

## Calcification of the Coronary Arteries in the Absence of Atherosclerotic Plaque

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Arterial calcification in the coronary arteries frequently indicates concomitant atherosclerotic plaque but can be present in the medial layers with no evidence of plaque. Calcification of the medial layer of arteries is seen most often in the peripheral arteries but also is widely recognized in the coronary arteries. We describe 2 patients who had marked medial and intimal calcification of the coronary arteries with little or no accompanying atherosclerosis.

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Atherosclerotic plaques frequently contain intimal calcium deposits. Arterial calcification also can occur in the medial layer of arteries in the absence of atherosclerotic plaque. This medial calcification, sometimes referred to as Mönckeberg sclerosis, is seen most often in the peripheral arteries and is particularly common in the setting of metabolic disorders such as diabetes mellitus and end-stage renal disease.<sup>1,2</sup> Medial calcification in the coronary arteries is widely recognized.<sup>3,4</sup> We describe 2 cases showing that coronary artery calcification can occur in the medial layer of human coronary arteries that are devoid of atherosclerotic plaque.<sup>3,4</sup>

### REPORT OF CASES

#### CASE 1

A 6-year-old boy with a long-standing history of anemia and failure to thrive had a 2-year history of end-stage renal disease of undetermined etiology requiring peritoneal dialy-

sis. One year before death, the patient was noted to have hyperparathyroidism (parathyroid hormone, 512 pg/mL; reference range, 10-55 pg/mL) and hypercalcemia (calcium, 10.2 mg/dL) that resulted in bony degeneration. Elevated levels of parathyroid hormone and calcium normalized after subtotal parathyroidectomy. Eight months before the patient's death, he presented with a 4-month history of increasing fatigue, diaphoresis, and abdominal distention. Chest radiography revealed cardiomegaly, and echocardiography showed a large left ventricle with globally decreased systolic function and abnormal diastolic function. Previous chest radiographic and echocardiographic findings had been normal. Markedly elevated levels of serum urea nitrogen (62 mg/dL) and creatinine (6.4 mg/dL), hypercalcemia (calcium, 12.8 mg/dL), and hyperphosphatemia (phosphorus, 9.1 mg/dL) were observed, with attendant renal failure requiring hemodialysis. Serum levels of 1,25-dihydroxyvitamin D were decreased (10 pg/mL; reference range, 24-65 pg/mL). The patient was treated with captopril, and his blood pressure was monitored closely. Follow-up echocardiography showed improved cardiac function. Nevertheless, during the next 2 months, the patient exhibited persistent diaphoresis and shortness of breath, especially when supine. While receiving an intravenous infusion of pamidronate, the patient had a hypotensive episode along with chest pain and body aches. His heart sounds became extremely faint, and cardiac arrest ensued. Resuscitative measures were unsuccessful.

Autopsy gross examination showed a heart weighing 130 g with dilated ventricles. The microscopic sections showed multifocal calcifications of myocardial fibers including the papillary muscles. Calcification was also present in the annulus of the mitral valve. The aorta was free of calcification, but the medium and large coronary vessels showed diffuse medial calcification. Microscopic foci of calcification were seen occluding the small coronary vessels of the myocardium. The coronary arteries showed only mild intimal proliferation, with no evidence of atherosclerotic plaque (Figure 1). Autopsy also revealed small kidneys with extensive calcifications.

#### CASE 2

A 62-year-old woman had mild nonobstructive coronary artery disease, idiopathic cardiomyopathy with left ventricu-

