International Journal of Biomedicine 13(2) (2023) 357-360
http://dx.doi.org/10.21103/Article13(2)_CR5

CASE REPORT

INTERNATIONAL JOURNAL OF BIOMEDICINE

The Persistence of COVID-19-Related Pancytopenia as A Possible Sign of Hairy Cell Leukemia: A Case Report

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Abstract

COVID-19 is known to cause many hematological abnormalities, such as thrombocytopenia, leucopenia, and lymphopenia. Pancytopenia, a decrease in all peripheral blood cell lines, is a rare complication not commonly seen in patients with COVID-19. We report a case of a patient who experienced COVID-19 infection with mild clinical symptoms like fever, fatigue, and muscle and bone aches. The laboratory examinations revealed pancytopenia, mainly neutropenia, thrombocytopenia, mild anemia, and relative lymphocytosis, which persisted after infection resolution. The splenomegaly in abdominal echography and the characteristics of lymphocyte elements in peripheral blood smear examination raised suspicion of the presence of hairy cell leukemia (HCL); therefore, the patient was further examined with a bone marrow biopsy, which confirmed the diagnosis. The persistence of pancytopenia after recovery from COVID-19 infection, especially in patients with splenomegaly, should raise suspicion of another hematological coexistence diagnosis like HCL.(**International Journal of Biomedicine. 2023;13(2):357-360.**)

Keywords: COVID-19 • hairy cell leukemia • pancytopenia

For citation:Barbullushi (Rucaj) A, Kristo A, Davidhi A, Kullolli I. The Persistence of COVID-19-Related Pancytopenia as A Possible Sign of Hairy Cell Leukemia: A Case Report. International Journal of Biomedicine. 2023;13(2):357-360. doi:10.21103/Article13(2)_CR5

Abbreviations

HCL, hairy cell leukemia; **RBC**, red blood cells; **WBC**, white blood cells.

Introduction

A novel coronavirus, SARS-CoV-2 [an enveloped, positive sense, single-stranded RNA virus], causing COVID-19, has produced an ongoing pandemic in many countries.[1] Although the main target of the virus is the human respiratory system, it can affect other systems of the organism, especially the hematopoietic system and hemostasis.[2-4]

COVID-19 is known to cause many hematological abnormalities, such as thrombocytopenia, leucopenia, and lymphopenia.[5] Pancytopenia, a decrease in all peripheral blood cell lines, is a rare complication not commonly seen in patients with COVID-19. The common causes of pancytopenia are drug-induced bone marrow toxicity, tumors, autoimmune processes, and viral infections, including human immunodeficiency virus, parvovirus B19, cytomegalovirus, or Epstein–Barr virus.[6] In the case of a viral infection, the etiological mechanism is bone marrow aplasia, which is caused by various mechanisms. In COVID-19 infection, in rare cases, persisting pancytopenia may reveal a coexisting hematological disorder.[7,8]

Case Presentation

A 53-year-old woman without previously known diseases was diagnosed with COVID-19 infection in

September 2021 after an investigation for clinical signs of fever, fatigue, myalgia, and arthralgia. A blood test detected leucopenia (WBC - 3.47×10^3/μL) with moderate neutropenia (neutrophils - 0.63×10^3/μL), lymphocytosis (lymphocytes - 2.57×10^3/μL), thrombocytopenia (platelets - 64×10^3/μL), and mild anemia (RBC 3.81×10^6/μL, Hb - 10.4 g/dl). Blood iron (168.1 μg/ml) and ferritin (14.45 ng/ml) were normal, while the D-dimer value was slightly elevated (762 ng/ml). After the COVID-19 infection was resolved, the pancytopenia, especially leucopenia with neutropenia and thrombocytopenia, persisted; therefore, a peripheral blood smear examination and an abdominal echography were performed. In the peripheral blood smear, we detected a clonal group of lymphocytes that presented fine cytoplasmic extensions (Figure 1), while abdominal echography revealed the presence of splenomegaly. In these conditions, a diagnosis of HCL was suspected.

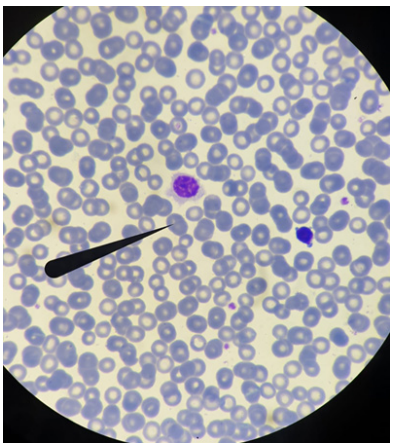

Fig 1. *Hairy cell leukemia, cytological features. Peripheral blood smear showing characteristic lymphoid cells with pale blue or blue-gray cytoplasm and hair-like cytoplasmic projections. The nucleus is often eccentrically placed and is oval or indented, with loose, spongy chromatin.*

The patient preferred to have further examinations to establish the diagnosis and undergo treatment at Pisa University Hospital. By this time (November 2021), neutropenia with lymphocytosis and thrombocytopenia persisted in the blood test.

The patient has received the osteo-medullary biopsy in which discreetly cellulated preparations were characterized by an infiltration of lymphoid elements equal to 70%, about half of which presented thin membrane protrusions compatible with the "hairy" phenotype. Normal hematopoietic lines were markedly reduced.

