Uremic Tumoral Calcinoses in Hemodialysis Patients: Clinicopathological Findings and Identification of Calcific Deposits

JUN’ICHIRO HAMADA, KAZUYA TAMAI, WATARU ONO, and KOICHI SAOTOME

ABSTRACT. Objective. Extraskeletal calcifications generally develop in uremic patients. Periarticular massive calcifications, referred to as uremic tumoral calcinoses (UTC), represent solitary or multifocal calcium phosphate deposits. Our objectives were to clinically analyze a series of 8 patients with UTC undergoing hemodialysis, and to characterize calcium deposits in UTC.

Methods. The clinical, radiological, and pathological features of 8 consecutive patients (4 men and 4 women, mean age 49 yrs) with UTC were analyzed, and treatment and outcome were evaluated. Calcific specimens from the 8 patients were analyzed by x-ray diffraction, Raman spectroscopy, and infrared spectroscopy.

Results. Unifocal UTC was observed in 5 patients, whereas multifocal lesions occurred in 3 patients. The most common sites of UTC were the shoulders, elbows, and hands. Elevated serum calcium and phosphorus and intact parathyroid hormone were detected in 63% (n = 5), 100% (n = 8), and 63% (n = 5) of the patients, respectively. An increased calcium-phosphorus (Ca×P) product was observed in 6 patients. Medical intervention to decrease the Ca×P product achieved complete remission in 3 of 5 patients with solitary UTC, whereas this treatment was ineffective for multiple UTC. The 8 calcium deposits were identified as carbonate apatite.

Conclusion. The most important pathogenic factors in UTC are an increased Ca×P product and hyperphosphoremia, which is not necessarily related to hyperparathyroidism. Medical intervention is effective for solitary UTC, but combined treatment (surgery and medical therapy) is required for multiple UTC. Calcium deposits in UTC are composed of carbonate apatite. (J Rheumatol 2006; 33:119–26)

Key Indexing Terms:
UREMIC TUMORAL CALCINOSIS
CALCIUM PHOSPHATE
HEMODIALYSIS
CARBONATE APATITE

Uremic patients undergoing hemodialysis frequently exhibit visceral, vascular, or periarticular extraskeletal calcifications. Uremic tumoral calcinosis (UTC) resembles idiopathic tumoral calcinoses in its predilection for periarticular sites, tumoral development, and clinicopathological features. UTC composed of massive calcium-phosphate deposits is observed only rarely, even in dialysis patients, in whom the prevalence of UTC has been reported to range from 0.5% to 3%.

The etiology of UTC remains unclear. Elevated serum phosphorus3, a high calcium phosphorus (Ca×P) product3-5, and secondary hyperparathyroidism4,5 have been recognized to play a major role in pathogenesis, while other factors, such as aluminum intoxication4,6 or local tissue injury7, have been proposed to be involved in development of UTC.

Although various treatments have been used to reduce UTC, these have not always been successful. Surgical removal of isolated masses has been the preferred treatment; however, complete excision cannot be accomplished in cases involving extensive infiltration into soft tissues and adjacent structures, and consequently recurrence is almost inevitable. Therefore, other medical interventions, such as phosphorus deprivation, have been recognized as treatment strategies that may be preferable to surgical excision.

Calcific deposits in UTC have been variously identified as calcium phosphate8, hydroxyapatite (HAP)9, carbonate-substituted apatite9, or a mixture of carbonate apatite and calcium carbonate10. HAP is the most stable and least soluble among calcium-phosphate salts, whereas carbonate-substituted apatite is much more soluble. Reduction of tumoral masses by medical treatment usually follows resolution of calcium deposits. Identification of the properties of the calcific deposits may contribute to an understanding of the dissolution of lesions, because calcium-phosphate crystals reported previously possess various dissolution behaviors11.

Our objective was 2-fold: to clinicopathologically ana-
lyze a series of 8 patients with UTC undergoing hemodialysis, and to characterize the calcific deposits in these cases of UTC.

