CLINICAL IMAGE

Impaired humoral immune response in a COVID-19 patient with chronic lymphocytic leukemia complicated by spontaneous pneumomediastinum and hemophagocytic lymphohistiocytosis syndrome

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A 37-year-old man was admitted to the hospital with a 2-day history of dry cough and a fever of 40 °C. His medical history included chronic lymphocytic leukemia, which had been diagnosed 6 months before and treated with 6 cycles of rituximab and cyclophosphamide. He tested positive for COVID-19 by a polymerase chain reaction (PCR) test (June 2020).

On admission, the patient was in good general condition, without features of respiratory and cardiovascular failure. His laboratory tests indicated pancytopenia and a moderate elevation of inflammatory markers. A radiographic examination of the chest (computed tomography [CT] angiography, X-ray) displayed extensive bilateral ground-glass opacities in the lungs, with no features of pulmonary embolism. Flow cytometry revealed a severe depletion of B lymphocytes, which was consistent with prior rituximab therapy for chronic lymphocytic leukemia. Additional analysis of B-cell subpopulations was also performed (FIGURE 1A–1C).

Over the course of hospitalization, a bacterial coinfection was suspected due to clinical deterioration and increasing levels of inflammatory markers, which prompted initial treatment with ceftriaxone. No clinical improvement provoked switching the antibiotic regimen to ceftazidime and amikacin, and then to meropenem, levofloxacin, and linezolid. Enoxaparin in an intermediate dose was also adopted. Trimethoprim / sulfamethoxazole, acyclovir, and antifungal therapy were then added. Extensive microbiological tests of the blood, urine, and bronchoalveolar lavage fluid repeatedly showed negative results. Due to a further decrease in the neutrophil count and recurrent high fever, neutropenic fever was suspected and a granulocyte colony–stimulating factor was administered.

Dexamethasone was administered because of progressive respiratory failure. On day 9 after admission, the patient required passive oxygen therapy. Due to increasing levels of D-dimers and a high risk of thromboembolism, a regimen with therapeutic-dose enoxaparin was started. Control chest X-ray showed a significant progression of infiltrative lesions in the left lung. Furthermore, abdominal CT indicated hepatosplenomegaly. Anti–SARS-CoV-2 immunoglobulin A and immunoglobulin G tests that were performed on day 12 and 24 after symptom onset continued to show negative results. However, repeated PCR tests of nasopharyngeal swab specimens were positive for SARS-CoV-2 infection.

On day 17 of hospitalization, chest CT and X-ray were performed due to a sudden clinical deterioration. Spontaneous pneumomediastinum, subcutaneous emphysema, and progression of lung lesions were found (FIGURES 1D–1F). After laryngological and thoracic surgery consultations, a conservative treatment was adopted. Two days later, convalescent plasma was transfused. Afterwards, the patient's respiratory failure worsened and he was relocated to the Intensive Care Unit.

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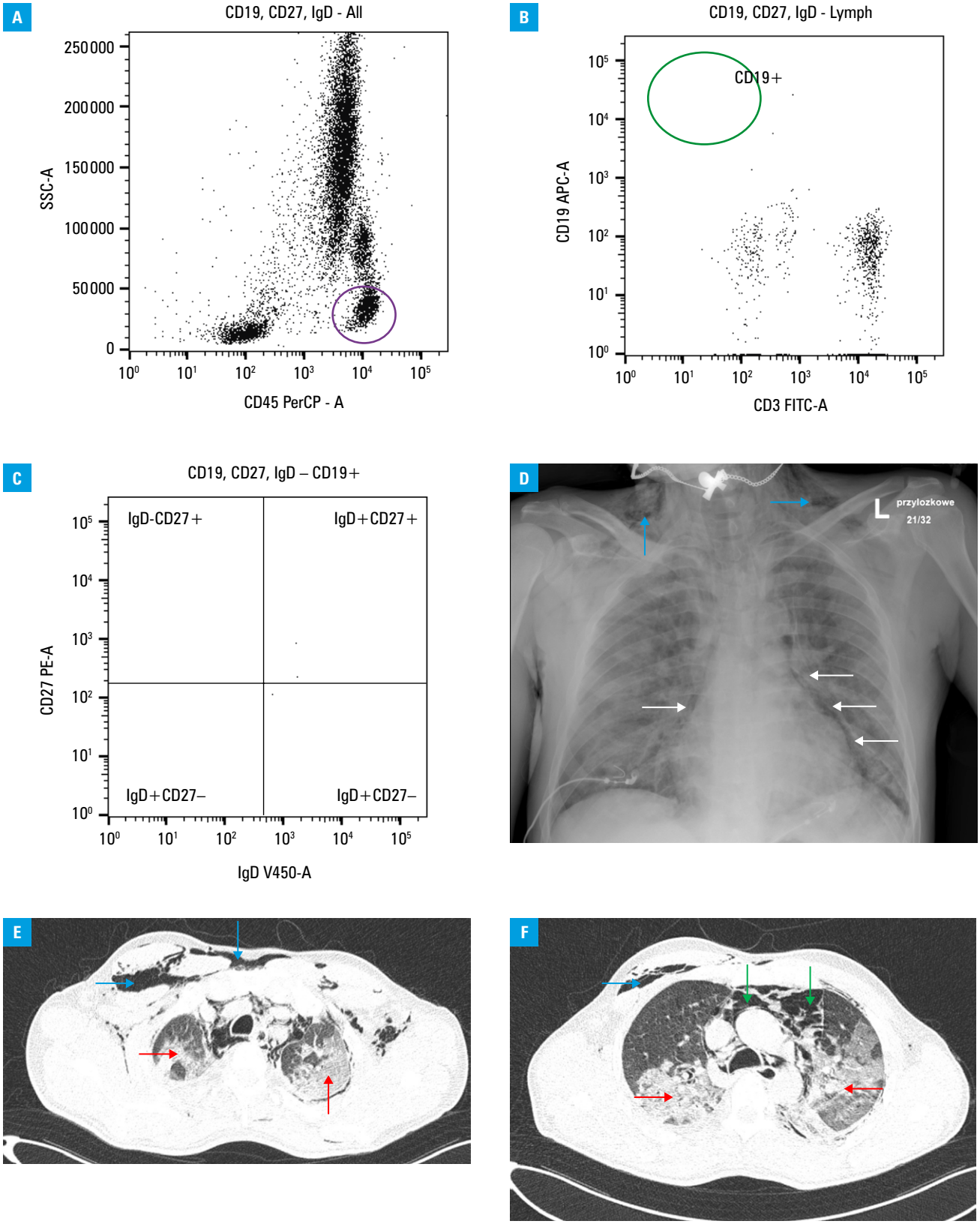

