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A cholestatic syndrome may be a surprising cause of medical error

M. Pătrășescu[1], P. Nuță[1], Raluca S. Costache[1,2], Săndica Bucurică[1,2], B. Macadon[1], Andrada Popescu[1], Mariana Jinga[1,2], Florentina Radu Ioniță[1,3]

Abstract: *Autoimmune cholangitis defines a spectrum of cholestatic liver diseases that are characterized by inflammation of bile ducts and a reasonable response to immunosuppressive therapy. The two most common diseases associated with this term in the literature are: an overlap syndrome of primary biliary cirrhosis and autoimmune hepatitis and a form of hyper IgG4 syndrome (currently associated with autoimmune pancreatitis). Liver biopsy is mandatory for the diagnosis. There are, whatsoever, in clinical practice, many cases that do not meet current diagnostic criteria but that have a good response to corticosteroid treatment.*

Keywords: *autoimmune cholangitis, primary biliary cirrhosis, hyper IgG4 syndrome*.

Cholestatic syndromes are very often encountered in gastroenterology practice. The causes may be quite different but there is a largely accepted consensus of classification into two categories: extrahepatic and intrahepatic, rendering very different treatment and prognosis. A proper diagnosis is mandatory for a proper treatment. Conversely, a failure of a correct diagnosis may result in wrong treatment and medico-legal issues. The subject of malpraxis legal actions is often considered to be associated with an embarrassing professional failure with only punitive results. In fact, the conclusions of malpraxis cases may, as well, give very documented information to healthcare professionals in order to better improve medical care.

The differential diagnosis of the causes of cholestatic syndromes is quite challenging. An extrahepatic cause is an obstructive one, may it be acute (billiary colic) or slowly developing (benign or malign strictures, pancreatic head tumor, ampuloma). The imaging workup (CT scan, cholangioMRI) are sufficiently revealing for an extrahepatic obstructive cause in order to conduct a proper treatment. The intrahepatic cholestatic syndromes are even more challenging as there are a quite large array of very different causes with very different treatment and prognosis spanning from viral hepatitis to primary billiary cirrhosis and primitive sclerosing cholangitis. The rare the cause the frequent misdiagnosis and medico-legal consequences.

Among rare intrahepatic causes, autoimmune cholangitis is a term recently coined for a spectrum of

[1] Carol Davila Central Emergency Military Hospital, Bucharest
[2] Carol Davila University of Medicine and Pharmacy, Faculty of Medicine, Bucharest
[3] Titu Maiorescu University, Faculty of Medicine, Bucharest

cholestatic liver diseases where an immunologic pathological mechanism is highly suspected with regard to the cause of inflammation of bile ducts. This term implies also a fare response to immunosuppressive therapy. There is, though, some confusion in literature regarding this disease as it may refer to several ailments: an overlap syndrome between primary biliary cirrhosis AMA (antimithocondrial antibodies) negative and autoimmune hepatitis, a form of hyper IgG4 syndrome (associated with autoimmune pancreatitis), a separate entity as a transition form in spectrum of cholestatic disorders. This confounding data makes the diagnosis in this cases very difficult and, also, a potential source of medico-legal issues

The name autoimmune cholangitis was coined for the first time be Brunner et al[1] to describe the situation of three patients suffering of primary biliary cirrhosis AMA negative; all those patients had antinuclear antibody (ANA) and cholangiopancreatography showed no abnormality. The therapy with prednisolone and azathioprine was successful.

The antigen specificity for AMA was demonstrated to be an inner membrane mithocondrial antigen, a 74 kDa E2 subunit of pyruvate dehidrogenase complex (PDC-E2). The most sensitive lab test to assess the presence of these antibodies is an ELISA using recombinant or purified antigens.

5 to 8% of patients suffering of primary biliary cirrhosis lack AMA in spite of having typical clinical and histological features of this disease.[2] All of these patients had ANA (antinuclear antibodies), highly suggestive of autoimmune hepatitis. Moreover the level of serum IgM was significantly lower in these patients then AMA positive counterparts.

Considering the fact that AMA may have a role in the pathogenesis of the disease, a study by Kitami et al of patients AMA negative and AMA positive demonstrated that there is not truly AMA negative primary biliary cirrhosis. Kitami performed an exhaustive immunoblotting studies of various inner mithocondrial membrane antigens that are not currently looked for.[3]

From the pathologist's point of view AMA positive patients have an increased risk of cirrhosis comparing with AMA negative counterparts. Among histological features, the granulomatous destruction of bile ducts is the only histological marker highly specific for primary biliary cirrhosis AMA negative or positive, but this lacks sensitivity. These data further increases the difficulty of diagnosis.[4]

What about the treatment: ursodeoxycholic acid is the treatment of choice in both forms of primary biliary cirrhosis with equal efficiency.

