Extraskeletal calcifications in a dialysis-dependent teenager: A novel cause of acquired pediatric complete heart block

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Introduction

Complete atrioventricular (AV) block in children is most often congenital or acquired secondary to cardiac surgery or acute myocarditis. We present a case of a pediatric dialysis patient with new complete heart block discovered on routine outpatient electrocardiogram (ECG), ultimately attributed to calcium deposition within the conduction system. This phenomenon has never before been described in a pediatric patient with an otherwise normally functioning heart. This report highlights a potentially fatal occult risk that should be considered in the care of children with renal failure and expands the differential diagnosis of acquired AV block.

Case report

The patient is a 16-year-old female subject with peritoneal dialysis–dependent end-stage renal disease (ESRD) secondary to steroid-resistant nephrotic syndrome and calcineurin inhibitor toxicity. Her history additionally includes anemia of ESRD, malnutrition with gastrojejunal tube for supplementation, chronic kidney disease–mineral and bone disorder (CKD-MBD), wheelchair dependence for chronic pain and deconditioning, and medication nonadherence secondary to several psychiatric diagnoses including persistent depressive disorder.

KEY TEACHING POINTS

- Renal failure may lead to visceral calcium deposition resulting from secondary hyperparathyroidism, hypercalcemia, and hyperphosphatemia. These calcium deposits have been described in a variety of tissues, including the myocardium, coronary arteries, and cardiac valves.
- Calcium deposition in the region of the cardiac conduction system, including the location of the atrioventricular node, can lead to complete heart block. This calcium deposition may be due to renal failure or other etiologies such as Paget's disease, parathyroid gland neoplasms, or atherosclerosis-related calcification.
- Calcification of the atrioventricular node is a rare and potentially life-threatening complication of renal failure in both adults and children. Pacemaker implantation may be indicated.

At a routine dialysis clinic appointment, she was noted to be bradycardic. An ECG demonstrated a new finding of complete AV block with a junctional escape rhythm at 50 beats per minute. Her QTc was borderline prolonged at 465 milliseconds. All prior studies including an ECG 17 months earlier (Figure 1) and Holter monitor 13 months earlier demonstrated sinus rhythm with intact AV conduction. Her PR interval on prior ECGs ranged between 130 and 160 ms, with an interval of 136 ms noted on the ECG preceding the heart block. She denied any history of recent viral illness symptoms, fever, near syncope, or syncope. She reported

KEYWORDS Heart block; Hyperphosphatemia; Calcium; Atrioventricular block; End-stage renal disease; Dialysis
(Heart Rhythm Case Reports 2022;8:591–595)

Funding Support: Dr Miyake is supported by NHLBI K23HL136932. Disclosures: The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Christina Y. Miyake, Texas Children's Hospital, 6651 Main St, Houston, TX 77030. E-mail address: cymiyake@bcm.edu.

