



Case Report

Post-COVID-19 Lymphocytopenia and Opportunistic Pathogens Infection in a Thalassemia Major Patient

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Abstract: Transfusion-dependent thalassemia patients undergo transfusion immunomodulating effects, which result in a general immune response depression and, consequently, an increase in the frequency of infectious episodes and neoplastic events due to a reduction in phagocytic function. Altered natural killer functions and IL-2-mediated lymphocytic response, defects in antigen presentation due to monocyte-macrophage cells, and decreases in bone marrow precursors and HLA II+ cells all play key roles in immunodepression in thalassemia major. SARS-CoV-2 infection presents marked lymphopenia, occurring in 96.1% of severe cases. COVID-19-related lymphopenia is due to various mechanisms, which lead to an increase in lymphocytic apoptosis. Post-COVID-19 lymphocytic quantitative and functional disorders may compromise immune response and promote the onset of infections via opportunistic pathogens. Herein, we report a case of a thalassemia major patient who developed severe post-COVID-19 lymphocytopenia, which may have facilitated the onset of a severe Klebsiella Pneumoniae infection.

Keywords: thalassemia major; COVID-19; lymphocytopenia; opportunistic infections



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1. Introduction

In thalassemia major patients, regular transfusion therapy leads to a deficit in the immune response and, thus, to susceptibility to infections and neoplastic events [1]. In these patients, the immunological picture outlines the reduced functionality of phagocytes and natural killer cells; alterations in the IL-2-mediated lymphocyte response; defects in antigen presentation due to monocyte-macrophages; the altered production of white cell precursors in bone marrow; and severe changes in the major histocompatibility system (HLA) [2]. Lymphocytopenia occurs in 96.1% of severe cases of SARS-CoV-2 infection [3,4]. COVID-19-related lymphopenia is due to various mechanisms, which lead to an increase in lymphocytic apoptosis [5,6] by upregulating Fas and Fas ligands (a type-II transmembrane protein that belongs to the tumor necrosis factor TNF family) in T cells, especially IFN- γ sensitized virus-specific T cells (CD4+ and CD8+), or their redistribution caused by the chemotaxis of lung tissue [7]. Post-COVID-19 lymphocytic quantitative and functional disorders may compromise the immune response and favor the onset of infections from opportunistic pathogens [6], as described in our case.

2. Case History

A 50-year-old Caucasian woman affected by β thalassemia major, IVS1-6/IVS1-6 genotype, was subjected to regular hemotransfusions since she was 6 months of age to maintain a hemoglobin (Hb) concentration level of 9–10 gr/dL. At the time of the study, she received 2 units of packed red blood cells (RBC) every two weeks. Splenectomy and cholecystectomy were performed at ages 16 and 25 years, respectively. She had received regular chelation therapy with deferoxamine from 2 years of age to date at the dose of 2 g for 5 days a week with good compliance. However, her mean serum ferritin level

was 1000 ng/mL, and the iron burden was equal to <155 mL blood/kg/year. At age 20, she tested as serum positive for hepatitis C and hepatitis B; she was treated with PEG interferon and ribavirin, achieving a good response. On 14 October 2020, she was admitted to our COVID-19 Medicine Internal Unit as she developed SARS-CoV-2 infection with bilateral pneumonitis. Laboratory tests showed an increased number of white blood cells (21,100/mm³), neutrophilia (91%), and lymphocytopenia (9%). Hemoglobin levels were good (10 gr/dL).

The patient was treated with a remdesivir therapy with a dose of 200 mg on the first day followed by 100 mg on the second day; dexamethasone, 8 mg/day; enoxaparin, 6.000 UI/day; doxycycline, 200 mg on the first day followed by 100 mg from the second day to the fifteenth day; vitamin C; antioxidants; and anti-inflammatory drugs. Moreover, the standard transfusion regimen had to be increased during hospitalization as hemoglobin levels tended to decrease; thus, she received a blood transfusion with packed RBC every week until discharge. The clinical, instrumental, and laboratory picture of bilateral pneumonia regressed after about one month, and the patient was discharged from the hospital.

