IJIRR

International Journal of Information Research and Review
Vol. 12, Issue, 02, pp.7925-7928, February, 2025

RESEARCH ARTICLE

RECURRENT JAUNDICE AS A PRESENTATION OF SJOGREN SYNDROME

Aritra Panja[1], Megha Majumder[1,*], Kausik Bhar[1], P. Gopi Krishna and [2]Manodeep Barai

[1]Institute of Post Graduate Medical Education and Research, Kolkata, India
[2]All India Institute of Medical Sciences, Raipur, India

ARTICLE INFO

Article History:
Received 18th November, 2024
Received in revised form
24th December, 2024
Accepted 25th January, 2025
Published online 27th February, 2025

Key words:

Sjogren, Autoimmune
Hepatitis, Jaundice.

ABSTRACT

Primary Sjogren Syndrome is one of the most common auto immunedisease with a prevalence rate ranging between .06% and 1.5%. Sjogren syndrome occurs mainly due to loss of immunological tolerance to self-antigens leading to autoimmune destruction of mainly salivary and lacrimal glands. Soxerostomia and xerophthalmia are the predominant features of the disease. Extra-glandular manifestations such as fatigue, arthralgia, peripheral neuropathy, purpurea, pulmonary infiltrates are also not so uncommon. Here we want to discuss a case of 33 years old lady presented to the clinic with repeated (4 episodes) episodes of hepatitis in last 6 and ½ years without predominant features of dry eyes and dry mouth. After thorough clinical and investigational workup, we have found out that recurrent hepatitis is due to acute exacerbation of autoimmune hepatitis and Sjogren syndrome is the underlying disease. In this report, we are going to present unusual presentation of this relatively common rheumatological disorder, Sjogren and difficulties facing diagnosis of Autoimmune hepatitis in the setting of concomitant rheumatological disorder.

INTRODUCTION

Autoimmune hepatitis is a type of chronic hepatitis with continuous hepatocellular inflammation and necrosis which ultimately can lead to fibrosis, cirrhosis and liver failure.It was first known in 1951 (1). It is characterized by hyperglobulinemia, presence of serum autoantibodies and abnormal liver function test.Both environmental factors (e.g. drugs, chemical or viral) and genetic predisposition have role in the aetiopathogenesis of autoimmune hepatitis in the background of failure of native immune system to clear autoantibodies (2) (3) (4). AIH is mainly classified into 2 types, AIH 1 &2. AIH 1 is associated with presence of Antinuclear Antibody (ANA) and/or Anti-smooth muscle antibody and in the minority of population presence of autoantibodies against actin, atypical perinuclear antineutrophilic cytoplasmic antibodies (pANCA), soluble liver antigen are also can be present. Clinically it can present variedly from asymptomatic patient to acute hepatitis (recurrent bouts of acute hepatitis possible) or cirrhosis (5). So high clinical suspicion is required for its diagnosis. In autoimmune hepatitis liver biopsy has a role not only for its diagnosis but also to predict the prognosis of the disease (6). Sjogren syndrome is a chronic, multisystemic autoimmune disease characterised by lymphocytic infiltration of salivary and lacrimal glands leading to keratoconjunctivitis sicca and dryness of mouth with some extra-glandular manifestation (7) (8) (9). It is mainly of 2 types – primary and secondary Sjogren syndrome. Primary Sjogren syndrome is more prevalent in

female population (female to male ratio 10:1)with peak incidence between fifth and sixth decade of life (10). Secondary Sjogren syndrome is associated with presence of other autoimmune disease mainlyrheumatoid arthritis (with a prevalence ranges from 4% to 31%), systemic lupus erythematosus and systemic sclerosis (7) (11) (12). Autoimmune hepatitis is uncommon in Sjogren syndrome affecting only 1% of the patient (13). Because of the rarity of this association diagnosis is quite difficult. Here we report a case of Sjogren syndrome presented with recurrent episodes of acute hepatitis which is quite unusual presentation and poses challenge in diagnosis of this syndrome.

