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CASE REPORT

Unusual causes of intrahepatic cholestatic liver disease

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Abstract

We report five cases with unusual causes of intrahepatic cholestasis, including consumption of *Teucrium polium* (family Lamiaceae) in the form of tea, Stauffer's syndrome, treatment with tamoxifen citrate for breast cancer, infection with *Coxiella Burnetii* (acute Q fever), and infection with *Brucella melitensis* (acute brucellosis).

Key words: Brucella melitensis; *Coxiella Burnetii*; Cholestasis; Hepatitis; Stauffer's syndrome; Tamoxifen; *Teucrium polium*

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INTRODUCTION

The term "cholestasis" indicates stoppage or *stasis* of bile. Cholestasis is not a disease but a symptom of many diseases. It is defined as a pathologic state of reduced bile formation or flow. This definition applies more to the experimental situation, where the rates of bile formation and flow can be measured, than to human cholestasis, where neither can be assessed. Therefore, the clinical definition of cholestasis is any condition in which substances normally excreted into bile are retained. The mechanisms of cholestasis can be broadly classified into intrahepatic, where an impairment of bile formation occurs, and extrahepatic, where impedance to bile flow occurs after it is formed[1]. Intrahepatic cholestasis occurs in certain instances of viral, alcoholic, drug-induced, and chronic liver diseases, such as genetic defects[2] (Table 1). Gallstones, bile duct strictures, and tumours are the most frequent causes of extrahepatic (mechanical) bile duct obstruction[2] (Table 1). Cholestatic liver disease is characterised by a predominant elevation of serum alkaline phosphatase and bilirubin, although serum bilirubin may be normal until a late stage of the disease. In this paper we discuss five patients with unusual causes of intrahepatic cholestatic liver disease.

CASES REPORT

We retrospectively studied the case notes of 100 patients with intrahepatic cholestatic liver disease who were hospitalised in two divisions of internal medicine for investigation in 2002-2004. Five unusual causes of intrahepatic cholestasis were revealed in our patients. The causes of intrahepatic cholestasis were defined as unusual with a prevalence < 10%. The medical histories of five representative patients with these causes of cholestasis are reported below:

Case 1

A 67-year old man was admitted to hospital for a 5-d history of painless jaundice, pruritus, dark urine and light stools. His medical history included fatty liver, associated with hyperlipidemia and the consumption of ethanol, which was confirmed by an abdominal ultrasound scan and liver biopsy performed in the previous year. Consumption of *Teucrium polium* (family Lamiaceae) in the form of tea for the treatment of hyperlipidemia during the previous 6 mo (increasing to 2 litres per day in the preceding month) was also mentioned. Physical examination revealed yellow pigmentation of the sclera and skin. Laboratory tests showed the following values: haematocrit (Ht) 46%, white blood cell (WBC) count 7000 cells/mm^3 (neutrophils 53%, lymphocytes 29.3%, monocytes 10.2%, eosinophils 6.6%), MCV106 fL (normal range: 80-99 fL), platelet (PLT) count 133 000/mm^3 (normal range: 150 000-450 000/mm^3), international normalized ratio (INR) 2.9 (normal value: < 1.7), alanine aminotransferase (ALT) 1272 U/L (normal range: 5-40 U/L), aspartate aminotransferase (AST) 1739 U/L (normal range: 5-40 U/L), γ-glutamyl transpeptidase (GGT) 302 U/L (normal range: 10-75 U/L), alkaline phosphatase (ALP) 190 U/L (normal range: 35-125 U/L), total bilirubin (Bil) 11.37 mg/dL (normal range: 0.1-1.3 mg/dL), direct-bilirubin (d-Bil) 7.97 mg/dL, albumin (Alb) 3.3 gr/dL (normal range: 3.5-5.0 g/dL), lactate dehydrogenase (LDH) 380 U/L (normal range: 80-230 U/L), bilirubin and urobilinogen in the urine. Serological and immunologic tests, such as tests for hepatotropic

