

# Malignant Pheochromocytoma Simulating Meningioma: Coexistence of Recurrent Meningioma and Metastatic Pheochromocytoma in the Base of the Skull

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For Editorial see page 817

Meningiomas are among the most common intracranial tumors. However, even though some reports have suggested a possible association between meningioma and a clinical syndrome resembling pheochromocytoma, to the best of our knowledge, the association between meningioma and authentic pheochromocytoma was documented only twice before [1,2].

We describe a patient with metastatic pheochromocytoma invading the base of the skull, which was clinically and radiologically indistinguishable from a coexistent contralateral recurrent meningioma. We discuss the possibility that despite its rarity, the association between meningioma and pheochromocytoma may not be fortuitous.

## Patient Description

In January 1992 a 47 year old man was referred for evaluation of suspected recurrent meningioma. Fourteen years earlier, in 1978, a large left frontal meningioma was discovered and surgically removed.

Four years after the removal of the meningioma, in the course of a routine work-up for newly discovered hypertension, abnormally increased urinary VMA secretion was detected. A computerized tomography scan revealed a large, encapsulated, retroperitoneal mass that displaced the right kidney and the right hepatic lobe. The mass contained areas of low density suggestive of tissue necrosis. An arteriographic study established the adrenal origin of the tumor and revealed enrichment of numerous pathologic vessels. The tumor, which was encroached on the right

kidney, was surgically removed along with the right kidney and was identified as pheochromocytoma with no indications of malignancy in the resected specimen. Following surgery, blood pressure returned to normal values and the patient was lost to follow-up.

Eight years after the initial removal of the meningioma, a CT scan revealed a large tumor extending from the left anterior fossa to the middle infra-temporal fossa. The tumor reached the lateral margin of the left orbit, eroding the floor of the middle cranial fossa, invading the left infra-temporal fossa and displacing the ventricular system from left to right. The cerebral portion of the tumor appeared edematous. An additional tumor occupied the right frontotemporal area, infiltrating the right orbit and the right infra-temporal fossa, eroding the floor of the middle fossa. The CT findings were interpreted as compatible with bilateral recurrence of the meningioma [Figure A]. An operation was recommended, which the patient initially declined.

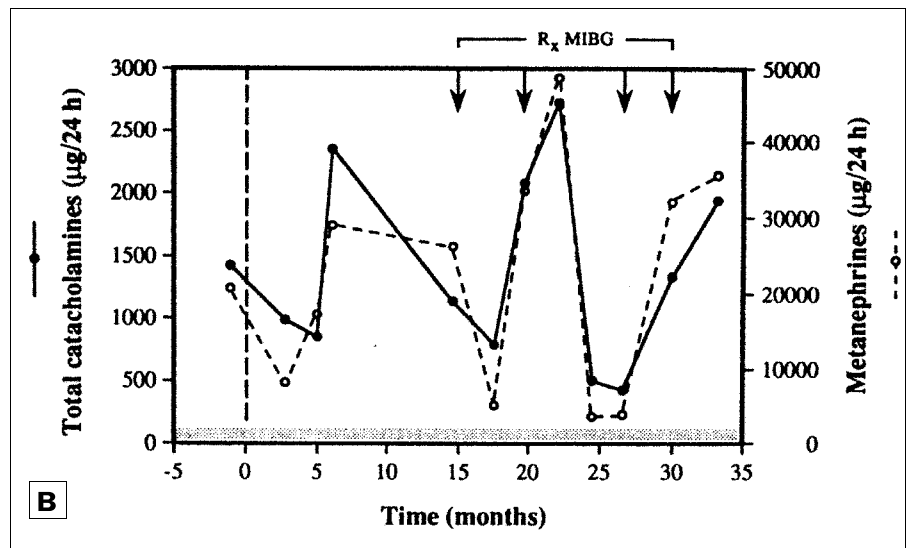
In January 1992, removal of the left-side tumor was carried out through a temporal transcranial approach. During surgery the systolic blood pressure increased abruptly to 300 mmHg and was controlled with nitroprusside infusion. The postoperative course was uneventful. Histopathologic examination revealed a typical meningioma of the meningiothelial type, including occasional foci containing psammoma bodies, and some areas displaying fibroblastic features and other foci of transitional type (between meningio-epithelial and fibroblastic types). One portion of the tumor was attached to skeletal muscle and

was histologically shown to infiltrate it. The tumor expressed estrogen receptors, progesterone receptors and epithelial membrane antigen on immunochemical staining, but was negative for chromogranin.

One month post-surgery, several semi-quantitative urinary VMA determinations revealed abnormally increased excretion. Metanephrine excretion at 24 hours was >20,700 µg (normal <1,000) and 24 hours total catecholamines excretion was 1,420 µg (normal <275), diagnostic of pheochromocytoma. A meta-iodo-benzyl-guanidine scan revealed an intense concentration corresponding with the right frontotemporal mass (not shown). Four months later, following preparation with phenoxybenzamine and atenolol, a second operation was performed to remove the right frontotemporal mass. Microscopic examination showed a tumor composed of polymorphic polygonal cells with abundant granular cytoplasm. The tumor cells invaded bony trabeculae and dense collagenous tissue. On immunohistologic staining the tumor cells expressed chromogranin; they were negative for progesterone receptors and epithelial membrane antigen. The histopathologic findings were compatible with a metastatic pheochromocytoma. The post-operative course was uneventful.