On 27 December 2020, she developed a fever (T 39 °C); pharyngodynia; odynophagia; sinusitis; and a voluminous, hard, and painful pseudo-tumoral lesion adhering to the superficial and deep planes of the right lateral cervical region, which did not regress after therapy with amoxicillin and clavulanic acid. Molecular SARS-CoV-2 diagnostic molecular tests were negative. A marked post-COVID-19 lymphocytopenia persisted upon blood count (white blood cells: 16,300/mm³; neutrophils: 86%; lymphocytes: 4%; monocytes: 8%; eosinophils: 2%). She was admitted into the Otolaryngology Unit and subjected to Neck Contrast Computed Tomography (CT).

Contrast CT showed that the pseudo-tumoral lesion of the right lateral cervical region measured about 6 × 5 × 6 cm and was characterized by a hypodense probably necrotic–colliquative core, hyperdense internal shoots, thick walls, and jagged edges (Figure 1).



Figure 1. Contrast CT of the neoplasm. Description is given in the main text.

Fine needle aspiration showed that the pseudo-tumoral lesion had a fibrous wall with lively vascular neogenesis and intense lymph plasma cell infiltration, without atypical elements. It found positivity for piperacillin- and tazobactam-sensitive *Klebsiella Pneumoniae*. The patient followed antibiotic therapy, resulting in the resolution of the infection. On 30 June 2020, we observed that lymphocytopenia resolved 6 months after discharge from the COVID-19 Medicine Internal Unit, as shown by the blood count (WB: 14,000/mm³ N 65% L 30% M 5%). The patient's transfusion requirements decreased with reasonable well-being.

3. Discussion and Conclusions

COVID-19 is a viral infection with a high impact on the hematopoietic system and hemostasis. Lymphopenia might be seen as a cardinal laboratory finding. A retrospective

study showed that lymphopenia persisted in a remarkable percentage of patients who had recovered from SARS-CoV-2 infection [8]. Post-COVID-19 lymphocytopenia is due to transient immune suppression, affecting innate and acquired immunity. Hence, there is a loss of self-tolerance characterized by the development of autoantibodies, and impaired immune reconstitution, which amplifies immune damage [9]. It has also been found that regulatory T lymphocytes are suppressed by the activation of lymphocytes with lineages of self-reactivity [10]. Furthermore, a high percentage of co-expression Tim-3 + PD-1 + T subset existed both in CD4+ and CD8+ T lymphocytes, especially in intensive care unit (ICU) patients, which suggested that T cells were in an exhausted state from activation, leading to a depletion of immune functions [11].

Regular blood transfusion exerts an immunosuppressive effect on thalassemic patients. Dzik et al. showed at least two categories of immunosuppressive effects, HLA-dependent mechanisms directed against adaptive immunity and another unspecified against innate immunity. The non-specific mechanism could be due to the infusion of apoptotic blood cells and transforming growth factor beta (TGF- β) by blood transfusion [12]. Recent studies have shown that regular and continuous blood transfusions cause the downregulation of cellular immune functions, with an increased frequency of relapses of solid tumors, post-operative bacterial infections, and greater severity of viral infection [13]. Thalassemic patients also display enhanced susceptibility to infections as a consequence of several complex biological processes. The most important factors promoting thalassemia-induced alterations of the immune system are disease-related factors, such as decreased levels of complement, properdin, and lysozyme; reduced absorption and phagocytic abilities of polymorphonuclear neutrophils; disturbed chemotaxis; and altered intracellular metabolism and therapy-related factors, such as blood transfusions related to iron-overload and allo-genic stimulation, iron chelation therapy and obviously splenectomy when applicable [14]. Splenectomy also causes a predisposition to infections and changes in the immune system. It is a therapeutic intervention used in thalassemia in order to avoid an increased consumption of red blood cells caused by hypersplenism [15]. The spleen is a primary organ of immunological surveillance as it is a reservoir of immunocompetent lymphocytes. Thus, its removal causes alterations in the immunological system, such as a decrease in the activity of natural killers and a weakened IgM memory B-cell response. In addition, an exacerbation of immunological alterations caused by multiple transfusions was found in splenectomized thalassemia patients [16].

The observations in our case support the hypothesis that post-COVID-19 lymphocytopenia in thalassemia patients may facilitate the onset of severe infections from opportunistic pathogens. Additional studies performed on a large sample of patients are needed to replicate our findings.

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