Venous thrombosis in a child with ulcerative colitis in remission : a case report

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Abstract

Over the past 70 years, an association between venous thromboembolism and inflammatory bowel disease has been described. We report on a thirteen year old boy with ulcerative colitis and venous thrombosis. Literature on incidence of venous thromboembolism in inflammatory bowel disease (IBD) is reviewed as well as the possible pathogenetic mechanisms of this 'hypercoagulable state' : role of acquired risk factors, inflammation, coagulation abnormalities and platelets. Finally, treatment of IBD and thrombosis is discussed. (Acta gastroenterol. belg., **2014**, 77, **71-74**).

Key words : thrombosis, inflammatory bowel disease, children.

Case description

We report on a thirteen year old boy with known ulcerative colitis. Since 2.5 years, patient was in clinical and biochemical remission, he was admitted to the hospital because of a ten day course of right-sided neck pain. Especially active movement was painful.Complaints had started two days after patient had fallen on his back. Algipan®, a local NSAID, had been administered without bringing any relief. In the weeks before admission, no illness was noted. Patient had no fever, no abdominal pain, diarrhoea or bloody stools. He was on a maintenance therapy of Colitofalk® 500 mg three times daily.

Further personal history was negative apart from relapsing urticaria/itch for which in the past cetirizine was used.

Family history was negative for bleeding disorders and thrombotic disease. There was no history of inflammatory bowel disease or other auto-immune diseases.

At clinical examination we saw a boy in good general health. Weight and heigth were situated at the tenth percentile. No fever was noted. Examination of heart and lungs was unremarkable. There was no abdominal tenderness and the skin was unremarkable. A discrete swelling could be noticed at the right side of the neck. There was no overlying redness or apparent local warmth.

Ultrasound of the neck was performed, showing partial thrombosis of the right jugular vein over a distance of approximately 5 centimetres. CT angiography confirmed the diagnosis (Fig. 1). Figure 1. CT angiography showing partial thrombosis of the right jugular vein as indicated by white arrow.

Laboratory investigation showed normal hematocrit and haemoglobin. White blood cell count was 16.400/mm^3. Inflammatory markers were elevated with CRP 1.52 mg/dl and sedimentation rate 33 mm/h. Broad screening of

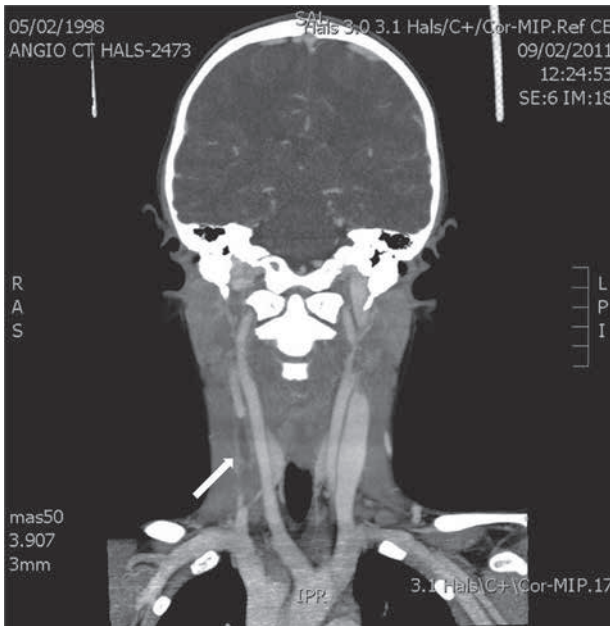

Fig. 1. —

thrombotic factors was performed. Results are listed in table 1. Patient was heterozygous for Factor V Leiden mutation. Factor II G20210A mutation was negative. aPC resistance was withheld as diagnosis. Protein S was decreased as a secondary phenomenon because of thrombosis. It was repeatedly measured afterwards, showing normal values.

