EXTENSIVE SPECIFICALLY LOCALIZED MYOCARDIAL CALCIUM DEPOSITION IN A HEMODIALYSIS PATIENT

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A 51-year-old female who was hospitalized for evaluation of frequent episodes of hypotension, died unexpectedly. At autopsy, there were many fine, white granular deposits in the myocardium, which were more prominent in the subepicardium of the left ventricle than in the subendocardium.

Pathologic calcification is sometimes seen in chronic hemodialysis patients and in some organs the sites of calcium deposition are quite specific. There have been few reports concerning the pattern of calcium deposition in the myocardium and, to our knowledge, the reason for this characteristic distribution is unknown. However it may relate to hydrogen ion concentration in the myocardium. (Jpn Circ J 1992; 56: 27-31)

MYOCARDIAL calcification is a serious and fairly common1, 2 complication of long-term hemodialysis that can cause intractable heart failure and conduction disturbance. We present the case of a 51-year-old female found to have focal calcium deposits within the heart after 5 years of hemodialysis leading to long-standing hypertension and proteinuria. She had a history of gestosis. After delivery proteinuria continued and hypertension developed at the age of 35. The diagnosis of chronic renal failure was made and hemodialysis was begun at another hospital 5 years before admission. She was treated with Elctonin® 4 years and Alfarol® 2 years before entry because of secondary hyperparathyroidism. One year before entry, hypotension developed, especially during hemodialysis, and became more frequent. The patient was hospitalized for evaluation.

On admission, blood pressure was 108/60 mmHg and pulse rate 82/min and regular. The palpebral conjunctiva was slightly anemic. A third heart sound and a grade III pansystolic murmur were audible at the apex. Urinalysis showed proteinuria and microhematuria. The following laboratory values were obtained: red cell count 240×10^6/mm^3; hemocrit 20.5%; white cell count 7000/mm^3; platelet count 24.1×10^9/mm^3; Blood urea nitrogen 74 mg/dl; creatinine 7.2 mg/dl; sodium 140 mEq/L; potassium 5.6 mEq/L; chloride 106 mEq/L; calcium 8.6 mg/dl; phosphate 7.3 mg/dl; alkaline phosphatase 31.6 KAU; serum aspartate aminotransferase 31 IU; lactate dehydrogenase 413 IU; and creatine kinase 41 IU. The pH of arterial blood was 7.395; partial pressure of oxygen 66.5 torr; partial pressure of carbon dioxide 33.8 torr;

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and base excess -3.5 mEq/L. An electrocardiogram demonstrated low voltage in limb leads and poor progression of the R wave, with ST-segment depression in leads V1 through V3. Small q waves were found in leads I and aV1. There was ST-segment elevation in leads I, II, III, aVF and V4–5 (Fig. 1). Chest x-ray disclosed cardiac enlargement (cardiothoracic ratio: 58%) with normal bronchovascular markings and no pulmonary congestion. Two-dimensional echocardiography revealed left atrial enlargement, prominent calcification of the posterior leaflet of the mitral valve, and reduced motion of the left ventricular wall. Moderate mitral regurgitation was detected by pulsed Doppler imaging.

Although asymptomatic on admission, the patient died unexpectedly the following morning. At autopsy, the heart weighed 480g. Macroscopically, the left atrium was moderately dilated, and the left ventricle (LV) was hypertrophic. The posterior leaflet of the mitral valve was thickened and nearly rigid because of calcifications covering it and extending to the posterior wall of LV. The mitral chordae were also thickened and partially fused. The aortic, tricuspid and pulmonary valves were intact. There were many fine, white granular, deposits in the myocardium, which were more prominent in the subepicardium of the LV than in the subendocardium. Pericardium was smooth and was not adherent (Fig. 2).

Histologically, the affected posterior leaflet of the mitral valve showed fibrous thickening with neovascularization and severe calcification. The middle and subepicardial...
layers of the LV and the interventricular septum exhibited loss of myocardial fibers, dense fibrosis, and massive calcification (Fig. 3). The most advanced lesions contained dense fibrous tissue with large, confluent calcium granules. In milder lesions, remnants of myocardial fibers showed cytoplasmic degeneration and fine calcium granules. The walls of arteries and arterioles in the subepicardium of the LV showed fine to dense calcification, and severely affected vessels displayed intimal fibrosis and luminal stenosis. Calcification of veins was mild. In contrast most myocardial fibers in the subendocardial region appeared intact. Only focal edema or fibrosis was seen in the interstitium. Microscopic examination for amyloid under polarized light after congo red staining was negative. However, von Kossa staining disclosed fine calcium granules scattered throughout the fibers. Vascular involvement was milder than that in the subepicardium. The right ventricular wall was intact but some fibers contained fine calcium granules. There were no significant stenotic lesions in the coronary arteries in the epicardium. Calcification and fibrosis were scattered throughout the conducting system.

Pathologic calcification is classified as either dystrophic, which occurs in degenerating or necrotic tissue in the event of systemic calcium and phosphate imbalance; or metastatic, which involves calcification of normal tissue due to metabolic disturbance and may involve any organ, visceral or nonvisceral. Hyperphosphatemia, elevation of the calcium-phosphorus product; rapid hemodialysis-induced acid-base changes, and secondary hyperparathyroidism are thought to predispose to metastatic calcification. Annual changes in serum calcium, phosphorus, and alkaline phosphatase, including the data concerning serum parathyroid hormone concentration, during last 6 years are shown in Fig. 4. Progressive elevation of serum calcium developed after Alfarois prescription. Most studies have revealed a beneficial effect of vitamin D analogues on biochemical, radiological and histological signs of hyperparathyroid bone dis-
ease. However hypercalcemia is also known as a rather common side effect of vitamin D therapy. Reports presenting therapeutic strategies using vitamin D analogues have not universally resulted in adequate suppression of parathyroid hormone secretion and have often noted significant hypercalcemia. In our patient, inadequate control of serum calcium may be related to the significant calcium deposition in the myocardium.

In some organs, the sites of deposition are quite specific. As Terman et al reported, there have been few reports concerning the pattern of calcium deposition in the myocardium. The reason for this characteristic distribution is unknown and have not ever been discussed. In our case, calcium deposits were most extensive in the subepicardium of the LV. Under some circumstances, such as under partial coronary occlusion, hydrogen ion concentration was lower in the subepicardium than in the subendocardium. An alkaline milieu in the presence of a calcium-phosphorus product exceeding plasma saturation is a favorable setting for calcium phosphate precipitation. So the characteristic distribution of calcium deposits in the myocardium may be related to the hydrogen ion concentration in the myocardium. Recently, advances in hemo-dialysis have led to prolonged survival among patients with chronic renal failure. However, many new problems have emerged in associated with long-term hemodialysis, such as metastatic myocardial calcification. Thus it is important to investigate the mechanisms of such complications and look at how they might be prevented. Our case is very rare and interesting. It may hint at the mechanism of myocardial calcification.

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