Spontaneous right ventricular thrombus in a patient with active ulcerative colitis and protein C deficiency: a review with a case report

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**Abstract.** – **Background:** Inflammatory bowel disease (IBD) is an idiopathic condition of gastrointestinal tract whose pathogenesis results from the complex interaction of genetic susceptibility and environmental influences. It is well known how IBD patients have an increased risk of thrombosis.

**Objectives:** To assess the frequency and characteristics of thromboembolic events (TEE) in IBD and the role of certain etiopathological factors in such thrombotic patients.

**Material and Methods:** We report the case of a young woman affected by protein C deficiency, who during a clinical recurrence of ulcerative colitis (UC), developed a spontaneous right ventricular thrombus and pulmonary embolism. Then, we made a review of literature that documented thromboembolic events in IBD patients.

**Results:** A search using the PubMed database identified 65 case reports documenting thromboembolic events in patients with known UC and 7 documenting thromboembolic events in known Crohn’s disease.

**Discussion:** The data of the literature confirm that IBD patients have an approximately three fold greater risk for developing a TEE compared with the general population. The risk for thrombosis correlates well with disease activity in Crohn’s disease, and to lesser extent in ulcerative colitis.

**Key Words:**

Inflammatory Bowel Disease; Ulcerative colitis; Ventricular thrombus; Thromboembolic events.

**Introduction**

Extraintestinal manifestations are common in the inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn’s disease, occurring in at least 25-40% of patients. They can be classified as related to disease activity or not. If secondary systemic effects of therapy on disease and complications are also included, almost all the patients have extra intestinal manifestations.

Patients with IBD are at increased risk of developing thromboembolic complications. In fact, the deep vein thrombosis and pulmonary embolism are a major cause of their mortality in IBD. Venous thrombembolism is more frequent than arterial embolism. More than 60% of the vascular complications are accounted for by peripheral venous thrombosis. Unusual sites of thrombosis include mesenteric, portal, cerebral veins and cardiac cavities. Arterial thrombosis is extremely uncommon. In severe disease, thrombocytosis and increased concentrations of many clotting factors that behave as acute phase proteins, lead to a procoagulatory status. The majority of IBD patients with thromboembolic events show an active disease2.

We report the case of a young woman, who during a clinical recurrence of UC, developed a spontaneous right ventricular thrombus and pulmonary embolism.

**Case Report**

A 38-year-old female patient with 15 years history of UC, in chronic treatment with mesalazine and azathioprine, suffering from abdominal pain, bloody diarrhea (4-6 stools per day) and weight loss (6 kg in the previous 3 months) was admitted in the hospital in October 2008. On admission, her body temperature was 37°C. Her physical examination revealed no abnormalities. The patient was conscious, thin, well nourished, and pale. Her blood pressure was 130/70 mm Hg, pulse rate was 110/min, and respiratory rate was normal. Cardiovascular
and abdominal examinations were within normal limits. Respiratory examination showed medium crackles. The blood and stool cultures obtained on her first day of admission did not reveal any pathogen. Microscopic stool examination revealed abundant leukocytes and erythrocytes. Laboratory data showed elevated C reactive protein (CRP) levels and ESR (12 mg/dl and 98 mm, respectively), severe thrombocytosis (1,157,000/mm³), total white blood cells count of 6300/mm³ and severe ipochromic anemia with a Hb value of 6.9 g/dL. Her colonoscopy revealed loss of mucosal vascular pattern, granularity and friability of the whole colonic mucosa. Histopathology of the rectal mucosa showed an abundant infiltration of neutrophils, lymphocytes and plasma cells, cryptitis and crypt abscess in some areas. The patient’s ECG and abdominal ultrasonography were normal. Chest x-rays revealed an area of opacity representing consolidation. Based on these findings, the patient was diagnosed with pneumonia and moderately active ulcerative pancolitis and started combined antibiotic therapy with metronidazole and ciprofloxacin. Anemia was treated with 2 blood transfusions. Nutritional support was also provided. During hospitalization the patient developed a gradually increasing exertional dyspnea. There were no conventional risk factors for deep vein thrombosis.

