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Occurrence of pulmonary thromboembolism during infliximab therapy

Sirs,

Infliximab therapy is an effective treatment for rheumatoid arthritis and ankylosing spondylitis. The occurence of positive antinuclear-antibodies (ANA) during infliximab is relatively common but development of systemic lupus erythematosus (SLE) is very rare. Patients are commonly screened for the presence of ANA before anti-TNF therapy but their presence in the absence of clinical symptoms is not considered to be a contraindication for the therapy (1).

The described patient is a 55-year old woman with a psoriasis arthritis since 1992. SLE had been previously suspected based on the occasional spontaneous leukopenia and positive ANA (titer > 5000). DNA antibodies had been negative and she had no clinical features of SLE. Since 1995, she has been treated with methotrexate.

Her arthritis was more active during 2001 and infliximab therapy was begun in the fall of 2001. Six months earlier her ANA-titer was negative, but just before institution of the infliximab therapy the titer of ANA was >5000 with a homogenous pattern. Anti-DNA antibodies were not tested immediately prior the therapy. She also had mild leukopenia ($2.5x10^9$/l) and because of that her methotrexate dose was only 7.5 mg per week. She received two infliximab infusions of 3 mg/kg each at two weeks apart, without complications. The arthritis responded well to the therapy.

However, one week after the second infusion she developed inspiratory pain on right side of the chest with slight shortness of breath and she had pain in the left leg for a few days. Chest x-ray and blood tests were checked and excluding moderately increased CRP (61 mg/l), other laboratory tests were non-diagnostic and a diagnosis of respiratory infection was made. Symptoms gradually disappeared, control x-ray was normal and she received the third infliximab infusion 4 weeks later. Six days after the third infusion pain reappeared in the right side, with marked shortness of breath and pain now in her right leg. She was admitted to the emergency unit. Spiral TT disclosed a filling defect in the right lung in accordance with pulmonary em-bolism. Ultrasound disclosed a thrombus in both fibular veins and also superficial veins in the left leg. The ultrasound of abdomen was normal. After admission to the hospital a spiking fever (ad 39.8ºC) appeared and also an urticarial rash over the entire body. A SLE-type reaction was suspected or alternatively a rash due to antibiotic treatment (clindamycin) which had been begun 4-5 days before admission to the hospital for prophylaxis after a tooth root dental procedure. Blood cultures, repeated chest x-rays, ultrasound of the abdomen and orthopantomography were non-diagnostic. The results of the relevant laboratory tests are shown in Table I. Decreased C4, clearly increased anti-DNA antibodies and slightly increased cardiolipin antibodies could be observed but no other predisposing factors for thrombosis. Anticoagulation with warfarin was started and prednisone was increased to 20 mg/day. Fever and rash gradually disappeared and she was discharged from hospital.

The present case is the first to associate anti-TNF-therapy with pulmonary embolism. Positive anti-DNA-antibodies and borderline increased anticardiolipin antibodies were also detected. However, the antibodies were not screened prior to therapy and even though they disappeared after discontinuation of infliximab their relationship with infliximab remains unclear. Drug-related pulmonary thromboembolism has been described in association with procainamide-induced SLE and positive anticardiolipin antibodies (2). Development of a hypercoagulable state and circulating anticardiolipin antibodies has been described during infliximab therapy (3). Appearance of anticardiolipin antibodies has been described also during etanercept therapy but their appearance was associated with concomitant infections (4). In conclusion, although the role of the anticardiolipin antibodies in the development of thromboembolism is in this case uncertain,screening of anti-DNA and anti-phospholipid antibodies before and during anti-TNF-therapy should perhaps be warranted.

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Table I. Clinical parameters before and during infliximab therapy. Cardiolipin-Ab (IgG) were measured using an ELISA assay and lupus anticoagulant using phospholipid sensitive APTT and Russel viper venom test methods.

	Normal range	Baseline	During the therapy
WBC	(3.6-10.1 x E9/l)	2.3	2.7
B-Tromb	(150-400 E9/l)	173	98
P-D-Dimeer	(< 0.5 mg/l)	ND	7.1
B-FII-D	(pos/neg)	ND	neg
FVIII	(47-146 %)	ND	187
P-ATIII	(84-10 %)	ND	74
P-APCres	(2-6)	ND	2.2
C3	(0.71-1.41 g/l)	ND	0.77
C4	(0.12-0.34 g/l)	ND	0.04
Antinuclear-Ab	(< 320, titer)	> 5000	> 5000
Anti DNA-Ab	(< 10, titer)	ND	50
Anti-cardiolipin Ab	(< 11 EU)	ND	16
Lupus anticoagulant	(pos/neg)	ND	positive*

*Sample taken during warfarin treatment. P-APCres: activated protein C resistence, B-FII-D: prothrombin II gene mutation analysis, P-ATIII: antithrombin III.