CASE REPORT

Thromboembolism in active ulcerative colitis

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SUMMARY

Inflammatory bowel disease (IBD) has a range of both intestinal and extraintestinal manifestations. Thromboembolism involving the arterial and/or venous systems is rare. Early recognition and treatment of thrombosis in patients with IBD may prevent progression and minimise complications. However, clear guidelines on the duration of treatment and indications for primary prophylaxis need to be established. We report a case of a young patient with ulcerative colitis, who developed multiple site arterial and venous thrombosis, all occurring within short intervals of each other.

BACKGROUND

Inflammatory bowel disease (IBD) is associated with a range of extraintestinal manifestations, though their pathogenesis is poorly understood. The most common are sacroiliitis and peripheral arthritis. Ocular, mucocutaneous and vascular complications are rarely seen.¹

The elevated risk of thromboembolism in patients with IBD has been well documented. Patients with IBD have an overall threefold increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism (PE) compared with the general population.² In those with an active flare, this risk is eightfold.³ The arteries and veins in the upper and lower limbs, digits, cerebral and retinal vasculature, pulmonary, portal, hepatic, retinal, mesenteric and cardiac systems have all been reported to be involved with thromboembolic events.⁴

CASE PRESENTATION

A 47-year-old man presented to Nambour General Hospital following a witnessed generalised tonic-clonic seizure. This was on the background of newly diagnosed and poorly controlled ulcerative colitis (UC), with symptoms of urgency, frequency (between 8 and 12 motions per day) and intermittent haematochezia stretching back 30 years. He never smoked, consumed less than two standard drinks weekly and had a normal body mass index.

He had been diagnosed with UC 5 months prior to his hospitalisation and was given 50 mg 6-mercaptopurine (6-MP). This was increased to 75 mg after 3 months, but due to side effects (severe nausea, vomiting and dysgeusia), he ceased his medication. His disease control suffered, evidenced by increased stool frequency (8–12 motions per day), raised inflammatory markers (C reactive protein 105 mg/L, erythrocyte sedimentation rate 90 mm/

hour) and normocytic anaemia (Hb 97 g/L). He was convinced to restart a regimen of 50 mg 6-MP with 10 mg prednisolone daily, 3 weeks prior to his hospital admission.

Two weeks prior to hospitalisation, he developed acute severe left wrist and forearm pain after lifting a heavy object. His pain progressed and his limb became pale and cool. No symptoms of left-sided weakness or paraesthesia developed.

A plain film radiograph and soft tissue ultrasound scan of the left wrist were normal. MRI demonstrated mild synovitis of the first carpometacarpal joint. A subsequent duplex ultrasound scan confirmed a left radial artery occlusion from its origin to the wrist, with a patent ulnar artery. Before anticoagulation treatment could be initiated, he suffered a generalised tonic-clonic seizure lasting 5 min. He was admitted to Nambour General Hospital under a general medicine team, with input from the vascular, neurology and gastroenterology teams.

While neurological examination was normal, he was given levetiracetam as an electroencephalogram demonstrated epileptiform discharges over the left fronto-temporal regions.

The left hand had reperused and was warm with a palpable ulnar pulse but no radial pulse. No sensory or motor deficit was evident. An MRI of the left arm did not show evidence of vasculitis, but again confirmed the radial artery occlusion (figure 1).

In hospital, an initial non-contrast CT brain demonstrated a focus of hypoattenuation within the left frontal lobe with no evidence of haemorrhage. A postcontrast CT showed no enhancement within the area (figure 2). An MRI 2 days later revealed a dural sinus venous thrombosis with cortical extension and evidence of postinfarct petechial haemorrhage (figure 3). Anticoagulation was again deferred due to the potential risk of further bleeding.

Three days after admission, his right upper limb had become swollen, erythematous and tender. Radial and ulnar pulses were preserved. A duplex ultrasound scan revealed superficial thrombophlebitis of the cephalic vein in the forearm and DVT involving the radial, basilic and axillary veins. A CT of the chest, abdomen and pelvis was performed, and while no evidence of neoplasm or lymphadenopathy was identified, multiple subsegmental pulmonary emboli were found. He was, therefore, given a heparin infusion and bridged to warfarin.

INVESTIGATIONS

Our patient had no previous personal or family history of venous thromboembolism (VTE).

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Figure 1 Three-dimensional time resolved magnetic resonance angiogram (time-resolved angiography with stochastic trajectories) left arm. The thick white arrow indicates an abrupt cut-off of the proximal radial artery, with no flow distally. The thin white arrow indicates the normal ulnar artery and the arrow head the interosseous artery.

Figure 3 Susceptibility weight image (sequence of MRI brain. White arrow indicates a tortuous thrombosed cortical vein.

Vasculitis and thrombophilia screens (antinuclear antibody and extractable nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibodies and cytoplasmic anti-neutrophil cytoplasmic antibodies, rheumatoid factor, anticardiolipin antibodies, Protein C and S, Factor V Leiden mutation, lupus anticoagulant, antithrombin III, JAK2 V617F mutation and hyperhomocysteinaemia) were normal, other than an atypical P-ANCA (160).

