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LETTER TO THE EDITOR

Pleural effusion as a rare sign of anaplastic large-cell lymphoma in a COVID-19 patient: A case report and literature review

Dear Editors,

COVID-19 can induce pleiotropic symptoms and laboratory abnormalities. With this case report, we would like to raise awareness that COVID-19 is not a "catchall" diagnosis.

A 58-year-old man presented to the emergency department for dyspnea worsening since the last 5 days. In his history, he suffers from chronic obstructive pulmonary disease (COPD) GOLD II due to active smoking, arterial hypertension, atrial fibrillation, and obesity. He presented with bilateral pneumonia in October 2019 of unknown etiology treated successfully empirically with amoxicillin/clavulanic acid and clarithromycin. At that time, a chronic lymphopenia (around 400 lymphocytes/µL) is already present, but not explored. On admission, the patient was apyretic and had a blood pressure of 106/76 mmHg, 106/min heart rate, and oxygen saturation at 86%. Laboratory main findings showed a worsening of his lymphopenia (40 lymphocytes/µL, reference value: 1.2-3.5 10^3/µL), high D-dimer level (3570 ng/mL, reference value 0-500 ng/mL) normal platelet and white blood cell count, negative serology for HIV, treponema, hepatitis B and C, and a positive SARS-CoV-2 RT-PCR. Chest scan showed no pulmonary embolism, a pleural effusion, and 35% of lungs surface lesions highly suggestive of COVID-19 infection. Patient was hospitalized, and azithromycin, hydroxychloroquine, cefuroxime, and oxygen therapy were administered. A pleural tap was performed, showing 2900 red blood cells/µL and 1710 leukocytes/µL with 93% lymphocytes and 7% neutrophils. Lymphocytes displayed a highly basophilic cytoplasm, and clearly visible nucleolus (Figure 1). Those atypical lymphocytes were, together with the laboratory results, compatible with COVID-19. Nonetheless, puzzled by the number and the aspect of pleural cells, the pathologist performed an immunophenotype on pleural tap which showed an infiltration of T lymphocytes $CD3^+$, $CD7^+$, $CD2^-$, $CD16/56^-$, $CD57^-$, $CD5^-$, TCR gamma/delta, $CD45RO^+$, $CD45RA^-$, $CD25^+$, $CD30^+$, $CD4^-$, and $CD8^-$ compatible with anaplastic large-cell lymphoma (ALCL). At that time, no immunohistochemical analysis was requested or performed. TAC-PET and bone marrow biopsy were scheduled but could not be performed due to patient admission to intensive care unit (ICU) following a severe desaturation (76% of SaO_2). A second pleural tap was performed and sent to the pathologist for immunochemistry staining.

Patient condition worsened in the ICU with an increased pyrexia to 38.9°C, low blood pressure 88/59 mmHg, and a productive cough. The current diagnosis was a secondary pulmonary infection with *Klebsiella pneumoniae* and *Staphylococcus aureus* isolated on nasopharyngeal aspirate. Unfortunately, patient passed away due to the severity of his condition. Complementary immunohistochemical results showed positivity for CD7, CD3, CD30 and negativity for CD5, CD4, CD8 and no expression of ALK protein (Figure 2). A T cell clonality test performed by PCR on paraffin-embedded tumor material and targeting the *TCRG* gene demonstrated a T cell monoclonality.

SARS-CoV-2 can be responsible of pleiotropic hematological abnormalities such as lymphopenia, with or without reactive lymphocytes, neutrophilia, and thrombocytopenia.[1] Among them, lymphopenia is the most common in COVID-19 patients. Huang & al. conducted a study in Wuhan showing that 63% of COVID-19 patients had a lymphopenia.[2] Lymphopenia is slightly reduced during the incubation period and worsens during the cytokine storm that may occur in some patients usually 7-14 days after onset of the symptoms.[1] The pathophysiology of COVID-19-associated lymphopenia is multifactorial. It is attributed to a direct toxicity of the SARS-CoV-2 on lymphocytes thanks to their membrane ACE2 receptor, to apoptosis induced by TNF-alpha released during the cytokine storm, to an inhibition of proliferation due to acid lactic acidosis, and to a

