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CASE REPORT

Autoimmune haemolytic anaemia secondary to COVID-19 infection presenting as anaemia-induced unstable angina

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Abstract

Autoimmune haemolytic anaemia (AIHA) is a condition characterised by antibody mediated haemolysis. COVID-19 infection has been associated with multiple extra pulmonary complications of autoimmune origin, including AIHA. We report a case of a 72-year-old man who presented with unstable angina induced by severe anaemia secondary to autoimmune haemolysis. His direct antiglobulin test was positive with IgG, C3d and IgM positivity denoting a mixed type AIHA. After exclusion of other known associations of AIHA, a possible diagnosis of COVID-19 infection presenting as mixed AIHA with severe symptomatic anaemia, was made. He was managed successfully with oral prednisolone and cautious blood transfusions.

Key words: Mixed autoimmune haemolytic anaemia, COVID-19, AIHA

Introduction

Autoimmune haemolytic anaemia (AIHA) is a condition characterised by autoantibodies directed against red blood cells causing extravascular or intravascular haemolysis. The reported global incidence is 1 to 3 per 100,000 / year. (1,2) AIHA can be divided into warm, cold, or mixed-type according to the type of autoantibodies present. Out of these, mixed-type accounts for 5% of all AIHA cases. (2) Nearly half of AIHA cases are primary, and the rest are secondary to another underlying disorder. COVID-19 infection, despite its primary target being the respiratory system, is known to cause a wide spectrum of extrapulmonary clinical manifestations. A considerable proportion of these manifestations has an underlying autoimmune process. One such rare association is AIHA. Here, we report a case of a 72-year-old man presenting with severe anaemia and anaemia-induced myocardial ischaemia following a mixed type AIHA in possible association with COVID-19 infection.

Case presentation

A 72-year-old man presented to medical casualty with acute onset constricting type central chest pain associated with nausea and sweating, lasting for approximately 30 minutes. This acute presentation was preceded by easy fatigability and exertional chest pain for four days. He gave a history of mild nonproductive cough and poor appetite during the past week. He denied any fever, and the rest of the systemic inquiry was unremarkable. His medical history included diabetes, stage 3 chronic kidney disease, dyslipidaemia and chronic coronary syndrome. He had undergone a coronary angiogram 12 years back which showed dual vessel disease with

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bridging collaterals. He was on optimum medical treatment at the time of evaluation. He was pale, mildly icteric, and haemodynamically stable. He was not in respiratory distress, and his lungs were clear on auscultation. He did not have hepatosplenomegaly or lymphadenopathy. Electrocardiograms showed partial right bundle branch block with inferior and lateral dynamic T inversions and ST segment depressions. Troponin levels were repeatedly negative. His initial blood investigations showed severe anaemia with a haemoglobin (Hb) level of 4.8 g/dL with an elevated mean corpuscular volume (MCV) of 102 fL. A diagnosis of anaemia-induced unstable angina was made, and the rest of the workup showed indirect hyperbilirubinaemia, elevated reticulocyte count and high LDH level supporting a haemolytic process with macrocytes and polychromasia in peripheral blood smear. The direct antiglobulin test (DAT) was positive, indicating an autoimmune aetiology. All 3 of IgG, C3d and IgM-cold-agglutinins were positive , further refining the diagnosis as mixed-type autoimmune haemolytic anaemia.

The results of the initial investigations are summarised in table 1.

Table 1 - Summary of initial investigations

Test	Result	Reference range
WBC	11240x10^6/L	4,500 - 10,000
Haemoglobin	4.8 g/dL	11-16
MCV	102 fL	80-100
MCH	32.2 pg	27-34
RDW	59.4 fL	35-56
Platelets	375,000 x10^6/L	150-450
Peripheral smear	Macrocytes with the appearance of granulocytic red cells and reduced RBC mass. neutrophilic leukocytosis with toxic changes. Platelets are normal.	
Reticulocyte count	18.69%	0.3-3.0
LDH	522 U/L	125-220
Total bilirubin	4.4 mg/dL	0-1.5
Direct bilirubin	1.0 mg/dL	0-0.2
AST	46 U/L	10-35
ALT	36 U/L	10-40
DAT and DAT profile	Positive with IgG, IgM and C3d positivity	
Serum creatinine	1.93 mg/dL	0.5-1.1
Chest x ray	Normal	
CRP	30 mg/L	< 5

