NOTE

A Malignant Pheochromocytoma with Ileus, Polyuria and Hypercalcemia: A Case of Recurrence 17 Years after the Initial Operation

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Abstract

A case of malignant pheochromocytoma, with a recurrence 17 years after the initial diagnosis of benign pheochromocytoma, was presented. The autopsy revealed multiple metastases of pheochromocytoma to the bone marrow of the thoracic and lumbar vertebrae. Of particular note is the fact that the patient was associated with paralytic ileus, polyuria and hypercalcemia and that he died of hypercalcemia crisis. Cases like this appear to be very rare.

Malignant pheochromocytoma is a rare disease and the prognosis of the disease is usually poor (Palmieri *et al.*, 1961). Decreased motility of the gastrointestinal tract and resultant constipation are uncommon symptoms of pheochromocytoma (Gifford *et al.*, 1965). Moreover, paralytic ileus is a rare complication of the disease (Cruz and Colwell, 1972). Though hypercalcemia may uncommonly be seen in the disease (Miller *et al.*, 1975), pheochromocytoma associated with hypercalcemic crisis has not been reported yet, as far as we know. This paper presents a case of malignant pheochromocytoma who was found to have multiple metastases of the tumor 17 years after the initial diagnosis of benign pheochromocytoma and expired after developing paralytic ileus, polyuria and prominent hypercalcemia.

Case Report

A 41-year-old Japanese man was admitted to Hirosaki University Hospital with pain in the left chest and right hip in 1982.

At the age of 15 years, he visited a clinic with palpitation and headache, and high blood pressure was pointed out. In 1965, at the age of 23 years, his blood pressure was 195/130 mmHg and urinary excretion of catecholamines was excessive (norepinephrine 1,047 $\mu\text{g/day}$ and epinephrine 124 $\mu\text{g/day}$). Under a diagnosis of pheochromocytoma, abdominal surgery was done and a tumor, which abutted on the right adrenal gland and weighed 43 g, was excised. The histological examination revealed that the tumor was pheochromocytoma. Since no metastasis of the tumor was found, it was diagnosed as benign pheochromocytoma. During the 5 years

following the operation his blood pressure remained normal. However, he did not come to hospital thereafter, and neither his blood pressure nor urinary excretion of catecholamine was measured till 1982.

He was first admitted to the department of orthopedics of our hospital on September 7, 1982. Bone scintigrams revealed concentrations of ^{99m}Tc and ^{201}Tl at the sites of the right 5th rib, the left 7th rib and the right ischium. The plasma norepinephrine concentration was 12.0 ng/ml and epinephrine was 0.04 ng/ml. Urinary excretion

of norepinephrine was more than 2,000 μg /day and epinephrine was 8.3 μg /day. Under a diagnosis of metastatic pheochromocytoma, excision operation of the ribs and the ischium was done on October 18. Histological examination revealed that the tumors were pheochromocytoma.

When he was transferred to our ward on February 17, 1983, the blood pressure averaged 200/130 mmHg in the supine position. The heart rate was 120 beats per minute. A grade 2/6 systolic murmur was heard in the third left intercostal space, but

Fig. 1. Angiogram of inferior adrenal artery showing the hypervascular mass.

the heart size and rhythm were normal. He was 167 cm tall, weighed 62 kg, was pale and restless and showed excessive sweating. The plasma norepinephrine concentration was 14.9 ng/ml and epinephrine 0.04 ng/ml. Basal supine plasma renin activity (PRA) was elevated to 6.8 ng/ml/h. Findings from the other hormonal studies, ie, T_3 , T_4 , somatostatin, methionine- and leucine-enkepharin were all within the normal range except for the elevated level of plasma gastrin (240 pg/ml).

Computed tomography revealed a mass posterior to the inferior vena cava at the level of the upper pole of the right kidney. The mass was hypervascular as seen in Fig. 1. Blood was sampled serially from the vena cava in the locations shown in Fig. 2. A markedly high level of norepinephrine concentration was demonstrated in the superior vena cava just above the level of the right atrium and in the inferior vena cava just below the level of the renal veins. An adrenal scintigram revealed a normal concentration of ^{75}Se at the site of the left adrenal gland. However, the concentration was reduced or almost eliminated at the site of the right adrenal gland.

He was treated with 5 mg of prazosin hydrochloride and 60 mg of propranolol hydrochloride. The systolic blood pressure was mostly held under 180 mmHg, but the pulse rate remained rapid at over 100 per minute. Oral administration of nifedipine (10 mg) was effective when the blood pressure spontaneously rose to over 250 mmHg.

Loss of appetite, nausea, hypoactive bowel sounds and progressive abdominal distension developed shortly after he had been transferred. Severe constipation persisted and paralytic ileus was then diagnosed on March 4, 1983, and was relieved by 1 to 2 liters of warm water enema with soap every day. A contrast medium, which had been given for the stomach examination on February 21, was still observed in the cecum area in the plain roentgenogram of the

abdomen on March 14. Besides the severe constipation, an increase in the volume of urine was observed. His daily urine output was 2 to 3 liters during the first few weeks in our ward, but increased gradually until it exceeded 5 liters per day by March 2. Blood urea nitrogen and serum creatinine were normal. The mean specific gravity of the urine was 1,012 in February and 1,008 in March and the plasma antidiuretic hormone (ADH) level was within the normal range (3.2 pg/ml).

