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Case Report

Exacerbation of Autoimmune Hemolytic Anemia after COVID-19 in a Relapsed/Refractory Hodgkin Lymphoma Patient: A Case Report

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INTRODUCTION

In December 2019, a novel pneumonia syndrome was identified in China Zhu *et al.*[1]. This novel coronavirus was known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The clinical spectrum of symptomatic COVID-19 cases varied from mild to severely ill Zhu *et al.*[1]. Now, we are becoming more aware of the new disease complications. This includes renal impairment, thrombosis, cardiac injury and 'long COVID-19'.

Autoimmune Hemolytic Anaemia (AIHA) is a rare autoimmune disease in which autoantibodies react with self-red blood cells causing their hemolysis. The warm subtype is responsible for the majority of AIHA cases and is mediated by IgG autoantibodies to the red blood cells Rh system Barcellini *et al.*[2].

There have been a few case reports of Autoimmune Hemolytic Anaemia (AIHA) associated with COVID-19. To the best of our knowledge, this is the first report showing exacerbation of AIHA occurring during COVID-19 in a relapsed/refractory Hodgkin lymphoma case in sustained complete response.

The case report documents that AIHA is one of the discovered complications of COVID-19 infection. The presentation of post COVID AIHA shows a typical presentation of the disease.

No published guidelines for the treatment of autoimmune hemolytic anaemia secondary to COVID-19 up till now. In this case report, we try to mention treatment options for this COVID-19 sequelae.

Work up for newly diagnosed AIHA patients now-a-days should include a lung CT scan and PCR for SARS-CoV-2.

To establish guidelines for the management of AIHA with COVID-19 we need to study much more cases.

MATERIALS AND METHODS

Study area: The study was carried out at the Hematology Unit, Oncology Centre, Faculty of Medicine, Mansoura University, Egypt from February, 2019 to November, 2020.

Case report: A 19 years old female patient presented to our outpatient clinic in February, 2019 with low-grade fever, night sweets and right neck swelling. She had a past medical history of primary autoimmune hemolytic anaemia, managed by oral steroid and splenectomy 10 years ago. Standard blood test after admission showed that Hgb13.7 g dL^{-1}, total leukocytic count 17×10^9 mm^{-3} and platelet 477×10^9 mm^{-3}. Liver and renal function tests were within normal range. The LDH was 233 U L^{-1} (range 100-190).

Positron Emission Tomography-Computed Tomography (PET/CT) scan revealed metabolically active supra and infra diaphragmatic nodal, hepatic, osseous and pulmonary lymphomatous infiltrates (Deauville V). Histologic examination and immunohistochemical analysis of the right cervical lymph node made the diagnosis of classical Hodgkin's lymphoma (mixed cellularity, MC subtype) by finding the diagnostic Reed-Sternberg cells and CD30 (+) and CD15 (+). The bone marrow biopsy was positive for lymphoma. Based on the complete staging workup the final diagnosis was classical HL, mixed cellularity, stage IV B. Her international prognostic score was 2.

She was administered 2 cycles of doxorubicin, bleomycin, vinblastine and dacarbazine chemotherapy (ABVD). Reassessment by PET/CT in, June, 2019 showed complete remission. That is why bleomycin was omitted and the patient continued 4 cycles of AVD.

The PET/CT on, October, 2019 revealed residual metabolic re-activated mediastinal LN and pulmonary infiltrates Deauville IV. So, the Patient planned for brentuximab+gemcitabine, dexamethasone and cisplatin (GDP) protocol. However, the cycles were interrupted because of repeated attacks of neutropenia (grade 4), gastroenteritis and fungal pneumonia confirmed by bronchoalveolar lavage. After 4 cycles of combined Brentuximab-GDP, reassessment by PET/CT March, 2020 showed complete response. She continued on single-agent Brentuximab and was planned for Autologous stem cell transplantation.

Unfortunately, after the 8th Brentuximab cycle, in August, 2020, she presented with productive cough, fever 38°C, pulse 109/min and respiratory rate of 19 breaths/min, her SpO_2 on ambient air was 94%. The C-reactive protein level was negative and serum ferritin of 255.8 ng mL^{-1} (20-200 ng mL^{-1}).

