

Between a Rock and a Hard Place: Metastatic Calcinosis of Left Ventricular Outflow Tract Secondary to Renal Failure Resulting in Symptomatic Aortic Regurgitation



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INTRODUCTION

Cardiovascular complications are the most common cause of death in dialysis-dependent chronic renal failure (CRF) patients. The array of cardiovascular complications in CRF patients is vast and includes processes such as coronary artery disease, arrhythmias, heart failure, and valvular disease.¹ Of those patients with valve calcification, the mitral annulus, mitral valve, and aortic valve are the classic sites predisposed to metastatic calcification in CRF patients.² Valvular calcification can then lead to secondary complications, which include valvular dysfunction, conduction abnormalities, and embolization.^{3,4} Several factors have been proposed to play a role in valve calcification, primarily calcium-phosphorus imbalance and aging, among others.⁵ Here we present an exceptionally interesting case of moderate aortic regurgitation secondary to metastatic calcinosis involving the left ventricular outflow tract (LVOT) in a peritoneal dialysis-dependent CRF patient and a review of metastatic calcinosis.

CASE PRESENTATION

A 68-year-old man with a history of hypertension, diabetes, and CRF on peritoneal dialysis for 2 years presented to our hospital as a direct admission from the nephrology clinic due to progressively worsening fatigue, generalized weakness, and falls in recent weeks. He reported no issues with his peritoneal dialysis routine. He denied any other symptoms. Physical exam demonstrated a temperature of 98°F, blood pressure of 101/49 mm Hg, heart rate of 77 bpm, and a diastolic murmur at the left sternal border. A transthoracic echocardiogram demonstrated an ejection fraction of 45%–50% with severely increased left ventricular end-diastolic volume of 261 mL by modified biplane with a large cylindrical echo density of 3.4 cm × 0.9 cm, projecting into the LVOT from the hinge point of the left coronary cusp (LCC) with independent mobility resulting in moderate aortic regurgitation (see [Videos 1–4](#)). Given the echo-bright presentation and smooth contour of the density, it was more suggestive of calcification rather than a vegetation or thrombus (see [Figures 1 and 2](#)). Furthermore, the patient had no fevers or other findings supportive

of an infectious process, although there was associated mitral annular calcification. Interestingly, the echo findings are completely new when compared with his most recent echocardiogram from 2018. His echo at that time demonstrated an ejection fraction of 50%–55% with a left ventricular end-diastolic volume of 158 mL by modified biplane and no evidence of aortic valve, mitral valve, or LVOT pathology (see [Figure 3](#)). Of note, it was around this time that the patient first became dialysis dependent. On physical exam during this admission, multiple dark spots were noted on his hands and feet (see [Figure 4](#)), which had developed in recent months. In addition, x-rays of hands and feet demonstrated extensive calcifications throughout (see [Figure 5](#)). A recent computed tomography chest scan confirmed a heavily calcified aortic valve ([Figure 6](#)). Laboratory evaluation demonstrated the following: white blood cell count, 7.4/mm³; hemoglobin, 10.0 g/dL; platelet count, 164,000/mm³; calcium, 8.4 mg/dL; phosphorus, 8.5 mg/dL; blood urea nitrogen, 52 mg/dL; creatinine, 14.30 mg/dL; parathyroid hormone level, 1,042 pg/mL (reference range 16–65 pg/mL); vitamin D-25 level, 12.85 ng/mL (reference range 12–52 ng/mL); and thyroid-stimulating hormone, 2.2 mIU/L. Multiple blood culture draws returned negative. The cardiothoracic surgery team evaluated the patient and, given a modified frailty index of 54.5%, deemed him a poor surgical candidate.

