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Case Report

Recurrent Pheochromocytoma With Bone Metastasis Eight Years After Bilateral Adrenalectomies in a Patient With Neurofibromatosis Type 1

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ABSTRACT

Background/Objective: Pheochromocytoma can recur years after curative surgical resection. Rarely, it may reoccur as metastasis. Here, we present a case of metastatic pheochromocytoma to the bones in a patient with neurofibromatosis type 1 (NF1), 8 years after initial resection of primary bilateral adrenal pheochromocytomas without metastases.

Case Report: A 44-year-old woman presented with diffuse body pain and palpitations. Her past medical history included NF1 and hypertension. Eight years prior to her current presentation, she had undergone a bilateral adrenalectomy for the management of bilateral adrenal pheochromocytomas. Her plasma metanephrines normalized after surgery and remained normal at her 1-year postoperative visit. She was subsequently lost to follow-up until her current presentation. Our evaluation revealed significantly elevated urine and plasma metanephrines as well as innumerable DOTATATE avid lesions along the axial and perpendicular spine compatible with a metastatic neuroendocrine tumor. She was started on doxazosin and metoprolol and discharged home with a plan to be seen by Oncology to discuss systemic therapy.

Discussion: Predicting malignant disease in patients with primary tumors without metastases is challenging. There is no single factor that can reliably predict tumor behavior. It is unknown if individuals with NF1, who have a genetic predisposition for developing pheochromocytomas, are at an increased risk of malignant disease.

Conclusion: Due to a lack of accurate predictors, annual biochemical testing is recommended after primary tumor resection and in patients with a genetic predisposition. Strict lifelong follow-up should be strongly considered due to a possible higher risk of malignant disease.

Introduction

Pheochromocytoma is a rare neuroendocrine tumor that arises from adreno-medullary-chromaffin cells.[1] Following initial surgical resection, pheochromocytoma may recur in approximately 6% to 16.5% of cases.[2] Recurrence can manifest locally in the adrenal tissue, distally in the contralateral adrenal gland, or as metastases to sites without chromaffin cells, such as the lymph nodes, liver, bones, or lungs.[3] In the literature, studies show a median time for the development of metachronous metastases was 5.5 years after the primary tumor diagnosis.[4] Neurofibromatosis type 1 (NF1) is a common autosomal dominant neurocutaneous disorder and is one of the most common hamartoma neoplastic syndromes.[5] Although the most common malignancies associated with NF1 are intracranial gliomas and malignant peripheral nerve sheath tumors, an increased risk of pheochromocytomas has also been demonstrated in the literature.[6,7] The incidence of pheochromocytoma among NF1 patients is estimated to be between 0.1% and 5.7%; however, due to the relative rarity of pheochromocytomas in NF1 patients, the majority of what is known of the management and follow-up for this entity is based on case reports and small case series.[6,8] Additionally, it is unknown if there is an increased risk of malignant

Abbreviation: NF1, neurofibromatosis type 1.

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pheochromocytoma in patients with NF1 compared to the general population. Here, we present a case of recurrent pheochromocytoma with bone metastasis, 8 years after initial resection of primary tumors without metastases in a patient with NF1.