CASE PRESENTATION

31 years old female without any comorbidity presented with yellowish discolouration of eyes and urine for last 1 month which was insidious onset, gradually progressive in nature. Patient also reported nausea and recurrent episodes (6-7 episodes) of vomiting with right hypochondrial discomfort for the same duration. Stool was yellowish in colour and no history of itching of skin. Patient also complained of low-grade

Corresponding author:** ***Megha Majumder,
Institute of Post Graduate Medical Education and Research, Kolkata, India

fever associated with fatigue and weakness for the same duration but fever was not associated with chill, rigor, arthralgia, myalgia, any localising symptoms, alopecia, frothy urine, hematuria, oral ulcer but history of decreased appetite was present. Past history revealed that patient had 3 similar episodes in last 6 and 1/2 years. Each episode of jaundice was milder than recent episode, persisted for about 2 months associated with nausea, vomiting, pain abdomen, fever and relieved on its own without medication. 1st episode was in October,2017; 2nd in December 2018 and the last episode occurred in May, 2022.

In between each episode patient complained fatigue which is still persisting and slowly progressive in nature. She is non-alcoholic, non-smoker, no history of intake of any hepatotoxic drug including ayurvedic medication. Family history(including autoimmune disease) is non-contributory. Patient complained of increased requirement of water during normal eating but she denied any history suggestive of dryness of eyes. Menstrual history is within normal limit and she has 3 children. No history of complication during pregnancy was found.

INVESTIGATION

Complete blood count showed a haemoglobin of 11.7 mg/dL, mean corpuscular volume 88fL, total leukocyte count7200/microlitre with neutrophil 60%, lymphocyte 40% and platelet 2.2 lakh/microlitre. Liver function test suggested hyperbilirubinemia; total bilirubin 6.4mg/dL, direct bilirubin 2.9mg/dL, indirect bilirubin 3.5mg/dL (suggesting hepatocellular jaundice), normal serum albumin 4.1gm/dL; elevated aminotransferase (normal value <40IU/L), aspartate aminotransferase 77IU/L, alanine aminotransferase 103IU/L, alkaline phosphatase 75IU/L, normal prothrombin time: 12sec. However total serum protein was 9.5mg/dL and hypergammaglobulinemia was noted. Serum IgG level was elevated, around 2730mg/dL.

To rule out infectious aetiology of hepatitis, we sent blood for serum HBsAg, anti-hepatitis C (IgM anti-HCV), hepatitis B core antibody IgM, IgM anti hepatitis A, IgM anti hepatitis E, HIV, cytomegalovirus and subsequently all came out to be negative. Autoimmune profile suggested: ANA positive with titres of 2 + (fine speckled with cytoplasmic pattern), positive anti-Sjogren syndrome-A antibody with high titres of 3+, negative double stranded DNA, normal complement protein (C3, C4, C1q protein), agglutination seen on direct coomb test with titre of 2+ but autoimmune hepatitis profile and anti-Sjogren syndrome-B antibody came out to be negative. Further workup suggested normal ultrasonography of whole abdomen (Liver- 12cm with normal echotexture of liver, no splenomegaly).

Next, we planned for liver biopsy and it suggested- chronic hepatitis with mild portal lymphoplasmacytic infiltrate, marked interface activity, moderate lobular necro-inflammatory activity; consistent with autoimmune hepatitis. As patient has high titres of anti-Sjogren syndrome-A antibodies we proceeded with Schirmer test and minor salivary gland biopsy to look for oral and ocular involvement. Minor salivary gland biopsy showed diffuse inflammatory cell infiltrate around the ducts mainly composed of lymphocytes (approximately 100 in number) and histocytes within the salivary gland tissue with presence of numerous plasma cells, features consistent with Sjogren syndrome. Schirmer test came out to be positive in right eye (7mm in left eye, 3 mm in right eye).

