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A Rare Case of Reynolds Syndrome Revealed by Hematemesis

Dr. Soukaina Jiddi*, Lairani Fatima-Ezzahra, Soukaina Elyazal, Imane Haraki, Khadija Krati

*Department of Gastro-Enterology, Mohammed VI hospital, Marrakech, Morocco.
Soukainajiddi@gmail.com

***Corresponding Author:** Dr. Soukaina Jiddi, Department of Gastro-Enterology, Mohammed VI hospital, Marrakech, Morocco.*

Abstract

Reynolds syndrome (RS) is an autoimmune disorder characterized by overlapping primary biliary cholangitis (PBC) and systemic sclerosis (SSc) [3]. Diagnosing overlap syndrome remains a challenge, During systemic sclerosis, the prevalence of liver injury is approximately 1% [6]. Few RS case reports were published. The diagnosis is usually based on clinical, immunological and histological findings, and mainly focused on dermatologic features [8]. Our aim is to make the physicians aware of this rare association and help with its diagnosis.

***Case Presentation:** We here report, the case of a 45-year-old woman who was diagnosed with scleroderma one year before her admission, treated by Corticotherapy, colchicine and methotrexate. She was admitted to our department for hematemesis. Her vital signs on admission were normal; her conjunctiva was pale with icteric scleras. Skin inspection revealed hyperpigmentation predominant in face, sclerosis predominantly on the back of both hands. Upper gastrointestinal endoscopy test was performed, reporting a grade III esophageal varices and congestive hypertrophic gastric mucosa. Abdominal ultrasound revealed a splenomegaly and a cirrhotic liver morphology . Immunoflorecence reported mitochondrial and centromere patterns of antinuclear-antibodies. Therefore, RS was diagnosed and ursodeoxycholic acid was started. She has had no further complications during follow-ups.*

***Conclusion:** In summary, it should be kept in mind that PBC is commonly associated with extrahepatic autoimmune diseases; This is why we must perform hepatic function tests in these patients to detect abnormalities that can often coexist silently.*

Keywords: *systemic sclerosis; Primary biliary cholangitis; Overlap syndrome; Reynolds syndrome; Autoimmunity; hematemesis.*

Introduction

Reynolds and al. described in 1971, 6 patients with classical primary biliary cholangitis, who presented concomitantly with varying degrees of scleroderma [4].

PBC is a chronic and progressive disease which shows a slow and progressive destruction of small intrahepatic bile ducts, impaired biliary secretion and stasis of bile acids within the liver which when untreated will culminate in end-stage biliary cirrhosis [4]. The liver symptoms are almost unnoticed by patients and, this is the reason why the medical consultation is delayed [4].

Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular endothelial damage in small vessels, autoimmune response associated with specific autoantibodies, and progressive fibroblast dysfunction leading to an increased deposition of the extracellular matrix [1]. The systemic manifestations of the disease include circulation abnormalities, such as Raynaud's phenomenon, and multiple organ involvement with fibrotic and vascular complications .It may be classified as diffuse cutaneous SSc or limited cutaneous SSc (lcSSc) on the basis of the extent and distribution of skin involvement. [4-6].

Due to the fact that it is a rare and underdiagnosed disease, the authors present the case of a female patient who consulted for scleroderma, and subsequently, presented during follow up hematemesis and elevated liver enzymes.

Case Report

This paper reports the case of a 40-year-old woman who was diagnosed, based on clinical and immunological features, with sceleroderma one year before her admission. It was revealed by sclerodactyly, Raynaud's phenomenon and strongly positive antinuclear antibodies. She was then put under corticosteroids, colchicine and methotrexate. This patient got admitted to our department due to multiple episodes of hematemesis. Her vital signs on admission were normal. Skin inspection revealed hyperpigmentation predominant in face (Figure 1), sclerosis predominantly on the back of both hands (Figure 2) and hypo and hyperpigmented lesions with the appearance of salt and pepper (figure3) . In the rest of the skin there is generalized xerosis. In addition, pale conjunctivae with icteric scleras. A digital rectal examination found melena.