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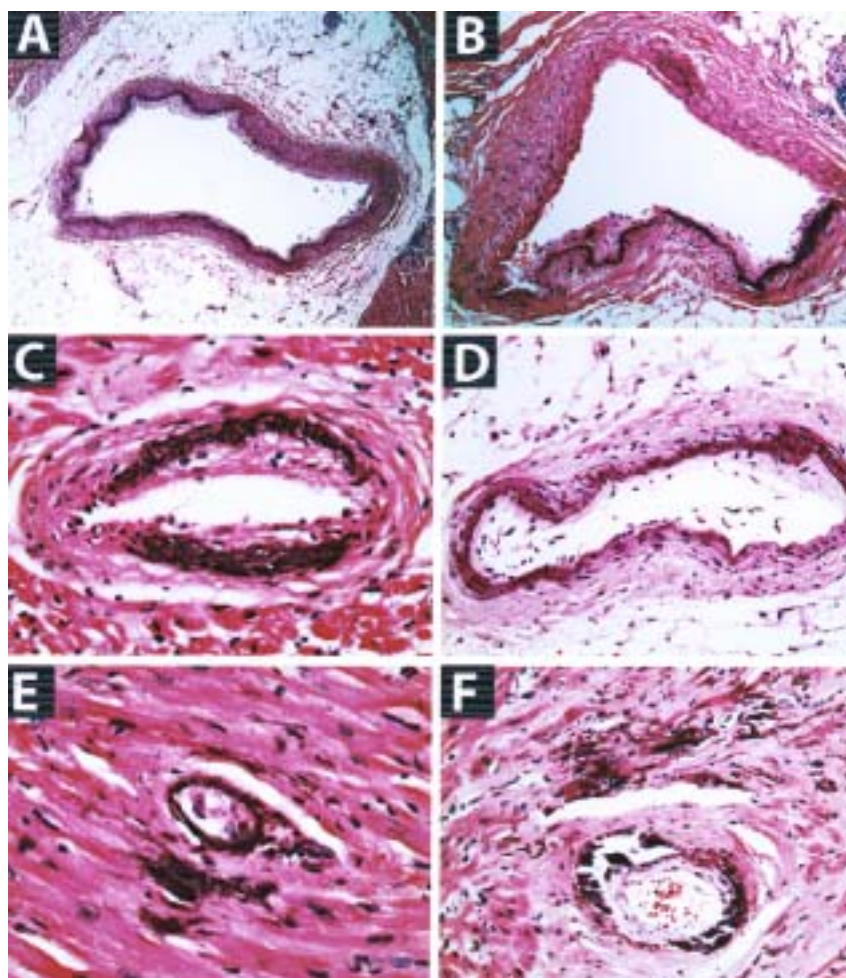


FIGURE 1. Case 1. Medial coronary artery calcification in the absence of intimal calcification or atherosclerotic plaque. A and B, A large epicardial coronary artery is seen with diffuse medial calcification and minimal intimal fibromuscular hyperplasia. The artery is surrounded by epicardial adipose tissue (white region). At least one third of the circumference of the arterial tunica media is calcified (dark stained region). Intimal hyperplasia is present just internal to the medial calcification, but no foam cells are seen. Such intimal hyperplasia is composed predominantly of fibromuscular cells and proliferating myofibroblasts and does not represent atherosclerotic plaque. C and D, Medium-sized intramyocardial coronary artery with prominent medial calcification that is almost circumferential. C, Myocardial tissue (red-pink) surrounding the artery. D, The artery is adjacent to adipose tissue (white). E, A small, distal intramyocardial coronary artery with prominent medial calcification and dystrophic myocyte calcification (dark stain at 7 o'clock position). The lumen is almost totally occluded. F, Circumferential medial calcification of a distal intramyocardial coronary artery with marked perivascular and interstitial fibrosis and dystrophic myocyte calcification (hematoxylin-eosin, original magnifications: A and B,  $\times 40$ ; C and D,  $\times 200$ ; E and F,  $\times 400$ ).

lar systolic dysfunction, an ejection fraction of 15%, and moderate mitral and tricuspid regurgitation. The patient's medications included angiotensin-converting enzyme receptor blockers, angiotensin-converting enzyme inhibitors, and  $\beta$ -blockers during the past 2 years, and she had developed progressive symptoms of shortness of breath and intermittent lower extremity edema. Her medical history was remarkable for mild systemic hypertension for 15 to 20 years and type 2 adult-onset diabetes mellitus (non-insulin-

dependent diabetes mellitus) for 5 years. The patient had experienced a stroke 4 years previously. She also had undergone orthotopic heart transplantation for her severe left ventricular systolic dysfunction. Laboratory test results revealed hyperglycemia (glucose, 306 mg/dL), elevated levels of serum urea nitrogen (49 mg/dL) and creatinine (1.8 mg/dL), and hyperphosphatemia (phosphorus, 5.9 mg/dL).

