Malignant Pheochromocytoma Lacking Clinical Features of Catecholamine Excess Until the Late Stage

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Abstract

A malignant pheochromocytoma is described in a 71-year-old man. Osseous metastases became manifest 12 years after successful removal of the primary tumor which originated in paraganglionic tissue near the right adrenal gland. Although the patient had no symptoms of catecholamine excess initially, hypertension, tachycardia and excessive sweating appeared several months before his death, concomitantly with a sharp increase in noradrenaline secretion due to an accelerated growth of metastatic tumors. Since there is no histologic criterion of malignancy in this neoplasm, it would be prudent to consider every case of pheochromocytoma as potentially malignant and to follow-up carefully for a long time after removal of the primary tumor.


Key words: paraganglioma, hypertension, osseous metastasis, noradrenaline

Introduction

Malignant pheochromocytoma is a rare neoplasm. The reported incidence varies from less than 1% to 19% of all pheochromocytomas (1-5), and when the primary lesion is extra-adrenal, this may rise to 24% (6) or 30% (7). Recurrence usually occurs several years after removal of the primary tumor (5, 8, 9), and bone is the most common site for metastases (8). The diagnosis of malignant pheochromocytoma is difficult, because it cannot be defined based on histologic criterion, and the clinical manifestations overlap those seen in benign pheochromocytoma except for the mass effect of tumors in the late stage.

We report here a patient with malignant pheochromocytoma which recurred 12 years after successful removal of the primary tumor. The patient had been asymptomatic and normotensive until several months before his death, when hypertension, tachycardia and excessive sweating appeared with a concomitant increase in noradrenaline secretion due to an accelerated growth of metastatic bone tumors.

Case Report

A 71-year-old man was admitted to Teikyo University Mizonokuchi Hospital on February 2, 1998 complaining of neck pain and numbness in the right hand (2nd admission). There was no family history of clinically overt endocrine diseases. In 1986, the patient had episodes of right upper quadrant pain after taking fatty dishes. He underwent abdominal ultrasonography, which demonstrated, in addition to gallbladder stones, a right adrenal mass. Although the pain was shortly relieved by the use of spasmolytics, he was admitted to a hospital for evaluation of the incidentally-discovered adrenal tumor on April 30, 1986 (1st admission). The patient had never experienced paroxysms of headache, palpitation, excessive sweating, apprehension, flushing or other symptoms commonly observed in pheochromocytoma before.

1st admission

Physical examination revealed no gross abnormality. No stigmata of Cushing’s syndrome were present. The skin was normally perspirated, and was free of eruption and pigmentation. No goiter or any other abnormal mass was found in the neck. There was no tumor palpable in the abdomen. His blood pressure on the day of admission was 138/88 mmHg with a pulse rate of 80/min, which was not changed significantly by palpation of the abdomen. The blood pressure was 128/66 mmHg (pulse rate 72/min) on the 2nd hospital day, and had remained normal during the whole period of hospitalization. Optic fundus did not show any hypertensive change.

The results of admission urinalysis and hematologic studies were normal. Liver function tests, blood urea nitrogen, serum creatinine, lipid profile and electrolytes including calcium were normal.

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all within normal limits. A 75-g oral glucose tolerance test gave normal results with an appropriate insulin response. Chest X-ray films revealed normal cardiac silhouette and normal pulmonary markings. An electrocardiogram showed regular sinus rhythm without evidence of ischemic changes.

Plasma levels of noradrenaline were elevated, while those of adrenaline and dopamine were normal (Table 1). In accordance with these results, 24 hours urinary excretion of noradrenaline and its metabolites, normetanephrine and vanillylmandelic acid (VMA), was clearly increased. Plasma renin activity and aldosterone concentration were normal and responded normally to stimulation by 2 hours of upright posture. Plasma cortisol, calcitonin and thyroid hormones as well as urinary 17-hydroxycorticosteroid excretion were within normal limits.