Table 1 Causes of cholestasis[2]

Intrahepatic cholestasis	Extrahepatic biliary tract diseases
Primary biliary cirrhosis (PBC)	Choledocholithiasis
Primary sclerosing cholangitis (PSC)	Bile duct tumours (benign and malignant)
Drugs and toxins	Ampullary tumours (benign and malignant)
Sepsis	Pancreatic carcinoma
Malignancy	Mirizzi's syndrome
Granulomatous liver disease (infections, chemicals, drugs, miscellaneous)	AIDS cholangiopathy
Intrahepatic cholestasis of pregnancy	Parasites
Hepatitis (viral and alcoholic)	PSC (primary sclerosing cholangitis) (see left)
Genetic disorders	
Total parenteral nutrition associated cholestasis	
Graft versus host disease	
Post liver transplant cholestasis	

viruses were negative. Histopathology of a liver biopsy revealed cholestatic hepatitis compatible with drug-induced hepatitis. The management of the patient was successful mainly consisted of careful parenteral administration of suitable fluids and vitamin K, per os administration ursodeoxycholic acid and a frequent assessment of the liver function tests. Liver dysfunction was restored one month after his admission.

Final diagnosis: Acute cholestatic hepatitis caused by *Teucrium polium* L.

Case 2

A 50-year old man [farmer, smoker (40 packs/year)] was admitted to hospital because of a 5-d history of high-grade intermittent fever (up to 38.5℃) associated with mild left abdominal pain, fatigue, and anorexia. Weight loss (approximately 12 kg) during the previous two months was also mentioned. His medical history included Hashimoto thyroiditis and vitiligo. Physical examination revealed a palpable abdominal mass on the left kidney that was confirmed by ultrasound and CT scans of the abdomen. Laboratory tests showed the following values: Ht 31%, WBC 9000 cells/mm^3 (neutrophils 53%, lymphocytes 27%, monocytes 13%, eosinophils 7%), PLT 470 000/mm^3, erythrocyte sedimentation rate (ESR) 140 mm/h, C-reactive protein (CRP) 8 mg/dL (normal range: 0.08-0.8 mg/dL), ALT 260 U/L, AST 227 U/L, GGT 140 U/L, ALP 187 U/L, Bil 2.1 mg/dL, d-Bil 1.8 mg/dL, Alb 3.2 gr/dL, LDH 370 U/L, INR 2.9, microscopic haematuria in urinalysis. Serological and immunologic tests were negative. A left radical nephrectomy was performed. Pathologic examination revealed stage Ⅱ renal cell carcinoma (RCC). Six weeks after the nephrectomy, the liver function tests, the ESR and CRP level were normal. There was no recurrence or metastasis throughout the 3-year follow-up period.

Final diagnosis: Non-metastatic cholestatic paraneoplastic syndrome associated with RCC stage Ⅱ (Stauffer's syndrome).

Case 3

A 60-year old woman was admitted to hospital for the check of elevated liver function test levels in blood examinations. Her medical history included fatty liver confirmed by an abdominal ultrasound scan and liver biopsy performed in the previous year (steatohepatitis). She had a previous history of modified mastectomy with axillary lymphadenectomy for a retroareolar, canalicular breast carcinoma 6 months ago. She received adjuvant radiation and started tamoxifen citrate (20 mg daily) two months before admission. Physical examination revealed hepatomegaly that was confirmed by an abdominal ultrasound and CT scan. No hepatic metastasis or main bile duct obstruction was detected. Laboratory tests showed the following values: Ht 43%, WBC 7600 cells/mm^3 (neutrophils 60%, lymphocytes 28%, monocytes 8%, eosinophils 4%), MCV 102 fl, PLT 142 000/mm^3, INR 1.9, ALT 377 U/L, AST 284 U/L, GGT 342 U/L, ALP 290 U/L, Bil 1.5 mg/dL, d-Bil 1.2 mg/dL, Alb 3.2 gr/dL, LDH 320 U/L. Serological and immunologic tests, tumour markers, such as tests for hepatotropic viruses were also negative. Histopathology of a liver biopsy revealed cholestatic hepatitis compatible with drug-induced hepatitis. Tamoxifen was withdrawn and methylprednisolone (1 g daily) was administered for 3 d. Thereafter, 0.5 mg/kg prednisone was indicated for 7 d and subsequently decreased. Five weeks after the discontinuation of tamoxifen citrate, serum ALP and GGT levels were normalized, while serum ALT and AST concentrations were approximately a little above the normal limits. Currently she is receiving anastrazole (aromatase inhibitor).

