CASE REPORT

Vascular calcification in a young patient with end-stage renal disease

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Vascular calcification in children with long-standing dialysis is a unique phenomenon. Hyperphosphataemia and hyperparathyroidism are the major pathogenic risk factors. We describe a young patient with end-stage renal disease diagnosed since childhood and underwent prolonged dialysis therapy. He was admitted for recurrent episodes of acute joint pain. Investigations confirmed diffuse periarticular, vascular, and intracardiac calcifications which were rarely seen in the young population. He underwent parathyroidectomy and incidentally found to have a co-existing papillary carcinoma of thyroid. After parathyroidectomy, serial X-rays showed resorption of these calcifications.

Introduction

Although extraskeletal calcifications had been recognised as a complication of uraemia, the emphasis in the past was on skeletal changes and bone disease. With greater awareness of cardiovascular mortality and morbidity in end-stage renal disease (ESRD), vascular calcification becomes a focus of studies even in the paediatric population. We report on a dialysis patient with diffuse vascular calcification and review the literature on its pathogenesis.

Case report

The patient was a 5-year-old boy who presented with proteinuria and chronic renal failure in September 1991. Radiological workup revealed a non-functioning left kidney and hypoplastic right kidney. He reached ESRD after reaching 11 years old and was started on peritoneal dialysis. He received regular growth hormone therapy, erythropoietin injections, oral calcium carbonate, and oral calcitriol (Rocaltrol; RP Scherer, Baden, Germany) for his growth failure, anaemia, and renal bone disease. Peritoneal equilibration tests showed high average transport rates for urea and creatinine, so he was put on home-automated peritoneal dialysis with a 10-hour regimen every night. The fill volume of each cycle was adjusted according to his body weight and his final regimen was 2.5% peritoneal dialysis fluid, 2 L per cycle, 4 cycles per night with a last dwell of 2 L (total therapy volume of 10 L). His initial renal plus peritoneal dialysis Kt/V urea was 1.86 and creatinine clearance was 38 mL/min/1.73m^2. As his urine output dropped to less than 100 mL/day, his Kt/V urea was only 1.38. Despite having an extra mid-day ultrabag exchange prescribed, he never performed that exchange. His compliances with oral medications and erythropoietin

TABLE. The yearly average of serum calcium, phosphate, calcium-phosphate product, and parathyroid hormone (PTH) of the patient*

Duration of dialysis (years)	Mean ± standard deviation			
	Serum calcium (mmol/L)	Serum phosphate (mmol/L)	Calcium-phosphate product (mmol/L)^2	PTH (pmol/L)
6	2.46 ± 0.07	2.17 ± 0.20	5.33 ± 0.57	152.85 ± 38.22
7	2.58 ± 0.06	2.48 ± 0.24	6.40 ± 0.73	199.05 ± 5.44
8	2.58 ± 0.05	2.65 ± 0.56	6.86 ± 1.61	231.00 ± 22.49
9	2.53 ± 0.10	2.99 ± 0.15	7.59 ± 0.60	298.05 ± 3.60
10	2.55 ± 0.09	3.02 ± 0.20	7.70 ± 0.68	293.35 ± 30.62
After parathyroidectomy	1.80 ± 0.25	1.07 ± 0.22	1.88 ± 0.20	2.40

* Reference ranges with respect to age and sex:
Serum calcium for age: (16-18 years) 2.1-2.57 mmol/L and (>19 years) 2.1-2.62 mmol/L
Serum phosphate for age: (16-18 years) 0.85-1.6 mmol/L and (>19 years) 0.88-1.45 mmol/L
Serum PTH: 1.1-6.9 pmol/L

