Cytokines in Collagen Disease–Related Atherogenesis

To the Editor:

We read with interest the report of Asanuma, et al. and the excellent editorial of Shovman, et al. describing the role of proinflammatory cytokines in the pathogenesis of atherosclerosis in systemic lupus erythematosus (SLE). Two interconnected pathogenic systems are involved: a complex array of proinflammatory factors found in collagen diseases per se, and a similar in part but different complex of proatherogenic factors in atherosclerosis. Indeed, in the last decade, our knowledge of proinflammatory and immunological factors in the pathogenesis of atherosclerosis has markedly expanded. One of the important factors, not mentioned in the editorial, is the group of secretory phospholipases A2 (sPLA2). Low molecular weight nonpancreatic secretory PLA2 catalyze the hydrolysis of the sn-2 group in glycerophospholipids, producing lysophospholipids and nonesterified fatty acids. The best investigated sPLA2 is the group of secretory phospholipase A2 enzymes in atherogenesis. Curr Opin Lipidol 2005;16:341–4.

We thank Dr. Pruzanski and colleagues for their letter regarding our report showing that interleukin 6 is associated with burden of atherosclerosis in patients with systemic lupus erythematosus (SLE). They comment on the relationship between inflammation and atherosclerosis and suggest that, in addition to the comprehensive list of biomarkers presented in the editorial by Shovman, et al, increased concentrations of secretory phospholipases A2 (sPLA2) should be a candidate marker or mediator for atherosclerosis in patients with inflammatory disease. This suggestion is based on the increased concentrations of sPLA2 in patients with SLE and rheumatoid arthritis, and its role in atherosclerosis. Thus, indeed, sPLA2 should be considered as a mediator and, if so, as a potential target. In addition, other mechanisms that may be common to inflammation and atherosclerosis such as oxidative stress are of interest. However, because associations do not always imply causation, the challenge facing future research will be defining whether markers are also mediators.
Dr. Shovman, et al reply

To the Editor:

We thank Dr. Pruzanski and coworkers for their interest in our editorial1 and welcome their comments. We agree that the group of secretory phospholipases A2 (sPLA2) and especially sPLA2 IIA are involved in the pathogenesis of atherosclerosis through their proinflammatory and proatherogenic effects. Recently several new studies provided evidence that the protective function of sPLA2 IIA in inflammation is also indicated. In particular, the efficient bactericidal properties of sPLA2 IIA resulting in decreased persistence of microbial pathogens in the vessel wall have been reported2-4. It is presumed that the ability of sPLA2 IIA to attack Staphylococcus aureus and other Gram-positive bacteria lies primarily in the enzyme, in the binding to the bacterial cell wall, the penetration of the wall, and the hydrolytic attack on the phospholipids of the bacterial cell membranes.2,3 The protective effect of sPLA2 IIA against Gram-positive and Gram-negative bacteria was verified also in vivo through investigations of sPLA2 IIA-transgenic mice. The transgenic mice showed a significantly higher resistance to Staphylococcus aureus compared with the control animals.5

Along with antibacterial characteristics, the antithrombotic properties of sPLA2 IIA have been described and associated with the inhibition of thrombin synthesis, decreasing the probability of thrombus formation.6-8 On the other hand, the local expression of sPLA2 IIA may have a protective effect associated with bactericidal activity and inhibition of thrombin synthesis. Systemic expression of sPLA2 IIA may engender the protective effect through removal of oxidatively modified lipoproteins from the bloodstream via the liver and adrenals.6-8 Recently, the antiinflammatory properties of sPLA2 IIA were established in an experimental model of carrageein-induced pleurisy in rats.9

The extent to which an expression of sPLA2 IIA has pathogenic or protective functions with respect to atherosclerosis depends possibly on whether expression of the enzyme as the consequence of an inflammatory reaction is induced locally in the vessel wall or systemically as the result of an acute-phase reaction9-10. Thus, local sPLA2 IIA expression in the vessel wall may be connected with several pathogenic effects, and generally through increased phospholipolysis of oxidatively modified lipoproteins by sPLA2 IIA, resulting in cellular lipid accumulation and foam cell formation.9 On the other hand, the local expression of sPLA2 may have a protective effect associated with bactericidal activity and inhibition of thrombin synthesis. Systemic expression of sPLA2 IIA may engender the protective effect through removal of oxidatively modified lipoproteins from the bloodstream via the liver and to a lesser extent via the adrenals.6-8

The insightful discussion by Pruzanski, et al is timely and highly relevant from the scientific and clinical points of view, and additional investigations regarding the role of the sPLA2 group in the pathogenesis of atherosclerosis are required.