MATERIALS AND METHODS

Patients. We retrospectively reviewed the records of 8 dialysis patients with UTC who were treated in Dokkyo University Hospital between 1989 and 2000. Collagen vascular disease was not observed in any of these patients. We defined UTC as the presence of periarticular calcified masses of size > 2 cm, according to previous reports of UTC. The 8 patients (4 men and 4 women aged 21 to 62 yrs, mean age 49 yrs) were treated in our department and were followed for more than 4 years. The total dialysis population in our hospital during the period of the study comprised 423 patients.

Methods. Clinical characteristics such as age, sex, duration of dialysis, location and size of UTC, etiologic and histopathologic factors, radiographic findings, type of treatment, and outcome were analyzed in the 8 patients.

The pathogenesis of UTC was evaluated on the basis of serum calcium and phosphorus concentrations, Ca×P product, parathyroid hormone (PTH) level, and previous trauma or inflammation. Secondary hyperparathyroidism in dialysis was diagnosed according to the widely used criterion of an intact PTH concentration > 4 times the normal level (50–70 pg/ml). A Ca×P product > 70 was considered to be high.

Preparation of calcific samples. Calcific samples obtained from the 8 patients by biopsy or during surgery were washed with distilled water, dried at room temperature, and then analyzed by x-ray diffraction, Raman spectroscopy, and Fourier transform infrared spectroscopy (FTIR). Synthetic HAP served as a control, and was provided by Sumitomo Cement (Tokyo, Japan).

X-ray diffraction. The powder x-ray diffraction patterns of all samples were recorded with a diffractometer (Ru 200B, Rigakudenki, Akishima, Japan) using CuKa radiation generated at 30 KV and 30 mA from a graphite monochromator. The detector was scanned between 3° and 90°. A data processor (RAD-B, Rigakudenki) was used to record radiation counts. Specimen components were defined according to the database of the Joint Committee on Powder Diffraction Standards (JCPDS).11

Raman spectroscopy. Laser Raman spectra were collected from powdered samples with a spectrometer (Ramanor U-1000, Jobin Yvon, Longjumeau, France) using argon ion laser excitation at 5145 Å with an NEC GLG3300 exciter. Laser power determined at the samples ranged from 100 to 150 mW. The spectrum scan speed was 120 cm⁻¹/min and scans were repeated 30 times. Spectral ranges from 3800 to 120 cm⁻¹ were used.11

Infrared spectroscopy. We obtained FTIR spectra between 4000 and 480 cm⁻¹ using a spectrometer (FTS-60, Bio-Rad, Cambridge, MA, USA) in conjunction with a microscope (IR-Plan, Spectra Tech, Shelton, CT, USA). The collected specimens were placed on a KRC-5 plate and direct measurements were performed without the use of any dispersion material such as KBr. Spectra were obtained at 8 cm⁻¹ resolution and averaged 256 scans11.

RESULTS

Clinical presentation. Symptomatic UTC was identified in 1.9% of patients with chronic renal failure on hemodialysis in our hospital. The demographic characteristics of the 8 UTC patients are summarized in Table 1. The duration of hemodialysis ranged from 4 to 111 months (mean 63 mo), and 6 patients had been receiving dialysis for more than 4 years.

The main symptoms in the UTC patients were localized swelling (100%), pain (75%), pruritus (63%), ulceration (25%), fistula (13%), and infection (25%). The duration of symptoms ranged from 2 months to 7 years (mean 1.5 yrs). Unifocal UTC occurred in 5 patients, whereas multifocal lesions were observed in 3 patients. The predominant areas involved were the shoulders (25%), elbows (19%), hands (19%), hips (13%), and thighs (13%) (Table 2). The size of calcium deposits ranged from 4 to 25 cm (mean 10 cm).

Roentgenographic examinations showed extensive soft tissue calcification in the UTC patients (Figures 1 and 2). These massive calcific tumors were located in periarticular sites, and there were no bony abnormalities, except for subperiosteal resorption on the sacrum in one patient.

Laboratory findings. Laboratory findings are shown in Table 3. Fistula or ulceration with infection occurred in 3 patients with high C-reactive protein concentrations (> 5 mg/dl). The serum phosphorus level was elevated in all patients, hypercalcemia was present in 5 patients (63%), and a Ca×P product > 70 was observed in 6 patients (75%). The serum aluminum concentration was < 40 µg/l in all 8 patients. The intact PTH level was increased in 5 patients, but diagnosis of secondary hyperparathyroidism was only possible in one patient, according to the universal criterion for this condition.

