MATTERS ARISING

Exposure to chemicals and systemic sclerosis

Occupational exposure to various chemicals, including vinyl chloride, silica dust, epoxy resin, benzene, trichloroethylene, propylene oxide, and a large solvent, has been described as a potential provoking factor of systemic sclerosis (SSc) and scleroderma-like disorders. However, the precise contribution made by occupational environmental factors to the occurrence of scleroderma remains unknown.

Susceptibility to these agents may differ widely in distinct areas of Europe, as a result of the long history of employment of the chemicals and the occupational exposure to various solvents. Several cases of exposure to solvents have been described, including that reported by García-Zamalloa and colleagues in the Annals. Patients developed scleroderma-like symptoms from exposure to vinyl chloride disease in the north of Hungary (Kazincbarcika). The disease seemed to be limited to female workers from rural areas, who were employed to do menial jobs in the urban areas, with a concomitant higher risk of exposure to solvents and other chemicals. After a latent period of several years, these patients developed SSc indistinguishable from 'true' systemic sclerosis. Now, with the improvement of working conditions in Hungary, the number of cases with exposure to chemicals is decreasing.

Vinyl chloride disease seems to be relatively frequent among British workers exposed to this agent. Conversely, in Hungary, vinyl chloride disease has been found to be extremely rare, in spite of the presence of well detectable exposure to this chemical: 464 workers were exposed to vinyl chloride in Kazincbarcika (north eastern Hungary) for more than 10 years on average, but only one case of vinyl chloride disease has been described, despite regular and well documented screening for the presence of this disorder. Another group of 60 workers has been exposed to trichloroethylene without any signs of scleroderma related disease.

Genetic markers are useful tools for relating chemically induced SSc-like vinyl chloride disease. Susceptibility to this disorder is increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it and an antigen associated with the haplotype A1 B8, while DR3 favours the progression over the disease, as seen among the British workers.

The heterogeneity of clinical symptoms, distribution of major histocompatibility complex alleles, and autoantibody profiles in SSc suggest that this disorder may represent a group of distinct diseases, and that the characteristic genetic and environmental pre-disposing risk factors can be totally different in these subgroups. The environmental contribution to scleroderma is unknown, raising the need for a European multicentre case-control study to determine the groups at risk.

LETTERS TO THE EDITOR

Acquired scleroderma anaemia associated with penicillinase therapy for rheumatoid arthritis

Penicillinase has been successfully used in the treatment of rheumatoid arthritis since 1964. Most of the serious reactions have been haematological and include agranulocytosis, thrombocytopenia, and aplastic anaemia. The incidence of some adverse side effects, such as thrombocytopenia, rashes and proteinuria, has been shown to be unacceptable high with high dose treatment.

We report a case of acquired scleroderma anaemia following treatment with penicillinase for rheumatoid arthritis. A 50 year old man with a five year history of rheumatoid arthritis and non-insulin-dependent diabetes mellitus developed more active joint disease associated with rheumatoid nodules and erosive changes revealed by radiography. His joint disease had been controlled on ibuprofen 600 mg three times daily, but in June 1988 penicillinase 125 mg once daily was added to his regimen. The dose was gradually increased, by 125 mg at monthly intervals, to 500 mg once daily. At no stage was he taking phenacetin or paracetamol.

Before he commenced taking the penicillinase, the patient's full blood count had been stable, with a haemoglobin concentration of 13-2 g/dl, platelet count 351 x 10^9/l, leukocyte count 9-3 x 10^9/l and erythrocyte sedimentation rate 35 mm/1st h. The film was mildly microcytic with a discocyte count (MCV 75 fl) and hypochromic. The white cell differential was normal.

Two months after he started treatment, his haemoglobin had decreased to 9-9 g/dl and showed hypochromia and microcytosis (MCV 78 fl). He then began a course of iron therapy and the haemoglobin temporarily increased to 12 g/dl in November 1988. By January 1989 his haemoglobin decreased back to 10-8 g/dl with a microcytic picture (MCV 70 fl) and by February 1989 it had decreased further, to 7-0 g/dl. At this stage, the film showed a dimorphic picture with some hypochromia, target cells, and dyserythropoiesis. There were some nucleated red cells and the white cells and platelets were normal. Because of the appearance of the blood film, the possibility of scleroderma anaemia was raised.

