Transient cryofibrinogenaemia with acral digital necrosis, secondary Raynaud's phenomenon and polyarthritis

Sirs,

A search for cryoprecipitable plasma proteins is warranted in Raynaud's phenomenon and cold-induced acral symptoms. Cryoproteins are categorized into types I-III (1, 2). A special type of cryoprotein is cryofibrinogen, which may be detected using citrated or EDTA-chelated blood keeping fibrinogen soluble.

A 51-year-old woman had pain and paraesthesia in the fingers and three-phase Raynaud's phenomenon 6 weeks after flu-like symptoms. Her medical history included a mild chronic obstructive pulmonary disease and nicotine abuse. She had not used any medication. Physical examination showed: blood pressure 120/70 mmHg, heart rate 80 pm; bilateral cold-induced Raynaud's phenomenon of the 2nd - 4th fingers, and acral cyanosis ultimately leading to necrosis of the fingertips. She had developed non-erosive arthritis of the 1st - 3rd metacarpophalangeal (MCP) joints bilaterally, the carporadial joints, as well as of the shoulders and knees. Tinel's sign was positive over the left wrist. There were no pathognomonic signs. Abdominal ultrasonography and X-rays of the heart/lungs, hands and forefeet were normal. Biopsy of skin muscle and fascia from the non-lesional lower leg revealed minimal perivascular inflammation

Laboratory examination results were: ESR 40 mm/hr (normal < 20 mm/hr), C-reactive protein 23 mg/l (normal < 9mg/l) ,IgG 10.0 g/l (normal 8.0-17.0 g/l), IgA 2.54 g/l (normal 1.00-4.90 g/l), and IgM 1.65 g/l (normal 0.60-3.70 g/l). Cryoglobulins were positive for cryofibrinogen. Other serological results including IgM rheumatoid were negative.

Cryofibrinogen was demonstrated in two consecutive plasma samples, taken 3 weeks apart in the period when the clinical symptoms were most severe (Table I). Blood was collected as serum and plasma (tubes containing Li-heparin, K_3-EDTA or Na-citrate). Samples were centrifuged at 37ºC, and supernatants were divided into two parts and incubated at either 4ºC or 37ºC for 48-72 hours. A precipitate formed in the Li-heparin-plasma sample after incubation for 48 hours at 4ºC, and after 72 hours in the EDTA plasma. Precipitation did not occur in the citrate plasma nor in samples incubated at 4ºC or 37ºC.

The samples incubated at 4ºC were centrifuged (10 min 1500 x g, 4ºC), and the sediments were washed with ice-cold buffer, taken up in buffer (same volume as the original serum) and incubated at 37ºC for solubilisation.

In the unseparated samples, total protein in the sediments and supernatants was measured using nephelometry (BN100, Behringwerke, Marburg, FRG) to determine copper complexation in alkaline solution (Boehringer Mannheim, FRG). Immunoglobulins G, A and M were quantified by turbidimetry (Tina Quant, Boehringer Mannheim and Behring BN100), and fibrinogen by means of a clotting assay (AMAX CS 190, Hamburg, FRG). Additionally, samples were analyzed by electrophoresis followed by densitometric scanning for quantification.

The precipitate formed in heparin plasma incubated at 4ºC contained the highest protein concentration (1.8 g/L). This consisted almost exclusively of fibrinogen. About 66% of the fibrinogen remained in the supernatant. Less protein precipitated in the EDTA- and citrate-plasma samples incubated at 4ºC (0.45 g/L and 0.22 g/L, respectively); these sediments also consisted predominantly of fibrinogen, with a small amount of immunoglobulins (data not shown). Insignificant sediment was obtained from serum (Table I).

Because of the severity of her disease, the patient was advised to stop smoking, and nifedipine was prescribed. Intra-articular corticosteroids were injected into the carpal tunnel (CTS confirmed by electromyography). Due to intolerance she took diclofenac, hydroxychloroquine (HCQ; pruritic dermatosis) 200 mg daily and sulphasalazine (SSZ; nausea) only for short periods.

Two months later the polyarthritis and Raynaud's phenomenon had gradually vanished. Laboratory examination at this time showed: ESR 10 mm/hr, CRP 2 mg/l, cryoproteins no longer detectable. During a follow-up period of more than 18 months neither cryoglobulins nor arthritis recurred.

The laboratory demonstration of cryoprecipitable protein in this patient with transient RF proved to be complex. Cryoprecipitable fibrinogen such as this has been reported before (3). Its demonstration is strongly dependent on the conditions of blood sampling and the anticoagulants used. The presence of cryofibrinogen in the patient apparently was transient, suggesting the disappearance of the cryoprecipitability inductor (probably an immunoglobulin). Normalisation in this patient occurred semi-spontaneously, and proved to be permanent. We believe that the recovery was independent of the treatment given.

