Clinical Characteristics of Concomitant Primary Biliary Cirrhosis and Graves’ Disease: A Literature Review

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Abstract

Although, Hashimoto’s thyroiditis (HT) is commonly characterized by extrahepatic manifestation of PBC, the coexistence of primary biliary cirrhosis (PBC) and Graves’ disease (GD) is uncommon. Here, we conducted a review of the English and Japanese literature, including proceedings, regarding the coexistence of PBC and GD. Of 24 reviewed patients, all of who were female, there was no clear tendency of one disease to precede the other. Of two patient deaths, one was due to liver failure as a result of PBC progression.

Keywords: Primary biliary cirrhosis; Graves’ disease; Hyperthyroidism; Thyrotoxicosis; Hashimoto’s thyroiditis

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune liver disease of unknown etiology, although the causes appear to involve both environmental and genetic factors [1,2]. PBC is characterized by chronic progressive cholestasis with destruction of the small intrahepatic bile ducts, particularly the interlobular bile ducts [3-7].

Autoimmune thyroid diseases include Graves’ disease (GD) and Hashimoto’s thyroiditis (HT). HT is one of the most common autoimmune endocrine diseases and is characterized by autoimmune-mediated destruction of the thyroid gland [8]. Moreover, HT is a relatively common extrahepatic manifestation of PBC. However, the coexistence of PBC and GD is comparatively uncommon. Moreover, it is unclear whether patients with concomitant PBC and GD occur by chance or have a common immunological or genetic basis.

To date, there have been few systematic literature reviews of patients with concomitant PBC and GD. Here we performed a literature search and reviewed patients with concomitant PBC and GD.

Methods

We reviewed the English and Japanese literature, including proceedings, to retrieve reports of concomitant PBC and GD since 1980, and summarized the findings of all relevant published reports. A literature search was performed using the following keyword combinations: (1) “primary biliary cirrhosis” and “Graves’ disease (or Basedow’s disease)” and (2) “primary biliary cirrhosis” and “hyperthyroidism (or thyrotoxicosis).” The English literature searches were performed using the PubMed and Embase databases, while the Japanese literature search was conducted using the Japana Centra Revuo Medicina.

For case discussion of concomitant PBC and GD, we excluded non-autoimmune causes of thyrotoxicosis, such as leakage of thyroid hormones or overproduction or release of thyroid hormones from adenomatous goiters.

PBC

PBC is considered an autoimmune disease characterized by chronic progressive cholestasis with destruction of the small intrahepatic bile ducts, particularly the interlobular bile ducts [3-7]. PBC affects middle-aged women more commonly than men (ratio of 9-10:1) [9,10].

The clinical features and natural history of PBC among individual patients significantly vary from asymptomatic to progressive disease [11]. Jaundice, pruritus from cholestasis, and general fatigue are typical symptoms of PBC. However, up to 60% of patients present with no clinical symptoms. Histopathologically, PBC is diagnosed by florid bile duct lesions, such as chronic, nonsuppurative destructive cholangitis, and epithelioid granuloma formation [11].

A diagnosis of PBC is established when two of the three following objective criteria are present [11]: (1) elevated serum alkaline phosphatase levels, (2) presence of antimitochondrial antibodies (AMA), which are useful for serological diagnosis of PBC (90%-95% of patients with PBC are AMA-positive [6]), and (3) liver histology findings.

Prognosis of PBC is often dependent on the development of portal hypertension or cirrhosis, indicating liver failure. Disease progression in some patients can be significantly inhibited by treatment with ursodeoxycholic acid [11,12]. Patients with end-stage liver failure require organ transplant [10].

GD (Basedow’s disease)

GD, also known as Basedow’s disease in Europe, is the most common cause of hyperthyroidism [1,2], with an annual incidence of 14–21 patients per 100,000 individuals [13,14]. Although, individuals can be affected at any age, it is most commonly seen in middle-aged women [14].
GD is caused by circulating anti-thyroid stimulating hormone (TSH) receptor autoantibodies that mimic the action of TSH, thereby resulting in increased synthesis and release of thyroid hormones [13,14]. GD is associated with extrathyroidal manifestations, including orbital disease (ophthalmopathy), skin changes, and rarely, fingertip and nail abnormalities [14]. However, its coexistence with other autoimmune liver diseases, such as PBC, is uncommon.

**GD Complicated With PBC**

Sjögren’s syndrome (SjS) appears to be the most common autoimmune disorder concomitantly present with PBC [15-18]. Similarly, HT, rheumatoid arthritis, systemic sclerosis, and Raynaud syndrome may coexist with PBC [17-19]. Silveria et al. [20] reported that among 67 patients with PBC, 32 (48%) had at least one extrahepatic autoimmune diseases and nine (13.4%) had thyroid dysfunction. However, the incidence of GD in PBC patients was not reported in this study [20].

