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Case Report

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Acute Autoimmune Hepatitis with Amyopathic Dermatomyositis: "A Diagnostic and a Therapeutic Dilemma" : A Case Report

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ABSTRACT

Autoimmune hepatitis(AIH) is a rare, immune-mediated inflammatory liver disorder, while its acute form has a spectrum of clinical manifestations including acute-icteric AIH, acute severe AIH (AS-AIH) and AS-AIH with acute liver failure (ALF) (1). A subset of patients with dermatomyositis (DM) presents with characteristic skin findings but without muscle involvement, termed clinically amyopathic dermatomyositis (CADM). This subgroup includes patients with amyopathic DM(AMD), who are devoid of all clinical and laboratory findings of muscle involvement (2). We report a case of a previously healthy 54-year-old woman who presented with acute icteric AIH and features of AMD, rapidly progressing to AS-AIH with ALF and the diagnostic and therapeutic challenges encountered while managing the patient.

Keywords: Acute Autoimmune hepatitis, Amyopathic dermatomyositis, Acute liver failure, Plasma Exchange

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare, immune-mediated inflammatory liver disorder marked by the presence of circulating autoantibodies, elevated levels of gamma globulins, and unique histological features in liver biopsy (1). AIH is characterized by a sudden onset of symptoms and laboratory abnormalities that are identified at the time of diagnosis, without any clinical or laboratory indicators of liver failure. It has a spectrum of clinical manifestations including acute-icteric AIH, acute severe AIH (AS-AIH) and AS-AIH with acute liver failure (ALF)(1). Clinically amyopathic dermatomyositis (CADM) is a subset of patients who develop specific skin findings of DM without any muscle symptoms, while patients who lack all signs of muscle involvement is referred to as amyopathic DM(ADM). The co-existence of acute AIH with ADM is rare, and the rapid progression of acute AIH to AS-AIH resulting in ALF is also infrequently documented.

CASE REPORT

53-year-old lady, who was working in Kuwait for 6 years as a house maid, presented with nausea, vomiting and yellowish discoloration of eyes for 1-week duration.

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The patient developed nausea and vomiting for one week while in Kuwait. She did not experience hematemesis, blood-stained vomitus, abdominal pain, or loose stools. There was no fever, chills, rigors, dysuria, or urinary symptoms. She noticed yellowish discoloration in her eyes for one week but did not have body itching, pale stools, or tea-colored urine. There was no abdominal distension, lower limb swelling, altered bowel habits, melena, loss of appetite, or weight loss. There was no altered sleep. She did not experience chest pain, palpitations, shortness of breath, exertional dyspnea, or fatigue. Prior to the onset of her illness, she had been well and three days before becoming ill she had traveled to a nearby city with her employers, consuming food from outside. She has lived in Kuwait for the past six years and has been separated from her husband for the same duration. She reported no high-risk sexual behaviors, history of blood transfusions, or IV drug use. She does not consume alcohol and had not taken any long-term or short-term medications, including Ayurvedic treatments.

She had also noticed a dark purplish discoloration around her eyes with swelling which appeared within one week. The skin around her eyes was not itchy. Additionally, she noticed dark discoloration over the joints of her fingers but did not observe any other rashes. She did not report arthralgia, myalgia, or swelling in either small or large joints. She denied having difficulty in combing her hair, climbing stairs, or standing up from a squatting position. There were no complaints of dry, gritty eyes, dry mucous membranes, hair loss, or oral ulcers.

She had no history of liver, rheumatological, hematological, or cardiac diseases, nor did she have diabetes or dyslipidemia. She did not have any history of miscarriages and was a mother of two sons. She had reached menopause at the age of 49 and denied any post-menopausal bleeding. Her allergy history was unremarkable. The patient reported no family history of hematological, autoimmune, vascular, gastrointestinal, or liver diseases, nor any history of malignancies.

On examination, her BMI was 26 kg/m², and she was afebrile. She appeared deeply icteric. There were no oral ulcers, and cervical or axillary lymphadenopathy was not present. There was a violaceous discoloration of the eyelids and periorbital area accompanied by edema, suggestive of a heliotrope rash (Figure 01 A). Additionally, erythematous, slightly raised violaceous papules were observed over the joints on dorsal aspects of fingers of both hands, suggestive of Gottron papules. (Figure 01 B). There were no signs of peripheral stigmata of chronic liver cell disease, finger clubbing, joint swellings, or thickened skin. Her abdomen was non-tender, without hepato-splenomegaly or palpable masses. No free fluid was noted. There was no proximal or distal muscle tenderness or weakness observed on examination and the rest of the systemic examination was unremarkable.

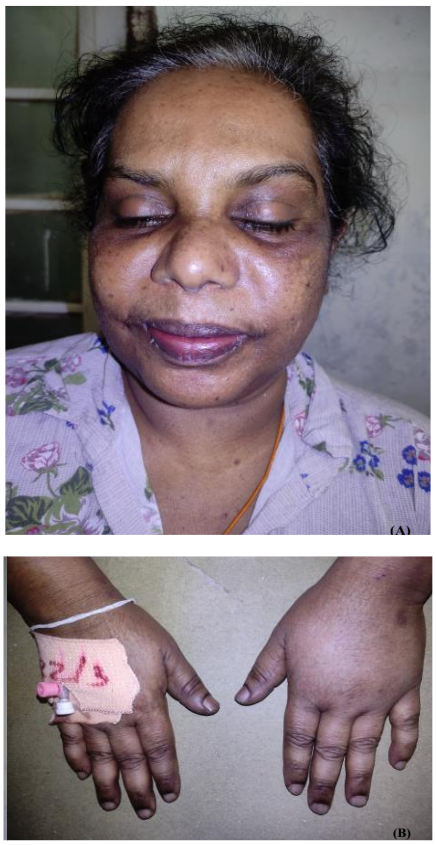

Figure 01: (A) Shows a characteristic cutaneous feature of DM called heliotrope rash (violaceous erythema of the eyelids or periorbital skin) (B) Gottron papules (purple papules and plaques over the tops of the small joints of the hands)

Investigations wise, Full Blood Count (FBC) indicated WBC at 9.75 x 10^9/L, Neutrophils at 5.13 x 10^9/L, Lymphocytes at 3.4 x 10^9/L, Hb at 12.3 g/dL, HCT at 36.6%, MCV at 88.6 fL and platelets at 230 x 10^9/L. The blood picture revealed normochromic normocytic cells,

occasional target cells, and round macrocytes, with normal WBC and platelet counts, suggesting evidence of liver pathology.

Her Random Blood Sugar and HbA1C levels were within normal limits. Serum Creatinine was 58 µmol/L, Serum Sodium (Na) was 144 mmol/L, and Serum Potassium (K) was 4 mmol/L, with a normal urine full report.

Liver function tests showed AST at 1398.3 U/L, ALT at 497 U/L, ALP at 209 U/L, direct bilirubin (DB) at 81.64 µmol/L, indirect bilirubin (IB) at 26.1 µmol/L, gamma GT at 129.2 U/L, total protein at 7.88 g/dL, albumin at 2.8 g/dL, globulin at 5.1 g/dL, PT/INR at 1.06, and APTT at 30 seconds. Her CRP was 33.6 mg/L and ESR was 85 mm/hour, while her Serum IgG level was markedly elevated at 4511 mg/dL (normal range: 700-1600)

The ultrasound of the abdomen revealed normal liver size and echo texture, a partially distended gall bladder with wall edema, pericholecystic fluid, soft calculi, and sludge, suggesting sub-acute cholecystitis. The spleen, pancreas, kidneys, bladder, and para-aortic lymph nodes were normal, with no ascites. A contrast-enhanced CT scan of the abdomen indicated acalculous cholecystitis, with fluid in the right iliac fossa/pelvis suggesting possible inflammation.

Her Creatinine kinase levels were within normal limits at 95 U/L (<145). Electromyography(EMG) findings were normal, without evidence of myopathy or myositis. Skin biopsy indicated epidermal spongiosis, lymphocytes, moderate perivascular and dermal lymphocytic infiltration, significant mucin accumulation, and no signs of red cell extravasation or leucocytoclastic vasculitis, suggesting the need to exclude dermatomyositis or SLE (Figure 02 A).

She had a positive ANA at 1/640 with a cytoplasmic filamentous fluorescence pattern (Actin AB), while dsDNA, anti-mitochondrial antibodies, and Rheumatoid factor were negative. The viral panel, including CMV IgM and IgG, EBV IgM, Hepatitis A IgM, Hepatitis B sAg, Hepatitis C RNA, and HIV 1 and 2 antibodies, was negative.

Liver biopsy revealed inflamed liver tissue with sheets of plasma cells admixed with lymphocytes with interface hepatitis, without any signs of suppuration or malignancy (Figure 02 B).

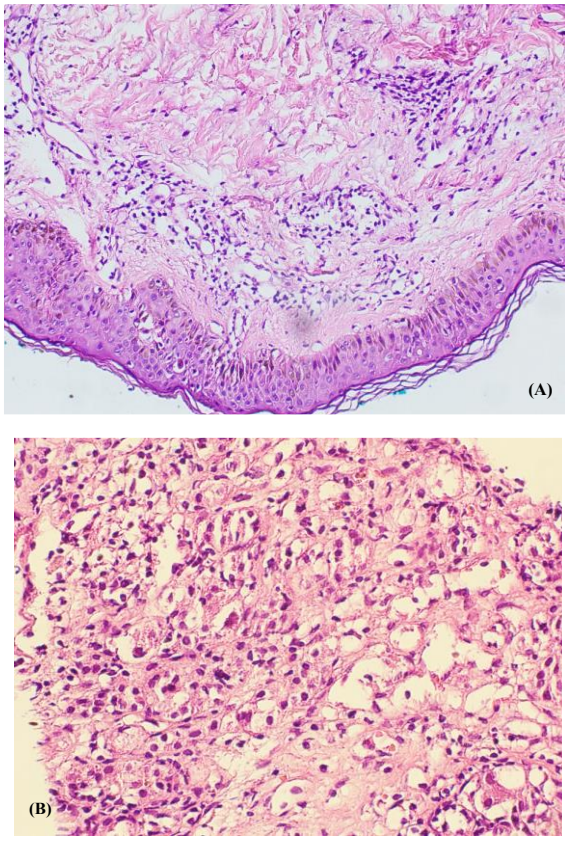

Figure 02: (A) The section show skin tissue with epidermis and dermis. Epidermis shows spongyosis and lymphocytes. Dermis shows moderate perivascular and dermal infiltration of lymphocytes admixed with significant mucin accumulation. (100x H&E) (B) The section of liver tissue shows sheets of plasma cells admixed with lymphocytes with interface hepatitis. (100x H&E))

Based on the short history and investigation findings, the diagnosis of acute icteric autoimmune hepatitis with amyopathic dermatomyositis was made. The patient was started on oral prednisolone 60 mg daily, liaising with Gastroenterology and Rheumatology teams. With treatment, her transaminase levels gradually decreased, but her bilirubin levels increased, and PT/INR got prolonged. The patient developed mild hepatic encephalopathy and ascites, and her condition progressed to acute severe autoimmune hepatitis with acute liver failure (ALF), while she was on high dose Prednisolone. Due to ongoing liver failure, it was not possible to start azathioprine or mycophenolate mofetil.

With the transfusion medicine opinion, plasma exchange was attempted twice, but both attempts resulted in hemodynamic instability and abandonment of the procedure, and the patient was deemed unsuitable for plasma exchange. Consequently, she was transferred to a specialized center for liver diseases for a liver transplant. Unfortunately, the patient succumbed to the illness within four weeks of disease onset.

