CASE REPORT

Acute coronary syndrome after infliximab therapy in a patient with Crohn's disease

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Abstract

Infliximab is a potent anti-TNF antibody, which is used with great success in Crohn's disease patients. Since its release in clinical practice, several adverse reactions have been observed. The interest in possible consequences of its administration is still high because of the recent introduction of the drug for the long-term maintenance therapy of refractory luminal and fistulizing Crohn's disease. We present a case of acute coronary syndrome (non-STEMI) in a patient with corticoid resistant Crohn's disease after his first dose of infliximab. By reviewing the scant articles that exist in the literature on this topic we made an effort to delineate the possible mechanisms of this phenomenon.

INTRODUCTION

Serious adverse events (infections, malignancies, serum sickness, lupus syndrome) that need hospitalization have been reported with a divergent frequency of 6%-18.9% for patients with inflammatory bowel disease (IBD) treated with infliximab[1,2]. We present a case of acute coronary syndrome (non-ST myocardial infarction) that occurred after infliximab administration in a patient with corticoid-resistant Crohn's disease.

CASE REPORT

The patient was a 40-year-old male Caucasian who visited the emergency department of our hospital because of chronic diarrhea with 10 watery bowel movements per day. After admission, the patient's history, symptoms, physical signs, laboratory, endoscopic and pathological findings during an extensive diagnostic work up, were compatible with the diagnosis of ileocolonic Crohn's disease (CDAI score: 320). The patient was started on mesalamine orally (1 g t.i.d), metronidazole (500 mg t.i.d) and prednisolone (25 mg b.i.d) intravenously along with parenteral fluids. Five days later 15 mg of prednisolone as well as budesonide enemas (2.3 mg b.i.d) were added to the treatment regimen. The unremitting course of his clinical status on the 12th d of hospitalization was the reason to administer infliximab (5 mg/kg) at a total dose of 375 mg. The infusion of infliximab was well tolerated without any acute adverse reactions. On the first day of treatment the patient's laboratory findings were the following: Ht: 31%, leucocyte count: 9900 (normal), platelets: 314 000, CRP: 143 mg/lt and all biochemicals including basic coagulation tests [prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)] were within normal values except serum glucose: 146 mg/dL. Chest X-ray showed only a slightly elevated cardiothoracic ratio. The next day azathioprine 50 mg t.i.d *po* was added to the therapeutic regimen and prednisolone was reduced to 40 mg iv. On the third day after infusion the patient experienced pain in the chest. The electrocardiogram showed T-wave inversion at the V4, V5, V6 precordial leads and at I, II limb leads with sinus rhythm. Cardiac enzymes [creatinine phosphokinase, creatinine phosphokinase isoenzyme MB, aspartate aminotransferase, lactate dehydrogenase, troponine] related to myocardial infarction were measured and troponine I was found increased: 2.2 ng/mL (normal: < 2 ng/mL). The patient was transferred to the emergency coronary care unit where a diagnosis of acute coronary syndrome implying non-STEMI myocardial infarction was made. During his stay he also suffered an episode of atrial fibrillation, which was reset by amiodarone. He received metoprolol, nitrates, low molecular weight heparin and clopidogrel, which permitted him to recover and return to our Unit after 4 d. Fifteen days after the administration of infliximab the patient's clinical and laboratory status has been improved, with 3 bowel movements per day, absence

of abdominal pain, better general state of health, CRP: 106 mg/lt and CDAI score: 160.

The patient had no family or personal history of heart disease, hypertension, hyperlipidemia, diabetes mellitus, smoking or obesity and was not taking any drugs before his admission. The physical examination of the heart and ECG at the time of presentation was normal. Fifteen days after the coronary episode the patient was subjected to echocardiography, which showed hypokenesia of the interventricular septum and overall impaired systolic function of the heart with an ejection fraction of 45%. A triplex of the carotids and vertebral arteries did not reveal any atherosclerotic lesions. Our patient also had elevated fibrinogen level (6.55 g/L, normal: 2-4.5 g/L), low protein S activity (41.9%, normal: 75%-130%, Protein S Ac test by Dade Behring), abnormal resistance to activated protein C (APCR) (PCAT: 66.6 s, normal: 85-200 s, Pro C Global protocol assay by Dade Behring) and normal antithrombin III and D-dimers levels under mild systemic inflammation with CRP levels of 32.5 mg/lt. One month later a cardiac exercise stress test was performed and found normal. Protein S activity and APCR were also normal at that time.

