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Research Article

Coexistence of Crohn's Disease and Autoimmune Hemolytic Anemia

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Abstract

Coexistence of Crohn's Disease (CD) and Autoimmune Hemolytic Anemia (AIHA) is uncommon, whereas concomitant cases of Ulcerative Colitis (UC) and AIHA have been relatively well-documented. This report reviews the English literature regarding the coexistence of CD and AIHA and discusses seven cases of concomitant CD and AIHA. The seven cases were predominantly male. There was no clear tendency of one disease preceding the other. Other complicating autoimmune diseases included Primary Sclerosing Cholangitis (PSC), which occurred in two of the seven cases.

Keywords: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Autoimmune hemolytic anemia; Hemolytic anemia

Abbreviations

AIHA: Autoimmune Hemolytic Anemia; CAD: Cold Agglutinin Disease; CD: Crohn's Disease; CMC: Colonic Mononuclear Cells; DAT: Direct Antiglobulin Test; IBD: Inflammatory Bowel Disease; Ig: Immunoglobulin; ITP: Immune Thrombocytopenic Purpura; PCH: Paroxysmal Cold Hemoglobinuria; PSC: Primary Sclerosing Cholangitis; RBC: Red Blood Cell; SCID: Severe Combined Immunodeficient; UC: Ulcerative Colitis

Introduction

Crohn's Disease (CD) and Ulcerative Colitis (UC) are the two most common Inflammatory Bowel Diseases (IBD). Both are chronic and recurrent conditions, characterized by intestinal inflammation that is a result of environmental, genetic, and immunological factors [1-3]. CD may affect any part of the gastrointestinal tract, and it involves the entire bowel wall. CD is histologically characterized by transmural inflammation and the presence of granulomas; endoscopy typically reveals discontinuous lesions, strictures, and linear ulcerations [3]. Moreover, the incidence of CD has increased overall in Europe from 1.0/100,000 person-years in 1962 to 6.3/100,000 person-years in 2010 [4]. Furthermore, extraintestinal manifestations such as autoimmune disease may develop during the course of CD. Besides affecting the gastrointestinal tract, a variety of extraintestinal manifestations have been recognized in 20%–40% of patients with CD [5].

Autoimmune Hemolytic Anemia (AIHA) is caused by hemolysis that is induced by the reaction of autoantibodies with Red Blood Cells (RBCs) [6-9]. Concomitant cases of CD and AIHA are rare, whereas concomitant cases of UC and AIHA have been relatively well-documented. Moreover, it is unclear whether cases of concomitant CD and AIHA occur incidentally or have a shared genetic or immunological basis.

To date, there have been few systematic literature reviews on concomitant CD and AIHA. In this report, we performed a literature search and reviewed cases of concomitant CD and AIHA.

Methods

We aimed to review the English and Japanese literature available in regarding concomitant CD and AIHA and 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 autoimmune hemolytic anemia, (2) Crohn's disease and Evans syndrome, and (3) inflammatory bowel disease and autoimmune hemolytic anemia. Literature searches were performed using PubMed and Japana Centra Revuo Medicina (IgakuChuoZasshi), respectively.

AIHA

AIHA is caused by hemolysis induced by a reaction between autoantibodies and RBCs [6-9]. Events that lead to AIHA include extravascular hemolysis caused by phagocytosis of erythrocyte-bound IgG in the spleen (hemolytic mechanism), activation of polyclonal B cells, reactions induced by molecular mimicry of exogenous antigens, breakdown of immune tolerance, and abnormal cytokine expression (autoimmune mechanism) [6-8]. The peak incidence of AIHA is seen in patients of 60–70 years of age with a male to female ratio of 40:60 [9]. The annual incidence of AIHA is approximately 1–3 per 100,000 [9,10].

