Acute renal artery occlusion following infliximab infusion

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Abstract

We report the case of a 44-year-old male patient who presented with acute renal artery occlusion, 3 d after first injection of infliximab for steroid refractory attack of ulcerative colitis. Extensive work-up provided no evidence of predisposing factors for arterial thrombosis. Infliximab was thus suspected in the genesis of thrombosis. At month 3 after thrombosis with ongoing anticoagulation, angio-tomodensitometry showed complete revascularization of the left renal artery with renal atrophy. Renal function remained normal and the patient was still in steroid free remission on mercaptopurin monotherapy.

Key words: Ulcerative colitis; Acute renal artery occlusion; Infliximab; Anti-tumor necrosis factor agent

Core tip: To the best of our knowledge, it is the first case reported of renal artery thrombosis after infliximab infusion. Evidence for drug induced toxicities are usually lacking and the diagnosis in our patient was based on both intrinsic and extrinsic criteria in favour of a direct consequence of infliximab administration. In the literature, only few reports have been published on arterial or venous thrombosis with these drugs. The arterial thrombosis are unusual and are mostly myocardial infarction or cerebrovascular accident. Renal arterial thrombosis in patient receiving infliximab is possible and clinician should be aware of this challenging unusual condition.

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INTRODUCTION

We report the case of a 44-year-old male patient who presented with acute renal artery occlusion, 3 d after first injection of infliximab for steroid refractory attack of ulcerative colitis.

CASE REPORT

A 44-year-old European male was diagnosed with ulcerative colitis (UC) in 2004. He presented with corticosteroid dependent pancolitis, with ongoing prednisolone treatment at 40 mg/d from the first flare. Azathioprine was introduced, at a daily dosage of 2.25 mg/kg but rapidly withdrawn due to intolerance. The patient was then administered mercaptopurin at a daily dosage of 50 mg, allowing steroid withdrawal. From 2005 to 2009, the patient remained asymptomatic with mercaptopurin at...
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Lemaître C et al. Acute renal artery occlusion following infliximab infusion

At day 5 after admission, infliximab rescue treatment was decided and the patient received a 2-h infusion of infliximab at 5 mg/kg. The symptoms rapidly responded to treatment, with complete disappearance of abdominal pain, bleeding and diarrhea. The patient was then discharged 4 d later, mercaptopurin was reintroduced and a second infusion of infliximab was scheduled at week 2 after the first infusion. However, the day after discharge, he was readmitted to emergency room for acute pain in the left iliac fossa, radiating to the genital organs. He had neither fever, nor signs of UC flare. Microscopy urine analysis found microscopic hematuria without leukocytes or bacterial colony. Renal ultrasound found no urinary obstruction. Contrast-enhanced abdominal computer tomography (CT) showed multiple areas of acute renal infarction on the left side, secondary to thrombosis of the renal branch arteries (Figures 1 and 2). Intravenous anticoagulation was introduced first, using non-fractioned heparin then relayed, at day 3 by vitamin K antagonists aiming at an international normalized ratio between 2 and 3. No attempt at revascularization was made as recommended by the vascular surgeon. Extensive etiologic work-up in search of any predisposing condition was performed and remained negative. It included search for antithrombin III, protein S or C deficiency, test for JAK 2, factor II and factor V mutations and paroxysmal nocturnal hemoglobuninuria as well as homoecystein, anticoagulation and antiphospholipid, and anti-nuclear antibody dosage. Transthoracic echography and rhythm holter recordings ruled out embolic disease. At month 3 after thrombosis with ongoing anticoagulation, angio-tomodensitometry showed complete revascularization of the left renal artery with renal atrophy. Renal function remained normal and the patient was still in steroid free remission on mercaptopurin monotherapy at maximal dosage. Transthoracic echo-angiography and antithrombotic treatments were recommended by the vascular surgeon. Extensive etiologic work-up in search of any predisposing condition was performed and remained negative. It included search for antithrombin III, protein S or C deficiency, test for JAK 2, factor II and factor V mutations and paroxysmal nocturnal hemoglobinurinah as well as homoecystein, anticoagulation and antiphospholipid, and anti-nuclear antibody dosage. Transthoracic echography and rhythm holter recordings ruled out embolic disease. At month 3 after thrombosis with ongoing anticoagulation, angio-tomodensitometry showed complete revascularization of the left renal artery with renal atrophy. Renal function remained normal and the patient was still in steroid free remission on mercaptopurin monotherapy at maximal follow-up. We concluded that renal artery thrombosis was related to infliximab infusion in this UC patient. We then made a formal declaration to the local French pharmacovigilance and drug safety authorities.

