Case Report: Clinical Pathological Correlations in a Case of Primary Parathyroid Carcinoma

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ABSTRACT

Carcinoma of the parathyroid accounts for one to two percent of patients with primary hyperparathyroidism. A patient admitted to our medical center gave us the opportunity to follow the course of the clinical laboratory findings and the effect of treatment modalities on these laboratory measurements. The clinical course included hypercalcemia, hypophosphatemia, pancreatitis, consumptive coagulopathy, pancytopenia, and sepsis. As vitamin D3 plays an important role in calcium homeostasis, 1,25-(OH)2-vitamin D3 was measured at several points during the clinical course. These findings may serve to help understand some of the underlying control mechanisms involved in the hypercalcemic state.

Introduction

Carcinoma of the parathyroid was originally described in 1938.1 Since then, there have been approximately 100 case reports in the English literature (for a more detailed review, see references 9 and 13). There is an equal male/female incidence, with the average onset late in the fourth decade. The highest reported serum calcium concentration to date has been 24 mg per dl, with an average concentration of 15.5 mg per dl. The five-year mortality rate is 50 percent, increasing to 90 percent by ten years. Death is almost always secondary to the complications of hypercalcemia. Radiotherapy is ineffective5,12 and, up to now, chemotherapeutic agents have had very limited success.6,11 The present authors recently studied a patient admitted to Loyola University Medical Center with an admitting diagnosis of primary parathyroid carcinoma. This afforded the opportunity to determine the effect of several treatment modalities on the characteristic biochemical changes in primary hyperparathyroidism. At the same time, determinations of serum immunoreactive...
parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D$_3$ [1,25-(OH)$_2$D$_3$] were made to assess the role of PTH, hypophosphatemia and hypercalcemia on 1,25-(OH)$_2$D$_3$ production rates.

Report of a Case

The patient was a 33 year-old white female who was in good general health until August, 1981 when she developed polyuria, fatigue, and a right-sided neck mass. Hypercalcemia, hypophosphatemia, and elevated PTH levels supported the diagnosis of primary hyperparathyroidism. A right-parathyroidectomy was performed and a histologic diagnosis of adenoma was made. Her post-operative serum calcium ranged from 9 to 10 mg per dl.

In February, 1982 she was referred to Massachusetts General Hospital where a right-neck exploration revealed multiple sites of parathyroid carcinoma. The tumor was debulked, but her post-operative calcium level remained above 12 mg per dl.

In April, 1982 she was admitted to Massachusetts General Hospital for treatment of hypercalcemia with calcitonin (to which she proved allergic), hydration, oral neutral phosphate, and mithramycin. Selective neck vein catheterization localized PTH-producing tumor in the right-neck and so a right-radical resection was performed in June, 1982. Her calcium level on discharge remained elevated at 12 mg per dl.

In August, 1982 she again developed fatigue, malaise, and a serum calcium of 25.1 mg per dl. She was started on palliative therapy and was transferred to Loyola University Medical Center.

Methods

Total calcium in serum and urine were measured by atomic absorption spectroscopy using a spectrophotometer.* Serum phosphorus and amylase determinations were performed.† Calcitonin was measured by radioimmunoassay using a kit.‡ Serum ionized calcium was measured by microelectrode.§ Serum electrolytes were measured.§ Blood gas analysis was performed,¶ and platelet counts were done.** Prothrombin time (PT) was

* Perkin Elmer Model 4000, Perkin Elmer Corporation, Norwalk, CT.
† ACAIII Clinical Analyzer, DuPont Company, Wilmington, DE.
‡ Immuno Nuclear Corporation, Stillwater, MN.
§ Orion Biomedical Space Stat 20, Cambridge, MA.
¶ Astra 4, Beckman Instruments, Inc., Fullerton, CA.
** Coulter Model S-plus II, Coulter Electronics, Inc., Hialeah, FL.
Figure 1. Levels of intact PTH. Surgical debulking of the tumor is indicated by "S". Chemotherapy regimens are indicated by "C". Measurement of serum PTH concentration is as described in the Methods section.

Results and Discussion

This patient afforded us the opportunity to examine some of the clinical laboratory findings during the course of a rarely observed tumor and how these findings were affected by the various treatment modalities.

