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Seronegative Autoimmune Hepatitis- A Diagnostic Challenge

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ABSTRACT:
Autoimmune hepatitis (AIH) is a complex autoimmune chronic liver disease of unknown etiology that occurs as one's immune system attacks liver cells and creates a chronic inflammatory state which may cause acute liver failure or progress to cirrhosis. Seronegative AIH follows a similar course to auto-antibody positive AIH and diagnosis may be challenging (1). There is no single test to identify seronegative AIH and hence a delay in diagnosis and appropriate treatment may lead to progression of the liver disease. If not fully worked up, AIH may even increase the risk of malignancy. Therefore, a liver biopsy is a crucial step in the workup for AIH (2). We report a rare case of severe AIH associated with negative antibodies.

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I. INTRODUCTION:

Autoimmune hepatitis (AIH) is a complex liver disease of unknown cause which results in immune-mediated liver injury with varied clinical presentations. The cause of liver cell destruction in this disease is unclear, but may be related to an imbalance in some of the immune system cells (effector and regulatory). The persistent inflammation within the liver observed in AIH can result in scarring, ultimately leading to cirrhosis, liver failure requiring a liver transplant, and even death. AIH is about 4 times more common in females than males and is commonly associated with other autoimmune conditions. However, an average of 10% of AIH cases have AIH symptoms and pathology but lack autoimmune serology (3). For such seronegative AIH (snAIH) cases, there is currently no established diagnostic algorithm for diagnosis and improper or delayed diagnosis of snAIH can lead to no or inappropriate treatment that results in progression to fulminant hepatitis or cirrhosis. The revised conventional diagnostic criteria (RDC) scoring for AIH is complex and not routinely used in the clinical practice. The more recent simplified diagnostic criteria (SDC) scoring proposed by International Autoimmune Hepatitis Group in 2008 has wider application in routine practice facilitating the diagnosis of AIH with a specificity and sensitivity of ~90%. SDC scoring may not be applicable in patients with seronegative autoimmune hepatitis. These patients should be reassessed by using RDC. Immunosuppression and liver transplantation are our therapeutic weapons. While corticosteroids alone or in combination with azathioprine are effective and prolong survival, treatment failures to this standard of care are still a challenge (4).

II. MATERIALS:

A 42-year-old female presented with complaints of abdominal distension and bilateral lower limb swelling since 3 months, yellowish discolouration of skin and eyes since 2 months, facial puffiness and easy fatiguability since 1 month. She is a known case of Type 2 Diabetes Mellitus since 6 months, not on any medication. History of jaundice one year ago for 1 month duration, took ayurvedic medications for the same and was not evaluated.

On examination, patient had pallor, icterus, bilateral pitting pedal oedema upto knee joint, spider naevi present (image 1: spider naevi viewed through a dermoscope). Her vital parameters were within normal limits.

Per abdominal examination showed distended abdomen with flanks full, no organomegaly, shifting dullness present. Other system examination was within normal limits.

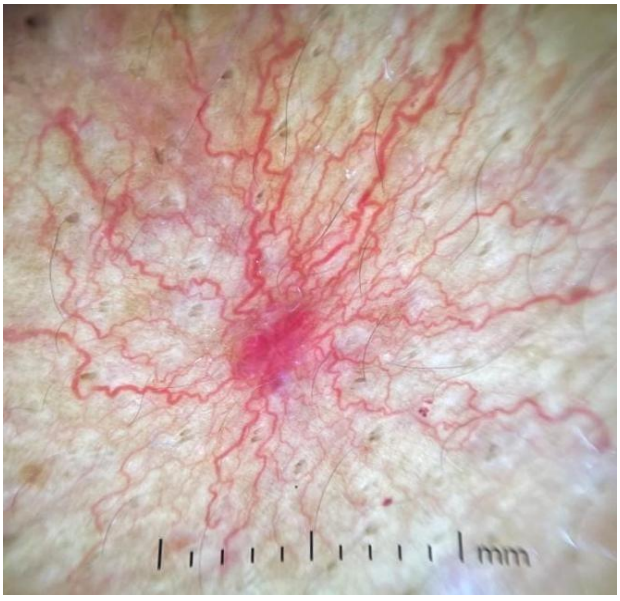

Figure 1: Spider naevi: https://d.docs.live.net/57661550751dcfc4/Desktop/spider%20naevi%20video.mp4

