Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection

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**Recommended Citation**

Patil NR, Herc ES, and Girgis M. Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection. *Hematol Oncol Stem Cell Ther* 2020.
CASE REPORT

Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection

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Received 12 May 2020; received in revised form 1 June 2020; accepted 14 June 2020

KEYWORDS
Anemia; Autoimmune; Cold agglutinin disease; COVID-19; Hemolytic; Pulmonary embolism

Abstract

Background: Lymphopenia, thrombocytopenia, and elevated D-dimer and ferritin levels are frequently reported in patients with severe coronavirus disease 2019 (COVID-19). Here we report a case of cold agglutinin disease (CAD), autoimmune hemolytic anemia (AIHA), and pulmonary embolism as a presentation of COVID-19 infection.

Case report: A 51-year-old African–American woman presented to the emergency room with fever and shortness of breath. She was tachycardic, febrile, and had an oxygen saturation of 88% on room air. Laboratory studies showed hemoglobin (Hb) 5.1 g/dL, D-dimer 4.55 mg/mL, and C-reactive protein 12.3 mg/dL. Computed tomography scan of the chest showed acute pulmonary embolism involving the bilateral lower lobe segmental branches. Her influenza test was negative, but her SARS-CoV-2 test returned positive. Due to severe anemia, she was not started on any anticoagulation. Haptoglobin was low. Direct antiglobulin test returned positive for anti-complement and negative for anti-immunoglobulin G. Cold agglutinin titer was 80. Mycoplasma, Epstein–Barr virus, parvovirus, human immunodeficiency viruses, and acute hepatitis screen were negative. Abdominal and pelvic computed tomography showed a normal liver and spleen without lymphadenopathy. Peripheral blood smear showed red blood cell agglutination. On Day 2, she became hypoxic requiring 6 L oxygen. Since her Hb remained...
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain that causes coronavirus disease 2019 (COVID-19). While most patients have mild disease, some develop severe disease. Comorbidities including chronic lung disease, diabetes, malignancy, immunosuppression, and obesity, and the elderly are at higher risk of severe outcomes. Lymphopenia, thrombocytopenia, and elevated D-dimer and ferritin levels are frequently associated with severe disease [1–3]. Disseminated intravascular coagulation [4] and venous thromboembolism (VTE) [5] have also been reported.

We report a case of cold agglutinin disease (CAD), autoimmune hemolytic anemia (AIHA), and pulmonary embolism (PE) as a presentation of COVID-19 infection at our institution.

CAD is very rare with a prevalence of 16 cases per million persons. In CAD, extravascular hemolysis causes acute hemolytic anemia where agglutination of red blood cells occurs at below normal core body temperature [6,7].

The two main types of CAD are primary (idiopathic) and secondary. Secondary CAD is associated with viral infections, autoimmune disorders, and hematologic malignancies. The most common infectious causes associated with CAD are Mycoplasma pneumoniae and Epstein–Barr virus [7,8]. Patients may develop hemolysis 2 weeks after the initial infection. Laboratory abnormalities typically improve with resolution of infection [7,9].

Case report

Our patient is a 51-year-old African–American woman with a past medical history of right breast ductal carcinoma in situ diagnosed in 2012 status post lumpectomy, radiation and tamoxifen for 2 years. She was diagnosed with recurrent stage IA right breast cancer in 2019 and underwent a nipple-sparing mastectomy on January 16, 2020, with breast reconstruction on February 26, 2020. She also has a history of left breast sparing mastectomy on January 16, 2020, with breast reconstruction and was started on hydroxychloroquine.

As her workup was consistent with CAD and cold AIHA, we started her on folic acid and recommended to use warm therapeutic pills.

Peripheral blood smear showed red blood cell agglutination. Complement was positive. Cold agglutinin titer was 80. Anemia workup including vitamin B12 level and folate level were normal. Antinuclear antibody and rheumatoid factor were negative. Monoclonal protein evaluation showed an inflammatory pattern. Glucose-6-phosphate dehydrogenase level was normal. Mycoplasma, Epstein–Barr virus, parvovirus, human immunodeficiency viruses, and acute hepatitis screen were negative. Occult blood stool test was negative. Abdominal and pelvic computed tomography showed a normal liver and spleen without lymphadenopathy.

Direct antiglobulin test returned positive. Anti-immunoglobulin G Coombs serum was negative and anti-complement was positive. Cold agglutinin titer was 80. Peripheral blood smear showed red blood cell agglutination. As her workup was consistent with CAD and cold AIHA, we started her on folic acid and recommended to use warm intravenous fluids and blood products.

On Day 2, she became more hypoxic requiring 6 L oxygen and was started on solumedrol 60 mg twice daily. Her Hb remained stable, and she was started on low-intensity unfractionated heparin without boluses for PE with close monitoring of her Hb. By Day 4, her D-dimer and ferritin levels increased to 7.54 µg/mL and 1471 ng/mL, respectively.

