CASE REPORT

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Metastatic Calcification of the Cardiac Conduction System with Heart Block: An Under-Reported Entity in Chronic Renal Failure Patients

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ABSTRACT: Systemic metastatic calcification is a common complication of chronic renal failure. Cardiac involvement is particularly ominous, especially when the cardiac conduction system is affected. Conduction defects, arrhythmias, and sudden death have all been reported with conduction system calcification; however, these are relatively under-reported or unrecognized causes of cardiac morbidity and mortality. We describe a 40-year-old man with Von Hippel-Lindau disease who had been maintained on hemodialysis for two years following bilateral nephrectomies for renal cell carcinoma. The patient presented with symptomatic complete heart block that had progressed from Mobitz type I atrioventricular block. Two months later, while being internally paced, the patient died unexpectedly after a complicated hospital admission. Postmortem revealed extensive vascular, myocardial, and conduction system calcification. Conduction system calcification may cause sudden death in chronic renal failure patients during hospital admission, or unexpectedly while the patient is in the community. Knowledge of this condition is necessary to detect it, as the conduction system is not routinely examined. A routine abbreviated conduction system examination is warranted for patients with systemic metastatic calcification, especially if they have sudden death or a known history of heart block.

KEYWORDS: forensic science, renal failure, sudden death, heart block, metastatic calcification, conduction system

This 40-year-old man had Von Hippel-Lindau disease complicated by multiple and recurrent cerebellar hemangioblastomas and paraplegia, secondary to a thoracic spinal cord hemangioblastoma. He had been maintained on hemodialysis for two years following bilateral nephrectomies for renal cell carcinoma. He presented with acute pre-syncopal symptoms and severe fatigue. He was found to be in third degree heart block with a ventricular rate of 40 beats per minute and had emergent placement of a transthoracic pacemaker. Three weeks earlier, the patient had been asymptomatic, but had a slow pulse and an electrocardiogram that revealed Mobitz type I atrioventricular block.

Over a two-month hospital admission, the patient had hypotensive episodes despite internal cardiac pacing, placement of a superior vena cava (SVC) stent for central venous thrombosis, and delirium related to moderate hypercalcemia. Although hypercalcemic, the patient's parathyroid hormone serum level was within laboratory reference intervals. He had not been significantly hypercalcemic prior to the admission and, in fact, had taken oral calcium supplements. He developed *Enterococcus faecalis* infection of a sacral ulcer that responded to antibiotic therapy. Despite adjustment of his pacemaker rate four days previously, in order to prevent any further hypotensive episodes, the patient was unexpectedly found dead. The death was considered unexplained, as he had been responding to antibiotics and his pacemaker had been functioning well.

Pathological Findings at Autopsy

An unrestricted autopsy confirmed healing decubitus sacral ulcers, prior bilateral nephrectomies, and an uncomplicated patent SVC stent. Hemangioblastomas of the thoracic spinal cord and cerebellum, a multiloculated pancreatic cyst, a schwannoma of the cauda equina, and an adrenal pheochromocytoma were evidence of Von Hippel-Lindau disease. Multiple cranial nerves showed entrapment neuropathy, secondary to extensive calcification of cranial dura. The parathyroid glands were normal size with no adenomas or hyperplasia. Due to the patient's history of third degree heart block and his unexpected death, the heart had detailed cardiac examination.

The heart weighed 450 g and there was fibrinous pericarditis related to chronic renal failure (CRF). There was moderate biatrial hypertrophy, moderate right atrial dilatation, mild right ventricular dilatation, and mild left ventricular hypertrophy and dilatation. Prominent calcific deposits of the myocardium were identified. There were no cardiac valve abnormalities. The coronary circulation was right dominant and the arteries had normal origin, course, and patent ostia. There was mild atherosclerosis of the aorta and

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epicardial coronary arteries. An epicardial pacemaker was attached to the heart and functioned normally upon testing.

