Letters to the Editor

Persistent Raynaud's phenomenon after exposure to vinyl chloride monomer: Assessment of endothelial damage

Sirs,

Vinyl chloride monomer (VCM) (C.A.S. No. 75-01-4), a colourless gas under ambient conditions, is involved in the manufacture of Polyvinyl chloride (PVC), a widely used plastic. VCM exposure can induce scleroderma-like diseases including osteolysis of the phalanges, scleroderma skin changes and Raynaud's phenomenon. Since these symptoms occur together during exposure, a common pathogenesis based on injury to the endothelial cells has been proposed (1,2). Indeed VCM exposure is toxic for the vascular endothelium, as shown by angiographic studies and by hand artery and capillaroscopic examinations (2,3). After removal of the affected workers from further VCM exposure, cessation or reversibility of the disease process has been described.

However, in a previous study we observed that some former VCM-exposed workers employed in the same VCM plant still had RP attributable to VCM at least 10 years after their last exposure. Furthermore, capillary abnormalities were discrete and no sclerodermatous changes were observed (4). We therefore compared vWf levels Ag, a product of endothelial cells which has been proposed as a marker of endothelial dysfunction or damage to the endothelium (5), in formerly VCM-exposed workers with RP and in formerly VCM-exposed workers without RP, to establish whether the persistence of these RP could result from endothelial injury. VWf has previously been shown to be increased in patients with secondary PR (6-8).

Subjects were recruited from among former workers employed in the same VCM plant, including two workshops: VCM polymerisation and PVC product manufacturing. All subjects were males and had worked at least one year in one or both of the plant units. Based on interviews with the workers and available atmospheric VCM concentration readings and due to the old technological process used, we estimate that the level of exposure may have been high, especially in the polymerisation unit.

Two groups were studied after their informed consent was obtained: 25 subjects formerly exposed to VCM with RP secondary to this exposure (mean age 65.4 ± SE 1.20 years) and 67 subjects formerly exposed to VCM without RP(mean age 65.6 ± SE 0.72 years). VWf in the blood was quantified by an enzyme-linked immunoabsorbent assay (ELISA), essentially according to Albin *et al.* (9). The $\chi 2$-test and the Mann-Whitney U test were used as appropriate. A significance level of 0.05 was chosen.

Both groups were similar in terms of their main characteristics: smoking habits, alcohol consumption, medical history and occupational exposure expressed as the duration of employment in the plant and their presence in the polymerisation unit. No differences were observed in the mean serum concentrations of vWf between the two groups (RP 1.47 ± S.E. 0.11 units of vWf /ml versus without RP1.45 ± S.E. 0.08 units of vWf /ml).

As with other environmental agents, VCM could represent a component in the pathogenesis of scleroderma (10). Vascular changes are thought to be an important event leading to scleroderma-like disease or scleroderma. RPis the most common feature of vascular disease in scleroderma. Small vessel injury resulting in proliferative and obliterative vasculopathy, and extensive fibrosis in the skin lead to RP. A deficiency in the endothelial–dependent vasodilatory mechanism has also been suggested.

Abnormalities in endothelial cells have previously been associated with secondary RP (6,7). Thus the endothelial cell probably has a range of important roles in the physiopathological process of scleroderma-like disease or scleroderma and secondary RP. Increased circulating levels of vWf are a consistent finding in patients with secondary RP and are explained as a sign of endothelial cell damage (6-8). For these reasons, using vWf as a marker we investigated whether persistent RP secondary to VCM could be caused by persistent endothelial cells injury/activation.

These and our previous results make this hypothesis improbable. Indeed we observed no association between the presence of RP and increased vWf levels. Previously we observed no correlation between the pattern of capillaroscopic abnormalities and persistent RP appearance and no skin abnormalities in former VCM-exposed workers with RP(4).

A neurogenic mechanism could be proposed and VCM could act on the peripheral nerves. Indeed, paraesthesiae of the fingers occurs independently of attacks of vasospasm in VCM-exposed workers (1). Moreover, Carpentier *et al.* observed an alteration of the peripheral nervous conduction velocities of the median and cubital nerves in VC-exposed patients with RP(11). Similarly Perticoni *et al.* described peripheral nerve pathology in workers with long exposure to VCM (12). According to Carpentier *et al*. this peripheral dysfunction could play a role in the physiopathology of RP in VC disease (11).

Organic chlorinated solvents such as trichloethylene and perchlorethylene, which both have a similar chemical structure to VCM, are known to induce scleroderma-like illness and to be neurotoxic (10,13). Furthermore, some cases of RP following exposure to trichlorethylene or perchlorethylene have been described among another clinical features (13). Thus the similarity of clinical manifestations between VCM and organic chlorinated solvents may reflect a common physiopathological mechanism, requiring metabolic activation to produce neurotoxic metabolites. However the mechanism of the possible VCM toxicity on peripheral nerves remains unknown.

