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Case Report

Malignant Pheochromocytoma Diagnosed by Fine Needle Aspiration: Report of a Case with Unusual Clinical Presentation and Review of the Literature

Nadine Shabti*, Andressa Balbi, Taylor Avakian, Phillip Pearson, and Mohamad Aziz

Department of Pathology, American University of the Caribbean, USA

***Corresponding author**
Nadine Shabti, Department of Pathology, American University of the Caribbean,10129 Zion Drive, Fairfax, VA, USA, Tel: (571) 484 -1359; Email: nadineshabti@gmail.com

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Abstract

Pheochromocytoma (PCC) is the most common neuroendocrine tumor of the adrenal medulla in adults and is characterized by over-secretion of neurogenic amines resulting in the classical triad of symptoms including episodic headaches, sweating, and elevated blood pressure. In the rare case of malignant pheochromocytoma however, the clinical presentation becomes highly variable based on the targets of distant metastasis. Reported here, is a case of a 53-year-old African-American male with typical symptoms of a malignant PCC in addition to bilateral sensorineural hearing loss. This case highlights the unusual symptoms that can arise from metastasis of malignant pheochromocytoma while also considering the potential differential diagnosis of paragangliomas.

ABBREVIATIONS

PCC: Pheochromocytoma; US-FNA: Ultrasound Fine Needle Aspiration

INTRODUCTION

Adistinctproblemofdiagnosingmalignantpheochromocytoma is the significant variation in clinical presentation that can arise from distant metastasis and local infiltration in many systems including the auditory canals. Classical guidelines state that 10% of pheochromocytomas are malignant and 10% are extra-adrenal as these tumors can present anywhere along the sympathetic chain [1]. PCC is mostly sporadic, but may also be associated with familial disorders such as Neurofibromatosis I, Von Hippel Lindau disease, and multiple endocrine neoplasia type II [1]. Malignant pheochromocytoma is defined clinically by metastasis of chromaffin tissue to at least one non-chromaffin site with the most commonly involved areas including liver, lymph nodes and bone.Malignantpheochromocytoma is an uncommon tumor. There are few reports of its clinical course in the literature and thus, increased awareness of this possible diagnosis by pathologists and clinicians makes it important to include in the initial differential diagnosis.

CASE PRESENTATION

A 53-year-old African American man presented with one month of diffuse abdominal pain associated with nausea, emesis and anorexia. He also reported 15 pounds of recent unintentional weight loss and fatigue. He denied any past medical history beyond an episode of Bell's palsy of the left side several years prior to his current presentation, anda smoking history of 35 pack-years. Vital signs were stable upon admission and physical examination revealed normoactive bowel sounds, abdominal tenderness to palpation with guarding. No masses were appreciated due to pain on minimal palpation. Initial laboratory studies included normal complete blood count, renal and liver function tests, amylase, lipase, lactate, uric acid, and coagulation panel. However lactic dehydrogenase (LDH) levels were found to be elevated at 1222 U/L; although high LDH is a nonspecific indicator of neoplasia it is also viewed as a useful clue in the diagnosis of pheochromocytoma [2].

Evidence of malignancy and metastasis of suspected pheochromocytoma was apparent viaimaging studies. Computed tomography imaging of the abdomen/pelvis revealed a centrally necrotic cystic right adrenal mass (14 x 19 cm) with marked mural nodularity, and no significant calcification. In addition, multiple necrotic mesenteric lymph nodes, a 4.3 cm retroperitoneal necrotic mass inferior to the cecum, two cavitated masses in the right upper lung lobes, and scattered nodules in the left upper lobes were also noted.

Enhancing lytic lesions consistent with diffuse bony metastases were identified involving the left scapula, transverse process of C7, L3 spinous process, iliac bone, 9th and 6th ribs, and T10-11 vertebral bodies. The impression was a right adrenal mass, most likely a primary adrenal carcinoma with widespread pulmonary and osseous metastases.