Histologic examination of the heart revealed a recent medium-sized subendocardial left ventricular infarct with mild involvement of the anterolateral papillary muscle. Small, healing, subendocardial infarcts of the right ventricle were also present. In addition to recent ischemia, patchy, old microinfarcts were found throughout the atria and the ventricles. The intramyocardial arterioles had calcification of their internal elastic lamellae, some with prominent medial calcification (Fig. 1). Most affected arterioles showed fibrointimal thickening and lumen narrowing. Diffuse left ventricular perivascular fibrosis with foci of myocardial metastatic calcification was present.

An abbreviated conduction system examination sampled the sinoatrial (SA) and atrioventricular (AV) nodes. Sections of the SA node showed extensive perinodal fibrosis with metastatic calcific deposits involving both perinodal fibrous tissue and adjacent myocardium. These calcific deposits directly impinged on the SA node (Fig. 2). Arterioles supplying the SA node exhibited fibrointimal thickening. Examination of the AV node revealed similar histologic findings to the SA node, including severe perinodal fibrosis and metastatic calcification impinging on the AV node itself. Myocytes within the region of the AV node also had foci of metastatic calcification. The arterioles supplying the AV node showed severe calcification of internal elastic lamella and media along with intimal thickening. The His bundle and the proximal left bundle branch were both identified and they were unremarkable (Fig. 3).

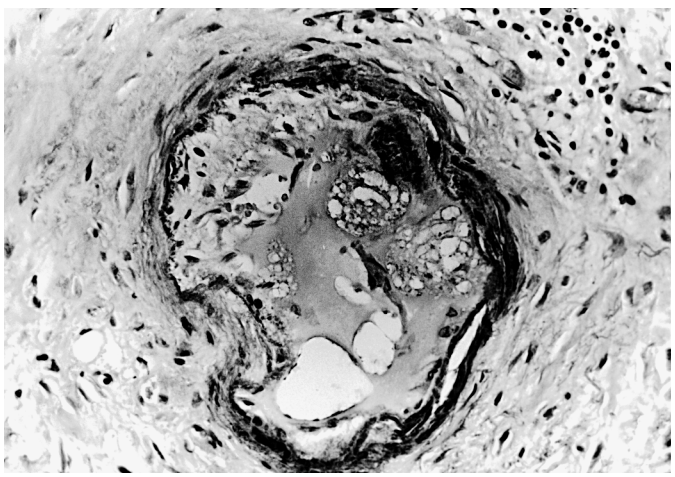

FIG. 1—*High power photomicrograph of a typical intramyocardial arteriole with calcification of the internal elastic lamina, medial calcification, and intimal thickening. (× 250, Hematoxylin Phloxine Saffron).*

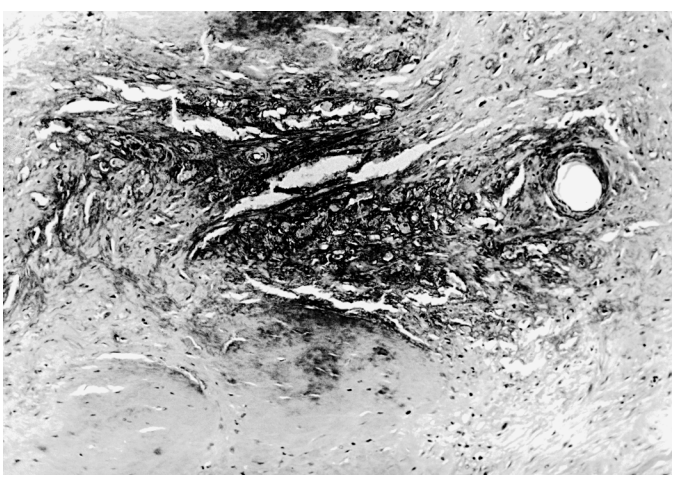

FIG. 2—*Calcific deposits in the myocardium that directly impinge upon the sinoatrial (SA) node. Vascular calcification can also be identified. (× 100, Hematoxylin Phloxine Saffron).*

