REVIEW

Thrombosis and Inflammatory Bowel Disease

PETER M. IRVING,* K. JOHN PASI,† and DAVID S. RAMPTON*
*Centre for Gastroenterology and †Centre for Haematology, Institute of Cell and Molecular Science, Barts and The London NHS Trust, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Interaction between thrombosis and inflammation is increasingly recognized. With this, interest has arisen in the role of thrombosis in inflammatory conditions, including the inflammatory bowel diseases. Although the association between active inflammatory bowel disease and thromboembolic complications has long been known, there has been a resurgence in research into the role of thrombosis and the hemostatic system in the pathogenesis of both ulcerative colitis and Crohn's disease. Here we review the increased frequency of thromboembolic complications occurring in patients with inflammatory bowel disease; whether thrombosis might play a part in the initiation and maintenance of inflammation in inflammatory bowel disease; abnormalities of the coagulation system found in patients with inflammatory bowel disease; platelet dysfunction in inflammatory bowel disease; the mechanisms by which hemostatic processes might be proinflammatory in inflammatory bowel disease; and how these interactions might impact not only on the prevention of complications, but also on the treatment of the underlying inflammation in inflammatory bowel disease.

An association between IBD and thrombosis has been recognized for more than 60 years. Not only are patients with IBD more likely to have thromboembolic complications, but it has also been suggested that thrombosis might be pathogenic in IBD. Here we review the relationship between thrombosis and the complications, pathogenesis, and treatment of IBD.

Thromboembolism as a Complication of Inflammatory Bowel Disease

Thromboembolic complications of IBD are well recognized and were first described in UC in 1936.[1] Although pulmonary embolism (PE) and lower limb deep vein thrombosis (DVT) are the most common thromboembolic phenomena seen in IBD, case reports of thrombosis of most other veins and arteries can be found in the literature. Indeed, thrombophlebitis migrans, a cutaneous problem thought to be due to a prothrombotic state and more usually associated with pancreatic malignancy, has been described in association with UC.[2,3]

The quoted frequency of thromboembolic events in patients with IBD varies widely (Table 1); in clinical studies, thromboembolic events are said to occur in 1%–8% of patients, whereas in postmortem studies, rates reach 41%. Many of these studies, however, are from an era in which the management of IBD was more invasive than it is now; in one study, more than half of the group surveyed (patients with UC) had undergone surgery.[4] Moreover, the introduction of prophylactic measures against thromboembolism, such as heparin, antithrombotic stockings, and early postoperative mobilization, postdates some of the earlier reports. Although postmortem data overcome the problem of failing to diagnose subclinical thromboembolic events, it is difficult to interpret the results of these as well as other studies without an appropriate control group.

Two recent studies have addressed these difficulties and provide more robust evidence of the increased risk of thromboembolism in IBD; in these, patients with IBD had a 3-fold increased risk of either DVT or PE compared with the general population.[5,6] Bernstein et al[5] performed a population-based cohort study and calculated incidence rates of DVT or PE of 40/10,000 person years for CD and 50/10,000 person years for UC. Moreover, in the other study, an inflammatory control group (rheumatoid arthritis) and a gastroenterologic disease control group (celiac disease) both had fewer episodes of thromboembolism than the IBD patients,[6] even after adjustment for confounding variables such as operations, oral

Abbreviations used in this paper: ADP, adenosine diphosphate; CD, Crohn's disease; DVT, deep venous thrombosis; EPCR, endothelial protein C receptor; IBD, inflammatory bowel disease; OCP, oral contraceptive pill; PE, pulmonary embolism; PLA, platelet-leukocyte aggregate; TF, tissue factor; TFPI, tissue factor pathway inhibitor; UC, ulcerative colitis.