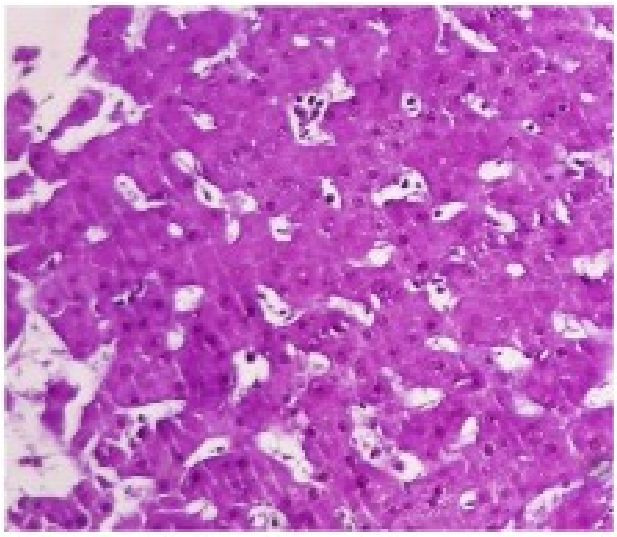

Figure 1. Masson Trichome stain oF liver biopsy

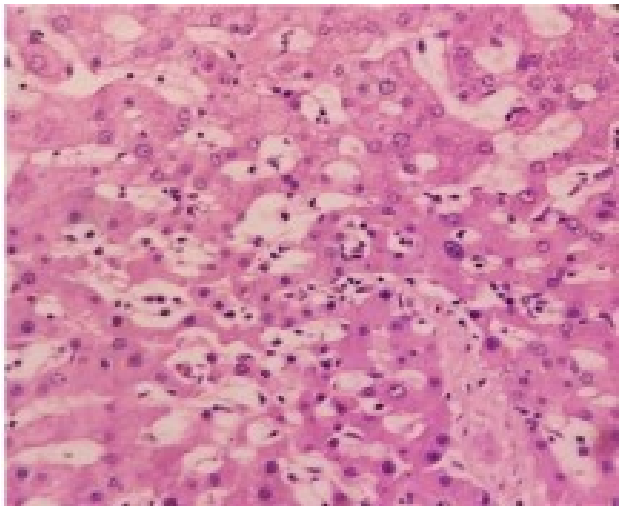

Figure 2. HE stain of liver biopsy with lymphocytic infiltration

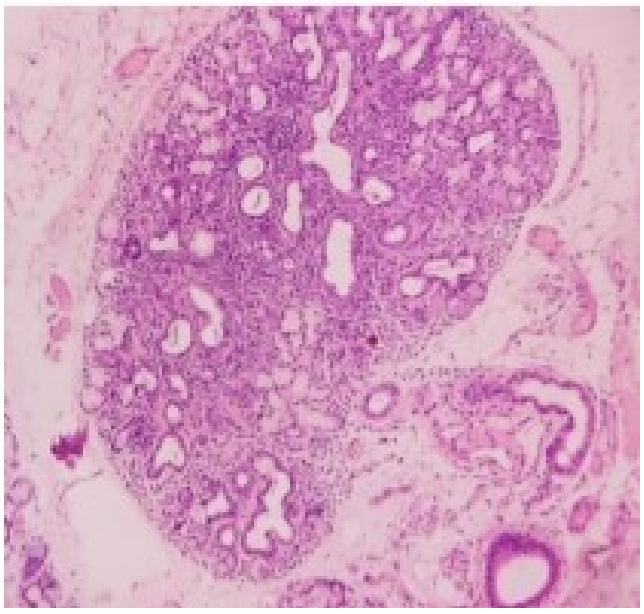

Figure 3. minor salivary gland biopsy with lyphocytic infiltration around the duct

DISCUSSION

Autoimmune hepatitis: The exact pathophysiologic mechanism in autoimmune hepatitis is not understood. However; in genetically susceptible individual, autoimmune attack is maintained by molecular mimicryand loss of regulatory T cell control (5). Drugs, herbal compounds and viral antigens can act as triggering factor (5) (14). If untreated it can lead to cirrhosis.A simplified diagnosticcriteriais used for autoimmune hepatitis which mainly depends on autoantibodies, IgG levels, liver histopathology and the exclusion of viral hepatitis.

- Autoantibodies:Antinuclear antibody (ANA) or anti Smooth muscle antibody (ASMA) of Liver Kidney Microsomal antibody in titre of >1:80 – score 2
- ANA or ASMA or LKM antibody in titre of >1:40- score 1
- Soluble Liver antigen (SLA)/Liver pancreas (LP) positive (>20 units)- score 1
- IgG level: >1.1 times of upper normal limit– score 2
- >upper normal limit- score 1
- Exclusion of viral hepatitis: Give 2 points if viral hepatitis has been excluded
- Liver histopathology- Histologic features typical of autoimmune hepatitis- score 2

Histologic features compatible with autoimmune hepatitis- score 1. If total points are 6, probable diagnosis of autoimmune hepatitis can be made whereas we can say definite autoimmune hepatitis if total score is 7 or more (5) (15). This scoring system has sensitivity of 81% and specificity of 97% (16). Here in our patient; ANA has come out to be positive in 1:160 dilution with titre of 2+ (score 2), IgG elevated- 2730mg/dL (upper normal limit 1700mg/dL, so >1.1 times upper normal limit and score 2), absence of viral hepatitis (score 2), liver histopathology consistent with autoimmune hepatitis (score 1). So here total score is 7 and patient can be diagnosed as autoimmune hepatitis.

