Cold Agglutinin Disease Unmasked by COVID-19 Vaccination

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Introduction

Cold agglutinin disease (CAD) is a form of autoimmune hemolytic anemia defined by the production of monoclonal IgM cold agglutinins that target surface antigens of erythrocytes. These agglutinins lead to complement mediated hemolysis in the absence of a primary infection or malignancy. Cold agglutinin syndrome (CAS), in contrast, refers to a cold agglutinin mediated hemolysis occurring in association with or secondarily to an identifiable trigger, mainly infections (EBV, CMV, *Mycoplasma pneumoniae*), malignancy, or vaccines. It is a transient process that typically resolves with treatment of the underlying condition. Therefore, distinguishing CAD from CAS is important in terms of clinical management, as CAD reflects a chronic intrinsic clonal process that may require targeted therapy, while CAS is often a transient disorder and managed primarily by addressing the cause and providing supportive care.

Case Presentation

A 53-year-old previously healthy woman presented to the emergency department with a two-week history of dark urine, body aches, and severe fatigue. One week prior to the onset of her presentation, she received her first dose of the Pfizer COVID-19 vaccination. In the emergency department, she was found to be severely anemic with a hemoglobin level of 6.9 g/dL and a mean corpuscular volume of 112 fL. Further evaluation revealed a reticulocyte count of 11.3% and a haptoglobin level <1 mg/dL. Direct antibody testing was positive for cold agglutinins. She was initially diagnosed with CAS presumed to be secondary to COVID-19 vaccination. She was treated conservatively without transfusions and demonstrated gradual improvement in hemoglobin over the ensuing weeks. However, over the next few months, she continued to have moderate anemia with evidence of hemolysis. This prompted bone marrow evaluation to exclude CAD or an underlying lymphoproliferative disorder. Bone marrow biopsy demonstrated a small clonal kappa restricted CD5+ B-cell population without evidence of an overt lymphoproliferative malignancy. A diagnosis of CAD was then made.

Discussion

This patient's hemolysis occurring shortly after COVID-19 vaccination suggests immune activation as a possible precipitating event rather than the initial onset of disease. CAD is characterized by monoclonal IgM production, a process that evolves over months to years and is unlikely to arise within days post vaccination. Furthermore, the discovery of a kappa restricted CD5+ B-cell population from the bone marrow points toward the presence of a preexisting lymphoproliferative process. COVID-19 vaccination induces a marked immune response, including transient B-cell stimulation and complement activation, which potentially stimulated cold reactive antibody activity and resulted in clinically significant hemolysis. This case suggests the origin of the patient's CAD to be vaccine associated immune triggering of previously subclinical CAD rather than vaccine induced generation of a novel clonal disorder.