Journal of Medical Case Reports and Reviews
Received 12 Aug 2021 | Revised 20 Aug 2021 | Accepted 24 Oct 2021 | Published Online 26 Oct 2021

DOI: https://doi.org/10.52845/JMCRR/2021/4-10-3
JMCRR 4 (10), 1011–1015 (2021)

ISSN (O) 2589-8655 | (P) 2589-8647 IF:2.964

CASE REPORT

Hairy cell leukemia unmasked by COVID-19 associated autoimmune hemolytic anemia

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Abstract

Hairy cell leukemia (HCL) belongs to a heterogeneous group of B-cell malignancies, which can occasionally be detected in asymptomatic patients. Herein, we report a case of HCL discovered due to the management of the hemolytic episode of cold-antibody autoimmune hemolytic anemia (cAIHA) developed during the course of a mild form of coronavirus disease 2019 (COVID-19). Neither the AIHA nor the underlying HCL did affect the course of COVID-19, but the indolent course of HCL showed to have been changed into a clinically overt disease.

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Running head: Hairy cell leukemia in a COVID-19 patient and anemia

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Keywords: : Hairy cell leukemia, COVID-19, Cold-agglutinin autoimmune hemolytic anemia

1 | INTRODUCTION

Hairy cell leukemia (HCL) is a very rare chronic B-cell lymhoproliferative disorder characterized mostly by an indolent course. Some patients have signs and symptoms common to a number of diseases and present with fatigue, fever, infections; most of them have splenomegaly and pancytopenia at diagnosis (1). During the coronavirus disease 2019 (COVID-19), only a few patients with indolent B-lymphoid malignancies with autoimmune hemolytic anemia (AIHA) as a primary complication were reported (2). Cold-antibody AIHA (cAIHA), is better known as a complication

of chronic lymhocytic leukemia and non-Hodgkin lymhoma (3, 4). This form of AIHA belongs to the so-called secondary cold agglutinin syndrome which can occur secondary to infection also, typically after Mycoplasma pnemonia and Epstein-Barr virus infections (5).

We added to this list our patient with a mild clinical form of COVID-19 and cAIHA, with no underlying disease, but who, during the course of the infection was diagnosed as indolent hairy cell leukemia.

2 | CASE REPORT

A 55-year-old man with no significant medical history presented himself to his general practitioner complaining of anosmia, high fever and cough for a few days and was treated with azithromycin and paracetamol. After 10 days, the patient was examined in the emergency department due to progressive fatigue, persistent fever, dark urine, but with no symptoms of respiratory insufficiency. The nasopharyngeal swab by polymerase chain reaction (PCR) test was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the patient was admitted at the COVID-19 department.

The blood tests showed macrocytic anemia, leukopenia, and lymphocytosis. Further investigation revealed raised values of LDH, transaminases and bilirubin, a positive direct antiglobulin test (DAT), and also cold agglutinin antibodies. Haptoglobin and reticulocyte count were in the normal range. There was no presence of shizocytes on the peripheral blood smear, so microangiopathic hemolytic anemia (MAHA) was excluded. Table 1 outlines a summary of a few selected results before and after the treatment protocol was conducted.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to authorized users.

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*Hematologic treatment: cladribine/rituximab first dose followed by rituximab monthly

The patient was initially treated with methylprednisolone of 1mg /kg. Transfusion support was also initiated but without significant improvement. Further immunological diagnostic tests were performed: anticardiolipin, antiphospholipid antibodies, ADNA, ANA, C3, C4 were negative. Serology for HBV, HCV and C, HIV was also negative. Sternal puncture with immunophenotyping was also performed and immunophenotyping revealed the expression of CD103 marker of hairy cells, pan B markers CD19, CD20, CD22, and CD10 marker of follicular cells. The level of monoclonal kappa B cells with hairy cell phenotype was 2%. MSCT of the thorax showed radiological findings typical for COVID-19 pneumonia (Figure 1), while MSCT of the abdomen showed no splenomegaly or significant lymphadenopathy. The treatment of hairy cell leukemia was not started due to the low number of hair cell clones on flow cytometry and no significant splenomegaly.