Case Report

A 44-year-old female presented to the hospital with a 2-week history of palpitations and worsening generalized body pain that was accompanied by dizziness and presyncope. Her medical history included NF1 and hypertension, both of which were diagnosed approximately 20 years previously. Eight years prior to the current presentation, she presented to another institution with sudden onset shortness of breath without a clear precipitating event. Her initial vital signs included a heart rate of 140 beats per minute and a systolic blood pressure of 240 mmHg. Her respiratory status deteriorated shortly afterwards, and she was intubated for increased work of breathing. Imaging at the time revealed a 13.9 cm × 12.2 cm right adrenal mass and a 4.7 cm × 4.3 cm left adrenal mass with a density of 35 Hounsfield units. Metanephrines were 14.861 pg/mL (≤57 pg/mL), normetanephrines were 91.178 pg/mL (≤148 pg/mL). Due to worsening respiratory status despite intubation, she was transitioned to extracorporeal membrane oxygenation for severe cardiac dysfunction with cardiogenic shock due to catecholamine storm which she remained on until her adrenalectomies. Following pretreatment with phentolamine, the patient underwent a right total adrenalectomy and a left subtotal adrenalectomy. The final pathology for the left and right adrenalectomies reported a 5.4 cm and 18.5 cm pheochromocytoma respectively with tumors present at the inked resection margins, extensive necrosis, lymphovascular invasion, and positive succinate dehydrogenase-B immunostaining on both samples. Imaging prior to surgery did not reveal any distant metastases outside of the primary bilateral adrenal tumors. One month after surgery, her plasma metanephrines values were <25 pg/mL (≤57 pg/mL), and normetanephrines were 65 pg/mL (≤148 pg/mL). One-year follow-up after surgery, her plasma metanephrines level was 10 pg/mL (0-62 pg/mL), and plasma normetanephrines level was 98 pg/mL (0-145 pg/mL). Thereafter, she was lost to follow up.

On her present admission, her vitals were notable for a blood pressure of 151/97 mmHg and a heart rate of 111 beats per minute. Multiple café-au-lait spots were observed on her upper extremities and trunk. Initial laboratory testing was unremarkable. A full-body computed tomography scan revealed multiple pulmonary nodules, diffuse mixed lucent, and sclerotic lesions affecting both the axial and appendicular skeleton, as well as a 1.7 cm breast mass (Figs. 1 and 2). It is notable that on imaging, her remaining partial left adrenal gland did not have evidence of any localized tumor recurrence. On further lab testing, plasma metanephrines were 2.83 nmol/L (0-0.49 nmol/L), plasma normetanephrines were >50 nmol/L (0.00-0.89 nmol/L), the urine metanephrines/creatinine ratio was 3156 μg/g (0-300 μg/g), and the urine normetanephrine/creatinine ratio was 114 828 μg/g (0-400 μg/g).

A Ga-68-DOTA PET/computed tomography revealed numerous DOTATATE avid lesions scattered throughout the axial and appendicular skeleton (Fig. 3). The lung nodules did not show DOTATATE uptake. Due to high clinical suspicion for pheochromocytoma recurrence with metastatic disease, the patient was initiated on doxazosin for alpha blockade, followed by metoprolol for beta blockade. She was discharged home with a blood pressure below 130/80. After her hospitalization, the patient had follow-up appointments scheduled with oncology and endocrinology specialists at a separate institution to consider systemic therapy options as she was unable to follow-up in our clinic due to lack of insurance coverage. Unfortunately, she passed away 4 months after hospital discharge before receiving treatment for metastatic pheochromocytoma.

Highlights

- Screening should be considered in neurofibromatosis type 1 (NF1) patients presenting with hypertension.
- NF1 patients have increased risk of developing pheochromocytoma.
- NF1 patients may also be at a higher risk for pheochromocytoma recurrence.
- NF patients may require a more aggressive initial resection.
- In patients with hereditary predisposition, vigilant monitoring is encouraged.

Clinical Relevance

Pheochromocytoma can recur despite curative treatment with surgery. Especially in patients with a genetic predisposition to develop pheochromocytoma, such as patients with NF1, lifelong follow-up, and biochemical testing should be done to ensure vigilant monitoring for any potential recurrence.

Discussion

We present a case of pheochromocytoma recurrence with bone metastases 8 years after initial bilateral primary tumor resection without evidence of distant disease. There are several areas of clinical interest in this case where due to the relative paucity of literature, there are very few guidelines on the appropriate management of pheochromocytoma in NF1 patients.

