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Cold Agglutinin Disease in the Setting of Pancreatic Adenocarcinoma

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Introduction

Autoimmune Hemolytic Anemia (AIHA) is caused by antibody-mediated destruction of red blood cells. There are two broad categories of AIHA: warm and cold, both categorized by the thermal reactivity of the autoantibodies [1]. Cold AIHA, or Cold Agglutinin Disease (CAD), occurs at temperatures below normal body temperature and primarily involves IgM antibodies. Primary cold agglutinin disease is often seen as a distinct, clonal lymphoproliferative disease while secondary cold agglutinin syndrome typically occurs in the setting of infections, autoimmune disorders, or aggressive lymphomas. In the context of solid organ malignancies, however, CAD is a rare association with only 52 cases reported in literature [2]. We report a case of a 65-year-old man diagnosed with pancreatic ductal adenocarcinoma who also presents with concomitant CADin the setting of multifactorial etiologies.

Case Presentation

A 65-year-old man to the Emergency Department (ED) with complaints of dyspnea, worsening lethargy, and generalized weakness. The patient also endorsed an unintentional weight loss of over 20 pounds in the last two months along with constipation, and pale, greasy-colored stoolsfor the past month.

On initial presentation, the patient was afebrile with BP 155/84 mmHg, HR 86/min, and RR 16/min, oxygen saturation of 98% on room air. 7 days before, he went to urgent care for complaints of dysuria and urinary hesitancy. Labs at the time were significant for a hemoglobin of 21.9 with characteristics suggestive of high titer cold agglutinin, neutropenia, elevated creatinine of 1.31, and urinalysis showing large blood and proteinuria. Physical exam was remarkable for bilateral non-pitting lower extremity edema. Initial laboratory work-up showed elevated lipase of 267, hyperbilirubinemia at 2.1, elevated LDH at 406, and macrocytic anemia with a hemoglobin of 7.6 and MCV of 118. 5. Given his initial presentation and history, a CT abdomen and pelvis with contrast was ordered, which showed findings suspicious for primary pancreatic neoplasm with nodal metastases and early carcinomatosis (Figure 1). The patient was subsequently admitted to the internal medicine service for further work-up of pancreatic cancer.

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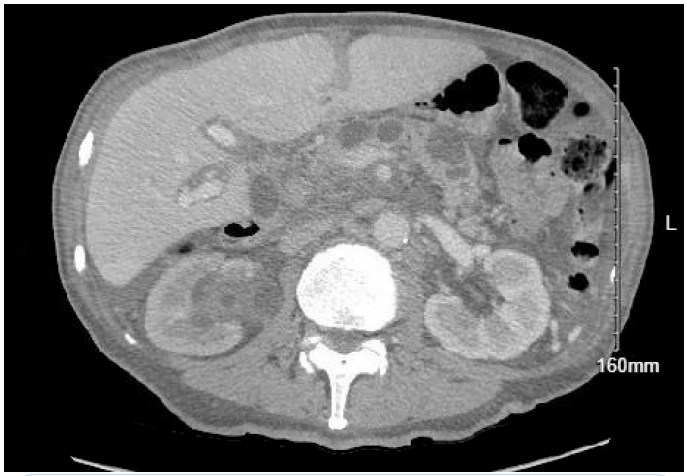

Figure 1: Abdominal CT highlighting the cystic lesions with septations in the pancreatic head and diffuse ductal dilatation.

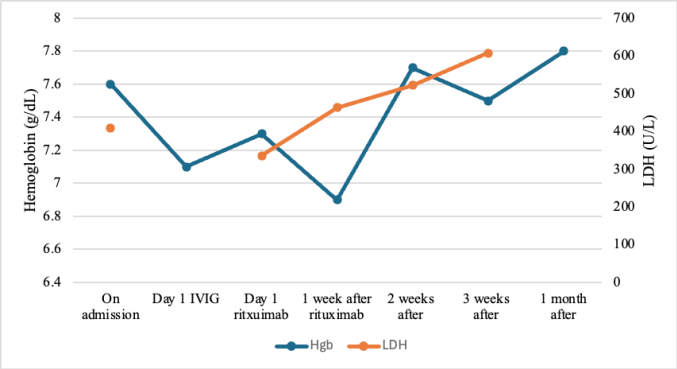

Figure 2: Graph showing hemoglobin and LDH values following treatment with IVIG and rituximab.