Final diagnosis: Acute cholestatic hepatitis caused by Tamoxifen citrate.

Case 4

A 39-year old man presented with a one-month history of painless jaundice and after a 5-day period of dark urine without fever. His personal and family medical history was unremarkable. Physical examination revealed yellow pigmentation of the sclera and skin. Laboratory tests showed the following values: Ht 47%, WBC 6700 cells/mm^3, PLT 215 000/mm^3, ALT 762 U/L, AST 735 U/L, GGT 167 U/L, ALP 417 U/L, Bil 3.19 mg/dL, d-Bil 2.15 mg/dL, LDH 390 U/L, urobilinogen in the urine. Immunologic tests, such as tests for hepatotropic viruses were negative. A four-fold increase was found by comparing the titers of IgG antibodies to phase Ⅱ antigen of *Coxiella Burnetii* in two consecutive assays (indirect immunofluorescence antibody technique, IFAT). Histopathology of a liver biopsy revealed acute hepatitis. The patient was treated successfully with doxycycline (100 mg per os twice daily) for 2 wk. Liver dysfunction was restored two months after his admission.

Final diagnosis: Acute cholestatic hepatitis caused by *Coxiella Burnetii* (acute Q fever infection).

Case 5

A 47-year old man shepherd was admitted to hospital, because of a 2-wk period of intermittent low-grade fever, fatigue, malodorous sweating and headache. His personal

and family medical history was unremarkable. A record of the consumption of unpasteurised dairy products during the previous months was reported. Physical examination revealed hepatomegaly that was confirmed by an abdominal ultrasound scan. Laboratory tests showed the following values: Ht 36, WBC 7900 cells/mm^3 (neutrophils 60%, lymphocytes 30%, monocytes 7%, eosinophils 3%), PLT 123 000/mm^3, ESR 53 mm/h, CRP 4.43 mg/dL, ALT 672 U/L, AST 769 U/L, GGT 432 U/L, ALP 342 U/L, Bil 2.3 mg/dL, d-Bil 2 mg/dL, Alb 3.3 gr/dL, LDH 380 U/L. Brucella agglutinin titter was positive at 1/320 and growth of *Brucella melitensis* in blood culture after 5 d. After a putative diagnosis of brucellosis, the patient was administered doxycycline (100 mg per os twice daily) for six weeks plus 1 g streptomycin im for the first 21 d, beginning on the third day of hospitalisation, while waiting the serological and cultural confirmation. Liver dysfunction was restored five weeks after his admission.

Final diagnosis: Acute cholestatic hepatitis caused by *Brucella melitensis*.

DISCUSSION

Case 1

The final diagnosis was based on the excessive consumption of *Teucrium polium* tea during the month before admission, and the exclusion of other cholestatic syndromes. The histopathological change in the findings of the liver biopsy, taken before and after the consumption of the excessive amount of tea was also conclusive evidence of the cause of cholestatic hepatitis. Although the mechanism of *Teucrium polium* hepatotoxicity is unclear, teucrin A and several neoclerodane diterpenoids, present in the aerial parts of the plant, have been reported as the probable hepatotoxic precursors of this herb[3]. In some instances, liver injury has been associated with the presence of autoantibodies in the serum[4,5]. It has also been reported that some flavonoids have antihyperlipidemic properties, while some terpenoids could inhibit lipid peroxidation[3]. In 1995 Mattei *et al*[6] reported massive hepatocyte necrosis predominantly in the centrilobular areas of the liver in a patient with acute liver failure after the consumption of *Teucrium polium*.