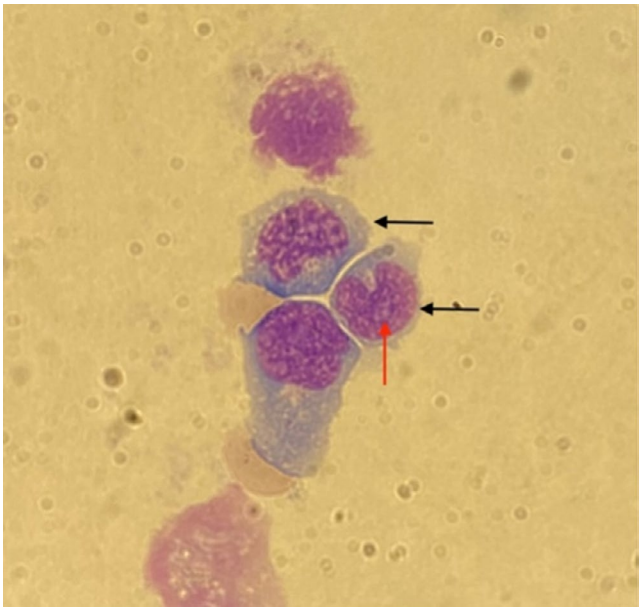

FIGURE 1 Pleural effusion tap of the patient showing lymphocytes displaying reactive morphology (black arrow) with a visible nucleolus (red arrow) (MGG × 1000)

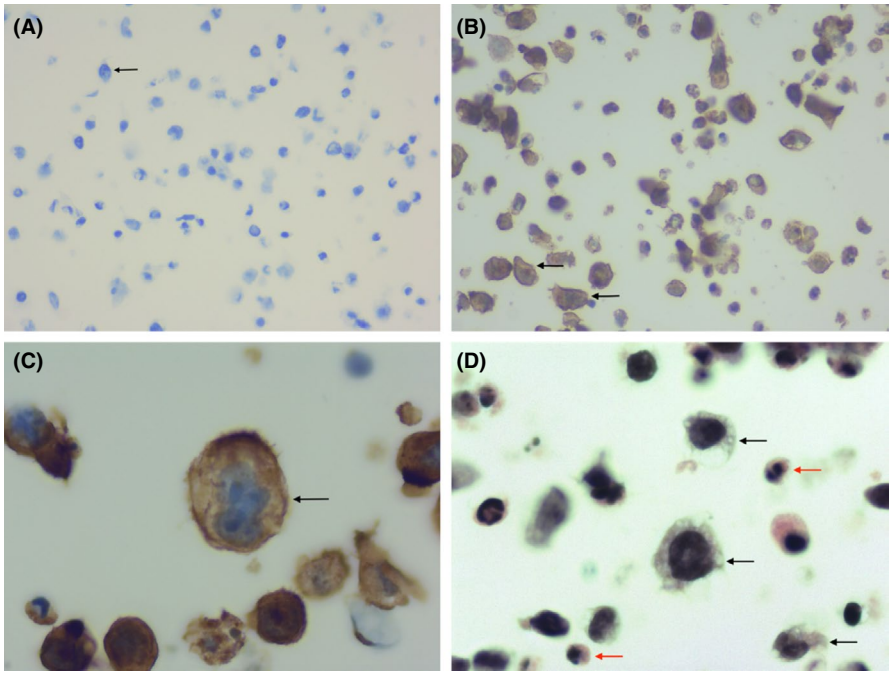

FIGURE 2 Immunohistochemical staining for CD30 and ALK. Pathological cells (black arrows) show negative ALK staining (A: ×400) and strong CD30 staining (B: ×400 and C: ×1000). Hallmark and "doughnut" cells (D: H&E staining × 1000) can be found and are targeted with black arrows. Neutrophils are marked with red arrows and can be used as a scale to assess hallmark cells width

direct virus toxicity on lymphoid organ resulting in lymphoid organ atrophy.[1,2] Nevertheless, lymphopenia is also frequently encountered in lymphoma, as observed in our patient.

Anaplastic large-cell lymphoma (ALCL) is a non-Hodgkin lymphoma (NHL) discovered in 1985.[3] Strong positivity for CD30 (also named Ki-1) is characteristic of ALCL. It is commonly a T-lymphocyte-type pathology but 15% are of B-type phenotype[4] and are considered as a variant of large B-cell lymphoma (DLBCL).[5] ALCL is classified by the World Health organization (WHO) in four entities: systemic anaplastic lymphoma kinase (ALK) positive or negative ALCL, primary cutaneous ALCL, and the breast implant-associated ALCL (occurring as a reaction to the silicone).[3]