Clinically, there was no evidence of blood loss and an endoscopy was normal. His arthritis was considered to be well controlled on therapy, with a C-reactive protein 29 mg/l (normal range 0-20 mg/l) and C3 degradation product 15 U/ml (NR 5-12 U/ml); vitamins B12 and folate levels were normal, serum iron 33 mmol/l (NR 14-34 mmol/l), and iron binding capacity 34 mmol/l (NR 43-72 mmol/l). Bone marrow aspirate and trephine revealed a hypocellular marrow with markedly reduced erythropoiesis, gross dyserythropoiesis and 24% ringed sideroblasts. The karyotype of the bone marrow was normal. The appearance of the hyperplastic and megakaryocytic series was normal. During the period of investigation the haemoglobin decreased to a minimum of 4-9 g/l. The patient's penicillinase regimen was continued and he began taking pyridoxine 100 mg twice daily. He required a blood transfusion to control his symptoms, but subsequently maintained his haemoglobin at about 12-5 g/dl, with a normal MCV (81 fl). A repeat bone marrow aspirate at two months was hypercellular, and although there was mild dyserythropoiesis, ringed sideroblasts were not present.

During subsequent follow up, the patient's joint disease flared. In order to control this problem, it was decided initially to treat him with prednisalone 5 mg once daily and, more recently, with hydroxychloroquine.

Patients with acquired idiopathic skin sclerosis are anaemic. Aplastic anaemia is a rare complication of all three haematopoietic cell lines. The changes are most marked in the red cell lineage, with at least 15% of nucleated erythroid cells in the marrow being ringed sideroblasts. The peripheral blood shows a dimorphic picture with poikilocytosis, basophilic stippling and some hypochromic features, although the overall MCV is often slightly increased. The karyotype may be abnormal and there is a predisposition to develop acute leukaemia.

Secondary scleroderma change occurs in a wide variety of conditions, but the number of...
ringed sideroblasts is generally many fewer than 15%. The white cell and megalokaryocyte series are not affected. Occasionally, patients develop severe sideroblastic anaemia secondary to drug therapy or severe alcohol abuse which may revolve on stopping the offending drug. In the case of isoniazid the mechanism is thought to be inhibition of pyridoxine related haemassynthesis; isoniazid binds pyridoxine and the complex is excreted via the kidney. Penicillamine may have a similar mode of action.

A number of haematological side effects of penicillamine therapy have been reported. Sullivan et al. reported a case of sideroblastic anaemia in a patient with biliary cirrhosis who was taking 1000 mg of penicillamine daily. The features of sideroblastic anaemia developed over 12 months and resolved after cessation of penicillamine and introduction of pyridoxine treatment. The patient later recommenced taking penicillamine with pyridoxine cover, without further problems. This patient had abnormal liver function and this may have contributed to the situation.

Ramselaar et al. reported a patient who developed aplastic anaemia secondary to penicillamine. The leucopenia resolved, but the patient remained anaemic and thrombocytopenic with bone marrow features of sideroblastic anaemia. The patient did not respond to pyridoxine therapy and subsequently died of a septicemic episode.

In our patient, the development of sideroblastic anaemia was closely associated with the introduction of penicillamine therapy and his rheumatoid arthritis was relatively quiescent as judged by clinical and laboratory parameters. On introduction of pyridoxine, the patient's anaemia resolved and the abnormal sideroblasts disappeared from the bone marrow. Thus the sudden onset of anaemia and the response to withdrawal of penicillamine strongly implicate penicillamine as the causal agent. The follow up bone marrow analysis showed only minor dysplastic features—a frequent finding in pyridoxine sensitive sideroblastic anaemia.

