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Case report

Thrombophlebitis migrans including Mondors' syndrome and autoimmune hemolytic anemia in ulcerative colitis; case report and review of the literature

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SUMMARY

Thromboembolic events occur in UC and Crohn's disease. Activation of clotting factors and thrombocytosis are common. In ulcerative colitis, increased levels of factor V, factor VIII and fibrinogen and decreased levels of antithrombin III have been demonstrated. Deep vein thrombosis and pulmonary emboli affect patients with severe disease and may occur after colectomy. Thromboembolic events in the eye or intracranial vessels have been described. Coombs positive hemolytic anemia has occasionally been reported in patients with ulcerative colitis. In some of these rare cases, hemolytic anemia was the main problem of the patient and was cured by colectomy.

A case of a young female patient with ulcerative colitis, autoimmune hemolytic anemia, recurrent deep vein thromboses including Mondors' syndrome and menstrual abnormalities is reported. There are several convincing reports that associate UC with Coombs positive hemolytic anemia and this co-existence should be considered in every UC patient with persisting or severe anemia. Before relating autoimmune anemia to UC, other causes of hemolysis should be excluded.The treatment of persistent autoimmune hemolytic anemia in UC patients could probably include administration of cyclosporine as there is a report of improvement of anemia after weeks of treatment. Methotrexate or azathioprine are alternative agents. Anti-influenza vaccination should invariably be performed in all IBD patients treated with immunosuppressive agents. Steroids should not be withdrawn or administered at reduced doses in cases of severe autoimmune hemolytic anemia.Patients with hypercoagulable states, thrombotic events and IBD usually require careful administration of anticoagulant agents. Sulfasalazine or azathioprine may reduce the effect of oral coumarin anticoagulants, while heparin is usually effective. Low molecular weight heparin may be used as a chronic regimen if required, balancing the dose at safe levels.

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INTRODUCTION

Although ulcerative colitis (UC) and Crohn's disease primarily involve the bowel, they are both associated with other extraintestinal manifestations. For some patients, especially those with sclerosing cholangitis or ankylosing spondylitis, the extraintestinal manifestations may be more troublesome than the bowel disease. The extraintestinal manifestations can be divided into two major groups: those in which the clinical activity follows the activity of the bowel disease and those in which the clinical activity is unrelated to the clinical activity of bowel disease. Most extraintestinal manifestations seem to occur more frequently in ulcerative colitis (UC) or Crohn's colitis patients than in those patients with Crohn's disease restricted to the small intestine. Thromboembolic events occur in UC as well as in Crohn's disease; activation of clotting factors and thrombocytosis are common in this disease.[1] In ulcerative colitis, increased levels of factor V, factor VIII and fibrinogen and decreased lev-

els of antithrombin III have been demonstrated. Acquired antithrombin III deficiency in two UC patients has also been reported.[2] Deep vein thrombosis and pulmonary emboli affect patients with severe disease and may also occur after colectomy.[3] In addition, thromboembolic events in the eye or intracranial vessels have been described.[4] Coombs positive hemolytic anemia has occasionally been reported in patients with ulcerative colitis.[5-8] In some of these rare cases, hemolytic anemia was the main problem of the patient and was cured by colectomy.[9]

Young female patients with inflammatory bowel disease (IBD) may experience abnormalities in their menstrual cycle or even amenorrhea. In all such cases, the patient should be treated as a unique entity and all additional manifestations should be investigated.

Herein we report a case of a young female patient with ulcerative colitis, autoimmune hemolytic anemia, recurrent deep vein thromboses and menstrual abnormalities.

CASE REPORT

An eighteen-year-old female patient with a 2-year history of ulcerative colitis (UC) was admitted to the Department of Internal Medicine because of disease relapse, thoracic superficial vein thrombophlebitis and severe anemia (hemoglobin 7.9 g/dl). She reported one bloody solid bowel movement per day and a history of recurrent deep vein thromboses of the lower extremities.

