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COLD AGGLUTININ DISEASE IN THE SETTING OF PANCREATIC ADENOCARCINOMA

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ABSTRACT

Autoimmune haemolytic anaemia (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. Cold agglutinin disease (CAD) occurs at temperatures below normal body temperature and primarily involves IgM antibodies. CAD typically occurs secondary to other processes: lymphoproliferative disorders or infection, although it can be rarely idiopathic.

We present a case of a 65-year-old male with no past medical history who initially presented with haematuria and proteinuria, along with thrombocytopenia and leukopenia. He reported an unintentional weight loss of more than 9 kg, constipation, and pale-greasy coloured stools. Computed tomography (CT) scan of the abdomen and pelvis revealed findings suspicious for primary pancreatic neoplasm with nodal metastases and early carcinomatosis, severe right hydronephrosis, and distended gallbladder. Direct antiglobulin test (DAT) screening was negative, but an antibody screen was positive. The patient had a positive cold agglutin screen and elevated CA 19-9, carcinoembryonic antigen (CEA), and cyclic citrullinated peptide (CCP) levels, tumour markers used typically for diagnosis of pancreatic cancer.

The patient presented with symptoms and laboratory findings suggestive of a complex interplay between haemolytic anaemia and a suspected solid organ malignancy, specifically pancreatic cancer. His elevated tumour markers and positive antibody screen and cold agglutinin screen suggested the possibility of paraneoplastic syndrome secondary to his pancreatic cancer. However, his infectious and autoimmune panel findings further complicated the picture and underscored the multifactorial nature of his condition.

KEYWORDS

Pancreatic adenocarcinoma, anaemia, paraneoplastic, gastroenterology

LEARNING POINTS

- This case highlights a rare association between autoimmune haemolytic anaemia (AIHA) and pancreatic adenocarcinoma.
- While AIHA is a known paraneoplastic syndrome of hematologic malignancies, this case report suggests that it may also be a paraneoplastic syndrome for solid tumours.
- This case report highlights the difficulty of treating AIHA in the setting of comorbidities, suggesting that standard treatment guidelines may not be effective.

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INTRODUCTION

Autoimmune haemolytic anaemia (AIHA) is caused by antibody-mediated destruction of red blood cells (RBCs). There are two broad categories of AIHA: warm and cold, both categorized by the thermal reactivity of the autoantibodies[1]. 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 the literature[2]. We report a case of a 65-year-old man diagnosed with pancreatic ductal adenocarcinoma who had concomitant CAD in the setting of multifactorial aetiologies.

CASE DESCRIPTION

A 65-year-old man presented to the emergency department with complaints of dyspnoea, worsening lethargy, and generalized weakness. The patient also reported an unintentional weight loss of over 9 kg in the last two months along with constipation, and pale, greasy-coloured stools for the past month.

On initial presentation, the patient was afebrile with a blood pressure of 155/84 mmHg, a heart rate of 86 bpm, and a respiratory rate of 16 breaths per minute, oxygen saturation of 98% on room air. Seven days before presentation, he went to urgent care for complaints of dysuria and urinary hesitancy. Labs at the time were significant for a haemoglobin of 21.9 g/dl with characteristics suggestive of high titre cold agglutinin, neutropenia, elevated creatinine of 1.31 mg/dl, and urinalysis showing haematuria and proteinuria. Physical exam was remarkable for bilateral non-pitting lower extremity oedema. Initial laboratory work-up showed elevated lipase of 267 U/l hyperbilirubinemia at 2.1, elevated LDH at 406 U/l, and macrocytic anaemia with a haemoglobin of 7.6 g/dl and MCV of 118. 5 fl *(Table 1)*. Given his initial presentation and history, a CT scan of the abdomen and pelvis with contrast was ordered, which showed findings suspicious for primary pancreatic neoplasm with nodal metastases and early carcinomatosis *(Fig. 1)*. The patient was subsequently admitted to the internal medicine service for further work-up of pancreatic cancer.

Upon admission, gastroenterology, haematology and oncology teams were consulted. Magnetic resonance cholangiopancreatography was 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. Elevated levels of markers CA 19-9 and carcinoembryonic antigen (CEA) levels further confirmed pancreatic malignancy with levels at 221 U/ml and 7 ng/ml, respectively. Given these findings, an endoscopic ultrasound (EUS) in one month was ordered by gastroenterology to reassess.



Figure 1. Abdominal computed tomography scan highlighting the cystic lesions with septations in the pancreatic head and diffuse ductal dilatation.

Simultaneously, work-up for his cold agglutinin disease revealed that the patient had a positive direct Coombs test with elevated LDH at 409 U/l 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 Epstein-Barr virus (EBV) Autoimmune work-up showed an ANA titre 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 subsequent labs, however, showed persistent anaemia at a haemoglobin level of 7.2 g/dl, alongside persistently elevated LDH and decreased haptoglobin *(Fig. 2)*.

Given that the patient remained stable, he was discharged with recommendations for outpatient follow-up with haematology, oncology and gastroenterology. Three weeks later, however, he was readmitted to the hospital for adult malnutrition. 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 thrombosis. Given his functional status, oncology did not recommend chemotherapy. The patient ultimately transitioned to hospice and passed away 5 days later.