DISCUSSION

It is already known that thromboembolic events occur more frequently in IBD patients (up to 8%) than in normal controls (up to 2%)[3]. Arterial thrombosis is an uncommon feature of IBD in relation to the far more frequent venous thrombosis. One third of IBD patients develop thrombosis while being in remission, weakening the hypothetical association of active inflammation and abnormal coagulopathy. There are a number of acquired risk factors related with IBD that may predispose to thrombosis. These include immobility, surgery, central venous catheters, parenteral feeding, deficits of vitamins B12 and folic acid as well as hyperhomocysteinemia, increased lipoprotein (a) and anticardiolipin antibodies. Inherited thrombophilic factors like V Leiden and G20210A prothrombin gene mutations have also been implicated in the thrombogenesis of IBD patients. Our patient had none of the above-acquired risk factors as specific investigation of the lipid panel, vitamin B12, folic acid, homocysteine and antiphospholipid antibodies (anticardiolipin, lupus) rendered normal results. The patient was also not subjected to any surgical intervention or parenteral nutrition and because of his young age and self-supporting clinical status was relatively active and not totally immobile. Our patient was also examined for inherited thrombophilic mutations with negative results. It is common for IBD patients to demonstrate abnormal laboratory values of thrombophilic factors in as many as 60% of the cases, a proportion far surpasses the prevalence of thromboembolism in IBD estimated at 8%[4]. In a study of IBD patients and healthy controls, although 21.4% and 9.5% of patients had reduced free protein S and abnormal APCR respectively, only 4.8% (4 patients out of 84) had a history of thromboembolism and furthermore in two of the patients with thrombosis there were none thrombophilic abnormalities detected[5]. The abnormal APC resistance in our patient is probably due to the low levels of activated protein S as the patient was not carrying the factor V Leiden mutation. High plasma fibrinogen level has been associated with increased risk of vascular and non-vascular mortality in a recent meta-analysis study including prospective trials with baseline fibrinogen values and subsequent monitoring of adverse events during at least 1 year of follow up[6]. The association of increased fibrinogen level with nonvascular events (mainly cancer) weakened the specificity of association with vascular diseases.

Among the other drugs administered to the patient, only steroids have been reported to be associated with coronary heart disease, either myocardial infarction or coronary spasm. These adverse events are related to treatment schedules either with long-term high dose steroid administration (120 mg depomethylprednisolone im for 2 years) or to bolus infusion of high dose steroids (as high as 250 mg methylprednisolone). Our patient was given only 40 mg of prednisolone daily divided into two doses. On the other hand, steroids as well as mesalamine are considered to confer an anti-coagulant effect in patients with Crohn's disease[7]. This protective role derives from the reduction of proinflammatory cytokines, namely the platelet-activating factor (PAF), TNF-α and IL-1.