Based on the optimum temperature of autoantibody reactivity, AIHA is categorized as cold [Cold Agglutinin Disease (CAD) or Paroxysmal Cold Hemoglobinuria (PCH)], mixed, or warm type [6-10]. The latter is most common and is frequently Direct Antiglobulin Test (DAT) (or Coombs test)-positive. Warm AIHA is considered partially DAT-negative, and DAT-negative AIHA occurs in 2%–4% of the cases [9]. Kamesaki et al. [11] reported that patients with DAT-negative AIHA respond equally well to corticosteroids therapy and have comparable 1-year survival rates compared with patients with DAT-positive AIHA. AIHA is also classified as being either primary (idiopathic) or secondary, and approximately half of the AIHA cases are considered idiopathic [12]. Secondary AIHA is induced by medicines (e.g., methyldopa and penicillin), lymphoproliferative diseases, autoimmune diseases, infectious diseases, or vaccine administration [6-8].

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

Case (Year)	Gender	Age at diagnosis of CD (years)	Age at diagnosis of AIHA (years)	CD prior to AIHA	Site of lesion (CD)	Type of AIHA	DAT	Complications	Treatment of AIHA	Reference
1 (1993)	M	41	34	–	colon?	warm	positive	PSC	Corticosteroids, splenectomy	[13]
2 (2002)	M	9	11	+	ileum colon	warm	positive		Corticosteroids	[12]
3 (2004)	M	44	44	Sim	ileum	warm	positive		Corticosteroids	[14]
4 (2005)	M	29?	29	+	ileum colon	warm	positive		Corticosteroids, immunoglobulin	[15]
5 (2009)	M?	21	21 or 22	+	ileum colon	warm	positive	PSC	Corticosteroids	[16]
6 (2009)	M	57	?	–	ileum colon	warm	positive		Corticosteroids	[17]
7 (2014)	F	37	41	+	ileum	warm	negative		Corticosteroids	[5]

CD: Crohn's Disease; AIHA: Autoimmune Hemolytic Anemia; DAT: Direct Antiglobulin Test; M: Male; F: Female; Sim: Simultaneous; PSC: Primary Sclerosing Cholangitis.

Symptoms associated with AIHA include primarily symptoms caused by the anemia itself, but also symptoms such as e.g., jaundice, and fever [9,10]. The diagnosis of warm AIHA is generally based on the following findings: 1) presence of hemolysis and anemia, 2) exception of other causes of hemolysis, and 3) serological findings of DAT and elevated reticulocyte count [10]. Administration of corticosteroids is the mainstay of treatment for warm AIHA with a two-third response rate [9,10]; however, relapse is common. Second-line treatment includes splenectomy, rituximab (the anti-CD20 monoclonal antibody), danazol, intravenous immunoglobulin (Ig), and plasmapheresis [9,10].

AIHA in IBD patients

One-third of IBD patients have recurrent anemia [5]. The types of anemia in CD include iron deficiency and anemia of chronic disease, vitamin B12 deficiency, folic acid deficiency, and therapeutic agents for CD such as sulfasalazine and methotrexate [5]. However, complications of hemolytic anemia in CD patients are rare. Case reports on AIHA [5,12-17], drug-induced hemolytic anemia [18], and hemolytic-uremic syndrome [19,20] in patients with CD have been sporadically reported.

Moreover, concomitant cases of AIHA and CD are rare, and the prevalence of AIHA in CD patients remains unclear. On the other hand, it has been reported that AIHA can be found in 0.2%–1.7% of UC patients [12,14,15,17,21,22].

In a study by Lakatos et al. [23], the prevalence of AIHA in UC patients was 0.65% (4/619) (average disease duration, 11.2 years), while the prevalence in patients with CD was 0% (0/254) (average disease duration, 9.2 years). Similarly, in a study by Snook et al. [22], the prevalence of AIHA in UC patients was 0.47% (4/858), while the prevalence in patients with CD was 0% (0/378).

Suspected etiology of AIHA in IBD patients

The exact mechanisms underlying the development of AIHA in IBD are poorly understood, and it is uncertain whether some patients with concomitant IBD and AIHA may have shared genetic susceptibility and/or immunological background favoring the development of these diseases.