Serum calcium, which had continued to increase since his transfer, was elevated to 14.0 mg/dl by March 12. Serum inorganic phosphate was 2.9 mg/dl. The serum calcitonin level was 120 pg/ml (normal range: below 300 pg/ml) and PTH was 0.2 ng/ml (normal range: below 0.5 ng/ml). Ionized calcium was 3.27 mEq/L (normal range: 2.10 to 2.35 mEq/L). Urinary excretion of calcium was 800 to 1,170 mg/day. Urinary excretions of prostaglandin E_1 and E_2 were both within the normal range. Drip

Fig. 2. Norepinephrine concentrations of blood sampled serially from the vena cava.

infusion of saline, intramuscular injection of calcitonin and oral administration of predonin every day were started on March 14 to lower the high calcium level. Serum calcium was then lowered to 12.0 mg/dl on April 6 and 11.2 mg/dl on May 4. However, serum calcium again increased gradually thereafter in spite of the same treatment for hypercalcemia. And it was elevated to 16.6 mg/dl on May 31. Shivering, vomiting, drowsiness, paralysis of extremities, cyanosis and arrhythmia developed. Drip infusion of mithramycin (1.25 mg) lowered the serum calcium level to 11.0 mg/dl on June 2. However, his general condition remained unchanged and he died suddenly in the morning of June 3.

Pathology

At autopsy a light brown thumb's head-sized tumor with focal hemorrhage and necrosis was found in the location between the inferior vena cava and the upper pole of the right kidney. The tumor had 2 modules; one was a little finger's head-sized and the other was cherry-sized. The latter nodule projected into the lumen of the vena cava (Fig. 3). The histologic pattern was typical of pheochromocytoma (Fig. 4). Remnants of the adrenal gland was not seen. An analysis for catecholamine revealed 558,000 μg of norepinephrine per gram of the tumor tissue. However, epinephrine was below the detectable level. Norepinephrine and epinephrine levels in the left adrenal gland were 34,500 μg and 110,000 μg per gram of the tissue. The bone marrow of the thoracic and lumber vertebrae was replaced by brown tumors (Fig. 5), which

Fig. 3. Pheochromocytoma projected into the lumen of the vena cava.

Fig. 4. Microphotograph of malignant pheochromocytoma arising from the area of the right adrenal gland, showing large polygonal cells. (H & E $\times 100$)

Fig. 5. The bone marrow of the lumbar vertebrae was replaced by metastatic pheochromocytoma.

tissue contained 107,000 μg per gram of norepinephrine. The thyroid gland and 3 parathyroid glands found were normal. The colon was filled with a large amount of impacted stool and distended with a thinned-out wall. It was accompanied with congestion, focal bleeding and necrosis. The nerve plexuses of Auerbach in the colon wall were normal. No occlusion was found in the superior and inferior mesenteric arteries. The histological examination of the kidneys revealed slight hyalinization of glomerulus and prominent metastatic calcification in the epithelial cells of proximal tubules, loops of Henle and distal tubules.

Comments

The present case of malignant pheochromocytoma is unique because of his long survival and of extremely rare complications.

The prognosis of malignant pheochromocytoma is usually poor (Palmieri *et al.*, 1961; James *et al.*, 1972). The 5-year survival rate subsequent to treatment was 96 % for benign tumors and 44 % for malignant tumors (Remine *et al.*, 1974). The mean interval between the primary tumor and the recurrence was from 5.6 (Remine *et al.*, 1974) to 8 years (Mahoney and Harrison, 1977). Meanwhile, some cases with a long survival were also reported (Scharf *et al.*, 1973; Mahoney and Harrison, 1977). Remine *et al.* (1974) recorded 4 patients who were alive with the disease at 5, 20, 20 and 21 years. In Japan 69 cases of malignant pheochromocytoma had been reported by the end of December in 1983 (Miura and Ishizuka, 1984). And as far as we know, the case reported here survived longer than any other recorded in Japan. One cannot be certain whether a tumor is benign or malignant even after removal of the tumor (Priestley *et al.*, 1963), unless a metastasis is found. In that sense, Mahoney and Harrison (1977) recommended all patients with

pheochromocytoma to have a detailed follow-up for 15 years. In our patient the recurrence developed 16 years after the initial operation. Therefore, we recommend that close follow-ups of the patients should be done every 6 months for more than 15 years. We think that the follow-up study should at least include measurements of blood pressure, pulse rate and urinary excretion of catecholamines.

