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Immunoglobulim G4 (Igg4)-Associated Autoimmune Hepatitis: A New Entity Found In African Countries

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Abstract
IgG4-related disease (IgG4-RD) is a chronic fibro-inflammatory condition affecting a wide range of organs. Elevation of serum IgG4 concentrations and abundant infiltration of IgG4-expressing plasma cells are the main diagnostic characteristics of this autoimmune disease. Salivary glands, pancreas and biliary tract are the organs commonly affected by IgG4 disease, but liver involvement is less well documented. Recently, 5 studies have identified a subtype of autoimmune hepatitis (AIH), called IgG4-associated AIH (IgG4-HAI). IgG4-HAI is diagnosed on the basis of a significant accumulation of IgG4-expressing plasma cells in the liver in patients who met the diagnostic criteria for classical AIH [1]. We report here the case of a 70-year-old patient with newly discovered autoimmune hepatitis diagnosed on the basis of classical autoimmune hepatitis criteria and scores and with an elevated igg4 level, and marked igG4 positive plasma cell infiltration of the liver.

Keywords: *Liver, auto immune hepatitis, IGG4 disease, IgG4-associated AIH*

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I. Introduction

Autoimmune hepatitis (AIH) is an immune-mediated inflammatory liver disease that is common in women and characterized by elevated serum IgG levels, presence of serum autoantibodies, and interfacial hepatitis in liver histology [2,3]. Clinically, some AIH patients have elevated serum IgG4 levels but are not diagnosed with IgG4-related diseases (IgG4-RD) or IgG4-related autoimmune hepatitis (IgG4-related-AIH). In this work, we describe the clinico-pathological characteristics of this entity while comparing them to the characteristics of classical AIH. The aim is to know if IgG4-AIH should be considered as a subtype of AIH or as a hepatic involvement of a systemic IgG4-RD We report here the case of a 70-year-old patient with newly discovered autoimmune hepatitis diagnosed on the basis of classical autoimmune hepatitis criteria and scores and with an elevated igg4 level.

II. Case report

We report the observation of a 70-year-old male patient with antecedents of intercostal herpes zoster treated 6 years ago, operated for hemorrhoidal pathology. This patient was referred to the hepato gastroenterology department for the exploration of an atypical abdominal pain associated with cholestatic icterus. He presented asthenia and weight loss. An abdominal ultrasound was performed showing a chronic hepatopathic liver without dilatation of the intrahepatic bile duct and the main bile duct with multi lithiasis VB. The biological work-up showed cytolysis with ASAT 8.67 N (295) and ALAT

4.87N (268) as well as anicteric cholestasis with Gamma-glutamyl-transferases (GGT) at 1.2 N (66 U/L) and normal alkaline phosphatases (PAL) (146 U/L). Serological profile: HBV(hepatitis B virus), HAV, HIV,HCV, and HEV came back negative, immunoglobulin G (IgG): 22. 41 g/l (8,7-17).

The antinuclear antibodies (AAN) was positive The anti smooth muscle antibody (SMA), anti Soluble Liver Antigen (SLA), anti Liver and Kidney Microsome(LKM1) anti liver cytosol antigen (LC1) and antimitochondrial antibody (AMA) were negative.

A liver biopsy was performed and revealed a significant fibrosis (F3) with a piecemeal necrosis and lymphoplasmacytic infiltrates enriched with IgG4 plasma cells, and moderate tissue eosinophilia.

Serum IgG4 level returned back elevated with a rate to 3. 53 times the upper limit of normal (3.051 IU).

An association with autoimmune diseases was searched, however, no dysthyroidism, Primitive Biliary Cholangitis, diabetes, Sjögren's syndrome, celiac disease, biermer's disease or chronic inflammatory bowel disease were founded at the etiological assessment.

A search for other systemic disorders of IgG4 disease was carried out systematically and was negative:

- No biliary tract abnormalities: MRI: normal and liver biopsy analysis revealed no biliary tract lesions.
- No pancreatic abnormality: radiological pancreas normal in appearance,
- No renal involvement: normal renal function with negative 24h proteinuria
- No thyroid involvement: thyroid examination normal, with normal TSH, T3 and T4 values.
- No pulmonary or mediastinal involvement: chest CT scan revealing no parenchymal or vascular abnormalities
- No skin, salivary gland, lacrimal or neuromeningeal involvement.