Key words
Kidney failure, chronic; Vascular diseases

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injection were also poor. He refused living-related renal transplantation nor was he inclined to wait for cadaveric renal transplant. Despite repeated interventions by a clinical psychologist, there was no improvement in his compliance. His condition remained stable and he was asymptomatic for years, but his serum parathyroid hormone (PTH) level increased exponentially. At the age of 15 years, oral pulse calcitriol at 2 μg 3 times per week was started as his PTH level increased to 186 pmol/L with serum calcium of 2.24 mmol/L, phosphate 1.69 mmol/L, and alkaline phosphatase 1268 IU/L. His PTH responded and dropped back to 31 pmol/L initially. However, his non-compliance to medication continued and became even worse during his adolescence. His PTH level increased markedly and his calcium-phosphate product remained elevated (Table). The use of intravenous calcitriol, parathyroid scan, and parathyroidectomy were suggested but he refused. He has had no bone pain, fracture, or muscle weakness. However, serial X-rays showed generalised decrease in bone density with coarse bony trabeculation, bony erosions over distal aspects of bones, distal femur, proximal tibia, and acromioclavicular joints.

Ten years after the commencement of dialysis (aged 22 years), he was admitted for left wrist pain. Physical examination showed a cystic lesion over the left wrist and aspiration yielded a chalky fluid. The fluid contained no pus cells or urate crystals, and Gram stain and culture were negative. X-rays showed extraskeletal calcification (Fig a). Parathyroidectomy was advised for refractory hyperparathyroidism, but the patient refused. His phosphate binder was changed to aluminium hydroxide and low calcium peritoneal fluid solution was used for his dialysis. He received intensive dialysis therapy during his stay in hospital, and after discharge, he remained on his usual dialysis regimen. Five months later, he was hospitalised for severe left knee pain, which interfered with walking. His left knee was hot, tender, and swollen. X-rays showed bilateral diffuse periarticular knee calcification (Figs b and c), diffuse linear calcification over both hands (Figs d and e) and abnormal calcification in the chest X-ray (Fig f). Serum biochemical tests showed urea 24.2 mmol/L, creatinine 1170 μmol/L, calcium 2.44 mmol/L,

一名年輕的末期腎病患者的血管鈣化

需長期接受透析的兒童出現血管鈣化是一種獨特的現象，而高磷血症和副甲狀腺功能亢進症是主要的致病危險因素。本文報告一名自幼年開始已診斷患有末期腎病的年輕患者，他須長期接受透析治療。病人因反覆出現急性關節痛而入院，檢查後證實病人有瀰漫性的關節旁、血管及心內鈣化，這種情況很少會發生在年輕的病人身上。病人接受副甲狀腺切除術時，同時發現有乳突性甲狀腺癌。病人術後的放射影像顯示鈣化已被吸收溶解。