Sjogren syndrome: Sjogren syndrome is autoimmune disease characterised by dysfunction of T and B lymphocytes, development of autoantibodies to autoantigens mainly anti-SSA and anti-SSB, increasing apoptosis of cells, lymphoid migration of glandular tissue leading to inflammation and destruction of exocrine glands (17) (18) (8) (5). Extra-glandular features are possible in Sjogren syndrome which include peripheral arthritis, secondary Raynaud's phenomenon involving digits, pulmonary involvement- Interstitial Lung Disease(most common pattern Non-Specific Interstitial Pneumonia but most specific pattern Lymphocytic Interstitial Pneumonia), renal involvement- mainly tubular involvement (distal Renal Tubular Acidosis is very specific), peripheral neuropathy (8). One of the most significant complications is malignant transformation to lymphoma. So, follow up is very necessary (8).

For diagnosis of Sjogren syndrome most simplified criteria is 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for Sjogren syndrome. According to this-criteria

- Histopathology of minor salivary gland showing focal lymphocytic sialadenitis with a focus score more than equal to 1 – assign score 3
- The presence of anti-Ro/SS-A antibodies- score 3
- Schirmer's test less than or equal to 5 mm per 5 minutes in atleast 1 eye- give score 1
- Unstimulated whole salivary flow of less than 0.1 mL per minute- assign score 1
- SICCA ocular staining score more than or equal to 5 using lissaminegreen or fluorescein dye – give score 1

Patient may be classified as primary Sjogren syndrome if total score is more than or equal to 4 and patient has fulfilled first or second criteria. Here in our patient total score is 7 (patient has high titre of anti-SSA antibody, minor salivary gland biopsy showing focal lymphadenitis with focus score 1, Schirmer test showing positivity in right eye). So, this patient can be diagnosed as primary Sjogren syndrome (20,21). Patient was started with Prednisolone (20mg) and Azathioprine (25mg). It has been planned to taper Prednisolone and escalate Azathioprine gradually.

CONCLUSION

We reported a case where 31 years old female presented with recurrent episodes of acute hepatitis and fatigue for last 6 and ½ years and thereafter was ultimately diagnosed with autoimmune hepatitis associated with Sjogren syndrome. The uniqueness of this case was patient did not complain any classical features of Sjogren syndrome such as dryness of eyes or mouth except some amount of increased requirement of water intake during food swallowing.

This diagnosis is not only important to prevent further episodes of hepatitis or hepatocellular failure this is particularly important to prevent dreaded long-term complications of Sjogren syndrome. As the association of autoimmune hepatitis with Sjogren syndrome is relatively rare, diagnosis is quite challenging. In our case persistently raised globulin and direct coombs test positive anaemia are the clues to think about some autoimmune etiology.

REFERENCES

1. WALDENSTROM J. Leber, Blutproteine und Nehrungseiweiss (Liver, blood proteins and food proteins). Dtsch Z VerdauStoffwechselkr. 1952;12(Spec No):113-21. Undetermined Language. PMID: 12979911.
2. Silva J, Brito BS, Silva INN, Nóbrega VG, da Silva MCSM, Gomes HDN, Fortes FM, Pimentel AM, Mota J, Almeida N, Surlo VC, Lyra A, Rocha R, Santana GO. Frequency of Hepatobiliary Manifestations and Concomitant Liver Disease in Inflammatory Bowel Disease Patients. Biomed Res Int. 2019;2019:7604939. (PMC free article) (PubMed) (Reference list)s
3. Palle SK, Naik KB, McCracken CE, Kolachala VL, Romero R, Gupta NA. Racial disparities in presentation and outcomes of paediatric autoimmune hepatitis. Liver Int. 2019 May;39(5):976-984. (PubMed) (Reference list)
4. Linzay CD, Sharma B, Pandit S. Autoimmune Hepatitis. (Updated 2023 Aug 14). In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459186/