A computed tomography (CT) performed for the appearance of these symptoms showed a clot in the right ventriculum and pulmonary embolism. Echocardiography confirmed the presence of a moderately mobile, homogenous, pyramidal-shaped mass with irregular surface, attached by a broad stalk to the right ventricular wall compatible with a thrombus (Figure 1). It did not interfere with blood flow or with tricuspid and pulmonary valve function. We started immediately a therapeutic dose of low molecular weight heparin (LMWH). Laboratory tests for coagulation abnormalities and trombophilic assessment revealed a deficiency of protein C and of protein S (PC activity 31%, PS activity 137%, a PCR ratio 0.96). After a month of anticoagulation therapy, a new echocardiography documented the disappearance of the ventricular thrombus. The heart was otherwise structurally normal. The patient was discharged home with long-term warfarin. At the time of discharge laboratory tests, chest X-ray were normal; platelet count was 322,000/mm³, level of Hb 9.77 g/dL, INR 2.72.

**Discussion**

A search using the PubMed database identified 65 case reports documenting thromboembolic events in patients with known UC and 7 documenting thromboembolic events in known Crohn’s disease. These are summarized according to the site of involvement and are presented in Table I.

The cerebral district is the most common location of thromboembolic events (TEE) (involvement in IBD), accounting for 34.7% of all cases reviewed. Secondly hepatic and mesenteric vessels ac-

**Table I. Summary of case reports of TEE in IBD patients.**

<table>
<thead>
<tr>
<th>Site of involvement</th>
<th>N° Case report</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral district</td>
<td>25</td>
<td>34.7</td>
</tr>
<tr>
<td>Hepatic and mesenteric vessels</td>
<td>12</td>
<td>20.8</td>
</tr>
<tr>
<td>Pulmonary vasculature</td>
<td>6</td>
<td>9.7</td>
</tr>
<tr>
<td>Cardiac cavities</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>Other sites involvement of variable severity</td>
<td>25</td>
<td>34.7</td>
</tr>
</tbody>
</table>

**Figure 1.** Right ventricular thrombus.
counting for 20.8% and respiratory TEE occurring in 9.7%. Most of the patients presenting respiratory TEE are female and nearly all are affected by UC. In only four cases (3 UC and one case of Crohn’s disease) the involvement of cardiac cavities has been reported, and the age of onset of the disease in these patients is remarkably younger. Out of 2 of these four patients underwent colectomy before the thrombotic events. Because of this temporal link between colonic resection and onset of disease some authors speculated how the colectomy may have induced thrombotic diseases in these patients. Alternatively, this phenomenon may be related to the discontinuation of therapies after presumed surgical cure of the disease.

Thromboembolic events (TEE) in IBD patients were first described in 1936 when Bargen and Barker reported 18 incidents among 1500 patients with UC (1.2%). The prevalence was higher at autopsy where thromboembolism was diagnosed in 14 of 43 cases (32%). The severity of thrombosis is documented by the fact that it is the third cause of death for patients with UC: peritonitis 38%, malignant neoplasms 12%, thrombosis and thromboembolic disease 9%.

In IBD, the comparisons between the different studies are further complicated by several factors, such as the differences in the clinical and demographic features of the patients studied and in their disease activity evaluation. Despite these limitations, both the prothrombotic nature and the hypercoagulability state are established features of IBD as well as the implication of endothelial cells. The thrombotic condition is identified as an increase in risk factors for thrombosis and/or a decrease in the natural anticoagulant factors.

Thrombosis is characterized by focal microthrombi in the vasculature of the inflamed intestine and systemic TEE, leading to extensive morbidity and mortality within two years of a TEE. The overall incidence of TEE is ~6.5% in both Crohn’s disease and ulcerative colitis patients, with a three-fold increase in the risk of a systemic TEE compared with the general population. However, the fact that in autopsies the prevalence of systemic thromboembolism is nearly six-fold higher than that seen in clinical studies suggests that a large fraction of cases remains undiagnosed.