DISCUSSION

To the best of our knowledge, this is the first reported case of renal artery thrombosis after infliximab infusion. Evidence for drug-induced toxicity is usually scarce but in our patient diagnosis was suspected based on both intrinsic and extrinsic criteria in favor of a direct consequence of infliximab administration.

Infliximab is a chimeric monoclonal antibody against tumor necrosis factor-α (TNF-α). In the literature, only a few reports have been published on arterial or venous thrombosis with these drugs. Arterial thrombosis is unusual and presents mostly as myocardial infarction (MI) or cerebrovascular accident (CVA). In 2011, Korswagen reported 8 thromboembolic events (TEE) in a retrospective cohort of 272 patients treated by adalimumab, including 4 cases of deep vein thrombosis (2 pulmonary embolisms, 1 plebitis, and 1 optical vein thrombosis) and 4 cases of arterial thrombosis (1 CVA, 1 MI, 1 CVA and
MI, and a transient ischemic attack)[1]. Anti-adalimumab antibodies were detected in four of these eight patients. The incidence rate of TEE was respectively 26/1000 and 8.4/1000 persons per year for patients with and without anti-adalimumab antibodies, with an adjusted hazard ratio of 7.6 and a median period of occurrence of 78 and 156 wk respectively for patients with and without antiadali-
umab antibodies)[3]. Mehta et al)[2] described a right common femoral artery thrombosis 3 d after a second dose of infliximab in a patient with Crohn’s disease. Thrombo-
philia screening and immunologic biology were negative in this report. The patient presented spontaneous arterial revascularization and underwent right hemicolectomy to treat severe disease flare. Pettipain et al)[1] reported 85 TEE, which were declared in drug safety records between 2000 and 2006, in patients treated by TNF-α inhibitors for inflammator
ey bowel disease (IBD) or rheumatoid arthri-
tis. Forty-two arterial TEE were observed in this series including 20 MI, 7 CVA, 6 lower limb arterial thrombo-
oses, 1 CVA with MI, 1 renal thrombosis, and 7 other thromboses. Mean duration of TNF-α inhibitor therapy was 10.6 months and 79 out of 85 patients received con-
comitant systemic corticosteroids or methotrexate or COX (cyclo oxyge
nase)-2 selective inhibitors. Sixteen of the 42 patients with arterial TEE had two or more ad-
ditional risk factors for cardiovascular events, including tobacco addiction, arterial hypertension, or dyslipidemia. Anti-TNF agent was reintroduced in 18 patients without complication, after complete or partial patency. Regarding acute vascular events involving renal vascularization, only Tabibian et al)[3] described combined inferior vena cava and bilateral renal vein thrombosis in a woman with UC, 4 wk after the third injection of infliximab.

IBD and TEE have been associated since 1936[13]. The relative risk of TEE is increased by around 3 in IBD[14] and exceeds 15 during flares[7]. Although the physiopathology remains unclear, previous studies have sought to explain this association. Immobiliation of in-patients, surgery, indwelling catheters, and hyperhomocysteinemia associated with folate or vitamin B12 deficiencies or bleeding disorders may be part of the explanation in some patients. However, systemic inflammation is proba-
ably the main culprit through activation of the coagula-
tion cascade with increased thrombin and platelet activa-
tion[15]. The formation of immune complex might also have contributed to the occurrence of TEE. Immune complex can activate platelets via the Fcy-receptor and complement system, through induction of aggregation and procoagulant particle release. This factor induces more venous TEE[15].