Discussion

Over the past 70 years, numerous case reports and case series have described an association between venous thromboembolism (VTE) and inflammatory bowel disease. In 2001, a large Canadian population-based cohort study of adults with inflammatory bowel disease showed

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Table 1. — **Screening for thrombotic factors**

Marker	Value	Reference values
PT	84%	70-130%
aPTT	37.1 s	26.6-36.8 s
D-dimers	0.73 mg/l	< 0.50 mg/l
Fibrinogen	3.71 g/l	2.20-4.96 g/l
Protein C	72%	69-134%
Protein S	52%	72-123%
Antithrombine activity	91%	83-128%
Von Willebrand factor ag	113.5%	50-150%
aPC ratio	1.78	> 2.14
Lupus anticoagulans	negative	
Anticardiolipine antibodies	negative	
homocysteine	8.9 μmol/l	5.5-16.2 μmol/l

comparable incidence rates of thrombosis in patients with Crohn's disease and ulcerative colitis : 30/10.000 person-years for deep vein thrombosis and 20/10.000 person-years for pulmonary embolus (1). A more recent Danish population-based study showed incidence rates of venous thromboembolism of 24/100.000 person-years in IBD. Compared to a control group, the incidence was twice that of the general population (2). An important finding in this latter study was the strong effect of patient age on thromboembolic risk. In patients with IBD aged twenty years or younger, the annual incidence of VTE was low : 8.9 per 10.000 person- years, 85% less than that of persons 60 years of age or older. On the other hand, the relative risk of venous thromboembolism was approximately four times higher in children than in the elderly.

The pathogenesis of thrombosis in inflammatory bowel disease is probably multifactorial. Kappelman *et al*., in their study found that patients with IBD had a 50 % higher risk of VTE than controls, after adjusting for additional thromboembolic risk factors, suggesting that IBD is an independent prothrombotic risk factor (2). It is noteworthy that thrombosis is more frequent when IBD is in an active phase and the occurrence correlates with the extent of disease, suggesting inflammation playing a role in the pathogenesis. Particularly pancolonic involvement in ulcerative colitis and colonic involvement in Crohn's disease patients is correlated with thrombosis (3,4,5). Some authors suggest that as far as the risk for thrombosis is concerned, the IBD population might be divided into two sub-groups : the first and most prevalent one in which thrombotic complications develop during an active disease phase and where acquired risk factors play an important role and the second one, in which thrombosis develops during clinical remission and where hereditary risk factors appear to play a role similar to that in the general population (8). The patient we presented here probably belongs to the second group. In this patient, thrombosis occurred after recent trauma in a context of pre-existing aPC resistance. Moreover, this IBD patient was in clinical and biochemical remission for a long period.

Transient abnormalities of the coagulation system, including thrombocytosis, elevated factor V, factor VII, factor VIII, fibrinogen and lipoprotein a all have been reported, as well as deficiencies in protein S and antithrombin III (6). In a 2003 review article, Papa *et al*. demonstrated no differences in the prevalence of Factor V Leiden mutation, the prevalence of the Prothrombin gene mutation G20210A and the prevalence of the C677T mutation in the MTHFR gene (causing moderate hyperhomocysteinemia) in thrombotic IBD and thrombotic non-IBD patients (7). A recent study, comparing the prevalence of Factor V Leiden and G20210A mutation in the Prothrombin gene in thrombotic IBD and thrombotic non-IBD patients even showed a lower prevalence of inherited prothrombotic risk factors (8). This might suggest that acquired risk factors play a more important role in the pathogenesis of thromboembolism in IBD. Indeed, many acquired risk factors are present in IBD (Table 2) (9) and moreover, most of these acquired risk factors apply to an active/inflammatory disease state. Hyperhomocysteinemia, which is significantly more common in IBD patients compared to the general population is to be seen as an acquired risk factor because of its low levels of folate, vitamin B6 and vitamin B12 (3) and not due to gene mutations, such as C677T in the MTHFR gene (8). The frequently observed vitamin deficiencies in IBD patients are a result of low dietary intake, malabsorption, hypercatabolism and/or drug interference (3).

Thrombosis in IBD thus seems to be the result of multiple acquired risk factors and inflammation of the gut, which seems to be a risk factor per se (2). It is, however not very clear if coagulation abnormalities are the result of (chronic) inflammation or, play a role in mucosal inflammation and even in the pathogenesis of IBD.

