Systemic sclerosis and organic solvents: early diagnosis in industry

In 1957 Rein and Walder described the first cases of systemic sclerosis (SS) after contact with organic solvents. An increasing number of cases have subsequently been reported, the most frequent involving aliphatic hydrocarbons (vinyl chloride, perchloroethylene, trichloroethylene), and 20 cases related to aromatic hydrocarbons (benzene, toluene, xylene, white spirits and diesel). Aromatic amines (cyclohexylamine and m-phenyleneendiamine) and formaldehyde derivatives were involved in about 10 cases.1-3

Our 56 year old patient developed SS with skin, lung and pericardial involvement after intense and prolonged exposure to toluene (aromatic hydrocarbon), heptane (aliphatic hydrocarbon), dimethylbuthylphenyldiamine, (aromatic amine), and octylphenol formaldehyde (formaldehyde (derivate), curability, and by it's regularity. Exposure to nonchlorinated hydrocarbon and sulphated substances was also assessed.

For 23 years he had worked in the rubber trade, production of a tyre factory. However, a period of eight years he developed progressive thickening of the skin of the fingers, Raynaud's phenomenon and progressive effort dyspnoea. He was first seen by us in May 1991 because of dyspnoea on minimal exertion.

Clinical findings on admission were sclerodactyly, mild generalised cutaneous sclerosis (more intense on both shoulders and some on the front of the chest.) Despite the upper trunk and palm telangiectasia. A trunk skin biopsy showed a severe sclerosis of the dermal collagen, with few fibroblasts, sclerosis of the sweat glands and subcuticular dermis, with poor vessel calibre and epidermal thickening and subcutaneous tissue. Fine cracks were present in both lung bases. A chest radiograph showed cardiomegaly. Echocardiography revealed a small pericardial effusion and enlargement of the right caviy with mild tricuspid insufficiency that yielded a pulmonary arterial hypertension of 46 mm Hg. Cardiac catheterisation showed it to be pre-arteriolar. Respiratory function tests showed moderate-severe restriction, (FEV1:1960 cc-59%; VC-IN:2:260 cc-52%) alteration on diffusing capacity (TLCO 57, 5%) and arterial gasometry with hypoxaemia (PaO2 73 mm Hg) and increased of the alveolar-arterial O2 gradient (A-aO2 = 43) compatible with moderate long fibrosis. A radiograph of the right hand showed small subcutaneous calcification in one digit. A barium swallow only showed reflux. Renal function was normal. Antinuclear antibodies were positive at a 1:400 titre with a nucleolar pattern. Anticientromere and antiScI 70 antibodies were negative.

The patient was treated with nifedipine (30 mg/day) and prednisone (1 mg/kg a day initially with subsequent tapering). A few months later he complained of dyspnoea at rest, and clinical signs of right sided heart failure. PAP control by echocardiography (Doppler) had raised to 80 mm Hg. He died 12 months after diagnosis from cardio-respiratory failure. Renal function remained normal until his death. Necropsy was refused.

SS is a multisystem disorder characterised by an overproduction of collagen with involvement of the skin, blood vessels and visceral organs.

Over the past 25 years there have been increasing reports of environmentally induced SS. 1 Organic solvents penetrate the skin, can be absorbed, and may produce metabolic changes in many organs, due both to a direct toxic effect and a possible immunogenetic susceptibility to SS.1-9 In most cases, avoiding exposure does not result in clinical improvement. Nevertheless, early diagnosis should be achieved. Raynaud's phenomenon is the first symptom in up to 70% of patients with SS.2 We suggest that a review of solvent exposure should include an immunological reactivity test (immunoblot check up) of workers from relevant industries. In patients in whom Raynaud's phenomenon is present a complete physical examination, a nailfold capillaroscopy and a selective autoimmunie study (anticentromer and antiScI 70 antibodies) should be carried out,1-9 and further exposure avoided if positive.

5. Yamakaga H, Czirjak L, Dank6 K, Crickx K, Kohn S. Systematic study (anticentromer and antiScI 70 antibodies) for his assistance.
arthritis involving *I. belli* and *Cryptosporidium* infestation in patients with AIDS are not yet well known. Further studies should help clarify these questions. We are not aware of any previous report of reactive arthritis after enteric infection due to *I. belli* and we believe this to be the first such report.

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**AUTHORS’ REPLY.** We are pleased that the first article in *Letters of the Month* has attracted interest and correspondence.

In reply to Dr Edgar *et al*, we feel that the use of Bence-Jones protein (BJP) as a descriptive term for urinary monoclonal light chains is in such standard usage as to be fully acceptable; few clinicians or laboratory scientists would be in any doubt as to the meaning of this term.

