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Coexistence of Inflammatory Bowel Disease and Graves' Disease

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Abstract

The coexistence of Graves' disease (GD) and inflammatory bowel disease (IBD), particularly Crohn's disease (CD) and ulcerative colitis (UC), has not been well documented. Therefore, this report reviews the literature regarding coexisting IBD and GD. Reported cases of concomitant IBD and GD are rare; 16 cases of concomitant UC and GD and 3 cases of concomitant CD and GD were found. Among the 19 reported cases of concomitant IBD and GD, IBD developed before GD in 8 (42.1%) cases, GD developed before IBD in 9 (47.4%) cases, and both conditions coexisted in 2 (10.5%) cases. Therefore, there was no evidence for a tendency of a preceding disease between IBD and GD. The interval between diagnoses of IBD and GD varied from 0 year to 20 years. Furthermore, there was no evidence indicating that patients with concomitant IBD and GD had poorer prognoses than those with IBD but without GD.

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

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of inflammatory bowel disease (IBD). IBD is characterized by chronic recurrent conditions and intestinal inflammation. IBD is estimated to be a multifactorial disease that may result from a number of causes such as genetic and environmental factors, microbiota, and immunological factors [1,2]. Crohn's disease can affect any portion of the gastrointestinal tract, whereas UC is characterized by inflammation that is confined to the large intestine [1]. Microscopically, CD affects the entire bowel wall, whereas UC is restricted to the epithelial lining of the gut [1]. The development of extraintestinal manifestations or coexistence of autoimmune disorders during the course of IBD is well known; however, the coexistence of IBD and autoimmune thyroid diseases, such as Graves' disease (GD), has not been well documented. Here we summarize the reported cases of concomitant IBD (UC or CD) and GD.

Prevalence of Concomitant Hyperthyroidism in Inflammatory Bowel Disease

The reported prevalence of hyperthyroidism in patients with UC was 0.62%-3.7% [3-9]. Although Järnerot et al. [9] reported that the prevalence of hyperthyroidism in patients with UC was significantly higher than that in healthy controls (3.7% vs. 0.8%; $p<0.01$), other studies have found no difference in the prevalence of hyperthyroidism between patients with UC and the general population [5]. However, the prevalence of UC in patients with hyperthyroidism was 1.34% [10].

Few studies have investigated the prevalence of thyroid dysfunction in patients with CD. In a study by Snook et al. [4], the prevalence of hyperthyroidism in patients with CD was 0.3%. In a study by Yakut et al. [11], the prevalence of hyperthyroidism in patients with CD was 0% (0/33), although this study included a limited number of patients.

The prevalence of hyperthyroidism in IBD has been investigated; however, the prevalence of GD in patients with IBD has not been well documented, despite the fact that the most common cause of hyperthyroidism is GD [3,12,13].

Graves' Disease

GD, termed Basedow's disease in Europe, is one of the most common autoimmune disorders, with an annual incidence of approximately 14 per 100,000 individuals [14]. Approximately 3% of women and 0.5% of men develop GD during their lifetime [13]. It is a polygenic and multifactorial disease that develops because of a complex interplay between genetic susceptibility and environmental and endogenous factors [15]. GD is caused by circulating antibodies (antithyroid stimulating hormone receptor autoantibodies) that mimic the actions of thyroid stimulating hormone, resulting in the increased synthesis and release of thyroid hormones [14].

Characteristics of Cases of Concomitant Ulcerative Colitis and Graves 'Disease

Cases of concomitant UC and hyperthyroidism, such as GD, are rare [6,7,16]. In general, the pathophysiology of UC is associated with the Th2 cytokine phenotype, and there is increased Th2 activity in GD [6]. Therefore, GD and UC are associated with a Th1/Th2 imbalance, with a dominance of Th2 responses [6,10,12,17,18]. However, it is unclear whether GD is an extra intestinal manifestation of UC [7]; therefore, it is unclear whether concomitant GD and UC occur by chance or reflect a common immunological basis [19].

