

Viral infections and systemic sclerosis

Sirs,

We read with great interest the review by Moroncini *et al.* (1) dealing with the possible role of viral infections in the etiopathogenesis of systemic sclerosis (SSc). The disease is characterised by particularly complex pathogenesis, including immune-system, fibroblast, and endothelial dysfunctions. (1, 2). Their effects are responsible for the large variety of phenotypic expressions: the skin sclerosis may present from very limited to markedly diffuse extent, as well as severity and composition of visceral organ involvement are extremely variable among patients. Similarly, a variety of immune-system alterations, including different autoantibody specificities are detectable (1, 2). All together these findings suggest a variable combination of triggering, infectious and/or environmental, and predisposing genetic factors. In this scenario, it is not surprising that one or more infectious agents may play a causative role in SSc. In particular, human Cytomegalovirus (HCMV) and Parvovirus B19 (PV-B19) show some biological peculiarities that may fit together the pathogenetic mechanisms responsible for SSc (3, 4). With regards the PV-B19, the ability of this virus to persistently infect both fibroblasts and endothelial cells, as well as its chronic latency in the bone marrow of scleroderma patients it is quite compelling (3, 4). The PV-B19 tropism for haematopoietic stem cells might represent a clue for the explanation of the defective production of endothelial cell progenitors with impaired vasculogenesis largely demonstrated in SSc patients (5, 6). We agree with Moroncini *et al.* that such hypothesis, mainly suggested by our group, is still awaiting confirmation, possibly by wider and collaborative researches.

The role of HCMV has been also investigated given its ability to infect both endothelial cells and fibroblasts, as well as the bone marrow of SSc patients, with consequent immune-mediated alterations through molecular mimicry mechanism (1, 7, 8). This hypothesis may represent one

model of linking between infections and autoimmunity. In this respect, we would like to recall our previously published observation of a 33-year-old woman developing SSc after recently acute HCMV infection (9). Five months after this episode, the patient progressively developed weakness, polyarthralgias, cutaneous hypermelanosis, puffy hands, Raynaud's phenomenon, followed by digital ulcers, sclerodactyly, esophageal dysmotility, mild interstitial lung involvement, capillaroscopic scleroderma pattern, and serum anti-nucleolar antibodies. Moreover, the presence of HCMV RNA was demonstrated by *in situ* hybridisation technique in the skin biopsy, with nuclear and cytoplasmic endothelial cell localisation. On these basis, diagnosis of SSc was done; of note, the patient's mother was affected by systemic lupus erythematosus (9). The observation of scleroderma following recent HCMV infection may strongly support the hypothesis of a possible triggering role of this virus in SSc, with the important contribution of the patient's genetic background (mother affected by another connective tissue disease). A coincidental association between HCMV infection and SSc cannot be totally excluded in this single case; however, the striking sequence of events, the presence of viral genome in endothelial cells, in a setting of clear genetic predisposition, are strongly suggestive for a pathogenetic link between HCMV infection and SSc in this patient. SSc is the result of multifactorial and multistep pathogenetic process; in the large majority of cases the first stages of the disease are clinically indistinct, mainly with regards to possible causative agents. Successively, specific triggering factors might be hidden by predominant self-perpetuating autoimmune process. In this respect, the analysis of large series of patients with very early SSc (10), recruited in a multicenter study, might identify a significant number of individuals with clinical and infectious characteristic able to definitely establish the actual role of viral infections in scleroderma.

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