Primary biliary cirrhosis in a patient with Turner syndrome

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An increased prevalence of X chromosome monosomy has recently been demonstrated in patients with primary biliary cirrhosis (PBC). Chronic cholestasis of unknown etiology is a common clinical feature in patients with Turner syndrome who reach the fourth and fifth decades of life. A 37-year-old patient with Turner syndrome who presented with clinical and biochemical features of chronic cholestasis is described. Subsequent investigations confirmed the diagnosis of PBC. The patient did not respond to the medical treatment and was referred for liver transplantation. The present case may support the importance of X chromosome genes in the development of genetic predisposition to PBC, and emphasizes the necessity for a systematic study of the prevalence of PBC in patients with Turner syndrome.

Key Words: Primary biliary cirrhosis; Turner syndrome

Turner syndrome (TS) is a disorder associated with complete or partial monosomy of the X chromosome. TS occurs in phenotypic females and presents with short stature and features secondary to gonadal dysgenesis (1). An increased prevalence of X chromosome monosomy in peripheral white blood cells was recently reported in patients with primary biliary cirrhosis (PBC) (2). Epidemiological reports in TS indicate an association with chronic cholestatic liver disease of unknown etiology and the risk of liver cirrhosis in patients with TS is approximately six times higher than in the general population (3). In the present report, we describe a patient who presented with both TS and PBC.

CASE PRESENTATION

A 37-year-old woman with TS diagnosed in her childhood and a history of type 2 diabetes mellitus, hysterectomy and breast implants presented in 1999 with recurrent episodes of right hypochondrial pain. She underwent cholecystectomy but her symptoms persisted, and she had an endoscopic retrograde cholangiopancreatography in 2000. Although it was normal, she underwent sphincterotomy because she was thought to possibly have biliary dyskinesia, but it did not relieve her symptoms. Her serum biochemistry at that time was as follows: aspartate aminotransferase 75 U/L (normal range 3 U/L to 30 U/L), alanine aminotransferase 142 U/L (normal range 3 U/L to 45 U/L), alkaline phosphatase 345 U/L (normal range 30 U/L to 120 U/L), bilirubin 31 µmol/L (normal range 3 µmol/L to 17 µmol/L), albumin 42 g/L (normal range 38 g/L to 45 g/L), hemoglobin 126 g/L, leukocytes 0.0075 × 10^9/L (normal range 4 × 10^9/L to 10 × 10^9/L) and platelets 284 × 10^9/L (normal range 150 × 10^9/L to 400 × 10^9/L). She was referred to a tertiary referral liver clinic. Her major complaints were persistent right upper quadrant pain, mild pruritus, dry eyes and fatigue. On examination, she was noted to be short in stature and had other phenotypic features of TS. There were no stigmata of chronic liver disease. Laboratory investigations, apart from results mentioned above, showed a positive antimitochondrial antibody (AMA) level of 69 U/mL (determined by ELISA, normal value less than 5 U/mL) and an elevated immunoglobulin (Ig)M of 15 g/L (normal range 0.7 g/L to 3 µmol/L to 17 µmol/L), UFC testosterone and alpha-1-antitrypsin were all normal. Screening for viral hepatitis was negative, and an abdominal ultrasound was essentially normal. She underwent percutaneous liver biopsy which showed the presence of delicate septation with portal fibrous expansion and moderate (approximately 50%) duct loss with ductular proliferation, thought to be compatible with stage 2 PBC. Bone densitometry showed osteopenia. She was prescribed ursodeoxycholic acid at a dose of 15 mg/kg body weight but her biochemistry

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continued to deteriorate (Figure 1). Because she complained of progressive and disabling fatigue, she was referred for liver transplant assessment. Upper gastrointestinal endoscopy performed at that time showed features of mild portal gastropathy.

**DISCUSSION**

There is only one report (4) published in English language literature describing a patient with TS who also had PBC. There are two other reports on simultaneous occurrence of TS and PBC, one published in Spanish (5) and another one published in proceedings to a medical meeting (6). The prevalence of PBC in TS has never been studied, despite the fact that chronic cholestasis with elevated liver biochemistry can be observed in 80% of patients with TS over the age of 35 years (7). It has also been reported that patients with TS may have positive anti-liver-kidney microsomal (LKM) antibodies (detected with indirect immunofluorescence, a method frequently associated with misinterpretation of AMA as LKM) (8). Systematic analysis of the presence of AMA has not been reported in the majority of clinical studies on patients with TS. However, TS and PBC share several similarities (9). In both disorders, cholestasis is age-related (i.e., develops in older rather than younger subjects). Both conditions are strongly associated with autoimmune disorders. Antithyroid antibodies are found in approximately 40% of patients with TS and more commonly in those who also have abnormal liver biochemistry (10). Also, the risk of inflammatory bowel disease in TS, estimated to be between 2.6% and 3%, is much higher than in the general population (11). Celiac disease shows a similar prevalence in both PBC and TS (12). Osteopenia, which often complicates PBC, is also associated with TS. Typically, bone mass improves but does not normalize on hormonal therapy in patients with TS; thus, estrogen deficiency cannot be considered the only responsible factor. Therefore, the presence of an unknown 'intrinsic bone defect' has been postulated to explain decreased bone mass in these patients (1). Because chronic cholestasis may contribute to abnormal bone density, its role in the development of osteopenia in TS can be contemplated. It has also been demonstrated that as many as 78% of patients with TS have bile duct changes typically seen in small duct primary sclerosing cholangitis, a disease in which histology could be difficult to differentiate from PBC (13).

If the prevalence of TS is one in 2500 (this frequently quoted proportion is probably an overestimation, because recent reports [14] have shown that prenatal diagnosis of TS leads to abortion in 71% to 100% of cases), then there should be approximately 5000 patients with TS in the province of Ontario, where we practice. Even if we saw all patients with PBC from our province (which is quite unrealistic) and the patient in the present study represented the only case of TS with PBC in Ontario, the calculated prevalence of PBC in TS would be 10 times higher than in the general population of Ontario (15). Because the life expectancy in TS is significantly lower than in general population (mostly due to cardiovascular abnormalities), many patients with TS may not survive to the age at which PBC manifests itself clinically. This figure may therefore be much higher than only 10-fold.

A recent report (2) demonstrated that X chromosome monosomy occurred significantly more commonly in patients with PBC than in controls and patients with hepatitis C (in particular, affecting cells involved in adaptive immune reactions). The authors suggest that the deficiency of genes localized to the X chromosome may predispose to altered immune responses, thus increasing the risk of PBC. Because genetic predisposition to PBC has been supported by several reports (16), systematic studies, including autoimmune markers in cholestatic patients with TS, may help in the elucidation of the etiology of PBC.

**Figure 1** Liver biochemistry of described patient. A Alanine aminotransferase (ALT) (normal range 3 U/L to 30 U/L) and alkaline phosphatase (ALP) (normal range 30 U/L to 120 U/L). B Bilirubin (normal range 3 µmol/L to 17 µmol/L) and albumin (normal range 38 g/L to 45 g/L).
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