5. Shrestha M, Subedi SC, Shah S, Acharya J, Regmi M, Mehta N. Autoimmune Hepatitis Leading to Liver Cirrhosis: A Case Report. JNMA J Nepal Med Assoc. 2022 Dec 1;60(256):1059-1062. doi: 10.31729/jnma.7808. PMID: 36705108; PMCID: PMC9795117.
6. Hubscher SG. Role of liver biopsy in autoimmune liver disease. Diagnostic Histopathol. 2014 Mar 1;20(3):109–18. doi: 10.1016/j.mpdhp.2014.01.009. (CrossRef) (Google Scholar)
7. Baldini C, Talarico R, Tzioufas AG, Bombardieri S. Classification criteria for Sjögren's syndrome: A critical review. J Autoimmun. 2012;39(1-2):9–14
8. Fox, R.I. C.M. Fox (Eds.), Sjögren's syndrome: practical guidelines to diagnosis and therapy, Springer Science & Business Media (2011), 10.1007/978-1-60327-957-4
9. Ottoman, B.A. R.A. Ali A rare case report of Sjögren's syndrome in a young female with clinicosonographical characterization and literature review Am J Ultrasound, 2 (1) (2015), pp. 1-8
10. Qin B, Wang J, Yang Z, et al.: Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis, Ann Rheum Dis 74:1983–1989, 2015.
11. Jadhav S, Jadhav A, Thopte S, Marathe S, Vhathakar P, Chivte P, Jamkhande A. Sjögren's Syndrome: A Case Study. J Int Oral Health. 2015 Mar;7(3):72-4. PMID: 25878484; PMCID: PMC4385732.
12. Patel R, Shahane A: The epidemiology of Sjogren's syndrome, Clin Epidemiol 6:247–255, 2014.
13. Autoimmune hepatitis in patients with primary Sjögren's syndrome: a series of two-hundred and two patients. Karp JK, Akpek EK, Anders RA. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907119/ Int J Clin Exp Pathol. 2010;3:582–586. (PMC free article) (PubMed) (Google Scholar)
14. Oh HJ, Mok YM, Baek MS, Lee JK, Seo BS, Kim TH, Choi KH, Hwang IK, Ra JE, Oh YR, Kim YS, Cho EY, Kim HC, Sohn YW. Co-development of autoimmune hepatitis and Sjögren's syndrome triggered by the administration of herbal medicines. Clin Mol Hepatol. 2013 Sep;19(3):305-8. doi: 10.3350/cmh.2013.19.3.305. Epub 2013 Sep 30. PMID: 24133669; PMCID: PMC3796681.
15. Autoimmune hepatitis. Lohse AW, Mieli-Vergani G. J Hepatol. 2011;55:171–182. (PubMed) (Google Scholar) (Ref list)
16. Autoimmune hepatitis—immunologically triggered liver pathogenesis—diagnostic and therapeutic strategies. Sucher E, Sucher R, Gradistanac T, Brandacher G, Schneeberger S, Berg T. J Immunol Res. 2019;2019:9437043. (PMC free article) (PubMed) (Google Scholar) (Ref list)
17. Sjögren's syndrome. Fox RI. Lancet. 2005;366:321–331. (PubMed) (Google Scholar)
18. Subgroups of Sjögren's syndrome patients categorised by serological profiles: clinical and immunological characteristics. Kontny E, Lewandowska-Poluch A, Chmielińska M, Olesińska M. Reumatologia. 2018;56:346–353. (PMC free article) (PubMed) (Google Scholar) (Ref list)
19. Neville, B. D. Damm, C. Allen, J. Bouquot (third ed.), Oral and maxillofacial pathology, 3, Saunders/Elsevier, St. Louis (2009), pp. 466-470
20. Shiboski CH, Shiboski SC, Seror R, et al.: 2016 American College of Rheumatology/European League against Rheumatism classification criteria for primary Sjogren's syndrome A consensus and data-driven methodology involving three international patient cohorts, Ann Rheum Dis 76:9–16, 2017.
21. Shiboski CH, Shiboski SC, Seror R, et al.: 2016 American College of Rheumatology/European League against rheumatism classification criteria for primary Sjogren's syndrome A consensus and data-driven methodology involving three international patient cohorts, Arthritis Rheumatol 69:35–45, 2017.

****