The multiple bone metastases are most likely a cause of the hypercalcemia in our patient. The metastases in the vertebral column may explain the dispersed peaks of norepinephrine levels obtained at the time of the vena caval blood sampling. Hypercalcemia associated with pheochromocytoma is mostly attributable to concomitant primary hyperparathyroidism (MEN type 2) (Miller *et al.*, 1975). However, in our patient the serum calcitonin level was not elevated and the pathological examination revealed neither medullary thyroid carcinoma nor parathyroid hyperplasia. Moreover, a normal level of PTH also can rule out the possibility that an increased level of catecholamine might have stimulated PTH release from the parathyroid gland (Swinton *et al.*, 1972; Kukuraja *et al.*, 1973). Still there is the question whether the bone metastases were the only cause of the hypercalcemia and hypercalcemic crises. In previous reports malignant pheochromocytoma with bone metastases did not always accompany hypercalcemia (Herrera *et al.*, 1980; Scott *et al.*, 1982) and the correlation between the extent of bony lesions and hypercalcemia was poor. As to this, Kimura *et al.* (1982) suggested that the velocity of bone destruction was an important factor in developing hypercalcemia in malignant tumors in general. It is possible that the tumor produced other osteolytic substances such as prostaglandins (Finlayson and Casey, 1975; Plean *et al.*, 1976), or some PTH like substance which cannot be detected by the present radioimmunoassay. Mithramycin was effective in reducing the

serum calcium concentration in this case. The level of serum calcium was decreased from 16.6 mg/dl to 11.0 mg/dl in 2 days. Our experience supported the previous observation that this cytotoxic substance was useful in the treatment of hypercalcemia which had been resistant to treatment with combinations of saline, calcitonin and glucocorticoids (Kimura *et al.*, 1982).

Decreased gastrointestinal motility and resultant constipation are uncommon symptoms of pheochromocytoma (Gifford *et al.*, 1964). In a series of 68 cases constipation was recorded in only 8% (Hume, 1960). Paralytic ileus is, moreover, a rare complication of the disease. A review of the English literature revealed only 8 previously described cases (Cruz and Colwell, 1972). In Japan only 2 cases with paralytic ileus have been recorded in literature (Okuno *et al.*, 1983; Ishizuka *et al.*, 1983). Decreased motility of the gastrointestinal tract can be predicted from the pharmacological effects of catecholamines, which appeared to be mediated through α_2 - and β_2 -adrenergic receptors (Mayer, 1980). Besides the action of catecholamines, hypercalcemia might have played a role in developing the obstinate constipation. It is known that ionized calcium is essential in neuromuscular transmission. Therefore, the loss of smooth muscle tone and decreased activity of the autonomous nerve due to the hypercalcemia, as well as the action of catecholamines, might have developed the paralytic ileus. The absence of clinical symptoms, such as severe abdominal pain and shock, and the pathological findings can rule out the possibility that an occlusion of the major vessels in the mesentery might have caused the paralytic ileus.

Polyuria is another uncommon symptom of pheochromocytoma (Graham, 1951; Stackpole *et al.*, 1963). Norepinephrine is known to increase the renal water excretion (Schrier *et al.*, 1975). This action is considered to be mediated by suppression of ADH release

(Schrier *et al.*, 1975). In our case the ADH level was not elevated in spite of the marked polyuria and of possibly decreased total blood volume (Sjoerdsma *et al.*, 1966). On the other hand, hypercalcemia is known to inhibit the effect of ADH on water flow across the renal tubules (Epstein, 1968). The metastatic calcification in the tubular epithelial cells might indicate the disturbance of tubular function (Cotran, 1981). The urine volume appeared to have increased rather in parallel with the rise in the serum calcium level. Therefore, the marked polyuria observed in this case seemed to be attributable to the effects of both hypercalcemia and increased secretion of catecholamine.

An elevated level of gastrin was observed in our patient. Hypergastrinemia has been reported in patients with pheochromocytoma (Hayes *et al.*, 1972; Sagara *et al.*, 1981; Tatsuta *et al.*, 1983). Intravenous infusion of epinephrine increased gastrin secretion (Christensen and Stadil, 1976; Hayes *et al.*, 1978) and this response was prevented by the administration of propranolol (Hayes *et al.*, 1978). Intravenous infusion of neither norepinephrine (Christensen and Stadil, 1976) nor phenylephrine (Hayes *et al.*, 1978) stimulated gastrin secretion. Therefore, stimulation of gastrin release by catecholamine was considered to be a β -adrenergic effect (Hayes *et al.*, 1978). Tatsuta *et al.* (1983) observed that the serum gastrin level was elevated in pheochromocytoma with a high serum epinephrine level, but not in those with a normal epinephrine level. In our case, the plasma epinephrine level was within the normal range although the norepinephrine level was high. Norepinephrine is known to have the effects of α_1 -, α_2 - and also β_1 -adrenergic agonist (Lee, 1981). Therefore, a very high level of norepinephrine might have stimulated gastrin secretion by its β -adrenergic action in our patient.

Acknowledgements

The authors are grateful to Mitsubishi Yuka Laboratory of Medical Science (Tokyo, Japan) for measurements of tissue catecholamine contents.

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