The disease presenting symptom a couple of years earlier had been bloody diarrhea. The diagnosis was established by total colonoscopy with terminal ileum inspection. The disease affected the whole length of the colon and rectum, while the terminal ileum had a normal appearance. Biopsies taken throughout the colon and ileum and were compatible with ulcerative colitis. Enteroclysis revealed a terminal ileum of normal appearance, with no signs of inflammation. No parasite, enteroviruses or bacteria was found in stool cultures and stool examination for ova and parasites was negative.

Eight months after diagnosis, the patient was diagnosed with deep vein thrombosis of her right leg. She had not been bedridden for a long period at that time nor been operated on before this event. The thrombosis was treated with low molecular weight heparin resulting in complete revascularization. During hospitalization the patient had to be transfused because of severe autoimmune hemolytic anemia. Meanwhile she was receiving methylprednizone (16 mg/dl), ferrous sulfate, folic acid and intramuscularly vitamin B12.

A second deep vein thrombosis took place one year later in the left leg and in the front part of the chest wall veins (Mondors' syndrome) while the patient required blood transfusions from time to time due to persisting anemia. An indirect Coombs test was found positive (two crosses), while iron deficiency was corrected at that time. Disease activity was remarkably low during these phenomena but complete remission proved difficult to achieve. The patient was discharged with methylprednizone 16 mg per day, heparin (dalteparin 5,000 UI/0.2 ml daily s.c), lactulose, benzodiazepine, ferrous sulfate, folate, vitamin B12 and recombinant human erythropoietin alpha (10,000 UI/ml, s.c, 3/week). She was also started on azathioprine 125 mg per day (2,5 mg /kg). During the first year of diagnosis the patient was started on sulfasalazine without any improvement of her symptoms and this drug was discontinued because of its potential effect on hemolysis.

In this last admission, the patient had laboratory evidence of autoimmune hemolytic anemia, with increased indirect bilirubin and dehydrogenase lactate, a Coombs positive test and decreased serum haptoglobulins. She had no fever or other evidence of infection. She had not had menses for 1 year. As reported, she had blood in the stool, but no diarrhea. Physical examination showed signs of anemia. On laboratory analysis, she had anemia, thrombocytosis and elevated erythrocyte sedimentation rate. Nothing remarkable was noticed after complete testing for hypercoagulable states including proteins C and S, anti-cardiolipin antibodies, antithrombin III and factor V (Leiden) mutations. A gynecological evaluation was performed including ultrasound, which was within normal limits.

The patient was informed about the potential benefits of a total colectomy with or without splenectomy, but preferred to try conservative measures in order to delay or avoid surgery and is now starting infusions (5mg/kg) with anti-tumor necrosis factor alpha (anti-TNFa) monoclonal antibody (Remicade, Schering Plough).

DISCUSSION

We reported the rare case of a young female patient with UC, who was diagnosed with autoimmune hemolytic anemia and recurrent deep vein thrombosis including Mondors' syndrome. These manifestations were more troublesome to control than the intestinal disease itself

and diagnostic and therapeutic dilemmas were faced mainly due to the continuing steroid dependency of the patient.

Anemia is sometimes a significant problem in IBD. Iron deficiency and anemia of chronic disease are the main causes of anemia in UC, while in Crohn's disease vitamin B_{12} deficiency is quite common in severe ileal disease or after surgery. Sulfasalazine treatment is a cause for folic acid deficiency anemia, or even autoimmune hemolytic anemia.[10] Apart from that, there are several convincing reports that associate UC with Coombs positive hemolytic anemia and this co-existence should be considered in every UC patient with persisting or severe anemia.[11-13] Before relating autoimmune anemia to UC, other causes of hemolysis should be excluded. Hemolysis due to frequent transfusions, hereditary spherocytosis, hereditary elliptocytosis, G-6-PD (dehydrogenase of glucose 6-phosphate) deficiency, pyruvate 6 kinase deficiency, infections, microvasculitic hemolytic anemia are other common causes of hemolytic anemia that should be considered in the differential diagnosis. G-6-PD deficiency is the commonest cause of Coombs negative hemolysis and should be excluded in patients receiving sulfasalazine.[14] Ulcerative colitis patients with evidence of anti-erythrocyte antibodies has also been reported.[15,16]