DISCUSSION

Valvular calcification in hemodialysis patients is increasingly recognized. The majority of valvular lesions in these patients are acquired, mostly secondary to complex mineral-metabolic derangements.^{5,6} As a result of the various metabolic disturbances associated with CRF and hemodialysis, the prevalence of valvular calcification is up to eight times higher in patients undergoing hemodialysis than in the general population.^{6,7} Furthermore, valvular calcification is detected up to 10–20 years earlier in CRF patients than in the general population. Once present, it progresses up to 10 times faster in this population.^{7,8} Unfortunately, valvular calcification is correlated with higher cardiovascular and all-cause mortality risk in dialysis patients.^{9,10} Urena *et al.*⁸ reported a mean survival time of 23.0 ± 9.5 months after diagnosis of valvular calcification in dialysis patients. With an increasingly dialysis-dependent and aged population, valvular calcification is expected to be ever-more omnipresent.^{9,10}

Until recently, metastatic calcinosis was attributed to passive deposition of calcium as part of a chronic degenerative process. Various studies have since shown that derangements in mineral metabolism correlate most strongly with the development of malignant calcinosis.⁴ There remains, however, controversy over the impact conferred by other derangements, such as calcium-phosphate product, iPTH, RANKL, and so on. By extension, calcium supplements and calcium-based phosphate binders have also been associated

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VIDEO HIGHLIGHTS

Video 1: Parasternal long-axis view demonstrating a large, echo-dense mass projecting in and out of the aortic valve throughout the cardiac cycle.

Video 2: Parasternal long-axis view with color Doppler demonstrating the aortic regurgitation secondary to interference from the independently mobile LCC echo density.

Video 3: Parasternal short-axis view demonstrating the aortic valve and the echo-dense mass as it interferes with cusp motion.

Video 4: Parasternal short-axis view with color Doppler highlighting the associated regurgitation.

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with more rapid progression of calcinosis. This is further supported by the fact that non-calcium-based phosphate binders are associated with improved survival in these patients.⁶ Other supplements, such as vitamins D, K, and A, have also been shown to increase calcifications, but the exact mechanisms remain unclear.⁶ Other researchers postulate that, like in atherosclerosis, valvular calcification may be a result of immunoinflammatory dysregulation secondary to metabolic syndrome, hyperlipidemia, and diabetes—all of which are strongly associated with the development of CRF and the need for hemodialysis in the first place.⁶

Just as the cardiac effects of metastatic calcinosis are diffuse, so are the secondary complications that arise. Metastatic calcinosis affecting the valves and perivalvular anatomy can manifest as stenosis and/or regurgitation. This can lead to the development of heart failure in some patients. While most valvular complications are chronic and progressive, Jang *et al.*¹¹ report a case of abrupt, severe aortic regurgitation secondary to metastatic calcinosis. Left-sided valvular calcification can result in devastating embolic sequelae including strokes, mesenteric ischemia, and myocardial infarction, to name a few.² Furthermore, calcification of the electrical system of the heart can present as conduction abnormalities and/or various arrhythmias.² Based on available literature, there are no data available for risk stratification based on echocardiographic appearances of metastatic calcinosis.

While suspicion for metastatic calcinosis should be elevated in dialysis patients, it is important to remember common mimickers that could present similarly. A wide variety of diseases can manifest as vegetations, including cardiac tumors, infectious diseases, and marantic endocarditis, to name a few.² While the incidence of infective endocarditis increases in CRF,^{12,13} our clinical suspicion for this was low as our patient remained afebrile, maintained a normal white blood cell count, and had negative cultures. Papillary fibroelastomas are often attached to the aortic valve and surrounding structures and can result in embolic complications as well. The highly echogenic and overall structural appearance of the mass was more consistent with a calcification, rather than a papillary fibroelastoma. Highly echogenic cardiac masses in dialysis patients can be further broken down to metastatic calcinosis, calcified thrombus, or calcified amorphous tumor, which is a relatively new and rare entity, first described in 1997.¹⁴ Histologically a cardiac CAT consists of calcification and