In total, 16 cases of concomitant UC and GD [5,7,8,12,17-27] have been reported in the English and Japanese literature since 1980 (Table 1). Hyperthyroidism is more common in females than in males, with a female-to-male ratio of 10:1 [12]. In contrast, UC is not a sex-specific disease [28]. However, of the 16 previously reported cases of concomitant GD and UC, 6 (37.5%) were male and 10 (62.5%) were female. UC developed before GD in 6 (37.5%) cases, GD developed

before UC in 9 (56.3%) cases, and both conditions coexisted in 1 (6.3%) case. The diagnoses of the concomitant diseases occurred between the ages of 18 years and 61 years, and the intervals between diagnosis of the primary and concomitant diseases were 0–20 years. Three cases of concomitant UC and GD were complicated by other autoimmune diseases, with one case each for dermatomyositis, primary sclerosing cholangitis, and IgA nephropathy.

Case	Sex	Type of IBD	Interval between the diagnosis of the primary and concomitant disease (years)	IBD prior to GD	Remarks	Reference
1	F	UC	0-1	-	-	[8]
2	M	UC	0-1	-	-	[8]
3	F	UC	1	+	dermatomyositis	[26]
4	M	UC	10	-	-	[23]
5	F	UC	20	-	-	[27]
6	F	UC	0-1	-	-	[24]
7	M	UC	7	+	primary sclerosing cholangitis	[21]
8	F	UC	2	-	-	[25]
9	F	UC	0	Sim	-	[17]
10	M	UC	12	+	-	[20]
11	F	UC	4	-	familial GD	[18]
12	M	UC	2	+	-	[19]
13	F	UC	5	+	-	[7]
14	F	UC	1	-	-	[5]
15	M	UC	4	+	familial UC	[12]
16	F	UC	20	-	IgA nephropathy	[22]
17	M	CD	0	Sim	-	[29]
18	M	CD	0-1	+	-	[30]
19	F	CD	16	+	familial GD	[10]
UC: Ulcerative Colitis; CD: Crohn's Disease; GD: Graves' Disease; F: Female; M: Male; Sim: Simultaneous						

Table 1: Characteristics of the patients with concomitant inflammatory bowel disease and Graves' disease.

In most cases in which GD developed in patients with pre-existing UC, GD did not cause UC flare-up. One patient had familial UC [12] and another had familial GD [18]. However, genetic or immunological backgrounds were not investigated in the reported case studies regarding concomitant UC and GD. In most cases of concomitant UC and GD, UC was treated with pharmacotherapy, such as amino salicylates and corticosteroids. Only three of these cases required surgery (colectomy) for persistent colitis, despite pharmacotherapy [5,12,20]. In most cases, GD was treated with antithyroid agents and only one case required surgery (subtotal thyroidectomy) [7]. No deaths were reported with regard to concomitant UC and GD, and no patient with concomitant UC and GD had a poorer prognosis than those with UC but without GD.

There was no tendency of either UC or GD to be the preceding disease, and moreover, there may be no clear correlations between GD development and UC flare-up. There is no indication that patients with concomitant UC and GD have poorer prognoses than those with UC but without GD.

Characteristics of Cases of Concomitant Crohn's Disease and Graves'Disease

Three cases of concomitant CD and GD have been reported in the English and Japanese literature since 1980 [10,29,30]. The characteristics of the three reported cases are shown in Table 1; two patients were male and one was female. In two cases, CD was diagnosed before the GD development, whereas CD and GD were simultaneously diagnosed in the remaining case. The intervals between the diagnosis of CD and GD were 0–16 years. Only one case required surgery (ileotomy) for perforation of the ileum, which had occurred 22 years before GD development [10]. However, genetic or immunological backgrounds were not investigated in the reported case studies. In one case of concomitant CD and GD, the onset of GD and

exacerbation of CD were approximately coincidental [30]. One patient had familial GD [10]. There were no deaths because of CD or GD.

Conclusions

A total of 19 previous case reports of concomitant IBD and GD (16 with UC and GD, 3 with CD and GD) were identified and summarized. Some previous studies have reported that the prevalence of hyperthyroidism in IBD may not be significantly higher than that observed in the general populations. To date, it is uncertain whether concomitant IBD and GD are caused by common immunological or genetic backgrounds or if these cases occur by chance. This is partially because common immunological or genetic backgrounds have not been well documented in previously reported case studies. Therefore, GD cannot currently be considered as an obvious complication in patients with IBD. However, additional data are required to clarify these conditions.

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