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Rare co-occurrence of probable pernicious anemia and autoimmune hepatitis in a 55-year-old male patient: A case report

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Abstract

This is a case of probable pernicious anemia in the setting of autoimmune hepatitis. A 55-year-old male patient presented to the Emergency Room at Dr. Ruth K.M. Pfau Civil Hospital, Karachi with complaints of diarrhea and fever and was subsequently transferred to the medicine ward. The patient also had signs of unexplained anemia. We performed laboratory tests and were able to rule out the common causes of liver pathology, including viral hepatitis. For blood, the values showed decreased hemoglobin levels and an elevated Mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) (114 fL), indicating macrocytosis. Finally, we were able to conclude autoimmune pathology after the results of antibody testing demonstrated positive lab values for anti-smooth muscle antibodies, antinuclear antibodies, and anti-gastric parietal cell antibodies. The patient had developed pernicious anemia in the setting of autoimmune hepatitis, which is an extremely rare case and documented instances are scarce in the available literature regarding such cases.

Keywords

Pernicious anemia, autoimmune hepatitis, anemia, antibody testing, liver pathology

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Introduction

Autoimmune hepatitis (AIH) represents an infrequent form of chronic liver inflammation, which evolves from an initial acute hepatitis episode. Its clinical presentation spans a spectrum from acute to chronic liver diseases. The disease is categorized as autoimmune hepatitis-1 and autoimmune hepatitis-2 based on distinct antibody profiles.[1] The prevalence of autoimmune hepatitis in Asia is 12.99, lower than in other regions of the world.[2] People with autoimmune hepatitis are at risk of having other autoimmune diseases. Examples include celiac disease, thyroid conditions such as Graves' disease or Hashimoto's disease, ulcerative colitis, rheumatoid arthritis, lupus, or Sjogren's syndrome.[3] However, it is rarely observed with pernicious anemia (PA), another autoimmune disease characterized by the formation of antibodies against parietal cells or intrinsic factors, leading to impaired absorption of vitamin B12.[4]

Here we present a unique case of probable PA with autoimmune hepatitis.

Case description

This is a case of a 55-year-old Pakistani male patient with type 2 diabetes mellitus (DM) who presented to the emergency department with complaints of loose stools and fever for 1 month. He also reported significant weight loss since the onset of his symptoms and complained of generalized weakness and shortness of breath on exertion. Orthopnea and paroxysmal nocturnal dyspnea were not reported. Upon further questioning, the patient reported significant joint pain and stiffness in small hand joints for the last few months and experienced painful ulcers in the mouth. He provided a history of on and off jaundice in the last few months. The patient

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also reported multiple admissions with similar complaints in the past.

The diarrhea was described as greasy, foul smelling, yellow in color, and difficult to flush. It did not contain blood and was not associated with abdominal pain. The patient experienced 5–6 episodes per day. Fever was low-grade, intermittent, and not associated with rigor and chills. The patient experienced joint pain and deformity in the small joints of the hands bilaterally, with significant morning stiffness lasting around 30 minutes. The pain and stiffness improved with activity. The chest was clear on percussion and auscultation, and the cardiovascular system examination was unremarkable.

On examination, the patient had a Glasgow Coma Scale score of 14/15 and was fully oriented. Vitals were slightly unstable including tachycardia, low blood pressure, and increased respiratory rate. Signs of anemia and raised jugular venous pressure were seen. The patient had a capillary refill time of >2 s. No cyanosis or clubbing was present. The patient appeared dehydrated, with dry mucosal surfaces. The abdomen was soft and distended. Gross ascites were visible and non-tappable, and the lower borders of the liver and spleen were palpable. Scleral icterus was noted. There was significant joint deformity at the metacarpophalangeal joints bilaterally. The patient had multiple oral ulcers and loss of lateral thirds of eyebrows. There was no Raynaud's phenomenon or photosensitivity.[5] The patient also had bilateral pedal edema which began 15 days ago, was gradual in onset, and had progressively increased. Significant temporal wasting was also noted.

