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Special Article - Inflammatory Bowel Disease

Coexistence of Inflammatory Bowel Disease and Graves' Disease (Basedow's Disease)

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Abstract

The coexistence of inflammatory bowel disease (IBD) and Graves' disease (GD), also known as Basedow's disease, is uncommon although both conditions involve the autoimmune process. This report reviews the English- and Japanese-language literature, including proceedings, on coexisting IBD [ulcerative colitis (UC) and Crohn's disease (CD)] and GD, and discusses cases of concomitant IBD and GD reported since 1980. Of the 33 cases of concomitant IBD and GD that were identified, 29 cases (87.9%) were UC and GD, and four cases were CD and GD (12.1%). 16 patients with concomitant disease were male (48.5%) and 17 (51.5%) were female. In four cases (12.1%), IBD and GD were diagnosed almost simultaneously. In 13 cases (39.4%) GD was diagnosed before IBD and in 16 cases (48.5%) IBD was diagnosed before GD. The interval between the development of the primary and the concomitant disease ranged from 0 to 37 years. The main treatments for concomitant IBD and GD were pharmacotherapy or surgery, and there were no deaths due to either IBD or GD.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Graves' disease; Basedow's disease; Hyperthyroidism

Abbreviations

CD: Crohn's Disease; GD: Graves' Disease; IBD: Inflammatory Bowel Disease; TSH: Thyroid Stimulating Hormone; UC: Ulcerative Colitis

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of inflammatory bowel disease (IBD). Both are chronic recurrent conditions and are characterized by intestinal inflammation that appears to result from a combination of environmental and immune factors [1,2]. A recent systematic review indicated a prevalence of UC and CD of 319 and 249 per 100,000, respectively, in the US and 322 and 505 per 100,000, respectively, in European countries [1,2]. Approximately 25% IBD patients develop symptoms before 18 years of age. However, diagnosis is often delayed until later in life [1,2].

Graves' disease (GD), also known as Basedow's disease in Europe, is the most common cause of hyperthyroidism [3,4]. It is one of the most common autoimmune disorders, with an annual incidence of approximately 14 per 100,000 [5]. GD is caused by circulating antibodies [anti-thyroid stimulating hormone (TSH) receptor autoantibodies] that mimic the action of TSH, resulting in increased synthesis and release of thyroid hormones [5]. Other causes of hyperthyroidism include toxic adenoma, toxic multinodular goiter, and non-thyroid disease [4].

The development of extra-intestinal manifestations during the course of IBD is well known. Although chronic thyroiditis (Hashimoto's disease) is known to be an extraintestinal manifestation of UC, cases of concomitant UC and GD are uncommon [6-8]. Moreover, cases of concomitant CD and GD are particularly rare [9].

To date, there have been few systematic literature reviews of concomitant IBD and GD or hyperthyroidism. For this report, we performed a literature search and a review of cases of concomitant IBD (UC and CD) and GD.

Methods

We aimed to review the English- and Japanese-language literature, including proceedings, on concomitant IBD and GD, and to summarize the findings in such reports published since 1980. A literature search was performed using following keyword combinations: (1) ulcerative colitis and Graves' disease (or Basedow's disease), (2) ulcerative colitis and hyperthyroidism, (3) Crohn's disease and Graves' disease (or Basedow's disease), (4) Crohn's disease and hyperthyroidism, (5) inflammatory bowel disease and Graves' disease (or Basedow's disease), and (6) inflammatory bowel disease and hyperthyroidism. The English- and Japanese-language literature searches were performed using PubMed and Japana Centra Revuo Medicina (Igaku Chou Zasshi), respectively.

For the discussion of cases of concomitant IBD and GD, we excluded cases in which the cause of thyrotoxicosis was unclear, and cases with non-GD hyperthyroidism, such as those with overproduction or release of thyroid hormones from adenomas [4,6]. Some reports discussed cases of UC induced or aggravated by the administration of rituximab used to treat GD, although it remains unclear whether rituximab can induce UC de novo in a previously healthy bowel [10]. Therefore, we also excluded the suspected rituximab-induced UC cases [11,12] from our concomitant IBD and GD cases.