In IBD, systemic TEE occur mainly in the venous circulation, but can also develop in the arterial circulation. The most common types of TEE, deep vein thrombosis (DVT) and pulmonary embolus, but thromboses are also reported in unusual sites such as cerebral, innominate, retinal, hepatic, and mesenteric veins.

The degree of activity and the extent of inflammatory intestinal disease are generally considered to correlate well with the risk for a TEE. In several series of IBD patients, the control of the disease activity led to a partial normalization of the disturbed coagulation factor profile and the platelet activity, and, conversely, the anticoagulation therapy attenuated the inflammation. On the other hand, at least two lines of evidence suggest that intestinal inflammation cannot account for the hypercoagulable state in these patients: firstly, one-third of IBD patients experience TEE in the absence of active bowel disease or, in ulcerative colitis patients, even after undergoing proctocolectomy; secondly, the hypercoagulable state is not found in other autoimmune diseases such as celiac disease. Thus, factors other than inflammation need to be considered for the prothrombotic state.

The cellular basis that underlies the hypercoagulable state is complex and includes impaired function of all three components that rule hemostasis: platelets, coagulation, and fibrinolysis. In particular, spontaneous platelet aggregation or platelet hypersensitivity to low concentrations of aggregating agents occurs in nearly 50% of IBD patients. Although this feature of IBD platelets may be independent of the disease activity, recent evidence suggests that platelet hyperactivation is, in part, mediated by the CD40-CD40 ligand (CD40L) pathway. This pathway is increasingly recognized to play a central role in the chronic inflammation that promotes atherosclerosis and platelet activation. IBD platelets overexpress CD40L protein up to four times more frequently than normal platelets and release more soluble CD40L (sCD40L) to the plasma. Elevated levels of sCD40 are associated with an increased risk for developing a TEE. At the mechanistic level, CD40L overexpression in IBD platelets is likely to originate from the interaction with the activated endothelium of the microvasculature of the inflamed mucosa. The platelet CD40L overexpression and increased plasma levels of sCD40L correlate with the extent of bowel disease.

Hyperhomocysteinemia (hyper-Hcy) is a risk factor for arterial and venous thrombosis, hav-
ing a prevalence of about 5% in the general population. Hyper-Hcy is approximately three times more frequent in IBD than in the normal population. This can be secondary to nutritional causes or medications (methotrexate, salazopyrine, corticosteroids), but a comparison between the homocysteine levels of IBD patients with a TEE and those without TEE history shows no significant difference in Hcy levels. However, this lack of correlation likely reflects the multifactorial basis for hypercoagulability in IBD patients.

Other sites of the coagulation cascade are also altered in IBD patients, including increased fibrinogen, increased prothrombin fragments and thrombin-antithrombin complexes, and increased factors V, VII, and VIII. This increase favours clot formation, and therefore predisposes to thrombosis. The levels of several proteins that regulate the coagulation cascade are also altered. The level of antithrombin III (AT III), is significantly lower in the plasma of IBD patients.

Under normal conditions, activated protein C with its cofactor protein S inhibit activated factors V and VIII, and thereby prevent uncontrolled thrombosis. A few reports show a deficiency of protein C and of protein S during active bowel disease. IBD patients also have significantly lower expression of endothelial protein C receptor and thrombomodulin, which impair protein C activation and consequently lead to lower effective protein C activity.

Moreover, the prevalence of factor V Leiden mutation is more frequent in IBD than in the general population. Two other common inherited thrombophilias (prothrombin G20210A mutation and C677T variant of the methylenetetrahydrofolate reductase, MTHFR) are as frequent in IBD patients as in the general population.

Impaired systemic fibrinolytic capacity is another potential contributor to the hypercoagulable state in IBD patients. The plasma levels of tissue plasminogen activator (tPA), the principal activator of the fibrinolytic system, are significantly lower in IBD patients than in the general population. Besides, an increase in plasminogen activator inhibitor and thrombin-activatable fibrinolysis inhibitor, proteins that inhibit fibrinolysis, have been reported. Thus, both decreased activation and increased inhibition of the fibrinolytic system can contribute to hypofibrinolysis.