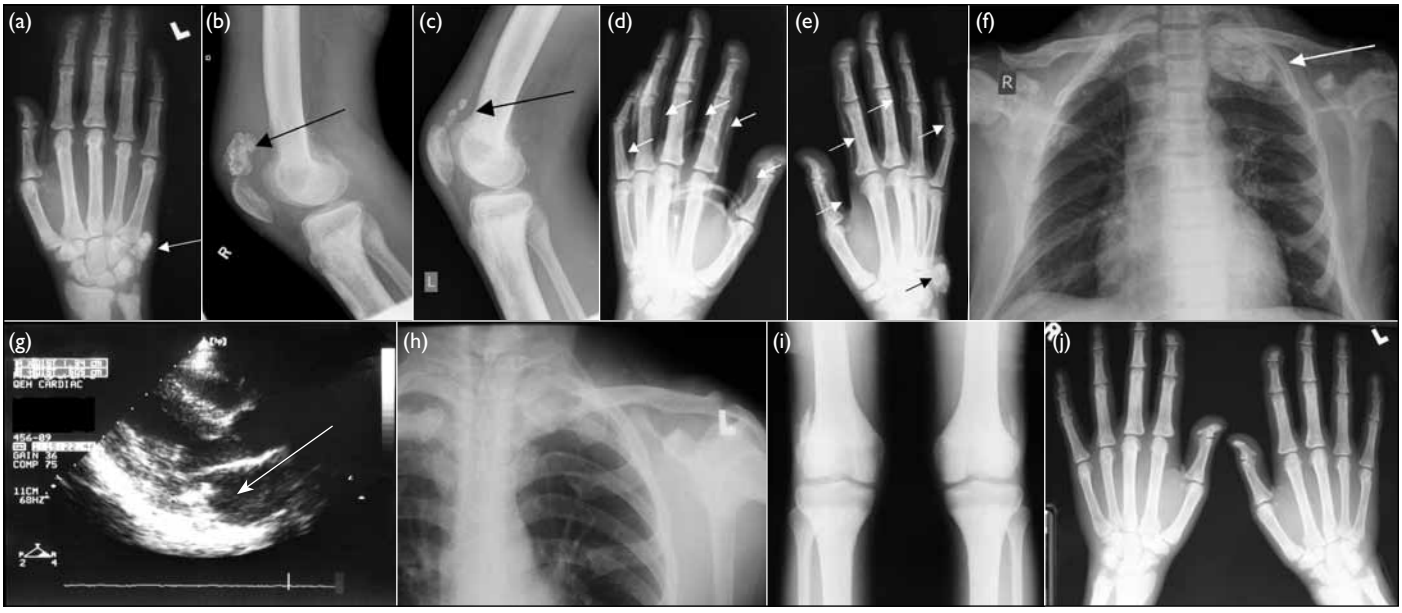

FIG. (a) An X-ray of left hand taken on first admission showed extraosseous calcification over left wrist (white arrow) with resorption of distal tufts of left thumb and fingers. Diffuse osteosclerosis was also noted. (b) The lateral view of right knee with calcification over suprapatellar region (black arrow). (c) The lateral view of left knee with calcification along the prepatellar tendon (black arrow). Oblique views of (d) left and (e) right hands with periarticular calcification over right wrist (black arrow). Apart from the calcification over left wrist, linear calcifications along the digital vessels were seen (white arrows). (f) A chest X-ray shows abnormal subcutaneous calcification and a large tumoural calcinosis over left sternoclavicular junction (white arrow). The lung field was congested. (g) Echocardiogram (parasternal long axis view) shows an echo-dense mass (white arrow) measuring 2 x 1.4 cm at mid-posterior left ventricular wall. (h, i, j) Resolving calcification over chest X-ray; the linear vascular calcifications over both hands and tumoural calcification over left wrist had resolved and disappeared 1 year after parathyroidectomy. Some abnormal calcification is still observed at periarticular region of both knees

phosphate 2.76 mmol/L, calcium-phosphate product 6.73 (mmol/L)^2, and PTH 242 pmol/L (reference range, 1.1-6.9 pmol/L). Echocardiography revealed increased echo density over the posterior mitral valve leaflet and an echo dense mass measuring 2 x 1.4 cm in size at the mid-posterior left ventricular wall that was compatible with intracardiac calcification (Fig g). Cardiac contractility and atrioventricular valve function were not impaired. His electrocardiogram showed nil abnormality. The sestamibi parathyroid scintiscan showed hyperplasia of parathyroids. The patient agreed to a total parathyroidectomy, but during surgery biopsy of a suspicious lymph node yielded metastatic papillary carcinoma of thyroid, which was an unexpected co-existing finding. Total thyroidectomy was then performed 1 month later. The patient received I^{131} treatment and recovered uneventfully from both surgeries. One year later, repeated X-rays (Figs h, i and j) showed resorption of the abnormal calcifications. Follow-up echocardiography showed a decrease in the extent of the echo dense signal.

Discussion

Although renal transplantation is the mainstay of treatment for children with ESRD, many children and adolescents are still on long-term dialysis therapy and do not enjoy the advantages of renal transplantation. Following a prolonged period of renal failure and dialysis, cardiovascular complications become a major cause of mortality and morbidity, which occurs at an earlier age than in adult counterparts.[1,2] Milliner et al[3] reported systemic calcifications observed at autopsy in approximately one fourth of paediatric ESRD patients; 76% had soft tissue calcification, 28% had coronary artery calcification, and 44% showed evidence of myocardial infarction. The longer the duration of dialysis, the higher the risk.

