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Perioperative management of patients with glioblastoma copresenting with pheochromocytoma: illustrative case

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BACKGROUND Undiagnosed pheochromocytoma can present with hemodynamic instability during surgical procedures. Here, the authors discuss a 69-year-old male with isocitrate dehydrogenase (IDH)–wildtype glioblastoma copresenting with undiagnosed pheochromocytoma, which, to the authors' knowledge, is the second reported case in the literature.

OBSERVATIONS The patient presented to the emergency department with a 1-month history of coordination difficulties, progressive morning headache, and mild left-side weakness. Imaging showed a 5-cm peripherally enhancing intra-axial right parietal mass with surrounding vasogenic edema. Intraoperatively, the patient had significant uncontrollable hypertension up to 240/120 mm Hg, and the operation was promptly aborted. Contrast-enhanced computed tomography imaging of the chest, abdomen, and pelvis identified a 4.9-cm left adrenal mass of indeterminant etiology. Endocrinology diagnosed the incidentaloma as a pheochromocytoma, initiating alpha blockade followed by beta blockade, and the urology service performed a laparoscopic adrenalectomy after patient stabilization. The neurosurgery service removed the intra-axial brain lesion 2 days after adrenalectomy, which was diagnosed as IDH-wildtype glioblastoma. The patient was discharged home after 6 days in stable condition.

LESSONS This case highlights the importance of preoperative screening for pheochromocytoma in neurosurgical patients with adrenal incidentalomas, especially in incidentalomas > 4 cm, even without high clinical suspicion.

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KEYWORDS glioblastoma; GBM; pheochromocytoma; perioperative management

Pheochromocytomas are catecholamine-secreting tumors that typically develop in the adrenal medulla, with the potential to induce paroxysmal hypertension and life-threatening cardiovascular complications.[1] The clinical manifestations of pheochromocytoma range from asymptomatic to acute hypertensive crises, presenting a challenge in perioperative management.[2,3] Their clinically significant and often paroxysmal symptoms underscore the importance of preoperative screening, particularly in patients with incidental adrenal masses, termed "adrenal incidentalomas," identified during imaging studies.

Adrenal incidentalomas are reported in approximately 4% of adult imaging studies,[4,5] with growing incidence with the increased availability and frequency of abdominal imaging.[6] Of these lesions, approximately 7% are pheochromocytomas,[6–8] which are characteristically lipid poor (< 10 Hounsfield units [HUs])[1,6,9,10] and tend to be larger than nonsecretory adenomas with an average size of 4–6 cm.[7,10–12] Pheochromocytoma symptoms include the classic triad of episodic headache, sweating, and tachycardia, and related clinical manifestations remembered with the 5 Ps: painful headache, palpitations, perspiration, pallor, and pressure (i.e., hypertension).[1,13] However, given the baseline prevalence of these signs and symptoms and the clinical variability of pheochromocytoma presentations, the presence and absence of these features have not been shown to be reliably sensitive or specific in the diagnosis of pheochromocytomas.[14,15] Thus, diagnosis can be difficult and is ideally made during the screening of

ABBREVIAITONS CNS = central nervous system; CT = computed tomography; [^{18}F]DOPA = [^{18}F]dihydroxyphenylalanine; HU = Hounsfield unit; IDH = isocitrate dehydrogenase; MRI = magnetic resonance imaging.

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known familial germline mutations (which account for up to 40% of tumors[16]) or investigation of an adrenal incidentaloma prior to potentially life- or organ-threatening clinical manifestations. In the context of brain neoplasms, computed tomography (CT) scans of the chest, abdomen, and pelvis are inconsistently ordered to investigate the etiology of new-onset brain masses, aiming to differentiate between primary brain tumors and metastatic disease.[17,18] While screening for pheochromocytoma is commonplace in suspected hemangioblastoma cases due to its association with von Hippel–Lindau disease, it is not a standard procedure for new intracranial masses, as the detection of adrenal incidentalomas in the preoperative neurosurgical setting is rare. However, if not appropriately addressed, the presence of a pheochromocytoma could precipitate a hypertensive crisis during surgical interventions.

