Retroperitoneal Hematoma in a Hemodialysis Patient Receiving Low Molecular Weight Heparin

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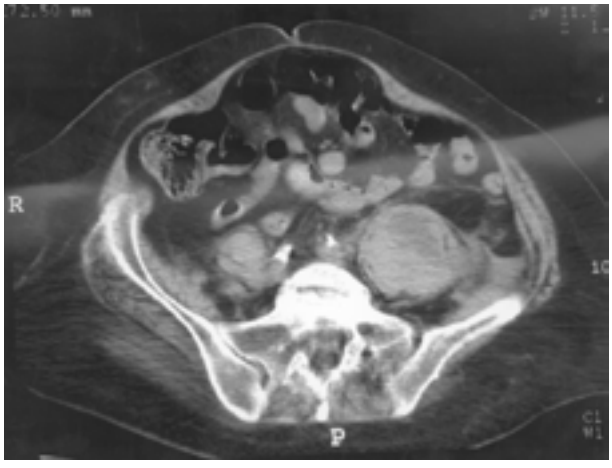
Low molecular weight heparin represents a significant advance over unfractionated heparin for venous and arterial thrombosis. Developed in the late 1980s, LMWH has become an excellent alternative to unfractionated heparin because it offers superior efficacy and safety, shows improved pharmacokinetics, has a longer half-life, and permits once- or twice-daily subcutaneous administration, without the need for laboratory monitoring [1]. Enoxaparin, a LMWH, is indicated for ischemic complications of unstable angina, non-Q wave myocardial infarction, and the prevention and treatment of venous thromboembolism [2]. Spontaneous retroperitoneal hematoma associated with the use of enoxaparin has not been widely reported. We describe a patient on hemodialysis who developed retroperitoneal hematoma while on enoxaparin.

Patient Description

A 70 year old patient with acute renal failure was admitted to the hospital. She had been seen and treated for transitional cell carcinoma of the bladder 3 years previously. Kidney biopsy showed pauci-immune crescentic glomerulonephritis. Hemodialysis was begun and the patient received pulses of methylprednisolone and cyclophosphamide and was discharged. Five days later she was readmitted due to thrombosis of the right iliac vein and Klebsiella sepsis. The patient was treated with antibiotics and subcutaneous enoxaparin 1 mg/kg twice a day. During the following week hemoglobin level fell progressively to 7 g/dl. Swelling of the left leg occurred. A computerized tomography scan demonstrated a hematoma that involved the groin and the left side of the retroperitoneum [Figure]. LMWH was stopped. A Tenckhoff catheter for peritoneal dialysis was placed until renal function improved. Today the patient is dialysis-free.

Comment

We describe a hemodialysis patient under anticoagulation with enoxaparin, complicated with severe retroperitoneal hematoma. Determinations of anti-factor Xa were not done. Unlike unfractionated heparin, which has equivalent activity against factor Xa and thrombin, low molecular weight heparin has a greater activity against factor Xa, produces a more predictable anticoagulant response, and has better bioavailability, longer half-life and dose-independent clearance. LMWHs cause less bleeding than unfractionated heparin in laboratory animals, for several reasons: it binds less to platelets; unlike unfractionated heparin LMWH does not increase microvascular permeability. It has lower affinity for endothelial cells and high molecular weight forms of Von Willebrand factor. Anti-Xa activity can be used as a biologic marker of LMWH activity. Because of the more predictable anticoagulant response to subcutaneous administration of LMWHs compared with unfractionated heparin, routine monitoring of anti-Xa activity in clinically stable adults with uncomplicated disease is not recommended. Data on the pharmacokinetics of LMWH in patients with renal failure are controversial. In early single-dose studies, after subcutaneous or intravenous administration [3], the authors concluded that end-stage renal disease has little effect on the pharmacokinetics of enoxaparin,



Axial pre-contrast enhancement pelvic CT image at the level of the iliac bones showed enlargement of the left psoas muscle with a hypodense mass.

LMWH = low molecular weight heparin

and dosing adjustments are unnecessary. In contrast, in other studies, the half-life of anti-factor Xa activity was significantly prolonged in patients with differing degrees of renal dysfunction, including hemodialysis patients [4].

There are pharmacokinetic differences between the various types of LMWH. Indeed, enoxaparin has a greater plasma anti-Xa activity and more renal excretion as compared to dalteparin and nadroparin. The use of enoxaparin may result in increased bleeding complications in patients with renal insufficiency. A case of fatal abdominal and retroperitoneal bleeding in a dialysis patient receiving tinzaparin and aspirin was recently described by Farooq et al. [5]. They advise that the initial enoxaparin dose be reduced by 16% of the recommended dose in patients with chronic kidney disease stage 3, by 44% of the usual treatment in stage 4, and possibly even more in stage 5 to avoid severe or even fatal outcomes.

Since excessive anticoagulation has been described even in patients with mild renal insufficiency during treatment with enoxaparin, it has been advised that physicians monitor anti-factor X activity in these patients to avoid a possible accumulation phenomenon. Because the optimal dosage of LMWHs has not been established for patients with renal insufficiency or extremes of body weight, during pregnancy, or for premature newborns, anti-Xa activity monitoring may be warranted in these subsets. Whether this monitoring can prevent major bleeding in these subjects remains to be clarified in further studies.

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Recurrent and Bilateral Deep Vein Thrombosis in a Crohn's Patient

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Clinical assessment of patients presenting with a thromboembolic event necessitates an evaluation of probable risk factors including immobilization, occult neoplasms, prior surgery, or an existing hypercoagulable disorder. Although a significant body of evidence suggests inflammatory bowel disease as a risk factor for TE events, clinical guidelines to date are yet to include this condition as a risk factor. We report a patient with Crohn's disease who developed recurrent deep vein thrombosis (DVT).