In the analysis of immunophenotype, the clonal lymphocytes were positive for pan-B-cell markers CD19, CD20, and positive for specific markers of hairy cell phenotype CD103, CD11c, and CD25. Considering these results, the diagnosis of HCL was established.

In December 2021, the patient started therapy for HCL with cladribine followed by rituximab (a cycle of cladribine injection for five days and one injection a week of rituximab for four weeks), and the response has been very good. Two months after treatment completion (March 2022), the blood elements were significantly improved: WBC - 5.44×10^3/μL, neutrophils - 3.54×10^3/μL, lymphocytes - 1.39×10^3/μL, RBC - 3.89×10^6/μL, Hb - 12.6 g/dl, and platelets - 216×10^3/μL. In the control abdominal ultrasound, the spleen was within normal limits. By this time, in the bone marrow cytology, the lymphoid line was reduced to 9% without hairy phenotype, while the analysis of immunophenotype resulted in a 4% lymphocytic population and a clonal of 0.1% of total cellularity with the phenotype of hairy cell (CD103/CD25/CD 11c) suggestive for MDR (minimal residual disease). The patient is in remission with MDR, in good clinical and hematological condition, and under periodical controls.

Discussion

As previously mentioned, the most common cytopenia referred to in COVID-19 infection is leucopenia with lymphopenia and thrombocytopenia. Lymphopenia is found in many COVID-19 patients, about 80%-85%, with a higher proportion in severe cases.[9,10] The presence of lymphopenia is explained mainly by two mechanisms: First, the COVID-19 virus invades human cells by binding to the angiotensin-converting enzyme 2 receptor (ACE-2), which is found primarily in the lungs, heart, and gastrointestinal tract but also expressed on the surface of lymphocytes. Consequently, the virus may bind directly to these cells and cause lysis. The second mechanism is related to the fact that virus infection induces the production and release of a number of pro-inflammatory cytokines, such as IL-6, IL-10, IL-1β, IL-2,TNF-α, and IFN-γ, which cause a very strong immune response to SARS-CoV-2 infection, referred to as the "cytokine storm."[11,12] The cytokine storm, especially the strong activation of IL6, is shown to induce lymphocyte apoptosis, atrophy of lymphoid organs, and decrease lymphocyte regeneration.[13] This exaggerated immune response also leads to an increase in neutrophil production in COVID-19 infection, especially in more severe cases complicated with a secondary bacterial infection.[14,15]

Thrombocytopenia is another important laboratory feature in COVID-19 patients, encountered in 20%-55% of cases and related to the severity of the disease.[16] The low platelet count is explained by different mechanisms, such as a decrease in platelet production either from SARS-CoV-2 infection myelosuppression or a strong inflammatory response,[17,18] platelet consumption in microthrombi induced from endothelial damage due to the potent COVID-19 inflammatory response,[19] or direct destruction of platelets by the immune system, as in an immune thrombocytopenic purpura-like state.[20] On the other hand, different studies have demonstrated that anemia is not common in COVID-19 infection, even in severe cases.[21,22]

Our case report showed that typical laboratory signs of COVID-19 infection were mild leucopenia and thrombocytopenia. The presence of lymphocytosis and not lymphopenia, which is a prominent laboratory feature in this infection, the presence of neutropenia and anemia, the persistence of these blood alterations after infection resolution, and finally, the hairy-like projections in a peripheral

blood smear of lymphocytes associated with splenomegaly in abdominal echography raised a strong suspicion for a simultaneous diagnosis of HCL, a rare lymphoproliferative neoplasm characterized typically by pancytopenia associated with splenomegaly.[23] It is slightly more common in females with a median age of presentation of 55 years old.[24] Most cases present the *BRAF* V600 mutation in memory B cells, which activate the mitogen-activated protein kinase (MAPK) pathway, promoting growth, survival, and the differentiation of the clonal of hairy cells.[25,26] The reticuloendothelial organs are infiltrated from the clonal of hairy cells, which morphologically are presented as small lymphocytes with fine hair-like cytoplasmic extensions, expressing immunophenotypically in addition to pan-B cell antigens, specific markers of CD11c, CD25, and CD103.[27]

Hairy cells release cytokines, such as IL-6 and TNF-α, that prevent regular hematopoiesis and promote bone marrow fibrosis leading to pancytopenia[28] similar to COVID-19 infection. The clinical course of the disease is usually indolent, mainly presenting with weakness and fatigue (80%), infections, pancytopenia, and splenomegaly, similar to our case.[24,29]

To our knowledge, few cases are reported in the literature to be diagnosed with HCL or reactivated HCL during COVID-19 infection,[8,30,31] but a recent cohort study found an elevation of new cases diagnosed with HCL, revealed by splenomegaly and/or cytopenia in the situation of COVID-19, emphasizing the importance of investigating cytopenia when present at COVID-19 diagnosis.[32]

In conclusion, persisting pancytopenia after COVID-19 infection may reveal that a coexisting hematological disorder probably exists; in particular, persisting neutropenia and thrombocytopenia associated with splenomegaly should raise suspicion of the presence of HCL, a rare form of leukemia characterized by these features.

Competing Interests

The authors declare that they have no competing interests.

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