INSIDIOUS COMPLICATION OF ULCERATIVE COLITIS - CLINICAL DETERIORATION DUE TO OCCULT AND UNEXPECTED EXTRAINTESTINAL COMPLICATION

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ABSTRACT

***Introduction**: Thromboembolic disease, including venous thrombosis and pulmonary embolism, is a well-established extraintestinal complication of inflammatory bowel disease (IBD). The frequency of these potentially lethal events mandates improved vigilance in clinical practice.*

***Case presentation**: A 28-years old man with no prior medical history was admitted through our Emergency Room for the first flare of extensive ulcerative colitis of moderate-severe activity. Due to a complex disease course requiring prolonged hospitalization, he was started on low dose low-molecular-weight heparin as a primary prophylaxis of venous thromboembolism. He became febrile after four weeks reporting just slight chest discomfort with no other symptoms. The occurrence of fever coincided with the ongoing study at our Department that included measurements of levels of blood coagulation factors and fibrin degradation products. Laboratory findings were consistent with acute thrombosis and despite low probability of pulmonary embolism according to Wells' criteria, no signs of peripheral deep venous thrombosis and no known accountable predisposing factors, we decided to do pulmonary angiography that revealed pulmonary embolism.*

***Discussion**: In the presented case, suspicion of pulmonary embolism was raised merely by the accidental laboratory findings suggestive of acute thrombosis, since our patient's clinical symptoms were initially ascribed to a more probable hospital-acquired pneumonia. However, clinical presentation of pulmonary embolism is often nonspecific. Whether a high-grade fever was atypical presentation of pulmonary embolism or was due to obscure infectious complication remains difficult to determine retrospectively.*

***Conclusion**: Our case illustrates how most atypical and unexpected scenarios are possible in IBD patients with thromboembolic complications. It also raises the question of need to alleviate the diagnostic criteria for pulmonary embolism in this high-risk group of patients in order to reduce mortality by prompt diagnosis and therapy.*

***Key words**: Colitis, ulcerative, inflammatory bowel disease, pulmonary embolism, thromboembolism.*

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Introduction

The two major forms of idiopathic inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease, are disorders of uncertain etiology characterized by inflammation of the gastrointestinal tract and numerous extraintestinal manifestations, thromboembolic disease being one of them[1,2].

The prothrombotic tendency in IBD, resulting mainly in pulmonary embolism (PE) and deep venous thrombosis (DVT), was recognized over seventy years ago[3], the exact pathogenetic mechanisms are still unclear today. In contrast to general population, where the incidence increases exponentially with age[4], IBD patients that develop thrombosis tend to be younger. In addition to well-established acquired risk factors for venous thromboembolism (VTE) and specific coagulation defects and gene mutations that account for hereditary trombophilia, the trigger for thromboembolism in IBD can not be identified in more than a half of those affected[5].

It is estimated that thromboembolic events are three-fold more likely in IBD patients compared to controls[6], with the risk being even higher during disease flares[7]. Incidence of these events in different clinical studies was reported at rates ranging

from 1% to 7%[3,5,6] with VTE mortality rates in this population ranging from 8% to 25%[5,8]. Some studies indicate that the colonic involvement in Crohn's disease and extensive disease in ulcerative colitis, in addition to disease activity, influence the overall risk[7]. However, thromboembolic events are also reported in patients with well-controlled disease as well as after proctocolectomy[5]. Therefore, since these events are neither infrequent nor can be foreseen, the initial diagnosis of IBD should trigger routine assessment of thrombosis risk in order to prevent these potentially lethal complications[9]. Even though clinical practice guidelines recommend VTE prophylaxis during the acute phase of inflammatory bowel disease, there is no standardized approach among gastroenterologists regarding this issue[10,11].

We present a case that demonstrates unpredictability and insidious nature of thromboembolic events occurring in IBD patients: a young man diagnosed with occult pulmonary embolism without demonstrable concomitant deep vein thrombosis during the first flare of severe, extensive ulcerative colitis while on prophylactic doses of low-molecular-weight heparin, whose only provoking factor seems to be the disease itself.

