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Autoimmune Thyroid Diseases Concomitant with Crohn's Disease and Ulcerative Colitis

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Abstract

The coexistence of Crohn's disease (CD) and autoimmune thyroid diseases [Graves' disease (GD) and Hashimoto's thyroiditis (HT)] is uncommon, although these conditions involve autoimmune processes. This report reviews the English and Japanese literature, including proceedings regarding coexisting CD and the autoimmune thyroid diseases GD and HT, and discusses cases of concomitant CD and GD (six cases) and CD and HT (12 cases), compared with reported concomitant cases of ulcerative colitis and GD.

Keywords: Autoimmune thyroid diseases; Graves' disease; Hashimoto's thyroiditis; Crohn's disease; Ulcerative colitis; Inflammatory bowel disease

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two most common forms of inflammatory bowel disease (IBD). Although both are chronic recurrent conditions characterized by intestinal inflammation that results from a complex of environmental, genetic, and immunologic factors [1-3], there are several differences between CD and UC. CD can affect any part of the gastrointestinal tract, whereas UC is characterized by inflammation confined to the large intestine [3]. Microscopically, CD affects the entire bowel wall, whereas UC is restricted to the epithelial lining of the gut. Moreover, CD is characterized histologically by transmural inflammation, presence of granulomas, and endoscopicy typically reveals discontinuous lesions, strictures, and linear ulcerations [3].

Furthermore, extraintestinal manifestations can develop during the course of CD. However, cases of concomitant CD and autoimmune thyroid diseases [Graves' disease (GD) and Hashimoto's thyroiditis (HT)] are uncommon [4]. Moreover, it is unclear whether cases of concomitant autoimmune thyroid diseases and CD occur by chance or have a common immunological basis.

To date, there have been few systematic literature reviews of concomitant CD and these autoimmune thyroid diseases. In this report, we performed a literature search and reviewed the cases of concomitant CD and autoimmune thyroid diseases (GD and HT), comparing our findings with our previous reports of concomitant cases of ulcerative colitis and GD [5].

Methods

We aimed to review the literature available in English and Japanese languages including proceedings in Japanese language, regarding concomitant CD and GD or CD and HT and to summarize the findings of all relevant reports published since 1980. A literature search was performed using the following keyword combinations: (1) Crohn's disease and Graves' disease (or Basedow's disease), (2) Crohn's disease and hyperthyroidism, (3) Crohn's disease and Hashimoto's thyroiditis (or autoimmune thyroiditis), (4) inflammatory bowel disease and Graves' disease (or Basedow's disease), (5) inflammatory bowel disease and hyperthyroidism, and (6) inflammatory bowel disease and Hashimoto's thyroiditis (or autoimmune thyroiditis). The English and Japanese literature searches were performed using PubMed and Japana Centra Revuo Medicina (Igaku Chou Zasshi), respectively.

For the discussion of cases of concomitant GD and CD, we excluded cases in which the cause of thyrotoxicosis was non-autoimmune thyroid disease such as leakage of thyroid hormones, overproduction, or release of thyroid hormones from adenomatous goiters [6]. For the discussion of cases of concomitant GD and HT, we excluded cases in which the cause of hypothyroidism was uncertain.

Autoimmune thyroid diseases

GD, which is known as Basedow's disease in Europe, is the most common cause of hyperthyroidism and one of the most common autoimmune disorders [7,8], with an annual incidence of approximately 14 cases per 100,000 individuals [9]. GD is caused by circulating antibodies [anti-thyroid stimulating hormone (TSH) receptor autoantibodies] that mimic the action of TSH, thereby resulting in an increased synthesis and release of thyroid hormones [9]. Other causes of hyperthyroidism include toxic adenoma, toxic multinodular goiter, and non-thyroid disease [8].

HT, which is also known as autoimmune thyroiditis, is one of the most common autoimmune endocrine diseases, characterized by an autoimmune-mediated destruction of the thyroid gland. HT is sometimes also characterized by an enlarged thyroid and histologically by lymphocytic thyroid infiltration and positive antibody tests for anti-thyroglobulin and/or anti-thyroid peroxidase antibodies [10]. HT is a common cause of hypothyroidism. However, some cases exhibit normal thyroid hormone (including TSH) levels, whereas others exhibit subclinical hypothyroidism in the presence of increased TSH levels. HT can also cause thyrotoxicosis due to destructive (painless) thyroiditis.

Genetic associations between CD and GD

Some studies have assessed possible common genetic factors

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between GD and CD. The role of non-HLA genes such as PTPN22, CTLA4, and CD40 in GD patients has been extensively investigated [11]. Although some studies reported that PTPN22 does not influence the risk of IBD, including CD [12], other studies reported that PTPN22 may influence the risk of developing CD [13,14]. Moreover, some studies reported that CTLA4 may also influence the risk of developing CD [15,16]. Moreover, in a Spanish meta-analysis, the frequency of the minor allele rs1883832T of the CD40 gene was observed to be significantly higher in CD patients than that in control individuals, but it was not significantly higher in UC patients [17].