The patient hadn't gone through a recent medical review, and at the time of presentation, he wasn't diagnosed with any active medical condition. Appropriate tests were ordered, including Complete Blood Count, iron studies, vitamin B12, folic acid levels, and Liver function tests (LFTs) as shown in (Tables 1 and 2). Low levels of vitamin B12 and folic acid (<150 pg/mL and 2.4 ng/mL respectively), were seen. IgG levels were raised (3100 mg/dL). C-reactive peptide levels were also raised (58 mg/L), indicating an inflammatory response. The patient's lipid profile, urinary copper, and ferritin levels were normal. The thyroid function tests were also ordered, and the thyroid profile was normal. Total IgA levels were also tested, and they turned out to be normal. The patient's serum amylase and lipase levels, and alkaline phosphatase levels were also within the normal range. Testing for human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 were also negative. A provisional diagnosis of malabsorption syndrome was made.

The LFTs were remarkably deranged. There were low levels of albumin of 2.1 g/dL; elevated bilirubin of 2.1 mg/dL; elevated direct bilirubin of 1.2 mg/dL. Alanine aminotransferase and aspartate aminotransferase levels were also significantly elevated, with values of 108 and 138 U/L respectively. Viral hepatitis was excluded after serum levels of markers of viral hepatitis turned out negative.

Table 1. Shows the hematologic lab values.

Test	Result (on admission)	Result (at discharge)
Hemoglobin (Hb)	3.1 g/dL	8.3 g/dL
Mean corpuscular volume (MCV)	114 μm^3	N/A
Platelets	12,000 cells/nm^3	82,000 cells/nm^3
White blood cells (WBCs)	4.8 × 10E9/L	11.9 × 10E9/L

Table 2. Shows the live function test.

Test	Result
Albumin	2.1 mg/dL
Total bilirubin	2.1 mg/dL
Direct bilirubin	1.2 mg/dL
Aspartate aminotransferase (AST)	138 U/L
Alanine aminotransferase (ALT)	108 U/L
Alkaline phosphatase (ALP)	78
Serum amylase	14

The patient was in critical condition upon arrival and blood transfusions were performed on the patient, and the patient received two packs of red blood cells. Intravenous vitamin B12 therapy was implemented after oral therapy had failed. Significant improvement in the patient's condition was noted following these interventions, with stabilization of vital signs and an increase in hemoglobin levels.

Further diagnostic tests were ordered including tests for hepatitis B and C, Human Immunodeficiency Virus, celiac disease, and tuberculosis (TB), all of which came out to be negative. To rule out celiac disease, we performed appropriate tests including serum antibody levels of anti-tissue transglutaminase (anti-tTG), anti-gliadin, and anti-endomysial antibodies. Testing for HLA-DQ2 and HLA-DQ8 was also done. These tests turned out negative. The TB screening test was also negative (tuberculin skin test).

We performed an abdominal echo ultrasound (US) to assess the morphology of the liver. The liver was normal in size, with *irregular margins* and *coarse echotexture*. The portal vein diameter measured 1.2 cm. Shear wave elastography was also performed and it demonstrated mild to moderate fibrosis of the liver. We proceeded with autoimmune profile evaluation and found that our patient had positive lab values for antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-parietal cell antibodies (APCA). The anti-citrullinated peptide (Anti-CCP) antibodies also returned positive, implying that the patient had a high probability of rheumatoid arthritis. Anti-double-stranded DNA antibodies were negative as shown in (Table 3). *Helicobacter pylori* testing also came out to be negative.

The patient was noncompliant and refused invasive gastric procedures for further investigation and management;

Table 3. Shows the autoimmune profile.

Test	Result
Antinuclear antibody (ANA)	Positive
Anti-smooth muscle antibody (ASMA)	Positive
Anti-parietal cell antibodies (APCA)	Positive
Anti-cyclic citrullinated peptide (Anti-CCP)	Positive
Anti-double-stranded DNA (Anti-dsDNA)	Negative
Immunoglobulin G (IgG)	3100 mg/dL

therefore, a biopsy could not be performed. However, based on the results, we concluded that the patient had developed autoimmune hepatitis using the simplified autoimmune hepatitis scoring system, with a score of 6 (raised IgG, ANA, and ASMA positive, negative hepatitis viral markers) as shown in Table 3, along with PA.

He was discharged with supportive treatment including IV vitamin supplements, and immunosuppression with prednisolone. Exclusion of the presence of esophageal varices was not possible due to the refusal of invasive procedures, but propranolol was prescribed to prevent variceal bleeding. The patient was advised to follow-up, which he didn't comply with, and the patient never returned for re-evaluation.

