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Coexistence of Graves' Disease (Basedow's Disease) and Ulcerative Colitis

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Abstract

The coexistence of Graves' disease (GD), also known as Basedow's disease, and ulcerative colitis (UC) is uncommon although both conditions involve the autoimmune process. This report reviews the English- and Japanese-language literature on coexisting hyperthyroidism and UC, and discusses cases of concomitant GD and UC reported since 1980. Of the 16 cases of concomitant GD and UC that were identified, 10 were female (62.5%). In one case (6.3%), GD and UC were simultaneously diagnosed. In nine cases (56.3%) GD developed before UC and in six cases (37.5%) UC developed before GD. The time interval between the development of the primary and the concomitant disease was 0–20 years. Most cases of concomitant GD and UC were treated with pharmacotherapy and there were no deaths reported.

Keywords: Graves' disease; Basedow's disease; Hyperthyroidism; Ulcerative colitis

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of inflammatory bowel disease (IBD). UC is a chronic recurrent condition that is characterized by intestinal inflammation resulting from a complex interaction between environmental and immune factors [1,2]. A recent systematic review revealed that the prevalence of UC in Western and European countries is 90–505 per 100,000 [2]. In Japan, the prevalence of UC has been reported to be low compared with Western and European countries [3].

Autoimmunity is believed to have a role in the pathogenesis of UC, and different autoimmune diseases may coexist in an individual [4]. The development of extraintestinal manifestations during the course of UC is well known. In a controlled study by Snook et al. [5], 6.6% UC patients had at least one autoimmune disorder, compared with 2.0% patients in the control group and 1.9% CD patients. If primary sclerosing cholangitis (PSC) was considered as an autoimmune disorder, the percentage of patients with at least one disorder increased to 9.4% UC patients and to 2.6% CD patients [5]. Other diseases that may occur as extraintestinal manifestations in patients with UC include arthropathies, skin diseases (erythema nodosum), eye disorders (uveitis), spondyloarthritis, and osteoporosis [2,6].

Although autoimmune thyroid diseases, such as chronic thyroiditis (Hashimoto's disease), are known to be extraintestinal manifestations of UC [7-9], cases of concomitant hyperthyroidism and UC are uncommon. Graves' disease (GD), also known as Basedow's disease in Europe, is the most common cause of hyperthyroidism [3,10]. 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. Other causes of hyperthyroidism include toxic multinodular goiter, and nonthyroid disease [10].

To date, there are few systematic literature reviews of concomitant UC with GD or hyperthyroidism. For this report, we conducted a literature search and a review of cases of concomitant UC and GD (Basedow's disease).

Methods

We aimed to review the English- and Japanese-language literature on concomitant hyperthyroidism and UC, and to summarize the findings in case reports of concomitant of GD and UC published since 1980. A literature search was performed using 4 keyword combinations: (1) Graves' disease and ulcerative colitis, (2) Basedow's disease and ulcerative colitis, (3) hyperthyroidism and ulcerative colitis, and (4) thyrotoxicosis and ulcerative colitis. 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 GD and UC, we excluded cases in which the cause of thyrotoxicosis was leakage of thyroid hormones, overproduction or release of thyroid hormones from adenomas [10], excessive supplementation of thyroid hormones [9,10], or nonthyroid diseases.

Some reports discussed cases of UC induced or aggravated by the administration of rituximab, although it remains unclear whether rituximab can induce UC de novo in a previously healthy bowel [11]. Rituximab is a chimeric monoclonal antibody directed against the surface CD20 antigen on B cells, and rituximab therapy is sometimes indicated for GD. Therefore, we also excluded the suspected rituximab-induced UC cases [12,13] from our discussion.

Common immunological or genetic pathogenesis in UC and GD

One of the accepted hypotheses for the pathogenesis of UC (IBD) is that the mucosal immune system exhibits an aberrant response towards luminal antigens such as commensal bacteria [4,14]. For example, a chronic low-grade portal infection caused by UC, which leads to chronic biliary tract inflammation and fibrosis, has been

suggested as a pathogenic mechanism [15]. However, because the colon and the thyroid do not have the same embryological origin, the same trigger antibodies may not be the cause of the association between GD and UC [8,16].

In many autoimmune diseases, including UC and GD, the CD8+ T-cell count in the peripheral blood is decreased and that the CD4/CD8 ratio is increased [17]. Moreover, the pathophysiology of UC is strongly associated with a Th2 cytokine phenotype, and there is also increased Th2 activity in GD [8]. Therefore, both GD and UC are associated with a Th1/Th2 imbalance, with a dominance of Th2 responses [3,8,16,18,19]. However, this immunological imbalance also occurs in many other autoimmune conditions [17]. Therefore, it has not yet been determined whether UC and GD develop through a common immunological basis [7].

