., myasthenia gravis).^{2,3} These cells were described a century ago but Litwins and Leibowitz⁴ in 1951 first proposed the term "virocyte" to describe them in viral infections other than infectious mononucleosis. Compared with normal circulating lymphocytes, atypical lymphocytes are larger and have abundant cytoplasm, which often spreads around and gets indented by neighboring red calls.⁵ Infection by Epstein-Barr virus leads to lymphocytosis due to direct infection of B-lymphocytes by the virus. In contrast, infection by the coronavirus causing the Middle East respiratory syndrome (MERS), leads to lymphopenia. This is due to the direct infection of Middle East respiratory syndrome coronavirus of T-lymphocytes leading to cell apoptosis while no viral replication can occur.⁶ Lymphocytopenia was noted in our patient, as seen in patients with COVID-19 in China.⁷ There is preliminary evidence that SARS-CoV-2 can also infect T-cell lymphocytes leading to apoptosis.⁸ Zini et al⁹ described morphological findings of circulating white blood cells in COVID-19 afflicted patients in Italy. They observed large atypical lymphocytes, dysplastic myelocytes with azurophilic granules, and apoptotic cells of both lymphocyte and neutrophil origins.

During this emerging pandemic by SARS-CoV-2, clarifying all aspects of COVID-19 pathogenesis is an understandable urgency. Not surprisingly, this viral infection causes the production of "virocytes," which are visible in the peripheral smear. Although lymphocytopathic changes seen in atypical reactive lymphocytes are usually not unique for specific pathogens—including SARS-CoV-2—their mere presence in COVID-19 suggests the need for



FIGURE 1. Portable chest x-ray with bilateral airspace opacities.

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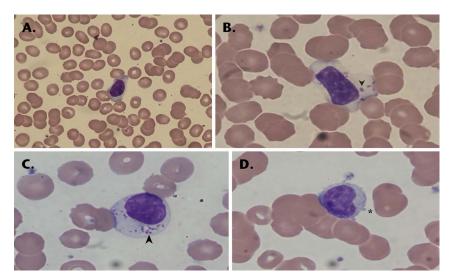


FIGURE 2. (A) Atypical lymphocyte; (B and C) large granular lymphocytes with azurophilic granules (arrow heads); (D) monocytoid cell with budding (asterisk) of the peripheral membrane.

further studies to elucidate the role of this novel coronavirus in myelopoiesis and overall disease pathogenesis.

REFERENCES

- Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91:157–160.
- 2. Simon MW. The atypical lymphocyte. Int Pediatr. 2003;18:1.
- Murray JC, Gresik MV, Serabe BM, et al. Pathological case of the month. Peripheral blood "virocytes" associated with respiratory syncytial virus bronchiolitis. *Arch Pediatr Adolesc Med.* 1995;149:1033–1034.
- Litwins J, Leibowitz S. Abnormal lymphocytes ("virocytes") in virus diseases other than infectious mononucleosis. *Acta Haematol*. 1951;4: 223–231.

- Lichtman MA, Kaushansky K, Prchal JT, et al, eds. The Mononucleosis syndromes. In: *Williams Manual of Hematology*. 9e ed. New York, NY: McGraw- Hill; http://hemonc.mhmedical.com/content.aspx?bookid= 1889§ionid=137389740 accessed April 24.2020.
- Lim YX, Ng YL, Tam JP, et al. Human coronaviruses: a review of virus-host interactions. *Diseases*. 2016;4(3):26.
- Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis.* 2020; https://doi. org/10.1093/infdis/jiaa150.
- Wang X, Xu W, Hu G, et al. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cell Mol Immunol.* 2020. https://doi.org/10.1038/s41423-020-0424-9.
- Zini G, Bellesi S, Ramundo F, et al. Morphological anomalies of circulating blood cells in COVID-19. *Am J Hematol.* 2020. Published ahead of print. https://doi.org/10.1002ajh.25824.