Discussion

AIH represents an acute autoimmune liver condition that can be further categorized into two types; Type 1 and type 2, each associated with distinct antibody profiles. Type 1 AIH is associated with ANA and ASMA while the lesser common type 2 contains liver-kidney microbiota and/or liver cytosol antibodies.

The precise pathophysiology of AIH remains ambiguous. The prevailing theory relating to AIH is that it develops in a genetically susceptible population, triggered by certain environmental factors. Consequently, the autoimmune attack is sustained, possibly through molecular mimicry, and may be exacerbated by loss of regulatory T-cell control. Viral antigens, drugs, and herbal compounds have been identified as triggers.[6]

Patients can be diagnosed with AIH at any age however type-1 AIH tends to occur most frequently between the ages of teenage and adulthood. In addition to hepatitis with varying degrees of liver damage, fibrosis, and cirrhosis. AIH can present with other autoimmune and inflammatory conditions like rheumatoid arthritis, Grave's disease, ulcerative colitis, celiac disease, Systemic lupus erythematosus (SLE), and other similar conditions.[7]

This is a 55-year-old patient who presented with a history of type 2 DM and complained of gastrointestinal symptoms associated with fever, fatigue, and weight loss for a month. Upon further inquiry, it was found to have joint pain, jaundice, pancytopenia, and deranged vitals. He also had a history of multiple hospital visits with similar complaints in the past. Although the symptoms would seem unrelated at first a history of treatment for similar problems pointed to a deeper underlying issue.

Gastrointestinal manifestations, especially fat, foul-smelling ulcers, combined with markers of malabsorption (low vitamin B12, folic acid, and impaired liver function) led to the assumption of malabsorptive syndrome, hence confirming, or ruling out the diagnosis of celiac disease was a vital step. Since invasive diagnostic techniques were denied by the patient, we had to perform important laboratory investigations which included serology for celiac disease which consisted mainly of anti-tTG, anti-endomysial, and anti-gliadin antibodies. These antibodies have a high level of sensitivity and specificity in patients with celiac disease. Additional testing was done for HLA-DQ2 and HLA-DR8, which are also highly sensitive to celiac disease. All these lab investigations turned out negative, which enabled us to rule out celiac disease with confidence.

Although the initial symptoms gave the impression of celiac disease or another small bowel disease, it is likely that in this case, the malabsorptive symptoms were due to another etiology.[8] We performed additional tests to assess pancreatic and biliary function and were able to rule out the possibility of pancreatic and biliary insufficiency based on the results of these tests. The patient had normal serum levels of pancreatic enzymes and markers of biliary insufficiency.

A hepatic etiology was likely considering the US findings demonstrating evidence of end-stage liver disease. Different common causes of this condition were considered, including viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease.[7] The patient also exhibited no other symptoms suggestive of conditions such as hemochromatosis or Wilson disease. The patient had a normal BMI and no history of alcohol abuse. Testing for viral markers was negative. The diagnosis of AIH was a challenge due to the patient's refusal of invasive procedures hence the biopsy was not performed. Therefore, the probable diagnosis was reached through an extensive process of exclusion. The patient had an obvious autoimmune predisposition, considering his lab results, history of oral ulcers, and symptoms and investigations consistent with rheumatoid arthritis. Despite the absence of biopsy, the positive laboratory tests for raised IgG and other pertinent autoimmune markers coupled with the patient's presenting symptoms collectively supported the probability of AIH with autoimmune hemolytic anemia. The positive lab values for ASMA are highly suggestive of autoimmune hepatitis. A meta-analysis conducted to determine the accuracy of ASMA for diagnosing AIH showed a high pooled specificity of 0.926 (95% CI: 0.917–0.934).[9] Normal levels of IgG fall within 600–1640 mg/dL for adults. Our patient demonstrated a significantly elevated IgG level (3100 mg/dL), which is considered a hallmark of AIH.[10]

For diagnosis, we used the simplified AIH scoring system, according to which a score of 6 is a probable diagnosis while a score of equal to or greater than 7 is a definitive

diagnosis.[11] From our lab evaluation, we reached a score of 6, suggesting a probable diagnosis of AIH in our patient. The symptoms of malabsorption in our case were most likely due to AIH. While it is a less typical presentation of liver disease than small bowel, pancreatic, or biliary disease, it is not uncommon to see these symptoms in hepatic dysfunction, acute or chronic.[8,12]

Autoimmune hemolytic anemia has been found to coexist with AIH.[13] and at times, with viral infections.[14,15] However, the patient additionally exhibited anemia characterized by an elevated MCV and deficiencies in vitamin B12 and folate. This occurrence suggests PA, an exceptionally uncommon association with AIH.[16]

Gastrointestinal manifestations, especially fat, foul-smelling ulcers, combined with markers of malabsorption (low vitamin B12, folic acid, and impaired liver function) led to the assumption of malabsorptive syndrome about but the simultaneous findings of pancytopenia, elevated MCV, and arthralgia prompted further investigation.

