Pheochromocytoma: Unusual Presentation of a Rare Disease

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Pheochromocytoma can mimic a number of other diseases, making diagnosis difficult. The common presenting signs and symptoms are paroxysmal hypertension, headache, excessive sweating, and palpitation. Ten percent of all cases of pheochromocytoma are familial, as indicated by its coexistence with familial multiple endocrine neoplasia [1]. We describe a rare case of low back pain as the only initial presentation of a patient with MEN type II A syndrome.

Patient Description

A 47 year old man was admitted to our internal medicine department because of low back pain of 4 weeks duration and a finding of a lytic bone lesion of the fourth lumbar vertebra on spinal computerized tomography scan. The patient's history was remarkable for smoking (50 pack-years) and cataract extraction in the left eye, with no history of hypertension. Family history was significant in that one sister had died of pancreatic carcinoma and another sister has adenocarcinoma of the breast.

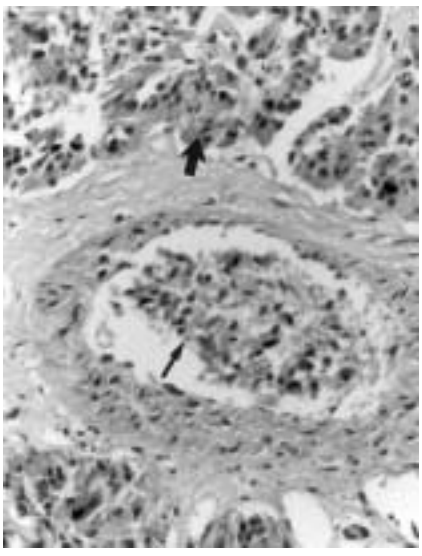
On admission, the patient's temperature was 36.5°C, pulse 80/minute, respiration rate 14/minute, and blood pressure 160/100 mmHg. Apart from a positive straight leg-raising test for the left leg, the physical examination was unremarkable. Laboratory findings on admission were as follows: hemoglobin 15 mg/dl; white blood cell count 6,400/mm^3, and platelet count 333,000/mm^3. Prothrombin and partial thromboplastin times were within normal range, as were serum creatinine, glucose, and electrolyte levels. Urine analysis revealed no abnormality. Chest X-ray and CT scan of the chest were normal. X-rays of the lumbar spine disclosed two large bilateral masses, and CT scan of the abdomen revealed bilateral adrenal masses (7x7cm each). At this stage, a tentative diagnosis of adrenal malignancy with metastatic lytic lesion of the L4 vertebra was made, and radiotherapy to L4 was initiated in order to prevent vertebral collapse. On the third day of radiotherapy, blood pressure rose to 200/100 mmHg accompanied by palpitations, headache and profuse sweating. Endocrinologic evaluation of the adrenal masses revealed elevated urinary levels of vanilylmandelic acid (236 g/24 hour) and metanephrine (30,000 g/ng creatinine). This finding was compatible with the diagnosis of malignant pheochromocytoma, which was confirmed by needle biopsy from the L4 vertebra.

Scintigraphy scan with meta-iodo-benzylguanidine coupled with I-131 revealed metastases in the lumbar spine and pelvis. Thyroid ultrasonographic examination revealed no masses, but there were fine calcifications in both lobes; plasma calcitonin level was elevated (182 ng/L, normal 3–100 ng/L).

The patient was treated with phenoxybenzamine and propranolol for 3 weeks, followed by bilateral adrenalectomy. The histopathologic analysis of the adrenal masses disclosed non-calcified large pleomorphic cells positively stained for synaptophysin, chromogranin and neuron-specific enolase. Some S-100-positive sustentacular cells were found. In addition, groups of tumor cells were identified in vascular spaces. This histologic finding was compatible with the diagnosis of malignant pheochromocytoma [Figure A].

The patient's DNA analysis revealed a RET-mutation at codone 634 in exon 11, a finding compatible with MEN type IIA. A genetic screening of the patient's family members was negative for these mutations. After bilateral adrenalectomy, the patient was asymptomatic, VMA returned to normal level (8.6 g/24 hour), and MTN significantly decreased (2,300 g/ng creatinine).