Primary systemic ALCLs account for 1%-3% of adults NHL, among which 50%-60% are ALK-positive and 40%-50% ALK-negative.[3,6] ALK-negative ALCL has a worse prognosis than ALK-positive ALCL, with a 5-year overall survival of 49% and 70%, respectively.[6] ALK-negative ALCL involves less commonly extranodal tissue compared to ALK-positive ALCL and most patients usually present with a stage III-IV disease, B symptoms, and abdominal lymphadenopathy.[3] Although 11% of ALCL involve lungs, pleural infusion as a presenting symptoms is very rare, with only few cases reported in the literature.[5,7] This clinical presentation was nevertheless observed in our patient. Morphological features of ALCL consist of small to large atypical cells known as hallmark or "doughnut" cells, displaying an eccentric "kidney"-shaped nucleus with possible multiple basophilic nucleoli.[8] As previously mentioned, ALCL immunophenotype has a strong $CD30^+$, with ALK-negative ALCL usually expressing T cell antigens positive such as $CD3^+$ (in 68% cases), $CD4^+$, $CD43^+$, $CD45RO^+$, and $CD5^-$. CD8 positivity is rare, and cases with *DUSP-22* rearrangement can display double negativity for CD4 and CD8.[3,7] *DUSP22-IRF4* and *TP63* rearrangements, present respectively in 30% and 8% of the cases, are described as important promoters of the ALK-negative ALCL oncogenesis.[3]

Morphological characteristics of ALCL are similar to atypical lymphocytes encountered in COVID-19 patients. COVID-19 atypical lymphocytes are pleomorphic cells with a wide blue basophilic cytoplasm displaying a prominent nucleoli, with a round or indented nuclei[9] or of lympho-plasmacytoid shape similar to those encountered in Epstein-Barr or cytomegalovirus infection.[10] Our patient being diagnosed with COVID-19, pleural atypical cells (Figure 1) were compatible with a SARS-CoV-2 infection. To our surprise, additional analyses performed on the pleural fluid cells were rather compatible with ALCL. Indeed, cell flow cytometry immunophenotyping showed positivity for CD30, CD3, CD45R0 and negativity for CD5, CD4, CD8 confirmed by immunohistochemical staining revealing hallmarks and "doughnut" cells negative for ALK, CD4, CD8 and positive for CD30 (Figure 2). The diagnosis of ALCL was further supported by postmortem T cell clonality analysis performed on the paraffin-embedded pleural liquid and displaying a *TCRG* monoclonal rearrangement. *DUSP22-IRF4* chimeric gene could not be assessed due to the insufficient sample quantity.

By this case report, we want to draw attention that symptoms of presentation of hemato-oncological diseases, for example, lymphopenia and abnormal cell morphology, may be similar to those of COVID-19 and that differential diagnosis must be kept in mind. Lymphomas and hematological neoplasms are important to be ruled out in a context of COVID-19 suspicion. Patients suffering from COVID-19 infection with an underlying cancer are at higher risk of more severe outcomes, with hematological cancers having the highest severity and death rates among all cancers.[11] Lymphomas may present with cough, with or without fever, and possibly with a pleural effusion, which is also being described and added to the clinical spectrum of COVID-19.[12]

In the particular context of the COVID-19 pandemic, our patient's symptoms have been integrated into a clinical picture of viral

infection. In retrospect, the initial chronic lymphopenia and possibly primary lesions should have been the subject of an initial assessment as the underlying diagnosis was probably present prior to the COVID-19 infection phase. The final diagnosis was already of poor prognosis, further complicated by a severe SARS-CoV-2 infection which explains the rapidly declining clinical evolution of our patient.

CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

LR, AD, and OK collected the data for the manuscript. SL and PH performed the immunohistochemical staining and genetic analysis, respectively. OK wrote the manuscript. All authors reviewed and approved submission of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Omar Kamel[1]
Laurence Rozen[1]
Sophie Lecomte[2]
Pierre Heimann[3]
Anne Demulder[1]

[1]*Hematology Department, Laboratoire Hospitalier Universitaire de Bruxelles (LHUB-ULB), Université Libre de Bruxelles, Brussels, Belgium*
[2]*Department of Anatomopathology, CHU Brugmann, Brussels, Belgium*
[3]*Laboratory of Oncomolecular Biology, Department of Haematology, LHUB-ULB, Brussels, Belgium*

Correspondence
Omar Kamel, CHU Brugmann, Laboratoire Hospitalier Universitaire de Bruxelles (LHUB-ULB site Horta) Université Libre de Bruxelles, Place A. Van Gehuchten 4, 1020 Brussels, Belgium.
Email: omar.kamel@lhub-ulb.be

ORCID

Omar Kamel https://orcid.org/0000-0002-2318-1102

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