The patient was respiratory sufficient and without complications throughout the hospitalization, i.e., there was no need for COVID-19-related treatment. Control blood tests revealed increased hemoglobin values and a decrease in LDH, aminotranspherases and bilirubin values; leukopenia and lymphocytosis persisted (Table 1). The dose of corticosteroids was gradually reduced due to the good treatment response and the patient was discharged after two weeks; the control PCR for SARS-CoV-2 still remained positive. However, at the time of last follow-up, two months after the beginning of COVID-19 the laboratory findings showed a progression of leukopenia, lymphocytosis and thrombocytopenia, while control immunophenotyping two months after revealed an increase in monoclonal kappa light chain CD103 to 19%, and he was readmitted for a revision for the possibility of hairy cell leukemia treatment. Five months from the beginnig of COVID-19 symptoms the concurrent cladribine/rituximab therapy was started, followed by rituximab monthly. The treatment resulted in a good response and today, after the fifth cycle of rituximab the patient feels well, with normal routine laboratory findings (Table 1), while control immunophenotyping showed no monoclonal B-cells.

TABLE 1: Laboratory course of patient with COVID-19 from admission to the hospital until the last check-up

Variable	range	Day of disease COVID-19 follow-up			Hematologic treatment*	
		15^{th}	21^{st}	2^{th} month	5^{th} month	10^{th} month
White blood cells ($\times 10^9$/L)	3.4-9.7	2.1	2.4	2.5	2.4	4.3
Lymphocytes (%)	20.0-46.0	43	43	88	75	31.1
Erythrocytes ($\times 10^{12}$/L)	4.34-5.72	1.80	2.27	3.45	3.03	4.27
Hemoglobin (g/L)	138-175	62	78	121	109	137
Platelets ($\times 10^9$/L)	158-424	136	170	83	74	162
Bilirubin (μmol/L)	3-20	106	14		9	15
Aspartate aminotransferase U/L	10-40	49	23	12	13	10
Alanine aminotransferase U/L	10-41	130	65	14	13	10
Haptoglobin (g/L)	0.30-2.0	1.87	1.73			
Lactate dehydrogenase (U/L)	124-241	262		132	135	130
D-dimer (mg/L)	<0.5	1.83	1.73			
C-reactive protein (mg/L)	<3	269	41	2	3	3
Reticulocyte($\times 10^9$/L)	22-97	10	84	30		

3 | DISCUSSION

Numerous hematological abnormalities in association with coronavirus 2019 disease (COVID-19), including rare cases of AIHA, were described (6–8). However, the prevalence and pathogenetic and clinical significance of these abnormalities remain to be further elucidated because each of these can be either a consequence of the viral response phase or an inflammatory response phase during COVID-19 infection. The pathophysiological mechanism of hemolytic anemia in COVID-19, like in other infections, probably includes the mechanism of ”molecular mimicry”- a cross-reaction between antigen determinants of an infectious agent and self -molecules. This resulted in the cross-activation of autoreactive T and B cells and the production of autoreactive antibodies (9, 10).

The timeframe of AIHA and HCL occurrence in our patient suggests that the development of AIHA was triggered by viral infection and the development of HCL from an indolent to overt disease probably by a prolonged host inflammatory response. On the other hand, the course of COVID-19 was unchanged by these immunological disorders. In this case, it was essential for the disease outcome, because during cAIHA complex interactions between the complement system, coagulation system, and inflammatory processes could lead to an increased frequency of thrombosis, which is also one of the crucial pathogenic process during the COVID-19 infection, responsible for most of the disease complications. It is important to note here a study of patients with untreated chronic lymphatic leukemia (CLL) and COVID-19 infection with fatal outcome in most of them, which suggests the existence of a greater risk for the development of a severe form of COVID-19 infection in patients with an indolent phase of this B cell lymhoproliferative disease (11).

In conclusion, our case calls for at least a more aggressive approach of AIHA management during COVID-19 infection, irrespective of the disease severity and in addition, the possibility of acceleration or induction of malignant B cell disease by COVID-19 must be taken into account.

Conflicts of interest

The authors declare that they have no conflict of interest.

Consent

Written patient informed consent was obtained to publish this case report.

