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BRIEF REPORT

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Cardiovascular calcifications in pediatric patients receiving maintenance dialysis

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Abstract Cardiovascular disease is a major cause of morbidity and mortality in adult patients with end-stage renal disease receiving maintenance dialysis. Coronary artery calcifications (CAC) contribute to the high prevalence of cardiac disease and are associated with hyperphosphatemia, an elevated calcium-phosphorus product (CaxP), and prolonged time on dialysis. Chronic inflammation and malnutrition are also associated with an increased risk for development of cardiac calcifications. Young adults receiving maintenance dialysis develop cardiac calcifications at a degree out of proportion to healthy adults of the same age and gender. Many of these young adults initiated dialysis as children or teenagers. Risk factors associated with the development of CAC are also seen in the pediatric dialysis population. To date, reports of cardiac calcifications in pediatric patients receiving maintenance dialysis are limited to post-mortem studies. We present two pediatric patients with ANCA-positive vasculitis diagnosed with cardiac calcifications while receiving maintenance dialysis. Hyperphosphatemia and an elevated CaxP product were seen in both patients and probably contributed to the development of extraskeletal calcifications. In addition, both patients had an underlying systemic inflammatory disease and significant weight loss/malnutrition that may have contributed to the early and rapid onset of cardiac calcifications.

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Introduction

Extraskeletal calcifications are a well-known complication of renal osteodystrophy in patients with end-stage renal disease (ESRD) maintained on chronic dialysis. Risk factors for the development of calcification include poorly controlled secondary hyperparathyroidism, hyperphosphatemia, elevated calcium-phosphorus (CaxP) product, prolonged history on dialysis, and possibly the use of certain vitamin D analogues and calcium-based phosphate binders [1, 2, 3, 4].

Metastatic calcification may occur in soft tissue, periarticular, pulmonary, and vascular sites, including calcification in the coronary arteries and cardiac valves. Coronary artery calcifications (CAC) are significantly increased in incidence and severity in adult patients with ESRD [5]. Cardiac calcifications contribute significantly to the high incidence of cardiovascular disease in patients with ESRD [6], which in turn is a major cause for the higher mortality observed in these patients [7].

Recent studies confirm the high incidence of overall cardiovascular disease in pediatric ESRD patients [8, 9]. The prevalence of cardiac and/or coronary calcifications in pediatric ESRD patients is yet unknown. While the same risk factors that predispose to CAC in adult patients are often seen in pediatric ESRD patients, Goodman et al. [10] did not detect CAC by electron beam computed tomographic (CT) scan in patients with ESRD younger than 20 years. The current report presents two pediatric ESRD patients, both younger than 20 years of age, discovered to have significant cardiac and vascular calcifications while on maintenance dialysis, with some of the traditional risk factors for developing extraskeletal calcifications.

Table 1 Biochemical and nutritional characteristics of two pediatric patients with cardiac and vascular calcifications (*Ca* calcium, *P* phosphate, *PTH* parathyroid hormone, *BMI* body mass index)[a]

	Patient 1	Patient 2
Mean serum Ca (mg/dl)	11.4±1.0	10.8±0.6
Mean serum P (mg/dl)	7.4±1.3	8.7±1.0
Mean CaxP product (mg^2/dl^2)	84.6±15.6	94.1±7.9
Mean intact PTH (pg/dl)	404±242	368±119
Mean serum albumin (g/dl)	4.13±0.27	3.95±0.25
% BMI change	–8.65%	–16.19%
%Weight change	–8.68%	–13.78%

[a] One year prior to diagnosis, based on monthly values

Case reports

Patient 1

Patient 1 is an 18-year-old Caucasian male with ESRD secondary to Wegener granulomatosis receiving chronic peritoneal dialysis (CCPD) since February 2000 (dialysis duration 30 months to date). His course on CCPD has been remarkable for chronic malnutrition with significant weight loss (weight loss of 7 kg; Table 1), necessitating prolonged hospitalizations for nutritional rehabilitation. In June 2001, he developed a chronic cough and a chest X-ray showed the presence of increased interstitial markings with possible worsening of his interstitial lung disease related to his Wegener granulomatosis. In September 2001, he developed severe acute chest pain with respiratory distress. Evaluation confirmed the presence of significant myocardial ischemia as noted by electrocardiographic changes with a rise in myocardial enzyme activity. A subsequent coronary angiogram failed to detect any lesions in his major coronary arteries, but an endomyocardial biopsy performed at that time showed the presence of extensive calcification of small vessels in his myocardium (Fig. 1). Echocardiography did not reveal calcification but did show the presence of mild left ventricular hypertrophy (LVH) with a depressed ejection fraction. A follow-up echocardiogram performed 1 month later showed an improvement in left ventricular function, with a normal ejection fraction and persistence of LVH.

Additional evaluation revealed extensive lung parenchymal calcifications (originally noted as increased interstitial markings on chest X-ray) detected by CT scan and confirmed by lung biopsy. CT scan showed scattered calcifications of the dura mater in the brain. He also developed soft tissue periarticular calcification on his hand.