Routine blood investigations complete hemogram revealed microcytic hypochromic anaemia, Liver function test was deranged with hyperbilirubinemia, hypoalbuminemia and transaminitis and deranged coagulation profile. Renal function test and electrolytes were within normal limits. HIV, HBs Ag, HEV and HCV were negative. Auto immune hepatitis panel of LKM-1, SLA, Anti-F Actin, ANA, anti-SMA, anti-alpha-1 antitrypsin and ANCA was negative.

USG abdomen and pelvis showed chronic parenchymal liver disease with features of portal hypertension, mild splenomegaly and ascites. Diagnostic ascitic fluid analysis showed high SAAG ratio of 1.4. Opthalmological evaluation showed no evidence of KF ring, serum ceruloplasmin levels and 24 hours urinary copper were within normal limit. Upper GI endoscopy showed early oesophageal varices and mild portal-hypertensive gastropathy.

Patient was subjected to trans-jugular liver biopsy which showed features suggestive of Chronic hepatitis with moderate activity, compatible with autoimmune hepatitis.

(**Figure 2a, 2b, 2c, 2d**)

Blood and urine culture and sensitivity were done showed no growth, Chest X ray was normal.

Patient was diagnosed to have sero-negative AIH and treated with steroids and immune-modulators.

III. INVESTIGATIONS

	Patient value	**Reference range**
White blood count(/mcL)	9200	4000-11000 /mcL
Hemoglobin (g/dl)	**8.7**	13-17 g/dl
Packed cell volume(%)	26.8	40-50 %
Platelet count (/mcL)	**100000**	150000-410000 /mcL
N/L/M/E/B (%)	52/36.6/8.8/2.1/0.4	40-80/20-40/2-10/1-6/0-2 %
MCV (fL)	64.1	83-101 fL
MCH (pg)	20.8	27-32 pg
MCHC (%)	32.4	31.5-34.5 %
RDW(%)	22.2	12-15 %
Urea (mg/dL)	21.19	16-40 mg/dl
Creatinine (mg/dL)	0.93	0.9-1.3 mg/dl
Uric acid(mg/dL)	6.6	2.6-6.0 mg/dL
TSH (mcIU/ml)	4.49	0.4-4.2mcIU/ml
ANA	1+ positive (1:100 dilution)	NEGATIVE
ESR (mm/hr)	39	0-15 mm /hr
Ceruloplasmin (U/L)	19.7	14-40U/L
Cortisol(ug/dL)	3.62	5-23 ug/dL
CRP(mg/dL)	0.408	0.3-1
C3 /C4(mg/dL)	61.5/10.3	75-175/15-45
P/C Ratio	0.19	<0.2
Magnesium(mg/dL)	2.13	1.7-2.2
Immunoglobulin G (mg/dL)	3330	600-1600
GGT	78	5-40U/L
Procalcitonin	0.14	<0.1ng/ml
25 OH VitaminD3 (ng/ml)	20.57	>20ng/ml