There has been some research on possible common genetic factors in GD and UC. The role of non-HLA genes (including the lymphoid protein tyrosine phosphatase gene (PTPN22), CTLA4, CD40, TSHR, and TG) in GD has been extensively investigated [20,21]. A single-nucleotide polymorphism (C1858T) causing an amino acid substitution (R620W) in PTPN22 has been implicated in GD, as well as in rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes mellitus [21,22]. PTPN22 is an important regulator of T-cell receptor signaling in memory and effector T cells, and polymorphisms in the PTPN22 gene might alter T-cell receptor signaling and T-cell activation [21]. In a British study, Prescott et al. [22] found no significant differences in genotype or allele frequencies between patients with UC and controls, suggesting that PTPN22 did not influence the risk of IBD in that population. Moreover, a meta-analysis conducted in China found a negligible association between PTPN22 C1858T and IBD including UC [23]. Conversely, a functional polymorphism located at the CD40 gene, rs1883832, has been consistently associated with GD in a number of studies [20,24]. A Spanish meta-analysis found that the frequency of minor allele rs1883832T was not significantly higher in UC patients than in controls, but it was significantly higher in CD patients than in controls [24].

It is not yet clear whether GD and UC share a common immunological or genetic basis, or whether GD is a true extraintestinal manifestation of UC [7]. In fact, some studies have found no differences in the prevalence of GD or hyperthyroidism between UC patients and the general population. Therefore, it is possible that GD and UC develop in the same individual purely by chance. However, further research is needed to determine whether concomitant GD and UC is indeed a chance occurrence or is the reflection of a common immunological or genetic basis [1].

Prevalence of concomitant thyroid disorders in UC patients

The studies identified by the literature search indicated a prevalence of thyroid dysfunction (hypo- or hyperthyroidism) in the general population, including the population in iodine-deficient countries, of 2%–8% [25].

Some studies reported a similar prevalence of thyroid dysfunction in UC patients (2.2%–8.0%) [1,25-28]. In a study conducted in Italy, Casella et al. [25] found that the prevalence of thyroid dysfunction in the general population was 7.5% (429/5721), which is significantly higher than the prevalence in UC patients (2.5%; 4/162). In Japan, the prevalence of chronic thyroiditis in UC patients was reported as 0.14% (8/5833) in the 1980s and as 0.07% (1/1433) in the 1990s [1,28]. Conversely, some population studies demonstrated a 2- to 4-fold increase in the prevalence of thyroid disorders in patients with UC, compared with the general population [16,29].

Prevalence of concomitant hyperthyroidism and UC

The most common causes of hyperthyroidism (or thyrotoxicosis) are GD, excessive supplementation of thyroid hormones, toxic adenoma, and toxic multinodular goiter, as well as nonthyroid disease [9,10]. The reported prevalence of hyperthyroidism (or thyrotoxicosis) in UC patients was 0.62%–3.7% [8,7,10,25,30]. Conversely, the prevalence of UC in patients with hyperthyroidism was 1.34% [19].

Casella et al. [25] 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. In a study by Snook et al. [5], the prevalence of hyperthyroidism and hypothyroidism in UC patients was 1.5% and 0.9%, respectively. In the same study the prevalence of hyperthyroidism and hypothyroidism in CD patients was 0.3% and 0.5%, respectively, and 0.7% for both hyperthyroidism and hypothyroidism in the control group (patients with nonautoimmune gastrointestinal disorders) [5]. Based on the findings of their study, Snook et al. [5] suggested that the development of autoimmune disorders, including thyroid disorders, did not show a clear temporal relationship with the onset or activity of IBD, with the exception of concomitant cases of autoimmune hemolytic anemia in UC patients.

In studies conducted in Japan, the prevalence of chronic thyroiditis in UC patients was reported as 0.14% in the 1980s and as 0.07% in the 1990s [1,28]. However, there were no reports on the prevalence of hyperthyroidism in UC patients in Japan [1,28]. Several reports found no significant difference in the prevalence of hyperthyroidism between UC patients and the general population. However, Järnerot et al. [31] reported that the prevalence of thyrotoxicosis in UC patients was significantly higher compared with that in controls (3.7% vs. 0.8%; $p<0.01$).

In summary, a review of the literature suggests that there is no significant 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.

Characteristics of cases of concomitant GD and UC

According to Casella et al. [25], the first report of concomitant hyperthyroidism and UC was in 1968. We identified 27 reported cases of concomitant thyrotoxicosis and UC in English- and Japanese-language reports published since 1980 [1,3,7-10,16,18,25-30,32-39]. We excluded cases of concomitant UC and thyrotoxicosis caused by excessive supplementation of thyroxine after subtotal thyroidectomy for toxic adenoma, toxic multinodular goiter, or unknown causes. In total, we identified 16 reported cases of concomitant GD and UC (eight in the English language [7,16,25,29,30,34,36] and eight in the Japanese language [1,3,18,26-28,37,38]). The characteristics of these 16 reported cases of concomitant GD and UC are summarized in Table 1. Hyperthyroidism is more common in females than in males, with a female-to-male ratio of 10:1 [3,40]. In contrast, UC is not a sex-specific disease; the female-to-male ratio for UC ranges from 0.51 to 1.58 [2]. Of the 16 cases of concomitant GD and UC identified in this review, 6/16cases (37.5%) were male and 10/16 (62.5%) were female (Table 1).

