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• *CASE REPORT* •

Etiological role of brucellosis in autoimmune hepatitis

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Abstract

To show that brucellosis may trigger autoimmune hepatitis (AIH), in addition to nonspecific liver involvement and toxic hepatitis, due to a class effect of tetracycline family used for treatment. We present a female patient admitted to our hospital due to partially improved fatigue and elevated liver enzymes following doxycycline and streptomycin usage for brucellosis. Brucellosis is endemic in our country, Turkey. It may involve any organ in the body. Liver is frequently involved. Doxycycline used for treatment occasionally may lead to hepatotoxicity. AIH is a necroinflammatory disease of the liver. Certain drugs (e.g., minocycline), toxins, and viruses (hepatitis B, hepatitis C, EBV, *etc.*) can trigger AIH. Only one case of AIH probably caused by doxycycline and brucellosis was reported. We discuss the relationship between brucellosis, AIH, and hepatotoxicity of doxycycline. Brucellosis may trigger AIH.

Key words: Brucellosis; Autoimmune hepatitis; Doxycycline

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INTRODUCTION

Brucellosis can present with various manifestations and may involve any organ in the body. Hepatic pathology comprises noncalcified granulomas, suppurative abscesses, and mononuclear cell infiltration. Liver and spleen enlarge in 15-20% of cases. Elevated liver enzymes and bilirubin levels accompany these pathologies[1].

Doxycycline, used for brucellosis, can cause toxic hepatitis. Doxycycline may lead to microvesicular fatty infiltration as the other members of the tetracycline family. There is only one report about toxic hepatitis caused by doxycycline in human despite various studies done on rats by Böcker *et al*, showing microvesicular fatty infiltration with 50-100 mg/kg doxycycline[2-5]. Hepatocytes are filled with fat droplets that do not displace the nucleus. They occur as a result of beta oxidation of fatty acids. Fatty infiltration is either diffuse or zonal. It is partially correlated with dosage[6]. Streptomycin, another drug used for brucellosis, has no known hepatotoxicity.

Autoimmune hepatitis (AIH) is a necroinflammatory disease that may lead to chronic hepatitis and cirrhosis. Its etiopathogenesis is not clear. Various clues indicate that some viruses (HBV, HCV, coxsackie, EBV, *etc.*), some drugs (minocycline in type 1 AIH, *etc.*), and toxins can trigger AIH[7-9]. Histological findings of AIH are portal hepatitis, interface hepatitis, panacinar hepatitis, and cirrhosis; even there may be no pathologic features. Interface hepatitis is characterized by gamma globulin deposition in hepatic mesenchymal cells in periportal area with lymphocyte, plasmocyte, and histiocyte infiltration. Although these features are not entirely specific for AIH, they are frequently and most severely observed in AIH. Destructive bile duct injury does not support AIH while periductal lymphoid aggregates or mixed inflammatory infiltrates are acceptable in cases with interface hepatitis and appropriate clinical findings. Presence of destructive cholangitis and ductopenia suggests primary sclerosing cholangitis (PSC), while nondestructive cholangitis suggests primary biliary cirrhosis (PBC). Diagnosis of AIH is difficult not solely due to histopathologic findings but also due to alcohol usage, viral markers, biochemical and immunologic markers. Nevertheless a scoring system was developed to increase the specificity of diagnosis of AIH (Table 1). Some features (destructive cholangitis or ductopenia) of PBC or PSC may accompany those of AIH, namely overlap syndromes. Some infectious agents or some drugs may trigger overlap syndromes as well as AIH[10].

The case described below is a good example about difficulties in defining the etiology in a patient with impaired liver enzymes.

CASE REPORT

A woman, who was diagnosed with brucellosis by serological and clinical means three months ago, received a treatment regimen of doxycycline and streptomycin. She was admitted to hospital because of partially improved fatigue and elevated liver enzymes.

Biochemical tests yielded AST 140 IU/L, ALT 122 IU/L,

Table 1 AIH scoring system

Category	Feature	Score	Patient
Gender	Female	+2	+2
ALP:AST (or ALT) ratio	<1.5	+2	–2
	1.5–3.0	0	
	>3.0	–2	
Gamma globulin or Ig G levels over normal values	>2.0	+3	+3
	1.5–2.0	+2	
	1.0–1.5	+1	
	<1.0	0	
ANA, SMA, or anti-LKM1 titer	>1:80	+3	+3
	1:80	+2	
	1:40	+1	
	<1:40	0	
AMA	Positive	–4	–4
Viral markers	Positive	–3	+3
	Negative	+3	
Drugs	Yes	–4	–4
	No	+1	
Alcohol	<25 g/d	+2	+2
	>60 g/d	–2	
HLA	DR3 or DR4	+1	
Immune disease	Thyroiditis, colitis, synovitis, others	+2	0
Other liver-related antibodies	Anti-SLA/LP, anti-aktin, anti-LC1, p-ANCA	+2	0
Histologic features	Interface hepatitis	+3	+3
	Plasmocytes	+1	+1
	Rosette formation	+1	0
	None of the above	–5	0
	Biliary changes	–3	–3
	Other features	–3	0
Response to therapy	Complete	+2	+2
	Relapse	+3	
Score before therapy			
Absolute diagnosis		>15	6
Probable diagnosis		10–15	