In mixed cryoglobulinemia a low-antigen-containing diet has been shown to modify certain symptoms, possibly by decreasing the burden of circulating immune complexes (4). Treatments suggested for essential cryofibrinogenemia, mostly in case reports, include immune suppression with corticosteroids and/or alkylating agents (5, 6), fibrinolysis with ancrod or stanazol (7-9) and plasmapheresis (10). The disease course in our patient suggests that an expectative treatment regimen may be safely followed as well, particularly when the cryoprecipitable protein tends to vanish spontaneously.

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Table I. Total protein, immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), and fibrinogen in serum and heparin plasma samples collected at presentation and stored at 37ºC, supernatant at 4ºC, and precipitate at 4ºC. Data (in g/l) were confirmed by protein electrophoresis (not shown).

	Sample 37ºC	Supernatant 4ºC	Precipitate 4ºC
Serum			
Total protein	69.0	67.9	0.04
IgG	2.53	2.47	0.006
IgA	10.0	9.5	< 0.0001
IgM	1.85	1.66	0.006
Fibrinogen	NC	NC	NC
Plasma			
Total protein	76.2	72.9	1.8
IgG	2.60	2.50	0.135
IgA	9.9	10.0	0.032
IgM	1.75	1.71	0.039
Fibrinogen	3.5	3.6	1.4

NC: no clotting in the fibrinogen assay, indicating insignificant fibrinogen.

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Nimesulide: Is it only an anti-inflammatory, analgesic drug?

Sir,

Nimesulide (4-nitro-2-phenoxy-methanesulphonanilide) is a non-steroidal anti-inflammatory drug (NSAID), which is considered to be a preferential cyclo-oxygenase-2-blocker and has other anti-inflammatory actions in addition to its action on prostanoid formation (1-7). NSAIDs are largely used for relief of symptoms of rheumatic diseases, but they are considered to be ineffective in modifying disease activity; they are also considered to be ineffective (or at least to exhibit only slight and inconstant effects) on acute-phase reactants, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). A decrease in the values of acute-phase reactants is instead a typical effect induced by slow-acting antirheumatic drugs (SAARDs). We observed a case of polymyalgia rheumatica (PMR) which appeared especially interesting because nimesulide administration might have induced a marked decrease of acute-phase reactants.

We examined a 68-year-old Caucasian male who reported persistent pain localised in the muscles of the neck, shoulder and pelvic girdle. The onset of pain had been about 1 year before. Muscle or joint tenderness was not observed on clinical examination. ESR and CRP values were within the normal range (ESR: 10 mm/h; CRP serum level: 0.6 mg/dl). Rheumatoid factor was detected, with a titre of 441 IU. The patient had been taking low dose nimesulide (100 mg daily) for one month. Nimesulide induced only a slight and transient decrease in pain intensity. Nimesulide administration was then stopped. Seven days after nimesulide withdrawal ESR was 22 mm/h, the CRP level was 1.5 mg/dl, rheumatoid factor titre was 532 IU, and the fasting plasma glucose level was 157 mg/dl. The patient complained of strong pain interfering with daily activities and with nocturnal sleep. ESR and the CRP level measured again after 10 days were 80 mm/h and 7 mg/dl, respectively. The patient reported persistent strong pain, mainly felt during the night and the morning, localised in the shoulder and pelvic girdle, with morning stiffness lasting about 2 hours. Joint or muscle tenderness or reduced muscle strength were not detected on clinical examination. PMR was diagnosed and deflazacort was prescribed, with a daily dosage of 30 mg. Two months after the onset of deflazacort therapy, the patient reported complete pain relief. ESR and CRP values were in the normal range.

This case appears to be interesting for many reasons. The patient was affected by PMR: the diagnosis was based on typical clinical and laboratory findings, and was confirmed by the effect of the specific therapy for this disease, i.e. the administration of corticosteroids. When we first saw the patient, the diagnosis was not clear because the values of acute-phase reactants were within the normal range; the patient was taking nimesulide, which had induced only a slight analgesic effect. An increase in the values of acute-phase reactants occurred only after nimesulide withdrawal, which was also followed by an increase of pain. It may be deduced that nimesulide, though it was not effective in providing complete pain relief, could have a marked effect on acute-phase reactants. Complete relief of pain was achieved only by the administration of corticosteroids, which are considered to be the drugs of choice in PMR. We may suppose that the effect of nimesulide on acute-phase reactants is due to an as yet unknown mechanism of action, quite different from those studied previously and not related to the anti-inflammatory and analgesic actions.

Further investigations are necessary to confirm our hypothesis. A careful comparison between the effects of nimesulide and the effects of other NSAIDs in different clinical conditions may be useful to identify the pathophysiological mechanisms via which nimesulide exerts its specific actions.

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