In managing intracranial neoplasms with concurrent adrenal masses, preoperative identification of pheochromocytoma is important for optimizing patient outcomes, especially for intraoperative hemodynamic stability. This report highlights the case of a 69-year-old male with isocitrate dehydrogenase (IDH)-wildtype glioblastoma and an undiagnosed pheochromocytoma, prompting abortion of the neurosurgical procedure due to uncontrolled elevated blood pressure. The management of this patient included a workup and treatment for suspected pheochromocytoma prior to resection of the neoplastic brain lesion. We thus propose a management strategy involving initial history screening for neurosurgical candidates with adrenal incidentalomas, followed by endocrinological workup and treatment for suspected pheochromocytomas copresenting with brain lesions, with an emphasis on biochemical screening for patients with lipid-poor adrenal masses with either a positive family history or a tumor size larger than 4 cm, even in the absence of classic symptoms.

Illustrative Case

A 69-year-old right-handed male presented with a 5-week history of progressive morning headaches, mild cognitive impairment, decreased left-handed dexterity, and gait imbalance with deviation to the left. The headaches were described as right sided, with radiation from the right posterior neck, most severe in the mornings and were recently accompanied by nausea. The patient also reported a 2-year history of unintentional weight loss of approximately 20 pounds and occasional night sweats. He did not have any prior history of headache, palpitations, tremors, chest pain, or anxiety attacks. His medical history included hypertension, well controlled with hydrochlorothiazide and ramipril, as well as depression and dyslipidemia. His family history was negative for pheochromocytoma or the associated syndromes of multiple endocrine neoplasia, neurofibromatosis type 1, and von Hippel–Lindau disease.

Initial contrast-enhanced CT imaging of the head revealed a solitary heterogeneous, peripherally enhancing mass within the right parietal lobe, measuring 5.3 × 4.2 × 4.3 cm (anteroposterior by transverse by craniocaudal), with extensive surrounding vasogenic edema (Fig. 1). On brain magnetic resonance imaging (MRI) with gadolinium, the mass showed avid irregular peripheral enhancement on postcontrast images. Along with the surrounding edema, there was resulting mass effect, including sulcal effacement, subfalcine herniation, and mild right uncal herniation. The appearance was most suggestive of primary central nervous system (CNS) malignancy, with the differential diagnosis including brain metastasis. Contrast-enhanced CT of the chest, abdomen, and pelvis identified a 4.9-cm left adrenal mass that was indeterminate for benign or malignant characteristics, with a differential diagnosis of adrenal cortical carcinoma, adrenal metastasis, and pheochromocytoma (Fig. 2).

The size and mass effect of the brain lesion necessitated urgent resection, regardless of whether it was primary or metastatic. In the absence of typical symptoms of catecholamine excess, the patient was prepared for urgent craniotomy. On induction of general anesthesia and with positioning maneuvers, the anesthetist reported increases in blood pressure of up to 240/120 mm Hg, which were challenging to control. This prompted stopping the procedure and transferring the patient to the intensive care unit for blood pressure management and further investigation.

Endocrinology was consulted to guide therapy and workup. Biochemical investigation revealed elevated 24-hour urinary metanephrine (48.8 µmol/24 hrs, normal < 1.3 µmol/24 hrs) and normetanephrine (14.8 µmol/24 hrs, normal < 4.2 µmol/24 hrs). Other endocrinological workup was negative for abnormalities in serum cortisol, aldosterone, or renin. An [^{18}F]dihydroxyphenylalanine ([^{18}F]DOPA) scan demonstrated avid tracer uptake in the left adrenal mass, consistent with pheochromocytoma, with no sites of [^{18}F]DOPA avid metastatic disease. The brain lesion showed mild uptake, as seen in primary malignant brain tumors. Because of central photopenia of