We believe that this is the first reported case of acquired sideroblastic anaemia which was reversible with pyridoxine, in a patient with rheumatoid arthritis. As many of the adverse effects of penicillamine are dose dependent, it may be possible to reintroduce penicillamine under pyridoxine cover, particularly if a smaller dose controls the joint disease.

This report highlights the need for vigilance in patients with rheumatoid arthritis who are receiving maintenance penicillamine. The development of anaemia whilst on penicillamine treatment warrants careful investigation, including consideration of a bone marrow aspirate if other more common causes are excluded.

Homologous complement factor deficiency and primary antiphospholipid syndrome: a clinical and serological study

Complement factor 2 (C2) deficiency is the most common inherited complement deficiency. In 60% of cases the disorder is associated with a lupus-like disease, and to a lesser extent with recurrent bacterial infections. An isolated form of glomerulopathy is described in about 25% of patients. Here, we describe a patient with homozgyous C2 deficiency and primary antiphospholipid syndrome (PAPS). The APS manifestation was repeated cerebrovascular disease; another relevant feature was hypertensive nephropathy without overt nephritis. Bilateral cataracts were diagnosed in a 40 year old man in 1986; simultaneously, he was discovered to be hypertensive. There was no previous history of renal calculus or urinary symptoms. Blood analysis revealed creatinine 0.247 mmol/l, urea 27.8 mmol/l, triglycerides 226 mg/dl at the only limited parameters. Urinary sediment was normal; protein excretion was 0.2 g/24 h. The patient was treated with captopril 50 mg/day, with good blood pressure control.

Nine months later, the patient suffered a convulsive seizure without any residual neurological deficit. Laboratory studies showed low haemolytic complement activity (< 8 U/ml) with normal C3 and C4 concentrations. Antinuclear antibodies and antibodies to double stranded DNA, extractable nuclear antigens and rheumatoid factor were negative.

A percutaneous renal biopsy showed a segmental and focal glomerulosclerosis, without acute or chronic changes by fibrinoid or fibrinoid necrosis of the vessel wall. Immunofluorescence showed a weak positivity with IgA, C3, C4, and Cq antisera. In 1987, the bilateral cataracts were surgically removed. Subsequently, the patient became aware of a right visual field defect.

Three years later (May 1990) he showed clinical features of intermittent claudication with inadequate blood supply to the lower extremity. In July 1990 he suddenly experienced dysarthria, right distemalia and lateropulsion with mild right hemiparesis and hemihyypoesthesia. A right homonymous hemianopsia, matching the earlier visual complaint, was also detected. Antiplatelet drug treatment (aspirin) was started. Cranial computed tomography, performed 72 hours afterwards, showed a recent right cerebellar haemorrhage, with an old left occipital lobe infarct. Angiographic examination showed abnormally dilated basilar and left vertebral arteries.

At this stage, anticoagulant antibodies were detected by standard enzyme linked immunosorbent assay. Their values were moderate positive for IgM and low positive for IgG (according to the international standards for that assay); a year later IgG and IgM values were both positive. Coagulation studies showed normal prothrombin time and activated partial thromboplastin time. Thrombocytopenia was not found. HLA typing was performed using microlymphocytotoxicity, and completytophs assayed: agallro electrophoresis, immunofixation and Coomassie staining for C4; cellulose acetate electrophoresis, immunofixation and nigrin staining for factor B; and polyclamlyl isoelectrorephoresis, immunofixation and silvar staining for C2. The total haemolytic complement activity and C2 were undetectable, with normal C3 and C4 concentrations (table). Reconstitution of total haemolytic complement activity was possible by addition of C2. The results of completoype and haploype analysis were also compatible with this homozygous deficiency (table).

The proband had a sister who suffered repeated migraines and died at the age of 30 years from cardiac infarction; the father also died (aged 64 years) from cardiac infarction. The mother was asymptomatic and had negative autoimmune serology.

We present here the first description (Medline 1987–April 94) of a patient with a homozgyous C2 deficiency and PAPS. C2 deficiency is a molecular genetic deficiency with two variants; in the proband, the HLA haploype corresponded with the type I form, although the completoype was not typical.
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