Following surgery, an initial decrease in urinary catecholamines excretion was observed, albeit still in abnormally high amounts [Figure B]. A repeat MIBG scan revealed previously undetected pathologic concentrations compatible with metastases of pheochromocytoma in the skull,

MIBG = meta-iodo-benzyl-guanidine



**[A]** CT scan of the base of the skull. The patient underwent a previous resection of meningioma at the left anterior and middle fossae. A recurrent tumor, seen in the left anterior and middle fossae with tumor infiltration to the left infra-temporal fossa, was revealed to be a recurrent meningioma. A radiographically equivalent tumor in the right anterior and middle fossae turned out to be a metastatic pheochromocytoma. Arrowheads delineate the tumors' boundaries.

**[B]** Variation in urinary total catecholamines and metanephrines in response to therapeutic doses of MIBG. The stippled area indicates the normal limits. The "zero" time point indicates the time of surgical removal of a large right frontotemporal metastasis of pheochromocytoma. The four arrows mark the administration of MIBG (100, 160, 180 and 200 mCi respectively).

ribs and vertebrae (not shown). In an attempt to eradicate the metastases, MIBG was successively administered in therapeutic doses of 100, 160, 180 and 200 mCi fractions, on four separate occasions 4–8 months apart. Transient decreases in catecholamine excretion were observed following the two initial doses [Figure B]. Approximately 19 years after the initial removal of a malignant pheochromocytoma and 9 years after the resection of a large cranial metastasis, the patient is alive and well.

### Comment

This case illustrates several issues: a) the rare concurrent association of meningioma and pheochromocytoma; b) the unique malignant nature of the pheochromocytoma in the context of concurrent meningioma, and its unusual metastatic spread to the skull; c) insight into the role of MIBG as a therapeutic agent for treating metastatic pheochromocytoma, and the utility of monitoring catecholamine for the evaluation of the efficacy of therapy in patients with metastatic pheochromocytoma; and d) the slow progression of malignant pheochromocytoma.

Despite its rarity, the concurrent association of meningioma and pheochromo-

cytoma in the present case, as well as in the two previously reported cases, may not be casual. Meningioma and pheochromocytoma share a common embryologic origin. Meningiomas are tumors of the meninges, which originate from cells of the neural crest, as do pheochromocytomas, which arise from the adrenal medulla or from paraganglionic tissue that derives from embryonic cells of the neural crest. The idea of a common embryologic origin of the cells that give rise to meningioma and pheochromocytoma is reinforced by the separate association of pheochromocytomas and meningiomas with defined "neurocristopathies" (disorders of the neural crest) such as neurofibromatosis type 2, von Hippel-Lindau and the Rubinstein-Taybi syndromes. In addition, a patient with meningioma was identified from among eight individuals with pheochromocytoma who were identified in a prospective survey of a large kindred with familial pheochromocytoma [2]. The potential for coexistence of different neurocristopathies is further emphasized by a report of a patient with three tumors of neural crest origin: meningioma, neurofibroma and choroidal melanoma.

Several observations suggest a common genetic origin for pheochromocytomas and

meningiomas. Loss of heterozygosity on the long arm of chromosome 22 was detected in 9 of 17 pheochromocytomas. The mutations were localized between D22S10 and proximal to D22S22 [3]. The deleted region is closely related to regions that are believed to contain tumor-suppressor genes. In addition, mutations of the neurofibromatosis type 2 (NF-2) gene on the long arm of chromosome 22, which are associated with acoustic neuromas and meningiomas, were detected in a large proportion of meningiomas [4]. LOH at 22q11 was identified in three tumor types in a patient with NF-2, suggesting a common pathogenetic mechanism to those tumors [5]. All these data suggest that LOH on the long arm of chromosome 22 is a most likely candidate locus for the combination of pheochromocytoma and meningioma. In another report, LOH at the DIS7 locus on chromosome 1 was suggested as the critical locus in a pheochromocytoma from a patient with coexistent meningioma and pheochromocytoma [1], but since the constitutional genotype of that patient did not display heterozygosity at that locus, the LOH

LOH = loss of heterozygosity

theory could not be proven in that particular case. Unfortunately we were not able to study the genetics of our patient's tumors or his constitutional genotype.

The present case raised a significant diagnostic dilemma. Due to the history of a previously resected meningioma and the recognized tendency of recurrence, and because of its radiographic appearance, the right temporal tumor was originally suspected to be a meningioma. However, unexpectedly, it was associated with intense concentration of MIBG. In view of the rarity of cranial pheochromocytoma metastases we speculated on the possibility of meningioma-associated catecholamine secretion, but this was rejected by the histopathologic findings that were compatible with metastatic pheochromocytoma, as well as by the lack of secretory characteristics in the meningioma tissue.

Two previous reports on coexistent meningiomas and pheochromocytomas referred to benign pheochromocytomas [1,2]. To the best of our knowledge, the present case is the only available report of a patient with meningioma associated with malignant (metastatic) pheochromocytoma.

Following removal of the right fronto-temporal metastasis of pheochromocytoma, a marked decrease in urinary catecholamine excretion was observed; however, urinary catecholamines excretion subsequently increased beyond their pre-operative level [Figure B]. Administration of MIBG, used as a pharmacologic vehicle for conveying radioactive iodine to the pheochromocytoma metastases, produced an initial apparently encouraging response, based on an observed decrease in urinary catecholamines and metanephrine excretion after each administration. However, evidence for remission was short-term [Figure B], as post-MIBG scans failed to show regression of the metastases and catecholamine excretion subsequently increased. The discrepancy between the observed fall in catecholamine secretion on the one hand and the consistency of MIBG scans on the other underlines that caution should be applied to the interpretation of urinary catecholamines and metanephrine excretion as markers for monitoring the therapeutic response in patients with malignant pheochromocytoma.

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