However, it may be necessary for further investigations to identify common genetic factors in CD and GD. At present, it is uncertain whether concomitant cases of IBD and GD occur due to common genetic backgrounds.

Thyroid enlargement in CD patients

Ultrasonography has been used to assess thyroid volume in CD or UC patients in some studies. Messina et al. [18] reported that statistically significant thyroid enlargement was found in IBD patients compared with control individuals and that it occurred more frequently in CD (70.4%) than in UC (14.3%). Moreover, Bianchi et al. [19] reported that enlargement of the thyroid gland occurred more often in CD patients than in control individuals, although there were no differences between UC patients and control individuals. On the other hand, Neubauer et al. [20] reported that there were no differences in the enlargement of the thyroid between CD patients and control individuals, although enlargement was observed more commonly in UC patients than in control individuals.

Prevalence of thyroid diseases in CD patients

The reported prevalence of hyperthyroidism (or thyrotoxicosis) in UC patients was in the range of 0.62%–3.7% [8,21-25]. Moreover, in several reports [23,25], no significant difference in the prevalence of hyperthyroidism was found between UC patients and the general population, although Järnerot et al. [26] reported that the prevalence of thyrotoxicosis was significantly higher in UC patients compared with control individuals (3.7% vs. 0.8%; $p < 0.01$).

The rate of extraintestinal manifestation of CD is 20%–40%, although there may be geographical differences [27]. However, the rate of GD or HT in CD patients is unknown in detail. In a study by Snook et al. [23], the prevalence of hyperthyroidism and hypothyroidism in CD patients was 0.3% and 0.5%, respectively. In the same study, the prevalence of hyperthyroidism and hypothyroidism in UC patients was 1.5% and 0.9%, respectively, while the prevalence was 0.7% for both hyperthyroidism and hypothyroidism in the control group [23]. In a study by Pooran et al. [28], the prevalence of hypothyroidism was lower in CD patients [3.8% (8/210)] than that in control individuals [8.2% (17/206)], although the prevalence of hyperthyroidism was statistically similar between the groups. Therefore, our review of the literature suggests that there is no clear difference in the prevalence of hyperthyroidism or hypothyroidism between CD patients and the general population.

In a study by Bardella et al. [29], the prevalence of HT in CD and UC patients was 4.4% (4/90) and 2.2% (2/90), respectively. However, over the recent years, cases of concomitant CD and autoimmune thyroid diseases have been only scarcely investigated.

Iodine deficiency or low iodine intake may increase the incidence of non-autoimmune thyroid diseases. CD may sometimes be related to conditions of iodine deficiency [30]. Järnerot et al. [31,32] demonstrated the increasing of the turnover of thyroxine or thyroid ^{131}I uptake in CD patients, suggesting that these may be the cause of iodine deficiency that was not due to impaired iodine absorption. Simi et al. [33] reported an exaggerated response of thyrotropin to exogenous thyrotropin-releasing hormone in 13 patients, who had previous intestinal resection for CD, and in 42 healthy controls. An exaggerated and prolonged response curve was found in eight of the CD patients and one control ($p < 0.01$), while baseline hormone levels were normal in all CD patients [33]. CD is also characterized by malabsorption syndrome [30], and CD may be related to thyroid disorders via iodine malabsorption followed by iodine deficiency. However, to the best of our knowledge, no cases in which autoimmune thyroid diseases were induced by iodine deficiency via malabsorption syndrome complicated by CD have been reported.

Characteristics of cases of concomitant CD and GD

The characteristics of six reported cases (males, n = 2; females, n = 4) of concomitant CD and GD are summarized in Table 1 [4,34,35]. In three of the five cases, excluding one individual with an almost simultaneous diagnosis of CD and GD, CD was diagnosed before the development of GD.

Concomitant disease was diagnosed between the ages of 14 and 48 years, and the interval between the diagnosis of the primary and the concomitant disease was 0–20 years. Two cases required surgery for CD [4]. There were no fatalities due to CD or GD. At least 2/6 cases had a history of familial diseases [4].

Comparison between cases of concomitant CD and GD and cases of concomitant UC and GD

We previously reported a review of cases of concomitant UC and GD [5].

In our report, we identified 16 published cases of concomitant GD and UC (eight in English, and eight in Japanese; proceedings on cases of concomitant GD and UC were excluded). Of the reported 16 cases of concomitant GD and UC identified in this review, six cases (37.5%) occurred in males and 10 cases (62.5%) in females. In nine cases (56.3%) of GD developed before UC, and in one case (6.3%), the two diseases were simultaneously diagnosed. The diagnosis of the concomitant diseases happened between the ages of 18 (or 19)–61 years and the time interval between the diagnosis of the primary and the concomitant disease was 0–20 years [5].

Although the relevance of these findings is limited due to the numbers of cases, there was no clear tendency for one disease to precede the other in both cases of concomitant CD and GD and cases of concomitant UC and GD.

