Concomitant Immune Thrombocytopenic Purpura and Crohn’s Disease

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Abstract

The coexistence of immune (idiopathic) thrombocytopenic purpura (ITP) and Crohn’s disease (CD) is rare. We performed a review of cases of concomitant ITP and CD in the English and Japanese literature. Among 17 identified cases of concomitant ITP and CD, ITP was initially diagnosed in four cases and CD was initially diagnosed first in six cases. Simultaneous diagnoses were reported in the remaining seven cases. No fatalities were reported in any of the 17 cases. However, resistance or transient responses to standard therapies, such as glucocorticoids or intravenous immunoglobulin (IVIG), and splenectomy for the treatment of ITP were reported in a number of concomitant cases. Moreover, the administration of anti-tumor necrosis factor (TNF)-alpha antibodies was a commonly considered pharmacological therapy in cases of concomitant ITP and CD.

Keywords: Immune thrombocytopenic purpura; Idiopathic thrombocytopenic purpura; Thrombocytopenia; Crohn’s disease; Inflammatory bowel disease

Introduction

Crohn’s disease (CD) and ulcerative colitis (UC) are the commonest forms of inflammatory bowel disease (IBD). CD is a chronic recurrent disease characterized by intestinal inflammation due to genetic, immunological, and environmental factors [1]. Aberrant T lymphocyte autoreactivity (innate and adaptive immune responses to a subset of commensal enteric bacteria) is a major component of the immunological dysfunction observed in CD patients [2]. CD involves the entire bowel wall and may affect any part of the gastrointestinal tract. Furthermore, the development of extraintestinal manifestations, including a range of autoimmune diseases, is observed in 20–40% of patients with CD [2,3].

Common autoimmune hematological disorders include autoimmune hemolytic anemia (AIHA), immune (or idiopathic) thrombocytopenic purpura (ITP), and pernicious anemia [4,5]. ITP is characterized by the presence of autoantibodies against platelet surface antigens leading to immune-mediated platelet destruction and low platelet counts [4]. Concomitant ITP and CD appears to be uncommon, with only sporadic case reports in the literature. An immunological interaction between ITP and CD has long been suspected, however, whether concomitant ITP and CD has a common immunological basis or occurs by chance remains unclear. There have been few systematic literature reviews regarding concomitant ITP and CD. Therefore, we conducted a literature review of reported cases of concomitant ITP and CD.

Methods

We performed a review of cases of concomitant ITP and CD in the English and Japanese literature. Literature searches were performed using PubMed and Japana Centra Revuo Medicina (Igaku Chuo Zasshi) for English and Japanese manuscripts, respectively.

Thrombocytopenia in CD patients

Several conditions causing thrombocytopenia in CD patients have been reported: 1) ITP (autoimmune platelet destruction); 2) drug-induced thrombocytopenia, believed to induce autoimmunity or bone marrow suppression, reported following the use of anti-tumor necrosis factor (TNF)-alpha antibodies (i.e., infliximab) [6,7], 5-aminosalicylic acid [8], azathioprine [9], and low-molecular-weight heparin [10]; 3) the presence of thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS) in patients with CD [11-13]; 4) hematological malignancies [14] or portal hypertension (hypersplenism); and 5) deficiencies in minor elements, such as copper, during nutrition therapy for CD [15].

ITP

ITP is characterized by systemic hemorrhagic diathesis due to excessive thrombocyte destruction. ITP can be classified into acute (newly diagnosed) and chronic types according to clinical course [16]. In general, acute ITP is more common in infants than adults and often recovers spontaneously, whereas chronic ITP is typically recurrent and occasionally refractory to therapy [16]. ITP can also be classified according to the cause as either primary ITP or secondary ITP. Primary ITP is defined as an acquired autoimmune disorder characterized by isolated thrombocytopenia in the absence of other known causes that may be associated with thrombocytopenia [17,18]. In contrast, secondary ITP is defined as thrombocytopenia either associated with other disorders (e.g., hematological malignancies, collagen diseases, and infectious diseases) or induced by vaccination or drugs [17,18]. No single test can reliably diagnose ITP. ITP is rather a diagnosis of exclusion based on medical history, physical findings, serum tests (complete blood counts and antiplatelet antibody measurements), and peripheral blood smears [17].

The diagnosis of primary ITP requires only the presence of isolated thrombocytopenia (<100,000 cells/μL) in the absence of obvious underlying medical conditions [17]. Although the pathogenesis of ITP has yet to be fully elucidated, immune dysregulation and the development of autoantibodies appear to play major roles in the
development ITP [19]. Moreover, Evans syndrome is diagnosed on the basis of the simultaneous presence or sequential occurrence of AIHA and ITP in the absence of an underlying etiology [4]. Evans syndrome is characterized by hemolytic anemia, thrombocytopenia, and the production of antibodies, complement, or both against red blood cells (RBCs) and platelets [4].