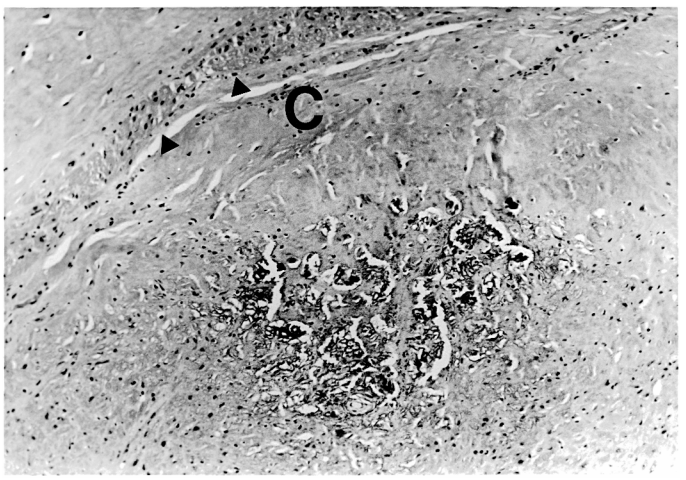

FIG. 3—*Myocardial calcific deposits in the area of the atrioventricular (AV) node, His bundle and Left bundle branch. The actual His bundle and left bundle branch (arrowheads) were not involved by the calcium deposits. (C = central fibrous body) (× 100, Hematoxylin Phloxine Saffron).*

The cause of death was attributed to probable arrhythmia (immediate cause), due to metastatic calcification of the cardiac conduction system and myocardium, due to chronic renal failure (underlying cause). Other significant conditions contributing to death would include recent and healing subendocardial infarcts, and Von Hippel-Lindau disease. The manner of death was natural.

Comment

Metastatic calcification, a common complication of CRF, has increased in incidence with the prolonged survival of dialysis patients (1–4). Disordered calcium-phosphate homeostasis is a major mechanism predisposing to metastatic calcification (4–6). In CRF, hyperphosphatemia, secondary to decreased renal excretion of phosphate, and decreased renal hydroxylation of 25-hydroxycholecalciferol, can both contribute to secondary hyperparathyroidism (4,5). The pathophysiologic mechanisms of CRF related secondary hyperparathyroidism are complex (5). The result may be increased parathyroid hormone synthesis causing metabolic bone diseases, including renal osteodystrophy and osteitis fibrosa cystica, as well as metastatic calcification (4,5). Metabolic complications of CRF are treated with phosphate binding agents, dietary phosphate restriction, and avoidance of excess dietary calcium (1). Poor therapeutic compliance, excess calcium supplement, antacid and vitamin intake, and plasma and tissue pH changes during dialysis may contribute to systemic deposition of calcium (1,2,4). The current patient had no biochemical or histologic evidence of secondary or tertiary hyperparathyroidism. His hypercalcemia, like the disordered calcium-phosphate metabolism of many CRF patients, was likely multi-factorial in origin.

Metastatic calcification may involve any tissue (1,7,8). CRF patients tend to have cardiac, renal, and vascular involvement, although pulmonary and gastrointestinal calcification also may occur (3,4,7). Cardiac metastatic calcification preferentially involves the mitral annulus and the mitral and aortic valves, however, calcification of the myocardium, endocardium, coronary arteries, and the cardiac conduction system are recognized (1–4,7–13). Annular and valvular calcification can both lead to significant morbidity and mortality with valve insufficiency and stenosis, bacterial endocarditis, periannular abscesses, calcific and thrombotic emboli, sudden death, and conduction defects ranging from atrial fibrillation to complete heart block (14–18). Conduction defects related to annular calcification usually result from contiguous extension of calcification from the valve annulus with direct impingement on the conduction system (14,16). Although our patient had prominent vascular and myocardial metastatic calcification, he had no cardiac valve or annulus involvement.

Vascular metastatic calcification in CRF can involve all vessel types including elastic and muscular arteries, arterioles, capillaries, and venules (7,9). Typically there is calcification of the internal elastic lamella with extension of calcific deposits into the media in severe cases (2,3,7,9,10). Coronary arteries and arterioles involved by metastatic calcification also commonly exhibit fibrointimal thickening that may lead to vessel stenosis (2,3,9). Myocardial ischemia may result from this luminal narrowing, especially if superimposed on significant pre-existing coronary artery atherosclerosis (19). In the present case, the patient had extensive calcification of his intramyocardial arterioles with fibrointimal thickening and stenosis. His myocardial microinfarcts that involved all cardiac chambers were likely related to his small vessel disease. Metastatic calcification also affected the myocardium and perivascular regions.