FIGURE 1 **A**–**C** – flow cytometry of the patient (EDTA-anticoagulated blood stained with the mixture of monoclonal antibodies, sampled on day 3 of hospitalization). The entirety of detected lymphocytes is indicated by the purple circle in the SSC vs CD45 PerCP plot (**A**). B cells were identified as $CD19^{+}CD3^{-}$ and their depletion related to dysregulated humoral immunity is marked by the green circle (**B**). $CD19^{+}$ B cells comprised only 0.3% of all lymphocytes (**C**). Subclasses such as nonswitched memory, switched memory, and double-negative B cells were not identified. **D** – chest X-ray performed on day 17 of hospitalization. Pneumomediastinum (white arrows) and subcutaneous emphysema (blue arrows) in the neck area as well as further progression of infiltrative lesions in both lungs were discovered. **E**, **F** – computed tomography scan performed on day 17 of hospitalization showing pneumomediastinum (**F**, green arrows) and subcutaneous emphysema (blue arrows) in the upper parts of the chest and in the neck. The distribution of airspace suggested perforation of the upper respiratory tract. Additionally, extensive ground-glass opacities in the upper lobes of both lungs were visualized (**E**, red arrows), with the greatest intensity in the peaks, and similar lesions with overlapping consolidations were found in the lower lobes (**F**, red arrows).

G

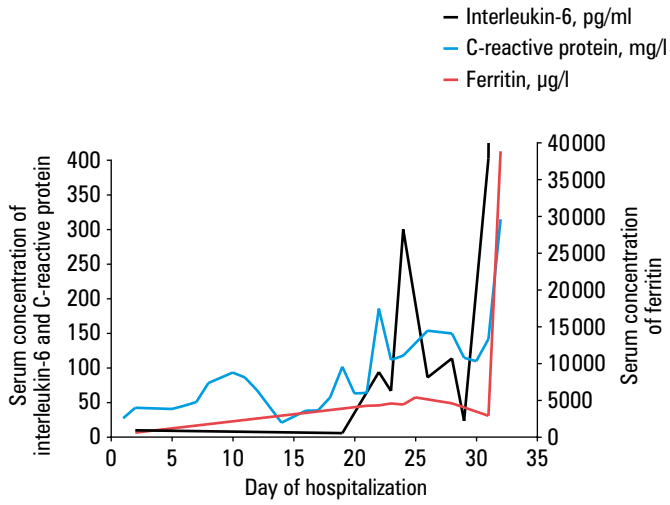

FIGURE 1 G – fluctuations of serum interleukin-6, C-reactive protein, and ferritin levels during hospitalization

A high-flow nasal oxygen therapy was initiated. After 10 days in the Intensive Care Unit, the patient was intubated and mechanical ventilation was started. However, his general condition continued to deteriorate. Finally, he experienced sudden asystolic cardiac arrest and consequently died.

Continuously elevated and increasing levels of interleukin-6, C-reactive protein, and ferritin (FIGURE 1G) which were observed during hospitalization synergize with the COVID-19 cytokine storm.[1] Furthermore, based on the HLH-2004 diagnostic criteria, rapidly increasing levels of ferritin, persistent fever, splenomegaly, and pancytopenia raised a suspicion of hemophagocytic lymphohistiocytosis syndrome.[2] The H-score estimated a 95.5% probability of hemophagocytic lymphohistiocytosis.[2] In accordance with the available literature, B-cell depletion, dysregulated humoral immunity, and a high H-score are independent predictors of mortality in COVID-19, which elucidates the unfavorable prognosis in our patient.[3,4] In contrast, it has recently been underlined that there is no association between the level of SARS-CoV-2–neutralizing antibodies as a single parameter and severity of the disease.[5] The adaptive immune response is a broad concept comprising also SARS-CoV-2 antigen–specific $CD4^+$ T cells and $CD8^+$ T cells enhancing viral clearance; therefore, only harmonized functioning of these 3 mechanisms may minimize the COVID-19 fatality.[5]

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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