The agarose gel electrophoretic assay used for the detection of urinary BJP in our laboratory has a sensitivity of 0.08 g/l, which after concentration of urine x20 gives a lower limit of detection of approximately 0.001 g/l of monoclonal BJP (Sheldon L, personal communication). In this case BJP was not quantified but was expressed as two faint bands of kappa protein at initial testing. The laboratory routinely expresses BJP calculated as a percentage of total urinary protein.

It is our experience, and that of our colleagues in the laboratory, that the term ‘benign’ can be applied to the presence of a monoclonal protein in persons with no evidence of myeloma, Waldenstrom macroglobulinaemia, amyloidosis or other related B cell malignancy. We suggest that the term can only be applied once the condition is shown to be stable with time — five years for IgG and IgA and 10 years for IgM paraprotein. An alternative term monoclonal gammopathy of unknown significance (MGU) is better used when any doubt exists.

We agree with Dr Edgar *et al*, and hope that *Letters of the month* highlights the need to follow up the findings of even a faint band of BJP with serial BJP measurements. It was this omission which led to the difficulties encountered in this case. However, we appreciate the concern expressed by Dr Edgar that early bone marrow examination be undertaken if any BJP is detected and there is general agreement that this decision should be based on clinical judgement. Most clinicians would find it impossible, for reasons of resource limitation and clinical acceptability, to perform bone marrow examination on every patient with any detectable BJP, although this is a moot point.

Certainly levels of >0.01 mg/l are more suggestive of malignancy and should be investigated with bone marrow examination. As far as other investigations are concerned plain radiographs are generally regarded as a more sensitive indicator of the presence of myeloma. Isotope bone scans can often be normal in myeloma even with significant bony deposits. Interpretation of the finding of increased uptake by the bone marrow needs to be aided also by assay of *β*, microglobulin. *β*, microglobulin may be elevated either with deterioration in renal function or with myeloma tumour mass; interpretation of elevated levels may be difficult.

If *Letters of the month* continues to draw attention to important clinical issues and to open areas of controversy then it will surely achieve its intended purpose.

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**MATTERS ARISING**

**Bence-Jones protein and vertebral osteoporosis**

We welcome the introduction of *Letters of the Month* and read with interest the case report submitted by Hughes *et al*. Regarding the investigation of patients presenting with back pain. As the authors rightly point out, the exclusion of occult lymphoproliferative disorders in this group of patients is of the utmost importance. There are, however, several points of concern arising from the case particularly in relation to the clinical interpretation of monoclonal urinary light chains.

The use of the term Bence-Jones protein (BJP) can cause confusion as it refers to the original heating test for the detection of urinary monoclonal free light chains. These are now best detected using the more sensitive techniques of immunoelectrophoresis or immunofixation. As this interesting case demonstrates, serum immunofixation levels can remain normal in a few cases, even in the terminal stages of disease. It is therefore imperative that paired serum and urine samples are sent for immunochemical analysis.

We feel it is potentially misleading to say “... Traces of urinary BJP in isolation can prove to be benign ...” It is generally agreed that their detection is highly suggestive of underlying lymphoproliferative disease in the majority of cases and it is wrong to dismiss such findings as benign. In addition the definition of “a trace” will depend heavily on the detection system employed in individual laboratories. Accurate quantitation of the free light chains should routinely be undertaken; measurement of total protein is less informative. These are the important lessons we must appreciate if patients with occult myeloma are to be detected and successfully treated.

We would emphasise that in patients presenting in this manner, a more aggressive investigational algorithm is indicated, including early bone marrow examination and radioisotope scanning of bone. Only when negative results from these investigations are available would it be advisable to monitor the patient over time remembering that a repeat bone marrow examination is always an option at a later date.

**Antiphospholipid antibodies (aPL) in systemic lupus erythematosus. Are they specific tools for the diagnosis of aPL syndrome?**

We read with interest the paper by Ghirardello *et al* on antiphospholipid antibodies (aPL) in systemic lupus erythematosus (SLE) but would suggest that their conclusion, “lupus anticoagulant (LA) but not anticoagulardip antibody (aCL) positivity is a specific tool for the diagnosis of thrombotic complications ... in SLE”, is interpreted with caution.

There are a number of methodological problems in setting up a study of this kind which should be highlighted:

1) This study was retrospective and it cannot be assumed that aPL-positive patient is aPL-ve at the time of study, they were also aPL-ve at the time of diagnosis of SLE. In fact, the authors do not specifically state in reference to the 47 patients who had experienced pregnancy, whether they were diagnosed as having SLE at that time. It is therefore likely that the recording of aPL complications using

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