Increased activity of coagulation factors and thrombocytosis have constantly been described in children and adults with IBD.[17,18] However, increased platelet counts have not been related to thomboembolism.[19] Arterial and venous thrombotic events have an average incidence of 1.3% in IBD patients, with deep vein thrombosis being the most common thombotic manifestation.[18] Deep vein thrombosis usually takes place after major surgery, prolonged bed-rest or during acute and severe disease exacerbation. This kind of thrombosis may present as recurrent, migrant[20] or in the form of rare syndromes such as the Mondors' syndrome[21] with cutaneous chest wall vein thrombosis. Other thrombotic events include myocardial infarct, pulmonary embolism,[22,23] intraventricular thrombi, and peripheral arterial and venous occlusions including cerebrovascular thrombotic events.[24] In addition, thrombotic skin gangrene has been reported in IBD patients.[25,26] These patients may be at risk for Budd-Chiari syndrome,[27] especially in the presence of anti-cardiolipin antibodies[28,29] or antiphospholipid antibodies.[30] Budd-Chiari syndrome has also been reported to complicate bowel surgery.[31] It has been proposed that activation of the endothelium and the coagulation pathway is central to this enhanced thrombotic tendency. An abnormal tendency to thrombosis may be due to increased activity of procoagulant forces such as coagulation cascade, platelet inhibitors, fibrinolytic activators.Under physiological conditions these forces are kept in homeostatic balance by the vascular endothelium. The exact time when this balance is disturbed and the nature of the triggering factor(s) still remain under investigation. However, investigation in those patients must always include complete testing for hypercoagulable conditions,[32] as previously mentioned, but not all factors that predispose to thrombosis can be identified. It is also wise to conduct an ophthalmologic evaluation in every IBD patient with thrombosis, not only to exclude retinal vascular abnormalities,[33] but also to look for cataract from steroids or iridocyclitis.

Menstrual abnormalities are common in female patients with chronic diseases. In our case the combination of chronic inflammatory activity in the bowel with severe anemia led to interruption of menses. The findings of ultrasound were not compatible with ovarian polycystic syndrome, because only small cysts were seen. Thrombosis of ovarian veins and prostatic plexus has been reported in ulcerative colitis,[34] with subsequent sexual abnormalities. The attending physician should never forget to ask the patient about menstrual or sexual abnormalities and should schedule a consultation with a gynecologist and an endocrinologist as required.

The treatment of persistent autoimmune hemolytic anemia in UC patients is likely to include cyclosporine administration as there is a report of improvement of anemia after weeks of treatment with this drug.[35] Methotrexate or azathioprine are alternative agents. Anti-influenza vaccination should be performed in all aged IBD patients treated with immunosuppressive agents. Steroids should not be withdrawn but administered at the minimal adjusted doses in cases of severe autoimmune hemolytic anemia.

Patients with hypercoagulable states, thrombotic events and IBD usually require careful administration of anticoagulant agents. Sulfasalazine[36] or azathioprine[37] may reduce the effect of oral coumarin anticoagulants, while heparin is usually effective.[38-40] Low molecular weight heparin may be used as a chronic regimen if required, balancing the dose at safe levels. An improvement of intestinal disease has been observed during heparin administration by some authors. Streptokinase use in extensive thromboses has also been reported.[41]

Total colectomy or splenectomy can improve severe autoimmune hemolytic anemia in UC as colectomy leads to remission of the autoimmune hemolytic anemia. Nev-

ertheless, a rare case of relapse of hemolytic anemia after colectomy for severe pancolitis and another one in which autoimmune hemolytic anemia developed after total colectomy in a UC patient have been reviewed.[42]

In conclusion, we reported a case with ulcerative colitis, autoimmune hemolytic anemia and recurrent thrombotic events including Mondors' syndrome .The strategy of investigating and treating such patients has been reviewed and discussed. In any case, the patient should be treated as a unique entity because extraintestinal manifestations may sometimes be more troublesome than the intestinal disease itself.

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