Besides these abnormalities in coagulation, platelets also seem to play a role in IBD thrombosis through their

Table 2. — **Acquired prothrombotic factors in IBD**

Prolonged Immobilization
Surgery
Fluid depletion
Steroid therapy
Central venous catheters
Hyperhomocysteinemia/vitamin deficiencies

actions as well on arterial as on venous vessel wall. Throughout the course of several inflammatory conditions, including IBD, the adherence of platelets to the endothelium of the arterial wall has been shown to be an early manifestation of regional immune reactivity (10,11). Changes to the mucosal microvasculature in IBD have been observed and include : vascular injury, focal arteritis, fibrin deposition, microinfarction and neoangiogenesis. In venous microvessels from the gut of IBD patients, a downregulation in the expression of thrombomodulin and endothelial protein C receptor has been observed and is likely to exert an effect on the conversion of protein C to its activated form, thus promoting coagulation. It is interesting to know that TNF-α also has been shown to downregulate the expression of thrombomodulin and endothelial protein C receptor, indicating the influence of coagulation and inflammation on each other (12). Besides TNF-α, a potential role for homocysteine in microvascular inflammation in IBD may exist. Treatment of gut-derived endothelial cells with homocysteine results in endothelial inflammation, indicated by upregulation of VCAM-1, production of MCP-1 and phosphorylation of p 38. As a consequence, the endothelium has a greater capacity to adhere to T cells and monocytes. The process is blocked by treatment with folic acid (13).

Very often, reactive thrombocytosis occurs during the active phase of IBD. The reason for this greater number of platelets is not well understood and is not a unique feature of IBD, as it can also be seen in other inflammatory conditions such as rheumatoid arthritis or systemic lupus. Platelets in patients with IBD typically have a smaller mean corpuscular volume, which has been proposed as a marker of disease severity as it inversely correlates with sedimentation rate and level of C-reactive protein. Despite their smaller size, platelets tend to have an augmented granular content (14,15). In vitro studies have shown platelets of IBD patients to spontaneously aggregate in more than 30%, compared to none of control individuals, independent of disease severity (16). Moreover, platelet aggregates have been found in vivo circulating in IBD patients, but not in other disease states of chronic inflammation (17), indicating this as a feature typical of inflammatory bowel disease. Furthermore, Collins *et al*. showed that in patients with IBD platelets circulate in an activated state, demonstrated by the expression of surface activation markers P-selectin and GP53 and serum measurement of the platelet activation marker β-thromboglobulin (17). This activated platelet state was more recently confirmed by the detection of surface CD40 ligand, an activation marker allowing platelets to interact with numerous immune and non-immune cells (18).

As acquired risk factors appear to play an important role in thrombosis in IBD, major efforts to prevent thrombotic complications should focus on prevention and/or correction of acquired risk factors. Every physician who cares for IBD patients should always keep in mind that an increased risk for thrombosis exists. Antithrombotic treatment should be started in all clinical conditions that are associated with a greater risk for thrombosis, such as surgery and immobilization. In order to prevent thrombosis in IBD, a good and continuous control of disease activity as well as vitamin supplementation is recommended. Furthermore, many of the drugs with anti-inflammatory activity also modify coagulation, for example infliximab, 5- aminosalicylic acid and azathioprine. In the case in which thrombosis has occurred, treatment is equal to that of thromboembolic events in the general population (9). In figure 2, a flowchart on the management and evaluation of deep venous thrombosis is proposed. Considering that in IBD patients acquired and inherited risk factors can coexist, it seems advisable that each patient's individual risk is being assessed. If necessary, a maintenance therapy with anticoagulants should be considered.

Conclusion

Thrombosis is a potential complication of IBD, in adults as well as in children. Discussion remains whether a 'hypercoagulable state' is the result of IBD itself or is due to a combination of acquired prothrombotic risk factors. However, it seems to be that disease extent and disease activity correlate best with this 'hypercoagulable state' and thus prevention of thrombosis is – at least partially – obtained by good disease control. If thrombosis does occur, treatment is no different than in non-IBD patients.

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