Several weeks later, the patient underwent total thyroidectomy. Histologic examination of the thyroid gland revealed medullary carcinoma with multiple foci in the right and left lobes.



[A] Adrenal pheochromocytoma with interstitial (thick arrow) and intravascular (thin arrow) tumor cells (hematoxylin and eosin x 100)

MEN = multiple endocrine neoplasia

Because of multiple symptomatic metastases in the lumbar spine and pelvis, a regimen of three cycles of MIBG therapy (100 μCm per cycle) for the first 6 months, at 2 month intervals, was begun. A decrease in the size of the metastatic lesions was noted on CT, technetium-99m bone scan as well as MIBG scan. The pain resolved and the patient returned to normal activities. Recently, after a disease-free interval of 2 years, new lesions were found in the anterior mediastinum, head of the right humerus, skull, and in the liver. MIBG therapy was resumed and radiotherapy to the skull was started.

Comment

Sometimes, rare disorders present in an atypical way, which may make the diagnosis difficult, as was the case in our patient. In our patient the sole presenting symptom of MEN IIA syndrome was back pain.

The typical presenting symptoms in more than 90% of cases with pheochromocytoma are headache, palpitation, perspiration or paroxysmal hypertension. The hypertension is usually sustained and resistant to conventional treatment, or alternatively there may be a hypertensive crisis accompanied by episodes of paroxysmal seizures, anxiety attacks, or hyperventilation. Hypertension is absent in some cases only.

There are a few case reports in the literature where low back pain was associated with pheochromocytoma [2,3]. In all these patients, back pain was the presenting symptom, and the characteristic symptoms of pheochromocytoma, including hypertension, were initially absent. Our case suggests that pheochromocytoma should be considered in the differential diagnosis of bone lytic lesion.

The increase in blood pressure following initiation of radiotherapy observed in our patient was reported in another case in which exacerbation of pheochromocytoma manifestations were associated with radiation therapy without prior medical adrenergic blockade [4].

The treatment of patients with pheochromocytoma consists of unilateral or bilateral total adrenalectomy. Pre-operative alpha blockade with phenoxybenzamine or prazosin with additional beta blockade is necessary to prevent hypertensive crisis, hypovolemia, and tachycardia during surgical removal of the tumor [1]. Patients with metastatic malignant pheochromocytoma or conditions in which pheochromocytoma cannot be totally removed, irradiation with MIBG is administered in order to achieve tumor regression and decrease catecholamine secretion. A combined chemotherapy with cyclophosphamide, vincristine, and dacarbazine may be an alternative therapy to MIBG-resistant tumor [1].

Familial pheochromocytoma accounts for 10% of cases [1]. The concurrence of large malignant bilateral adrenal pheochromocytoma masses should raise the possibility of a familial tumor syndrome (such as MEN type IIA and IIB, neurofibromatosis type I and Von Hippel-Lindau disease). Both MEN IIA and IIB are characterized by bilateral pheochromocytoma. MEN IIB is distinguished by its unusual phenotype of marfanoid habitus and ganglioneuromatosis [5]. The finding of a germline mutation in the RET proto-oncogene was compatible with the diagnosis of MEN II. In contrast to our patient's presentation, medullary thyroid carcinoma is the initial presentation in most patients with MEN II [5].

In summary, we present a patient who sought medical treatment for low back pain and evidence of a lytic bone lesion, which was the result of metastatic pheochromocytoma as part of the MEN IIA syndrome, which was confirmed by the evidence of germline mutation in the RET proto-oncogene. This case emphasizes that pheochromocytoma should be included in the differential diagnosis of lytic bone lesions, and its clinical features may be induced by radiotherapy of the tumor.

MIBG = meta-iodo-benzyl-guanidine

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Capsule

Vitamin D versus fat

Mechanistic insight into the epidemiologic relation between colon cancer, vitamin D, and a high fat diet is now offered by Makishima et al., who report that a receptor for vitamin D in the intestine also binds a bile acid called lithocholic acid (LCA). Increased amounts of LCA are associated with a high fat diet, and because it is poorly reabsorbed it passes into the colon. Binding to the vitamin D receptor stimulates the expression of CYP3A, an enzyme that can catabolize LCA. These results may explain how the enteric system protects itself from the toxic effects of LCA and how vitamin D may guard against colon cancer.

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