In an autopsy study of Kuzela et al., 58.9% of dialysis patients had myocardial calcification (3). They observed that increasing myocardial calcification was associated with severe intramyocardial vascular calcification with some vessels showing complete occlusion. Severe cardiac calcification is associated with myocyte degeneration and replacement of myocardial tissue by large confluent calcific deposits (3,4,9). It has been postulated that significant myocardial calcification may cause ventricular dysfunction, resulting in decreased cardiac output and congestive heart failure (CHF), (1,2,4,6,12). The current patient did have changes of CHF. Although severe myocardial calcification may occasionally be identified radiologically, antemortem diagnosis of cardiac calcification is uncommon (2,3,6).

Cardiac metastatic calcific deposits with fibrosis may impinge upon the cardiac conduction system and cause variable degrees of heart block, arrhythmias, and sudden death (2–4,9,11,12). Although calcification of the conduction system produces significant clinical effects, this pathologic entity has been under-recognized, especially as a cause of sudden death (3), with reports limited to individual cases and small series (2–4,11,12). Multiple factors contributing to this under-recognition include the difficulty in antemortem diagnosis of myocardial and conduction system calcification, the lack of electrocardiographic studies in most cases of sudden death, and lack of postmortem conduction system examination.

Terman et al. (2) determined that some chronic hemodialysis patients with suspected conduction system calcification showed progressive degrees of heart block. First degree heart block was followed by intraventricular block that could progress to complete heart block. Sudden death occurred in two out of their six patients. The present patient died suddenly with a documented history of progressive heart block that terminated in complete heart block.

Metastatic calcification of the cardiac conduction system, with impingement of both SA and AV nodes by perinodal fibrosis and calcific deposits, was the likely cause of our patient's conduction defects. The cardiac conduction system can also be directly calcified in CRF (2,3,9). Intramyocardial arteriole calcification, producing fibrointimal thickening and luminal stenosis, has been suggested to cause ischemia of the conduction system and may contribute to conduction defects and arrhythmias (2). Considering cardiac predisposition for involvement by metastatic calcification, we suggest an abbreviated examination of the cardiac conduction system be routine for patients exhibiting extensive systemic metastatic calcification.

It is interesting that the mitral annulus was not calcified in our patient. Since mitral annular calcification is well known and easily recognized by most pathologists, and may be detected by various imaging modalities, one would hope that this finding might reflect underlying myocardial and microvascular calcification. Unfortunately, however, at least in our patient, there did not seem to be a relationship.

With an aging population, continued success with dialysis, and the ambulatory nature of many CRF patients, it is reasonable to expect that the complications of CRF, including the fatal effects of metastatic calcification of the heart, will be more frequently encountered by the forensic and the hospital-based pathologist, both of whom study unexplained death. Chronic renal failure patients are not all in hospital when they die, and in many cases the death is unwitnessed and unexpected, hence forensic pathologist involvement. This cause of death may be missed if the condition is not recognized or the death is attributed to other co-morbid conditions. With chronic renal failure this would be easy to do so.

In summary, CRF is commonly associated with disordered calcium-phosphate metabolism and metastatic calcification. Metastatic calcific deposits of the myocardium, although uncommonly detected clinically, are common autopsy findings in CRF patients. Cardiac conduction system calcification is important to recognize as it may cause conduction defects and arrhythmias. It is likely under-diagnosed and should be recognized as a cause of sudden unexpected death. Postmortems of patients with extensive metastatic calcification, especially those for sudden death or with a history of conduction defects, should include examination of the cardiac conduction system. Conduction system examination may be useful in the investigation of sudden death in CRF patients. Unless this is thought of, death may be attributed to co-morbid conditions, with the true cause of death remaining undetected.

Acknowledgments

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