Tumoral Calcinosisssion Without Hyperparathyroidism in a Patient on Continuous Ambulatory Peritoneal Dialysis

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Reports of tumoral calcinosis (TC) in peritoneal dialysis (PD) patients are rare. Reported PD patients with TC also had hyperparathyroidism. A 67-year-old man on continuous ambulatory PD for almost 3 years developed TC of the right wrist and knee and both shoulders and feet. In the 2 years preceding the diagnosis of TC, this patient’s serum parathyroid hormone levels were consistently low (17 ± 12 pg/mL). Hypercalcemia had been found in 32% of the serum samples, hyperphosphatemia in 91%, and elevated $Ca \times P$ product in 78% of the samples. At presentation with TC, serum C-reactive protein was elevated, and serum levels of vitamin D compounds were below normal. Four months after the diagnosis of TC, the patient died with a combination of gastrointestinal and retroperitoneal bleeding episodes and septic events. Tumoral calcinosis may develop in PD patients without hyperparathyroidism. Sustained hyperphosphatemia and high $Ca \times P$ product are important in the pathogenesis of uremic TC. Elevated indices of inflammation may accompany TC. Studies are needed to identify other important factors in the pathogenesis of TC in PD patients and to evaluate treatment methods.

Keywords
Tumoral calcinosis, hyperphosphatemia, hypercalcemia, hyperparathyroidism, inflammation

Introduction
In patients on chronic dialysis, ectopic calcifications cause morbidity and, almost certainly, mortality. Arterial calcifications, the commonest ectopic calcifications, are linked to morbidity and mortality. Calciphylaxis is also recognized with increasing frequency and has a high mortality. Tumoral calcinosis (TC) is relatively uncommon and has been studied less intensively than have the other two conditions, but TC can cause discomfort and immobility. In hemodialysis patients, TC was initially described as a complication of hyperparathyroidism (1), but was subsequently found in patients with adynamic bone disease (2) or aluminum osteodystrophy (3). The few cases of TC reported in peritoneal dialysis (PD) patients were associated with hyperparathyroidism (4,5).

Here, we describe the development of TC in a patient on continuous ambulatory PD (CAPD). Hyperparathyroidism was absent, but hyperphosphatemia and elevated $Ca \times P$ product were sustained. Pathogenetic mechanisms and treatment of TC are discussed.

Case report
A 64-year-old man with end-stage renal disease secondary to diabetic nephropathy commenced CAPD with 4 daily exchanges, a 2-L fill volume, and 1.5% alternating with 2.5% dextrose content in November 2004. Peritoneal equilibration test revealed low-average transport. Urine flow rate exceeded 1 L in 24 hours and total (peritoneal plus renal) weekly $Kt/V$ urea was consistently above 2.0 throughout the CAPD period.

This patient had an early exit-site infection with methicillin-sensitive Staphylococcus aureus. In September 2005, he was hospitalized twice, once for severe hyperglycemia and once for accidental severing of the PD catheter without peritonitis. Following these admissions, he had several lower gastrointestinal (GI) bleeding episodes requiring transfusions of red blood cells and intravenous iron infusions. Colonoscopies revealed adenomatous polyps and bleeding internal hemorrhoids.

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In September 2007, the patient complained of a painless nodule in the extensor surface of the right wrist, stiffness and pain of the right knee, and pains in both feet causing a wheelchair existence. Radiographs and bone scan revealed extensive arterial calcifications and TC in the right wrist and knee, left elbow, both plantar areas, and both shoulders (Figures 1 and 2). The patient had not taken any vitamin D preparations. Calcium acetate, 667 mg with each meal was prescribed as the phosphate binder between December 2004 and February 2007, when sevelamer was substituted for calcium acetate because of hypercalcemia. He also consumed large amounts of calcium carbonate (Tums: GlaxoSmithKline, Philadelphia, PA, U.S.A.) for epigastric distress after September 2005, as was later discovered.

All oral calcium preparations were discontinued after the diagnosis of TC. Treatment with bisphosphonates was planned, but in rapid succession, he developed a duodenal ulcer, with severe upper GI bleeding requiring several transfusions of packed red blood cells; a cerebrovascular accident with right hemiplegia; *Klebsiella* pneumonia with bacteremia, endocarditis, and peritonitis necessitating transfer to hemodialysis; and a large spontaneous retroperitoneal hematoma. He died in January 2008 subsequent to intractable hypotensive shock.

Changes in the patient's laboratory values related to the development of ectopic calcifications occurred between the CAPD period before the two admissions in 2005 and the 2-year period preceding the diagnosis of TC. Table I shows these laboratory values in the pre-dialysis period (November 2000–October 2004), in the CAPD period between November 2004 and September 2005 (period A), in the CAPD period between October 2005 and September 2007 (period B), and in the CAPD period between October 2007 and January 2008 (period C). Periods A and B were compared statistically. Calcium, phosphorus, Ca$\times$P product, parathyroid hormone, glucose, and hemoglobin were higher in period A. Serum albumin and total CO$_2$ (tCO$_2$) were similar in periods A and B.

Hypercalcemia (>10.2 mg/dL), not found in periods A and C, was found in 7 samples (32%) in period B. Hyperphosphatemia (>5.0 mg/dL) was found in 5 samples (36%) in period A, 20 samples (91%) in period B, and 9 samples (36%), all during episodes of sepsis, in period C. Elevated Ca$\times$P product (>55) was found

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**Figure 1** (A) Total body bone scan and plain radiography of the right upper extremity showing tumoral calcinosis (arrows). The radiographic image also shows extensive arterial calcification.

