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Ulcerative Colitis Associated with Aplastic Anemia

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Running title: Ulcerative colitis with aplastic anemia

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INTRODUCTION

Anemia is the most common hematologic disorder in patients with ulcerative colitis (UC). In some cases, normochromic anemia results from the presence of a chronic disease; alternatively, blood loss or malabsorption may lead to an iron deficiency, resulting in hypochromic anemia. Other rare hematologic manifestations associated with UC include myelodysplastic syndromes and leukemia. Several investigators have suggested a clinical association between inflammatory bowel disease and myelodysplastic syndrome, since they share an immune dysfunction that impairs the activities of T-lymphocytes (3-6). UC is an inflammatory bowel disease of unknown etiology that mainly affects the mucosa of the rectum and colon. Immune mechanisms play an important role in UC, and immunogenetic factors have been implicated in the development of the disease. Aplastic anemia is a bone marrow stem cell disorder characterized by ineffective hematopoiesis, leading to pancytopenia. Although aplastic anemia is frequently idiopathic, the immune-mediated suppression of hematopoiesis may be implicated in at least half of patients, since more than half of these patients achieve hematological remission in response to immunosuppressive therapy. We report here a rare case of UC associated with pancytopenia requiring a blood transfusion in whom a bone marrow examination showed aplastic anemia. A common pathogenetic link between UC and aplastic anemia is suggested in this patient on the basis of the shared
immunologic impairment underlying both diseases.

CASE REPORT

A 33-year-old man presented in April 1998 with bloody diarrhea, fever, abdominal pain, and weight loss. His previous medical history was unremarkable, but his sister had been diagnosed as having UC. A colonoscopy showed petechial hemorrhage, shallow ulcerations surrounded by injected mucosa, and an abnormal vessel pattern in the sigmoid to transverse colon. The changes involved a length of 60 cm (Fig. 1). A biopsy specimen of colonic mucosa showed chronic inflammation. The patient was diagnosed as having UC with left-sided colitis. The patient’s hematological data are presented in Table 1. A blood count revealed thrombocytopenia (platelet count, \(70 \times 10^9/\text{liter}\)), normocytic anemia (hemoglobin, 11.9 g/dl; MCV 94.1 fl; reticulocytes \(9 \times 10^9/\text{liter}\)), and a normal white blood cell count of \(43 \times 10^9/\text{liter}\). A bone marrow aspirate and biopsy showed trilineage hypoplasia. The karyotype was normal. However, thrombocytopenia: (platelet count, \(73 \times 10^9/\text{liter}\)) was in fact already present in 1997, before the onset of UC. The patient’s serum IgG and IgA concentrations and C3 complement were normal. Serum anti-nuclear antibody and anti-DNA antibody were also negative. The patient was treated with mesalazine (4 g/day) and prednisolone (30 mg/day) for the exacerbation of UC. The bloody diarrhea resolved after 2 weeks of treatment; the steroid dose was reduced and eventually discontinued after 4
months of treatment. Subsequent UC relapses in December 1999 and April 2000 were alleviated using intravenous steroid therapy. In July 2001, the patient’s laboratory data showed a worsening of the pancytopenia without any gastrointestinal symptoms. The patient’s hemoglobin level was 5.9g/dl; WBC count was $3.1 \times 10^9$/liter; and platelet counts was $18 \times 10^9$/liter. A bone marrow aspirate and biopsy showed trilineage hypoplasia, and a diagnosis of aplastic anemia was made. The transfusion of 2 units of blood was required in August 2001, and the treatment with cyclosporine (CyA; 300mg/day) was initiated. The dose of CyA was adjusted to maintain a trough concentration between 200–250ng/ml in the whole blood. In December 2001, the patient’s hemoglobin level had increased to 10.2g/dl, his WBC count to $5.4 \times 10^9$/liter, and his platelet count to $32 \times 10^9$/liter. The colitis has remained in remission, and the patient’s blood counts are stable.

**DISCUSSION**

This is the first reported case of UC associated with aplastic anemia. Several cases of salazosulfapyridine or mesalazine-associated aplastic anemia have been reported in UC patients; according to current recommendations, these medications should be discontinued immediately in the event of bone marrow suppression (7). In our case, however, the thrombocytopenia was present before any diagnosis of UC or treatment with mesalazine. The clinical course of this case implies that the subsequent pancytopenia did not arise from
drug-induced aplastic anemia. Currently, the immune-mediated suppression of hematopoiesis has been considered as a potential etiology for bone marrow failure in patient’s with aplastic anemia, because more than half of aplastic anemia patients respond to immunosuppressive therapies, such as treatment with antithymocyte globulin or antilymphocyte globulin and CyA. Our patient’s aplastic anemia responded well to treatment with CyA, fulfilling the response criteria of Nakao (8) of “a rise in hemoglobin of 2g/dl or more compared to the pretreatment level after 4 months of CyA therapy”. This positive response strongly suggests an immunopathologic etiology in the present case. A response to monotherapy with CyA is suggestive of such a pathogenetic mechanism, since CyA acts by directly suppressing lymphokine production by T cells. Other groups (9, 10) have reported an increased frequency of positive HLA-DR2 test results in patients with aplastic anemia. 

