

## **BALANCING THE THROMBOTIC RISK AND THE HEMORRHAGIC RISK IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AND DEEP VEIN THROMBOSIS. CASE REPORT**

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**BALANCING THE THROMBOTIC RISK AND THE HEMORRHAGIC RISK IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AND DEEP VEIN THROMBOSIS - CASE REPORT (Abstract):**

The thrombotic events occurring in patients with inflammatory bowel disease are currently recognized as a form of extraintestinal manifestation of the disease. We present the case of a 35-year-old Caucasian male with inflammatory bowel disease and deep vein thrombosis, drawing attention to the particularities of the venous thrombotic events in this category of patients: high thrombotic risk, peak incidence at young age, high risk of recurrence. We state the correct anticoagulant treatment based on current evidence and guidelines recommendations, highlighting the importance of a careful assessment of both the thrombotic and hemorrhagic risk of the patient. Special attention has been paid to the new oral anticoagulants and to the latest recommendations of specialized guidelines.

**Keywords:** ANTICOAGULANTS, VENOUS THROMBOEMBOLISM, INFLAMMATORY BOWEL DISEASE.

Inflammatory bowel disease (IBD) is a chronic inflammatory condition characterized by local and systemic inflammation, predominantly affecting the gastrointestinal tract. The two major forms are Crohn's disease (CD) and ulcerative colitis (UC).

The association between IBD and venous thrombosis was first described in 1936 by Barger and Barker (1). Further studies (2,3) have shown that IBD patients have a 2 to 3 fold increased risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE) compared to the general population and the thrombotic risk

is almost three times higher in males than in females. No significant differences in the risk of venous thromboembolism (VTE) are found between UC and CD patients (4). The main sites of thrombosis are the deep veins of the lower limbs and the pulmonary system (5). Less frequently, the thrombosis may develop in the cerebrovascular system, hepatic, portal, retinal and mesenteric veins (4).

### **CASE REPORT**

We present the case of a 35-year-old Caucasian male who presented with pain in

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his right thigh with a 24-hour onset. The thigh was enlarged in volume, but without changes in color or local temperature. The patient denied any trauma in that area. At the age of 30 he was diagnosed with a limited form of ulcerative colitis (proctosigmoiditis) and at the time of the current presentation he was on treatment with mesalazine 1000 mg twice daily. He was a non-smoker. Venous ultrasound confirmed the deep vein thrombosis of the superficial femoral vein, the fresh thrombus occupying the lower third of the vein. Anemia was absent. The IBD was in remission. The patient's chronic treatment does not favor thrombosis; on the contrary, mesalazine has the advantage of reducing platelet activation.

The anticoagulant treatment was started with low molecular weight heparin (LMWH - enoxaparinum), with favorable outcome. Pain and swelling have rapidly diminished, being absent at discharge. Given the presence of UC, the main challenge was the management of the antithrombotic therapy, because patients with IBD are at high risk of both VTE and gastrointestinal bleeding.

### **DISCUSSION**

We started by evaluating the substrate of the prothrombotic state to fit the current thrombotic event into one of the two categories: provoked or unprovoked DVT.

The genetic mutations which are causes of inherited thrombophilia have similar incidence in IBD patients and in the general population, suggesting that the acquired factors play a crucial role in the occurrence of thrombosis. The clinical studies have shown no association between IBD and Factor V Leiden, prothrombin G20210, MTHFR or Factor XIII val34leu,

respectively. Therefore, the available guidelines do not recommend thrombophilia testing in patients with IBD and VTE, including the patients with unprovoked VTE while their IBD is in clinical remission (6). Accordingly, we did not do thrombophilia testing in our patient.

The role of inflammation in IBD pathogeny has been heavily debated over the years. Indeed, the inflammatory cytokines affect the coagulation cascade, fibrinolysis, and platelet functions. Because some of the coagulation factors are also acute-phase reactants, if the prothrombotic state is triggered by the inflammation or represent a feature of the intestinal disease per se is still a matter of debate. More recently, high levels of circulating microparticles have been found in IBD patients during active phases of the disease. Decreased natural anticoagulants (antithrombin III activity, proteins C and S, tissue factor pathway inhibitor) (7) and a disturbed fibrinolysis (reduction in fibrinolysis activators such as tPA and increase in inhibitors such as PAI-1 and TAFI) complete the complex anomalies of the coagulation system. Endothelial dysfunction and the quantitative, morphological and qualitative alterations in platelet characteristics also contribute to the prothrombotic state of this disease.

Despite the many above mentioned, inflammation does not seem to be the main player in this disease. Miehsler et al. (8) compared the thromboembolic risk of patients with IBD with that of patients with celiac disease and rheumatoid arthritis. While an association between the high frequency of thromboembolic events and IBD was established, no such association was found in patients with other systemic inflammatory conditions such as celiac disease and rheumatoid arthritis. A pro-

coagulant tendency unequivocally exists in IBD patients, but unfortunately no abnormality has been shown to be a marker for the thrombotic risk in IBD.

