

# Correspondence

## INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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## Cytokines in Collagen Disease–Related Atherogenesis

To the Editor:

We read with interest the report of Asanuma, *et al*<sup>1</sup> and the excellent editorial of Shovman, *et al*<sup>2</sup> describing the role of proinflammatory cytokines in the pathogenesis of atherosclerosis in systemic lupus erythematosus (SLE). Two interconnected pathogenetic 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<sup>3</sup>. One of the important factors, not mentioned in the editorial<sup>2</sup>, is the group of secretory phospholipases A<sub>2</sub> (sPLA<sub>2</sub>). Low molecular weight nonpancreatic secretory PLA<sub>2</sub> catalyze the hydrolysis of the sn-2 group in glycerophospholipids, producing lysophospholipids and nonesterified fatty acids. The best investigated sPLA<sub>2</sub>, called IIA, has been defined as an acute-phase reactant, since its circulating levels increase markedly in acute inflammatory and infectious conditions. It has, however, been recognized that sPLA<sub>2</sub> levels may remain elevated for long periods of time in several chronic diseases with inflammatory features. Several studies have shown that cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor, and some others induce *de novo* synthesis and extracellular release of sPLA<sub>2</sub>, thus suggesting that sPLA<sub>2</sub> serves as a common distal effector of these cytokines<sup>4</sup>. sPLA<sub>2</sub> IIA and a few other low molecular weight sPLA<sub>2</sub> (such as V and X) were found not only to participate in the metabolism of arachidonic acid but also in the hydrolysis of human high-density lipoprotein and low-density lipoprotein, releasing in turn a battery of proinflammatory factors.

We reported that a large proportion of patients with systemic lupus erythematosus<sup>5</sup> and rheumatoid arthritis<sup>6</sup> have high circulating sPLA<sub>2</sub> IIA. sPLA<sub>2</sub> IIA as well as other sPLA<sub>2</sub> such as V and X, along with lipoproteins, were found in the vascular wall and more so in the atheromatous areas<sup>7</sup>. sPLA<sub>2</sub> are not only hydrolyzing lipoproteins, but also induce mitogenesis and proliferation of human vascular smooth muscle cells and the release of prostaglandin E<sub>2</sub> and leukotriene B<sub>4</sub> from the cells<sup>8</sup>. Recently, sPLA<sub>2</sub> was found to play an important role in the pathogenesis of atherosclerosis<sup>7,9</sup>. Its level was found to serve as an independent predictive factor of recurrent

events in acute coronary syndromes<sup>10</sup>. Considering that the induction of sPLA<sub>2</sub> is mediated through a variety of cytokines and that sPLA<sub>2</sub> are released extracellularly along with the above cytokines, secretory PLA<sub>2</sub> should be included in the group of proinflammatory and proatherogenic factors, and may potentially serve as a novel target for the prevention of atherosclerosis in collagen diseases.

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## Dr. Chung, *et al* reply

To the Editor:

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 A<sub>2</sub> (sPLA<sub>2</sub>) should be a candidate marker or mediator for atherosclerosis in patients with inflammatory disease. This suggestion is based on the increased concentrations of sPLA<sub>2</sub> in patients with SLE and rheumatoid arthritis, and its role in atherosclerosis. Thus, indeed, sPLA<sub>2</sub> 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.

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### Dr. Shovman, *et al* reply

To the Editor:

We thank Dr. Pruzanski and coworkers for their interest in our editorial<sup>1</sup> and welcome their comments. We agree that the group of secretory phospholipases A<sub>2</sub> (sPLA<sub>2</sub>) and especially sPLA<sub>2</sub> 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 sPLA<sub>2</sub> IIA in inflammation is also indicated. In particular, the efficient bactericidal properties of sPLA<sub>2</sub> IIA resulting in decreased persistence of microbial pathogens in the vessel wall have been reported<sup>2-4</sup>. It is presumed that the ability of sPLA<sub>2</sub> 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<sup>2,3</sup>. The protective effect of sPLA<sub>2</sub> IIA against Gram-positive and Gram-negative bacteria was verified also *in vivo* through investigations of sPLA<sub>2</sub> IIA-transgenic mice. The transgenic mice showed a significantly higher resistance to *Staphylococcus aureus* compared with the control animals<sup>4</sup>.