Treatments for ITP

Although glucocorticoids and intravenous immunoglobulins (IVIg) remain the major therapeutic strategies for ITP, patients may eventually develop resistance to these approaches [20]. Splenectomy may also be considered in patients developing resistance to pharmacotherapy. A number of novel treatment options have been developed over the last decade, such as rituximab [20]. Helicobacter pylori infection has been shown to be associated with ITP. Significant increases in platelet counts are commonly observed following successful eradication therapy in ITP patients infected with Helicobacter pylori [21].

ITP in CD patients

The association between ITP and UC has been well described [5]. Although the prevalence of concomitant ITP in UC patients is reportedly 0.1–0.48% [22,23], the incidence of ITP in CD patients remains unknown. Zlatanic et al. [24] presented a series of 22 cases of concomitant ITP and IBD where 19 patients had UC and only three had CD (cases were reported up to 1997).

A systematic review (40 cases of concomitant ITP and UC) by Chandra et al. [5] suggested that ITP occurs during or after the onset of colitis. The age at diagnosis of both diseases ranged from 2 to 69 years, including five pediatric cases where both conditions were diagnosed before 16 years of age [30,32,33]. The interval between the diagnosis of primary and concomitant disease ranged from 0 to 28 years. No cases of concomitant Evans syndrome and CD were observed. All cases of CD predominantly affected the intestine except one case of gastric CD [35]. In two cases [22,27], the onset of ITP was apparently associated with an aggravation of CD. No fatalities were reported.

Treatment of ITP in concomitant ITP and CD cases

As described above, immunosuppressive therapies, such as glucocorticoids, IVIG, and splenectomy, are the front-line therapeutic approaches to ITP. The reported treatments and corresponding responses in reviewed cases of concomitant ITP and CD are summarized in Table 1.

All reviewed cases, except one refractory case [29], were successfully treated with the following management approaches: glucocorticoids only in 6 cases; IVIG only in 2 cases; glucocorticoids plus IVIG in 2 cases; splenectomy in 2 cases; glucocorticoids plus splenectomy in 1 case; infliximab in 2 cases; and rituximab in 1 case. Eradication therapy for Helicobacter pylori was not administered in any case following the diagnosis of ITP in concomitant cases.

| Case(year) | Sex | Age at diagnosis of CD (years) | Age at diagnosis of ITP (years) | CD prior to ITP | Response to glucocorticoids | Successful treatment of ITP | References |
|---|---|---|---|---|---|---|---|
| 1(1983) | F | 18 | 9 | - | + | glucocorticoids | [26] |
| 2(1987) | F | 37 | 65 | + | + | glucocorticoids, splenectomy | [27] |
| 3(1996) | M | 54 | 54 | - | + | glucocorticoids | [25] |
| 4(1997) | M | 43 | 43 | Sim | + | glucocorticoids | [28] |
| 5(1997) | F | 22 | 22 | Sim | + | glucocorticoids | [24] |
| 6(1998) | F | 19 | 19 | Sim | - | | [29] |
| 7(2000) | F | 8 | 17 | + | - | IVIG | [22] |
| 8(2001) | M | 12 | 14 | + | - | IVIG | [30] |
| 9(2001) | M | 2 | 2 | + | + | glucocorticoids | [30] |
Anti-TNF-alpha antibodies for the treatment of concomitant ITP and CD

The mucosal production of type 1 helper T cells (Th1) proinflammatory cytokines, such as TNF-alpha, is known to be increased in CD [2,21]. Moreover, Th1 responses may mediate both acute ITP and CD [21]. As discussed above, remission was achieved in two cases concomitant ITP and CD following the administration of infliximab (anti-TNF-alpha antibodies) [21,34].

Anti-TNF-alpha antibodies, such as infliximab, target both monocytes and activated T lymphocytes. Potential mechanisms of action of anti-TNF-alpha therapies include apoptotic and cytotoxic effects on monocytes and macrophages (the major producers of soluble TNF-alpha) and subsequent decreases in antiplatelet antibody production by B lymphocytes [2,21]. De Rossi et al. [34] proposed the use of anti-TNF-alpha antibodies as an efficient and relatively cost-efficient treatment in cases of ITP, particularly when concomitant with CD. Infliximab may be considered in patients refractory to standard therapies for concomitant CD and ITP [2,34,35].

Conclusion

Although there are currently a limited number of case reports describing concomitant ITP and CD, no clear tendency of one disease preceding the other, or differences in gender susceptibility, were found in our review of the literature. However, a number of reports suggested a correlation between the occurrence of ITP and CD activity. Whether concomitant ITP and CD occur incidentally or reflect a shared genetic or immunological basis remains unknown. Further investigations are required to fully elucidate the relationship between ITP and CD.

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