Upon admission, Gastroenterology, Hematology & Oncology teams were consulted. An MRCPwas performed which redemonstrated severe diffuse pancreatic ductal dilation with mild tail atrophy although no solitary mass was appreciated at the pancreatic head. Unfortunately, a biopsy was not taken as no solid obstructing mass was appreciated within the pancreatic head. CA 19-9 and CEA levels further confirmed pancreatic malignancy with levels at 221 U/mL and7 ng/mL, respectively. Given these findings, a repeat EUS in one month was ordered by Gastroenterology to reassess.

Simultaneously, work-up for his cold agglutinin disease revealed that the patient had a positive direct Coombs test with elevated LDH at 409 and low haptoglobin levels of <10 mg/dL. The patient had a positive cold agglutin screen at 4°C and 37°C. Infectious panel showed positive HBc IgM and positive IgG antibody for EBV. Autoimmune work-up showed an ANA titer of 1:320 with positive anti-SSO antibodies, elevated rheumatoid factor, and positive cyclic citrullinated peptide IgG antibody. Subsequently, the patient was given 1 unit of warm packed RBCs and Initiated on Intravenous Immunoglobulin (IVIG) and rituximab for treatment of CAD.His labs following, however, showed persistent anemia at a hemoglobin level of 7.2, alongside persistently elevated LDH and decreased haptoglobin (Figure 2).

Given the patient remained stable, he was discharged with recommendations for outpatient follow-up with Hematology/Oncology and GI. Three weeks later, however, he was readmitted tothe hospital for failure to thrive. During this hospitalization, an EUS-guided fine needle aspiration confirmed malignant pancreatic adenocarcinoma, stage 4. His subsequent hospital course was significant for diffuse abdominal distention requiring frequent paracentesis, malignant hydronephrosis requiring nephrostomy tube placement, and Superior Mesenteric Vein (SMV) thrombosis. Given his functional status, oncology did not recommend chemotherapy. Thepatient ultimately transitioned to hospice and passed away 5 days after discharge.

Discussion

CAD is a rare autoimmune hemolytic anemia, accounting for only 14% of AIHA [1]. The disease ischaracterized by cold agglutinins, autoantibodies that recognize antigens on RBCs at temperatures below normal human body temperature [3]. In healthy patients, these autoantibodies are typically only active at 3 to 4 degrees Celsius. However, in symptomatic patients, these agglutinins have higher thermal amplitudes, meaning they are active at higher temperatures, (around 28 to 30C). In cases where CAD occurs secondary to infections (such as Epstein-Barr Virus (EBV) mononucleosis or mycoplasma pneumoniae) or autoimmune disorders (such as Systemic Lupus Erythematosus, SLE), the hemolytic anemia resolves with resolution of the infection or treatment of the autoimmunity. In contrast, CAD secondary to a lymphoproliferativedisorder or primary CAD, often described as a lymphoproliferative disease, is chronic and minimally responsive to glucocorticoids or splenectomy.

We report the case of a patient presenting with concomitant pancreatic ductal adenocarcinoma and cold agglutinin disease in the setting of positive infectious and autoimmune screen findings.

Our patient exhibited both clinical and biochemical evidence of hemolysis: Dyspnea, fatigue, andgeneralized weakness alongside macrocytic anemia, low haptoglobin, and elevated lactate dehydrogenase, bilirubin, and absolute reticulocyte count. CAD was confirmed with positive cold agglutinin test and direct Coombs test, and pancreatic adenocarcinoma confirmed with EUSbiopsy, along with elevated tumor markers (CA 19-9, CEA).