DISCUSSION

Autoimmune hepatitis(AIH) is a rare, immune-mediated inflammatory liver disorder marked by the presence of circulating autoantibodies, elevated levels of gamma globulins, and unique histological features in liver biopsy (1). Acute AIH presents with sudden onset symptoms and laboratory abnormalities that align with the initial discovery of the disease, but without any signs of liver failure. In contrast, acute severe(fulminant) autoimmune hepatitis(AS-AIH) is a rare condition that progresses to hepatic encephalopathy within 26 weeks of symptom onset or disease detection, regardless of the presence of cirrhosis. (1)(3)

Acute liver failure(ALF) is characterized by onset of coagulopathy and any degree of hepatic encephalopathy(HE) within 26 weeks of symptom onset in patients without pre-existing cirrhosis (1).

Acute AIH has a spectrum of clinical features. In acute-icteric AIH, the patient exhibits jaundice without any coagulopathy or encephalopathy. In AS-AIH, the patient is jaundiced and coagulopathic (with an international normalized ratio [INR] >1.5), but there is no evidence of encephalopathy. In AS-AIH with ALF, the patient presents with jaundice, coagulopathy, and encephalopathy (1).

Regarding dermatomyositis (DM), most patients exhibit both skin involvement and muscle weakness, known as classic DM. However, a subset of patients develops the characteristic skin manifestations of DM without any muscle symptoms, termed clinically amyopathic dermatomyositis (CADM). CADM includes patients who lack clinical signs of myositis but show evidence of myositis through laboratory, radiologic, or electrophysiological studies (hypomyopathic DM), as well as those who have no signs of muscle involvement (amyopathic DM) for at least six months. Amyopathic dermatomyositis can be associated with late-onset muscle weakness, interstitial lung disease, and malignancy (2) and may be associated with autoimmune diseases, but the association with autoimmune hepatitis is rarely reported.

There are documented cases where multiple autoimmune diseases coexist, suggesting a potential genetic predisposition and shared immune dysregulation. These include primary biliary cirrhosis overlapped with AIH, associated with dermatomyositis, autoimmune thyroiditis and antiphospholipid syndrome (4), and AMD with autoimmune sclerosing cholangitis (5). These findings indicate that patients with one autoimmune disorder should be carefully monitored for signs of other autoimmune conditions, for early diagnosis and comprehensive management.

The coexistence of acute AIH and ADM in a single patient is a rare, likely due to the distinct underlying pathophysiological mechanisms involved. Among the two types of AIH, type 1 is more frequently associated with other autoimmune diseases; however, it is only occasionally linked with inflammatory myopathies (4).

AIH is characterized by a dense infiltration of lymphocytes, macrophages, and plasma cells in the liver. Despite the presence of circulating autoantibodies and plasma cell liver infiltration, AIH is classified as a T cell disease, since B cell activation depends on T cell activity. The critical role of T cells in the pathogenesis of AIH is highlighted by the disease's association with HLA class II polymorphisms (6).

In contrast, dermatomyositis results from a humoral-mediated attack targeting muscle capillaries and arteriolar endothelium. The initiating event involves the activation of complement factor 3 (C3), which generates C3b and C4b. This process leads to the formation of the membrane attack complex (MAC), which deposits on vascular walls, causing inflammation, resulting in hypoxic injury and atrophy of muscle fibers, especially those at the periphery, away from the vascular supply. Over time, the reduction in capillary density leads to necrosis and degeneration of the muscle fibers (7). However,

Cutaneous dermatomyositis is an inflammatory skin disorder classified as interface dermatitis. Diagnostic criteria require a skin biopsy that shows features of the disease, such as reduced capillary density, MAC deposition on small blood vessels at the dermo-epidermal junction, and variable keratinocyte staining for MAC (8).

Although AIH and dermatomyositis appear to have distinct pathophysiological features, further research is needed to explore potential connections between them. Additionally, understanding the pathophysiology of AMD is essential for understanding its unique clinical features and treatment strategies.

