

## Case report

# Life-threatening vasculo-Behçet following discontinuation of infliximab after three years of complete remission

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Received on January 28, 2013; accepted

in revised form on March 21, 2013.

*Clin Exp Rheumatol* 2013; 31 (Suppl. 77):

S96-S98.

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**Key words:** Behçet's disease, infliximab, thrombosis, vasculitis, tumour necrosis factor-alpha inhibitors

### ABSTRACT

*Behçet's disease (BD) is a chronic, complex multisystem vasculitis of unknown cause characterised for its ability to involve blood vessels of all sizes on both the arterial and venous sides of the circulation. It has been suggested that TNF-alpha plays a main role in the pathogenesis of BD. This hypothesis is supported by the efficacy of TNF-blocking antibodies in these patients, which have been shown to be very powerful in the induction of remission and as maintenance treatment on different BD manifestations, including severe vascular involvement. However, little is known about when and how to stop IFX after long-standing complete remission of these patients to avoid relapses. We describe a case of BD without previous vascular involvement that developed myocardial infarction and severe venous thromboses only four months after discontinuation of infliximab (IFX) after more than three years of complete remission. The patient did not respond to corticosteroids and intravenous cyclophosphamide and only recovered completely after reintroducing IFX.*

### Introduction

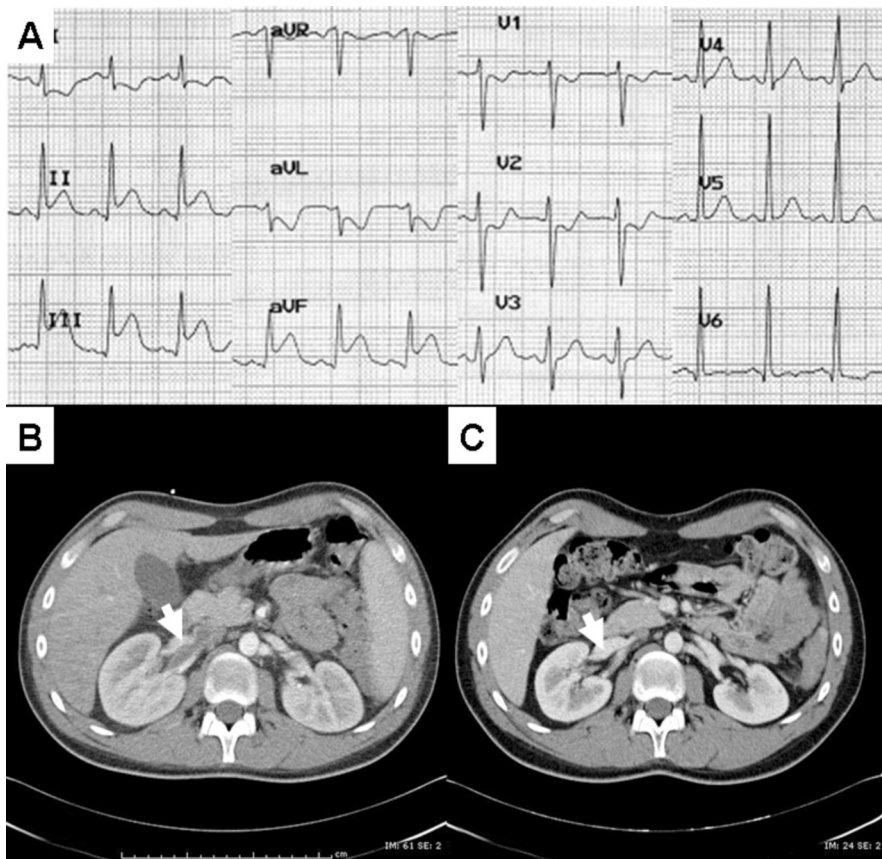
Behçet's disease (BD) is a chronic, complex multisystem vasculitis of unknown cause characterised for its ability to involve blood vessels of all sizes on both the arterial and venous sides of the circulation (1, 2). It has been suggested that tumour necrosis factor (TNF) alpha plays a main role in the pathogenesis of BD (3, 4). This hypothesis is supported by the efficacy of TNF-blocking antibodies, which have been shown to be very powerful in the induction of remission and as maintenance treatment on different BD manifestations, including severe

vascular involvement (5, 6). However, little is known about when and how to stop IFX after long-standing complete remission of these patients to avoid relapses. We describe a case of BD that developed myocardial infarction (MI) and severe venous thromboses only four months after discontinuation of infliximab (IFX) after more than three years of complete remission. The patient did not respond to corticosteroids and intravenous cyclophosphamide and only recovered completely after reintroducing IFX.