https://doi.org/10.1016/j.hrcr.2022.05.022

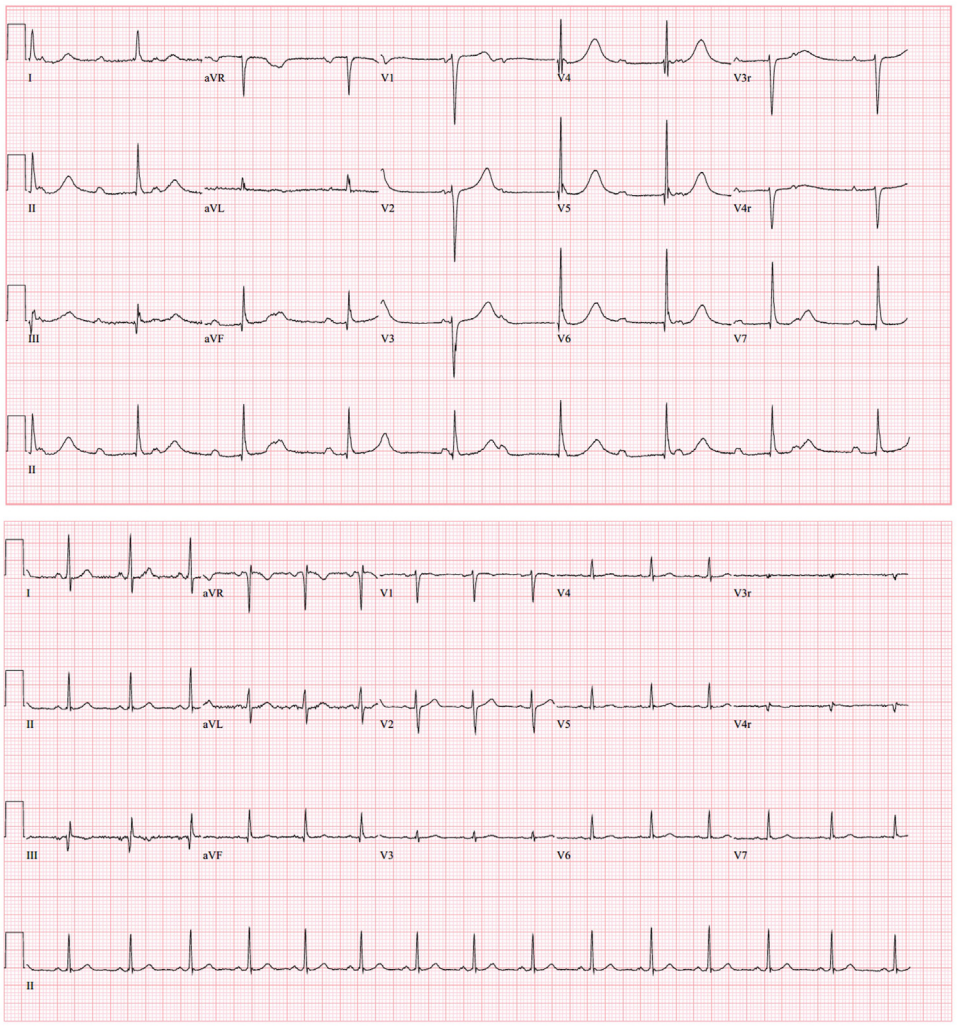

Figure 1 Complete atrioventricular block with junctional escape at 50 beats/min on outpatient electrocardiogram (ECG), with normal sinus rhythm on previous ECG 17 months prior.

possible increased fatigue but, wheelchair bound with limited physical activity, she could not provide further details regarding length of time regarding fatigue symptoms. She was admitted to the electrophysiology inpatient service for further workup of new-onset complete heart block. Inpatient telemetry monitoring revealed complete heart block upon admission and for the next 12 hours. Subsequently, she was noted to have some underlying conduction, although it oscillated unpredictably between high-grade second-degree block and rare episodes of first-degree block, with sudden resumption of complete heart block that was not associated with physical activity or other forms of adrenergic stimulation.

During this admission, a thorough workup for potential etiologies of conduction system dysfunction was pursued. Review of her cardiac history revealed that she had been followed intermittently by cardiology for subaortic hypertrophy with mild dynamic flow acceleration discovered on echocardiogram obtained for hypertension, as well as for a prolonged QTc in the setting of polypharmacy and electrolyte derangements. Her QTc was normal at baseline. Cardiac magnetic resonance imaging 18 months prior to the current presentation was normal, with the exception of moderate concentric left ventricular hypertrophy, with hyperdynamic biventricular function.

Review of all prescriptions identified aripiprazole, an atypical antipsychotic associated with AV block, as the only potentially contributing medication. However, the patient's mother had stopped administering this several weeks before admission. Hypercalcemia has been shown to cause complete heart block[1] and was certainly a consideration in this patient with known secondary hyperparathyroidism, but her calcium at admission was normal (8.9 mg/dL).

Review of her vital signs documented during an emergency room visit 1 week prior to her presentation revealed a normal heart rate. Given the acuity of onset, with the documented normal heart rate 1 week prior and a Holter monitor showing normal AV conduction 13 months earlier, myocarditis or infection were considered. However, she had no history of fever or other signs of infection, systolic function was

