Peripheral arterial thrombosis following administration of infliximab for Crohn disease

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Abstract

Infliximab is one of the most widely used tumour necrosis factor-alpha (TNF-\textalpha) inhibitors for control of Crohn disease. We report the case of a patient with ileocolonic Crohn disease developing major arterial thrombosis after treatment with infliximab. After conservative management and infliximab withdrawal, thrombus dissolution and vessel recanalisation were observed. Few cases of arterial thrombosis following infliximab treatment have been documented; continued vigilance in the reporting of adverse events of biological therapy is required given the development of newer biological agents.

Keywords

Crohn disease; infliximab; thrombosis.

Introduction

The TNF-\textalpha inhibitor infliximab has proven efficacy in, and is licensed for, the treatment of Crohn disease. Its use has become more widespread as clinicians become more experienced and comfortable with its indications. However, it has a significant side-effect profile, and well-recognised adverse events include hypersensitivity and infection. Reports of the less common complication of venous thromboembolism are increasing, but arterial thrombosis remains rare.

Although active inflammatory bowel disease is an established risk factor for peripheral arteriovenous thrombosis, we look at some of the evidence pointing towards an independent role of infliximab in this process. We report the case of a male patient with Crohn disease developing arterial thrombosis after infliximab administration.

Case report

A 48-year old man presented acutely with a 3-day history of pain, numbness and discolouration of the toes of his right foot, associated with a preceding 7-week history of worsening abdominal pain, anorexia and weight loss. He had been diagnosed with ileocaecal Crohn disease 2 years prior to this on the basis of ileocolonoscopy, computed tomography (CT) of the abdomen and small
bowel barium studies. Prior to this exacerbation, his disease had been controlled with use of azathioprine 2.5 mg/kg per day and mesalazine (Pentasa), but latterly had required addition of oral steroid for the deterioration. Despite 4 weeks of high-dose steroid, his Crohn disease remained active and refractory to conventional medical therapy, therefore he was initiated on the TNF-\(\alpha\) inhibitor infliximab at a dose of 5 mg/kg, followed by a second dose 2 weeks later. He presented to hospital 3 days after the second dose of infliximab. There was no significant cardiovascular or other past medical history, and he had stopped smoking a year previously, after a 26-year habit.

On admission, he was febrile, tachycardic and tender in the right iliac fossa with a reduced serum albumin level and an increased C-reactive protein (CRP) level. His right hallux, fourth and fifth toes were noted to be mottled and cool, with a capillary refill time of 3 s.

However, all lower limb pulses were palpable. He was treated with intravenous hydrocortisone for an exacerbation of Crohn disease and initiated on subcutaneous low molecular weight heparin. A CT angiogram of both lower limbs was performed, from which an axial image and coronal reconstruction are shown in Figs. 1 and 2, respectively.

A filling defect was demonstrated within the distal right common femoral artery and proximal right superficial femoral artery. Further images of the distal right common femoral artery demonstrated a crescentic plaque with a small focus of calcification at the margin, suggesting the presence of thrombus rather than embolus. In addition, the proximal vessels appeared patent, with no iliac or aortic disease seen. Normal distal run-off on the right was also visualised, including normal popliteal and tibial arteries. After a vascular review, arterial duplex of the right lower limbs showed 70% stenosis at the origin of the right superficial femoral artery with a 3-cm long echolucent thrombus. All vessels distal to this were patent. In view of the absence of critical

![Fig. 1. Contrast-enhanced axial CT image demonstrating a filling defect (arrow) within the proximal right superficial femoral artery.](image)

![Fig. 2. Contrast-enhanced coronal reconstructed CT image demonstrating a filling defect (arrow) within the proximal right superficial femoral artery (the left profunda femoris artery is patent but not visible on this image due to rotation).](image)
ischaemic symptoms (the patient had a viable extremity in the presence of all peripheral lower limb pulses with no sensory loss or muscle weakness), a conservative management strategy with anticoagulation was adopted over thrombectomy, which led to further improvement of his right lower limb symptoms and signs. A comprehensive thrombophilia screen prior to anticoagulation (including protein C, protein S, factor V Leiden, anti-cardiolipin antibodies, antithrombin III, homocysteine and fibrinogen) was negative.