Uncontrolled production of ACL, anti-phospholipid, and anti-nuclear auto antibodies, could be responsible for TEE. ACL antibodies are the most significant in terms of thrombogenicity and may contribute to a clinical “lupus-like” syndrome secondary to TNF-α-inhibitors[16]. The use of infliximab and adalimumab has been associated with an increasing number of autoimmune diseases[11]. This auto-
immunity is thought to be due to a decrease in apoptosis of inflammation bodies, a predominant Th2 response, and lack of control of some B cell populations[12]. A statistically significant increase in frequency is seen for Immunoglobulin M and Immunoglobulin G aCL after 3 mo of treatment with infliximab[19]. However, there is no established link between the presence of antibodies and the degree of activation of systemic inflammation responsible for risk of embolism[1]. TNF-α inhibitors may also impact the vascular system through other mechanisms. These latter could drive production of manganese superoxide dismutase, promote arterial vasodilatation by inducing nitric oxide production, induce endothelial dysfunction, alter lipid pro-
file and homocysteine rate, and be partially responsible for insulin resistance and subclinical atherosclerosis. All these effects might explain an increase in TEE[14].

Moreover, the role of glucocorticoids can not be excluded. Most of our patients who experienced throm-
bosis events were on concomitant corticosteroids at the time of thrombosis. Corticosteroids can induce changes in the coagulation and fibrinolytic pathways (elevated fi-
brinogen, and suppressed tPA activity)[18]. They limit the availability of arachidonic acid for prostocyclic synthesis, which may allow platelet thromboxanes to dominate on the endothelial surface, favoring vasoconstriction and thrombus formation. Theoretically, the ability of corti-
costeroids to reduce inflammation may offset these pro-
thrombotic risks. The odds ratio reported for thrombosis event is 1.87 (95%CI: 1.37-2.53)[14].

TNF-α, a proinflammatory and potential proco-
agulant cytokine, is elevated in IBD. TNF-α increases leukocyte adhesion, endothelial transmigration, vascular leakage, and alteration in the coagulation system. It in-
duces prothrombotic status. CD40/CD40 ligand links the inflammation and coagulation pathways. This couple is responsible for leukocyte recruitment and tissue dam-
age in the endothelial cells. In IBD, overexpression of this couple has been evidenced in mucosal microvascularization[13]. TNF-α inhibitors decrease the CD40/CD40L pathway. TNF-α inhibitors have been shown to drive production of manganese superoxide dismutase, which is a free radical scavenger. They promote arterial vasodilata-
tion by inducing mainly coronary nitric oxide oxide production. They are also responsible for endothelial dysfunction, alter-
tation of lipid profile, concentration of homocysteine,
inulin resistance, and subclinical atherosclerosis, which could all explain the increase in TEE[18].

Our case observation also highlights the difficulties involved in managing renal arterial thrombosis. In usual circumstances, thrombosis is trauma-related, requiring simple anticoagulation treatment. Revascularization does not impact unfavorable outcomes, such as hypertension or renal failure. Therefore, it should probably be reserved for patients with solitary kidney or bilateral thrombosis[19]. When an embolic event occurs, endovascular thromboly-
sis should probably be indicated. The success of this pro-
cedure in preserving renal function is partially dependent on the duration of renal artery occlusion, varying from 3 to 72 h according to the literature[19]. In other conditions,
especially if thrombosis occlusion occurs in previously damaged arteries the frequent presence of collateralization renders revascularization void [30].

In conclusion, renal arterial thrombosis is a possible risk of infliximab treatment. Clinicians should be aware of this unusual and challenging condition.

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