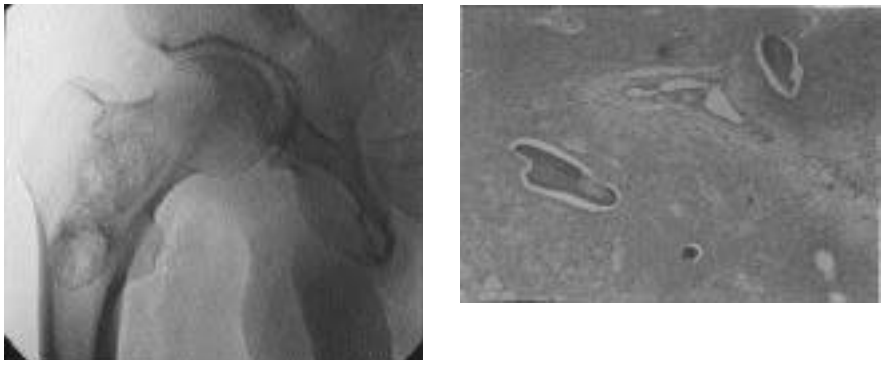
Letters to the Editor

Unrecognized seropositive RA and SS in a patient with associated familial hypercholesterolemia type IIa and osseous xanthoma of the proximal femur



(a) **(b)**

Fig. 1. (a) Digital radiography showing bone infiltrate (osseous xanthoma) in proximal portion of the right femur. **(b)** Trabecular bones around which are the xanthomatous cells (*top right corner, bottom left corner*). Opening blood vesels surround by fibrous cells (*center middle*). (H&E stain, 20x).

Sirs,

The clinical manifestations of hyperlipidemias may be varied: pancreatitis, premature arteriosclerosis, eruptive, tendon or osseous xanthomas, arthralgias, arthritis etc. (1, 2). In the literature, we have not found any data that some of the connective tissue disorders, such as: rheumatoid arthritis (RA),Sjögren's syndrome (SS),etc. may be associated with primary hyperlipidemias. There is only data that in systemic lupus erythematosus (SLE), hyperlipoproteinemia type I may be one of secondary clinical manifestations (1).

A patient, Caucasian, 51 years old, was admitted to the Institute of Rheumatology in Belgrade for hospital treatment. He was in pain, had swellings, and was limited in movement at: both shoulders, elbows, hands, knees and feet and he also had pain and stiffness in the hips. Besides that the patient complained of morning stiffness in the mentioned joints and xerophthalmia and xerostomia syndrome. The patient had these problems for about 5 previous months. During clinical examination, problems with joints were verified and xanthelasmas on eyelids, conjuctival hyperemia and dry tongue were noted. Significant laboratory results were: erythrocyte sedimentation rate (1st hour) 130 mm/h, leukocyte count 8.1 x 10^9 l,platelet count 441 x 10^9 l,total cholesterol 9.28 mmol/l (normal values (nv) < 5.20 mmol/l), low-density lipoprotein 7.40 mmol/l (nv < 3.36 mmol/l),triglyceride 1.05 mmol/l (nv < 1.8mmol/l), latex rheumatoid factor 100 I.U/ml (nv < 25 I.U/ml), Schirmer's test 4 mm in 5 minutes (nv 10 mm in 5 minutes). X-rays of the hands revealed several not completely differentiated subchondral cysts at the level of some of the MCP and PIP joints. X-rays of the hips showed bone infiltrate in the proximal part of the right femur (Fig. 1a). A curretage and a bone grafting of the femur lesion was performed. The microscopic appearance of the lesion (Fig. 1b) was thought to be compatible with an osseous xanthoma. We also performed skeletal scintigraphy to check for pathological infiltrates in the rest of the skeleton, but found none. Based on the patient's report of xerophthalmia and xerostomia syndrome and the positive Schirmer test we also performed minor salivary gland biopsy and found several foci, i.e. agglomerations of mononuclear cells of glandular tissue. We concluded that the patient fulfilled all of the criteria for diagnoses of RA and SS (3, 4). In addition typical hypercholesterolemia type IIa signs and xanthoma in the proximal part of the right femur were detected (1).

We have described a patient who was treated some 5 months with a diagnosis of hypercholesterolemic arthropathy although he had chronic, symmetrical, destructive polyarthritis of the peripheral joints associated with long-term morning stiffness, xerophthalmia and xerostomia syndrome. In addition to medicaments to lower the blood cholesterol level he was only taking NSAIDs.

One of possible reasons for not recognizing RA with associated SS in our patient was the similar clinical picture that might be present between early stage RA and some forms of hyperlipidemic arthropathies, because according to Mathon (5) there are some hyperlipidemic arthropathies that involve larger numbers of joints, have a symmetrical distribution, and are followed by strong pain. Otherwise, as Mason points out (2), patients with hyperlipidemias suffer from arthropathies more frequently than healthy persons and the occurrence of arthropathy is mostly episodic. Rheumatoid factor was not found in these patients and their arthropathies do not involve bone destruction.

We want to underline that we accidentally found osseous xanthoma in the proximal part of the right femur in our patient. This is rare clinical manifestation of hyperlipidemia, and has not often been described in the literature (6).

The question of a possible connection between hyperlipidemia and systemic diseases as RA and SS remains to be answered. Even though such an association has never been described in the literature, it is our opinion that the association seen in our patient was not accidental. We find strong support for this assertion in the work of Manzi *et al*. (7) and his associates. They attribute an important role in the development of arteriosclerosis of the blood vessels to cellular and humoral components of the immune system, i.e. a vasculities similar to the one that exists in systematic connective tissue disorders like RA and SLE. Given this and the fact that our patient had hyperlipidemia for a long time before he developed RA and SS, we would hypothesize that hyperlipidemia could be one of the risk factors for developing many systematic connective tissue disorders. If this assumption is correct,then it would not be unrealistic to expect similar cases in the future. For this reason we would recommend that rheumatologists carefully monitor any patients with hyperlipidemias, especially those with long-lasting arthropathies involving a large number of joints,because they are at risk of systemic conective tissue disorders. This question deserves further study.

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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.