Letters to the Editor

Three cases of Buerger's disease associated with hyperhomocysteinemia

Sir,

Buerger's disease or thromboangiitis obliterans (TAO) is a disorder of unknown etiology which affects young heavy smokers, primarily males. It is not clear why this disease affects only a small number of heavy smokers. The HLA DR4 antigen seems to be associated with TAO in Caucasian patients (1); it therefore may be hypothesized that a genetic predisposition contributes to the development of the disease.

Recently TAO has been associated with hypercoagulable states; a case of TAO with protein S deficiency (2) and 2 cases with very high levels of lipoprotein (a) (3, 4) have been described. Moreover, in a group of patients with TAO a fasting hyperhomocysteine level was observed in 5/9 patients and positive anticardiolipin antibodies in 6/17 (5). Very recently, laboratory investigations in 4 patients affected by TAO identified 2 cases with APC resistance and 3 cases with hyperhomocysteinemia after oral methionine loading, while fasting homocysteine levels were normal (6). These data lead to the hypothesis that the clotting process may play an important pathogenetic role.

In a group of 7 patients affected by typical TAO we found 3 males who were heavy smokers with fasting hyperhomocysteinemia; the most significant features of these patients are reported in Table I. The high level of fasting homocysteinemia (18.8 μmol/L in the first case, 28.6 in the second and 25.5 in the third; normal < 15) was associated with low plasma folate levels in all 3 cases (first case 8 nmol/l, second case 5.6, third case 5.4; normal > 11.5 nmol/l). The frequency of hyperhomocysteinemia in the normal Italian population is 5% (7). In all 3 cases protein C, protein S, anti-thrombin-III and LP(a) levels were normal and antiphospholipid antibodies were negative; the presence of activated protein C resistance was excluded.

In 2 cases a test for C677T methylene tetrahydrofolate reductase (MTHFR) mutation was performed; both subjects presented heterozygosity for this polymorphism.

Our patients were strongly urged to stop smoking and are being treated with iloprost and folate supplementation, even if it is not known whether the normalization of homocysteine levels with folic acid supplements may reduce the risk of vascular disease.

High levels of plasma homocysteine are caused either by genetic defects in the enzymes involved in homocysteine metabolism or by severe vitamin deficiency. The most common inherited cause of severe hyperhomocysteinemia is cystathionine β-synthase deficiency (8). Moderate hyperhomocysteinemia may be provoked by a frequent mutation (C677T) in the gene encoding for MTHFR when the folate status is inadequate (9). In recent years mild hyperhomocysteinemia, as observed in our patients, has been recognized as a strong independent risk factor for arterial vascular disease (8); an association between mild hyperhomocysteinemia and occlusive disease of coronary, cerebral and peripheral arteries has been reported (10). Homocysteine is directly toxic to endothelial cells (11) and modifies the thrombo-resistant properties of normal endothelium (12); moreover it may facilitate the atherogenic process by favouring the oxidation of low-density lipoprotein by arterial smooth muscle cells (13).

In our patients hyperhomocysteinemia might have facilitated the clinical expression of TAO, in which vascular injury may be directly caused by tobacco products or could be the consequence of secondary autoimmune phenomena (1). On the grounds of our observation and data in the literature (2-6), it is possible to hypothesize that different conditions predisposing to thrombotic events may further contribute to damage the endothelium of patients with TAO, thus favouring the onset of ischaemic events. In subjects with a history of heavy cigarette smoking, the presence of a prothrombotic condition might further alter the delicate balance of vascular homeosthasis.

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This work was supported by a grant from Progetto Sanità 1996-1997 Fondazione Cassa di Risparmio di Verona, Vicenza, Belluno ed Ancona.

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Table I. Salient clinical and laboratory features of 3 patients affected by Buerger's disease associated with hyperhomocysteinemia.

	Case 1	Case 2	Case 3
Age (yrs.)	29	36	34
Sex	Male	Male	Male
Symptoms at onset	Intermittent claudication	Pain at rest in the left foot	Phlebothrombosis in the right upper limb
Other clinical features	Acrocyanosis	Deep painful ulcer on the 5th toe of the left foot	Pain at rest in the right lower limb; multiple ulcers on the right hand
Angiography and/or Doppler study	Occlusion of the left superficial femoral, the left anterior tibial and the right radial arteries	Bilateral occlusion of anterior and posterior tibial arteries	Occlusion of posterior tibial artery on the right, of the anterior tibial artery bilaterally, of the ulnar artery bilaterally, and of the digital arteries of the right hand
Homocysteine level	18.8 μmol/l	28.6 μmol/l	25.5 μmol/l
Folate levels	8 nmol/l	5.6 nmol/l	5.4 nmol/l

Normal level of homocysteine < 15 μmol/l; normal level of plasma folate > 11.5 nmol/l.