Our hypothesis is that infliximab administration might be the cause of the myocardial infarction in this patient. There are three case reports that refer to patients with Crohn's disease (CD) who had venous adverse reactions related to infliximab. The first has reported a patient with retinal vein thrombosis[8], the second an extensive forearm deep venous thrombosis[9] and the third comes from a cohort study reporting deep venous thrombosis as well[2]. It has already been noted that infliximab can also aggravate heart failure if given at a dose of 10 mg/kg to patients with moderate or severe chronic heart failure[10]. Infliximab has also been found responsible for new onset heart failure in patients with rheumatoid arthritis (RA) or CD, some of them aged below 50 years. An acute coronary syndrome has been described in a patient with RA after infliximab therapy by Abedin et al[11]. However, there are substantial differences in the patient's clinical setting in comparison to our report. The patient in the aforementioned report was female and had a long-standing history of refractory RA starting 20 years ago and a 3-year history of hypertension. She needed multiple therapeutic interventions with corticosteroids, methotrexate, and leflunomide which is known to aggravate hypertension and lastly infliximab. The patient was also obese (95 kg) if we can postulate her weight from the infliximab dose (400 mg total dose, 4.2 mg/kg). Finally, the patient had multiple infliximab infusions in the last 2 years and had already received over 5 g of the drug in escalating dosage. It is obvious that an obese patient with hypertension and an active RA for several years, a disease, which by itself confers vascular compromise, is in danger for cardiovascular events even in the absence of infliximab administration, which already had been given in multiple doses without adverse events in the past. Our patient was a young male with newly presented Crohn's disease who suffered a non-ST myocardial infarction three days after his first dose of infliximab and without having any cardiovascular events in his medical history.

Although TNF has procoagulant properties mainly in high circulating concentrations it seems that during a re-

stricted production it may have antithrombotic activity[12] by reducing the expression of adhesion molecules like P selectin and the aggregation of platelets as well as their binding to fibrinogen. It has been found that TNF assists in the maintenance of myocardial vascular perfusion by producing vasodilation through the induction of nitric oxide (NO), which is also capable of inhibition of apoptosis of myocardiocytes and attenuation of the heart's stimulation by the sympathetic nervous system through the β-receptors[10]. TNF is also responsible for the release by myocytes of heat shock proteins (HSP 72, HSP 27)[13] that are considered to confer resistance against hypoxic stress as well as for the production of manganese superoxide dismutase, a scavenger of free radicals[14]. The administration of a potent anti-TNF antibody like infliximab, which neutralizes both soluble and membrane TNF can abrogate these homeostatic interventions causing deprivation of first line defensive mechanisms. Infliximab has been shown to cause vasoconstriction and increased wall shear stress in arteries of patients with RA after a dose of 3 mg/kg[15].

On the other hand, there are several reports of unaffected serum TNF-α concentrations despite administration of anti-TNF antibodies in patients with either RA, leucoclastic vasculitis or after myocardial ischemia. High levels of TNF-α in the serum have been associated with higher risk for myocardial infarction (OR: 1.7). It has been found in experimental models that endogenous production of TNF can downregulate its relevant receptors and therefore confer resistance to its continuous action. A counter-regulatory mechanism might upregulate the expression of mTNF and TNF-receptors on the cell membrane of endothelium, monocytes, vascular smooth muscle cells (VSMCs) and myocytes, at the time when anti TNF administration causes a reduction of the serum or tissue TNF levels, with the result of a rupture plaque or myocardial apoptosis. An increase in serum TNF-α levels has been noted in two studies of patients with RA and chronic heart failure respectively after the initial drop in TNF concentration following administration of infliximab[10,16]. In the former study the increase was noted on the 3rd till the 7th d after infusion. The authors inferred that TNF-α was not bioactive but rather was bound to anti-TNF antibodies. Because of the inability of TNF-α assays to measure free TNF, one can surmise that this paradoxical increase may not be so innocent and could activate monocytes to produce metalloproteinases or stimulate endothelial cells to become thrombogenic by releasing NO, thromboxane and platelet adhesion molecules.

There is therefore a need to study the TNF-receptor expression in Crohn's disease in the myocardium. Furthermore the study of TNF polymorphisms could offer an explanation for the susceptibility of some individuals to the cardiac effects of anti-TNF-α.

In conclusion, we support the notion that anti-TNF therapy is the "probable" cause of acute coronary syndrome in this patient because of the chronological sequence between its administration and the presentation of this adverse reaction (3 d). We also demonstrated that the drug was active for the patient's clinical condition and that the individual completely recovered one month later when the apparent effect of the drug was completely abolished. We could not find in the English literature an absolutely proven causal relationship between the pathogenesis of Crohn's disease and thromboembolic events. According to published criteria for the estimation of the probability of adverse drug reactions, this reaction could be rated as "probable"[17].

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