Ultrasound guided fine needle aspiration biopsy (US-FNA) of the 9thrib wasperformed. As cytopathology results were pending the patient developed precipitous sensorineural hearing loss. A slight left ear hearing difficulty he endorsed on presentation worsened to complete bilateral hearing loss over the course of one week. Magnetic resonance imaging (MRI) of the brain showed leptomeningeal disease with bilateral metastases to the internal auditory canals (Figure 1). US-FNA biopsy results revealed malignant cytomorphologic features (Figure 2A & B). Immunocytochemical studies performed on cellblock prepared from the cytology specimen were positive for chromogranin (Figure 2C) and Synaptophysin (Figure 2D). These findings were diagnostic of metastatic pheochromocytoma, and consistent with initial laboratory studies showing urine Metanephrines 541mcg/24h and Chromogranin A 261 ng/ml.

Extirpative surgery was performed with removal of the pelvic/abdominal mass as well as the lung nodules and surgery was uneventful as planned.Due to extensive disease, the patient also received high-dose combined chemotherapy using cyclophosphamide, vincristine and dacarbazine (CVD) as well as internal radiation. Patient was in a relatively stable condition and was determined not to be too ill to benefit from such aggressive therapy.

Our patient was alive with disease for two years after which recurrence was identified in both lungs. Patient refused any additional treatment andexpired one year later due to massive metastatic disease and multiple organ failure.

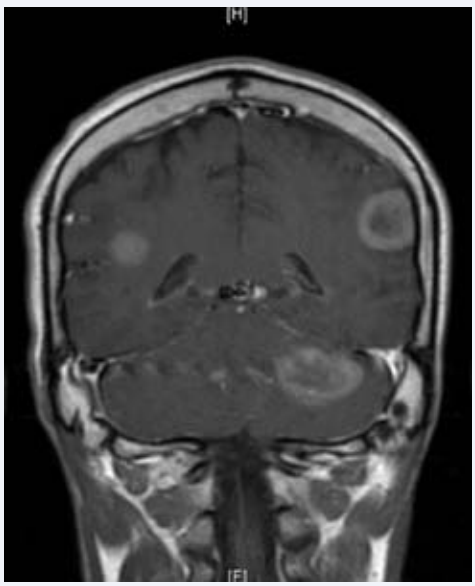

Figure 1 T1 weight post-contrast administration image. Enhancement within the ependymal surface of the lateral ventricles most pronounced in the periat rial regions, fourth ventricle as well as superior cerebellar sulci, and within the bilateral internal auditory canals.

DISCUSSION

Pheochromocytoma is an uncommon cause of hypertension in the general population, accounting for less than 1% of cases in hypertensive individuals [3]. In addition, of all pheochromocytomas, only 10% exhibit malignant behavior [4]. The most significant criteria that can definitively establish malignancy in a pheochromocytoma is recurrence of the tumor in sites devoid of chromaffin tissue [5]. Other considerations such as large size, extra-adrenal location, dopamine secretion, and a high ki-67 index are indicators for potential malignancy [5]. In our patient, malignant pheochromocytoma primarily produced a clinical syndrome of abdominal pain and nausea, dissimilar to the classic triad of hypertension, palpitations, and headache of PCC. The absence of these typical symptoms of PCC in the chief complaint drives the diagnosis away from benign and more towards malignancy [6]. A new mechanism to explain normotensive hypertension associated with PCC suggests a deficiency in dopamine-β-hydroxylase resulting in a decrease in norepinephrine [7]. However, the progressive hearing loss has not been described in the literature and may indicate malignant character as well as involvement of the auditory canals, an unusual site of distant metastasis.