Characteristics of cases of concomitant CD and HT

The characteristics of the 12 reported cases of concomitant CD and HT are summarized in Table 2 [4,36-42]. Of these, three cases (25%) occurred in males and nine (75%) in females. After excluding four cases with an almost simultaneous diagnosis of CD and HT, CD was diagnosed before the development of HT in five of the remaining eight cases. The concomitant disease was diagnosed between the ages of 10 and 55 years, and the interval between the diagnosis of the primary and concomitant disease was 0–27 years. Regarding thyroid function, there were five cases of hypothyroidism [36-38], four cases of thyrotoxicosis due to suspected destructive (or painless) thyroiditis [4,39,40,42]; one case exhibited normal function [36], and two were unclear because the results of thyroid function test (free T3/T4 levels and TSH levels) were

Case	(Year)	Gender	Age at diagnosis of CD (years)	Age at diagnosis of GD (years)	CD prior to GD	Site of lesion (CD)	Thyroid function tests			Remarks	Reference
1*	(1984)	F	48	28	–	colon?	?	?	?		
2*	(1996)	F	20?	31	+	?	<0.05	?	>6		
								→ normalization?			
3*	(1998)	F	32	27 or 28	–	small intestine	0.09	18.4	10.5	Familial CD	
										CD → small bowel resection	
4	(1999)	M	14	14	Sim	colon?	<0.1	?	?		[34]
								→ normalization?			
5	(2004)	M	19 or 20	20	+	ileum ?	0.05	5.6	3.7		[35]
								→ normalization			
6	(2005)	F	22	38	+	small intestine colon	0.017	>20	>12	Familial GD	[4]
								→ normalization		CD → ileotomy	

Table 1: The Characteristics of the Patients with Concomitant Crohn's Disease and Graves' Disease.

Case	(Year)	Gender	Age at diagnosis of CD (years)	Age at diagnosis of HT (years)	CD prior to HT	Site of lesion (CD)	Thyroid function tests (TSH:μU/mL, freeT:pg/mL, freeT4:ng/dL)	Remarks	Reference
1*	(1984)	F	48	48	Sim	colon?	hypothyroidism		
2*	(1987)	F	51	50 or 51	–	small intestine	?	malignant lymphoma	
								(small intestine•thyroid)	
3*	(1988)	M	17	44	+	small intestine colon	hypothyroidism (TSH 5.3)		[36]
							→ normalization		
4	(1988)	F	26	43	+	colon	normal		[36]
5	(1988)	F	43	55	+	small intestine colon	hypothyroidism (TSH 9.6)		[36]
6	(2002)	F	53	46	–	?	?	Sjögren's syndrome	[41]
7	(2005)	F	16	24	+	small intestine colon	thyrotoxicosis (TSH 0.036, freeT3 13.2, freeT4 5.6)		[4]
							→ normalization		
8	(2006)	F	26	26	Sim	colon	hypothyroidism (TSH 3.90, freeT4 1.39)	Turner syndrome	[38]
							→ normalization		
9	(2008)	F	15	15	Sim	colon	thyrotoxicosis (TSH<0.05, free T4 2.7)	beta-thalassemia	[40]
							→ subsequent hypothyroidism		
10	(2012)	F	14	10	–	small intestine	hypothyroidism		[37]
							→ normalization		
11	(2012)	M	10	10	Sim	small intestine colon	thyrotoxicosis(TSH 0.05, freeT4 31.5)	Bardet-Biedl syndrome	[42]
								Primary sclerosing cholangitis	
12	(2013)	M	35?	35?	+	small intestine	thyrotoxicosis?	primary biliary cirrhosis	[39]
							Familial CD	Familial CD	

Table 2: The Characteristics of the Patients with Concomitant Crohn's Disease and Hashimoto's Thyroiditis.

not mentioned in these papers [41]. There were no deaths due to CD or HT. One of the 12 cases represented familial CD

Among the 12 cases, a few remarkable reports noted were as follows: (1) Triantafillidis et al. [39] reported a rare case of a middle-aged male patient who developed primary biliary cirrhosis (PBC) after the diagnoses of CD and HT. In addition, his son was diagnosed with CD of the large intestine, indicating familial CD. To the best of our knowledge, this is the only male case of concomitant CD and HT concurrent with PBC. (2) Noto et al. [38] reported the case of a young female who was diagnosed almost simultaneously with CD and HT; she also had Turner syndrome. In contrast, in the cohort study of 2,459 patients, the risk of concomitant HT and CD was significantly increased in Turner syndrome patients compared with the general population [43]. This suggests that HT and CD might be a manifestation of Turner syndrome. (3) Halac et al. [42] reported a rare case of a young male who was diagnosed almost simultaneously with CD and HT; he also had Bardet-Biedl syndrome and primary sclerosing cholangitis.

Conclusion

We performed a literature search and reviewed six cases of concomitant CD and GD and 12 cases of concomitant CD and HT. At present, there is a limited number of case reports describing

concomitant CD and autoimmune thyroid diseases. It is uncertain whether these concomitant diseases occur by chance or reflect a common immunological basis.

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