III. DISCUSSION

Autoimmune hepatitis is a chronic inflammatory liver disease of unknown cause, occurring in a genetic predisposition to autoimmune diseases. Characterized by necrotic-inflammatory hepatocytic lesions, the presence of specific autoantibodies and high sensitivity to corticosteroid treatment. The diagnosis of HAI is based on a combination of clinical, biological, immunological and histological criteria, and the exclusion of other causes. It is not simply a matter of blindly and systematically applying a score.

IgG4 disease is characterized by multi-organ involvement, the histological features of which are a dense lymphoplasmacytic infiltrate (immunohistochemically positive for IgG4), organ fibrosis and obliterating venulitis. Serum IgG4 levels are often, but not always, elevated. Symptoms depend on the organs affected. Diagnosis typically requires biopsy.

The phenomenon of autoimmune hepatitis with elevated serum IgG4 levels has received little attention in clinical practice, and the possible mechanisms have received even less attention.

A first study of IgG4-associated autoimmune hepatitis in European and North African patients was carried out. These patients had similar basic clinical, biological and histological features, and followed similar disease progression characteristics to those of patients with classical autoimmune hepatitis. Of note, complete biochemical responses were similar between IgG4-associated AIH and classic AIH. Apart from a few case reports, only two studies in the literature have reported a case series of
IgG4-associated autoimmune hepatitis. [4]

In another study Immunoglobulin (Ig) G4 disease is a systemic autoimmune disease. Isolated liver involvement has been reported in Japanese patients and is known as IgG4 autoimmune hepatitis (HAI). IgG4 HAI" was defined according to Umemura's criteria: presence of at least 10 immunohistochemically-marked IgG4 plasma cells in a portal space. And its course seems similar to that of classic HAI [5].

Previous studies with a limited number of patients have indicated that IgG4-HAI and IgG4-unassociated HAI share laboratory results, pathological findings and glucocorticoid sensitivity. However, accumulation of IgG4-expressing plasma cells was only detected in IgG4-HAI. It should be noted, however, that the time to ALT normalization after glucocorticoid treatment might be shorter in IgG4-HAI than in unassociated IgG4- HAI [6-7] Confirmation of hepatic accumulation of IgG4-expressing plasma cells is absolutely necessary for the diagnosis of IgG4-HAI provided the patient meets the diagnostic criteria for HAI.

In our study, our patient presented the following clinical characteristics: male sex, advanced age at onset, development of fibrosis and absence of extradigestive manifestations, something which was also noted in a Chinese study, in fact in the latter compared to AIH patients with normal levels, AIH patients with high serum IgG4 levels had the clinical characteristics of a higher proportion of male patients, an older age at onset, a high prevalence of cirrhosis and a low prevalence of extra-digestive involvement at diagnosis. [8]

AIH is a frequent disease in women. The latest practice guidelines from the American Association for the Study of Liver Disease [9] indicate that female patients with autoimmune hepatitis may account for 71-95% , Further analysis concluded that high serum IgG4 levels and male gender were risk factors for HAI cirrhosis, suggesting the possible involvement of male susceptibility genes or abnormal male hormone and high serum IgG4 levels in regulating the progression of HAI cirrhosis.

Further analysis revealed that male gender was a risk factor for elevated serum IgG4 levels in AIH. Studies have reported that testosterone has an inhibitory effect on immune cells [10, 11], for example by inhibiting IgG production by B cells [12], while estrogen has a stimulatory effect on humoral immunity. Given that IgG4 is a subtype of IgG, we hypothesized that autoimmune hepatitis patients with high serum IgG4 levels might have significantly reduced androgen levels, thereby increasing serum IgG4 production.

Cirrhosis could reduce estrogen activation and lead to a relative decrease in androgen levels. Therefore, sex hormone imbalance may be involved in the development of cirrhosis, and elevated serum IgG4 levels may be a marker of sex hormone imbalance in HAI patients.

IV. CONCLUSION

A recent pathological clinic analysis identified IgG4-AIH as a subtype of AIH. Confirmation of hepatic accumulation of IgG4-expressing plasma cells is absolutely necessary for the diagnosis of IgG4-AIH, provided the patient meets the diagnostic criteria for AIH. Furthermore, another study revealed that the

proportion of male patients increased, and the prevalence of cirrhosis was high in HAI patients with elevated serum IgG4 levels at diagnosis.

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