The increased incidence of pheochromocytomas in NF1 patients is a known statistic with a reported incidence of nearly 20% to 50% in NF1 patients when hypertension is also present.[8] While

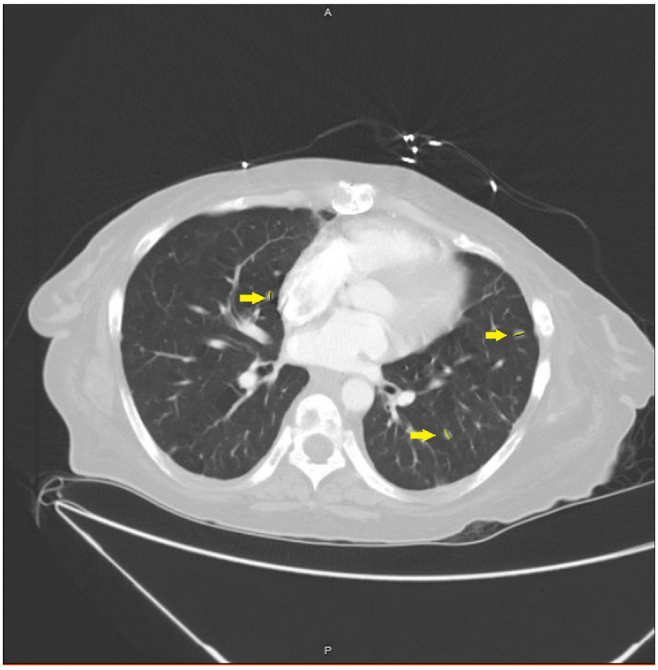

Fig. 1. CT scan of the chest demonstrated multiple pulmonary nodules (yellow arrows). *CT* = computed tomography.

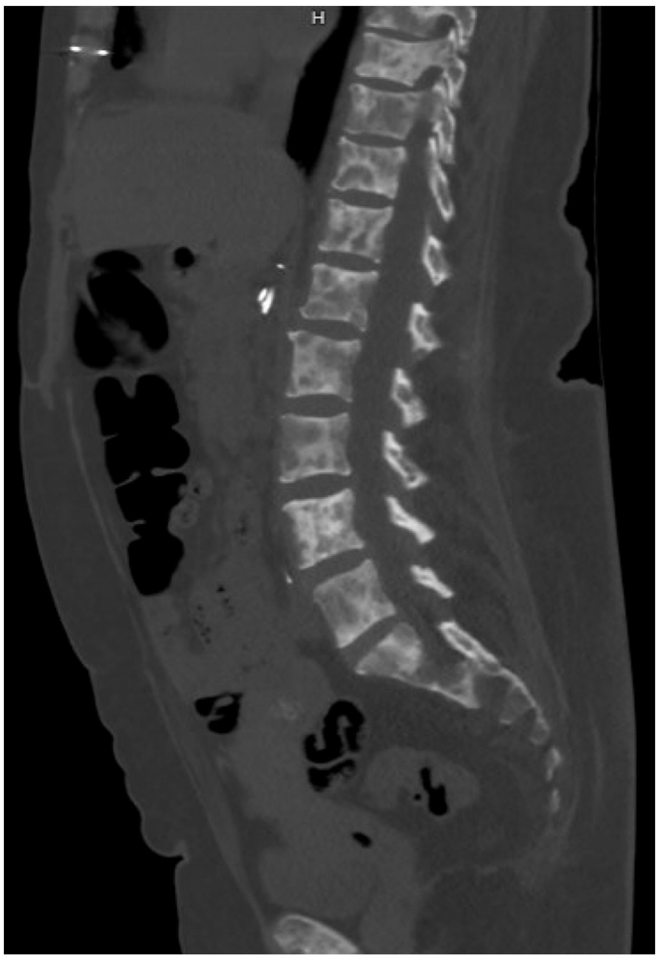

Fig. 2. Mixed lucent and sclerotic lesions Involving the vertebrae noted from CT scan. *CT* = computed tomography.