The pathogenesis of vascular calcification in uraemia is complex. Abnormally high phosphate and low serum calcium in renal failure trigger the secretion of PTH, leading to hyperplasia of parathyroid glands. The set-point for calcium-sensing receptors is altered, such that a higher level of serum calcium is required to suppress PTH secretion. The traditional practice was to use calcium-based phosphate binders and high-dose active vitamin D to keep serum calcium at the upper limit of normal and to replace the vitamin D deficiency. However, at this state of skeletal resistance to PTH, bone is unable to buffer the fluxes of calcium, which leads to extraskeletal calcification in various body tissues, including the heart and arteries. Deposition of calcium at periarticular soft tissues, tendons, and cartilages may cause acute pain, redness, and tenderness. Among all the extraosseous calcifications, vascular calcification is a uraemia-specific phenomenon and is the most devastating complication. It can be asymptomatic for a period of time before it suddenly reveals its presence as clinically serious calciphylaxis. Unlike endothelial type of arterial calcification, which is an integral part of atherosclerosis, uraemia causes medial wall calcification (Mönckeberg's sclerosis)[4] and the affected vessels become more rigid and less distensible. Intracardiac, valvular, and coronary artery calcifications may impair myocardial conduction, myocardial contraction, and the diastolic function of the heart. Affected patients are usually much younger than those with typical 'atherosclerotic' disorders. Our patient had a prolonged period of inadequate dialysis and uncontrolled tertiary hyperparathyroidism. As he was asymptomatic, he did not appreciate the importance of tight metabolic control, until he developed severe disabling knee pain.

High serum phosphate was known to increase intima-media thickness, vessel stiffness and left ventricular hypertrophy, and is a potent, independent predictor of cardiovascular mortality.[5] The pathogenesis of vascular calcification is not merely a process of passive precipitation due to the supersaturated state of calcium and phosphate in plasma. Raising the phosphate concentration in cell culture media of vascular smooth muscle cells (VSMCs) leads to deposition of hydroxyapatite. Hyperphosphataemia induces a phenotypic switch of VSMC to osteoblast-like cells (osteoblastic differentiation). There causes a dramatic loss of smooth muscle cell lineage makers and a gain in osteogenic markers, such as cellular core-binding factor alpha 1 and osteocalcin.[6] These osteoblastic reactions led to mineralisation of the extracellular matrix and of vascular calcification. Hypercalcaemia also induces osteogenic behaviour in VSMCs. The combination of high calcium and high phosphate synergistically induces formation of matrix vesicles and de-novo expression of specific bone-related protein.[7] A growing number of calcification inhibitors like fetuin A (α_2-Heremans-Schmid glycoprotein), matrix G1a protein, osteoprotegerin, pyrophosphates and bone morphogenetic protein 7 have been recognised in recent years. Dysregulation of these inhibitors and inducers probably plays a part in the pathogenesis of uraemic calcification.[8]

Hyperparathyroidism was also a risk factor for vascular and soft tissue calcification in animal models.[9] Partial or complete resorption of metastatic calcification was observed in uraemic patients after parathyroidectomy; significant decreases in both coronary and carotid artery calcification have been reported.[10] Hence, uncontrolled PTH release by itself may play a role. In our patient, apart from parathyroidectomy, newer pharmacological agents could have been deployed to control his metabolic disorder before it progressed to such a late stage. The latter agents include the non–calcium-based

phosphate binder, sevelamer hydrochloride (Renagel; Genzyme Corporation, US), new vitamin D analogues, and a calcimimetic agent (cinacalcet).

In recent years, the role of fibroblast growth factor 23 (FGF23) in uraemia is being increasingly recognised. This factor is a phosphaturic hormone secreted by osteocytes and osteoblasts in response to hyperphosphataemia. In order to exert its physiological effect, FGF23 requires the presence of Klotho in the receptor. The receptor complex (Klotho-FGFR) is found in the kidneys and parathyroid glands. It seems that FGF23 decreases renal reabsorption of phosphate and decreases the production of $1,25(OH)_2$ vitamin D. As glomerular filtration rate falls, FGF23 increases so as to maintain a normal phosphate balance. This drives down $1,25(OH)_2$ vitamin D levels and PTH levels increase.[11,12] Its role in uraemic metabolic bone disorder awaits further elucidation and may be the future target of therapy.

Conclusion

Uraemic patients with a long history of dialysis therapy may suffer from cardiovascular disease at a younger age than the general population. Tight control of metabolic disorders and awareness of the associated complications can help to improve patient outcomes.

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