# Concurrence of Hypernephroma and Hypercalcemia

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HYPERCALCEMIA is associated with a wide variety of diseases that have no direct relationship to calcium metabolism. Furthermore, malignant neoplasms of the lung, breast, or prostate may produce hypercalcemia in the absence of bony metastasis, by a mechanism not yet understood.

In 1948 Albright and Reifenstein [1] reported the first case of hypernephroma associated with hypercalcemia; hypophosphaturia, hypercalciuria, and normal serum alkaline phosphatase were noted in the presence of a single pelvic metastatic lesion. Transient reversal of laboratory abnormalities occurred after irradiation of the metastasis. In 1956, Plimpton and Gellhorn [4] added four additional cases. They also described a behavior pattern, similar to toxic psychosis, that reversed as calcium levels decreased. At the time of this writing, a total of nine cases have been reported.[2, 3]

It was our impression that this syndrome is more common than previously recognized. We reviewed our recent experience with hypercalcemia associated with hypernephroma to determine the incidence of this relationship and to examine the clinical circumstances accompanying it.

## Materials and Methods

The records of 400 consecutive patients with hypernephroma, operated upon at the Mayo Clinic during the years 1961 through 1968, were studied. Fifteen (4%) of these patients were found to have hypercalcemia (10.2 to 15.0 mg./100 ml.) preoperatively (Table 1). Because preoperative serum calcium determinations were made on only 118 of the 400 patients, the 15 patients with hypercalcemia represent an incidence of 13%.

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## Observations

The average age of the patients with hypercalcemia was 60 years (range, 45 to 73 years); there were eight men and seven women. Only one patient had had a seizure possibly related to hypercalcemia. The majority of the others had nonspecific and nonurologic symptoms such as anorexia, fatigue, nausea, and vomiting. The duration of symptoms ranged from 2 months to 2 years prior to diagnosis of the hypernephroma. Six patients reported significant weight loss.

Two asymptomatic patients were identified as the result of investigations for hypertension and renal calculi, respectively. Four patients had palpable renal masses.

Grade 1 microhematuria occurred in seven patients and grade 2 in three. No patient had gross hematuria. Thirteen patients were anemic; none were polycythemic.

Erythrocyte sedimentation rate was normal in three patients, slightly increased in one, and greatly increased in 11. Serum phosphorus values ranged from 2.2 to 3.9 mg./100 ml. (normal, 2.5 to 4.5 mg./100 ml.).

TABLE 1. *Serum Calcium Levels*

| Patient | Serum Calcium (mg./100 ml.)* | |
|---|---|---|
| | Preoperative | Postoperative |
| 1 | 12.4 | 8.6 |
| 2 | 14.6 | 8.9 |
| 3 | 10.2 | 9.0 |
| 4 | 10.5 | 9.0 |
| 5 | 10.9 | 9.0 |
| 6 | 10.6 | 9.7 |
| 7 | 10.5 | 9.9 |
| 8 | 11.0 | 11.0 |
| 9 | 10.8 | 11.1 |
| 10 | 10.9 | 11.4 |
| 11 | 12.9 | 12.5 |
| 12 | 10.5 | 15.5 |
| 13 | 12.8 | 15.9 |
| 14 | 13.2 | 9.4† |
| 15 | 13.6 | 9.3‡ |

* Hypercalcemia is defined as Ca > 10.1 mg./100 ml.
† Subsequently, 11.4 mg./100 ml.
‡ Subsequently, 11.6 mg./100 ml.

Six of the eight patients tested had the hepatic dysfunction syndrome,[6] including three patients with hepatomegaly and one with splenomegaly without evidence of metastasis.

Roentgenographic examination showed a nonfunctioning kidney in one patient and a mass in 14. In eight of the latter patients, roentgenologic criteria of hypernephroma were clearly present.

Urine calcium levels were increased (> 150 mg./24 hr.) in the four patients in whom calcium was measured.

On histopathologic examination, five tumors were grade 2, five were grade 3, and four were grade 4 (Broders).

The capsule was broached in 10 kidneys, and local spread with renal vein involvement was found in seven. Four patients had nonosseous metastasis at the time of operation. In two patients with small rib metastases demonstrated preoperatively, alkaline phosphatase levels were normal.

Postoperatively, serum calcium levels returned to normal in nine patients and remained increased in six. In two patients whose serum calcium values returned to normal, hypercalcemia again developed later; both of these patients are dead. Urine calcium levels returned to normal in the one patient studied.

Follow-up information is available for 14 patients. Only three are alive. They are patients in whom the serum calcium values returned to and remained within normal limits since operation. None of these patients has evidence of metastatic disease. They have been followed 2, 2, and 1 year, respectively.

## Comment

The association of renal cell adenocarcinoma and hypercalcemia is more common in our experience than previously recognized. Although we found an overall incidence of 4% in our series, the actual incidence among those patients studied preoperatively is 13%.

The discovery of hypercalcemia in a patient without urinary calculus disease or other manifestations of hyperparathyroidism should create concern about the presence of a malignant tumor, and search for renal carcinoma should be undertaken, along with other investigations.

We were unable to find any clinical or other laboratory differences between patients with hypercalcemia and the remainder of the group with hypernephroma. Most had nonspecific symptoms and no urologic findings of hypernephroma, which has been the recent trend noted with this neoplasm.

Serum calcium levels frequently reached high levels, but only one patient had symptoms that possibly could be related to hypercalcemia. Once the tumor was removed, serum calcium levels usually returned to normal in a few days.

Serial postoperative serum calcium determinations may prove to be of diagnostic value since return to normal probably indicates complete removal of the tumor and subsequent reversal to increased levels suggests recurrence of tumor.

The etiology of hypercalcemia in the presence of renal adenocarcinoma is obscure. Some extracts of tumor tissue have been found to contain a substance immunochemically similar to parathyroid hormone.[5] The presence of such a hormone would explain the clinical finding that reversal of hypercalcemia is related to removal of tumor tissue as well as the correlation of increased calcium levels with presence of tumor tissue. Indirect evidence for the existence of a parathyroid-like hormone in patients with hypernephroma can be obtained from consideration of two other syndromes associated with this tumor. Polycythemia is a well-recognized finding in approximately 4% of patients with hypernephroma,[7] seemingly based on elaboration of erythropoietin by the tumor. The relationship of hypernephroma and the hepatic dysfunction syndrome[6] with alteration in liver function also may be based on a hormonal mechanism. In both instances, removal of the tumor corrects the abnormality, and recurrence of the abnormality signifies further hormone-producing tumor.

## Summary

To determine the incidence and clinical usefulness of the association of hypercalcemia with hypernephroma, records of 400 consecutive patients who were operated upon for hypernephroma were studied. Fifteen of these patients (4%) were found to have hypercalcemia preoperatively. Although no other differentiating factors were found in these patients, serial determinations of serum calcium levels may be of prognostic value in assessing the completeness of tumor removal (calcium levels return to normal) and possible recurrence (calcium levels again increase).

## References

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