In conclusion it is quite likely that endothelial involvement occurs in RP due to VCM during exposure. However, ours results lead us to suppose that a physiopathological mechanism other than vascular changes or damage may play a role in the persistence of RPsecondary to VCM after exposure.

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Systemic lupus erythematosus and Crohn's disease: An uncommon association of two autoimmune diseases

Sirs,

The association of systemic lupus erythematosus (SLE) with inflammatory bowel disease is rare (1-3). Moreover, the differentiation between digestive manifestations of SLE and extra-digestive manifestations of Crohn's disease (CD) may be particularly difficult (2). Also, sulphasalazine therapy has been implicated in the development of lupus-like syndrome in patients with inflammatory bowel disease (4,5). We report a new case of the association between these two autoimmune diseases. In our case, SLE manifestations preceded the clinical manifestations of CD and, consequently, no drug therapy implication in SLE manifestations was found.

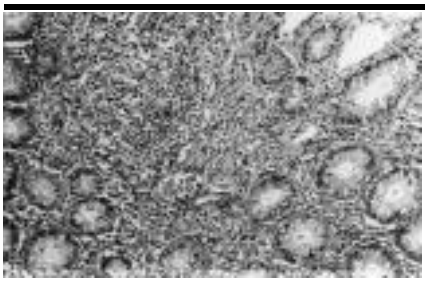

Fig. 1. Infiltration of lymphocytes and plasmatic cells, lymphoid hyperplasia and multinucleate giant cell granuloma formation.

A 41-year-old Caucasian woman presented at the hospital because of abdominal pain and diarrhea. She had been diagnosed 2 years earlier as having SLE because of a photosensitivity malar rash, oral ulcers, peripheral synovitis, positive antinuclear antibodies at 1/1280 (by indirect immunofluorescence using as substrate Hep2 cells), and positive anti-nDNA (by indirect immunofluorescence using as substrate crithidia luciliae) at 1/80. At the time of the onset of diarrhea she was also on treatment with non-steroidal anti-inflammatory drugs and chloroquine (250 mg/day). She recalled her symptoms having begun with abdominal pain and bloody diarrhea (8 times a day) 1 week before admission.

Physical examination showed abdominal distention, but no clinical features of SLE flare-up were observed. Apart from anemia (hemoglobin 9.04 g/dl) no other hematological abnormalities were found. Hepatic and renal function tests were normal. Antinuclear antibodies and anti-native DNA were positive at 1/320 and 1/40, respectively. Serum levels of C3 and C4 were within normal ranges. IgG and IgM anticardiolipin antibodies and ANCA tests were negative. Negative results for both stool cultures and parasitologic examinations of the feces ruled out enteric bacterial pathogens or amebiasis. Chest radiograph and electrocardiogram were also normal.

A colonoscopy showed edematous and hyperemic areas with aphthous ulcers, pseudopolyps and deep transversal and longitudinal fissures. These features were compatible with a moderately active CD. Biopsy specimens confirmed the endoscopic findings. Microscopic examination revealed a chronic inflammation affecting all layers of the colon, which was more severe in the lamina propia of the mucosa with infiltration of lymphocytes and plasmatic cells, aphthous ulcers in areas with lymphoid hyperplasia, fissures extending into the serosa, epithelial cells and multinucleate giant cell granulomas. Figure 1 shows the inflammatory infiltrate with granuloma formation. Neither thrombi in vessels nor any other evidence of ischemic colitis were observed. Once the diagnosis was established steroid therapy (prednisone 1 mg/Kg) and azathioprine (2 mg/kg) was started and a rapid improvement of symptoms was observed. At present, 6 months after the diagnosis the patient is free of symptoms.

The diagnosis of SLE in our patient was based on the criteria proposed by the American College of Rheumatology (formerly the American Rheumatism Association) (6). All parts of the gastrointestinal tract may be involved in SLE (7). However, the development of CD in patients with lupus unrelated to drugs is exceptional (2, 3). Although vasculitis in the bowel due to SLE may be difficult to distinguish from the onset of an inflammatory bowel disease, the onset of diarrhea and abdominal pain in our patient was not associated with a flare of her SLE. In this case, histological findings are the cornerstone to making the differential diagnosis between the two conditions. Evidence of immunofluorescence deposits of immunoglobulins and complement on the capillary wall and electrodense deposits on electronic microscopy are needed to establish a diagnosis of lupus vasculitis involving the gut.

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