Patients with end-stage renal disease (ESRD) receiving hemodialysis (HD) suffer from a number of metabolic derangements. Ectopic deposition of calcium in the skin, soft tissues, blood vessels, and viscera is a potentially devastating consequence of disorders of calcium and phosphorus homeostasis. We report the case of a patient with ESRD and secondary hyperparathyroidism receiving HD who developed metastatic pulmonary calcification and calciphylaxis following initiation of warfarin therapy after mechanical valve replacement. Because not all patients with ESRD receiving HD develop ectopic calcification, there appears to be a complex cascade of metabolic interactions that predispose patients to this process. Warfarin is a vitamin K antagonist with inhibitory effects not only on proteins of the coagulation cascade, but also on other important protein systems. Its role in ectopic calcium deposition has been the subject of theories and has been reported in the literature, but no link with metastatic pulmonary calcification has been made. Patients receiving HD have an increased incidence of conditions that require chronic anticoagulation with warfarin, such as VTE, atrial fibrillation, and valvular heart disease requiring valve replacement surgery. Bioprosthetic valves should be considered in these patients because of the potential risk of metastatic calcification when warfarin is used in the setting of mechanical valve replacement.
Abbreviations

ESRD  
end-stage renal disease

HD  
hemodialysis

MGP  
matrix Gla protein

VKDP  
vitamin K-dependent protein

Case Report

A 37-year-old man with end-stage renal disease (ESRD) and severe secondary hyperparathyroidism who was receiving hemodialysis (HD) since 2004 was admitted to our institution in August 2007 because of infective endocarditis requiring mechanical valve replacement of his mitral and aortic valves. Oral anticoagulation treatment with warfarin was initiated, and the patient was eventually discharged home. At that time, his chest radiograph showed only the postoperative changes (Fig 1A).
In March 2008, the patient was readmitted for a painful necrotic ulcer on his right calf. He had no other complaints except for mild dyspnea on exertion. His medications included nifedipine ER (90 mg daily), metoprolol (100 mg bid), multivitamins (one capsule daily), calcium acetate (2,001 mg tid), and warfarin (5 mg daily). Vital signs were normal with an arterial oxygen saturation of 94% on room air. His physical examination was remarkable for a 3/6 aortic systolic ejection murmur, few scattered crackles on both lungs, and trace bilateral lower extremities edema. Chest radiograph on admission revealed diffuse bilateral infiltrates (Fig 1B). Significant laboratory study values were as follows: international normalized ratio, 2.3; creatinine, 6.4 mg/dL; blood urea nitrogen, 48 mg/dL; calcium, 8.4 mg/dL (corrected); phosphorus, 6.0 mg/dL; alkaline phosphatase, 534 IU/L (normal range: 34-124); and albumin, 3.0 g/dL.

The patient was admitted with presumptive diagnoses of right leg cellulitis and pulmonary edema. Even though he underwent emergent HD with ultrafiltration challenge, a follow-up chest radiograph showed persistence of the infiltrates. A noncontrast chest CT scan was obtained (Fig 2). It revealed diffuse and confluent dense alveolar infiltration primarily in the upper lobes compatible with pulmonary calcifications. Subsequently, a CT scan of his right leg showed extensive vascular and soft tissue calcifications.
Metastatic pulmonary calcification and calciphylaxis on the right leg was diagnosed in the patient. He refused a skin biopsy to confirm the diagnosis of calciphylaxis. The intact parathyroid hormone level was 3,921 pg/mL (normal range: 12-65). The calcium-based phosphate binder was discontinued, and sevelamer was started instead. Cinacalcet and sodium thiosulfate after HD were also started to better control his secondary hyperparathyroidism. Anticoagulation therapy with warfarin was continued during his admission. He had a significant clinical improvement and was discharged home. Follow-up with surgery was arranged, and the patient subsequently underwent parathyroidectomy at our institution. His postoperative course was uneventful. Routine chest radiographs showed no interval change in the bilateral parenchymal infiltrates.

Discussion

Metastatic calcification is a process in which calcium deposition occurs in normal tissues. This is different from dystrophic calcification, which occurs when calcium salts are deposited into pathologically abnormal tissues. Patients with evidence of metastatic calcification can demonstrate both visceral and nonvisceral involvement. Visceral calcification may occur in the lungs, stomach, kidneys, heart, and muscles, whereas nonvisceral calcification (calciphylaxis) mainly affects the small to medium arteries of the dermis and subcutaneous tissues. Reported risk factors for metastatic calcification include hypercalcemia, hyperphosphatemia, elevated plasma calcium-phosphate product, hyperparathyroidism, chronic kidney disease, HD, protein C deficiency, and warfarin therapy.
The interplay of variables contributing to ectopic calcification in patients with ESRD seems to be linked specifically to the regulation of disproportionate levels of calcium, phosphate, and vitamin D compared with the normal population. In ESRD, systemic calcium and phosphate concentrations are typically elevated, leading to oversaturation and subsequent precipitation of mineral ions. Specific models looking at the alterations of vascular smooth muscle cells have shown that heterogeneous, uncloned populations of these cells do not mineralize in culture spontaneously, but can be induced to mineralize by elevating the phosphate levels within the culture.[2]