A CT scan showed a mass of 4 cm in diameter in the right adrenal gland, which was stained immediately after the infusion of contrast medium. An MRI examination revealed a high signal intensity lesion on T2-weighted images with multiple areas of low signal intensity inside suggesting necrotic changes (Fig. 1). No abnormal uptake was demonstrated in extra-adrenal sites by 131I-MIBG (metaiodobenzylguanidine) scintigraphy of the abdomen and chest.

Based on these findings, a diagnosis of pheochromocytoma was made, and the patient underwent laparotomy on September 16, 1986. A solid, encapsulated tumor, 50 g in weight, arising from the paraganglia adjacent to the right adrenal gland was found, and resected. No regional lymph nodes were enlarged. Cross sections of the tumor showed multiple areas of hemorrhage and necrosis. On light microscopy, the tumor was composed of relatively large chromaffin cells arranged in small or large alveolar patterns with a typical “Zellballen” appearance (Fig. 2A). Neighboring groups of tumor cells were separated by a reticulin-rich fibrovascular stroma. Nuclear pleomorphism, mitotic figures or vascular and capsular invasion was not evident.

Postoperative course was uneventful and without complications. After surgery, urinary VMA excretion fell to within the normal range (7.8 mg/day), although the blood pressure at bed rest in the morning measured by sphygmomanometry (133±8/<7.84±7.8, n=28) did not change significantly from that in the preoperative period (137±8/86±8, mean±SD, n=44). There was

<table>
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<tr>
<th>Table 1. Plasma Levels of Noradrenaline (NA), Adrenaline (A) and Dopamine (DA), and 24 hours Urinary Excretion of Noradrenaline, Adrenaline, Dopamine, Normetanephrine (NM), Metanephrine (M) and Vanillylmandelic Acid (VMA) during 1st and 2nd Admission</th>
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<tr>
<td>Date</td>
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<tr>
<td>Plasma*</td>
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<tr>
<td>NA (ng/ml)</td>
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<td>(0.04–0.35)</td>
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<td>A (ng/ml)</td>
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<td>DA (pg/ml)</td>
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<tr>
<td>Urine**</td>
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<td>NA (μg/day)</td>
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<td>A (μg/day)</td>
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<td>(&lt;21)</td>
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<td>DA (μg/day)</td>
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<td>(100–700)</td>
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<tr>
<td>NM (mg/day)</td>
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<td>(0.10–0.28)</td>
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<td>M (mg/day)</td>
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<td>(0.04–0.18)</td>
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<td>VMA (mg/day)</td>
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<td>(2.6–9.2)</td>
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Reference values are shown in parentheses. *Blood was drawn from the patient in the supine position for at least 30 minutes through a previously inserted indwelling intravenous needle, transferred to an ice-cold tube containing EDTA, and quickly centrifuged. The plasma was kept frozen at -70°C. **Urine samples were collected in containers with 20 ml of 6N HCl. Catecholamine and their metabolites in both plasma and urine were estimated by HPLC.
Figure 1. Magnetic resonance imaging of the abdomen (1st admission) showing a tumor mass in the right supra-renal area (arrows). A: T1-weighted image, B: T2-weighted image.

Figure 2. Photomicrographs of tumor tissues obtained at surgery. A, primary abdominal tumor tissue. B–D, metastatic cervical tumor tissue. Both primary abdominal (A) and metastatic cervical tumor tissue (B, C) composed of chromaffin cells, revealing essentially the same feature in histology. Grimelius stain (silver impregnation) for neurosecretory granule showed a positive reaction (D). A: HE stain (×20), B: HE stain (×20), C: HE stain (×10), D: Grimelius stain (×20).
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again no significant difference in simultaneously measured pulse rates before and after surgery (74±7 vs 80±7, mean±SD). The patient was followed-up annually. He had normal blood pressure and his urinary VMA excretion in random urine specimens remained normal during the period of observation. The patient had no pheochromocytoma-related symptoms during the period.