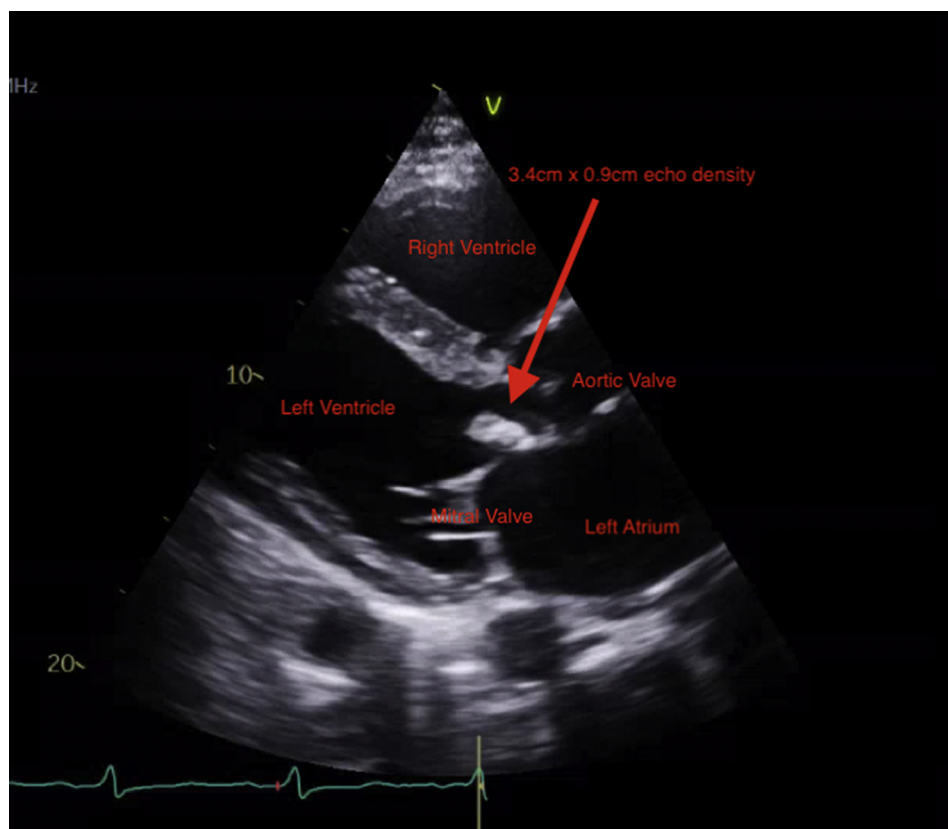


Figure 1 Large, cylindrical echo density of 3.4 cm × 0.9 cm (red arrow), projecting into the LVOT from the hinge point of the LCC.

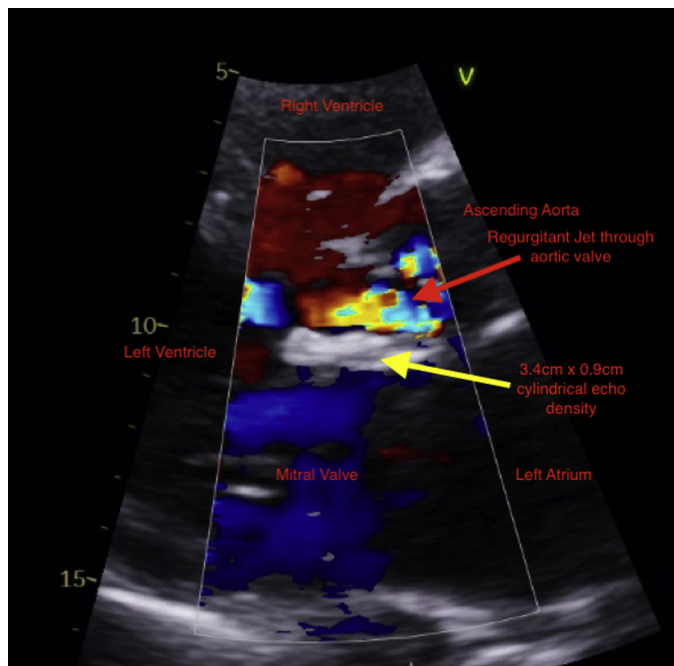


Figure 2 Color Doppler demonstrating aortic regurgitation (red arrow) secondary to interference from the independently mobile LCC echo density (yellow arrow).