Serum Ferritin (ng/ml)	26.8	21-35
U Copper 24 hrs (micro g/24hrs)	5.500	15-60
Total bilirubin (mg/dl)	**3.87**	0.30- 1.20mg/dl
Direct bilirubin(mg/dl)	**1.88**	0-0.2mg/dl
Total protein (g/dl)	7.73	6.4-8.30g/dl
Albumin (g/dl)	**2.55**	3.2-4.6g/dl
AST (U/L)	**248**	15-40U/L
ALT(U/L)	**123**	10-40U/L
ALP(U/L)	226	53-128U/L
Globulin(g/dl)	5.18	1.8-3.6g/dl
LDH (U/L)	318	100-190U/L
Prothrombim time (sec)	22.3	10.5-12.9
INR(sec)	**2.02**	0.8-1.2
aPPT (sec)	36.7	
Sodium (meq/L)	137	136-145meq/L
Potassium (meq/L)	3.56	3.5-5.10meq/L
Chloride(meq/L)	103.4	98-107meq/L
Calcium (mg/dl)	8.40	8.6-10mg/dl
HIV	Negative	
HBSAG	Non reactive	
HCV	Non reactive	

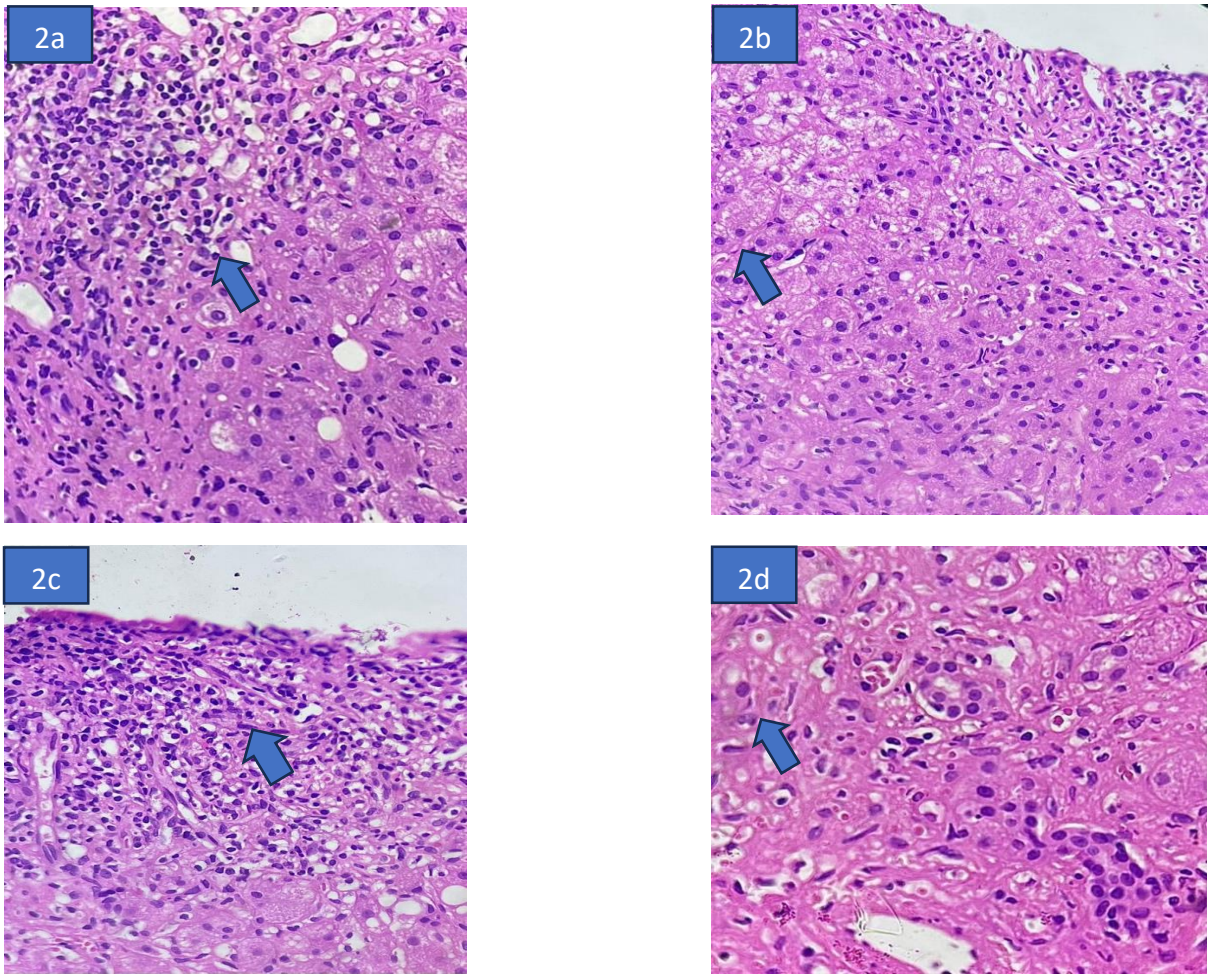

Figure 2: 40X, H and E stain, showing interface hepatitis(a,b) , inflammatory cells eroding the limiting plate between portal tract and liver parenchyma(c), hepatic rosettes(d).

IV. DISCUSSION:

There is an urgent need for general consensus on a specific definition and exclusion of confounding aetiologies with coordinated multicentre investigation of this rare condition to rule out other etiologies and develop therapies to reduce the significant mortality and need for emergency liver transplantation associated with this condition (5). AIH itself is a rare entity whereas sero-negative AIH constitute for 20% of cases, based on estimates of the natural history of autoimmune hepatitis, the 10-year survival is 80−98% for treated cases. Hence

proper evaluation and diagnosis of auto immune hepatitis is important especially cases of sero-negative where there is no specific diagnostic algorithm. Since, instances of reversal of fibrosis and cirrhosis have been reported in patients responding to treatment.

V. Conclusion:

