Ever-Changing Concepts of Calciphylaxis

Key words: calciphylaxis, uremia, vascular calcification

Calciphylaxis is clinically characterized as a serious condition with necrosis of the skin and adipose tissue, leading to a high mortality rate due to sepsis and ischemia (1). Although this abnormality is seen predominantly in patients with end-stage renal disease, it should be distinguished from simple metastatic calcification. Histologically, calciphylaxis is associated with medial calcification and intimal calcification of medial and small arteries with secondary gangrene of the tissue (2). Ever since the first clinical report in a uremic patient by Anderson in 1968 (3), the clinical features and concepts of calciphylaxis have been changing even recently. This sometimes leads to marked discrepancy in the discussion of cases with calciphylaxis. Furthermore, new entities have also been added to the list of predisposing factors for calciphylaxis. Such changes are partly due to the changing patterns of bone disease type and also those of therapeutic modalities such as vitamin D and calcium salts.

Calciphylaxis had been thought to involve almost exclusively distal sites in uremic patients with significant hyperparathyroidism and elevated Ca $\times$ P products (1). In such patients, surgical parathyroidectomy improves the signs and symptoms dramatically. By contrast, proximal lesions have been reported during the last decade (4). Obesity, female, hypoalbuminemia, diabetes and other factors have been suggested as new risk factors for the development of calciphylaxis (5). In such patients, parathyroidectomy may not be successful to control calciphylaxis as suggested by several reports. Although hyperbaric oxygen has been shown to reverse ulceration in some patients (6), it is much more important to recognize calciphylaxis at the early stage with non-ulcerating plaques as recently suggested by Fine and Zacharias (7).

In this issue of Internal Medicine, Oikawa and associates report a case of penile calciphylaxis (8).

See also p 63.

Although penile involvement has become popular as an example of proximal lesions (9), the development of calciphylaxis after parathyroidectomy seems to be a rare condition considering the pathogenesis. Decreased buffering capacity of bone after successful parathyroidectomy may partly explain the pathogenesis (10), however, such an observation supports the notion that factors other than high Ca $\times$

P are needed for the development of calciphylaxis.

Several proteins have been proposed as local inhibitor of calcification, such as matrix GLA protein and osteopontin. In addition, fetuin-A is another candidate protein of this category, which may act even systemically (11). Fetuin-A is also known as α 2-Heremans Schmid glycoprotein and is a potent inhibitor of Ca $\times$ P precipitation. It has been shown that the serum concentration of fetuin-A is decreased in dialysis patients, especially in those with a high CRP concentration (12). The serum from these patients was not so potent to inhibit Ca $\times$ P precipitation in vitro, which was rescued by the addition of recombinant fetuin-A. Lower serum fetuin-A was associated with more severe aortic calcification. Thus, abnormalities of such proteins may be involved in the pathogenesis of calciphylaxis. Further studies are certainly needed to establish a breakthrough for the early diagnosis and treatment of calciphylaxis.

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