Figure 2 Sagittal cerebral CT angiogram. Black arrow demonstrates normal sagittal sinus. White arrows indicate the absence of contrast within the anterior sagittal sinus, in keeping with dural sinus thrombosis.

Figure 4 Flexible sigmoidoscopy (rectum): erythematous mucosa with superficial ulceration, pseudopolyp formation and mild contact bleeding.

TREATMENT

An inpatient flexible sigmoidoscopy demonstrated moderate-to-severe inflammation, with features consistent with chronic UC (figures 4 and 5). He was given 12.5 mg prednisolone and 50 mg 6-MP one time per day and 2.4 g mesalazine two times per day.

OUTCOME AND FOLLOW-UP

Over the next 8 days, his left wrist pain settled, the swelling of his right arm resolved with elevation and compression, and he suffered no further seizures. The patient was then discharged, with on-going follow-up in vascular and gastroenterology clinics.

DISCUSSION

Extraintestinal manifestations are a recognised complication of IBD, with almost all organ systems implicated in the literature. The association between thromboembolism and IBD was first described by Bergen and Barker in 1936 as a rare extraintestinal manifestation.⁵ Compared with an estimated incidence of 10/10 000 in the general population,⁶ the incidence of DVT or PE has been reported to be 40/10 000 person-years for Crohn's disease and 50/10 000 person-years for UC.² Widespread VTE can have significant mortality and morbidity.⁷

Figure 5 Flexible sigmoidoscopy (sigmoid colon): moderate-severe mucosal inflammation with featureless, lead-pipe colon.

Cerebral venous thrombosis (CVT) is rare in IBD and presents with neurological manifestations. These are usually likely to be under-recognised and under-reported.⁸ The most common symptoms are headaches (69%–81%), focal neurologic deficits (38%–44%), seizures (28%–42%) and papilloedema (10%–51%).^{9–10} The precise incidence is unclear, although CVT appears to be more common in UC than in Crohn's disease,¹¹ and it carries an overall mortality rate of 4.3%–12.3%.^{12–14} Given this, Menon *et al* suggested that CVT must be considered in any patient with IBD who presents with neurological symptoms.¹⁵

Both acquired and genetic risk factors predispose patients to thromboembolic events, and the pathogenesis of this is not fully understood. Surgery, immobilisation, dehydration and central venous catheters all predispose patients to developing VTE.¹⁶ Inherited risk factors such as Factor V Leiden mutation and Protein C and S deficiency confer increased risks but, compared with the general population, are not more common in patients with IBD.¹⁷

Active UC, in particular, has been associated with increased factor VIII activity, elevated fibrinogen levels and accelerated thrombin generation¹⁸ and is likely due to the systemic inflammatory response during active disease. Patients have also been found to have increased platelet activation with evidence of spontaneous platelet aggregation and elevated thromboxane B2 and β -thromboglobulin levels.¹⁹ Cytokines (TNF- α , IL-1-3 and IL5) produced also contribute to thrombotic processes.^{20–21}

Our patient had poorly controlled UC and was having an active flare at the time of his presentation. His normocytic anaemia was likely due to chronic disease and haematochezia. Dehydration, coupled with a pro-inflammatory state, predisposed him to thrombosis. Early diagnosis and intervention might have prevented his condition from progressing.

The current practice in the treatment of VTE for patients with IBD is no different from patients with non-IBD. In the acute setting, anticoagulation with unfractionated heparin or low-molecular-weight heparin is recommended, with the eventual transition to oral anticoagulation.²² As always, the risk of bleeding must be considered when initiating patients on anticoagulant therapy. Warfarin therapy was chosen due to the ease of reversibility compared with novel oral anticoagulants.

The ideal duration of anticoagulation remains ill-defined. The Canadian Association of Gastroenterology has suggested that anticoagulant therapy be continued until 3 months after the IBD flare has resolved, citing the pro-inflammatory state as the provoking factor.²³

In regards to VTE prophylaxis for patients with IBD, no Australian guidelines exist to stratify patients with IBD into low-risk or high-risk categories. At present, most patients with IBD who are admitted are routinely given graduated compression stockings and subcutaneous unfractionated heparin or low-molecular-weight heparin. This is in accordance with the recommendation from Singh *et al*⁸ for strict mechanical and pharmacological DVT prophylaxis in patients with IBD.⁸

Currently, there are no data on the role of primary prophylaxis of VTE for patients with IBD in the community. Research into this area would be especially pertinent for patients with active flares and those with a previous history of VTE. Longitudinal case-control studies may help to identify patients with IBD who are at highest risk of recurrent VTE and determine whether they should be prophylactically anticoagulated. Furthermore, definitive treatment duration for patients with both first episode and recurrent VTE in the setting of IBD needs to be explored more thoroughly.

Learning points

- ▶ Venous thromboembolism remains an uncommon, although well-documented, extraintestinal manifestation of inflammatory bowel disease (IBD).
- ▶ Clear guidelines need to be established on the duration of treatment and the appropriateness of secondary prophylaxis for high-risk patients in the community.
- ▶ Clinicians should consider cerebral venous thrombosis as a differential in patients with IBD presenting with neurological symptoms, particularly in the setting of active disease.
- ▶ Early diagnosis can expedite investigation and management at a tertiary facility.

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