eosinophilic amorphous material in the background of dense collagenous fibrous tissue.¹⁴ Furthermore, patients with cardiac CAT share the same major risk factors as those in metastatic calcinosis—although, interestingly, cardiac CAT has a slight predominance in female patients per the literature.¹⁴ One important distinguishing factor is the echocardiographic heterogeneity noted with cardiac CAT.¹⁵ Unlike the typically uniform, hyperechoic features of metastatic calcinosis, a cardiac CAT is a mosaic of nodular calcifications, inflammation,



Figure 4 Multiple nodular lesions throughout all extremities.

and degenerated blood element, giving rise to a hyperechoic mass with accompanying partially hypoechoic or isoechoic components.¹⁵ While we, unfortunately, do not have a histological specimen to

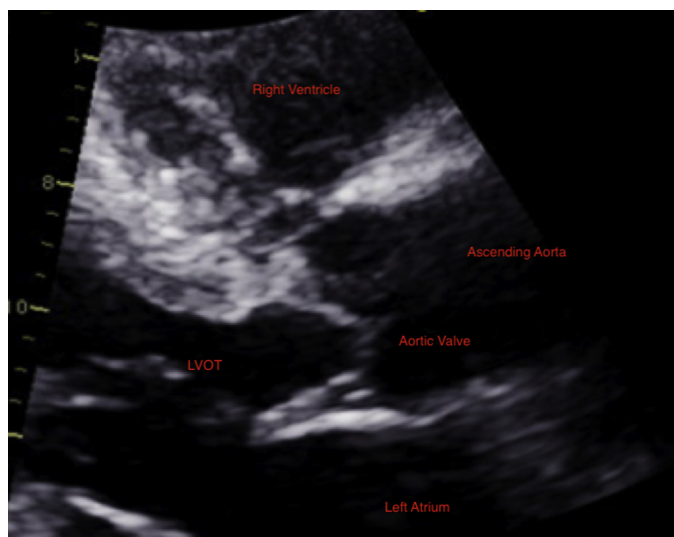


Figure 3 Parasternal long-axis view from 2018 demonstrating a structurally and functionally normal aortic valve.



Figure 5 X-rays of hands and feet demonstrating extensive calcification of peripheral vasculature.



Figure 6 Computed tomography chest scan demonstrating heavy calcification of the aortic mass and attached calcified mass.

confirm the diagnosis, the diagnosis of metastatic calcinosis is best supported given the patient's comorbidities, its uniform hyperechoic appearance on echocardiography, and evidence of diffuse, extracardiac calcification as well.

Based on current literature, guidelines for the management of valvular calcification in CRF patients do not differ from those for the general population.⁸ The standard monitoring and treatment guidelines for mitral and aortic stenosis and/or regurgitation apply for valvulopathy secondary to metastatic calcinosis. Tanaka *et al.*¹⁶ demonstrated that the postsurgical aortic valve replacement outcomes for dialysis-dependent patients did not differ from those of patients with normal renal function. While dialysis is not an outright contraindication to valve replacement, CRF patients in general have higher morbidity and mortality overall.⁶ Nevertheless, prevention is the cornerstone of management of metastatic calcinosis. Elevated phosphate levels correlate best with the development of metastatic calcinosis. Maintenance of calcium and phosphate levels is typically achieved through a combination of diet, increased dialysis, and phosphate binders.² While atherosclerosis has been postulated to play at least a partial role in metastatic calcinosis, optimized blood pressure and lipid control have not been demonstrated to slow the process.⁶ In fact, some studies have shown that statin use has been associated with increased calcium deposition, instead.¹⁷ In light of this, currently the guidelines advise against the use of statins solely for the treatment of valvular calcification.⁶

CONCLUSION

Valvular calcification is an ominous, yet unsurprising, finding in dialysis patients, as it is associated with higher cardiovascular and all-cause mortality.^{9,10} The complications of valvular calcification are vast and include valvular dysfunction, conduction abnormalities, and embolization.^{3,4} Several factors have been proposed, although not fully understood. With an increasingly dialysis-dependent and aged

population, the clinical suspicion for and management of valvular calcification are expected to be ever-more demanding.^{9,10}

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2021.01.001>.

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