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Septic arthritis caused by *Stenotrophomonas maltophilia* in a patient with acquired immunodeficiency syndrome

Sirs,

The Gram-negative bacillus *Stenotrophomonas maltophilia* is frequently isolated from clinical specimens in the absence of disease (1). Opportunistic infection occurs principally in individuals receiving immunosuppressive therapy, with underlying malignancy or with indwelling venous catheters (2, 3).

A 36-year-old man presented with fever and swelling and pain of 14 days duration in the right knee. He had been tested for human immunodeficiency virus infection (HIV) in 1985 with a positive result. He developed pulmonary tuberculosis in 1987, osteomyelitis of the right tibia due to *Salmonella* subgroup 1 in 1987, tuberculous osteomyelitis of the left tibia in 1990, cerebral toxoplasmosis in 1995, and HIV-associated encephalopathy in 1996. Both tibial osteomyelites were confirmed by bone biopsy.

On examination the patient was febrile and the right knee was enlarged. ESR was 120 mm/hr and haemoglobin 104 g/l. Blood and synovial fluid leukocyte counts were 11.1 10^9/l with 81% neutrophils and 35 10^9/l with 85% neutrophils, respectively. The number of CD4 positive lymphocytes was 0.11 10^9/l. Culture of the synovial fluid was negative. Simple x-rays and MRI showed findings compatible with osteomyelitis of the right femur and tibia and synovial fluid within the joint (Fig. 1).

Bacterial arthritis was suspected and the patient was empirically treated with intravenous (IV) gentamycin (180 mg/day for 2 weeks) and cloxacillin (2 g/day IV for 2 weeks followed by an oral regimen of 1 g/day for 4 weeks) with amelioriation of the pain and swelling. Two weeks after the cessation of antibiotics the patient once again became febrile and the knee was newly enlarged. Synovial fluid was aspirated and a bone biopsy of the right tibia was performed. Blood cultures and cultures of the bone biopsy were negative. Culture of the synovial fluid yielded *S. maltophilia*. The patient received oral trimethoprim (320 mg/12 hr) and sulfamethoxazole (1600 mg/12 hr) plus ciprofloxacin (750 mg/12 hr) for 6 weeks with resolution of the signs and symptoms.

HIV infection was present in 4 of 91 patients with *S. maltophilia* bacteraemia studied by Muder *et al.* (3). Manfredi *et al.* (4) described 54 episodes of *S. maltophilia* infection in 52 HIV-infected patients: bacteraemia in 44 cases, lower airway infection in 5 cases, urinary tract infection and pharyngitis in 2 cases each, and lymph node involvement in one case.

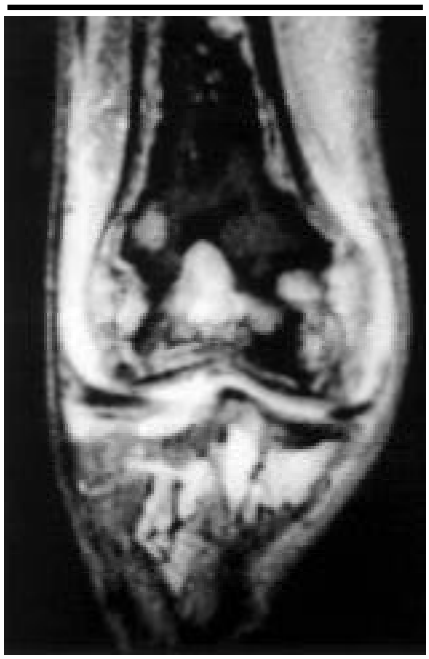

Fig. 1. MRI of the knee on T2-weighted images showing findings compatible with osteomyelitis of the femur and tibia.

Osteoarticular infections caused by *S. maltophilia* are rare. Osteomyelitis due to this organism has been reported in patients with wounds caused by corn-harvesting machines (5). Prepatellar bursitis due to *S. maltophilia* has been described in an elderly alcoholic man with heart disease, lung disease and adenocarcinoma of the stomach treated by gastrectomy (6).

In our patient diagnosis was difficult because he had received antibiotics for 6 weeks. Two weeks after the cessation of cloxacillin, an aetiologic diagnosis was made and a synergistic antimicrobial combination was administered with good results. Trimethoprim-sulfamethoxazole has traditionally been the most active agent used against this organism; the addition of another agent (in our case, ciprofloxacin) to which the isolate is susceptible should be considered in immuno-compromised patients (3).

We conclude that *S. maltophilia* should be included as a possible causative agent of septic arthritis in immunosuppressed patients.

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