Immunological association between UC and GD

In general, the pathophysiology of UC is associated with a Th2 cytokine phenotype, and there is also increased Th2 activity in GD [8].

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Table 1a: Characteristics of Patients with Concomitant Ulcerative Colitis and Graves' Disease (1980 ~ 2001).

Case	(Year)	Gender	Age at diagnosis of UC (years)	Age at diagnosis of GD (years)	UC prior to GD	UC type	Remarks	References
1	(1980)	F	46 or 47	46	-	Left-sided colitis?		[16]
2	(1980)	M	18 or 19	18	-	Pancolitis?		[16]
3	(1981)	F	53	53 or 54	+	?	Dermatomyositis	[26]
4	(1984)	M	46	36	-	Pancolitis		[23]
5	(1985)	F	66	46	-	Pancolitis		[27]
6*	(1989)	M	25?	30	+	?	Ankylosing spondylitis	
7*	(1993)	M	50	46?	-	Proctitis ?		
8	(1996)	F	31?	30	-	Left-sided colitis?		[24]
9	(1998)	M	17	24	+	?	Primary sclerosing cholangitis	[21]
10	(1999)	F	32	30	-	?		[25]
11*	(2000)	M	26	21	-	Pancolitis	type 1 diabetes	
12	2001	F	41	41	Sim	?		[14]
13	2001	M	14	26	+	Pancolitis?		[20]
14	2001	F	35	31?	-	Left-sided colitis	Familial GD	[13]
15	2001	M	24	26	+	Pancolitis		[15]
16*	2001	F	55	18	-	?		

UC: ulcerative colitis; GD: Graves' disease; F: female; M: male; Sim: simultaneous

* Japanese proceeding

Table 1b: Characteristics of Patients with Concomitant Ulcerative Colitis and Graves' Disease (2002~2013).

Case	(Year)	Gender	Age at diagnosis of UC (years)	Age at diagnosis of GD (years)	UC prior to GD	UC type	Remarks	References
17*	(2004)	F	37	37	Sim	Left-sided colitis		
18*	(2004)	F	28 or 29	30	+	Pancolitis		
19	(2005)	F	42	47	+	?		[7]
20*	(2005)	M	36	35?	-	Proctitis ?	Familial GD	
21*	(2007)	M	22	24	+	?		
22*	(2007)	M	19	27	+	?		
23*	(2007)	M	26 or 27	30	+	?		
24*	(2007)	M	57	67	+	?	Down syndrome	
25	(2008)	F	61	60	-	?		[17]
26	(2009)	M	22	26	+	Pancolitis	Familial UC	[3]
27*	(2010)	F	13	40	+	?		
28	(2012)	F	38	18	-	?	IgA nephropathy	[22]
29*	(2013)	F	20	20	Sim	?		

UC: ulcerative colitis; GD: Graves' disease; F: female; M: male; Sim: simultaneous

* Japanese proceeding

Therefore, both GD and UC are associated with a Th1/Th2 imbalance, with a dominance of Th2 responses [3,8,9,13,14]. Conversely, CD is associated with a dominance of Th1 responses [9].

However, it has not yet been determined whether GD is an extraintestinal manifestation of UC [7]. In fact, some studies have found no difference in the prevalence of GD or hyperthyroidism between UC patients and the general population. Therefore, it is unclear whether concomitant GD and UC occurs by chance or reflects a common immunological basis [15].

Prevalence of GD in UC patients

The reported prevalence of hyperthyroidism (or thyrotoxicosis) in UC patients was 0.62%–3.7% [4,7,8,16-18]. Conversely, the prevalence of UC in patients with hyperthyroidism was 1.34% [9].

Casella et al. [17] reported that the prevalence of hyperthyroidism in the general population in Italy was 1.05% (60/5721) and 0.62% (1/162) in UC patients. Several reports found no significant difference in the prevalence of hyperthyroidism between UC patients and the general population. However, Järnerot et al. [19] reported that the prevalence of thyrotoxicosis in UC patients was significantly higher compared with the prevalence in controls (3.7% vs. 0.8%; $p < 0.01$).

