Thyrotoxicosis Associated with Steatosis and Cholestasis; A Rare Association Case Report

Hind I. Fallatah MBCh B, ABIM, MACP
Hisham O. Akbar MBCh B, FRCPC

Department of Gastroenterology and Hepatology, King Abdul Aziz University Hospital, Jeddah Saudi Arabia

Abstract
Thyroid disorders especially thyrotoxicosis are commonly associated with hepatic dysfunction but cholestasis is rarely reported. We reported a 31-year lady with thyrotoxicosis-associated steatosis and cholestasis, the serological and the immunological markers were negative for chronic viral hepatitis and autoimmune liver diseases. She had significant improvement of the liver enzymes after treatment with radio active I^{131}. Over three years follow up, the liver enzymes were fluctuating with the changes in the thyroid status. In conclusion re-evaluation of the liver enzymes after treatment of thyrotoxicosis will differentiate patients with thyrotoxicosis induced hepatic dysfunction from those with underlying liver disease.

Key words: Hyperthyroidism, liver enzymes, Thyroid function tests, Non alcoholic fatty liver disease, I^{131}.

Journal of Taibah University Medical Sciences 2009; 4(1):

Correspondence to:
Dr. Hind I. Fallatah
Consultant Gastroenterologist and Hepatologist
King Abdul Aziz University Hospital
9714 Jeddah 21423 Saudi Arabia
+966 505623251
+966 2 6751149
hindfallatah@hotmail.com

Introduction
Hepatic involvement in systemic disorders is common with variable features from fulminant liver failure to cholestatic, hepatocellular or mixed pictures. Thyroid disorders are known to be associated with abnormal liver enzymes\(^1\). Autoimmune thyroid disorders like Hashimoto's thyroiditis and Grave's disease may be associated with autoimmune hepatitis as part of multiorgan autoimmune diseases. Treatment of hyperthyroidism with oral medication or radioactive iodine I^{131} may cause toxic liver injury\(^2,3,4\). Hyperthyroidism associated cholestasis was reported with both severe and mild hyperthyroidism. This form of cholestasis usually resolves after treatment of hyperthyroidism\(^5,6\). This case report is a description of rare association of thyrotoxicosis, cholestasis, and steatosis.
Case presentation

Thirty one year old lady diagnosed to have Grave's disease in 2001 based on clinical evidence of thyrotoxicosis, elevated thyroid function tests Thyroid stimulating (TSH) 0.005uiU/L, Free T4 hormone (T4) 67pmol/L, Free T3 (FT3)17pmol/L and positive thyroid antibodies she was treated with neomercazole but she was not compliant to the treatment and follow up. On March 2003 she presented to the out patients department with 2-year history of neck swelling, weight loss, heat intolerance, shortness of breath, dysphagia and secondary amenorrhea. There was no history of jaundice, no past or family history of liver disease and no history of blood transfusion. She was not receiving hepatotoxic medication or herbal medicine and she was off neomerccazole for more than one year. On physical examination, her weight 56.2Kg and height 134 cm, body mass index 31.18, blood pressure 118/70 mmHg, normal pulse rate with adequate volume and regular. She had exophthalamous, positive lid retraction and lid lag. She was not jaundiced. The neck examination revealed diffuse moderate size goiter, no bruit over it and the trachea was not deviated. She had hand signs of thyrotoxicosis (fine tremors and sweating), no proximal myopathy. The cardiovascular, chest and abdominal examination were normal. Complete blood count showed; White blood cells (WBC) 9.42kU/l, hemoglobin (Hb) 10.2 g/dl (Normal 11.5-16.5), and platelets (PLT) 368k/ul. Electrolytes, renal function and blood sugar were normal. Total protein 94g/l normal, albumin 44g/l, alkaline phosphatase 418U/L (Normal 50-136), gamma glutamyl transferase (GGT) 924U/L (Normal 5-85), Aspartate aminotransferrase (AST) 205U/L (Normal 5-50), alanin amino transferase (ALT) 234U/L (Normal 5-65), total bilirubin (TBil) was 7 (Normal). She had normal liver enzymes before the diagnosis of thyrotoxicosis.