WBC *- White blood cells,* ***MCV-*** *Mean corpuscular volume,* ***MCH-*** *Mean corpuscular haemoglobin,* ***RDW-*** *Red cell distribution width,* ***LDH*** *- Lactate dehydrogenase,* ***AST-*** *Aspartate transaminase,* ***ALT-*** *Alanine transaminase,* ***DAT-*** *Direct antiglobulin test*

Screening for causes of AIHA was done. He had a raised erythrocyte sedimentation rate (ESR) of 110 mm/ 1st hour. His anti-nuclear and anti-dsDNA antibodies were negative. The Contrast Enhanced CT chest, abdomen and pelvis showed no evidence of lymphoma. The peripheral blood smear was not suggestive of a haematological malignancy. Infections known to cause AIHA were screened for and hepatitis B, C, human immunodeficiency virus, epstein barr virus and mycoplasma infection were all negative. He denied any blood transfusions during the past three months and his medication did not reveal use of any drugs known to cause AIHA. As he complained of a mild cough and presented during the global pandemic of COVID-19 infection, we tested him for COVID. Even though his initial rapid antigen test was negative, the COVID PCR test became positive with a reactive COVID antibody titre suggestive of a recent infection. In the absence of other secondary causes and the clinical picture of mild cough followed by mixed-type AIHA, it was concluded that this was a case of mixed-type AIHA possibly secondary to COVID-19 infection.

He was transfused ABO, Rh and Kell compatible, indirect antiglobulin cross-matched, least incompatible leuko-depleted blood at 37°C. He was started on oral prednisolone 1mg/kg/day. His haemoglobin level gradually improved and stabilised at 9.7 g/dL over the next two weeks, followed by a reduction in indirect hyperbilirubinaemia and reticulocyte count. He was discharged on prednisolone and reviewed in 2 weeks, at which point he had a stable haemoglobin level.

Discussion

AIHA is diagnosed in the context of DAT positivity with ongoing haemolysis after excluding other alternatives. These include drug-induced haemolysis, recent blood transfusion within the past 3 months causing transfusion-related haemolysis, alloimmune haemolysis following organ or stem cell transplant and haemolytic disease of the newborn.(2) Warm AIHA is defined by the demonstration of DAT positivity for IgG alone or IgA + C3d, whereas cold agglutinin disease (CAD) is diagnosed by demonstrating the presence of a cold agglutinin, which is typically IgM.

Mixed-type AIHA is characterised by the presence of both a warm antibody and a cold agglutinin.(1,2) Our patient fulfilled all these criteria and was therefore diagnosed as mixed-type AIHA. Even in the presence of cold agglutinins, mixed AIHA does not typically show acrocyanosis or Raynaud's as in CAD.(2) The index patient lacked such symptoms. Mixed type has also been shown to cause more severe anaemia compared to other subtypes. In the GIMEMA study 63% of the severe anaemia cases were of mixed AIHA type.(3) This explains the degree of anaemia in our patient, which was severe enough to cause myocardial ischaemia.

As with other subtypes, mixed-type AIHA could be classified as primary or secondary. Shulman et al. described 144 patients with mixed-type AIHA, 50% of which were primary, whereas most secondary cases (42%) were associated with systemic lupus erythematosus (SLE).(4) One patient had mixed AIHA secondary to non-Hodgkin's lymphoma. In general, AIHA is known to be associated with other autoimmune conditions such as SLE, rheumatoid arthritis, autoimmune hepatitis, and scleroderma; infections such as EBV, hepatitis C, Hepatitis B, HIV, mycoplasma pneumonia and lymphoproliferative disorders such as chronic lymphocytic leukaemia or lymphoma.(1, 5, 6, 7) In our patient, we have excluded the above-known causes.

COVID-19 infection has been associated with multiple complications of autoimmune origin, such as Guillain-Barre syndrome, immune thrombocytopenia, vasculitis, autoimmune thyroid disease and AIHA. (8,9,10)

A systematic review described 50 cases of AIHA associated with COVID-19 infection, which appears to be a rare complication given the high disease prevalence.(11) However, it is important to recognise these patients early, as they reported a case fatality rate of 19%. Unlike other infections, which would typically predominantly cause one subtype of AIHA, COVID-19 infection was found to be associated with both cold (38%) and warm (28%) subtypes. Out of these 50 cases, only 3 showed mixed-type AIHA like our index patient. Most of these patients had one or more comorbidities, and only eleven patients had underlying lymphoproliferative disorders or other autoimmune conditions known to be AIHA triggers. (11) Lazarian et al. reported a case series of seven patients with COVID-19-associated AIHA.(12) Most of these patients had either moderate or severe disease. Authors observed that the onset of AIHA is compatible with the timing of cytokine storm, which may explain the pathophysiology behind the emergence of autoantibodies.(12) The proposed pathophysiology behind the occurrence of AIHA in COVID includes hyper stimulated immune response triggering autoimmunity and molecular mimicry.(13)