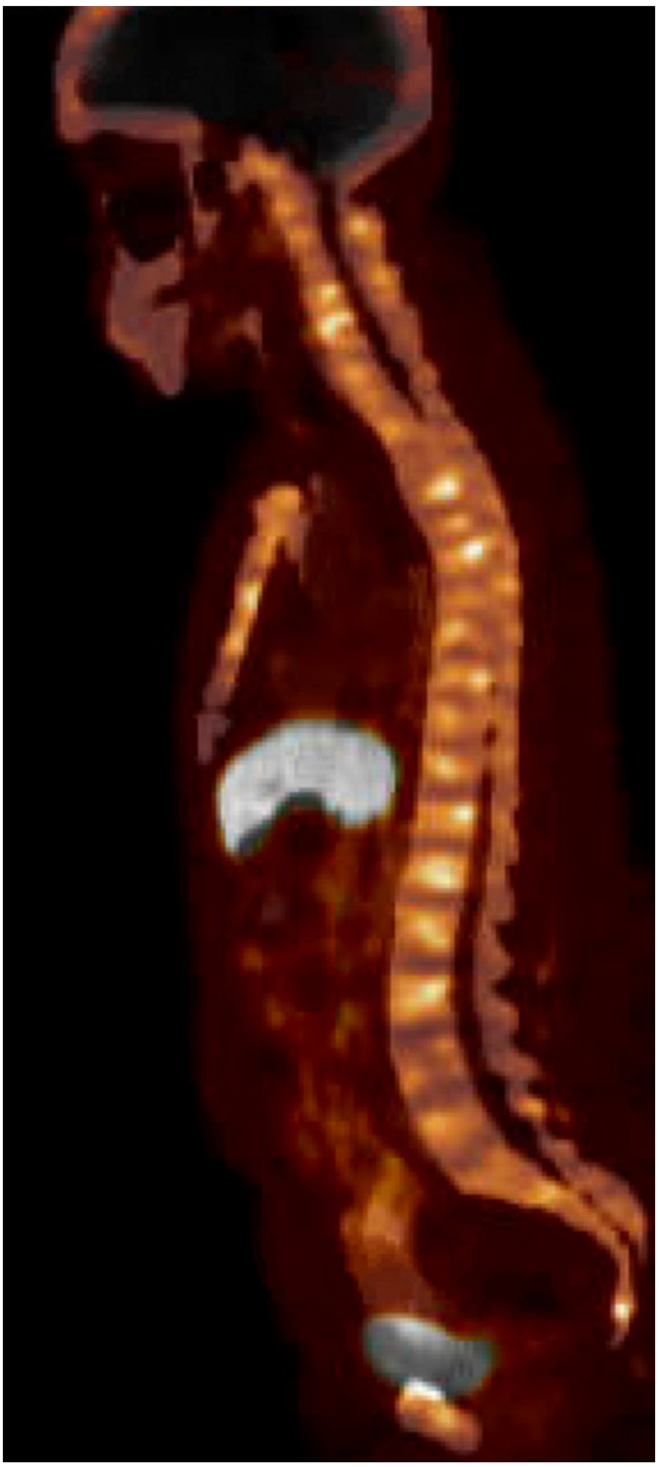

Fig. 3. Ga-68-DOTA PET/CT with innumerable DOTATATE avid lesions along the bones. *CT* = computed tomography.

pheochromocytoma is known to be associated with NF1, current guidelines do not recommend routine screening in asymptomatic individuals.[9] However, based on the high incidence of pheochromocytoma in NF1 patients with hypertension, it has been suggested perhaps in individuals with NF1 and hypertension, screening for pheochromocytoma should be encouraged. In our patient, who had a history of hypertension before being diagnosed with NF1, earlier screening for pheochromocytoma could have led to the timely detection and management, preventing life-threatening conditions such as congestive heart failure, and cardiogenic shock.