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REFERENCES


Muscle Cramps Associated with Localized Scleroderma Skin Lesions: Focal Dystonia, Neuromyotonia, or Nerve Entrapment?

To the Editor:

Localized scleroderma is a relatively benign and self-limited condition, with manifestations mostly restricted to the skin and subdermal tissue without vascular or visceral involvement. The pathogenesis and etiology of this disease remain controversial. It has been speculated that localized scleroderma may develop as a response to neurologic injury. We describe the occurrence of muscle cramps in the distribution of skin lesions in 3 patients with localized scleroderma and review the literature.

Case 1. A 36-year-old woman with established linear scleroderma developed a new hypo- and hyperpigmented skin lesion extending linearly from the dorsum of the right hand, over the forearm, and continuing in a band-like distribution to the biceps and deltoid areas. As the skin lesion enlarged over several months, she complained of muscle cramping involving the...
right triceps, biceps, and forearm muscles. Forearm cramps were elicited with chopping motions, and writing precipitated wrist and finger flexor muscle cramping. She was treated with hydroxychloroquine 200 mg bid. D-penicillamine and prednisone were previously discontinued. Cranial nerves, muscle strength, coordination, sensory examination, and deep tendon reflexes were normal. Cervical spine magnetic resonance imaging (MRI) revealed mild C5–C6 central disc herniation. Electromyography documented co-contraction of the right biceps and triceps muscles. Laboratory testing showed normal creatine kinase (CK) and a positive anti-single-strand DNA antibody test, and hypergammaglobulinemia.

Case 2. A 40-year-old woman with morphea complained of episodic right arm pain and cramping of the right third and fourth fingers, sometimes accompanied by sustained ulnar deviation of the wrist. These symptoms were elicited by writing. On examination she had hyperpigmentation and atrophy extending from just beneath the axilla down the inner aspect of the arm to the distal forearm. There was a pale, slightly indurated and thickened area over the right buttock. Cranial nerves, muscle strength, coordination, sensory examination, and deep tendon reflexes were normal. There were no spontaneous or inducible involuntary movements. Electromyography was normal. Cervical spine MRI was normal. Laboratory testing included normal CK and negative anti-single-strand DNA antibody test.

Case 3. A 19-year-old woman with linear scleroderma developed dysesthesias and muscle cramping of the right fourth and fifth fingers. Muscle cramping was not task-induced. She also complained of dysesthesias and “a pulling sensation” in the left upper quadrant of the abdomen. She was previously treated with hydroxychloroquine. Mental status, muscle strength, coordination, and deep tendon reflexes were normal. Hyperpigmented skin with atrophic subcutaneous tissue extended from the medi-al aspect of the right forearm to the right hypothenar area. Similar hyperpigmented skin lesions with atrophy were present in the left upper abdomen. There was also atrophy of the left side of the tongue. Sensation to light touch was decreased with hypersensitivity to pinprick in the right C8, T1 and T2, and left T8 and T9 dermatomes. There were no spontaneous or inducible involuntary movements. Three years earlier, at the onset of symptoms, nerve conduction studies showed mild distal right ulnar mononeuropathy. MRI of the cervical spine showed mild hypertrophy of the right C3–C4 and C5–C6 facets with mild foraminal narrowing at C6–C7. Laboratory testing showed normal CK and an elevated anti-single-strand DNA antibody (219 units/ml; normal < 60).

Muscle cramp is a sudden involuntary shortening of the muscle occurring at rest or with muscle activation (contraction). Shortened muscle is more susceptible to muscle cramps, as seen in atrophic regions affected by localized scleroderma. The presence of agonist-antagonist co-contraction in one of our patients is suggestive of focal dystonia. The peripheral origin of dystonia remains controversial, and proposed mechanisms include altered sensory input or increased spinal cord excitability after peripheral nerve injury (entrapment) and muscle cramps caused by continuous muscle fiber activity and neumyotonia have been reported in 3 other patients with contiguous scleroderma skin lesions (Table 1).