RESULTS

High-resolution chest computed tomography (CT) evaluation revealed multiple rounded ground-glass opacities of predominant peripheral distribution in both lungs coping with CO-RAD 5, no areas of consolidation nor bronchial dilation Fig. 1a and b. However, the nasopharyngeal swab qRT-PCR was negative, with positive results of serum procalcitonin and galactomannan. She was managed by antibiotics, antifungal and antiviral therapies.

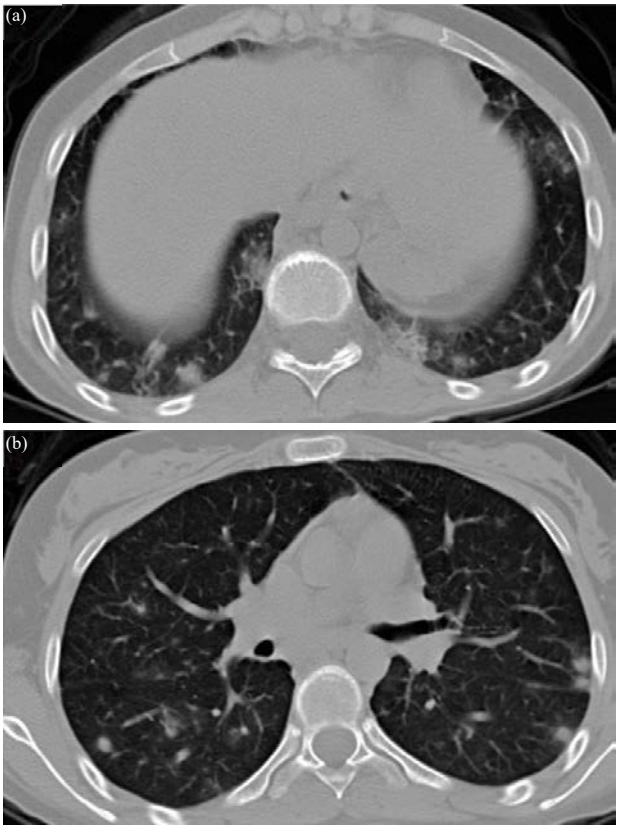

Fig. 1(a-b): Axial CT images, (a) Show multifocal bilateral rounded ground-glass opacities (GGO) of predominant peripheral distribution and (b) Largest is seen at the left lower lobe

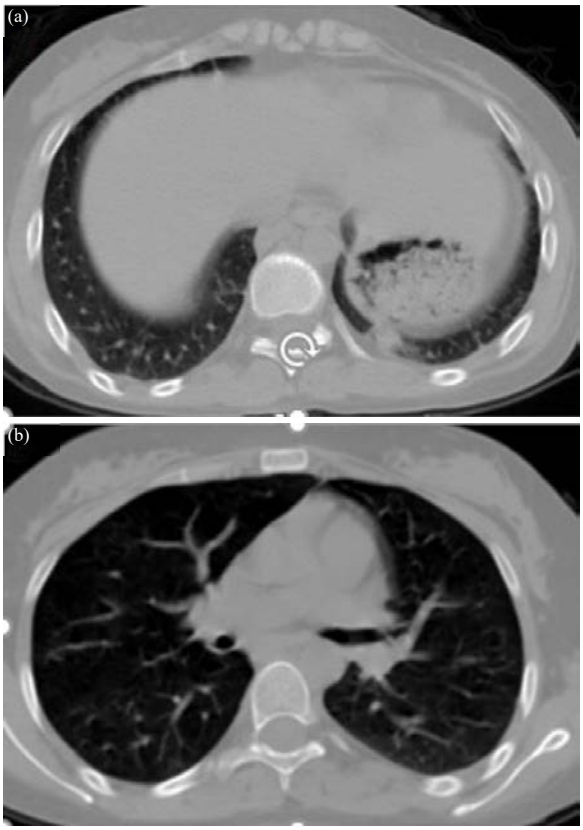

Fig. 2(a-b): Follow up axial CT images show less residual GGO

On follow up visit, she did not show any signs of improvement either clinically or radiologically, added to this, she complained of fatigue, low-grade fever and dark urine. Her CBC showed Hgb 5 g dL^{-1}, MCV 92.5 fL, MCH 33.5 pg, MCHC 36.3 g dL^{-1}, total leukocyte count of 35000 mm^{-3}, neutrophil of 20000 mm^{-3}, lymphocyte of 4800 mm^{-3} and platelet count of 358,000 mm^{-3}. The blood film showed spherocytes and agglutinated red blood cells. The corrected reticulocyte count was 7%. Liver function tests were normal except for indirect hyperbilirubinemia of 2 mg dL^{-1}, elevated LDH of 233 U L^{-1} (range 100-190). The diagnosis of recurrent autoimmune hemolytic anaemia was confirmed by positive direct antiglobulin tests (DAT) for IgG. Rapid detection of anti-SARS-CoV-2 IgG was negative and IgM was positive that confirm recent infection.