Cholesterol 7 mmol/L (Normal 1.2-5.2), and triglycerides 1.91 (Normal 0.6-2.3). The patient was considered for the statin (Simvastatin) therapy for her hypercholesteremia but this was deferred for the risk hepatotoxicity in the presence of abnormal liver enzymes. Thyroid stimulating hormone (TSH) 0.011ulU/L (Normal 0.27-4.2), Free T3 hormone (FT4) 94.16 pmol/L (Normal 12-22), Free T3 (FT3) 9.89pmol/L (Normal 2.8-7).

Antinuclear antibody (ANA) was moderately positive 1:160, double stranded DNA antibody was negative, Immunoglobulin-G (IgG) 11.8 which was normal Immunoglobulin-M (IgM) 1.19 was also normal. Antimitochondrial antibody (AMA2) was negative and smooth muscle antibody (SMA) was weakly positive. Serology for hepatitis A, B and C viruses were negative. Thyroid peroxidase antibody 1309 (Normal 0-34), Thyroid Thyroglobulin antibody (TG) 2263 (Normal 0-115). Human Immunodeficiency viruses 1, 2 (HIV) were negative. Ultrasound abdomen showed fatty liver changes but there were no evidence of intra or extra hepatic biliary dilatation. Thyroid ultrasound showed diffuse enlargement of the gland without focal lesions. Thyroid scan demonstrated diffuse increased uptake. Liver biopsy showed micro and macrovesicular steatosis, some hepatocytes showed intracytoplasmic cholestasis and mild fibrosis seen in the portal tract. No histological evidence of autoimmune hepatitis.

Because of the clinical and laboratory evidence of thyrotoxicosis and failure of previous medical treatment she received radioactive iodine therapy I131. Six month post I131 treatment the liver enzymes improved gradually with the reduction in T4 level AST 35U/L, ALT90U/L, Alk Pho248U/L. But with the progression to hypothyroidism which is expected after I-131 treatment the liver enzymes showed picture of hepatocellular derangements see Table 1. The serum lipids were still the same metformin 500mg twice daily was started as treatment for NAFLD together with thyroxin replacement therapy. The liver enzymes improved to the lowest level since she was diagnosed.
Table 1: Fluctuation of the patient’s liver enzymes before and after I\textsuperscript{131} therapy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Before I\textsuperscript{131}</th>
<th>6 month after I\textsuperscript{131}</th>
<th>9 month after I\textsuperscript{131}</th>
<th>Last follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.011</td>
<td>0.019</td>
<td>64.6</td>
<td>0.85</td>
</tr>
<tr>
<td>T\textsubscript{4}</td>
<td>94.16</td>
<td>24.19</td>
<td>2.47</td>
<td>29.68</td>
</tr>
<tr>
<td>T\textsubscript{3}</td>
<td>39.98</td>
<td>5.11</td>
<td>1.73</td>
<td>5.9</td>
</tr>
<tr>
<td>ALP</td>
<td>397</td>
<td>248</td>
<td>263</td>
<td>277</td>
</tr>
<tr>
<td>GGT</td>
<td>708</td>
<td>665</td>
<td>863</td>
<td>660</td>
</tr>
<tr>
<td>AST</td>
<td>205</td>
<td>35</td>
<td>132</td>
<td>90</td>
</tr>
<tr>
<td>ALT</td>
<td>234</td>
<td>90</td>
<td>202</td>
<td>117</td>
</tr>
<tr>
<td>T BIL</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

After three years of follow up the liver enzymes were still fluctuating but never back to normal pravastatin 10 mg daily was added and she was closely monitored, she had transient improvement of the liver enzyme but once again she had poor compliance to pravastatin. Currently the patient is receiving L thyroxin100 μg/day on the latest outpatient follow up the TSH 0.85, T\textsubscript{4} 29.68, T\textsubscript{3} 5.92. The liver enzymes showed hepatocellular derangement ALT117, AST90, ALP277 this most likely attributed to obesity associated non alcoholic fatty liver disease.