2nd admission

In September 1996, the patient developed neck pain and visited an orthopedist. X-ray films of the cervical spine were normal, which was confirmed later by us. He was diagnosed as having cervical spondylosis and was given analgesics. Because of persistent neck pain and numbness in the right hand that appeared in the last few months, the patient presented to the orthopedic department of our hospital on October 29 1997, and a neck tumor was discovered. He refused admission for assessment of the tumor at that time.

Finally, the patient was hospitalized on February 2, 1998. Upon physical examination, the blood pressure was 136/82 with a pulse rate of 84/min. A solid tumor, 5 cm in diameter, was noted on the right posterior side of the upper neck, which was attached to the spine and was not displaceable. Neurological examinations were negative.

The urine was normal, as were the results of routine hematologic, blood chemical and enzyme tests. Electrocardiogram and chest X-ray films were normal. Plasma levels of noradrenaline were markedly elevated, while those of adrenaline and dopamine were normal or marginally exceeded the upper reference limits (Table 1). Concurrently, 24 hours urinary excretion of noradrenaline, normetanephrine and VMA was definitively increased. Plasma renin activity and plasma levels of aldosterone, calcitonin and thyroid hormones were within normal limits. Serum neuron-specific enolase (NSE) concentration was 8.7 ng/ml (normal range: less than 10 ng/ml).

X-ray films of the spine showed destruction of spinous process of the 3rd cervical vertebra. An MRI revealed a high signal intensity mass on T2-weighted images, which encircled the right half of the 3rd cervical vertebra and partly extended in both superior and inferior directions (Fig. 3). The spinal cord was deviated to the left owing to compression by the tumor. A CT scan of the abdomen demonstrated, in addition, a 2-cm mass in the left iliac wing. An 123I-MIBG scintigraphy showed abnormal accumulation in the neck and the left iliac bone (Fig. 4).

On the 5th day of admission, the patient suddenly developed weakness of the muscles of the upper extremities, which rapidly extended to the shoulder, trunk and lower extremities. Examination disclosed a flaccid paresis and diminished tendon reflexes in the extremities, whereas pinprick, thermal and vibratory sensation were normal. Because of this progressive paraparesis, an emergency surgery was done on February 9, 1998, for decompression of the cervical spinal cord and the neck tumor was partially resected. Light microscopy of the tu-

Figure 3. Magnetic resonance imaging of the cervical spine (2nd admission) revealing a mass (arrows) which encircled the right half of the cervical vertebra. A: T1-weighted image, B: T2-weighted image.
Figure 4. $^{123}$I-MIBG scintigraphy (2nd admission) demonstrating, abnormal accumulation (arrows) in the neck (A) and the left iliac bone (B). A: posterior view, B: anterior view, L: left, R: right.

The patient described herein had malignant pheochromocytoma which originated in the paraganglionic tissue near the right adrenal gland. Gross and histopathologic characteristics of the primary tumor were not different from those of biologically benign pheochromocytomas. Surgical removal of the tumor was judged to be complete by the operating surgeon and pathologist. Serum NSE concentration, which has been claimed to be a sensitive marker of malignant pheochromocytoma (10), was not elevated. Metastases to the cervical spine and the iliac bone became manifest, however, 12 years after removal of the primary tumor. This is consistent with the view that the presence of secondary tumor deposits in sites where chromaffin tissue is not normally present is the only absolute criterion for malignant pheochromocytoma (11).

Of various prognostic factors surveyed by Nativ and coworkers (12), the most significant factors to predict a future malignant clinical course are large size and local extension of tumor at the time of surgery. In one report, malignant pheochromocytomas had a mean weight of 759 g, while the weight of benign
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One page of the document contains text discussing malignant pheochromocytoma. The text outlines the characteristics of malignant pheochromocytoma, its growth potential, and the importance of early detection. It also mentions the use of biochemical indices and imaging in the early diagnosis of metastases. The text highlights the importance of treatment options, emphasizing the role of surgery and the limitations of cytotoxic agents. The document references various studies and clinical cases, providing a comprehensive overview of malignant pheochromocytoma.

References