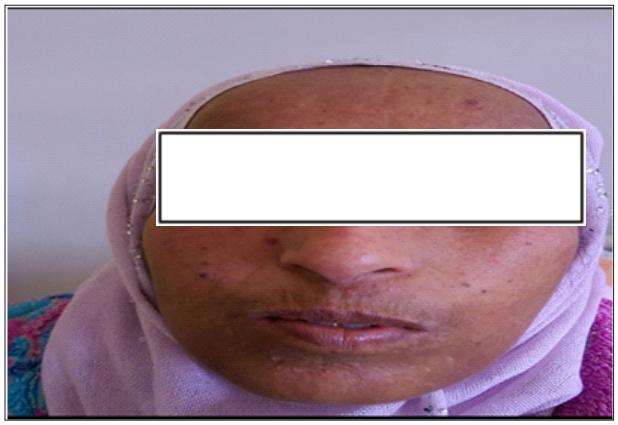

Fig1. *Hyperpigmentation lesions on face*

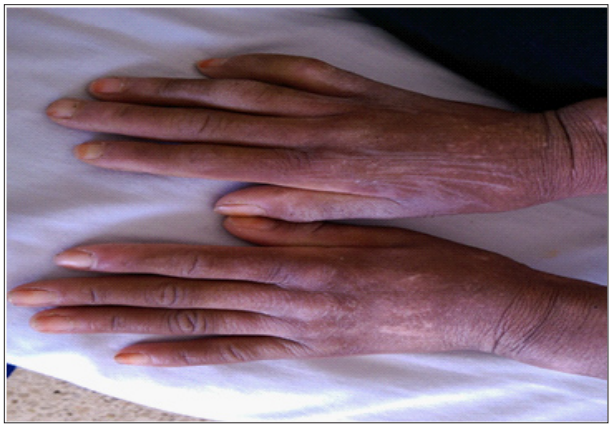

Fig2. *Slerosis lesions on hands*

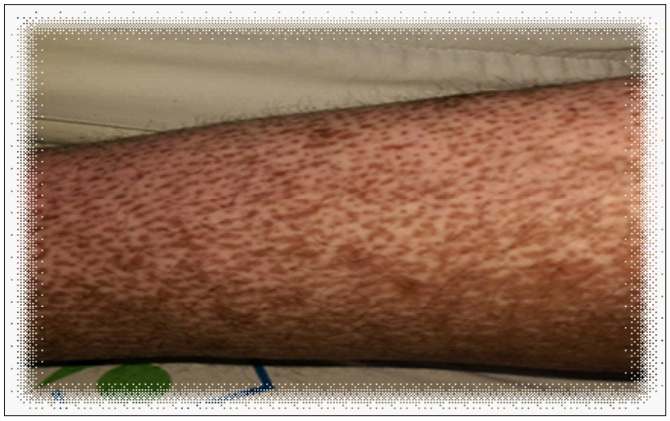

Fig3. *hypo and hyperpigmented lesions on legs*

Laboratory exams realized at the emergency room showed the following results : hemoglobin: 6.6g/dl, platelets: 215000 elements/mm3, Urea : 0.79g/l, Creatinine : 8.67mg/l . An upper gastrointestinal endoscopy was performed, reporting a grade III esophageal varices and congestive hypertrophic gastric mucosa. In addition liver function tests (table 1) showed hyperbilirubinemia with direct predominance and elevated liver enzymes: Total bilirubin: 2.4mg/dl, direct Bilirubin: 2.1mg/dl, aspartate aminotransferase: 75 U/L, alanine aminotransferase: 68 U/L, alkaline phosphatase: 679U/L), Gamma Glutamyl transferase: 397U/L and low serum albumin: 32 g/L.

We also requested an abdominal ultrasound revealing a splenomegaly with cirrhotic liver morphology. Due to the alteration of the liver function, we request tests hepatitis A, B and C serological tests, which were negative. Facing a patient with cholangitis without a history of chronic ingestion of alcohol or medication and without evidence of viral hepatitis, we suspected a picture of immune origin, so we requested anti-

mitochondrial antibodies that were strongly positive (80UI/l) as long as anti-centromere antibodies (1/80). All other autoimmune tests were negative. Thyroid-stimulating hormone and antitransglutaminase antibodies were normal. Consequently, the patient was diagnosed with coexistent primary biliary cholangitis and systemic sclerosis, also known as Reynolds syndrome. After controlling the esophageal bleeding by sandostatin and varices ligation, the treatment with ursodeoxycholic acid 13mg/kg/d and propranolol 40 mg. She has had no further complications during follow-ups.