In figure 1 are illustrated the changes in concentration of intact PTH as a result of surgery (indicated by "S") or chemotherapy (indicated by "C"). The patient presented to Loyola University Medical Center with a serum PTH level of approximately 5000 pg eq per ml (normal: 163 to 347 pg eq per ml). Surgical removal of tumor mass brought the concentration down to near the normal range. The PTH level was already rising, from 340 to over 1000 pg per ml, when chemotherapy was introduced. At this point, her PTH levels were expected to inexorably rise if chemotherapy was without effect. The introduction of chemotherapy, in fact, resulted in a reduction to nearly 500 pg per ml and values were maintained below 1000 pg per ml until complications (i.e., sepsis) prevented any further chemotherapeutic intervention. Subsequently, serum intact PTH levels rose rapidly.

In figure 2 is shown the efficacy of repeated i.v. administration of mithramycin on serum calcium concentration (normal calcium: 9 to 11 mg per dl). Mithramycin, probably acting via a direct cytolytic effect on osteoclasts, resulted in a temporary drop in serum calcium levels.

In the kidney, PTH causes a decrease in phosphate and bicarbonate reabsorption. There is an increase in chloride reabsorption as a result of bicarbonate losses. This expected effect of PTH on serum bicarbonate and chloride is illustrated in table I. Examination of repre-
TABLE I

Representative Serum Electrolyte and Arterial Blood Gas Determinations

<table>
<thead>
<tr>
<th>Electrolyte Levels</th>
<th>Blood Gas Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>135</td>
<td>4.2</td>
</tr>
<tr>
<td>135</td>
<td>4.1</td>
</tr>
<tr>
<td>134</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Normal ranges: Na = 134-147 mmol/L; K = 3.5-5.3 mmol/L; Cl = 95-105 mmol/L; CO₂ = 23-30 mmol/L; pH = 7.35-7.45; pCO₂ = 32-46 mm Hg; PO₂ = 74-108 mm Hg; HCO₃⁻ = 21-29 mmol/L.

Electrolyte levels are from three separate specimens; blood gas measurements are from three other specimens.

sentative electrolyte levels (panel A) reveals a lowered serum bicarbonate and the compensatory hyperchloremia. Blood gas analyses (panel B) also show a decreased bicarbonate with a compensatory respiratory alkalosis in order to maintain neutral blood pH.

On September 16, phosphate was added to the patient's intravenous fluids. On September 21, she complained of abdominal pain. In table II is documented an episode of acute pancreatitis with an initial amylase of 872 IU per L. In addition, changes in the platelet count, prothrombin time, partial thromboplastin time, and fibrin split products are consistent with the acute onset of a consumptive coagulopathy.

The pancreatitis resolved in approximately two weeks, despite the reduction in hypercalcaemia by surgery on September 24. The consumptive coagulopathy also appeared to resolve at the same time, but it could have persisted on a level undetectable except by measuring fibrin split products (which was not done).

In figure 3 is illustrated the relationship between serum levels of calcium, phosphorus, and 1,25-(OH)₂D₃ at representative points during the hospital course.

Column A data is from September 22, before the patient underwent surgical debulking of the tumor. The serum calcium was markedly elevated at 18.4 mg per dl, phosphorus was reduced to 2.0 mg per dl (normal: 3 to 4.5 mg per dl), and the 1,25-(OH)₂D₃ was 23 pg per ml (normal: 18 to 45 pg per ml). The intact PTH level was elevated (figure 1). A decreased concentration of serum phosphorus and an increased level of PTH, both well-known signals for increased production of 1,25-(OH)₂D₃, did not increase 1,25-(OH)₂D₃ under these conditions. A possible explanation for this phenomenon may be found in the result of studies carried out in several laboratories showing an inverse correlation between concentrations of ionized calcium and levels of 1,25-(OH)₂D₃ in rats. The ionized calcium at this point was markedly elevated at 3.1 mmol per L (normal: 1.1 to 1.3 mmol per L). This increased level of ionized calcium may have prevented the anticipated rise in 1,25-(OH)₂D₃ independent of PTH.