Case 2

Stauffer's syndrome is a non-metastatic cholestatic paraneoplastic syndrome usually associated with RCC, with an incidence of 3%-6% among these patients[7,8]. The syndrome is also associated with other malignancies, such as bronchial adenocarcinoma, leiomyosarcoma and prostate adenocarcinoma[9-11]. Stauffer's syndrome may result from tumour production of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and possibly interleukin-6 (IL-6)[12,13]. Nephrectomy may result in the amelioration of hepatic dysfunction, but persistent or recurrent elevations may herald local recurrence or metastatic disease[14]. It is remarkable that RCC was an unexpected finding diagnosed during the investigation of systemic symptoms and hepatic dysfunction in our patient. The hepatic dysfunction was returned to normal after nephrectomy.

Case 3

Tamoxifen is a synthetic antioestrogen with both agonist and antagonist properties and plays an important role in prevention and treatment of breast cancer[15]. It is believed to act primarily through binding to oestrogen receptors in breast cancer cells, acting as a competitive inhibitor of oestrogen. Several forms of drug-induced liver disease, such as clolestasis, benign liver tumours, hepatocellular carcinoma, acute hepatitis, submassive hepatic necrosis, steatosis, and steatohepatitis, have been attributed to tamoxifen[15,16]. Although tamoxifen is a known cause of cholestasis, very little attention has been focused on its use in patients with pre-existing liver dysfunction and the possible need for dose adjustment[17]. The pre-existing steatohepatitis might contribute to the early development of tamoxifen-induced cholestasis (2 mo after tamoxifen administration) in our patient.

Case 4

The final diagnosis was based on both serological and clinical criteria. *Coxiella Burnetii* has a worldwide distribution and reports from various countries show a variety of clinical and epidemiological features of Q fever from one area of the world to another[18]. Hepatic involvement is frequent in Greece as well as in France where it accounts for approximately 40%-50% of acute cases[19,20]. Usually hepatic involvement is asymptomatic with a mild increase (2-3 times the normal level) of ALP, AST, and ALT[21]. Jaundice is a rare finding in Q fever hepatitis while hepatomegaly is quite common[20]. The three clinical presentations of Q fever hepatitis are infectious viral-like hepatitis, fever of unknown origin with granulomatous hepatitis, and incidental finding of elevated transaminases in a patient with pneumonia. In patients with granulomatous hepatitis liver biopsy shows a typical doughnut granuloma with dense fibrin ring surrounded by a central lipid vacuole, that is highly suggestive of the disease caused by *Coxiella burnetii*[21,22]. Extensive destruction of liver tissue leading to hepatic coma and death have occasionally been reported[23,24].

Case 5

Brucellosis, a world-wide zoonotic disease, is a systemic infection caused by facultative intracellular bacteria of the genus *Brucella* that can involve many organs and tissues[25]. Brucellosis is a major public health concern in Greece, especially in areas where animal breeding is an important economic resource. *Brucella melitensis* is the most pathogenic and invasive species of *Brucella* and occurs more frequently in general human population than in other known species. Hepatic tenderness and mild elevation of transaminases and ALP may be found in acute disease[26]. Asymptomatic, mild cholestatic hepatitis accounted for approximately 16% of acute cases of brucellosis in a small study from Greece[27].

CONCLUSION

In conclusion, use of herbal remedies, as *Teucrium polium* must be considered a possible aetiology in the setting of clinical and/or biochemical manifestations of liver injury, since alternative medicine and herbal treatments

have growing appeal to many societies. Malignant diseases including hypernephroma, treatment with tamoxifen citrate, and infections with *Coxiella Burnetii* or *Brucella melitensis* are also unusual causes of cholestatic hepatitis. Clinicians should consider these causes during diagnostic workup of intrahepatic cholestatic liver disease.

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