Along with antibacterial characteristics, the antithrombotic properties of sPLA<sub>2</sub> IIA have been described and associated with the inhibition of thrombin synthesis, decreasing the probability of thrombus formation<sup>5</sup>. Moreover, it was established that sPLA<sub>2</sub> IIA may be responsible for enhanced clearance of oxidatively modified lipoproteins during inflammation via the liver and adrenals<sup>6-8</sup>. Recently, the antiinflammatory properties of sPLA<sub>2</sub> IIA were established in an experimental model of carrageenin-induced pleurisy in rats<sup>9</sup>.

The extent to which an expression of sPLA<sub>2</sub> 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 reaction<sup>10</sup>. Thus, local sPLA<sub>2</sub> IIA expression in the vessel wall may be connected with several pathogenic effects, and generally through increased phospholipolysis of oxidatively modified lipoproteins by sPLA<sub>2</sub> IIA, resulting in cellular lipid accumulation and foam cell formation<sup>10</sup>. On the other hand, the local expression of sPLA<sub>2</sub> may have a protective effect associated with bactericidal activity and inhibition of thrombin synthesis. Systemic expression of sPLA<sub>2</sub> 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<sup>6-8</sup>.

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 sPLA<sub>2</sub> group in the pathogenesis of atherosclerosis are required.

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### 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<sup>1</sup>. The pathogenesis and etiology of this disease remain controversial. It has been speculated that localized scleroderma may develop as a response to neurologic injury<sup>2</sup>. 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-nuclear antibody in a titer of 1:160 (normal < 40) with speckled staining, positive 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 medial 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<sup>3</sup>, 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)<sup>4,5</sup>. Muscle cramps caused by continuous muscle fiber activity<sup>6</sup> and neuromyotonia<sup>7,8</sup> 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<sup>2</sup>. The occurrence of muscle cramps in the distribution of skin lesions may be attributable to nerve hyperexcitability (leading to neuromyotonia or dystonia) or ephaptic transmission, similar to hemimasticatory spasm<sup>9</sup>. 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<sup>10</sup>.

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.

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

Study	Age/Sex	Type of Scleroderma (age of onset, yrs)	Latency, yrs	Symptoms	EMG results	Treatment Response
Our study	36 F	Linear (33)	2*	Cramps and posturing of right arm and hand	Dystonia	Baclofen; DNT
Our study	40 F	Morphea (19)	17*	Cramps of right hand	Normal	Tizanidine; good
Our study	19 F	Linear (9)	8	Cramps of right hand	Ulnar neuropathy	Baclofen; poor
Papadimitriou <sup>6</sup>	17 M	Morphea (17)	None	Twitching, painless cramps of the leg	CMFA	Gabapentin; DNT
Kumar <sup>8</sup>	32 M	Morphea (30)	None	Muscle twitching	Neuromyotonia	Phenytoin; good
Benito-Leon <sup>7</sup>	19 F	SSc (12)	4	Cramps of left arm and leg, task-elicited	Neuromyotonia	Carbamazepine; good

\* Muscle cramping in the setting of an exacerbation of scleroderma. SSc: systemic sclerosis; CMFA: continuous muscle fiber activity; DNT: did not tolerate.

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### 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<sup>1</sup>. We have also experienced similar cases in patients with severe Henoch-Schönlein nephritis (HSN) treated with azathioprine<sup>2</sup>.

We reported that azathioprine might be an effective therapy in children with severe HSN by ameliorating the progression of immunologic renal injury<sup>2</sup>. 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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