Abbreviations: ALP, serum alkaline phosphatase level; AST, serum aspartate aminotransferase level; ALT, serum alanine aminotransferase level; ANA, antinuclear antibody; SMA, smooth muscle antikoru; anti-LKM1, antibody against liver/kidney type 1; AMA, anti-mitochondrial antibody; anti-SLA/LP, antibody against soluble liver antigen/liver pancreas; anti-LC1, antibody against liver cytosole type 1; p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibody.

ALP 1 558 IU/L, GGT 1 190 IU/L and total bilirubin 2.48 mg/dL. Albumin/globulin ratio was reversed despite a normal level of albumin. Polyclonal gammopathy was detected on protein electrophoresis. Serum glucose, lipid, urea, creatinine levels and prothrombin time were normal. Anti-HBsAg, HBsAg, anti-HBc Ig G/M, anti-HBe Ag, HBeAg, anti-HCV, anti-HDV, anti-HEV, anti-HAV Ig G/M, and anti-HIV were negative. HBV-DNA and HCV-RNA were also evaluated; they were negative too. Immunologic markers of AIH (ANA, AMA, ASMA, p-ANCA, and anti-LKM1) were negative save ANA and AMA (1/640 and 1/320, respectively). Serologic tests for brucellosis were repeated; Rose-Bengal test was three positive and *Brucella abortus* titer was positive (1/320) for Coombs' test. Liver biopsy was performed and it yielded plasmocyte infiltration, interface hepatitis, and nondestructive bile duct injury suggesting PBC (Figure 1). AIH score was six. The case was diagnosed to be overlap syndrome that comprised AIH and PBC. Methyl prednisolone 40 mg/d and ursodeoxycholicacid (UDCA) 15 mg/(kg • d) were administered. All liver function tests returned to normal after a month. She is still taking maintenance treatment of steroid and UDCA.

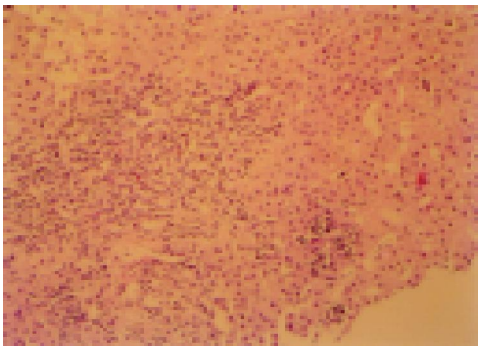

Figure 1 Areas of focal necrosis and periportal biliary piecemeal necrosis (HE ×440).

DISCUSSION

Liver involvement due to brucellosis recurrence and toxic hepatitis was suspected at admission. Microvesicular fatty infiltration, suggesting toxic hepatitis due to tetracycline and doxycycline, was not evident. Hence, histopathology did not support toxic hepatitis. Liver biopsy yielded bile duct injury, interface hepatitis, and plasmocyte infiltration. As a result we focused on AIH and evaluated immunologic markers of AIH. ANA positivity supported AIH. Increased gamma globulin levels, female gender, negative viral markers, and absence of alcohol usage also supported the diagnosis. Unfortunately anti-SLA/LP, anti-aktin, anti-LC1, and HLA tests were unavailable.

AST and ALT levels (3.5 and 3.0 times UNL) in our case were not in the range of a typical AIH case (more than 5.0 times UNL). In most cases of AIH, AST and ALT are below 500 IU/L. Bile duct injury and increased ALP/AST and ALP/ALT ratio indicated cholestatic component. Absence of ductopenia, nondestructive nature of cholangitis, and periductal infiltration supported PBC in spite of PSC component. AMA positivity was also valid for PBC. As in PBC, ALP was predominantly elevated than AST and ALT.

The case was diagnosed with an overlap syndrome according to the AIH scoring system probably triggered by doxycycline. Clinical and biochemical response to steroid and UDCA therapy is achieved.

Liver involvement in brucellosis is not restricted to granulomatous hepatitis; nonspecific cell infiltration (mononuclear cell and plasmocyte) is evident in most cases. This finding suggests that hepatic involvement of brucellosis may contribute to hepatic injury in our case. Furthermore, an overlap syndrome triggered by brucellosis is also open to discussion. Whether brucellosis or doxycycline is a trigger of overlap syndrome is an important question waiting for an answer. We think that our case demands attention since there is only one case in the literature about hepatitis developed after brucellosis infection and doxycycline usage[11].

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