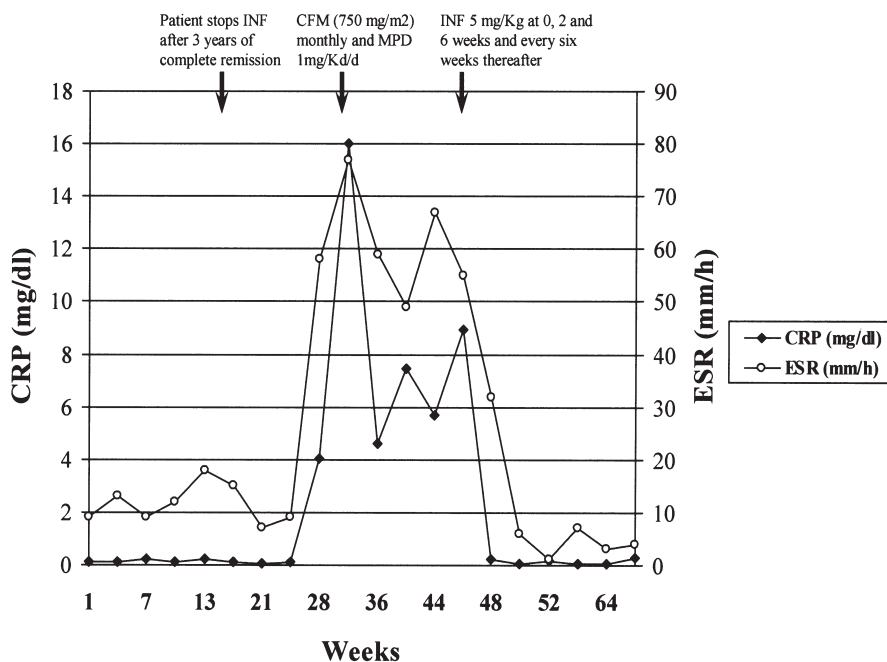
### Case report

A 26-year-old young man was referred to our department with a 10-day history of episodic high grade fever. Recurring painful oral and genital aphtae, erythema nodosum and an episode of bilateral panuveitis led to a diagnosis of Behçet's disease in January 2008, and he was started on colchicine, prednisone (PD) (5 mg/d) and methotrexate (MTX) (15 mg weekly). Vascular, neurological or other involvement at this time was excluded. Due to the poor control of eye involvement with MTX 15 mg and with methylprednisolone in combination with cyclosporine 3 mg/kg/day, IFX (5 mg/kg at 0, 2 and 6 weeks and every eight weeks thereafter) was started in co-therapy with methotrexate 15 mg weekly after a new episode of panuveitis in May 2008. He presented an excellent disease control since June 2008 and subsequently methotrexate was reduced to 7.5 mg weekly and prednisone dose was progressively tapered and stopped in August 2008. In July 2011, after almost three years without any symptom of the disease, our patient decided to withdraw his consent to infliximab therapy for personal reasons, maintain-

Competing interests: none declared.



**Fig 1.** A. Electrocardiogram of the patient showing changes compatible with an inferior wall myocardial infarction. B. Transverse computed tomography views of the abdomen in February 2012 after three months under monthly intravenous cyclophosphamide (750 mg/m<sup>2</sup>) and prednisone in a tapering dose (starting dose 1 mg/kg/d) showing the non-obstructing thrombus in the inferior vena cava extending into the right renal vein. C. Transverse computed tomography views of the abdomen in April 2012 after the third dose of infliximab (5 mg/kg at 0, 2 and 6 weeks) showing the resolution of the thrombus.



**Fig. 2.** Evolution of C-reactive protein (mg/dl) and erythrocyte sedimentation rate (ESR) (mm/h). CRP and ESR increased after discontinuation of infliximab and only returned to normal values after the reintroduction of this therapy.