There have been few reports regarding the incidence of GD or hyperthyroidism in patients with PBC. However, Floreani et al. [19] recently reported that among 361 patients with PBC who were followed-up for a mean period of 8 ± 6.9 years, 221 (61.2%) had at least one extrahepatic autoimmune disease. Further, they only found a significant positive association between female sex and extrahepatic manifestation of autoimmune conditions in PBC, while there were no significant correlations between AMA positivity, histological stage, mean age at diagnosis of PBC, and the presence of extrathyroidal autoimmune disease [19]. They also reported that among 361 patients with PBC, seven (3.2%) had GD and 45 (20.4%) had HT [19].

**Characteristics of Patients with Concomitant PBC and GD**

The characteristics of the 24 reported patients of concomitant PBC and GD, including one English and nine Japanese proceedings, are summarized in Table 1 [21-35]. All 24 patients involved females and, notably, both PBC and GD particularly occurred in middle-aged women. Of 10 patients simultaneously diagnosed with PBC and GD, PBC was diagnosed before GD in seven and GD was diagnosed first in seven of the remaining 14 patients. Hence, there was no clear tendency for one disease to precede the other. Concomitant disease was diagnosed in all patients between the ages of 35 and 64 years. The interval between diagnosis of primary and concomitant disease was 0–10 years and within five years in 19 (82.6%) of 23 patients, while the interval was unclear in one case. Therefore, the interval between the diagnoses of primary and concomitant diseases was relatively short. Among all 24 patients, one was familial GD [28]. The most common complicated disease was SjS, which occurred in four (17%) of 24 patients of concomitant PBC and GD [23,28,30].

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Sex</th>
<th>Age at diagnosis at PBC (Years)</th>
<th>Age at diagnosis at GD (years)</th>
<th>PBC prior to GD</th>
<th>Scheuer’s classification</th>
<th>Complications</th>
<th>Remarks</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1985</td>
<td>F</td>
<td>51</td>
<td>48</td>
<td>-</td>
<td>1 ~ 2</td>
<td>Sjögren’s syndrome</td>
<td>Reversible jaundice</td>
<td>[21]</td>
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<tr>
<td>2</td>
<td>1989</td>
<td>F</td>
<td>48</td>
<td>48</td>
<td>Sim</td>
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<td>[22]</td>
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<tr>
<td>3</td>
<td>1993</td>
<td>F</td>
<td>59</td>
<td>59</td>
<td>Sim</td>
<td>2 ~ 3</td>
<td>Mixed connective tissue disease</td>
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<td>[24]</td>
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<tr>
<td>4</td>
<td>1994</td>
<td>F</td>
<td>54</td>
<td>58</td>
<td>+</td>
<td>1 ~ 2</td>
<td>Sjögren’s syndrome</td>
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<td>[23]</td>
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<tr>
<td>5</td>
<td>1994</td>
<td>F</td>
<td>52</td>
<td>52</td>
<td>Sim</td>
<td>2 ~ 3</td>
<td>Polymyositis</td>
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<td>[25]</td>
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<tr>
<td>6*</td>
<td>1996</td>
<td>F</td>
<td>55</td>
<td>52?</td>
<td>-</td>
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<td></td>
<td>Sepsis → death</td>
<td>[26]</td>
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<td>F</td>
<td>54</td>
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<td>2000</td>
<td>F</td>
<td>55</td>
<td>55</td>
<td>Sim</td>
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<tr>
<td>9</td>
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<td>F</td>
<td>57</td>
<td>64?</td>
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<tr>
<td>10</td>
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<td>F</td>
<td>54</td>
<td>54</td>
<td>Sim</td>
<td></td>
<td></td>
<td>Familial GD case</td>
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<tr>
<td>11</td>
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<td>F</td>
<td>41</td>
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<td>Sim</td>
<td>1</td>
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<td>[31]</td>
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<td>F</td>
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<td>60?</td>
<td>Sim</td>
<td></td>
<td></td>
<td>Pulmonary hemorrhage → death</td>
<td>[32]</td>
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<tr>
<td>13</td>
<td>2007</td>
<td>F</td>
<td>53</td>
<td>59</td>
<td>+</td>
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<td>35</td>
<td>Sim</td>
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</table>
In three (13%) of 24 patients, jaundice was attenuated along with the normalization of thyrotoxicosis [23,33,35]. Although not yet clear, a possible mechanism of progression of jaundice or liver dysfunction after the onset of GD is reportedly hypoxemia due to a relatively decreased liver blood flow from increased oxygen consumption or circulatory disturbance that may be caused by high output heart failure or direct liver damage caused by increased thyroid hormone production [33].

In this cohort, two women died, one due to sepsis on the background of liver failure due to PBC [25] and the other due to pulmonary hemorrhage as a result of suspected vasculitis syndrome. There was no death due to the thyrotoxicosis itself.

**Conclusion**

In this literature review of 24 reported patients of concomitant PBC and GD, all involving females, there was no clear tendency for one disease to precede the other. There was one death from liver failure as a result of PBC. At present, it remains uncertain whether these concomitant diseases occur by chance or reflect a common immunological basis.

**References**