1542-3565/05/$30.00
PII: 10.1053/S1542-3565(05)00154-0

Table 1. Frequency of Thromboembolic Complications in Patients With IBD

First author	Year	Number of cases examined	Frequency of thromboembolic disease (%)
Clinical studies			
Bargen[1]	1936	1500	1.2
Ricketts[127]	1949	206	1.9
Dennis[4]	1952	261	7.5
Edwards[128]	1964	624	6.7
Talbot[11]	1986	7199	1.3
Webberley[69]	1993	104	7.7
Jankelson[129]	1997	145	2.8
Jackson[130]	1997	11,402	0.7[a]
Miehsler[6]	2004	618	6.2
Postmortem studies			
Bargen[1]	1936	43	31
Warren[131]	1949	180	6.7
Sloan[132]	1950	99	41
Graef[133]	1966	100	39

[a]Review of hospital admissions with first or second diagnosis of IBD, of which 0.7% had a thrombotic episode documented as a concurrent diagnosis.

contraceptive pill (OCP) use, smoking status, and body mass index. However, not all studies have shown an increased risk of thromboembolism in IBD, although one negative study showed that patients with IBD who do have thromboembolic events have them at a younger age than the general population.[7]

Further evaluation of patients with IBD who have experienced thromboembolic events has revealed disease characteristics associated with an increased risk of thromboembolism. In a review of 98 IBD patients with thromboembolism, most of the patients with CD had colonic disease, whereas those with UC had extensive disease, suggesting that the risk of thromboembolism might correlate with the extent of colonic involvement.[8] This observation had previously been noted in patients with UC by others.[9,10] Disease activity is also probably a risk factor for thromboembolism,[8,11] a fact supported by the relationship between thrombocytosis, coagulopathy, and disease activity (see below). However, it is of note that a third of thromboembolic complications occur while the disease is quiescent.[11]

Hence, although debated over the years, it is now apparent that IBD predisposes to thromboembolism. A more controversial issue is whether thrombosis contributes to the pathogenesis of IBD.

Thrombosis as a Pathogenic Mechanism in Inflammatory Bowel Disease

It has been suggested that thrombosis and ischemia might be involved in the pathogenesis of both UC and CD. Indeed, ischemic conditions of the bowel can present in a similar fashion to, and hence be mistaken for, both UC[12] and CD.[13] Although interest has recently moved away from the proposal that ischemia is a primary cause of IBD, it has become increasingly clear that inflammatory and thrombotic processes are linked, and current evidence suggests that thrombosis has some involvement, if not in the initiation, at least in the maintenance of the inflammatory process in IBD.

A vascular component to the pathogenesis of CD was first proposed only a year after Crohn et al. described the condition.[14] Subsequently, in 1989, a series of changes comprising vascular injury, focal arteritis, fibrin deposition, arterial occlusion, and then microinfarction or neovascularization was proposed as a possible pathogenetic sequence in CD.[15] In this study, resin casts of the intestinal vasculature showed changes ranging from intravascular fibrin deposition to complete thrombotic occlusion. Furthermore, the early vascular changes appeared to precede mucosal changes, suggesting that they were more likely to cause rather than result from the pathologic features of CD. Subsequent studies showed that intravascular fibrin deposition occurred at the site of granulomatous destruction of mesenteric blood vessels,[16] and positive immunostaining for platelet glycoprotein IIIa occurred in fibrinoid plugs of mucosal capillaries in CD.[17] In addition, intracapillary thrombus has been identified in biopsies from inflamed rectal mucosa from patients with CD.[18] When combined with evidence of ongoing intravascular coagulation in both active[19] and quiescent[20] CD, the above data point toward a thrombotic element contributing to the pathogenesis of CD.

The case for a thrombotic component in the pathogenesis of UC is less clear. In the 1960s, a study of the early histologic changes in UC identified intravascular platelet aggregates,[21] a finding supported by the discovery of intracapillary thrombus in rectal biopsies from patients with UC.[18] In addition, changes in the former study included thickening of the subepithelial capillaries with occlusion of their feeding vessels and intravascular fibrin deposition in association with platelet thromboses.[21]

Microvascular dysfunction might also contribute to ischemic changes in IBD; loss of vasodilatory ability,[22] decreased microvascular volume (in ileal CD),[23,24] and the presence of elevated levels of potent vasoconstrictors, such as endothelin-1, in both tissue and plasma[25,26] could contribute to the reduction in blood flow seen in chronic UC and CD.[23] Likewise, microvascular injury, as suggested by increased levels of circulating von Willebrand's factor[27] and anti–endothelial cell antibodies,[28] might contribute to localized thrombosis and, in the case