Finally, markers of endothelial damage, such as von Willebrand Factor (vWF) and thrombomodulin (TM), are increased in serum of IBD patients, with possible correlation with disease activity and/or acute phase reactants.

Autoantibodies against several components of the coagulation system are present at a higher frequency in IBD patients and may predispose for thrombosis. Antiphospholipid antibodies (anti-cardiolipin (aCL) antibodies and lupus anticoagulant (LAC)) facilitate thrombosis by activating endothelial cells and platelets and by impairing the activity of anticoagulation proteins. Antibodies against protein S were described in ~8% of IBD patients, but they were independent of protein S level. However, elevated titers of protein S antibodies, LAC, and aCL and β2-GPI antibodies, were not shown to be significantly different in IBD patients with TEE compared with IBD patients without history of TEE.

Despite numerous studies on the link between IBD and thrombosis, there are currently no distinct guidelines for the management of a TEE in these patients but only some recommendations for minimizing the risk of TEE. First, a critical step is minimizing modifiable risk factors like smoking, oral contraceptive therapy, and hormone replacement therapy that should be avoided. Immobility with other conditions that facilitate blood stasis needs to be avoided. Vitamins B6 and B12 and folate supplements should be included in the diet of IBD patients to avoid hyperhomocysteinemia.

Screening for inherited thrombophilia is a complex and controversial issue of great clinical significance but several factors such as the degree of bowel disease activity, patient history of a TEE, or family history of TEE may suggest a need for thrombophilia screening.

In IBD patients who have had a TEE, the concurrence of IBD activity and positive screening for thrombophilia justifies the inclusion of heparin in the therapy, as it is a relative indication for lifelong anticoagulation. Primary prevention with heparin or low-molecular-weight heparin in a patient with extensive and aggravated bowel disease that is steroid resistant is increasingly recognized as an acceptable treatment. This is a paradoxical effect of heparin, considering that aggravation of bowel disease is often accompanied by gastrointestinal bleeding. The emerging anti-inflammatory properties of heparin provide the basis for this therapeutic choice.
to avoid the systemic effects of heparins, a recent open-label study evaluated the safety and the efficacy of oral, colonic-release, low-molecular weight heparin-MMX™ for the treatment of mild to moderate left-sided UC. This appears to be a safe and effective treatment option in mild to moderate UC, and controlled studies are warranted to confirm its therapeutic effects. Obviously, more controlled studies are needed to define accurately the degree of bowel disease severity that justifies treatment with heparin.

To conclude, IBD patients have an approximately three fold greater risk for developing a TEE compared with the general population. The risk for thrombosis correlates well with disease activity in Crohn’s disease, and to lesser extent in ulcerative colitis. The cellular basis for hypercoagulability in these patients is multifactorial, and, therefore, there is no single laboratory marker that reliably correlates with the occurrence of thrombosis. Modifiable risk factors should be minimized, and folate and vitamin B supplementation should be prescribed to control homocysteine levels.

## Conclusion

In our case, the combination of coagulopathy (deficiency of protein C and S) associated with presence of piastrinosis despite immunosuppressive therapy and due to the pneumonia, has certainly facilitated the occurrence of cardiac TEE. Since the clotting system is potentially involved in IBD pathogenesis and/or in perpetuating and amplifying the inflammatory process, the use of anticoagulant or coagulation-related drugs can be considered for the treatment of IBD. The potential therapeutic value of both unfractioned heparin and low-molecular-weight heparin has been addressed in IBD, mainly in UC. Heparin is known for its anticoagulant indication, but it is also characterized by anti-inflammatory properties. Initial reports showed potential benefit of systemic heparin treatment in patients with IBD. However, data deriving from controlled studies overall suggest a lack of efficacy of these molecules. The elimination of removable risk factors is the first recommendable treatment in order to prevent thrombosis and heparin treatment may have a central role in the treatment of IBD patients with active bowel disease and/or increased risk for thrombosis.

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