Localized scleroderma may affect subcutaneous and deeper tissues, including muscles, ligaments, and bone, leading to stretching, angulation, or compression of nerves, followed by focal demyelination of motor nerve fibers. Dermatomal distributions of localized scleroderma skin lesions have been observed by some authors, and the skin lesions may follow a nerve injury. The occurrence of muscle cramps in the distribution of skin lesions may be attributable to nerve hyperexcitability (leading to neumyotonia or dystonia) or ephaptic transmission, similar to hemimasticatory spasm. In systemic sclerosis, distal axonopathy and focal nerve entrapment usually do not correspond to the distribution of skin lesions and are not associated with prominent muscle cramps.

Based on the temporal and spatial correlation of skin lesions and muscle cramps in our patients, we propose that localized scleroderma may precipitate muscle cramps, possibly caused by local nerve injury. Additional studies are needed to define the pathophysiology of such muscle cramps and to establish the spectrum of neurologic complications of localized scleroderma.

Table 1. Neurologic complications associated with cutaneous manifestations of systemic and localized scleroderma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age/Sex</th>
<th>Type of Scleroderma (age of onset, yrs)</th>
<th>Latency, yrs</th>
<th>Symptoms</th>
<th>EMG results</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our study</td>
<td>36 F</td>
<td>Linear (33)</td>
<td>2*</td>
<td>Cramps and posturing of right arm and hand</td>
<td>Dystonia</td>
<td>Baclofen; DNT</td>
</tr>
<tr>
<td>Our study</td>
<td>40 F</td>
<td>Morphea (19)</td>
<td>17*</td>
<td>Cramps of right hand</td>
<td>Normal</td>
<td>Tizanidine; good</td>
</tr>
<tr>
<td>Our study</td>
<td>19 F</td>
<td>Linear (9)</td>
<td>8</td>
<td>Cramps of right hand</td>
<td>Ulnar neuropathy</td>
<td>Baclofen; poor</td>
</tr>
<tr>
<td>Our study</td>
<td>17 M</td>
<td>Morphea (17)</td>
<td>None</td>
<td>Twitching, painless cramps of the leg</td>
<td>CMFA</td>
<td>Gabapentin; DNT</td>
</tr>
<tr>
<td>Kumar⁶</td>
<td>32 M</td>
<td>Morphea (30)</td>
<td>None</td>
<td>Muscle twitching</td>
<td>Neumyotonia</td>
<td>Phenyoit; good</td>
</tr>
<tr>
<td>Benito-Leon⁷</td>
<td>19 F</td>
<td>SSc (12)</td>
<td>4</td>
<td>Cramps of left arm and leg, task-elicted</td>
<td>Neumyotonia</td>
<td>Carbamazepine; good</td>
</tr>
</tbody>
</table>

① Muscle cramping in the setting of an exacerbation of scleroderma. SSc: systemic sclerosis; CMFA: continuous muscle fiber activity; DNT: did not tolerate.
Azathioprine and Tubulointerstitial Nephritis in Henoch-Schönlein Purpura

To the Editor:

We read with interest the report of Bir, et al, which suggests that azathioprine might have induced tubulointerstitial damage in their patient. We have also experienced similar cases in patients with severe Henoch-Schönlein nephritis (HSN) treated with azathioprine.

We reported that azathioprine might be an effective therapy in children with severe HSN by ameliorating the progression of immunologic renal injury. Nevertheless, 2 of the 10 patients with HSN who had been treated with azathioprine showed definite tubulointerstitial nephritis at followup biopsy. In these 2 patients, massive proteinuria rapidly improved after cessation of azathioprine therapy, and one of them also showed decreased mesangial depositions of IgG, IgA, IgM, and C3 at a second biopsy. However, mild proteinuria had persisted throughout the course of the disease, which might be related to tubulointerstitial nephritis. Although it is very difficult to prove that azathioprine might have caused severe tubulointerstitial damage, our patients did not receive any other nephrotoxic drugs, and the duration of severe proteinuria was not long enough to cause such a tubulointerstitial injury. However, we detected the tubulointerstitial nephritis by renal biopsy at the end of the course of azathioprine treatment, because our cases did not show the characteristics of rapidly progressive renal failure.

Therefore, clinicians should be more cautious in their use of azathioprine in patients with vasculitis, and further studies should be performed to elucidate the relationship between azathioprine and tubulointerstitial nephritis.

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