In most cases of concomitant GD and UC reported in the 1980s and 1990s, GD was diagnosed prior to 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 16 cases reported since 1980, in six cases (37.5%) UC developed before GD. In nine cases (56.3%) GD developed before UC, and in one cases (6.3%) the two diseases were simultaneously diagnosed (Table 1). The diagnosis of the concomitant disease was 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 (Table 1).

Case	Gender	Age at diagnosis of GD (years)	Age at diagnosis of UC (years)	GD prior to UC	UC type	Remarks	References (year)
1	F	46	46 or 47	+	Left-sided colitis?		[30] (1980)
2	M	18	18 or 19	+	Pancolitis?		[30] (1980)
3	F	53 or 54	53	-	?	Dermatomyositis	[37] (1981)
4	M	36	46	+	Pancolitis		[26] (1984)
5	F	46	66	+	Pancolitis		[38] (1985)
6	F	30	31?	+	Left-sided colitis	Primary sclerosing cholangitis	[27] (1996)
7	M	24	17	-	?		[34] (1998)
8	F	30	32	+	?		[28] (1999)
9	F	41	41	Sim	?		[16] (2001)
10	M	26	14	-	Pancolitis?		[29] (2001)
11	F	31?	35	+	Left-sided colitis	Familial GD	[18] (2001)
12	M	26	24	-	Pancolitis		[1] (2001)
13	F	47	42	-	?		[7] (2005)
14	F	60	61	+	?		[25] (2008)
15	M	26	22	-	Pancolitis	Familial UC	[3] (2009)
16	F	18	38	+	?	IgA nephropathy	[36] (2012)

Table 1: Characteristics of 16 Patients with Concomitant Graves' Disease and Ulcerative Colitis. UC: ulcerative colitis; GD: Graves' disease; F: Female; M: Male; Sim: Simultaneous

Clinical features of cases of concomitant GD and UC

The types of UC in the 16 cases of concomitant GD and UC included six cases of pancolitis and three cases of left-sided colitis. There were no cases of proctitis and the type of UC was unclear in seven cases (Table 1). There were no reports of a flare-up of UC soon after the onset of GD. In most cases of concomitant GD and UC, UC was treated with medications such as aminosalicylates and corticosteroids. Only three cases required surgery (colectomy), for persistent colitis despite pharmacotherapy [3,25,29]. There were no reports of severe complications of UC such as toxic megacolon. In most cases, GD was treated with antithyroid agents and only one case required surgery (subtotal thyroidectomy) [7]. There were no reports of death related to concomitant GD and UC and no evidence that patients with concomitant GD and UC had a poor prognosis compared with those with UC without GD.

Diarrhea is a common manifestation of both GD and UC. Therefore, concomitant GD should be considered in patients with UC with persistent diarrhea, despite otherwise well-controlled diseases [29].

Case reports of concomitant GD and UC

Of the 16 reports on cases of concomitant GD and UC, some were of particular interest. (1) Oshitani et al. [37] reported the case of a 53 year old female who developed UC, GD, and dermatomyositis within a 9 month period. (2) Janssen et al. [34] reported the case of a 24 year old male who developed GD 5 years after the diagnosis of PSC and 7 years after the diagnosis of UC. (3) Ku et al. [36] reported the case of a 38 year old female who developed GD and focal proliferative glomerulonephritis secondary to IgA nephropathy 20 years after the diagnosis of UC. (4) Terashima et al. [18] reported the case of a 35 year old Japanese female who developed UC 4 years after the diagnosis of GD. In addition, her brother was diagnosed with GD, indicating a case of familial GD. (5) Kohyama et al. [3] reported the case of a 26 year old Japanese male who developed GD 4 years after of the diagnosis of UC. In addition, his mother and cousin were diagnosed with UC, indicating a case of familial UC.

In another case worth noting (although it was not included in the 16 cases of concomitant GD and UC because it was not proven that the cause of hyperthyroidism was GD), Matsumura et al. [8] reported a 26 year old female with a flare-up of UC and hyperthyroidism that was

successfully treated with infliximab. In addition, they reported that the Th1/Th2 imbalance was improved 2 weeks after infliximab therapy. In most cases of GD developing in patients with preexisting UC, GD did not cause a flare-up of UC.

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