In summary, a review of the literature suggests that there is no clear difference in the prevalence of hyperthyroidism between UC patients and the general population. However, there have been few studies in recent years specifically investigating concomitant GD and UC.

Table 2: Characteristics of Patients with Concomitant Crohn's Disease and Graves' Disease.

Case	(Year)	Gender	Age at diagnosis of CD (years)	Age at diagnosis of GD (years)	CD prior to GD	Site of lesion (CD)	Remarks	References
1*	(1996)	F	20?	31	+	?		
2	(1999)	M	14	14	Sim	colon?		[28]
3	(2004)	M	19 or 20	20	+	ileum?		[29]
4	(2005)	F	22	38	+	ileocolon?	Familial GD, CD → ileotomy	[9]

CD: Crohn's disease; GD: Graves' disease; F: female; M: male; Sim: simultaneous
*Japanese proceeding

Characteristics of cases of concomitant UC and GD

In total, we identified 29 reported cases of concomitant UC and GD (eight in the English-language references [7,14,16,17,20-22], eight in the Japanese-language references [3,13,15, 23-27], and thirteen in the Japanese-language proceedings). The characteristics of these 29 reported cases of concomitant UC and GD are summarized in Table 1(1a and 1b).

Of the 29 cases of concomitant UC and GD identified, 14(48.3%) were male and 15 (51.7%) were female. In most cases reported in the 1980s and 1990s, GD was diagnosed before the development of UC. However, in cases reported in the 2000s there was no clear tendency in the order of diagnosis. In fact, of the 29 cases reported, in 13 cases (44.8%) UC was diagnosed before GD. In 13 cases (44.8%) GD was diagnosed before UC, and in three cases (10.3%) the two diseases were diagnosed almost simultaneously. The diagnosis of the concomitant disease was made between the ages of 18 (or 19) and 67 years, and the interval between the diagnosis of the primary and the concomitant disease ranged from 0 to 37 years (Table 1a and 1b).

The types of UC in the 29 cases of concomitant GD and UC included eight cases of pancolitis, four of left-sided colitis, and two of suspected proctitis. The type of UC was unclear in 15 cases (Table 1a and 1b). In most cases, UC was treated with medications, such as aminosalicylates and corticosteroids. Only four cases required surgery (colectomy), for persistent colitis despite pharmacotherapy [3,17,20]. There were no reports of severe complications of UC, such as toxic megacolon. There were no reports of death related to concomitant UC and GD and no evidence that patients with concomitant UC and GD had a worse prognosis than those with UC without GD.

Prevalence of GD in CD patients

Thyroid enlargement has been reported in 62%–70% CD patients, with antithyroid antibodies found in 12.5%–14.8% [9]. However, there have been few studies of the prevalence of autoimmune thyroid disease in CD patients. In a study by Snook et al. [18], 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, and 0.7% for both hyperthyroidism and hypothyroidism in the control group (patients with nonautoimmune gastrointestinal disorders) [18].

Characteristics of cases of concomitant CD and GD

The characteristics of four reported cases of concomitant CD and GD are summarized in Table 2 [9,28,29]. Of the four cases of concomitant CD and GD identified in this review, two cases were male and two were female. In three cases CD was diagnosed before the development of GD. The diagnosis of the concomitant disease was made between the ages of 14 and 38 years and the interval between the diagnosis of the primary and the concomitant disease was 0–16 years. Only one case required surgery (ileotomy) for perforation of the ileum, 22 years before the development of GD [9]. There were no deaths due to CD or GD.

Conclusion

We performed a literature search and a review of 33 cases of concomitant IBD (CD and UC) and GD. Of the 33 cases, the majority (87.9%; 29/33) were concomitant cases of UC and GD. There was no clear tendency for one disease to precede the other. In 13 cases GD was diagnosed before IBD and in 16 cases IBD was diagnosed before GD. In four cases the two diseases were diagnosed almost simultaneously. There were no deaths among the 33 cases. Therefore, there is no evidence that patients with concomitant IBD and GD had a worse prognosis than those with only IBD.

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