His average monthly CaxP product for 1 year prior to this event was 84.6±15.6 mg^2/dl^2 (median 87.4 mg^2/dl^2) with an average intact parathyroid hormone (PTH) of 404±242 pg/ml (median 457 pg/ml) (Table 1). In the year prior to the diagnosis of cardiac calcifications, treatment of his hyperphosphatemia consisted of calcium carbonate (mean prescribed daily dose of elemental calcium 5.6±1.4 g) until August 2001. He was then started on a non-calcium-based phosphate binder (sevelamer hydrochloride) and calcium carbonate was discontinued. Vitamin D therapy consisted of oral calcitriol (mean prescribed daily dose 0.93±0.96 µg), which was adjusted based on intact PTH values.

C-reactive protein values rose from a normal value of <0.5 in June 2000 to 9.8 mg/dl at the time of his acute myocardial ischemic episode. ANCA titers remained negative throughout this time. He remained on daily oral steroids for his underlying disease since his diagnosis.

Patient 2

Patient 2 is a 12-year-old Caucasian female diagnosed with ESRD secondary to ANCA-positive vasculitis receiving chronic dialysis (initially hemodialysis, then CCPD) since June 1999 (dialysis duration 38 months). She complained of a chronic cough lasting for approximately 2 months, for which she underwent a CT scan of her sinuses in August 2002 for further evaluation. Other clinical problems included severe malnutrition and weight loss (weight loss of 5.4 kg; Table 1) in the past 8 months.

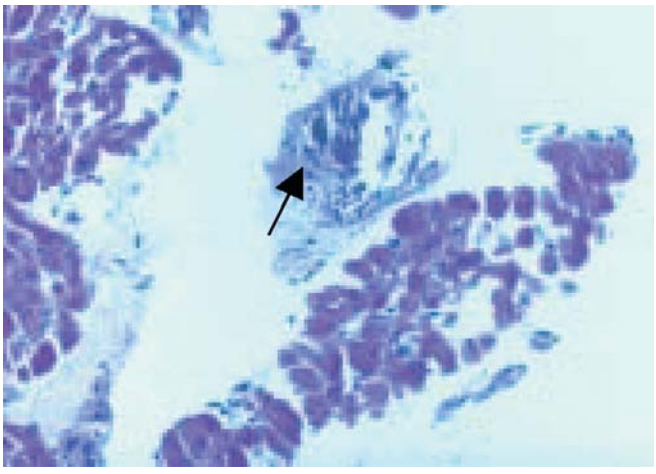

Fig. 1 Histopathology of myocardial calcification in patient 1. Metastatic calcification, as shown by the *arrow*, in the media of a small myocardial vessel

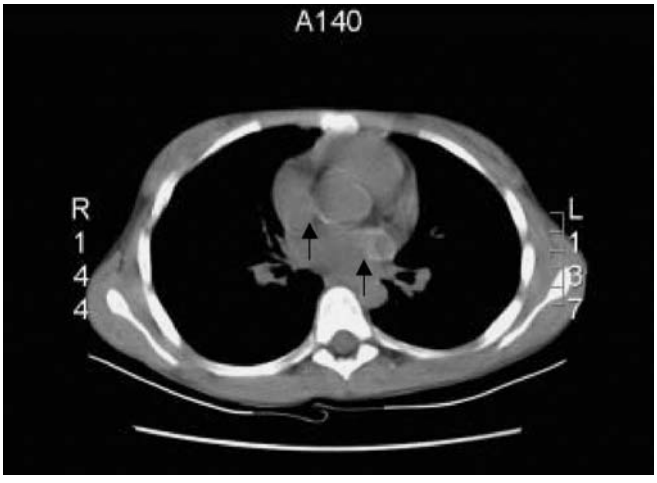

Fig. 2 Computed tomographic scan image of vascular and myocardial calcification in patient 2. *Arrows* show metastatic calcification at the base of the aortic root and in the myocardium of the left atrial appendage

Significant calcification of her carotid arteries was noted as an incidental finding on her sinus CT scan, and further evaluation with a chest CT scan demonstrated calcifications of her aortic root and in the myocardium in the area of the left atrial appendage (Fig. 2). Calcifications of her main bronchi were also detected, with no lung parenchymal involvement. Dura mater calcifications in the thoracic area and brain were also seen. Echocardiography did not detect any myocardial calcifications, but did show some calcifications in the mitral valve chordae tendinae. No LVH was noted.

Her average monthly CaxP product from 1 year prior to this was 94.1±7.9 mg^2/dl^2 (median 92.3 mg^2/dl^2) with an average intact PTH of 368±119 pg/ml (median 398 pg/ml) (Table 1). Calcium-based phosphate binders were prescribed until December 2001 and then discontinued. The patient was then switched to sevelamer hydrochloride (mean cumulative daily dose 6133±623 mg). The patient was prescribed oral calcitriol as a vitamin D analogue throughout the study period (mean daily dose 1.33±0.25 µg).

C-reactive protein has remained within normal limits to date. ANCA titers that had been negative became positive in February 2002 and increased in August 2002. She has been maintained on oral steroid therapy since diagnosis.