High levels of AST, ALT, and LDH, when assessed without checking CK, can lead to a misdiagnosis of liver disease in patients with myositis. Conversely, elevated levels of AST, ALT, and LDH, when accompanied by elevated CK, in patients with myositis may be indicative of muscle injury rather than liver involvement, especially in cases of AIH (4). Additionally, if direct bilirubin is elevated alongside elevated transaminases while considering obstructive pathology, it is crucial to consider AI-AIH with the history and examination.

AIH typically responds well to conventional corticosteroid therapy. The preferred treatment regimen is prednisone (30 mg daily, tapered over 4 weeks to 10 mg daily) in combination with azathioprine (50 mg daily) (3). However, patients with AS-AIH are often treated with high-dose prednisone (60 mg daily) or an equivalent dose of prednisolone. The rapid anti-inflammatory and immune-modifying effects of prednisone or prednisolone support the use of corticosteroids as initial therapy. The therapeutic effects of azathioprine occur gradually over three or more months, making it less effective for immediate treatment. In most instances, corticosteroids can be given orally, but in severe cases, intravenous therapy may be necessary (3). Early intervention with corticosteroids and immunosuppressive agents is crucial to halt the progression of liver damage and improve patient outcomes (9).

Manifestations of ALF can be so severe that immediate liver transplantation may be needed. A MELD score at presentation that qualifies for liver transplantation can help guide this decision (3). Potential rescue therapies for ALF include calcineurin inhibitors, mycophenolate mofetil, CD3 antibodies, rituximab, and abatacept. However, these are untested, unlicensed, and empiric for ALF, and may delay or complicate liver transplantation (3).

In ALF, liver dysfunction impairs biotransformation, excretion of toxins, and synthetic functions.

Plasma exchange(PE) is a therapeutic method that removes toxic substances and replenishes essential components by replacing a patient's plasma with fresh frozen plasma. For liver failure in adults, high-volume PE is considered a first-line therapy, used either independently or alongside other therapies (10).

Most case series involving children or adults with ALF suggest that PE can improve coagulation, decrease vasopressor support, and improve encephalopathy grade scores. By temporarily supporting liver function, PE can significantly lower mortality rates in patients with acute or chronic liver failure, providing time for liver recovery or transplantation. However, a case series involving pediatric patients indicated that performing PE more than six times may offer little benefit in terms of patient survival if a timely liver transplant is not available (10).

Nevertheless, systemic glucocorticoids, often combined with immunosuppressants, are the primary treatment for muscle involvement in dermatomyositis. While skin manifestations can be managed with sun protection, physiotherapy, and topical treatments like corticosteroids and calcineurin inhibitors, most patients require systemic medications such as hydroxychloroquine and methotrexate. Importantly, systemic glucocorticoids, although effective for muscle disease, have limited impact on skin involvement (7).

Therefore, managing a patient having both AIH and AMD requires treatment with steroids for liver disease along with specific skin therapies. This underscores the necessity of tailoring treatments for overlapping autoimmune diseases due to their varied responses. Also, these patients should be followed up for the complications of both autoimmune conditions while keeping an eye on the emergence of another different autoimmune

condition, emphasizing the value of a multidisciplinary approach involving hepatologists, dermatologists, and rheumatologists for effective management of complex autoimmune conditions (9).

In conclusion, the concurrent presence of acute AIH and ADM in this patient highlights the importance of increased clinical vigilance in diagnosing such overlapping conditions. Further research into the interactions between diverse autoimmune diseases is crucial to discovering the potential interconnections between them and developing more effective treatment approaches. Also, this case highlights the need for early identification of AI-AIH and prompt, aggressive treatment to prevent its progression and adverse outcomes. Understanding the shared immunopathogenic mechanisms underlying these conditions could lead to more targeted therapies, ultimately enhancing patient outcomes.

Author declaration

Authors' contributions:
Study concept and design: K.M.
Drafting of the manuscript: K.M., I.K., P.K., and S.B.
Study supervision: S.B.

Conflicts of interest:
The authors declare that there is no financial or non-financial conflict of interest.

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Data Availability Statement
Not applicable.

Consent for participation

Informed written consent was obtained from the patient and her family for publication of this case report.

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