Histological findings. Histological findings in 5 tissue specimens obtained from 5 patients showed multinucleated cystic and fibrogranulomatous proliferation with multifocal calcification in masses. The cyst walls were variably smooth and focally slightly papillary, and were lined by plump histiocytes and foreign body giant cells (Figure 3).

Treatment and outcome. Treatment and outcome are summarized in Table 2. Partial, subtotal, or complete surgical resection was performed in 4 patients, while 3 patients received medical treatment. One patient underwent only aspiration of calcific liquid once a week, due to his poor general condition. Only one patient who underwent surgery had recurrent calcific mass detectable by radiography 9 months postoperatively (Patient 2), whereas the other 3 patients who underwent surgery were apparently cured by additional medical treatment (Patients 3, 4, 6). No patient underwent parathyroidectomy. The medical treatment included calcium- or phosphorus-restricted diet, phosphorus deprivation, calcium carbonate or/and bisphosphonate administration, and hemodialysis with a low calcium dialysate, and these were effective in decreasing UTC in 5 patients.

Characterization of calcific deposits. Powder x-ray diffraction patterns of calcific samples from UTC patients are shown in Figure 4. All calcific samples revealed the same diffraction pattern in x-ray diffraction. The x-ray diffraction patterns appearing in the vicinity of 26.0°, 31.8°, and 33.0° of 29 were similar to those of HAP and carbonateapatite, while phases characteristic of calcium carbonate were not evident. The broader peaks displayed by the 8 samples indi-
Table 1. Demographic characteristics of patients with uremic tumoral calcinosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yrs</th>
<th>Nephropathy</th>
<th>Months on Dialysis</th>
<th>Dialysate Buffer</th>
<th>Parathyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52 M</td>
<td>Diabetic nephropathy</td>
<td>89</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>62 F</td>
<td>Unclassified</td>
<td>51</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>50 F</td>
<td>Diabetic nephropathy</td>
<td>66</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>49 F</td>
<td>Polycystic renal disease</td>
<td>92</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>51 M</td>
<td>Chronic glomerulonephritis</td>
<td>50</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>21 M</td>
<td>Chronic glomerulonephritis</td>
<td>44</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>41 M</td>
<td>Renal vascular disease</td>
<td>111</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>62 F</td>
<td>Diabetic nephropathy</td>
<td>4</td>
<td>Bicarbonate</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2. Clinical findings, treatment, and outcome of patients with uremic tumoral calcinosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thigh</td>
<td>Aspiration</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Shoulder</td>
<td>Complete resection</td>
<td>Recurrence</td>
</tr>
<tr>
<td>3</td>
<td>Shoulder</td>
<td>Subtotal resection, Ca, P restricted diet</td>
<td>Complete remission</td>
</tr>
<tr>
<td>4</td>
<td>Shoulder, hands, hip</td>
<td>Complete resection, P restricted diet</td>
<td>Complete remission</td>
</tr>
<tr>
<td>5</td>
<td>Elbow, sacrum, shoulder, hand, thigh</td>
<td>Complete resection, calcium carbonate and P restricted diet</td>
<td>No change</td>
</tr>
<tr>
<td>6</td>
<td>Elbow</td>
<td>Partial resection + bisphosphonate</td>
<td>Complete remission</td>
</tr>
<tr>
<td>7</td>
<td>Knee, hip, elbow</td>
<td>Bisphosphonate + low calcium dialysate</td>
<td>Partial remission</td>
</tr>
<tr>
<td>8</td>
<td>Wrist</td>
<td>Calcium carbonate</td>
<td>Complete remission</td>
</tr>
</tbody>
</table>

Figure 1. Radiograph of the elbow showing a calcified mass (Patient 6).

Figure 2. Radiograph of the wrist showing a calcified mass (Patient 2).
cate that UTC calcific samples possess a lower degree of crystallinity than synthetic HAP. Using x-ray diffraction alone, HAP and carbonate-substituted apatite could not be differentiated from each other.