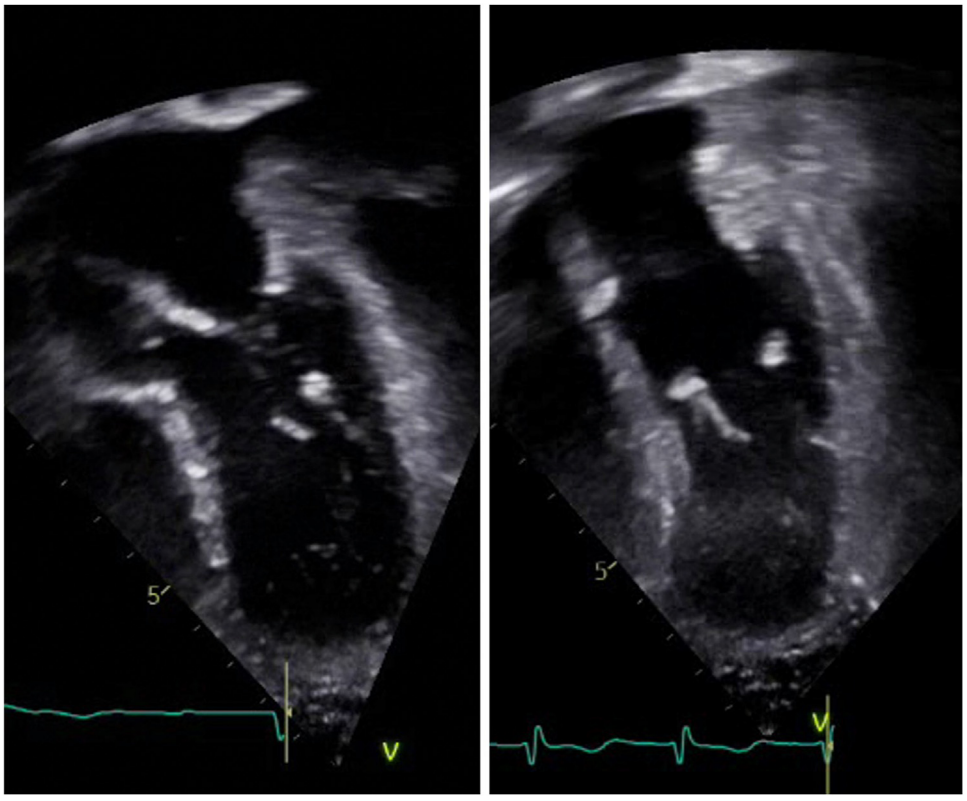

Figure 2 Echo-bright papillary muscles on echocardiogram suggesting possible calcium deposition.

preserved on echocardiogram, and inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, and ferritin, were normal. She tested negative for infections with known associations with AV node dysfunction, including COVID-19, Lyme disease, and tuberculosis. Anti–streptolysin O antibodies and anti-COVID antibodies were likewise negative.

Rheumatologic evaluation was undertaken to rule out autoimmune causes of heart block, in light of a maternal grandmother and maternal great-grandmother with systemic lupus erythematosus and a maternal aunt with hypothyroidism. This patient's fluorescent antinuclear antibody screen was positive at a titer level of 1:640 (>1:320 is considered significant). However, overall suspicion for autoimmune processes was low given the lack of additional systemic symptoms; confirmatory complement levels and anti-dsDNA, anti-SSB, anti-RNP, anti-Sm, anti-SSA, anti-Scl-70, and anti-Jo antibodies were all negative. Similarly, she had no additional features of syndromes such as Kearns-Sayre or Holt-Oram to suspect a genetic etiology.

In the absence of alternative explanations for her heart block, consideration was given to her most notable sequela of her renal disease: poorly controlled CKD-MBD. Although the patient was prescribed sevelamer for hyperphosphatemia and cinacalcet and vitamin D for hyperparathyroidism, her sporadic medication adherence had resulted in skeletal demineralization, with sclerosis of the carpal bones and epiphyses, and periostitis of her long bones. Her admission parathyroid hormone level was elevated at 726 pg/mL (upper limit of normal 80.1 pg/mL), phosphorous was high at 11.3 mg/dL (normal 2.5–5.0 mg/dL), and calcium-phosphate product was also elevated at 101.7 mg^2/dL^2 (normal <55.0 mg^2/dL^2), all suggesting increased risk of extraskeletal calcification. Examination of serial echocardiograms revealed echo-bright appearance of her papillary muscles, which had been initially mentioned in 2020, the year before the development of heart block, raising suspicion for potential cardiac calcium deposition (Figure 2). Therefore, cardiac computed tomography was obtained, confirming multiple calcifications along the aortic and mitral valves, the aortic root, and the central fibrous body where the AV node lies (Figure 3). The patient was thus diagnosed with acquired AV block most likely secondary to ectopic calcium deposition in the setting of uncontrolled CKD-MBD, though there was no safe way to obtain pathologic confirmation.

Having arrived at an irreversible and presumably progressive cause of this patient's complete AV block, the decision was made to perform implantation of a right ventricular leadless Medtronic A-V Micra pacemaker (Minneapolis, MN). She was observed overnight following implantation, and after confirmatory device interrogation, chest radiograph, and echocardiogram, was discharged home the following day. After 1 year of follow-up, the patient remains in complete heart block.

Discussion

Acquired complete heart block in nonsurgical pediatric patients is rare, most commonly caused by maternal

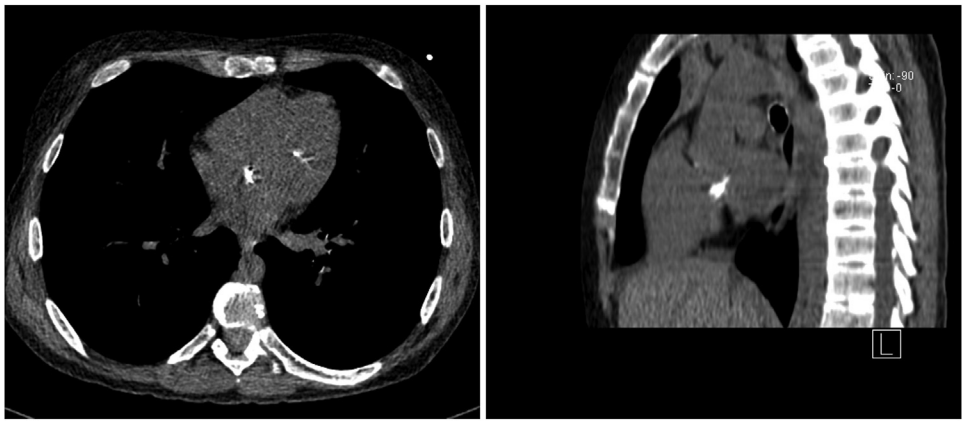

Figure 3 Cardiac computed tomography demonstrating calcium deposition at the level of the atrioventricular node, thought to be the cause of the patient's complete heart block.