Case presentation

A 28-years old patient with no prior medical history was admitted through our Emergency Room for frequent, loose, bloody stools, abdominal pain and tenesmus with unceasing symptoms during the preceding two months. He was a long-distance runner who led a healthy life, was a non-smoker and his family history was negative for thromboembolic events. At the time of admission, he reported five bloody stools/day with passage of mucus. His vital signs were stable with body temperature 37.2C, blood pressure 105/60 mmHg, heart rate 72/min and body-mass index of 22.2 kg/m^3. On palpation, there was a moderate tenderness in the left hemiabdomen. Initial laboratory tests revealed iron deficiency anemia (Table 1). Based on the clinical presentation and after ruling out the infectious etiology, the diagnosis of inflammatory bowel disease was made. No inflammatory changes were found on upper GI endoscopy and small bowel series with barium swallow. Rectosigmoidoscopy combined with biopsies findings were consistent with the diagnosis of ulcerative colitis. Total colonoscopy was not performed due to disease activity, but flat plate of the abdomen and multislice computed tomography indicated extensive colitis. Based on Truelove and Witts' criteria, our patient had moderate-severe disease and was started on oral (4g) and topical mesalazine (500mg), oral prednisolone (40 mg/day) and intravenous antibiotics (metronidazole 1500 mg/day, ciprofloxacin 400 mg/day), providing intravenous fluid and electrolyte replacement. Since there was no clinical response to initial therapy after nine days, he was switched to intravenous corticosteroids (methylprednisolone 60 mg/day). Follow-up endoscopy performed 15 days after admission revealed endoscopic improvement. Because of the prolonged hospitalization, he spent 45 minutes a day exercising under physiotherapist's observation and enoxaparin 0.6 ml subcutaneously once daily was given as a part of VTE prophylaxis.

		Normal range (adult)
Hemoglobin	78 g/L	138-175 g/L
Hematocrit	0.26	0.415-0.53
MCV	67.0 fL	83-97.2 fL
Iron, serum	3 umol/L	11-32 umol/L
Unsaturated Iron Binding Capacity	66 umol/L	25-54 umol/L
Total Iron Binding Capacity	69 umol/L	
Ferritin, serum	9.62 ug/L	30-400 ug/L
Platelet count	292x10^9/L	158-424x10^9/L
White blood cell (WBC) count	5.76x10^9/L	3.4-9.7x10^9/L
PT	0.76	>0.7
aPTT	26.0 s	24-33 s
Fibrinogen	2.6 g/L	1.8-4.1 g/L
AST	24 U/L	11-38 U/L
ALT	26 U/L	12-48 U/L
GGT	54 U/L	54 U/L
Alkaline Phosphatase	69 U/L	11-55 U/L
Total bilirubin	13 umol/L	3-20 umol/L
Creatinine	81 umol/L	79-125 umol/L
Blood Urea Nitrogen	6.4 mmol/L	2.8-8,3 mmol/L
C-Reactive Protein	3.45 mg/L	<5 mg/L

Table 1: Initial laboratory tests.

During the course of the disease, a significant weight loss was noted (BMI 19.6 kg/m^3, 8.5 kg loss in a 30-day period) in addition to low serum albumin levels (28.3 g/L) despite enteral nutrition supplements. He was therefore started on parenteral nutrition administered intravenously through a peripheral vein on 30th day of hospitalization, but

became febrile (39.0 C) the same day with no obvious localizing signs. Upon collecting samples for blood cultures (pathogens were not isolated), he was switched to empiric broad-spectrum antibiotic therapy (meropenem 3g/day).

At that time, there was an ongoing study at our Department that included measurements of the levels of blood coagulation factors and fibrin degradation products in hospitalized IBD patients. The testing of our patient coincided with the fever flare. Laboratory tests revealed high D-Dimers (3.45 mg/L, reference range <0.5) and factor VIII levels (2.42 kIU/L, reference range 0.5-1.49 kIU/L), low protein S (44.7%, reference range 65.0-140.0%) and low protein C activity (61.0%, reference range 70.0-140.0%). These findings indicated acute thrombosis which prompted us to perform additional testing. He negated dyspnea but, when asked precisely, mentioned only a slight chest discomfort that he failed to report since he regarded it irrelevant. His heart rate was normal (80/min), respiratory rate 12-15/min, blood pressure 95/60 mmHg, he showed no symptoms or signs of upper or lower extremity deep venous thrombosis, arterial hemoglobin saturation was >95% on room air and his electrocardiogram and chest x-ray showed no abnormalities. Routine laboratory findings were nonspecific (Table 2).