Gross examination of the explanted heart revealed concentric hypertrophy of the left ventricle with slight dilata-

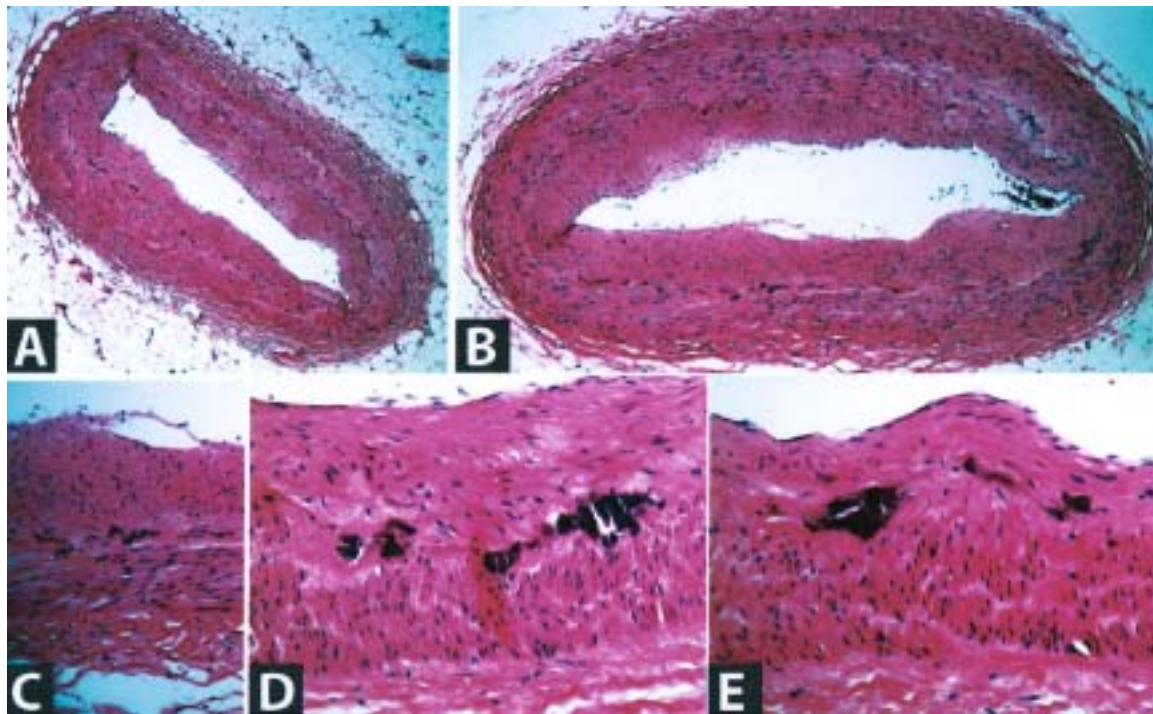


FIGURE 2. Case 2. A and B, Coronary artery sections from a patient with diabetes mellitus and renal dysfunction. C-E, Regions of calcification (black) involving the internal elastic lamina and the media. Note that although there is a typical amount of intimal thickening, no atherosclerotic plaque is present (hematoxylin-eosin, original magnifications: A and B,  $\times 40$ ; C-E,  $\times 200$ ).

tion. The right coronary artery showed mild atherosclerotic lesions with 20% stenosis. The left anterior descending coronary artery was free of atherosclerosis. Microscopic examination showed evidence of cardiomyopathy with myofiber hypertrophy, diffuse interstitial fibrosis, and patchy replacement fibrosis. Coronary arteries exhibited fibromuscular intimal hyperplasia and mild atherosclerosis. Surprisingly, diffuse medial calcification was present in the epicardial coronary arteries (Figure 2).

### DISCUSSION

Dystrophic and metastatic calcification in patients with renal dysfunction have been shown to be associated with

hyperparathyroidism and may improve with parathyroidectomy.<sup>5</sup> Such calcification frequently involves the tunica media of arteries, notably peripheral arteries. Both our patients exhibited evidence of renal dysfunction.

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