Column B data is from September 28, during the postoperative period. Serum calcium and intact PTH (figure 1) were nearly normal. Serum phosphorus was still decreased, and 1,25-(OH)₂D₃ was

TABLE II

Documentation of Pancreatitis and Consumptive Coagulopathy

<table>
<thead>
<tr>
<th>Date</th>
<th>Platelet Count (Norm: 150-400K)</th>
<th>PT (Norm: 9-10.6 Sec)</th>
<th>PTT (Norm: 25-36 Sec)</th>
<th>Amylase (Norm: 10-85 IU/L)</th>
<th>FSP (&lt;10 µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-21</td>
<td>70</td>
<td>12.6</td>
<td>28.3</td>
<td>872</td>
<td>40</td>
</tr>
<tr>
<td>9-22</td>
<td>27</td>
<td>14.2</td>
<td>645</td>
<td></td>
<td>&gt;10</td>
</tr>
<tr>
<td>9-23</td>
<td>41</td>
<td>12.6</td>
<td>202</td>
<td>&gt;10&lt;40</td>
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</tr>
<tr>
<td>9-24</td>
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<td>187</td>
<td></td>
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</tr>
<tr>
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<td>157</td>
<td>&gt;10&lt;40</td>
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<td>9-26</td>
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<td>40</td>
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<tr>
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<td>12.7</td>
<td>109</td>
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<tr>
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<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-6</td>
<td>10-12</td>
<td>26.3</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PT = prothrombin time
PTT = partial thromboplastin time
FSP = fibrin split products
slightly elevated at 60 pg per ml, perhaps owing to the effect of phosphorus and PTH.

Values obtained prior to the start of chemotherapy (October 5) are shown in column C. The expected rise in 1,25-(OH)₂D₃ owing to elevated PTH (figure 1) may have been overridden again by the continued hypercalcemia and to some extent by the rise in the level of serum phosphorus.

Column D data (from October 10) was obtained two days after the completion of a five day regimen of DTIC therapy and four days after the administration of mithramycin. The concentration of 1,25-(OH)₂D₃ was markedly reduced to 6 pg per ml. This could be an acute effect of DTIC on the production of the vitamin D metabolite, since one would have expected at least a normal level (if not an elevated one, owing to the increased concentration of PTH). Experiments are being carried out to investigate this possibility.

Results from November 16 (column E) were obtained five days after mithramycin treatment and 30 days after the completion of DTIC therapy. Elevated intact PTH (figure 1) and hypophosphatemia persisted. Here, there was a marked increase in the level of 1,25-(OH)₂D₃ to 76 pg per ml. Serum calcium was normal at this time.

The serum calcitonin concentration was increased during the course of her hospitalization, ranging from 100 to 150 pg per ml (normal: less than 60 pg per ml, data not shown). Since the physiological function of calcitonin in the human is not known with certainty, it is not possible to ascribe a significance to these calcitonin results.

**Conclusion**

Hyperparathyroidism owing to parathyroid carcinoma is a relatively rare condition that may cause sustained life-threatening hypercalcemia. Although the fraction of total serum calcium that was not protein-bound remained fairly normal, the severe degree of hypercalcemia resulted in a marked increase in serum ionized calcium. Because the tumor could not be completely removed (as it was adherent to the right common carotid artery), medical therapy was required. This included oral and intravenous phosphate, mithramycin, and finally, chemotherapy. Hemodialysis was used intermittently with limited success.

Review of the original surgical pathology section showed that the “adenoma” capsule had been amputated at the time of the initial surgery leading, unfortunately, to the subsequent chain of events. Parathyroid carcinoma is a sur-
gically curable disease if, at the first surgery, the surgeon is sufficiently alerted to that possibility and carefully removes the "adenoma" en bloc. A prevailing serum calcium level above 13 mg per dl should alert the physician to the real possibility of parathyroid carcinoma.

At least part of the hypercalcemia in primary hyperparathyroidism is due to increased renal production of 1,25-(OH)_{2}D_{3} in response to increased PTH and hypophosphatemia. However, severe hypercalcemia, as in rats, suppressed circulating levels of 1,25-(OH)_{2}D_{3} despite high PTH and low phosphorus (figure 3). This suggests the usual control mechanisms for 1,25-(OH)_{2}D_{3} production may be altered by extreme hypercalcemia.

References