As a result of continuing active Crohn disease with ongoing abdominal symptoms and poor nutritional status, he proceeded to a limited right hemicolectomy with administration of intravenous heparin infusion during the peri-operative period. After encouraging clinical progress, he was subsequently discharged on warfarin, azathioprine and a tapering dose of oral prednisolone. He remains well and asymptomatic, with restoration of strong femoral and distal pulses at follow-up along with confirmation of arterial recannalisation on repeat CT angiography.

Discussion

Infliximab is a chimeric monoclonal antibody against TNF-α. It has potent anti-inflammatory effects and is indicated in active and fistulating Crohn disease. The use of infliximab has increased in recent years and is now firmly established in the algorithm for management of Crohn disease.

A number of adverse reactions are associated with infliximab use. Susceptibility to infection and exacerbation of heart failure, as well as reactivation of tuberculosis, are well recognised. Infusion reactions, anaphylaxis and delayed hypersensitivity have also been reported. The development of thromboembolism is less well recognised. Several cases of venous thromboembolism have now been documented: one case of ipsilateral forearm deep vein thrombosis following an infusion reaction[1]; one case of hepatic vein thrombosis in a patient found to have underlying paroxysmal nocturnal haemoglobinuria[2]; one case of retinal vein thrombosis[3] and one case of pulmonary embolism[4]. Arterial thrombosis after infliximab infusion has only been reported in two cases, both presenting with acute coronary syndrome, one on a background of long-standing rheumatoid arthritis, hypertension and obesity[5], the other in a patient with acute severe Crohn disease[6].

Patients with inflammatory bowel disease have a four-fold increased risk of thromboembolic phenomena compared with normal controls[7]. A number of additional acquired risk factors exist that may predispose to clot formation, including surgery, immobility, placement of central venous catheters and folate and vitamin B12 deficiency. Our patient is an ex-smoker, and no exposure to these additional risk factors or underlying thrombophilic disorders was found.

Increased common carotid arterial wall thickness, as a marker of early atherosclerosis independent of classic cardiovascular risk factors, has been reported to be more common in patients with inflammatory bowel disease[8]. A recent Canadian population-based observational study has shown an increased risk of cardiovascular arterial thromboembolic disease in inflammatory bowel disease, but the predisposing factors in relation to this remain undefined[9].

There is little evidence to explain the putative role of infliximab in the development of thromboembolism. The uncontrolled production of autoantibodies to specific antigens by certain B cell lines is well reported [10], with anti-cardiolipin antibody being the most significant in terms of thrombogenicity. Moreover, this can progress to a clinical syndrome similar to systemic lupus erythematosus as a result of anti-TNF therapy. The development of anti-nuclear antibodies and antibodies against double-stranded DNA after infliximab administration have also been reported [11], but these are usually of the IgM class, as opposed to the high-affinity IgG class, which are more commonly responsible for the clinical features of the lupus syndrome. Anti-cardiolipin antibody as well as antibodies directed against other clotting factors were present in most other reports of infliximab-associated thromboembolism, but was notably absent from this case.

Although TNF-α has been considered to increase the risk of clot formation via its driving role in the chronic inflammatory process, some evidence points to the contrary, at least in the myocardium. TNF-α has been shown to drive production of manganese superoxide dismutase[12], a free radical scavenger, as well as certain heat shock proteins[13] in adult mammalian and feline cardiac myocytes, respectively. TNF-α also promotes coronary vasodilation by inducing nitric oxide[14]. It would follow that anti-TNF-α therapy would inhibit these regulatory mechanisms, and potentiate thromboembolism, which could contribute to the reported cases of acute coronary syndrome after infliximab use. Clearly further studies are required, not only to delineate the
mechanisms at work in peripheral vasculature, but also to explore further cellular processes independent of anti-cardiolipin antibody.

In conclusion, we consider that the cause of arterial thrombosis in this case was directly associated with the use of infliximab given the temporal relationship between administration and effect, in a patient with no underlying cardiovascular disease. There is emerging evidence for the independent role of infliximab in clot formation.

**Teaching point**

Infliximab has proven efficacy in the treatment of severe inflammatory bowel disease refractory to conventional treatment, as well as established indications in rheumatoid arthritis, ankylosing spondylitis and psoriasis. The spectrum of reported adverse effects continues to expand with increasing experience in the use of anti-TNF-α agents, which now includes peripheral arteriovenous thrombosis. Although concerns regarding long-term safety remain, the benefits of anti-TNF-α therapy appear to outweigh the risks identified. The continued development of novel biological therapies necessitates continued vigilance in the identification and reporting of less well-recognised adverse events.

**References**