DISCUSSION

CAD is a rare autoimmune haemolytic anaemia, accounting for only 14% of AIHA[1]. The disease is characterized 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,

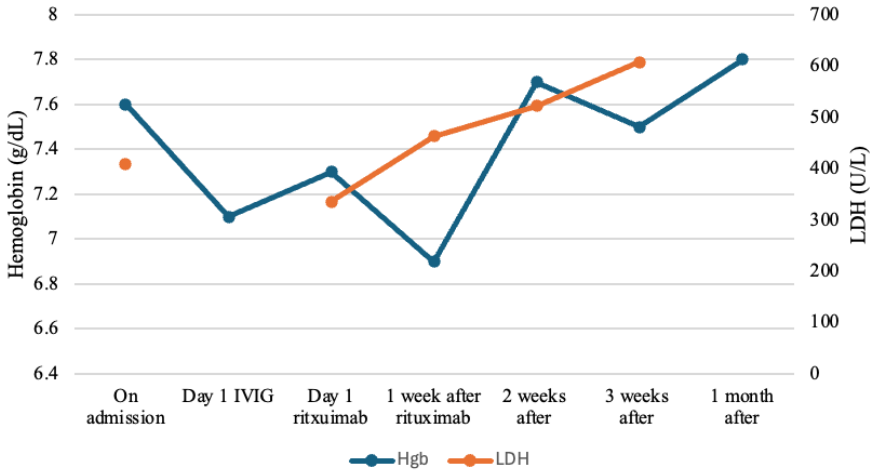


Figure 2. Graph showing haemoglobin and LDH values following treatment with IVIG and rituximab.
Abbreviations: LDH, lactate dehydrogenase; IVIG, on intravenous immunoglobulin.

meaning they are active at higher temperatures (around 28 to 30°C). In cases where CAD occurs secondary to infections (such as EBV mononucleosis or mycoplasma pneumoniae) or autoimmune disorders (such as systemic lupus erythematosus, systemic lupus erythematosus, SLE), the haemolytic anaemia resolves with resolution of the infection or treatment of the autoimmunity. In contrast, CAD secondary to a lymphoproliferative disorder 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 haemolysis: dyspnoea, fatigue, and generalized weakness alongside macrocytic anaemia, 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 EUS biopsy, along with elevated tumour markers (CA 19-9, CEA). While the patient's initial haemoglobin was 21.9 g/dl, we believe this is likely due to a lab error given that a repeat haemoglobin level 7 days later was noted to be 7.6 g/dl.

While the association of CAD with lymphoproliferative disorder is well established, there are few reports of AIHA in solid tumours, especially for pancreatic cancer. Puthenparambil et al. found that only 52 articles in the literature report AIHA as a paraneoplastic phenomenon in solid tumours, 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 a bone marrow biopsy which showed normocellular marrow and no morphologic evidence of lymphoma. Work-up of other possible aetiologies yielded positive HBc IgM and EBV IgG antibodies, alongside

Labs	Value	Normal Range
Haemoglobin (g/l)	7.6	13.5-17.5
Haematocrit (%)	20.5	41-51
MCV (fl)	116.5	80-99
Platelets (×10⁹/l)	315	140-440
Sodium (mEq/l)	137	135-145
Potassium (mEq/l)	4.5	3.5-5.3
Chloride (mEq/l)	98	98-108
Bicarbonate (mEq/l)	26	22-28
AST (U/l)	24	0-37
ALT (U/l)	16	6-45
Lipase (U/l)	267	16-63
Alkaline phosphatase (U/l)	94	40-129
Total bilirubin (mg/dl)	1.8	<1.2
BUN (mg/dl)	32	10-20
Creatinine (mg/dl)	1.31	0.6-1.2
Glucose (mg/dl)	108	70-100
CA 19-9	221	<35
CEA	7	<5
LDH (U/l)	409	94-250
Haptoglobin (mg/dl)	<10	30-200
Direct Coombs test	Positive	Negative
anti-CCP (U/ml)	421	<17
ANA titre	6:20	<1:40
ANA pattern	Speckled	-

Table 1. Tabulated lab values of patient's initial labs and normal lab ranges.

elevated autoimmune markers for SLE and rheumatoid arthritis. While autoimmune diseases can cause CAD, there have been cases reported that indicate paraneoplastic manifestations of pancreatic cancer can mimic autoimmune diseases, like rheumatoid arthritis[5,6]. Likewise, while EBV can also cause CAD, it is mediated by IgM antibodies, rather than IgG antibodies. Given that patient denies any clinical manifestations of related autoimmune diseases and active infectious mononucleosis caused by EBV, this strongly suggests his pancreatic cancer was the underlying trigger for the haemolytic anaemia.

While the mechanism for malignancy-associated AIHA is not well understood, improvement of anaemia in these cases occurred following definitive treatment of underlying malignancies in previously reported cases[7–10]. 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 anaemia with rituximab[11]. His haemoglobin levels improved minimally, with his highest level at 8.7 g/dl compared to 7.6 g/dl. Following his repeat EUS, the patient was diagnosed with stage IV pancreatic adenocarcinoma. Given his prognosis, the patient deferred treatment for 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 of patients whose clinical presentation is suggestive of autoimmune haemolytic anaemia, especially if there is no obvious underlying aetiology[12]. While linking AIHA to solid organ tumours is a diagnosis of exclusion, these investigations are necessary for early identification and treatment to help improve quality of life, and hinder mortality.

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