Urinary Metanephrines have been determined to be the most sensitive diagnostic aids in identifying pheochromocytoma with accuracy rates of 95% and their significantly elevated levels in our patient supported this diagnosis [8]. Due to the importance of differentiating typical signs and symptoms of malignant versus benign pheochromocytoma several parameters were investigated including computed tomography. Computed tomography (CT) has been found to represent a major step forward in the overall management of PCC with 90% accuracy and was subsequently performed on our patient who unveiled bilateral adrenal lesions and necrotic areas of metastasis suggesting malignancy and distant spread [8]. The pathological differentiation amid clinically benign and malignant pheochromocytoma can be arduous to make [9]. However, in a study of several sympatho-adrenal paragangliomas only four factors were found to meaningfully correlate with malignancy including (1) extra adrenal location, (2) coarse nodularity of the primary tumor, (3) confluent tumor necrosis, and (4) absence of hyaline globules [10]. In our patient, malignancy was further supported by ultrasound guided fine needle aspiration lymph node biopsy which revealed clusters of pleomorphic, hyperchromatic pheochromocytoma cells amidst a necrotic background positive for markers of neuroendocrine tumor origin [4].

An important consideration in the list of differential diagnoses for pheochromocytoma is paraganglioma, an entity composed of chromaffin-cell tumors located at extra-adrenal sites along the sympathetic and/or parasympathetic chain [11,16]. Paragangliomas commonly occur from the head and neck to the pelvis and thus depending on the site of tumors, acoustic symptoms can develop [12,13]. Jugulotympanic paragangliomas (JTP) is a paraganglioma that arises in the middle ear and mastoid. This neoplasm is thought to originate from the minute paraganglia at the middle ear and base of the skull. It usually develops in the 5th and 6th decade of life at either side with equal frequency. It grows along the course of Jacobson's nerve in the middle ear