Funding Statement

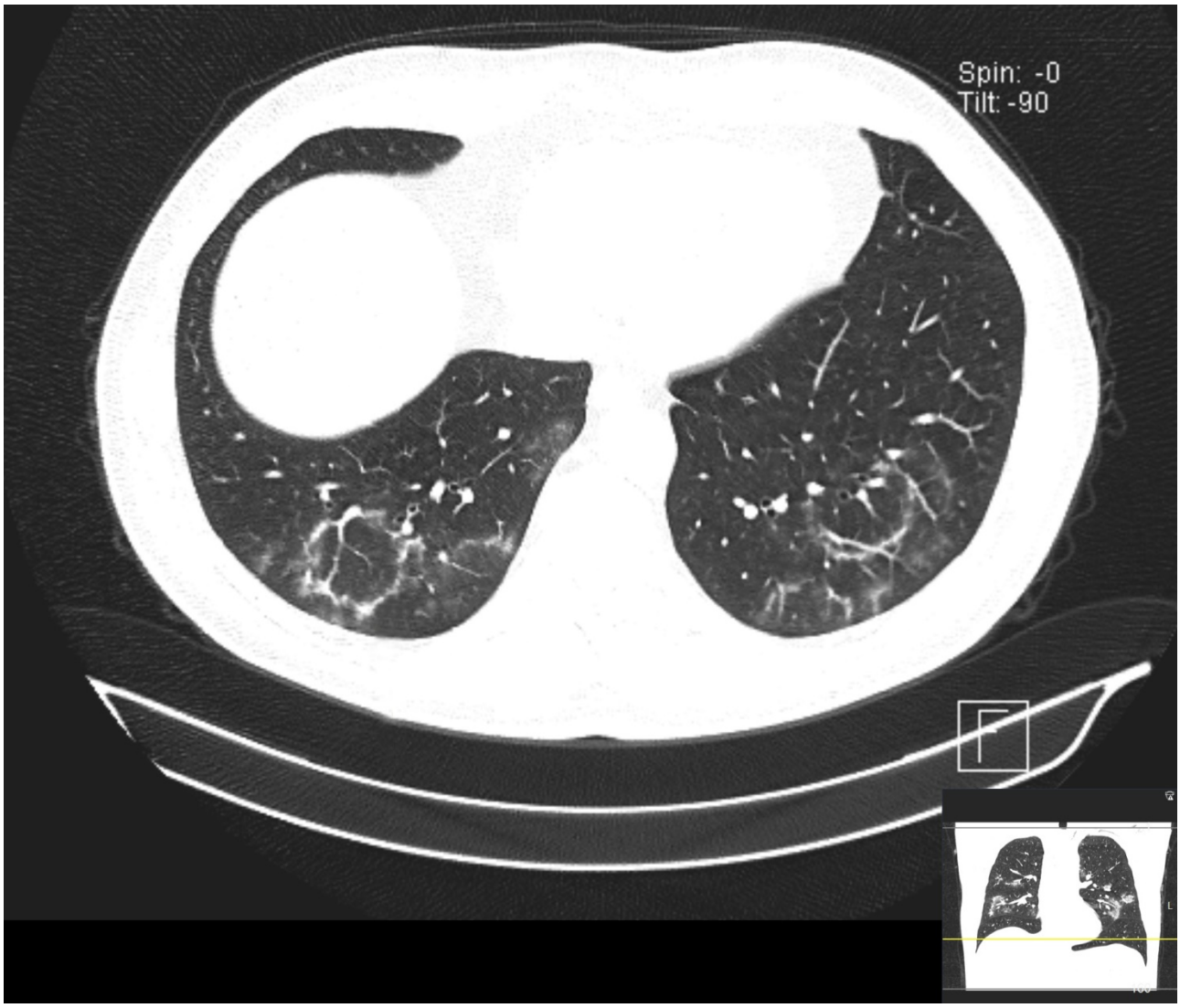

FIGURE 1: Chest CT findings of typical COVID-19 pneumonia (12^{th} day from the onset of symptoms; CT score 14)

The authors received no financial support for this study.

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How to cite this article: M.M.P., V.T., I.Z., M.M. **Hairy cell leukemia unmasked by COVID-19 associated autoimmune hemolytic anemia**. Journal of Medical Case Reports and Reviews. 2021;1011–1015. https://doi.org/10.52845/JMCRR/2021/4-10-3