As with many diseases suspected of having an autoimmune etiology or pathogenesis, the associations between UC and certain HLA class II genes have been investigated. Although HLA-class II genes do not explain all cases of UC, an association between HLA-DR2 and UC has been reported by several investigators (11, 12). Recent studies applying molecular techniques and typing for specific HLA-DRB1 subtypes have shown that within the HLA-DR2 group, the DRB1*1501 and DRB1*1502 alleles, but not the DRB1*1601 or DRB1*1602 alleles, are positively associated with UC (13, 14).
Other reports concerning HLA serologic typing in Japan have shown strong associations between a susceptibility to extensive or intractable UC and the HLA-DRB1*1502 allele (14, 15). The observation that the same HLA-DR2 haplotype is associated with both UC and aplastic anemia suggests a common immunologic impairment underlying the development of these diseases.

Primary sclerosing cholangitis (PSC) is an instructive example of an autoimmune disorder that appears to be associated with UC. Several reports have suggested that patients prone to develop PSC might represent a DR3 subgroup among patients with UC (16). In our case, the patient’s HLA serological type was HLA-DRB1*1502. Our patient’s clinical course showed a “relapse-remittance” pattern, consistent with a report that DRB1*1502 may favor an intractable condition. In contrast, UC associated with DRB1*1501 is less likely to show an intractable clinical course (15). Interestingly, DRB1*1501 is no only associated with a lower likelihood of intractability in UC patients, but with a good response to CyA therapy in patients with aplastic anemia. Recently, CyA has been used to induce remission in patients with UC who are unresponsive to conventional therapy, such as treatments with salazosulfapyridine and corticosteroids. A specific serologic HLA type may prove to predict the response to CyA therapy in UC patients, as has been seen in patients with aplastic anemia.

One plausible explanation for the association between UC and aplastic
anemia in the present case is that an underlying immunologic dysfunction may arise from certain cytokines regulated by specific HLA genes. Among the various cytokines, high concentrations of proinflammatory cytokine, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), have been noted in both inflammatory bowel disease and aplastic anemia (17-20). In particular, TNF-α has been implicated as a key mediator in the inflammatory process in UC and Crohn’s disease; for example, TNF-α antibodies are clinically effective in Crohn's disease and ulcerative colitis. On the other hand, an elevation of TNF-α have been reported in plasma from the bone marrow and peripheral blood in patients with aplastic anemia, but not from healthy individuals (20). The overproduction of TNF-α by T cells might explain the inhibition of hematopoietic precursor cells in aplastic anemia. The same overproduction of inflammatory cytokines may also account for the subsequent development of UC in the present case.

Several investigators have indicated that HLA genes can regulate the function or synthesis of cytokines. Miller and Kaplan (21) reported that serum IL-2 and TNF-α levels were elevated in patients with primary biliary cirrhosis and HLA-DR4, but were decreased in patients without HLA-DR4. Similarly, in systemic lupus erythematosus (SLE), a complex autoimmune disease with varied manifestations, the HLA-DR4 haplotype is associated with a high serum concentration of TNF-α, HLA-DR4 is also associated with a decreased
likelihood of nephritis. Further investigation regarding the associations between HLA-DR2 and inflammatory cytokines, including TNF-α and IL-1, are needed.

Myelodysplastic syndrome differs greatly from aplastic anemia. In most affected patients, myelodysplastic syndrome can not be explained by an immunological dysfunction, despite its association with UC. These patients do not respond hematologically to immunosuppressive therapies including treatment with CyA and antithymocyte globulin. Myelodysplastic syndrome is considered to be a monoclonal bone marrow stem cell disorder characterized by peripheral cytopenia and marrow dysplasia, rather than a disorder arising from immune-mediated suppression of hematopoiesis as in aplastic anemia. Why no previous cases of UC with aplastic anemia have been reported despite the apparent immunologic associations—in sharp contrast to the various reports of an association between UC and myelodysplastic syndrome—is puzzling.

Based on the findings seen in our case, aplastic anemia should be considered in a differential diagnosis of patients with UC in whom pancytopenia develops with no other evident cause, such as a drug reaction, hepatitis or other kind of viral infection. Bone marrow aspiration and biopsy are needed to diagnose and monitor both aplastic anemia and myelodysplastic syndrome. Although the association between UC and aplastic anemia may be coincidental, an
immunopathophysiological link seems plausible. We suspect that the elucidation of the underlying immune dysfunction will enhance our understanding of the pathogenesis of both UC and aplastic anemia.
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Fig 1. Endoscopic view of the sigmoid colon in December 1999 revealed numerous ulcers surrounded by injected mucosa. The ulcers were irregularly shaped and shallow. Lesions were present continuously from the rectum to the transverse colon, and endoscopic finding typical of ulcerative colitis.
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