		Normal range (adult)
Hemoglobin	101 g/L	138-175 g/L
Hematocrit	0.317	0.415-0.53
MCV	71.2 fL	83-97.2 fL
Platelet count	$265x10^9$/L	$158-424x10^9$/L
White blood cell (WBC) count	$9.5x10^9$/L	$3.4-9.7x10^9$/L
PT	0.71	>0.7
apTT	25.8 s	24-33 s
Fibrinogen	3.3 g/L	1.8-4.1 g/L
AST	41 U/L	11-38 U/L
ALT	54 U/L	12-48 U/L
GGT	47 U/L	54 U/L
Alkaline Phosphatase	37 U/L	11-55 U/L
Total bilirubin	9 umol/L	3-20 umol/L
Creatinine	92 umol/L	79-125 umol/L
Blood Urea Nitrogen	5.7 mmol/L	2.8-8,3 mmol/L
C-Reactive Protein	5.4 mg/L	<5 mg/L

Table 2: Laboratory tests, pulmonary embolism workup.

Although Wells' criteria classified him into low risk group for pulmonary embolism (1.3%) we decided to perform pulmonary angiography which showed endoluminal defects in the distal segment of the right lower lobe pulmonary artery as well as in its segmental branches indicating acute pulmonary embolism. Angiography excluded thrombosis of inferior vena cava, pelvic and femoral veins. Doppler ultrasound showed no signs of venous thrombosis in the lower extremities. Echocardiography was normal. Treatment with therapeutic doses of enoxaparine (0.6 ml subcutaneously twice daily) followed by administration of warfarin on the same day was initiated. We then performed screening for inherited thrombophilia, factor V Leiden mutation and prothrombin gene mutation, but no abnormalities were identified. Deficiencies in protein C, protein S and antithrombin could not be assessed due to ongoing anticoagulant therapy. Lupus anticoagulant was negative and anti-cardiolipin antibodies were detected in a moderate titers: IgG 26 U/ml (reference range: <10 negative, 10-20 weakly positive, 20-40 moderately positive, >40 strongly positive), IgM 13 U/ml (reference range: <10 negative, 10-20 weakly positive, 20-30 moderately positive, >40 strongly positive).

Over the following three weeks, INR was in the therapeutic range, symptomatic remission of inflammatory bowel disease was achieved and the patient was discharged with warfarin therapy, oral corticosteroids and azathioprine, which was started as medication for maintenance of remission.

Discussion

Acute pulmonary embolism (PE) is a common and often fatal manifestation of IBD patients, its occurrence being particularly high during the first year of disease[12]. The spectrum of clinical presentation ranges from asymptomatic to dramatic. Often nonspecific presentations represent a true diagnostic challenge.

In the case we presented, suspicion of PE was raised merely by the accidental laboratory findings suggestive of acute thrombosis. Patient's clinical symptoms, slight chest discomfort and fever in a setting of prolonged hospitalization, immunosuppression and heparin therapy pointed more to the hospital-acquired pneumonia rather than atypical PE[13].

The decision to perform additional diagnostic evaluation was based on a subjective risk assessment. According to clinical prediction rules (Revised

Geneva score, Wells score), there was a low clinical probability of PE; in fact, there were no accountable predisposing factors (recent surgery or trauma, personal or family history of VTE, malignancy, central venous lines, immobility, varicose veins, obesity, smoking, factor V Leiden and prothrombin gene mutation)[14], there were no signs of peripheral thrombosis and he was receiving primary VTE prophylaxis. On the other hand, PE may be unprovoked in 20% of cases[15] and when it comes to IBD patients, the percentage is even higher[5]. PE can occur from any site of DVT formation but in many instances, no peripheral source of thrombosis is ever identified[5,14]. Finally, the disease specific-risk factors were taken into consideration including the fact that IBD patients develop thrombosis at the younger age (<50 years) and that he was diagnosed with severe extensive colitis which further increases the relative risk of acute thrombosis in this patient population[5,7].

As mentioned above, the nonspecific clinical deterioration was not evocative of PE, and in retrospective it is difficult to determine whether it was due to thrombosis or concomitant obscure infectious complication. Therefore, the developed thromboembolic event itself can be regarded as asymptomatic. Occult PE is not infrequent, with the incidence of up to 30% in those with symptomatic DVT[16], however, the incidence in patients with occult peripheral thrombosis, as in the case we presented, is unknown[17]. Most fatal pulmonary emboli are never suspected and go undiagnosed[14]. Knowing that IBD patients have a three-fold increased risk[6], that the disease itself is an independent risk factor[2] and that symptoms of PE may be incorrectly interpreted in the setting of the underlying condition[17], we are impelled to alertness for PE while treating our patients. We also must address the question of need to alleviate diagnostic criteria for PE in IBD patients in order to reduce mortality by timely diagnosis and therapy.

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