

# Malignant Pheochromocytoma of the Urinary Bladder: Challenges in Diagnosis and Management

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**KEY WORDS:** extra-adrenal pheochromocytoma, urinary bladder, [<sup>123</sup>I] metaiodobenzylguanidine (MIBG) scintigraphy, 6-[<sup>18</sup>F] fluorodopamine PET scan, [<sup>131</sup>I] metaiodobenzylguanidine (MIBG) treatment

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**P**heochromocytoma may be either benign or malignant. These tumors produce and excrete significant amounts of catecholamines and their metabolites, thus giving rise to the well-known clinical picture of pheochromocytoma. If unrecognized, it may lead to death as the result of hypertensive crisis, arrhythmia or myocardial infarction. Therefore, a high index of suspicion is crucial for early diagnosis. We describe a case of malignant extra-adrenal paraganglioma, focusing on new modalities for its diagnosis and management.

## PATIENT DESCRIPTION

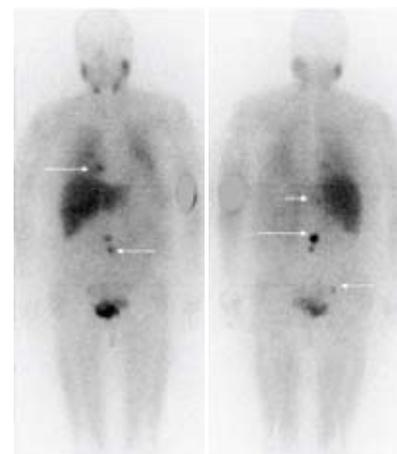
A 69 year old woman, a Russian immigrant, was hospitalized in 2006 because of recurrent syncope and episodes of severe headaches, dizziness and palpitations that had begun a few months earlier. Her medical history was remarkable for a 12-year hypertension that was relatively well controlled until 3 years before the current hospitalization. During those 3 years she experienced frequent paroxysms of severe hypertension, with blood pressure elevation up to 240/120 mmHg, which did not respond well to medical therapy despite

multiple anti hypertensive drugs. A cholecystectomy performed 3 years before the current admission was complicated by a severe life-threatening hypertensive crisis. Also noteworthy was urinary bladder neoplasm of unclear pathology that was diagnosed 8 years before the admission. At that time she was living in Russia and was treated with radiotherapy and chemotherapy. Computed tomography, performed one year before hospitalization, revealed a 6.5 cm mass in the right bladder wall. Repeated cystoscopies and biopsies demonstrated irritated mucosa with no evidence of malignancy.

On admission blood pressure was 200/110 mmHg in the supine position and 100/50 mmHg on standing; pulse was 110/minutes and regular. The rest of the physical examination was unremarkable. Laboratory tests demonstrated anemia (hemoglobin 8.7 g/dl) associated with chronic disease, prerenal azotemia (urea 116 mg/dl, creatinine 2.09 mg/dl) and hypokalemia (potassium 3.14 mmol/L). An electrocardiogram showed sinus tachycardia with non-specific ST-segment and T-wave abnormalities.

During hospitalization the recurrent elevations of blood pressure up to 240/120 mmHg accompanied by dizziness, headaches and palpitations raised the suspicion of pheochromocytoma. Levels of metanephrine, vanillylmandelic acid and catecholamines in 24-hour urine collections were significantly elevated. Treatment with phenoxybenzamine was started and propranolol was added later. A total body CT showed the 6.5 cm mass in the urinary bladder as well as a new right iliac lymphadenopathy, scattered pulmonary nodules and two solid masses in the right kidney. A

Anterior and posterior whole body images of the initial MIBG study show multiple MIBG avid foci in the right lower lung, liver, mid-abdomen spine and pelvis (arrows)



[<sup>123</sup>I] metaiodobenzylguanidine scanning showed multiple foci of increased uptake in the right lung, liver, abdomen and right pelvis adjacent to the bladder [Figure 1]. No pathological uptake was observed in the adrenals. A diagnosis of metastatic extra-adrenal pheochromocytoma, most likely of urinary bladder origin, was made. During surgery the external urinary mass could be only partially excised. Biopsy revealed multiple foci compatible with paraganglioma.