Raman spectra of calcific samples and synthetic HAP are shown in Figure 5. All calcific samples showed the same Raman spectra in Raman spectroscopy. The spectra of all calcific samples were characterized by a strong band at 960 cm\(^{-1}\) derived from the synthetic stretching mode of the PO\(_4\) base. Other Raman-active modes were seen at 1074, 590, and 434 cm\(^{-1}\). The weak bands at 1447, 1580, and 1650 cm\(^{-1}\) were derived from protein. The band at 3570 cm\(^{-1}\) is attributable to the OH base, and was clearly observed in calcific samples. Carbonate in calcific samples is not bound to proteins, but replaces hydroxyl or phosphate ions in the apatite structure\(^{11}\). The average carbonate content, calculated from spectra recorded in the linear absorption mode, was 9.3% for the calcific samples.

DISCUSSION
Calcinoise, or pathologic calcification of soft tissues, occurs in a variety of systemic and localized conditions. Ectopic calcification is generally classified into 3 types: metastatic calcification related to conditions that result from persistent hypercalcemia or hyperphosphoremia; dystrophic calcification related to conditions that follow a local metabolic or degenerative tissue abnormality; and calcinosis resulting from the deposition of calcium in skin, subcutaneous tissue, and periarticular tissue\(^{12}\). The causes of generalized calcinosis include collagen vascular disorders, such as scleroderma and dermatomyositis, idiopathic tumoral calcinosis, and idiopathic calcinosis universalis\(^{13}\). UTC, which is often referred to as tumoral calcinosis, should be differentiated from idiopathic tumoral calcinosis without metabolic abnormalities\(^5\). Although metastatic calcification is common in renal osteodystrophy, UTC is rare, even in patients undergoing dialysis. The prevalence of this lesion was 1.9% in our hospital, within the frequency range of 0.5% to 3% reported in the literature\(^{1,2}\).

Many factors, such as hyperphosphoremia, an elevated Ca×P product, hyperparathyroidism, duration of dialysis, vitamin D, and aluminum intoxication, have been implicated in the pathogenesis of uremic extraosseous calcification\(^1\). As pathologic calcium-phosphate deposition occurs mainly in tissues exposed to highly supersaturated body fluids, the pathogenesis of UTC may be understood to be similar to an aqueous solution model in which precipitation of calcium-phosphate salts occurs under conditions of high calcium and

Table 3. Laboratory data of patients with uremic tumoral calcinosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>CRP, mg/dl</th>
<th>Protein, g/dl</th>
<th>Albumin, g/dl</th>
<th>Calcium, mg/dl</th>
<th>Phosphorus, mg/dl</th>
<th>Ca × P Product</th>
<th>Ca/P Ratio</th>
<th>Intact PTH, pg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.8</td>
<td>6.1</td>
<td>3.1</td>
<td>8.5</td>
<td>7.1</td>
<td>60</td>
<td>1.20</td>
<td>278</td>
</tr>
<tr>
<td>2</td>
<td>4.1</td>
<td>6.7</td>
<td>3.3</td>
<td>10.2</td>
<td>7.6</td>
<td>78</td>
<td>1.34</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>5.6</td>
<td>7.0</td>
<td>3.4</td>
<td>11.1</td>
<td>7.3</td>
<td>81</td>
<td>1.52</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>1.7</td>
<td>7.2</td>
<td>3.9</td>
<td>9.4</td>
<td>9.1</td>
<td>85</td>
<td>1.03</td>
<td>148</td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>7.0</td>
<td>2.9</td>
<td>9.1</td>
<td>6.2</td>
<td>56</td>
<td>1.47</td>
<td>210</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>7.8</td>
<td>4.8</td>
<td>9.4</td>
<td>9.4</td>
<td>88</td>
<td>1.00</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>6.7</td>
<td>3.5</td>
<td>9.2</td>
<td>7.7</td>
<td>71</td>
<td>1.19</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>0.4</td>
<td>6.1</td>
<td>3.3</td>
<td>10.5</td>
<td>8.3</td>
<td>87</td>
<td>1.27</td>
<td>288</td>
</tr>
</tbody>
</table>

Protein (normal 6.6–8.4 g/dl), albumin (normal 3.8–5.3 mg/dl), calcium (normal 8.4–9.2 mg/dl), phosphorus (normal 4.4–5.2 mg/dl), Ca × P product (normal < 50). CRP: C-reactive protein, PTH: parathyroid hormone (normal < 70 pg/dl).
phosphate concentrations. Interestingly, recent studies have reported hyperphosphoremia to be a strong risk factor for extraskeletal calcification\textsuperscript{14,15}, and an increased $\text{Ca} \times \text{P}$ product to levels above 60 to 75 is reported to be an increased risk for metastatic calcification\textsuperscript{14,16}. UTC cases not associated with secondary hyperparathyroidism have been described, and secondary hyperparathyroidism has recently been recognized not to be a major contributor to the pathogenesis of UTC\textsuperscript{2,17}. In our cases, abnormalities of hyperphosphoremia (100\%) and a high $\text{Ca} \times \text{P}$ product (75\%) were observed, but secondary hyperparathyroidism occurred in only one patient.

Local factors, such as trauma, bleeding, inflammation, or production of a calcifiable matrix, may also be involved in development of UTC, because UTC patients often present with periarticular massive calcification\textsuperscript{4}. It is speculated that the tendon, tenosynovium, or bursa can cause the soft tissue to primarily precipitate calcium-phosphate salts, and the calcific mass subsequently develops to UTC. No preceding trauma or inflammation was recorded in our cases; however, unconscious soft tissue injury may create the local conditions for UTC development.

Various treatment strategies for UTC have been proposed. We have previously used surgical removal of calcific masses, but our strategy has shifted to medical treatment. Although surgical excision for UTC has been performed successfully in cases like ours, medical intervention to mobilize calcium and phosphate from tumoral deposits is favored. The most important pathogenic factor involved in UTC is an increase in the $\text{Ca} \times \text{P}$ product, as described above, and therefore medical treatment for reduction of the serum phosphorus level represents a noninvasive and fundamental

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Figure 4. X-ray diffraction patterns of calcific samples from patients with uremic tumoral calcinosis.
approach to UTC therapy. Patients with hyperphosphoremia can be administered phosphate binders or be placed on dietetic phosphorus restriction. Studies suggest that daily hemodialysis with a low calcium dialysate or daily nocturnal home hemodialysis successfully decreases and resolves massive UTC, by creating superior phosphate clearance. Vinpocetine, sodium thiosulfate, and bisphosphonate have been used to directly mobilize calcium and phosphate from calcific masses, thus reducing their size. Despite the many reports of treatment for UTC, no controlled clinical trials have been performed to guide evidence-based therapy, because of the rare occurrence of the lesion.

Calcific deposits of UTC have been variously identified as calcium phosphate, HAP, carbonate-substituted apatite, or a mixture of carbonate apatite and calcium carbonate. We analyzed 8 calcific samples with x-ray diffraction, FTIR, and Raman spectroscopy. X-ray diffraction is an analytical method used to characterize and identify crystals.

Figure 5. Raman spectroscopy of calcific samples from patients with uremic tumoral calcinosis.
based on their diffraction patterns, and the x-ray diffraction patterns of calcific samples were similar to those of synthetic HAP or carbonate apatite, while phases characteristic of calcium carbonate were not evident (Figure 4). The OH band at 3570 cm⁻¹ observed in synthetic HAP was not present in the Raman spectrum of any calcific deposits (Figure 5), indicating that they did not consist of HAP. Moreover, the FTIR spectra of calcific deposits had CO₃ bands around 870, 1410, and 1450 cm⁻¹. These data confirm that the calcific deposits in UTC are composed of carbonate apatite.

It is well known that HAP is the most stable form of calcium phosphate, and that the presence of carbonate in the apatite lattice decreases the stability of the apatite structure, thus increasing dissolution in body fluid. The solubility of carbonate apatite containing 6% of lattice carbonate by weight is about 10¹⁰ times greater than that of HAP²³. This means that a HAP solution after 3.8 days is comparable to that of a carbonate apatite solution after 30 s, with respect to
the degree of supersaturation. Calcific samples in UTC containing 9.3% of lattice carbonate by weight are much more soluble. If the calcific deposits in UTC were composed of HAP, medical treatment would be ineffective for reduction of the mass. The complete resolution of calcific deposits achieved by various conservative treatments is therefore attributable to the soluble carbonate apatite in UTC.

REFERENCES