Inflammatory markers subsequently improved. CRP decreased to 0.7 mg/dL, and she was weaned off oxygen. Her Hb remained stable at 9 g/dL, and she was discharged home in a stable condition. After 2 weeks of hospital discharge, her Hb increased to 11 g/dL. The WBC count was 6 K/µL with normal absolute neutrophil and lymphocyte counts.

Please cite this article as: N. R. Patil, E. S. Herc and M. Girgis, Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection, Hematol Oncol Stem Cell Ther, https://doi.org/10.1016/j.hemonc.2020.06.005
Discussion

The COVID-19 pandemic has caused significant morbidity and mortality. We are still in the process of understanding its pathogenesis, clinical manifestations, management, and prognosis.

High D-dimer levels and coagulopathy have been frequently reported in patients with severe disease. The prevalence of VTE in hospitalized patients with COVID-19 is 25–31% [5,10]. A study of 81 hospitalized patients with COVID-19 showed that 25% developed VTE. Of those, eight/20 patients died [10]. Klok et al. [5] reported regarding 84 patients with COVID-19 admitted in the Dutch university hospital who received thromboprophylaxis. The cumulative incidence of thrombosis was 31% (95% CI = 20–41). PE was the most frequent complication (81%) [5].

The International Society of Thrombosis and Hemostasis guidelines now recommend prophylactic-dose anticoagulation in all hospitalized patients with COVID-19 [11]. Some centers are now considering therapeutic-dose anticoagulation in patients with severe COVID-19, especially those with high D-dimer levels and coagulopathy.

Our patient had elevated levels of D-dimer (7.45 μg/mL), ferritin (1471 ng/mL), and CRP (12.3 mg/dL) at presentation, which were concerning for ongoing inflammation. There was no obvious provoking factor to her PE, and thus it was attributed to her COVID-19 infection.

With prompt COVID-19 and PE management using hydroxychloroquine, solumedrol, and heparin, our patient’s inflammatory markers and clinical condition improved in a few days. CRP decreased to 0.7 mg/dL (previously 12.3 mg/dL), she was weaned off oxygen (6 L to room air), and her Hb remained stable (9 g/dL) while in the hospital and increased to 11 g/dL at follow-up.

To our knowledge, this is the first case report of CAD with AIHA secondary to SARS-CoV-2 infection. Her workup for other etiologies including other viral and autoimmune studies was unrevealing. Her cold agglutinin titer was elevated at 80.

The management of her case was challenging as anticoagulation was held initially in the setting of severe anemia of Hb of 5.1 g/dL. Once bleeding was ruled out and her Hb remained stable after transfusion and with folic acid supplements, we implemented anticoagulation with low-intensity unfractionated heparin protocol and monitored her Hb every 8 h to ensure stability for 24 h.

Complete blood count with differential, D-dimer, coagulation studies, CRP, and ferritin should be assessed in all hospitalized patients with COVID-19. Hematologic abnormalities need close monitoring and prompt intervention if these parameters worsen. Hospitalized patients with severe COVID-19 are at high risk for VTE, disseminated intravascular coagulation, and subsequent mortality. Although bleeding complications are rare with COVID-19, bleeding risk needs to be considered on an individual basis.

Management of CAD includes cold avoidance, maintaining Hb at acceptable level, and treating underlying autoimmune, infectious, or bone marrow disorder. CAD commonly presents with hemolysis which could range from a mild form without anemia and compensated to a severe form requiring transfusions. Cold AIHA secondary to viral infections usually occurs within 2 weeks of the onset of primary infection and improves by the time of infection resolution.

In severely ill hospitalized patients, plasmapheresis or intravenous immunoglobulin can be used as a temporizing measure in addition to blood transfusion. Treatment is aimed at reducing antibody production. Patients with CAD due to infections usually have polyclonal cold agglutinin. Steroids are generally not effective.

Rituximab alone or in combination with bendamustine is usually administered to patients with chronic CAD, with or without underlying lymphoproliferative disorder [12]. These patients usually have a monoclonal cold agglutinin; thus, directed therapy against the clone of B cells or antibody-producing plasma cells is usually effective.

Rituximab is an anti-CD20 monoclonal antibody. It causes lymphopenia in about 48% of patients at a median of 14 days [13,14]. Thrombocytopenia, anemia, hypogammaglobulinemia, and prolonged neutropenia are also seen [15,16]. Most hospitalized patients with COVID-19 already have lymphopenia and thrombocytopenia. Therefore, administering rituximab to patients with COVID-19 may be risky because it can cause further B-cell depletion and can increase their risk for acquiring other infections.

Conclusion

Hematologic manifestations of COVID-19 infection remain to be completely defined. Our patient presented with CAD and AIHA in the setting of SARS-CoV-2 infection. SARS-CoV-2 should be recognized as a possible viral etiology to such rare diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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