**Discussion**

Thyrotoxicosis associated liver enzyme abnormality were reported in up to 37% of thyrotoxic patients\textsuperscript{1, 5, 6} The presence of cholestasis in association with thyrotoxicosis is rarely reported\textsuperscript{7,8}. This case represents a rare association of cholestasis and steatosis with thyrotoxicosis. The abnormality of the liver enzymes raises the possibility of autoimmune hepatitis in association with thyrotoxicosis is not supported by the finding on the liver biopsy and the IgG level, positive ANA is not specific and could be related to Grave's disease. Primary biliary cirrhosis (PBC) is another autoimmune disease that should be considered in an adult female with autoimmune thyroid disorder presenting with cholestasis, but this was excluded by negative (AMA2) antibody, normal (IgM) level and absence of PBC features on the liver biopsy. Chronic viral hepatitis (B or C) especially hepatitis C genotype 3 is well known to be associated with steatosis and high GGT level\textsuperscript{9,10} but negative viral markers and the liver biopsy findings were not supportive for the diagnosis of chronic viral hepatitis. Hepato-toxicity from previous Carbimazole treatment is another possibility but previously reported cases of carbimazole induced cholestasis developed during treatment or shortly after and were associated with clinical jaundice and hyperbilirubinemia\textsuperscript{2,3,11} which was not the case in our patient, she had normal bilirubin and on the other hand she stopped taking carbimazole more than one year before she had abnormal liver enzymes. I\textsuperscript{131} was reported to cause severe cholestatic hepatitis\textsuperscript{4} but in our patient the liver enzymes were abnormal before receiving treatment with I\textsuperscript{131}. In a report similar to our patient, Belassoued and colleagues reported a case of thyrotoxic hepatitis and steatosis with favorable outcome after I\textsuperscript{131} therapy\textsuperscript{12}. In the two reported cases by Hull and colleagues the jaundice resolve completely after thyroidectomy \textsuperscript{8}Toxic liver injury related to other drugs or herbal medicine was ruled out by history. The patient had normal liver enzymes before the diagnosis of thyrotoxicosis making hyperthyroidism
associated cholestasis the more likely cause of her liver abnormalities, but as compared to previously reported cases our patient did not had jaundice or hyperbilirubinemia and she had cholestatic rather than hepatocellular derangement of liver enzymes. Another form of thyrotoxicosis associated cholestasis was reported in association with thyroid storm. The patient did not have family history of hyperlipidemia but her base line serum cholesterol was high. In spite of low fat diet trials and pravastatin she maintained the same level of serum cholesterol during the follow up but the liver enzymes significantly improved after I^131 therapy. Non alcoholic fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH) usually present's with hepatocellular liver enzymes abnormalities (elevated ALT and AST) but NAFLD can sometimes present with cholestasis but ALP and GGT are poor markers for NASH. NAFLD and NASH are likely to be associated with hypothyroidism because of weight gain and hyperlipidemia this may explain the deterioration in the liver enzymes after initial improvement with the evolution from hyperthyroidism to hypothyroidism after I^131 therapy. The learning lesson from this case and from the reviewed literature that liver enzymes abnormality are commonly associated with thyrotoxicosis reassessment of the liver enzymes after achievement of euothyroid status is important to differentiate thyroid associated hepatic derangements from other liver diseases. To conclude, our patient had thyrotoxicosis associated cholestasis and steatosis with high body mass index, she had significant improvement of the liver enzymes after the treatment of thyrotoxicosis. The pattern of hepatic dysfunction changed from cholestatic to hepatocellular picture. Thyrotoxicosis associated cholestasis is a rare disorder with good response to the treatment of thyrotoxicosis. Its pathogenesis and the immunological back grounds are not clear. More data may be needed to understand thyroid associated liver abnormalities.

References

Thyrotoxicosis with steatosis and cholestasis