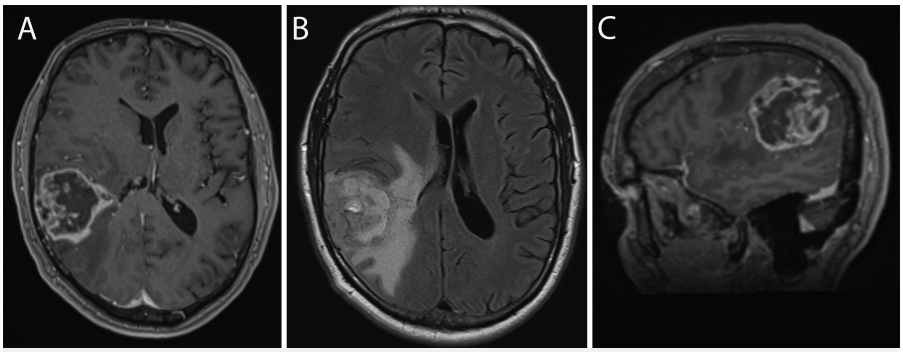

FIG. 1. Axial postcontrast T1-weighted (**A**) and T2-weighted fluid-attenuated inversion recovery (**B**) and sagittal postcontrast T1-weighted (**C**) MRI sequences demonstrating a large peripherally enhancing lesion in the right parietal lobe. A histopathological diagnosis was ultimately made of of IDH-wildtype glioblastoma.

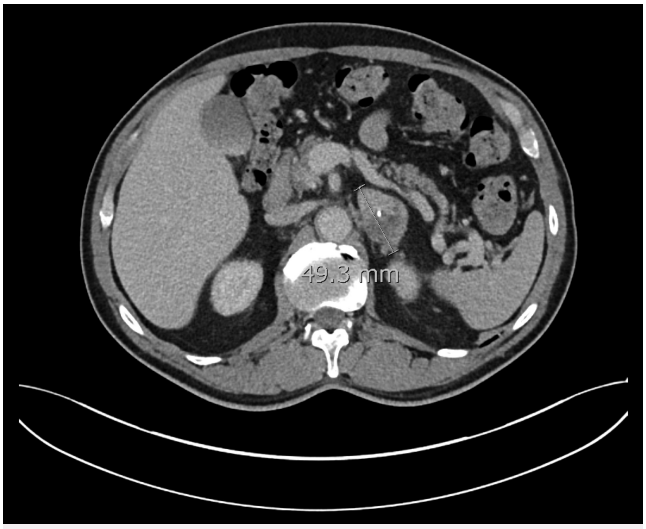

FIG. 2. Abdomen CT demonstrating a left adrenal mass, with histopathological confirmation of pheochromocytoma.

the adrenal mass in the [^{18}F]DOPA study, an [^{18}F]fluorodeoxyglucose positron emission tomography scan was obtained, which did not demonstrate metabolically active dedifferentiated adrenal disease. These investigations were expedited on an inpatient basis due to the intracranial malignancy with mass effect, during which time the patient was maintained on high-dose dexamethasone to control brain edema, with stabilization of neurological symptoms while awaiting neurosurgery.

Given the high clinical suspicion for pheochromocytoma, medical therapy was initiated for catecholamine excess, including alpha and beta blockades with terazosin and labetalol, respectively, and phentolamine as needed. A high-sodium diet and intravenous fluids were administered for intravascular expansion preoperatively. The urology team was consulted for the resection of the pheochromocytoma prior to rescheduling the craniotomy. When satisfactory control of the patient's heart rate and blood pressure was achieved over 9 days of medical titration (targets of < 90 bpm and < 120/80 mm Hg, respectively), left laparoscopic adrenalectomy was performed. Intraoperatively and briefly postoperatively, norepinephrine was required to treat hypotension, after which the blood pressure was well controlled with midodrine. Histopathological examination demonstrated a marginally excised, well-differentiated pheochromocytoma, with tumor cells staining diffusely and strongly positive for chromogranin and synaptophysin along with S100 staining of sustentacular cells. Genetic testing was negative for a hereditary pheochromocytom a-paraganglioma syndrome.

Two days later, right parietal craniotomy was performed with 5-aminolevulinic acid fluorescence guidance and intraoperative electrophysiological monitoring for the resection of the intracranial neoplasm. The blood pressure was stable throughout the procedure. Histopathological examination demonstrated a glioblastoma, IDH-wildtype, CNS World Health Organization grade 4. The patient recovered well, with improvement in preoperative motor deficits, and was discharged home on postoperative day 6.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

This report highlights the management of concurrent IDH-wildtype glioblastoma and pheochromocytoma. To our knowledge, this is the second case of concurrent glioblastoma and pheochromocytoma in the published literature.[19] The initial identification of an intracranial mass consistent with primary malignancy, alongside an indeterminate left adrenal mass on CT imaging, exemplifies a rare but clinically significant disease in the perioperative period.