Surgical resection of the tumor is the treatment of choice in pheochromocytoma; however, it may recur in a subset of cases[2]. Individuals with a hereditary predisposition have a 3.4-fold higher likelihood of developing recurrent pheochromocytoma compared to those with sporadic tumors.[10] Tumor size, exceeding 5 cm and right-sided pheochromocytoma are thought to be independent factors for pheochromocytoma recurrence and a pheochromocytoma of adrenal gland scaled score value >4 has been associated with a higher risk of malignant pheochromocytomas.[2,11] Many malignant pheochromocytomas may appear benign at first and do not present with metastases at initial presentation and because there is no single reliable method to predict the postoperative behavior of pheochromocytoma after resection, current guidelines recommend lifelong annual biochemical testing after surgery to monitor for recurrence.[1,3] Based on the available pathology data from her adrenalectomies, this patient would have had a minimum pheochromocytoma of adrenal gland scaled score of 3 (2 points for central necrosis and 1 point for vascular invasion) for both tumors.[12] This in addition to the size of the tumors (5.4 cm and 18.5 cm for left and right respectively) and the patient's NF1 status, likely placed her at a higher risk for tumor recurrence and malignant disease. Given the higher risk associated with her tumors based on size alone and her NF1 status, it is unclear if perhaps a

total bilateral adrenalectomy would have been more beneficial in preventing disease recurrence and metastatic disease.

Finally, it is not clear if the risk of malignant pheochromocytoma is higher in individuals with NF1 compared to patients with sporadic tumors. Based on the results from a single literature review, it seems the rate of malignant pheochromocytoma in NF1 patients is around 11.5% which similar to the reported rate for sporadic malignant pheochromocytomas of 2% to 13%.[8,13] This rate for malignant pheochromocytoma in NF1 patients should be interpreted with caution given it is the result from a single literature review of 148 case reports. The lack of large studies investigating the true incidence of malignant pheochromocytoma in NF1 patients makes it difficult to gauge if a more aggressive initial treatment plan or investigation into metastatic disease should be implemented in this patient subset.

In addition to pheochromocytoma, NF1 patients are also at an elevated risk of various neoplasms, including breast cancer. A cohort study conducted between 1985 and 2000 involving 1607 patients revealed that 47 patients (2.9%) developed breast cancer, while 20 patients (1.2%) developed pheochromocytoma.[7] Our patient presented with a right breast mass and multiple pulmonary nodules with no associated DOTATATE uptake. We considered 2 possibilities: primary breast cancer with lung metastases or metastatic pheochromocytoma too small for PET detection. Further assessment of the right breast mass through ultrasound, mammogram, and biopsy would have been needed to clarify the etiology. Metastatic pheochromocytoma to the breast is rare and has been reported in only a few case reports.[14,15]

As of the present date, there remains no curative treatment for metastatic pheochromocytoma. The primary goal of treatment is to mitigate disease progression and enhance the patient's quality of life. For individuals with asymptomatic or indolent pheochromocytoma, a strategy of vigilant observation is typically employed. However, in cases of disease advancement, various therapeutic approaches are available. These encompass surgical debulking, radionuclide therapy with meta-iodobenzylguanidine (I-131), or systemic chemotherapy involving a combination of cyclophosphamide, vincristine, and dacarbazine. Bone is the most common site of metastases from pheochromocytoma for which pathologic fractures are a significant cause of morbidity in patients with metastatic disease.[16] Patients with bone metastases may undergo conventional external beam radiation therapy, radiosurgery, and receive bisphosphonates or denosumab.[17] This patient's treatment plan included the commencement of tyrosine kinase inhibitor Axitinib for metastatic pheochromocytoma and denosumab for bone metastases. Unfortunately, she passed away before completing her treatment plan. Although the increased risk of developing pheochromocytoma is a known complication of NF1, there remains little in the literature on optimal timing and management for both screening and treatment of pheochromocytoma in NF1 patients. Given the increased risk, it may be reasonable to take a more aggressive approach with screening and evaluation for malignant disease.

Author Contributions

E.Y., X.N., M.P. conceived the manuscript. E.Y., X.N. wrote the manuscript with contributions from M.R.S. and M.P.

Patient Consent

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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