While the association of CAD with lymphoproliferative disorder is well established, there are few reports of AIHA in solid tumors, especially for pancreatic cancer. Puthenparambil et al reported that only 52 cases in literature report AIHA as a paraneoplastic phenomenon in solid tumors, one of which was linked to pancreatic cancer [2]. Additionally, there have been only two other case reports that associate AIHA with pancreatic adenocarcinoma [4]. Association between the two, therefore, often requires excluding other possible underlying diseases that could trigger cold agglutinin disease. In our patient's case, lymphoproliferative disorders were ruled out with abone marrow biopsy which showed normocellular marrow and no morphologic evidence of lymphoma. Work-up of other possible etiologies yielded positive HBc IgM and IgG antibodies for EBV, alongside elevated autoimmune markers for SLE and rheumatoid arthritis. However, given his history showed no potential exposure for Hepatitis B and patient denied any clinical manifestations of the autoimmune findings, this strongly suggests his pancreatic cancer was the underlying trigger for the hemolytic anemia.

While the mechanism for malignancy-associated AIHA is not well understood, improvement of anemia in these cases occurred following definitive treatment of underlying malignancies in previously reported cases [5-8]. In our patient's case, however, because of the delay in formal diagnosis of his pancreatic cancer, treatment was focused on symptomatic management of his anemia with rituximab [9]. His hemoglobin levels improved minimally, with his highest level at 8.7compared to

7.6. Following his repeat EUS, the patient was diagnosed with stage IV pancreatic adenocarcinoma. Given his prognosis, the patient deferred treatment of his cancer. Following extensive discussion with the palliative care team, he opted for hospice and passed away at home.

We report this case to highlight its rarity[4] and to demonstrate the importance of early investigation into patients whose clinical presentation is suggestive of autoimmune hemolytic anemia, especially if they have no obvious underlying etiology [10]. While linking AIHA to solidorgan tumors is a diagnosis of exclusion, these investigations are necessary for early identification and treatment to help improve quality of life, if not mortality.

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References

1. Berentsen S. Cold agglutinin disease. Hematology. 2016; 2016(1): 226-231. doi:10.1182/asheducation-2016.1.226.

2. Puthenparambil J, Lechner K, Kornek G. Autoimmune hemolytic anemia as a paraneoplastic phenomenon in solid tumors: A critical analysis of 52 cases reported in the literature. Wien Klin Wochenschr. 2010; 122(7): 229-236. doi:10.1007/s00508-010-1319-z.

3. Scheckel CJ, Go RS. Autoimmune Hemolytic Anemia: Diagnosis and Differential Diagnosis. Hematol Oncol Clin North Am. 2022; 36(2): 315-324. doi:10.1016/j.hoc.2021.12.001.

4. Hariz A, Hamdi MS, Boukhris I, Cherif E. Autoimmune haemolytic anaemia in pancreatic adenocarcinoma: a potential paraneoplastic presentation. BMJ Case Rep CP. 2019; 12(7): e229807. doi:10.1136/bcr-2019-229807.

5. Spira MA, Lynch EC. Autoimmune hemolytic anemia and carcinoma: An unusual association. Am J Med. 1979; 67(5): 753-758. doi:10.1016/0002-9343(79)90730-7.

6. Morris PG, Swords R, Sukor S, Fortune A, O'Donnell DM, et al. Autoimmune Hemolytic Anemia Associated With Ovarian Cancer. J Clin Oncol. 2008; 26(30): 4993-4995. doi:10.1200/JCO.2008.17.1231.

7. Jones E, Tillman C. A case of hemolytic anemia relieved by removal of an ovarian tumor. J Am Med Assoc. 1945; 128(17): 1225-1227. doi:10.1001/jama.1945.92860340001007a.

8. Loh KP, Kansagra A, Asik A, Ali S, Dahiya S. Paraneoplastic Autoimmune Hemolytic Anemia in Ovarian Cancer: A Marker of Disease Activity. Rare Tumors. 2015; 7(1): 4-7. doi:10.4081/rt.2015.5598.

9. Gertz MA. Updates on the Diagnosis and Management of Cold Autoimmune Hemolytic Anemia. Hematol Oncol Clin North Am. 2022; 36(2): 341-352. doi:10.1016/j.hoc.2021.11.001.

10. Hill A, Hill QA. Autoimmune hemolytic anemia. Hematol Am Soc Hematol Educ Program. 2018; 2018(1): 382-389.