The incidence of VTE in the general population increases with age, but in IBD patients the highest risk for VTE is observed among those less than 40 years of age, with an incidence rate ratio for VTE of 4.5 when compared with the non-IBD patients (9, 10). Our patient was 35 years old at the time of the thrombotic event, so he fit the pattern. The younger the age at the first thrombotic episode is, the higher the risk of recurrence (3). The thromboembolic complications occur more frequently during the active phases of the disease and in patients with extended disease (11). Moderate and severe disease flares significantly increase the risk of VTE in IBD patients and should be considered as a provoking factor. But the thromboembolic complications are also seen in almost one third of the patients with partial or full remission (11). In our case, the patient had a limited form of disease and he was in remission when the thrombotic event occurred, so disease flares were excluded as provoking factor. No other provoking factors have been identified. IBD patients who experience their first episode of unprovoked VTE have a 33% risk of recurrence within 5 years. The risk of recurrence is 2.5-fold higher than that of non-IBD patients after an initial episode of unprovoked VTE (3).

All these data suggest that IBD is a continuing risk factor for recurrent VTE and, therefore, indefinite anticoagulant therapy should be recommended in patients who are diagnosed with their first episode of unprovoked proximal DVT when in clinical remission (12). It seems that benefits of long-term anticoagulation in reducing re-

current VTE in IBD patients who have had unprovoked VTE outweigh the risks of the associated bleeding (2). The need for anticoagulation should be revised at least annually.

The first European evidence-based consensus on extraintestinal manifestations in inflammatory bowel disease (13) states that the treatment of VTE in IBD patients follows the same protocols as for non-IBD patients. So, we start the treatment with LMWH. Long-term anticoagulant treatment usually comprises a vitamin K antagonist (VKA) or a non-vitamin K antagonist oral anticoagulant (NOAC). Meta-analysis regarding efficacy and safety of NOACs as compared with VKA in the treatment of VTE have shown that NOACs have comparable efficacy to that of VKAs and are associated with a significantly lower risk of bleeding complications (odds ratio 0.63, 95% CI 0.44-0.90) (14). In terms of major gastrointestinal bleeding, a recent meta-analysis (15) reported low relative risk for rivaroxaban and apixaban and elevated relative risk for dabigatran when compared to warfarin. This might be explained by an individual drug effect or a difference between drug classes (FIIa inhibitors and FXa inhibitors). No separate data regarding bleeding risk were reported for edoxaban.

A meta-analysis of the clinical trials in the atrial fibrillation population confirmed a significantly increased risk of gastrointestinal hemorrhage with NOACs compared with VKA (16). Apixaban was not associated with this bleeding outcome in either the VTE or atrial fibrillation studies (17), so this medication may be more appropriate in patients who experienced a gastrointestinal hemorrhage or who are at risk for this complication. No significant difference was found between NOACs and comparators

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for extended treatment of VTE.

All studies on NOACs for VTE treatment suggest that they have comparable efficacy to that of VKAs with a more favorable safety profile, but there is no direct evidence for their use in IBD patients yet, so our treatment respected the so far existing evidence. We were able to find just one case report (18) of NOAC use (rivaroxaban) in a patient with VTE and IBD.

In terms of surgical recommendations, VTE is not an indication for an invasive procedure and despite a very limited experience colectomy per se seems not to be able to protect from recurrent thromboembolic events.

## CONCLUSIONS

We presented a case of IBD complicated with DVT as extraintestinal manifestation of the disease with the aim of raising awareness of the thrombotic risk in these patients. Considering that patients with IBD are at high risk of both VTE and gastrointestinal bleeding, we highlighted the importance of accurately assessing the duration of anticoagulant therapy. The latest guidelines mention that in the treatment and secondary prevention of VTE, NOACs have comparable efficacy to VKAs, with a more favorable safety profile, but it is also stated that there is no direct evidence for NOACs use in IBD patients yet.

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## NEWS

### ELECTROSPUN NANOFIBER ORIENTATION INFLUENCES WOUND CLOSURE

Nanofibers resemble the natural extracellular matrix of the human body. Furthermore, polymer nanofibers provide an ideal environment for wound healing. A recent study aimed to evaluate the pure topographical effects that an underlying scaffold material may have on fibroblast behaviour in a novel *in vitro* wound model, which included poly- $\epsilon$ -caprolactone scaffolds with different nanofiber alignment. A stencil based wound assay with L929 murine fibroblasts was used to study the closure of circular wounds over time. Triggering fibroblast migration into the wound accelerates the remodeling of the dermis. Cell viability, morphology and mobility – in fact a combination of proliferation and migration, since both occur during the natural wound healing process - were assessed. The study emphasizes the important effect of orientation on increasing cell mobility, polarization and elongating cell morphologies compared to random fiber scaffolds (Ottosson M, Jakobsson A, Johansson F. Accelerated Wound Closure - Differently Organized Nanofibers Affect Cell Migration and Hence the Closure of Artificial Wounds in a Cell Based *in vitro* Model. *PLoS ONE* 2017; 12(1): e0169419. doi:10.1371/journal.pone.0169419).

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