Yates et al. [24] reported regarding the characteristics of Colonic Mononuclear Cells (CMC) of a patient with UC and AIHA. CMC produced Ig when transferred to Severe Combined Immunodeficient (SCID) mice, and CMC transferred to SCID mice were able to produce IgG with anti-RBC activity. On the other hand, mononuclear cells extracted from draining lymph nodes, peripheral blood and spleen in transfected SCID mice were able to produce IgG, but no anti-RBC activity was demonstrable. The authors suggested that these results concur with clinical observations suggesting that the colon is the source of RBC autoantibodies in these patients [24]. Moreover, although the autoantibodies that develop in the colon in UC do not cross-react with RBCs, the most popular hypothesis with regard to the pathogenesis of AIHA in UC patients is that the absorption of non-RBC antigens through the diseased bowel causes the development of antibodies with cross-reactivity to the patient's RBCs, resulting in AIHA [17,21,25]. These suspected mechanisms may concur with the observations that in many cases of concomitant UC and AIHA, AIHA develops during or after the onset of colitis. Moreover, a systematic review by Chandra et al. [26] suggested that in many cases of concomitant UC and Immune Thrombocytopenic Purpura (ITP), ITP also occurs during or after the onset of colitis, and the proposed pathogenesis is antigenic mimicry associated with luminal antigen and platelet surface antigen.

However, AIHA may occur several years before the diagnosis of IBD (both UC and CD) [13,17] and AIHA rarely presents years after surgery for IBD [12,26], although extraintestinal manifestations went into remission after surgery such as colectomy, in some IBD patients [27].

Therefore, it is unclear whether cases of concomitant CD and AIHA occur by chance or by distinct mechanisms.

Characteristics of cases of concomitant CD and AIHA

The characteristics of the seven cases of concomitant CD and AIHA reported in the scientific literature in English are summarized in Table 1 [5,12-17]. To our knowledge, no literature or proceedings with regard to concomitant CD and AIHA available in Japanese have been reported. Among reported concomitant cases, six cases were male and one female. After excluding one case with an almost simultaneous diagnosis of CD and AIHA, CD was diagnosed before the development of AIHA in four of the remaining six cases. The concomitant disease was diagnosed between the ages of 11 and 57 years, and the interval between the diagnosis of the primary and concomitant disease was 0–7 years. All cases of concomitant CD and AIHA were categorized as warm type AIHA, and there were no cases of CAD, PCH, or mixed type. Six cases had DAT-positive AIHA; one had Coombs test-negative AIHA [5].

There was no clear correlation between AIHA and CD activity, although the number of case reports were limited. In two of the seven

cases, Primary Sclerosing Cholangitis (PSC) was a complicating autoimmune disease [13,16], although PSC is known to be associated more with UC rather than CD. There were no cases of concomitant CD and Evans syndrome, which is diagnosed by the simultaneous presence of AIHA, detected using a DAT, or ITP.

Pharmacotherapies for AIHA in concomitant cases of IBD and AIHA generally include administration of immunosuppressive drugs such as corticosteroids alone or in combination with azathioprine [21]. It is controversial whether splenectomy may be preferred in these concomitant cases [14,21,24]. In the seven reported cases of concomitant CD and AIHA, corticosteroids were administered, and one case underwent splenectomy for AIHA [13] in addition to corticosteroid treatment. On the other hand, another case underwent colectomy as treatment for CD [15]. There were no deaths due to CD or AIHA.

Conclusion

We performed a literature search and reviewed seven cases of concomitant CD and AIHA. Although there are a limited number of case reports describing concomitant CD and AIHA at present, we noticed that males were predominantly affected. There was no clear tendency of one disease preceding the other, and there was no clear correlation between the occurrence of AIHA and CD activity. It is uncertain whether these concomitant diseases occur incidentally or reflect a shared genetic or immunological basis. Further investigations are required to understand the potential relationship between these concomitant conditions.

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