TE = thromboembolic
DVT = deep vein thrombosis
IBD = inflammatory bowel disease

Patient Description

A 59 year old woman with Crohn's disease and a previous history of right leg DVT was admitted for a 3 week complaint of bilateral swelling below her knee and mild difficulty in walking. Two weeks prior to her present admission she had been hospitalized for exacerbation of her bowel disease with a diagnosis of small bowel obstruction, which was treated conservatively. On admission, physical examination revealed mild to moderate bilateral swelling and mild calf tenderness. The diagnosis of DVT was confirmed by Doppler ultrasound. Laboratory tests were unremarkable except for elevated D-dimer (391 µg/ml). Tests for hypercoagulable states including homocysteine, antithrombin-III, β2-glycoprotein I, protein S, protein C, anticardiolipin antibodies, lupus anticoagulant, anti-β2-glycoprotein I antibodies, activated protein C resistance (Factor V Leiden), prothrombin G20210A mutation and the C677T variant of methylenetetrahydrofolate reductase were all within normal range. The patient denied smoking and any family history of TE events. Menstruation was normal until the age of 49 and the patient did not use hormone replacement therapy.

Eight years prior to the mentioned hospitalization the patient had been diagnosed with Crohn's disease. No

extra-intestinal manifestations were ever documented. During the year prior to the current event, she reported five exacerbations of her Crohn's disease, three of which required hospitalization. At that time (8 and 12 months prior to her current admission), the patient was diagnosed with DVT of the right tibial and popliteal veins, with recurring thrombosis after anticoagulant therapy [Figure]. Interestingly, exacerbation of the bowel disease and recurrence of the thrombosis coincided [Figure].

Comment

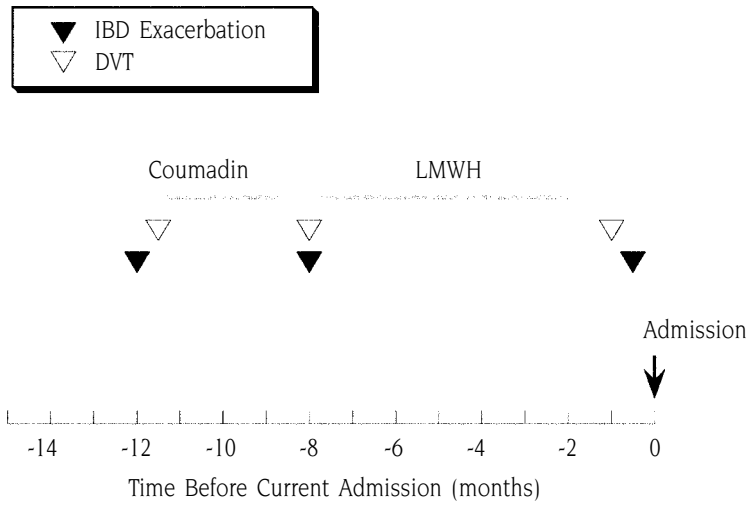
As in the patient presented here, the impression by clinicians that IBD patients have an increased risk for TE events has prompted several studies aimed at determining this relationship. Two large cohort studies have shown that the overall incidence of TE events is about 6.5% in both Crohn's disease and ulcerative colitis patients, with a threefold increase in the chance for a systemic TE event as compared to the general population [1,2]. However, the fact that in autopsies the incidence of systemic thromboembolism is nearly sixfold higher than seen in clinical studies [3] suggests that a large proportion of the cases remain undiagnosed. These figures raise the possibility that thromboembolism is a more common extra-intestinal manifestation than previously believed.

IBD patients have increased risk for both focal microthrombi in the vasculature of the inflamed intestine and systemic TE events, which leads to extensive morbidity and mortality. Systemic TE events occur mainly in the venous circulation but can also develop in the arterial circulation. Deep vein thrombosis and pulmonary embolus are the most common types of TE, but thromboses are also reported in unusual sites such as cerebral, innominate, retinal, hepatic and mesenteric veins [1].

The degree of activity and the extent of inflammatory intestinal disease in Crohn's patients correlate well with the patient's risk for a TE event. In two large cohort studies, about 70–90% of Crohn's patients who experienced a TE event had at least one clinical manifestation of active bowel disease, and in turn, normalization of the hypercoagulable state attenuated inflammation [1,4]. The present case is an extreme example of the tight coupling between active bowel inflammation and a hypercoagulable state, as evidenced by the synchronization between exacerbations in bowel disease and the occurrence of TE events [Figure].

It is well recognized that the development of a thrombotic process in IBD patients does not involve a single component of the clotting system but is multifactorial, including hyperhomocysteinemia, antiphospholipid antibodies, spontaneous platelet aggregation, endothelial dysfunction, hypofibrinolysis and increased level of the coagulation components [5]. In addition, the degree of bowel inflammation is a critical factor that contributes to hypercoagulability. Yet, the fact that it is absent in other chronic inflammatory diseases such as celiac disease and rheumatoid arthritis emphasizes its multifactorial nature [1].

We conclude that patients with IBD are at increased risk for thromboembolic events. As such, modifiable risk factors should be minimized, early mobilization should be encouraged, and supplementation with folate and vitamins B6 and B12 should be prescribed to control the homocysteine level. Furthermore, since execrations of bowel inflammation in these patients coincide with TE events, we suggest that clinicians be aware of the risk during and following these events.



Sequence of bowel exacerbation events (black triangles) and DVT (white triangles). Only bowel exacerbations that required hospitalization are indicated. Anticoagulation therapy with coumadin or low molecular heparin (LMWH) is indicated by a grey horizontal line.

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