Recent studies looking at the process of human smooth muscle vascular calcification found that two different proteins, serum fetuin-A (α2-Heremans-Schmid glycoprotein) and matrix Gla protein (MGP), act as potent endogenous inhibitors of calcification.[3] Fetuin-A is a circulating plasma glycoprotein produced by multiple tissues during fetal development and by the liver in adults.[4] It has been shown in vitro to be a potent inhibitor of hydroxyapatite formation. MGP is a vitamin K-dependent extracellular matrix protein synthesized by medial vascular smooth muscle cells and chondrocytes and is a potent inhibitor of vascular and cartilage calcification. Recent human studies have shown that fetuin-A and MGP levels are decreased in patients with ESRD receiving HD and chronic inflammatory states, leading to an increased risk for vascular calcification and calciphylaxis.[5]

There appears to be a complex process of converting vitamin K-dependent proteins (VKDPs), like the coagulation factors and MGP, to their biologically active form via carboxylation of glutamic acid residues. Although carboxylation is common to all VKDPs, the location and form of vitamin K used for activating VKDPs is variable. In hepatic carboxylation, the liver uses plant-synthesized phylloquinones (also known as vitamin K₃) to activate the coagulation factors. In a distinct process, vascular smooth muscle cells produce and activate MGP through a peripheral carboxylation process that depends on a family of menaquinones known as vitamin K₂. Deficiency of vitamin K₂, resulting from vitamin K₁ nutritional deficiency, malabsorption, or alteration of intestinal bacteria, can lead to vascular injury and calcification.[6]

Warfarin inhibits both the hepatic carboxylation of the coagulation factors and the peripheral carboxylation of MGP. In several animal models, extensive arterial calcification has been induced with the administration of high doses of warfarin. Observational studies in patients with ESRD suggest an association between warfarin exposure and accelerated calcification of the coronary arteries, aortic valve, and peripheral arteries. In a case control study[7] regarding the risk factors and mortality associated with calciphylaxis in ESRD, the use of warfarin was more prevalent in case subjects compared with control subjects (37% vs 1.8%). In addition, there seems to be a strong synergistic effect between warfarin and vitamin D in arterial calcification. A murine model[8] showed that concurrent warfarin treatment accelerated artery calcification in vitamin D-treated rats, even though warfarin treatment alone did not cause detectable artery calcification at treatment times of 1 week or less. This is significant because many patients with ESRD receive vitamin D supplementation.

From the pulmonary perspective, several authors have reported cases of pathologic tracheobronchial calcification associated with warfarin therapy after cardiac valvular replacement in both pediatric and adult patients.[9] In addition, fulminant metastatic pulmonary calcification and calciphylaxis have been reported in patients with ESRD and severe secondary hyperparathyroidism and after the initiation of HD and renal transplantation.[10]

This patient presented with both types of metastatic calcification: visceral (lungs) and nonvisceral (calciphylaxis involving his right leg). We were able to identify multiple risk factors, including ESRD receiving HD, severe uncontrolled secondary hyperparathyroidism, calcium-based phosphate binder therapy, and warfarin. However, we speculate that warfarin therapy after valve replacement surgery is the only precipitating factor that has a clear temporal connection to the rapid development of metastatic pulmonary calcification and calciphylaxis.

Patients receiving HD have an increased incidence of conditions that prompt chronic anticoagulation with warfarin, such as VTE, atrial fibrillation, and valvular heart disease requiring valve replacement surgery. The 1998 American College of Cardiology/American Heart Association guidelines recommended mechanical prostheses for valve replacement in patients with ESRD receiving HD because of the presumed accelerated degeneration of tissue valves in this specific population. However, subsequent studies found no superiority of mechanical valves over bioprostheses.[12] In fact, the incidences of thromboembolism, bleeding, and valve-related morbidity and mortality were significantly higher with mechanical valves. Interestingly, the latest 2006 American College of Cardiology/American Heart Association guidelines made no specific recommendations on the choice of valve.[13] Patients receiving HD who undergo mechanical valve
replacement surgery have an increased incidence of complications related to anticoagulation therapy with warfarin. Not only the risk of major hemorrhagic events, but also the alterations in calcium homeostasis create a real therapeutic dilemma. Bioprosthetic valves should be considered in patients with ESRD receiving HD because of the potential risk of bleeding and metastatic calcification when warfarin is used in the setting of mechanical valve replacement.

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REFERENCES: