The Effect of Thyrocalcitonin Therapy and Phosphate Deprivation on Tumoral Calcinosis

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SUMMARY

Six siblings were screened for clinical and biochemical evidence of tumoral calcinosis. The 3 brothers showed all the characteristic manifestations of this entity. Two of them were treated for an initial period of 6 months with large doses of thyrocalcitonin, with virtually no response. After a 9-month equilibration period they were treated by phosphate depletion, and at the end of 6 months they were re-investigated. There was no appreciable objective or radiological difference in the extent of the masses. It was concluded that, in these 2 patients, surgical excision of the tumours was the only feasible form of therapy.

Tumoral calcinosis is a rare metabolic disorder. Duret, in 1899, first described this condition. In 1943 Inclan et al. named the condition 'tumoral calcinosis'. It is characterized clinically by lobulated, calcified cystic masses, usually situated adjacent to major joints. They usually start as small and discrete tumours which tend to enlarge. The condition has been reported most frequently in coloured races — the majority of cases seem to have occurred in Blacks from Africa and America. Relatively few cases from South Africa have been described, and no White patients with this entity have been documented.

Systemic corticosteroids, surgical excision and local irradiation have proved to be of very little value. The first encouraging result in controlling this disease was achieved by Mozaffarian et al. by phosphate deprivation in a patient over a long control period. They were able to demonstrate a biochemical, objective and subjective improvement in the patient.

We had the unique opportunity of studying 6 siblings, 3 of whom were grossly incapacitated by this disease. Before we embarked on a controlled therapeutic trial, one of us (L.P.S.) used thyrocalcitonin on a patient (case 2) for a period of 2 months, after which some improvement in the patient's general condition was observed. It was decided to embark on a full thyrocalcitonin therapeutic trial on 2 of the siblings. During a 9-month equilibration period after thyrocalcitonin therapy, no therapy was given. At the end of this period both patients, treated by phosphate deprivation, were restudied for 6 months.

CASE REPORTS

Case 1

This patient, a 25-year-old White man, was first known to have subcutaneous nodules at the age of 3 years. These masses increased in size over the ensuing years until, in 1965, the patient came to the attention of L.P.S. At this time the patient had already had several areas of tumoral calcinosis excised from his right elbow, right foot and left buttck. On numerous occasions over the following 10 years it was necessary for L.P.S. to remove some of the masses surgically. In many areas a pseudocapsule formed, which was easily excised. In other areas, however, the diseased tissue infiltrated directly between muscle fibres and between individual muscles, completely enveloping vessels and nerves. Excision of these masses was particularly hazardous.

During August 1975, the patient was admitted to hospital for assessment before a trial with thyrocalcitonin therapy was started. He appeared chronically ill and was clinically anaemic. He had large masses associated with both shoulders and the left hip. A sinus from his left shoulder was discharging a white chalky material. The haematocrit value was 38% and the white blood cell count was 7,500/µl. The differential count was within normal limits. The sedimentation rate (Westergren) was 80 mm/h.

Bone marrow aspirate showed no abnormal infiltration, and staining for iron was within normal limits. The serum electrolytes, creatinine clearance, fasting blood sugar level, thyroid function tests, aspartate transaminase, acid and alkaline phosphatase and serum calcium levels were all within normal limits. The serum phosphorus level, the tubular reabsorption of phosphorus (TRP) and the 24-hour urinary hydroxyproline level are depicted in Table I. The responses of TRP and phosphate clearance after a parathyroid hormone (PTH) injection were also estimated (Table II). A skeletal bone survey showed numerous, large, calcific cystic structures in the region of the masses.

TABLE I. COMPARATIVE BIOCHEMICAL DATA

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Serum phosphorus (mg/100 ml)</th>
<th>TRP (%)</th>
<th>Urinary hydroxyproline*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>5.8</td>
<td>98</td>
<td>48.7</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>M</td>
<td>6.4</td>
<td>97</td>
<td>68.0</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>M</td>
<td>7.2</td>
<td>96</td>
<td>40.2</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>F</td>
<td>4.3</td>
<td>89.4</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>F</td>
<td>3.6</td>
<td>90</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>F</td>
<td>3.4</td>
<td>89</td>
<td>14</td>
</tr>
</tbody>
</table>

* Normal value: 6 - 22 mg/24 h.
TRP = Tubular reabsorption of phosphate.
the major joints (Fig. 1). The material coming from the sinus was found to be a combination of calcium carbonate and calcium phosphate. Histological examination of one of the masses showed lakes of crystalline material bounded by giant cells. Numerous collagenous fibrous trabeculae traversed this lesion and some new bone formation was seen. A radioactive scan and Ca studies were also done. On completion of the biochemical studies, thyrocalcitonin therapy was commenced for 6 months. At the end of this period the patient was readmitted to hospital.

TABLE 11. RENAL RESPONSE TO BOVINE PARATHYROID HORMONE

<table>
<thead>
<tr>
<th></th>
<th>Phosphate clearance (ml/min)</th>
<th>TRP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Before PTH: 2,44</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>After PTH: 21,4</td>
<td>76</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Before PTH: 0,19</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>After PTH: 14,36</td>
<td>88,6</td>
</tr>
</tbody>
</table>

TRP = tubular reabsorption of phosphorus; PTH = parathyroid hormone.

When admitted the second time, the patient again appeared chronically ill and there seemed to have been a general increase in the size of the masses. A comprehensive biochemical, radiographic and radio-isotopic study was again carried out. All therapy was now discontinued for a period of 9 months before it was decided to embark on phosphate deprivation. After 6 months the patient voluntarily stopped medication as he was certain that the masses had further increased in size.

He was admitted to hospital for a third time for further study. The serum calcium and phosphorus levels, TRP, 24-hour hydroxyproline excretion and 24-hour urinary calcium and phosphorus values were again evaluated.

Case 2

This patient, the 23-year-old brother of patient 1, first presented in 1968 with a large tumour situated on his buttock, but with no other obvious lesions. The large tumour was excised. Subsequently, at intervals of approximately 1 year, further masses were excised from different parts of his body. L.P.S. observed the patient, who was put on thyrocalcitonin for a short period. The initial response of the masses to medication was very promising. In 1975, before embarking on a prolonged trial of thyrocalcitonin therapy, he agreed to a limited assessment as an outpatient. The urinalysis was within normal limits. Creatinine clearance, serum calcium, urea and electrolyte values, and full blood count were within normal limits. The serum phosphorus level, TRP, and 24-hour urinary hydroxyproline level were estimated (Table I). The response of phosphate clearance and TRP to PTH injections was also assessed (Table II). Radiographs showed peri-articular deposits of calcium (Fig. 2). There was also evidence of soft-tissue calcification and possible calcification involving the vas deferens. He was then started on thyrocalcitonin therapy, which was continued for 6 months. At the end of this period he was restudied.
During the second period of study, the patient assured us that there had been no subjective improvement in the size or consistency of the masses. Radiographic studies confirmed that there had been no improvement. Serum calcium and phosphorus levels, TRP and urinary hydroxyproline excretion were again estimated. After a period of 8 months without therapy it was decided to commence with phosphate deprivation. We initially contemplated an 18-month trial period. After only 6 months he discontinued therapy. We assessed only the serum calcium and phosphorus levels, TRP and hydroxyproline excretion. The patient thought that the masses had not decreased in size; if anything, the one involving his hip had increased. A radiographic survey showed no decrease in the size of any of the masses.

Case 3

This patient is the eldest of the 3 brothers. His lesion is the mildest, as he has required surgery on one occasion only. He looks well and, other than a small mass involving his left hip, he appears to have no other lesion. He would not permit us to have any radiographs taken and would only agree to a limited number of blood estimations. His urinalysis was within normal limits. The packed cell volume was 45%, and the white blood cell count and differential count were normal. Creatinine clearance, and urea and electrolyte values were all within normal limits. Serum calcium, serum phosphorus and hydroxyproline levels and TRP are shown in Table I. He would not participate in either the thyrocalcitonin or the phosphate deprivation studies.

Methods

All routine laboratory tests were done in an autoanalyzer. Calcium was estimated by the EDTA titration method, and inorganic phosphorus by the routine method. Hydroxyproline was estimated with a Hypronosticon kit, supplied by Organon (Pty) Ltd. Alkaline phosphatase and other enzymes were estimated with Boehringer Mannheim reagent. For bone scanning, "Tc monofluorophosphate injections were given intravenously. For radioactive calcium studies 10 μCi of "Ca in the form of calcium chloride were given intravenously. On the first day after the injection blood samples were taken at 10 minutes, 1 hour, and 5 hours. Subsequent blood samples were taken at daily intervals for 6 days. All stool and urine samples were collected over the same period of time. Renal responsiveness to PTH was measured after an initial 4-hour period of forced diuresis; blood and urine samples were taken for measurement of phosphate, creatinine and calcium clearance, and TRP. At the end of this period a dose of 250 units of bovine PTH was administered intravenously to patients 1 and 2. At the completion of a further 4-hour study period, blood and urine were again sampled for phosphate, calcium and creatinine clearance, and TRP was again estimated. The percentage TRP was estimated by the following standard formula:

\[ \% \text{TRP} = 1 - \frac{\text{clearance of phosphorus}}{\text{clearance of creatinine}} \times 100 \]

The potency of PTH was established with a multidose vial and by repeating the above estimations on a normal volunteer who was sex- and age-matched with the patients. For 10 days during the study period patient 1 was given a diet containing 800 mg calcium and 1500 mg phosphorus. As the 2 other siblings refused hospitalization, no balance studies could be done. After completion of the initial baseline studies, salmon thyrocalcitonin was given in a dose of 80 MRC units 3 times weekly. After 3 weeks' therapy this dose was increased to 100 units daily. Therapy was continued for a period of at least 6 months before patient 1 was hospitalized for a further complete reappraisal, which included biochemical, isotopic and radiographic assessment. Because patient 2 refused hospitalization, only limited re-evaluation was possible. During the 3rd period of study, patients 1 and 2 were given a low calcium diet (± 250 mg/d) and oral antacid therapy was started. The latter consisted of 60 ml of aluminium hydrogen oxide suspension (Maalox) and 30 ml of aluminium hydroxide suspension (Amphojel), both given 4 times daily. Both phosphate-binding agents were taken 1 hour after meals. We had hoped for an 18-month therapeutic trial period, but both patients discontinued therapy after 6 months.

Results

The 3 siblings all showed the same biochemical abnormalities, i.e. a significantly raised serum phosphorus level, a normal serum calcium level, a significantly increased urinary hydroxyproline level and a slightly raised TRP. None of the other siblings studied showed any of these abnormalities (Table I).

Radio-isotope studies. In patient 1 the bone scan revealed abnormal areas of increased activity, which involved both the right and left shoulders, left and right hips and pelvis. The radioactive calcium studies showed that over the period of 6 days after an injection of "Ca the patient retained over 95% of the dose. The accretion rate was extremely rapid and high, and the specific activity remaining in the blood samples between the 1st and 6th days was immeasurable. We thought that the rapid decrease in serum-specific activity indicated a movement of the isotope into the calcium masses as well as accretion to the skeleton. There was no change in these findings after either phosphate deprivation or thyrocalcitonin therapy. Patients 1 and 2 showed a normal renal response to PTH, i.e. there was a significant increase in the clearance of phosphorus and a decrease in the TRP. Neither patient 1 nor patient 2 showed objective or subjective improvement at the end of the study periods. There was also no significant biochemical or radiographic improvement.

DISCUSSION

Tumoral calcinosis remains an obscure and rare condition. It occurs in both sexes and at all ages, with a special predilection for the coloured races. It has a tendency to involve more than one sibling in a family, but there are no documented cases of more than one generation of a family being involved. This suggests a
recessive autosomal mode of inheritance, and sex linkage may be of considerable significance in this study, although it was not thought relevant in other studies.

In numerous cases hyperphosphataemia has been documented. Wilber and Slatopolsky suggested that this could be attributed to an inherited reduction in tubular response to the phosphaturic action of PTH. In addition, there must be local factors which predetermine where and in which tissue calcium is deposited. Only connective tissue seems to be affected. Peri-articular and subcutaneous tissue, fascia and only occasionally the fat lobules surrounding individual fat cells are involved by the process. There is no calcification in any organ, which is pathognomonic of this condition. The characteristic cells in the cellular lining of the cystic spaces in cases of tumoral calcinosis resemble those found in bone.

Calcium phosphate accumulation in this entity differs markedly from that in bone, in that calcification does not take place in a collagen-osteoid framework. There is often an increased alkaline phosphatase activity in the lining of the cystic walls, and this, in conjunction with the relatively high pH concentration, might account for additional calcium phosphate accretion and retention by the masses.

Our findings in these 3 siblings were very similar to those of Lafferty et al., i.e. a raised serum phosphorus level and a raised urinary excretion of hydroxyproline; results of other biochemical tests, such as serum electrolyte, uric acid, urea and alkaline phosphatase estimations, were within normal limits. In 1 case we also demonstrated, with radioactive isotopes, a very rapid accretion rate and an extremely high level of activity over the masses. This is in agreement with findings in a previous publication. Over an 8-day period the calcified masses retained 82% of 99mTc, which is similar to the findings of Whiting et al.

Our finding of hyperphosphataemia in 3 siblings is also similar to that of Baldursson and co-workers. The above findings once again suggest that tumoral calcinosis is an inborn error of phosphorus metabolism. To account for the slight predilection for joints, bursae or bone prominences, chronic trauma could be significant. Maathuis and Koten suggest that there is a marked similarity between the entity known as Kikuyu bursa and tumoral calcinosis. In their series of cases they found that Kikuyu bursa developed only in pressure areas in certain Kikuyu tribesmen.

As the aetiology of tumoral calcinosis is obscure, it was decided initially to treat 2 of the siblings for a 6-month period with large doses of thyrocalcitonin. This was based on the assumption that the thyrocalcitonin would have a phosphaturic action on the kidney, or even influence the high urinary hydroxyproline values. The results in both siblings were particularly disappointing, as there was both a subjective and an objective increase in the size of the masses. It is, therefore, unlikely that a thyrocalcitonin deficiency is present, as suggested by Wilber and Slatopolsky. We are unable to explain the disappointing results after phosphate deprivation. Mozaffarian et al. had treated their patient for 18 months before their excellent result was achieved. We suggest, therefore, that if we had been able to persuade our patients to continue with the therapy for at least another year we might have achieved similar results.

Hug and Guncaga described a patient treated with diphosphonate (EHDP). They do not mention how long the patient was treated, but they do specify that there was no appreciable decrease in the size of the tumours. Therefore they re-instituted surgery. We have no personal experience in the use of EHDP, as it was not available when the trial was in progress. Therefore we relied on surgical excision or drainage to relieve symptoms when they became too severe, or if the tumours became secondarily infected.

REFERENCES