Autoimmune cholangitis may also be a manifestation of immunoglobulin G4 associated systemic disease, most commonly encountered in patients with autoimmune pancreatitis. Autoimmune pancreatitis (AIP) was first described by Yoshida and colleagues[5] in 1995 referring to a type of chronic pancreatitis with certain histopathologic and imaging features. Early or atypical manifestations of autoimmune cholangitis may not involve the pancreas, thus making the diagnosis even more challenging. There are no definitive diagnosis criteria so far, also some have been proposed like Mayo criteria (HISORt) and Asian Consensus Criteria. Two types of AIP have been described: type I which is a pancreatitis associated with immunoglobulin G4 systemic disease characterized by lymphoplasmocitic infiltration and elevated serum IgG4 levels; type II which is less commonly associated with elevated serum IgG4 levels and involves a granulocytic infiltration. 44% of all patients do not have hyper IgG4 serum levels.[6] The cholangitis is a sclerosing stricturing inflammation of bile ducts. The occasional absence of pancreatic involvement have been described. The natural course of AIP involves relapses. Low dose steroid treatment is very effective treatment.

Besides those two types of autoimmune cholangitis, the clinical practice may come along different situations where an intrahepatic cholestatic syndrome may not have sufficient diagnostic criteria to render a proper diagnosis also the response to corticosteroids is straight forward. These situations may be prevalent.

CASE PRESENTATION

Clinical data

We present the case of a male patient aged 48, living in country area, driver, who is admitted in an emergency department for biliary colic comprising of Charcot triad (colicky pain, fever, jaundice), intense itching, acolic stools and hyperchrome urine. This clinical picture is elicited by a fatty meal. The patient does not smoke cigarettes or drink alcohol and personal as well as family disease history are unremarkable.

Labs data

Labs indicates a cholestatic syndrome (increased total bilirubine – 7.5 mg/dL, direct bilirubine – 5.3 mg/dL, alkaline phosphatase – 190 UI/L, gammaglutamyl transpeptidase – 130 UI/L), hepatocytolitic syndrome (increased alanine aminotransferase ALAT – 300 UI/L, aspartate aminotransferase ASAT – 120 UI/L), minimum pancreatic reaction (increased serum amylase – 200 UI/L).

Abdominal US indicated an increased common bile duct (8 mm) with normal sized intrahepatic ducts, thickened gall bladder walls (3 mm) with multiple small (less than 1 cm) calculi. The clinical picture subsides progressively due to a treatment with: antispastics, antibiotics and proton pump inhibitors. The itching and jaundice didn't subside, though. The total bilirubine level reaches 5 mg/dL and direct bilirubine 2.7 mg/dL. In this particular moment the patient is referred to our clinic with the diagnosis of remitted biliary colic and with indication of elective endoscopic biliary sphincterotomy.

Clinical exam was remarkable for intense sclerotegumentary jaundice, pruritus, dark urine and white chalky stools.

Otherwise the patients had no complains.

Labs indicated normal CBC, cholestatic syndrome (increased total bilirubine – 7.7 mg/dL, direct bilirubine – 4.3 mg/dL, alkaline phosphatase – 199 UI/L, gammaglutamyl transpeptidase – 133 UI/L), hepatocytolitic syndrome (increased ALAT – 307 UI/L, aspartate aminotransferase ASAT – 107 UI/L), no pancreatic reaction (serum amylase – 49 UI/L), normal serum albumin, normal INR.

Imaging and and endoscopy data

Abdominal US indicated: normal size and ecogenicity of the liver, normal sized common bile duct (6 mm), normal gall bladder with minimal biliary sludge. We performed superior digestive endoscopy and side-view duodenoscopy which were unremarkable for pathologic changes, but indicated increased amount of intraluminal bile and a normal papilla major. CT scan with radiocontrast media was unremarkable. Colangio MRI was, also, unremarkable.

Immunology data

In the meanwhile the level of total bilirubine continued to increase to 8.5 mg/dL without the sharp predominance of direct fraction. An extended lab workup indicated: normal level of gammaglobulin, AgHBs negative, Ab antiHBc negative, Ab anti HCV negative, Ab anti HAV negative, CA 19-9 negative, alpha fetoprotein normal, CEA negative, AMA negative, Ab anti LKM1 negative, ANA negative, ASMA negative, pANCA negative, cANCA negative, Ab anti Ro negative, Ab anti La negative, Ab anti HIV negative.

Histopathology data

Liver biopsy was performed: liver tissue sample with marked biliary stasis predominantly intraductular, biliary clots, areas of hepatocellular steatosis, chronic inflammatory infiltrate of portal areas and intralobular areas, hepatocellular regeneration, interface hepatitis with bridging necrosis. (Figure 1, Figure 2).

This description fits into pathology diagnosis of autoimmune cholangitis.

Diagnosis and differential diagnosis

We agreed upon the final diagnosis: autoimmune cholangitis; remitted biliary colic by passage of microcalculi. Hence, it has been concluded that the patient had two different causes of jaundice (acute extrahepatic cholestasis and chronic intrahepatic

cholestasis), segregated by quite different prognosis and treatment. Considering the presence of interface hepatitis with chronic inflammatory infiltrate it had suggested that future evolution of clinical, serological, immunological and histopathology data may be in the direction of an overlap syndrome between AMA negative PBC and autoimmune hepatitis. The differential diagnosis included: primitive and secondary sclerosing cholangitis, primitive biliary cirrhosis, HIV cholangitis, Sjogren syndrome, non Hodgkin lymphoma.