autoimmune antibodies or myocarditis.[2] This is, to our knowledge, the first reported case of calcium deposition secondary to renal disease causing complete AV block in a child with previously normal cardiac conduction and function.

In adults, the link between renal failure and visceral calcium deposition is better established than in children. Generally thought to be related to secondary hyperparathyroidism, hyperphosphatemia, hypercalcemia, and elevated calcium-phosphate product,[3] calcium deposition in ectopic locations occurs in 40%–76% of adults on dialysis.[4] This "metastatic calcification"—or abnormal deposition in previously normal tissues[5]—has been described in the blood vessels, lung, kidney, myocardium, coronary artery, central nervous system, and gastric mucosa. High rates of cardiovascular disease in dialysis-dependent adults have been attributed to greater myocardial calcium content than in controls,[6] high rates of vascular calcification including high calcium content in the coronary arteries[7,8] and frequent calcification of the mitral and aortic valves.[9]

Though less common than the aforementioned types of cardiovascular calcification, conduction system involvement has been described in both dialysis patients and those with calcium deposition due to other causes. Two autopsy studies of adult dialysis patients identified frequent calcium deposits within the region of the AV node; death was attributed specifically to heart block caused by calcification in at least 3 of the patients examined.[10,11] Heart block has occurred in a 68-year-old male patient with ESRD and progressive mitral annulus calcium deposition[3]; a 40-year-old man with dialysis dependence and autopsy findings of extensive vascular, myocardial, and conduction system calcification[12]; a 63-year-old male patient with Paget's disease and presumed myocardial calcification[13]; a 66-year-old man with atherosclerosis-related aortic valve calcification[14]; and a 66-year-old patient with a parathyroid adenoma and resulting hypercalcemia.[15] The proposed mechanism for AV node dysfunction in each of these cases was calcium deposition within the conduction system.

While AV nodal involvement of metastatic calcification has been reported in adults, this is a novel finding in pediatric patients. Just 1 single-center study of 120 children with uremia, dialysis dependence, or renal transplant investigated the prevalence of soft tissue calcification in children, identifying a full 60% of their population with calcification of the blood vessels, lungs, kidneys, heart, and central nervous system.[4] There are 2 prior case reports of young people with calcification-related heart block, neither from renal failure. One was a 23-year-old patient with a bicuspid aortic valve and resulting calcification of both the valve and the intraventricular septum,[16] and the other was a 6-year-old with hyperphosphatemic familial tumoral calcinosis.[17] The sole pediatric patient previously described in the literature with chronic renal failure and possible conduction system calcification was an 11-year-old girl who was also known to have symptomatic cardiomyopathy related to chronic vascular calcification. She had no documented heart block but suffered a bradycardic arrest during anesthesia that was ultimately attributed to calcification of the conduction system.[18]

Greater awareness of this rare and potentially life-threatening complication of renal failure is critical for pediatric nephrologists and cardiologists alike. Particularly in patients with known elevated calcium-phosphate product or hyperparathyroidism, close attention must be paid to bradycardia, syncope, or ECG changes that could be the harbinger of cardiac calcification. Management is of course unprecedented, but since the calcification is presumed to be irreversible, and since most of the previously described adult patients received pacemakers or died, a pacemaker was the choice in our patient. A leadless device was chosen owing to her dialysis dependence, with sedentary lifestyle. We believe that the accumulation likely occurred over several years, facilitated by noncompliance. In retrospect, echo-brightness on the echocardiogram should have prompted further workup such as a Holter or cardiac magnetic resonance imaging. The quick progression of her disease

from normal conduction to complete heart block underscores a need for clinical vigilance.

Conclusion

Although soft tissue ectopic calcium deposition is a known complication of chronic kidney disease in adults, the phenomenon has been reported only once before in a pediatric patient with heart failure. This case emphasizes the need for attention to potential conduction abnormalities in patients with known risk factors for ectopic calcification. Annual ECGs, particularly in teenage years, could help with early identification of conduction delays in this population. In noncompliant patients or those in whom echo-brightness on echocardiogram is noted, biannual ECGs and further testing such as a 24-hour Holter and cardiac magnetic resonance imaging should be considered.

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