The pathophysiology of pheochromocytomas involves excess catecholamine production, with the downstream conversion of tyrosine to dopamine, norepinephrine, and epinephrine.[20] These catecholamines are released into the circulation, where they exert their effects through alpha and beta adrenoreceptors on various organ systems, most notably the cardiovascular system.[21] Norepinephrine, predominantly released in a continuous manner by these tumors, primarily causes persistent hypertension through vasoconstriction mediated by alpha-1 adrenoreceptors on vascular smooth muscle cells. Epinephrine, released in a paroxysmal pattern, can lead to tachyarrhythmias by stimulating beta-1 adrenoreceptors in the heart, enhancing cardiac contractility and rate. Beyond these effects, catecholamine excess can disrupt cerebral autoregulation and contribute to chronic conditions such as pressure natriuresis and intravascular volume depletion, further complicating the clinical presentation.[21] The detection of excess catecholamines and their metabolites, normetanephrine and metanephrine, in serum and urine are hallmarks of pheochromocytoma.[22] Treatment of pheochromocytoma involves an initial blockade of alpha adrenoreceptors to mitigate the risk of hypertensive crises, followed by beta adrenoreceptor blockade as indicated, prior to excision of the adrenal tumor.

In the context of neurosurgical procedures, the alpha and beta effects of pheochromocytoma have the potential to cause severe hemodynamic instability. Current urology and endocrine guidelines recommend the screening for pheochromocytoma in all lipid-poor (i.e., ≥ 10 HUs) adrenal masses ≥ 1 cm,[6,9] with either a 24-hour collection of urinary metanephrines (which has a sensitivity of 96% and specificity of 94%) or serumfree metanephrines (which has a sensitivity of 96% and specificity of 95%).[23,24] We thus propose a protocol for the timing of pheochromocytoma screening in patients with lipid-poor adrenal masses who are being evaluated for neurosurgical management of brain neoplasms, balancing diagnostic efficiency and surgical safety.

If the planned surgery is elective, it should be delayed until investigations rule out pheochromocytoma. If surgery is emergent, it should proceed with caution, ensuring anesthesia personnel are aware of the possibility of an untreated pheochromocytoma. If surgery is urgent, we propose that in the absence of a family history of pheochromocytoma or known pheochromocytoma/paraganglioma germline mutations, and with an adrenal mass of < 4 cm, screening can be performed after surgery. However, if a positive family history is identified or the adrenal mass is ≥ 4 cm, then screening should be carried out preoperatively using whichever assay can be returned most quickly. Our rationale is based on the high degree of heritability of pheochromocytomas,[1,10,16] the correlation between pheochromocytoma and large adrenal incidentaloma size,[7,10–12] and the poor predictive value of "classic" clinical features of pheochromocytoma.[14,15] Screening should be done even when brain imaging suggests a primary neoplasm unrelated to the adrenal mass. Confirmation of pheochromocytoma requires careful management, including alpha and beta blockade and adrenalectomy, to prevent severe hemodynamic fluctuations during neurosurgical interventions. These investigations and interventions need to be

expedited in the setting of a likely malignant intracranial tumor causing symptomatic mass effect.

Lessons

This case highlights the importance of accurate preoperative screening for pheochromocytoma in patients presenting with brain neoplasms and concurrent adrenal incidentalomas. Undertaking neurosurgical procedures with an untreated pheochromocytoma could lead to catastrophic intraoperative complications, including uncontrollable hypertension and cardiac arrhythmias. A comprehensive investigation of imaging findings, coupled with a screening of hemodynamic effects of any copresenting adrenal tumors, is essential for ensuring patient safety during brain neoplasm resection.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Au, Keough, Levine. Acquisition of data: Au, Hagen, Levine. Analysis and interpretation of data: Au, Guo, Hagen. Drafting the article: Au, Guo, Hagen. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Au. Study supervision: Au, Arnason.

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