Therapy with 150 mCi of [<sup>131</sup>I] MIBG was initiated. The headaches, palpitations, fainting episodes and paroxysms of hypertension gradually subsided. A repeated total body CT, performed a year later, did not show changes from the previous CT. Treatment with alpha and beta-blockers continued. Blood pressure

MIBG = metaiodobenzylguanidine

was well controlled and the patient felt well for 2 years after the operation when palpitations and paroxysms of severe hypertension recurred. Again, 24-urine free catecholamines and VMA levels were markedly elevated. A [<sup>123</sup>I] MIBG scan showed new metastatic foci in the left lung, liver and spine and another course of therapy with <sup>131</sup>I-MIBG was scheduled.

### COMMENT

Pheochromocytoma is a rare catecholamine-producing chromaffin cell tumor [1]. It can be sporadic or familial, the latter often being multifocal and appearing at an earlier age. Among the germline mutations are the von Hippel-Lindau gene causing the VHL syndrome, the RET gene leading to multiple endocrine neoplasia type 2, the neurofibromatosis type 1 gene associated with neurofibromatosis type 1, and the gene encoding mitochondrial succinate dehydrogenase subunit D and B associated with familial paraganglioma and pheochromocytoma.

While most pheochromocytomas are benign, malignancy accounts for up to 26–40% of all cases. There is no certain way to predict which tumors will progress to malignancy and no single histological feature alone is predictive of metastatic invasion [2]. Prognostic factors for malignancy include large size (diameter > 5 cm), local tumor extension at the time of surgery, and the DNA ploidy pattern with aneuploidy and tetraploidy having a more aggressive nature. A scoring system that combines histological, immunohistochemical and biochemical parameters was suggested to predict both the metastatic potential and the prognosis for patients with metastatic tumors [3]. In clinical practice, the only reliable criterion of malignancy is the presence of distant metastases. Since the overall 5-year survival in patients with malignant pheochromocytomas ranges from 40% to 74%, early diagnosis is of utmost importance.

VMA = vanillylmandelic acid  
VHL = von Hippel-Lind

Hypertension, occurring in 90% of patients, may be sustained or paroxysmal. It may cause encephalopathy, retinopathy, cardiomyopathy and proteinuria. A hypertensive crisis may be induced by trauma, exercise, various medications (such as antihypertensives, tricyclic antidepressants, glucagon, opiates) or surgery. The triad of headaches, palpitations and sweating should raise a high index of suspicion for pheochromocytoma. Other features are orthostatic hypotension, syncope and hyperglycemia. Aside from catecholamines and their metabolites, pheochromocytoma can also secrete various other peptides, such as parathyroid hormone-rP, ACTH, erythropoietin and interleukin-6, which contribute to clinical symptoms.

Diagnosis is confirmed by increased levels of free catecholamines and metanephrines either in urine or plasma. Urine levels, if determined during or shortly after a hypertensive crisis, have greater sensitivity. Plasma catecholamines have a sensitivity of 90% and a specificity of 95%, and plasma metanephrines are more sensitive than plasma catecholamine. The levels of chromogranin A and neuropeptide Y are increased in more than 80% of patients; however, their specificity for pheochromocytoma is low as they may be increased in other neuroendocrine tumors. Once the diagnosis is confirmed, the next step is localization by CT or magnetic resonance imaging.

Ninety-seven percent of extra-adrenal paragangliomas are found in the abdomen, mostly in the organ of Zuckerkandl, the sympathetic ganglia, or the urinary bladder. CT and MRI scans have similar sensitivity (98%–100%), but their specificity is only 70%. Therefore, functional imaging is needed to confirm that a tumor is a pheochromocytoma. Functional imaging by <sup>123</sup>I-MIBG scintigraphy (sensitivity 83–100%, specificity 95–100%), or by <sup>131</sup>I-MIBG scintigraphy (sensitivity 77–90%, specificity 95–100%) should be performed. False positive MIBG has been reported in cases of adrenal carcinoma, adrenal adenomas and anatomic varia-