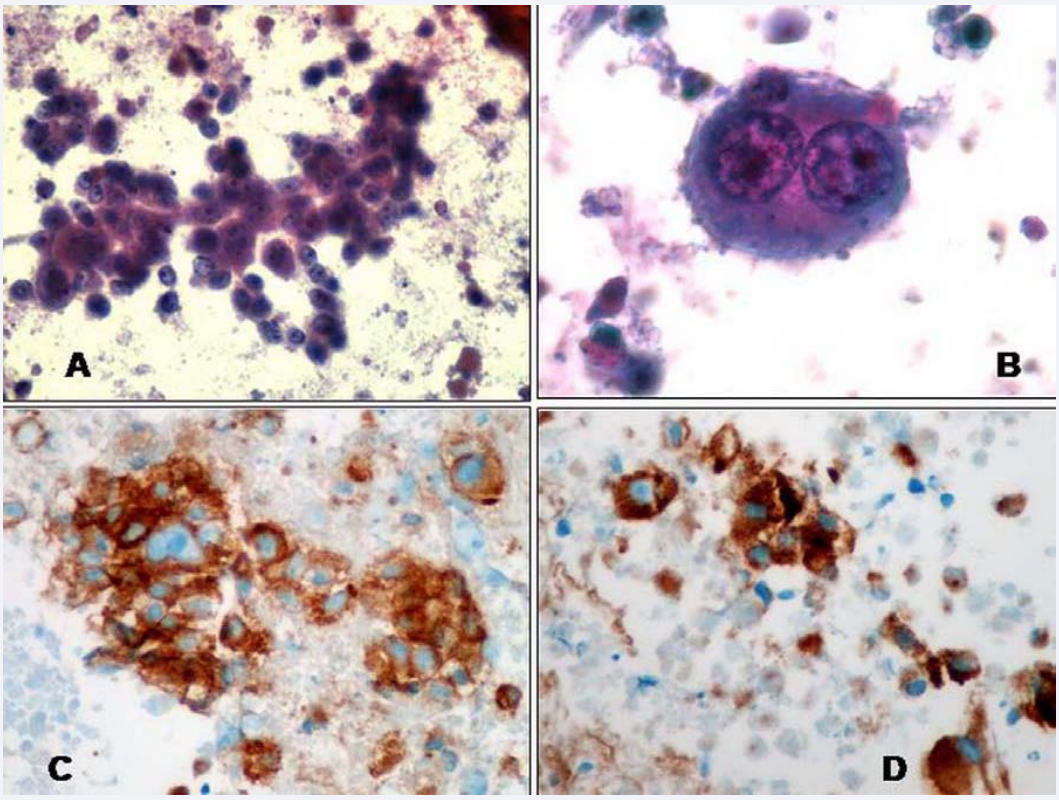

Figure 2 Pheochromocytoma cells arranged as loose clusters and single cells in a necrotic background. Papanicolaou, ×100(A). Pleomorphic large binucleated malignant Pheochromocytoma cell with prominent macronucleoli and stippled chromatin. Papanicolaou stain, ×200(B). Tumor cells are strongly positive for Synaptophysin (C). Tumor cells are strongly positive for Chromogranin (D).

cavity and can be associated with tinnitus, aural pulsations and conduction type hearing loss as it encroaches on the middle ear ossicles [14]. JTP can grow large enough to fill the middle ear cavity and bulge through the tympanic membrane, Eustachian tube or aditus ad antrum, with associated bony erosions. Given the similar syndrome of hearing loss that was seen in our patient, this neoplasm is an important entity to consider in the differential diagnosis of metastatic pheochromocytoma. One key difference is that these tumors are known to be mostly locally aggressive. In a study of JTP, regional and distant metastases were rare, with estimates by Alford and Guilford showing that less than 2% were metastatic and 3% were clinically malignant [14]. Inour patient, the nature of the hearing loss was sensorineural. Given the presence of the bulk of the tumor within the abdomen, with multiple sites of distant metastasis and bilateral middle ear involvement, the overall clinical presentation supported the diagnosis of malignant pheochromocytoma.

Since there is no definitive curative treatment for malignant pheochromocytoma and due to its poor prognosis, treatment initiatives are a prevalent topic of research. In a study conducted by Remine et al. reviewing 138 cases of pheochromocytoma encountered at the Mayo Clinic spanning the period offorty-four-year, the five-year survival rate subsequent to treatment for benign tumors was found to be 96% and for malignant tumors, 44% [17]. Currently a preoperative treatment regimen consisting of alpha and beta blockers followed by laparoscopic surgery to remove the tumor remains the gold-standard [3,16]. In a literature review conducted by Hartgrink et al., concerning the rare local invasion of the right atrium by a case of malignant pheochromocytoma, an aggressive surgical approach was always warranted as it provided relief of symptoms as well as prolonged survival [18].

To this day, there is much controversy over the parameters delineating malignant pheochromocytoma, with the general consensus identifying it based on metastasis to distant non-chromaffin sites. Consequently our case report serves to provide insight on a rare condition that strays from the classical textbook case. In addition, it is important to consider the differential diagnosis of a sympathetic/parasympathetic paraganglioma when investigating the potential for a malignant PCC as a similar clinical course can arise depending on the site of the tumor. While the populations involved in this etiology are a small subset of pheochromocytomas, no less attention should be given to this critical potential diagnosis. Exact survival has not been clearly reported, nor has an analysis of the efficacy of chemotherapy on survival time. Kaoru Nomura et al., analyzed the survival curves and survival times of patients with malignant pheochromocytoma and determined the efficacy of chemotherapy on prolongation of life. They reported an unexpected long survival time. They also noted that cyclophosphamide, vincristine, and dacarbazine (CVD) chemotherapy was not shown to extend survival, especially for women and patients with adrenal gland-derived primary tumors. They also reported that patients who already had metastases

at the time ofPheochromocytoma diagnosis had better survival than those whose metastases were found later [19].

Our case shows that definitive diagnosis of malignant pheochromocytoma can be based only on cytological specimens, especially when there is sufficient material to prepare a cellblock which can be utilized for immunohistochemistry studies as the case in our patient, and even molecular studies as needed. We also report this case with the unusual clinical presentation of seeding of the internal auditory canals and precipitous hearing loss, which may indicate additional feature of possible malignant disease.

It is our hope that this report raises awareness of what remain an unmet need in management of malignant metastatic pheochromocytoma and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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