The patient started prednisolone 1 mg/kg/day in addition to, antibiotics, antiviral, vit C and zinc as a treatment for COVID-19. She became transfusion independent and Hgb reached 13.5 g dL^{-1}. She recovered from COVID-19, she became clinically free, laboratory detection of anti-SARS-CoV-2 IgG that become positive with residual few ground-glass opacities in chest CT, Fig. 2a and b. In November, 2020, she finished 12 courses of Brentuximab and 4 cycles GDP and follow up PET/CT showed that the patient is in complete remission.

DISCUSSION

Autoimmune Hemolytic Anaemia (AIHA) is a rare autoimmune disease in which autoantibodies react with self-red blood cells causing their hemolysis. The warm subtype is responsible for the majority of AIHA cases and is mediated by IgG autoantibodies to the red blood cells Rh system Barcellini *et al.*[2].

Known pathogens supposed to cause warm AIHA to include hepatitis C virus, human immunodeficiency virus, infectious mononucleosis and COVID-19 virus Lopez *et al.*[3]. Till now, the mechanism of the AIHA association with the new coronavirus is not well known, but there are many factors, like

viral infections, which might trigger these types of diseases. It is reported that molecular mimicry between the viral protein spike and Ankyrin-1 in the red cell surface may be the precipitating event Angileri *et al*.[4].

Association of AIHA with COVID-19 infection has been rarely reported. In particular, Lazarian *et al*.[5] mentioned 7 cases of AIHA associated with COVID-19. In 4/7 patients, they detected warm antibodies, two patients were chronic lymphoid leukaemia cases and one patient was a monoclonal gammopathy of undetermined significance case.

Lopez *et al*.[3] reported a case of warm AIHA during COVID-19, but this patient was a case of congenital thrombocytopenia. finally, Hindilerden *et al*.[6] described a case of warm-AIHA during COVİD-19 without any underlying diseases.

Corticosteroids remain the mainstay of treating newly diagnosed primary AIHA Lechner *et al*.[7] but their impact on COVID-19 outcome is uncertain. Data have shown that COVID-19 patients receiving steroids have better results recommending that steroids might prevent the progression of COVID-19 disease to very severe forms. These results suggested steroid use in the early acute phase of COVID-19. Authors emphasize that more studies are still needed to affirm this hypothesis Russell *et al*.[8] and Gazzaruso *et al*.[9].

Nevertheless, 'WHO' does not currently support steroid use in viral diseases, like COVID-19 as the hypothalamic-pituitary-adrenal axis stimulation mediated by glucocorticoid can also aggravate lymphopenia, or exaggerate pro-inflammatory reactions that may worsen this pathogenic condition.

The randomized evaluation of COVID-19 (Recovery) trial compared dexamethasone with ritonavir/lopinavir, azithromycin and hydroxychloroquine and found that dexamethasone decreases the mortality rate in COVID-19 patients by a 30% reduction of the need for ventilation or oxygen supply Ortolani *et al*.[10].

To the best of our knowledge, this is the first report showing exacerbation of AIHA occurring during COVID-19 in a relapsed/refractory Hodgkin lymphoma case in sustained complete response. We support Liput *et al*.[11] suggested that the workup for newly diagnosed patients with AIHA should include a lung CT Scan and PCR for SARS-CoV-2. There are no guidelines for treatment, so the use of low dose steroids and also concurrent use of steroids with intravenous immunoglobulin could be an option as recommended by guidelines for the treatment of primary immune thrombocytopenia in the setting of COVID-19 infection.

CONCLUSION

This case report document that one of the discovered complications of COVID-19 infection is the exacerbation of Autoimmune hemolytic anaemia. The presentation of Post COVID AIHA show typical presentation of the disease and respond well to steroids as a first-line treatment.

SIGNIFICANCE STATEMENTS

This case report discovers one of the sequelae of COVID-19 infection. Further cases with AIHA after COVID-19 should be reported to know more details about this complication and make an approach for management.

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