tions of the renal pelvis. False negative MIBG examinations may be expected if the patient has not stopped taking medications that interfere with MIBG uptake, and if there are tumors that have undergone necrosis. Positron emission tomography imaging with 6-[<sup>18</sup>F] fluorodopamine positron-emitting analog of dopamine is a new useful technique. In addition, as compared with <sup>131</sup>I-MIBG, it has a lower radiation dose, and results are available on the same day in contrast to the 24–48 hour delay necessary for <sup>131</sup>I-MIBG imaging. Somatostatin receptor scintigraphy (Octreoscan), as compared with MIBG, is more sensitive only in metastatic pheochromocytoma, but not in benign tumors. Venous sampling coupled with the measurement of catecholamine gradient, a technically difficult invasive procedure performed in a few specialized centers, should be reserved only for selected cases when all other imaging methods have failed.

Therapy is based on antihypertensive control in adjunct to anti-tumor treatment. An alpha-blocker, phenoxybenzamine, starting with 10 mg once or twice daily and increasing the dose gradually up to a 1–2 mg/kg per daily in two divided doses, is the first-choice therapy. Beta-blockers should be instituted only after alpha-blockers have been started. This sequence is important since  $\beta$ -blockers lead to the loss of  $\beta_2$ -receptor-mediated vasodilatation and the unopposed effects of alpha-receptors cause vasoconstriction, arterial hypertension and increased afterload, causing myocardial infarction and pulmonary edema. Doxazosin, labetalol, dihydropyridine calcium channel blockers and metyrosine, may also be beneficial. After localization of the tumor, surgical removal should be performed. Symptom relief occurs in most patients with benign pheochromocytoma. Surgical treatment alone is seldom curative in malignant pheochromocytoma, but it may prolong survival by debulking, reducing metastatic spread and hormonal activity, and by removing metastases at life-threatening locations.

Other therapeutic options are radiation, by either  $^{131}\text{I}$ -MIBG, or a radioactive somatostatin analogue, and chemotherapy. For  $^{131}\text{I}$ -MIBG therapy to be effective, patients are chosen on the basis of significant radioisotope uptake (> 1% of the injected dose) as demonstrated during the diagnostic MIBG scans. The only limitation of this treatment is the total radiation dose to critical organs such as bone marrow. The initial  $^{131}\text{I}$ -MIBG dose is an important factor in the response and survival rate, as patients who received high initial doses lived longer than those who received lower doses [4].  $^{131}\text{I}$ -MIBG therapy is generally well tolerated, may yield partial remission in 24–54% of patients and has even been reported to produce complete remission. Similar to surgery,  $^{131}\text{I}$ -MIBG treatment alone is not curative; therefore, integration of  $^{131}\text{I}$ -MIBG with other therapeutic modalities should be considered in progressive disease. A somatostatin analogue therapy with octreotide is based on expression of somatostatin receptor in chromaffin cell tumors. As in therapy with

$^{131}\text{I}$ -MIBG, only patients showing a high uptake will benefit from this treatment. Hormone secretion and tumor growth have been reported to be stabilized in 25% of cases and even decreased in 20% of cases. Side effects are leukopenia and thrombocytopenia. Combined therapy of  $^{131}\text{I}$ -MIBG and  $^{177}\text{Lu}$ -octreotate might be more favorable and exert fewer side effects than a single high dose of  $^{131}\text{I}$ -MIBG with its potential severe bone marrow toxicity. Novel approaches, such as somatostatin analogues, combined with anti-angiogenic factors may become the therapeutic modality of the future. Chemotherapy should be considered for patients without avidity to radionuclide treatment or when there is progression of the disease despite conventional treatment. Combination of cyclophosphamide, vincristine and dacarbazine (CVD) in malignant pheochromocytoma showed symptomatic and hormonal responses (50–100%) but only a minimal tumoral response [5]. Combinations of etoposide and cisplatin or anthracycline, CVD and cytosine arabinoside showed some

success. However, in most patients with malignant pheochromocytoma, there is no curable therapy and the prognosis is unfavorable.

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