Discussion

Cardiovascular disease is the major cause of mortality in adults receiving maintenance dialysis. A recent study also identified cardiovascular disease as a significant cause of morbidity and mortality in pediatric ESRD patients, accounting for 38% of deaths in this population [8]. In the current report, we present two pediatric patients with cardiac and vascular calcifications. Thus, cardiac calcifications are not restricted to older adults with ESRD, but may also be seen in pediatric and adolescent patients receiving maintenance dialysis. Routine echocardiograms fail to show myocardial calcifications, which may account for the reason why data on pediatric cardiovascular disease are limited.

The high incidence of cardiovascular disease in adult ESRD patients is related to a number of underlying factors, including a high incidence of diabetes mellitus, hypertension, dyslipidemia, and accelerated atherosclerosis. Traditional risk factors for cardiovascular disease, including smoking and obesity, are often present. In addition, hyperphosphatemia has been noted to be an independent predictor of mortality [11], with the increase in mortality primarily secondary to cardiac causes [7].

The presence and degree of coronary calcification has been shown to correlate well with coronary artery atherosclerosis and plaque formation both in adults with normal renal function and with ESRD [12]. CAC has been noted in adult ESRD patients out of proportion to age-matched controls [5]. Thus, CAC is seen to a greater degree and at a younger age in patients with ESRD compared with age-matched controls with normal renal function. As reported by Goodman et al. [10], longer time on dialysis, older age, high CaxP product, and high doses of daily calcium intake were associated with a higher degree of CAC in young adults over the age of 20 years. No evidence of CAC was seen in patients younger than 20 years.

Another recent study on young adults with ESRD with childhood onset of chronic renal failure (CRF) noted the high prevalence of CAC and carotid artery thickening out of proportion to age-matched controls [13]. CAC was noted in 92% of 39 young adults aged 19–39 years with CRF duration ranging from 7 to 34 years and cumulative dialysis duration of 0–22 years.

In 1990, Milliner et al. [4] reported systemic calcifications at autopsy in approximately a quarter of pediatric ESRD patients at their institution from 1960 to 1983. Soft tissue calcifications were noted in up to 76% of patients with ESRD who had received dialysis. Of the 43 patients with systemic calcifications, mostly with multiple site involvement, 30 of 43 (69.8%) demonstrated vascular (non-myocardial) calcifications, 12 of 43 (27.9%) had coronary artery calcifications, and 19 of 43 (44.2%) had myocardial calcifications. Their analysis showed a significant association with the severity of calcinosis and the use of vitamin D therapy, age at onset of ESRD, sex, and the peak CaxP product.

Since this report, there have been many changes in the management of pediatric patients with ESRD. Use of various vitamin D analogues, calcium-based and non-calcium based phosphate binders has changed significantly over the years. In addition, we have seen significant changes in the ability to maintain patients with ESRD on maintenance dialysis, with improvements in the delivery of dialysis, management of anemia, and improvement of linear growth. No recent study has demonstrated systemic calcinosis, and specifically cardiac calcifications, in pediatric patients.

Both these patients demonstrated high CaxP products, hyperphosphatemia, and hypercalcemia; risk factors for the development of extraskeletal calcifications. However, other risk factors, such as severe hyperparathyroidism and prolonged time on dialysis, were absent. In fact, the severity of calcification despite the relative short duration of receiving dialysis is worrying. Both patients had an underlying diagnosis of a systemic vasculitis so it is possible that inflammation in association with vasculitis contributed to the vascular calcifications. ANCA-related aortitis, coronary arteritis, and accompanying aortic valvular disease have rarely been described in patients with active Wegener granulomatosis [14, 15, 16]. Davenport et al. [17] described two cases of aortic valve disease in patients with Wegener in remission.

Of note, both patients had significant weight loss in the months prior to the detection of cardiac and vascular calcifications. We have previously reported that malnutrition may be an additional risk factor for extraskeletal calcifications in ESRD patients on maintenance dialysis [18]. The association with malnutrition and atherosclerosis has also been noted in other reports [19, 20]. Wang et al. [21] also noted the link between cardiac valvular calcifications and malnutrition in adult ESRD patients receiving chronic peritoneal dialysis. It is possible that malnutrition and the underlying catabolic state have contributed to the development of cardiac and vascular calcifications in these pediatric ESRD patients.

In conclusion, pediatric ESRD patients receiving maintenance dialysis also face a high risk of cardiovascular disease, which may include cardiac and vascular calcifications. Routine screening for cardiac and vascular calcification by CT scan (ECG-gated EBCT or high-resolution helical CT) may be necessary in all pediatric ESRD patients receiving maintenance dialysis, irrespective of their age and duration of dialysis therapy. In addition, vigilant monitoring and therapy for hyperphosphatemia, hypercalcemia, and elevated CaxP products may be warranted to avoid complications of extraskeletal calcifications, which can occur even in pediatric and adolescent dialysis patients. Patients with systemic inflammation such as ANCA-related vasculitis may have additional risk factors for cardiovascular calcifications, which may be clinically manifested by myocardial infarction long after active vasculitis is detectable.

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