Treatment of AIHA consists of transfusions with least

incompatible blood for severe anaemia, immunosuppression, and treatment of the underlying disorder in secondary cases. In cases of mixed AIHA, caution must be taken to transfuse rewarmed blood at a temperature close to 37°C to avoid precipitating further haemolysis.

Management of mixed-type AIHA includes avoidance of cold exposure and glucocorticoids as first-line therapy, with good response rates to initial treatment. However, they typically progress to a chronic course with relapses. Second-line therapy recommended for mixed-type AIHA is similar to that of warm AIHA.(2) Rituximab is also now recommended as initial therapy as an adjunct to steroids or as a single agent by itself.(14)

Majority of the reported AIHA cases associated with COVID-19 have been treated with corticosteroids with good treatment response. In more severely ill patients, IVIG has been used as initial treatment in some case reports. Plasma exchange and rituximab have also been used as other treatment options. (11,15) Our patient responded well to initial treatment with oral prednisone reaching a haemoglobin target of 10 g/dL within one month.

Conclusion

Mixed-type AIHA is a rare complication associated with COVID-19 infection. It is important to beware of this condition as it can cause life-threatening haemolysis. Most such cases can be successfully treated with cautious blood transfusions and glucocorticoid therapy.

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References

1. Hill QA, Hill A, Berentsen S. Defining autoimmune hemolytic anemia: a systematic review of the terminology used for diagnosis and treatment. Blood advances. 2019 Jun 25;3(12):1897-906.
2. Hill QA, Stamps R, Massey E, et al. British Society for Haematology. The diagnosis and management of primary autoimmune haemolytic anaemia. British Journal of Haematology. 2017 Feb;176(3):395-411.
3. Barcellini W, Fattizzo B, Zaninoni A, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood, The Journal of the American Society of Hematology. 2014 Nov 6;124(19):2930-6.
4. Shulman IA, Branch DR, Nelson JM, et al. Autoimmune hemolytic anemia with both cold and warm autoantibodies. Jama. 1985 Mar 22;253(12):1746-8
5. Gupta V, Shukla J, Bhatia BD. Autoimmune hemolytic anemia. The Indian Journal of Pediatrics. 2008 May;75(5):451-4.
6. Sudha Reddy VR, Samayam P, Ravichander B, et al. Autoimmune hemolytic anemia: mixed type—A case report. Indian Journal of Hematology and Blood Transfusion. 2011 Jun;27(2):107-10.
7. Dacie JV. Autoimmune hemolytic anemia. Archives of Internal Medicine. 1975 Oct 1;135(10):1293-300.
8. Zulfiqar AA, Lorenzo-Villalba N, Hassler P, et al. Immune thrombocytopenic purpura in a patient with Covid-19. New England Journal of Medicine. 2020 Apr 30;382(18):e43.
9. Toscano G, Palmerini F, Ravaglia S, et al. Guillain–Barré syndrome associated with SARS-CoV-2. New England Journal of Medicine. 2020 Jun 25;382(26):2574-6.
10. Yazdanpanah N, Rezaei N. Autoimmune complications of COVID-19. Journal of medical virology. 2022 Jan;94(1):54-62.
11. Jacobs JW, Booth GS. COVID-19 and Immune-Mediated RBC Destruction: A Systematic Review. American Journal of Clinical Pathology. 2022 Jun;157(6):844-51.
12. Lazarian G, Quinquenel A, Bellal M, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. British journal of haematology. 2020 Jul 1.
13. Dotan A, Muller S, Kanduc D, et al. The SARS-CoV-2 as an instrumental trigger of autoimmunity. Autoimmunity reviews. 2021 Apr 1;20(4):102792.
14. Michel M, Terriou L, Roudot-Thoraval F, et al. A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study). American Journal of Hematology. 2017 Jan;92(1):23-7.
15. Brugnara C, Berentsen S. Cold agglutinin disease. UpToDate. Waltham, MA: UpToDate. 2021.

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