Table 1. *Hepatic and immunological tests*

Test	Value in patient	Reference value
Bilirubin Total	2.4mg/dl	0.3-1mg/dl
Conjugated	2.1 mg/dL	0.1-0.3mg/dl
Unconjugated	0.3mg/dl	0.2-0.7mg/dl
Alanine transaminase	68 UI/L	<42
Aspartate transaminase	75UI/L	<42
Gamma-Glutamyl transferase	397 UI/ml	women 7-38 UI/ml
Alkaline phosphatase	679U/L	40-100 IU/L
Serum Albumin	32 g/L	>35
Antibodies by indirect immunofluorescence	AMAs : 80UI/l ACAs : 1/80	
Hepatitis virus serologic tests	HBsAg: Negative. Anti HBc : Negative. AntiHVC: Negative.	

ACAs: anti-centromere antibodies; AMAs: antimitochondrial antibodies; HBsAg: hepatitis B surface antigen; Anti HBc: total hepatitis B core antibody; Anti HVC: hepatitis C antibody.

Discussion

This patient was diagnosed with scleroderma associated to primary biliary cholangitis. It's a rare association called Reynolds syndrome which diagnosis is usually not fortuitous [5]. In fact, PBC is the most frequently reported liver disease associated with scleroderma [7]. Data on the survival of patients with this overlap syndrome are contradictory [8].

Although the subjacent immune mechanisms are not yet completely known, Mayo and al reported that antigen-stimulated T-cells play an important role and described bigger prevalence of clonal populations of CD8+ TCRBV3 in Reynolds syndrome than in both conditions alone. [4].

Tojo et al[5] reported that, compared with PBC alone, patients with coexistent primary biliary cholangitis and CREST syndrome had a higher association of esophageal varices in earlier stages of primary biliary cholangitis, higher titers of anticentromere antibody, lower titers of antimitochondrial antibody, and a higher prevalence of HLA-DR9 [9].

PBC is a chronic cholestatic disease, probably caused by a yet unknown immunological mechanism [**4**]. Mid and late 50s is the average age of onset in various studies, and women are affected more frequently **[1]**. Systemic sclerosis also affects mostly women (5:1 female-to-male ratio), generally between the 3rd and 5th decades and with annual incidence of 14.1 cases per million [4].

PBC begins insidiously, with frequent pruritus accompanied by fatigue, or may accidentally be discovered when performing a liver profile that evidences high concentrations of alkaline phosphatase plus the presence of antimitochondrial antibodies. According to the American Association for the Study of Liver Diseases (AASLD) guidelines on PBC, the diagnosis can be established when two out of three criteria are met: 1) biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation;

2) presence of AMA; 3) histologic evidence of non suppurative destructive cholangitis and destruction of interlobular bile ducts [10]. The presence of autoantibodies in asymptomatic patients usually indicates a possible future development of PBC [11].

In our case, 2 of the 3 criteria listed above were met with our patient allowing confirmation of PBC without needing hepatic biopsy. Although liver biopsy allows diagnostic confirmation and disease staging, it is not mandatory for diagnosis once the other two criteria are met. Survival of patients with primary biliary cholangitis without treatment is about 10 years [4]. The prognosis of the disease has changed drastically with the introduction of ursodeoxycholic acid treatment (13-15 mg/kg/day) [11]. Other drugs used are immunosuppressants and antifibrotics **[1].**

In the case presented in this paper, PBC was overlapping SSc : the patient had systemic scleroderma that preceded on average 1 year the signs of PBC. This was discovered following occurrence of hematemesis. Laboratory findings confirmed the diagnosis with positivity of mitochondrial antibodies and cholestasis. Treatment with ursodeoxycholic acid was initiated. However, liver transplant remains the only treatment that truly improves PBC's natural history [4].

Reynolds syndrome prognosis depends of PBC's severity [12]. The regular evaluation of liver function tests is useful for monitoring disease progression. Advanced age, hyperbilirubinemia, low serum albumin and stage 4 (cirrhosis) liver biopsy indicate worse prognosis [4, 13]. According to Stadie , the coincidence of progressive systemic sclerosis and primary biliary cirrhosis seems to be a favorable association for the progression of PBC **[1]**.

Conclusion

All the peculiarities of this association require an increased surveillance in order not to ignore the impact of the liver injury on the overall prognosis of scleroderma [5]

The severity is variable. The disease may be manifested only with mild asymptomatic elevated liver enzymes or might debut with cirrhosis with severe hepatic insufficiency [**4**]. This is why we must perform hepatic function tests in these patients to detect abnormalities that can often coexist silently[4].

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