ing methotrexate 7.5 mg weekly, colchicine and PD (5 mg/d). Four months later the patient suffered from malaise, episodic high grade fever, coughing and mild dyspnea. He was admitted to our hospital to rule out an infection before starting immunosuppressants. Physical examination revealed a poor general condition, fever (39.2°C), pale skin, oro-genital aphthae and hepatomegaly. Laboratory tests revealed increased ESR (77 mm/h; normal <10) and CRP (16 mg/dl; normal <0.5), 17350 leukocytes/mm<sup>3</sup> (84% neutrophils), haemoglobin 11.1 g/dl (14-18), ALT 61 U/l (0-40) and GGT 403 U/l (7-50). An electrocardiogram (EKG) and a chest x-ray were normal. In the morning of the second day of admission the patient complained of having suffered from mild retrosternal pain during the whole night and an EKG showed ischaemic changes (Fig. 1A). Ultrasensitive cardiac troponin was 711 ng/l (0-14). A coronary angiography showed complete stenosis of a distal branch of the right coronary artery not susceptible to revascularisation and the patient was treated medically. Blood and urine cultures, SeptiFast multiplex PCR analysis for detection of DNA pathogens, an echocardiogram and studies for prothrombotic states were negative. A thoracic-abdominal-pelvic angioCT scan showed a 3 cm thrombus in the right common iliac vein (CIV) and a 4 cm non-obstructing thrombus in the inferior cava vein (ICV) extending into the right renal vein, without any evidence of pulmonary or other peripheral arterial aneurysms. Published evidence points out the inflammatory nature of thrombi in BD, and we decided to start PD 70 mg (1 mg/kg/d) with tapering dose and monthly intravenous cyclophosphamide (750 mg/m<sup>2</sup>) without anticoagulation. In February 2012, after three doses of cyclophosphamide, a new angioCT scan showed persistence of thrombosis in the right ICV and CIV, in spite of partial clinical and laboratory improvement (Fig. 1B, Fig. 2). Reintroduction of IFX was then decided (5 mg/kg at 0, 2 and 6 weeks and every six weeks thereafter). One week after the first dose of IFX the patient

was totally symptom free and all the lab tests were completely normal. At a 2 months and 1 year follow-up visit, a new angio-CT showed resolution of thrombosis (Fig. 1C), and the disease remained in complete remission (Fig. 2). Azathioprine was added to the treatment with the intention of reducing immunogenicity of infliximab.

Vascular involvement is common in BD (up to 40–50% of patients), presenting as venous, arterial thrombosis and as arterial aneurysms, particularly of the pulmonary tree (2, 7). It has been frequently associated with fever, constitutional symptoms and increased acute phase response, what makes imperative to rule out possible infections, delaying diagnosis and treatment (8, 9). Venous involvement has been described to be more common than arterial disease which occurs in <5% of cases and has been found to occur after a median of 4–7 years (7, 10, 11). Although mostly associated with aneurysms and less commonly with occlusion of the major arteries, combinations are possible (11). In the literature, only several reports describe coronary artery vasculitis in BD. This involvement has a poor prognosis, affects mainly young male subjects and is often manifested by MI, as in our case (12). Furthermore, our patient presented with thrombosis of the ICV and CIV as the first vascular event.

There is no agreement on how to treat major vascular disease in BD. The prompt initiation of steroids, alone or in combination with immunosuppressive treatment such as azathioprine or cyclophosphamide, has been associated with remission. Additionally the use of these immunosuppressants has been related with a decrease in the annual incidence of arterial events and recommended to prevent recurrences and death (5, 11, 13, 14). In our case, after three doses of intravenous cyclophosphamide and high doses of pred-

nisone in a tapering dose, only partial response was achieved.

The precise mechanisms underlying the thrombotic risk of BD remain unknown, although TNF and soluble TNF receptors have been found to be increased in BD patients with active disease and proposed to be crucial on thrombi formation (3). Additionally, anti-TNF-alpha therapy has also been described as an effective treatment in inducing and maintaining remission in BD (1, 4, 6, 13). In the present case, the extremely severe vascular involvement four months after IFX interruption and the rapid response after its reintroduction including the resolution of thrombosis, support the idea of the important role played by this therapy against the inflammation and thrombi formation in these patients.

Little is known about when and how to stop IFX complete remission of BD. In patients with vascular involvement several case reports suggest that remission after IFX can persist for a long time after stopping this therapy, however relapses have also been described. Ongoing therapy after infliximab discontinuation consisted of a combination of immunosuppressants and low dose glucocorticoids, although a patient that did not take any treatment has also been reported (4, 15). Controlled studies are needed to identify when and which patients are most likely to discontinue anti-TNF-alpha therapy successfully and reduce the risk of life-threatening relapses.

We describe the risk of developing multiple vascular thromboses in BD after IFX stopping after more than three years of complete disease remission. The impressive response of our patient after reintroduction of IFX supports the idea that this therapy should be considered in severe extensive cases of vasculo-Behçet as an early aggressive therapy or in patients not responding to regular immunosuppressants.

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