Suspicion of autoimmune hemolytic anemia prompted testing epidemiological association with AIH.[17] The combination of laboratory tests, autoimmune profile studies, and imaging studies revealed a strong association between autoimmune hepatitis and PA with positive ANA, ASMA, APCA, and anti-CCP antibodies the presence showed autoimmune hepatitis, in conjunction with low levels of vitamin B12 and folic acid suggest PA.

The patient also had joint pain, which followed a pattern like the one that is expected in rheumatoid arthritis, with pain in small joints of hands bilaterally with significant morning stiffness that lasted more than 30 min and improved with activity. The suspicions of RA were substantiated when the antibody screen demonstrated an elevated level of anti-CCP antibodies. This is the most specific lab test for rheumatoid arthritis (with a specificity of 95%–96%).[18] Autoimmune diseases tend to co-occur in predisposed individuals,[3] making it plausible that this patient has developed multiple autoimmune manifestations. Further diagnostic testing for RA wasn't deemed necessary due to the high clinical suspicion of RA, and the patient was managed appropriately.

Management of this case was difficult due to the complexity of the patient's condition and his refusal to be involved in invasive procedures. However, the patient was initially stabilized through swift blood transfusions and intravenous vitamin B12. AIH is found to be extremely sensitive to immunosuppressive therapy[6,19] and subsequent implementation of prednisolone immunosuppressive therapy yielded favorable results, leading to the stabilization of the patient's condition and subsequent discharge.

Prednisolone use in the long term is, however, associated with side effects, including acne, weight gain, hyperglycemia, hypertension, osteoporosis, and cataracts[20] Therefore, other Disease-Modifying Antirheumatic Drugs (DMARDs) may be prescribed to patients as an alternative to glucocorticoids, such as Azathioprine, Methotrexate, and Mycophenolate mofetil.[20] These medications are also associated with various side effects. Our patient was not administered DMARDs because his symptoms showed a positive response to prednisolone initially and long-term follow-up was not possible because the patient didn't return to follow-up.

In patients with cirrhosis, the likelihood of presence of esophageal varices is high as it is an important complication of end-stage liver disease.[21] Testing for varices is of paramount importance in such patients as the bleeding can be life-threatening.[22] The most accurate and widely used diagnostic method for suspected varices is esophagoscopy, which can directly visualize the varices. In our patient, there was no history of hematemesis, so the treatment options that are used to stop the variceal bleeding, such as band ligation and sclerotherapy, were not used.[21] Esophagoscopy was not performed due to the patient's refusal, but due to high risk, the patient was prescribed propranolol, a beta-blocker medication, which is the recommended treatment for variceal prophylaxis.[21,22]

Nevertheless, this case presentation raises important questions about long-term use, especially given patient noncompliance. Early diagnosis and access to specialist consultation should improve AIH management and outcome.[23] Ongoing assessment with regular follow-ups and patient education is critical in ensuring adherence to treatment regimens, reducing disease progression, and further prevention.

A limitation of this case report is that despite advising the patient to follow-up, they did not comply with this recommendation. Subsequently, the patient never returned for re-evaluation, resulting in a lack of further clinical data or assessment beyond the initial encounter.

Conclusion

Though the presentation of immune conditions in an overlapping fashion is a common occurrence in medicine, having autoimmune hepatitis concomitantly with PA is a rarity. Such a case requires thorough investigation to come to a conclusion, especially in the absence of a biopsy. The overlapping immune conditions present a challenge in the diagnosis and subsequent specialized care of patients with autoimmune hepatitis and warrant a multidisciplinary approach to address the underlying problems and provide treatment options. Collaborative efforts of a multidisciplinary team can provide optimal outcomes with a tailored approach to the specific needs of the patient.

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Author contributions

Ahmed Ibrahim Siddiqui: contributed to the conceptualization, writing – original draft, final approval, and agreeing to the accuracy of the

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