The typical presentation of AIH tends to be chronic with mild elevation of AST and ALT levels; however, it is essential to recognize seronegative AIH because of its atypical presentations. At first presentation, the diagnosis of AIH may be missed because of the mild symptoms. If there is a delay in diagnosing AIH, it could increase the risk of liver cirrhosis and even liver cancer. We encourage an emphasis on liver biopsy once the common etiologies are ruled out regardless of antibodies specific to AIH. There is no clear-cut algorithm for diagnosis of sn-AIH, and understanding the strength of each scoring system is vital to making the proper diagnosis. SDC and RDC have very similar diagnostic accuracies for patients with typical features of AIH. Diagnostic criteria used for conventional AIH may not be applicable to cases with seronegative autoimmune hepatitis. Current report suggests that RDC is more helpful in diagnosing patients who are negative for conventional autoimmune serology. We hope this case report improves the index of suspicion among clinicians for seronegative AIH.

References:

[1]. Sherigar, J. M., Yavgeniy, A., Guss, D., Ngo, N., & Mohanty, S. (2017). Seronegative Autoimmune Hepatitis A Clinically Challenging Difficult Diagnosis. Case Reports In Medicine, 2017, 3–6. Https://Doi.Org/10.1155/2017/3516234

[2]. Memon M B, Duplan P, Iska S, Et Al. (July 15, 2022) Acute Severe Seronegative Autoimmune Hepatitis With Undiagnosed Graves' Disease. Cureus 14(7): E26884. Doi:10.7759/Cureus.26884.

[3]. Bhumi Sa, Wu Gy. Seronegative Autoimmune Hepatitis. J Clin Transl Hepatol. 2023;11(2):459-465. Doi: 10.14218/Jcth.2022.00235.

[4]. Manns, M. P., Lohse, A. W., & Vergani, D. (2015). Autoimmune Hepatitis - Update 2015. Journal Of Hepatology, 62(S1), S100–S111. Https://Doi.Org/10.1016/J.Jhep.2015.03.005

[5]. Brennan, P. N., Donnelly, M. C., & Simpson, K. J. (2018). Systematic Review: Non A-E, Seronegative Or Indeterminate Hepatitis; What Is This Deadly Disease? Alimentary Pharmacology And Therapeutics, 47(8), 1079–1091. Https://Doi.Org/10.1111/Apt.14566