CLINICAL VIGNETTE

Cold Agglutinin Induced Hemolytic Anemia as Initial Presentation of Large B-cell Lymphoma

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Background

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent form of non-Hodgkin lymphoma globally, accounting for 30–40% of cases. Patients generally present with an identifiable mass, often with nodal or extra-nodal involvement.[1] It rarely presents with Coombs negative hemolytic anemia and Cold Agglutinin disease, with few cases reported in the literature.[2] We describe a recent case at a tertiary care center.

HPI

Our patient was a 67-year-old female who presented to the emergency department with dyspnea and fatigue with recently diagnosed hemolytic anemia. Past medical history includes: coronary artery disease with prior myocardial infarction status post left anterior descending artery stent in 2003; heart failure with ejection fraction (EF 48%) status post automatic implantable cardioverter-defibrillator (AICD) in 2022; hypertension, and hypothyroidism.

The patient reported fatigue and dyspnea on exertion after testing positive for COVID-19 for the second time in 4 months and receiving Paxlovid for 5 days. She had recently returned from a 7-day cruise of Italy, Spain, and Greece. She did not drink the local water nor bathe in fresh or salt water and mostly ate at restaurants. She shopped but denies other exposures. She initially saw her primary care physician and was diagnosed with hemolytic anemia of unknown origin. After diagnosis, she was seen in the emergency department about every two weeks due to persistent fatigue and dyspnea, secondary to recurrent anemia. She received several blood transfusions for hemoglobin values below 7. Two months ago, the patient was started on a steroid taper for presumed autoimmune hemolytic anemia, which she reported provided no significant relief and stopped a few weeks prior. She was uncertain of exact duration of treatment and denied bleeding symptoms including gingival bleeding, easy bruising, hematuria, melena, hematochezia, or hematemesis. She did not note any dyspnea at rest.

Patient was born in the Philippines and had extensive travel history, including Boston, New York and the Philippines in the prior year. She also traveled to Kenya and Tanzania for safaris. After her trip to Africa, she was evaluated at a hospital for fatigue and found to have pancytopenia: Hgb 6, WBC 3, and platelets of 60k. She received an unknown number of pRBC transfusions and reported resolution of her fatigue. Patient denied any insect bites or feeling ill during her travel.

Past medical history included a long history of hypertension, treated with daily amlodipine 5 mg and benazepril 10 mg. She reported a myocardial infarction in 2003 with LAD stent placement. In 2022, she developed symptomatic bigeminy. She was also told told that she had heart failure and started on metoprolol succinate 25 mg daily and furosemide 10 mg daily one month prior to admission.

Family and social history were non-contributory without alcohol, tobacco, and other substance use. Prior to her illness she was very active with substantial walking. She lived alone and was independent in all activities of daily living.

Hospital Course

In the emergency department, the patient was appeared well, with non-remarkable vital signs and normal room air oxygen saturation. Physical exam showed no jaundice, splenomegaly, or lower extremity edema. She received one unit of pRBC for Hgb of 7.3, without significant response in hemoglobin. Platelets were 128 and WBC 8.1. Other labs included undetectable haptoglobin, LDH of 760, and low reticulocyte count of 2.57, consistent with hypoproliferation. PT, INR, fibrinogen, vitamin B12, and folate were within normal limits. Cold agglutinin was positive with a titer of 1:8 and she was admitted to the Medicine Service.

She received additional pRBC transfusions and Hematology performed a bone marrow biopsy. Chart review noted recent normal colonoscopy.

Quantiferon Gold was positive and flow cytometry showed 11% monotypic B-cell population with kappa light chain restrictions (kappa/lambda 3.42, kappa free light chain 47.05). UPEP revealed monoclonal bands in gamma region: M-protein = 7.7%; M protein 2 = 3.2%). Repeat Hgb was 6.7 and the patient received another unit of pRBCs. She reported continued fatigue. Bone marrow biopsy results were consistent with diffuse large B-cell lymphoma. Hematology-Oncology recom-

mended 6 cycles of R-EPOCH chemotherapy. Echocardiography revealed an ejection fraction of 40-45%, with left lateral wall motion abnormalities, and pulmonary systolic pressure to 52. Quantiferon Gold was positive and isoniazid was started for latent tuberculosis.

Cardiology was consulted prior to EPOCH chemotherapy. After initiation, the patient reported chills and was hypothermic with elevated lactate level. She was cultured and started on piperacillin/tazobactam.

PET CT showed moderate diffuse FDG update of the axial and visualized proximal appendicular skeleton. Mediastinal lymphadenopathy had been previously noted on imaging but there was no FDG uptake was noted on PET CT. The patient received filgrastim and prophylactic acyclovir and levofloxacin. She was discharged with outpatient Hematology/Oncology follow up.

Discussion

Classically, lymphomas with hemolytic anemia have been associated with warm-agglutinin positive Coombs tests.[3] Our patient developed cold-agglutinin positive hemolytic anemia with a negative warm-type Coombs test. Cold-agglutinin associated hemolytic anemia results from binding of monoclonal cold agglutinins, primarily IgM with κ light chains, to the I antigen on the surface of erythrocytes. Binding triggers agglutination of red blood cells and activates the complement system, with phagocytosis of complement-coated red blood cells by the reticuloendothelial system.[4,5] Typically, bone marrow involvement in cold agglutination patients differs from that in other small cell variants of B-cell non-Hodgkin lymphomas, such as follicular lymphoma, chronic lymphocytic leukemia, and mantle cell lymphoma. The typical cytological and immunophenotypic features of these lymphomas are absent in cold agglutination-associated lymphoproliferative disease. Follicular lymphoma typically exhibits paratrabecular infiltration with cleaved cells, often expressing BCL6 and CD10. Chronic lymphocytic leukemia and mantle cell lymphoma may display both nodular and diffuse infiltration by small round cells.[6] In contrast, our patient's bone marrow was only significant for CD19, CD20, PAX5, BCL1, BCL2, IgM, and kappa with Ki67 proliferation index ~30%; negative for CD5, CD10, CD30, BCL6, and SOX11.[6] The atypical presentation on both the laboratory tests and bone marrow biopsy encouraged expanded evaluation. Patients initially showing signs of hemolytic anemia can be the first presentation of large B-cell lymphoma.

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