**Figure 2** Details of the bone scan, further illustrating areas of tumoral calcinosis.
in 5 samples (36%) in period A, 16 samples (78%) in period B, and 5 samples (20%) in period C. Values of blood glycosylated hemoglobin and serum lipids, which were measured only once in period A, were numerically lower in period B than in period A. At presentation with TC, serum C-reactive protein (CRP) was 58.5 mg/L (normal range: <10 mg/L), serum 1,25-dihydroxycholecalciferol was 5.5 pg/mL (normal range: 25.1 – 66.1 pg/mL), and serum 25-hydroxycholecalciferol was 9.4 ng/mL (normal range: 20.0 – 100.0 ng/mL).

**Discussion and conclusions**

The main points of this case report are that

- hyperparathyroidism was not necessary for the development of TC, and
- sustained elevation both of serum phosphorus and of Ca × P product preceded development of TC.

The development of arterial calcifications depends to some extent on the same factors, but with significant differences. Arterial calcifications are also frequent in diabetic patients without renal failure or Ca × P product abnormalities. In patients on PD, such calcifications do not respond to treatments that otherwise have some effect on TC, including reduction of Ca × P product, parathyroidectomy, or agents solubilizing the calcium salts from the ectopic calcifications (6).

Although the idea that ectopic calcifications result from an elevation of Ca × P product above a threshold value represents an oversimplification (7), the fundamental biochemical abnormality leading to TC in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-dialysis</th>
<th>Period A</th>
<th>Period B</th>
<th>Period C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.5±0.9</td>
<td>8.3±0.8</td>
<td>9.3±1.1c</td>
<td>7.4±0.8</td>
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<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.6±0.9</td>
<td>4.5±1.5</td>
<td>6.7±1.7d</td>
<td>6.4±2.6</td>
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<td>Ca × P</td>
<td>48±9</td>
<td>38±15</td>
<td>62±15d</td>
<td>48±20</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.7±0.4</td>
<td>3.0±0.4</td>
<td>2.8±0.3e</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>iPTH (g/mL)</td>
<td>87±29</td>
<td>82±68</td>
<td>17±12e</td>
<td>141±12</td>
</tr>
<tr>
<td>tCO₂ (mmol/L)</td>
<td>21.1±1.8</td>
<td>27.4±3.1</td>
<td>26.5±2.2e</td>
<td>24.4±5.2</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>162±75</td>
<td>259±152</td>
<td>156±49d</td>
<td>139±78</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.5±1.3</td>
<td>16.0</td>
<td>6.6±0.2</td>
<td>5.8±0.8</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>256±21</td>
<td>202</td>
<td>143±18</td>
<td>174</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>39±6</td>
<td>32</td>
<td>50±10</td>
<td>53</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>158±15</td>
<td>106</td>
<td>64±17</td>
<td>94</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>262±26</td>
<td>253</td>
<td>146±55</td>
<td>131</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.6</td>
<td>12.7±1.2</td>
<td>9.9±2.8e</td>
<td>9.7±2.2</td>
</tr>
</tbody>
</table>

| a Mean ± standard deviation (samples studied). |
| c p < 0.05 as compared with period A. Comparisons used the Student two-tailed non-paired t-test. |
| d p < 0.001 as compared with period A. |
| e Nonsignificant as compared with period A. |

PTH = intact parathyroid hormone (normal range: 11 – 67 pg/mL); tCO₂ = total carbon dioxide; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
dialysis patients is thought to be an elevated Ca × P product (3). Sustained elevation of Ca × P was noted in the 2 years preceding the diagnosis of TC in the patient reported here (Table I). However, only a fraction of the patients with similar elevations in Ca × P develop TC (8). This suggests that other influences, in addition to an elevated Ca × P, have critical roles in the pathogenesis of TC (9). Administration of vitamin D derivatives leads to ectopic calcifications in uremic animals (10). Associations between TC and intake (11) or aberrant metabolism (12) of vitamin D have been reported. However, our patient never took vitamin D preparations. Vitamin D levels in his serum were below normal when TC was diagnosed.

The association between chronic inflammation, which reduces the levels of endogenous inhibitors of calcification in body fluids, and arterial calcifications (13) or calciphylaxis (14) has been recognized. Induction of inflammation by TC has been reported (15,16). Serum CRP was elevated in the patient reported here when TC was diagnosed. However, whether inflammation can lead to the development of TC is not currently known.

Hyperlipidemia and diabetes have been associated with arterial calcifications. Metabolic acidosis has a protective effect on ectopic calcifications in uremic animals (17). The association of these three factors with TC has not been studied. In our patient, control of both serum glucose and lipids improved in the 2 years preceding the development of TC as compared with the first 10 months of CAPD, but serum tCO₂ was consistently on the high side (Table I).

Finally, mutations in several genes have been reported in familial TC (18,19), which has variants with and without hyperphosphatemia (20). The pathogenesis of uremic TC may be further elucidated by studies of the effects of uremia on these genes and on the metabolism of their products.

Decreases in the Ca × P product, parathyroidec-
tomy, sodium thiosulfate (6) [which can be adminis-
tered intraperitoneally in PD patients (21)], calcimimetics and bisphosphonates (16,22) have all been used in the treatment of TC. The characteristics of removal of certain bisphosphonates by hemodialy-
sis have been studied (23). Studies of their removal by PD are needed.

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