The treatment was highly effective (32 mg of methylprednisolone daily – 0.5 mg/kg prednisolon equivalent – with tapering to 8 mg daily in one month and ursodeoxicholic acid 10 mg/kg daily), resulting in disappearance of cholestasis and hepatocitolysis after 2 month. The dosage of Medrol reached 4 mg per day in the 4th month of treatment, the current clinical and biological status of the patient being excellent.

Figure 1. Biliary clots (hematoxilin-eosine dye)

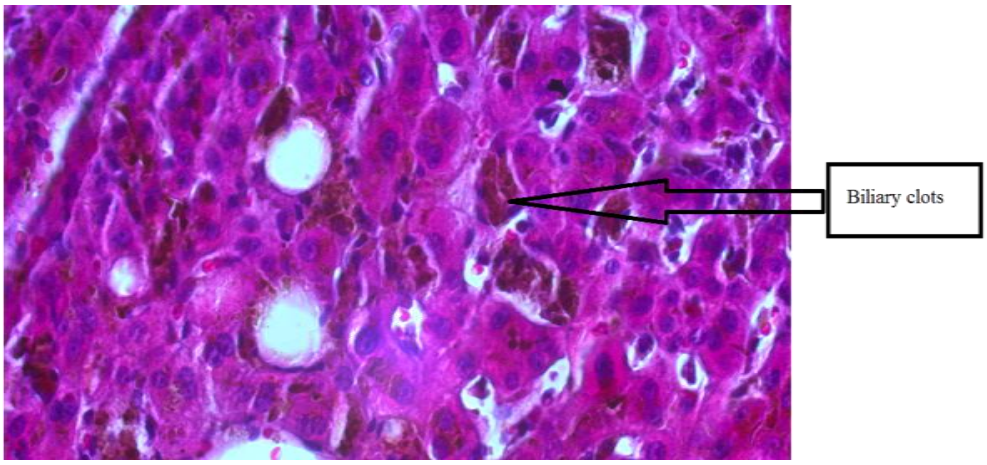
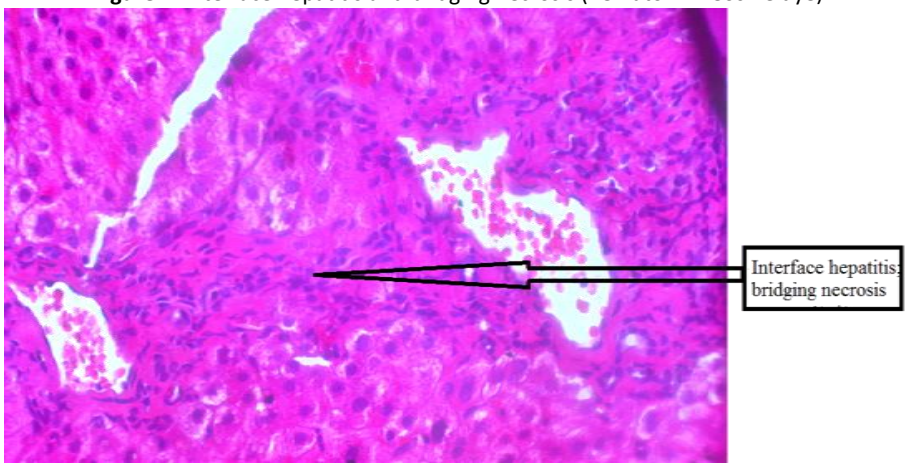


Figure 2. Interface hepatitis and bridging necrosis (hematoxilin-eosine dye)



DISCUSSION AND CONCLUSION

Autoimmune cholangitis is a very challenging diagnosis in the face of a lack of international consensus on terminology used in the literature. This very particular confounding situation may come in defense of the practitioner in case of a malpraxis legal action as it may occur. On the other hand should the diagnosis be late the disease may progress to complications such as cirrhosis, liver failure and, even, death. Referral of patient to a tertiary center of hepatology may be a reasonable course of action to

fully benefit medical care act. This is not always very handy.

A diagnosis workup involves various differential diagnosis of cholestasis syndrome; among these diagnosis AMA negative primary biliary cirrhosis, primitive sclerosing cholangitis of small ductules and hyperIgG4 cholangitis are the most important. Liver biopsy, high definition imaging workup and immunology panels are mandatory for a proper diagnosis.

The response to corticosteroid treatment is highly suggestive of immunologic process involved in the pathogenesis of liver ailment but it is not, whatsoever, pathognomonic as some are tempted to consider. The diagnostic criteria may uncover progressively in time, endorsing the idea of a continuum in a spectrum of autoimmune cholestatic diseases.

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