

Metachronous Metastasis of Pheochromocytoma to the Clivus: Report of an Exceptional Case

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Abstract

Pheochromocytomas (PCC) are rare neuroendocrine tumors of the medulla of adrenal glands. Malignant pheochromocytomas are even rarer and forming 10-25% of all PCC. The only criterion to establish malignant behaviour being distant metastasis to site without chromaffin tissue. We report an exceptional case of metachronous intracranial metastasis of pheochromocytoma to the clival bone in a 59-years-old patient. The patient was managed surgically for a right adrenal pheochromocytoma ten years before. Only six cases of intracranial metastasis of pheochromocytoma have been reported in the literature, and to the best of our knowledge, this is the seventh case and the first clival bone metastasis of this rare condition.

Keywords: Pheochromocytoma; Metastasis; Malignant; Clival bone

Introduction

Pheochromocytoma (PCC) is a rare catecholamine-producing tumor, which derives from the chromaffin cells of the adrenal medulla but may develop from extra adrenal paraganglionic tissues too [1-3]. On histopathological findings a PCC can initially be diagnosed as benign, however it is possible for metastasis to occur in other organs after resection [4-6]. PCC occur in less than five per million of the general population [2,7], and affect less than 1% of the hypertensive population [7]. The malignant forms of this condition are even rarer and form only 10-25% of all pheochromocytomas, with a median overall survival of 24.6 years and a median disease specific survival of 33.7 years [1]. Clinically, the symptoms are nonspecific which make pheochromocytoma an undiagnosed condition. Herein, we report an exceptional case of metachronous clival bone -metastasis of a right adrenal pheochromocytoma which was managed sequentially by partial excision ten years ago.

Case Presentation

The patient was a 59-years-old man who had a long history of adrenal pheochromocytoma disease that was discovered (at the age of 49). when he presented to an outside hospital with headaches, elevated systolic blood pressure above 160 mmHg at rest, extremely elevated blood pressure on mild and elevated catecholamines; at the admission Investigations revealed normal urinary epinephrine levels (1.7-22.4 mg/24 h), norepinephrine levels (12.1-85.5 mg/24 h). Family history was negative for Multiple Endocrine Neoplasia (MEN) and Von Hippel-Lindau (VHL) syndrome. MRI of the abdomen at that time demonstrated a large right-sided adrenal mass. A preliminary diagnosis of pheochromocytoma was suggested. Metaiodobenzylguanidine scan was negative, and surgical resection was recommended. The patient underwent resection of the adrenal tumor. A ¹³¹I Metaiodobenzylguanidine (MIBG) scan done at that time revealed no extra-adrenal hotspots. The diagnosis of pheochromocytoma was entertained and he underwent a left adrenalectomy with total excision of the tumor.

Grossly, the tumor measured 6.8 cm × 6 cm × 5.3 cm. Histology revealed a pheochromocytoma with characteristic immunohistochemical findings: Positive for, synaptophysine, chromogranine and PS100. MIB1 nuclear labelling was 8-10% suggesting malignant process. The tumor did not demonstrate local vascular invasion or evidence of extension outside the capsule. The PASS-score established was about 4, meaning high risk of malignancy. The patient remained asymptomatic for ten

years later. He developed progressive headache resistant to usual drugs and discrete diplopia. On examination, there were no neurological deficits noted. Urinary epinephrine and norepinephrine levels were in the normal range. Cranial MRI showed a Clival involvement by a process with encasement of the two vertebral arteries in T1 signal, and hyperintense central areas suggestive of degeneration or central necrosis, evoking metastasis (Figure 1).

The lesion was biopsied by transphenoidal approach by the neurosurgeon in our hospital. Grossly, the resected specimen matched with a red-brown bloody tissue. The most common histopathological morphology of PCC is a Zellballen growth pattern, separated by delicate fibrovascular stroma. However, in some cases of PCC, the Zellballen pattern is not seen, and a diffuse growth type pattern is detected. In our case, haematoxylin and eosin stain displayed atypical cells with eosinophilic cytoplasm and hyperchromatic nuclei and diffuse

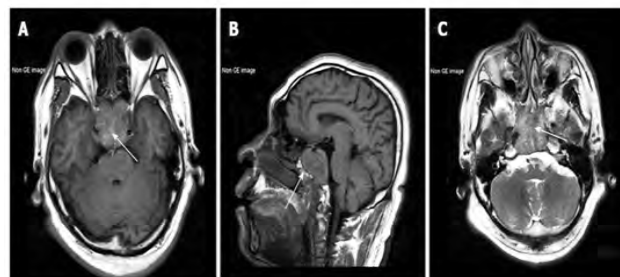


Figure 1: Brain magnetic resonance images. A: Axial T1-weighted magnetic resonance imaging (MRI) showing isointense mass (white arrow) with encasement of the bilateral carotid arteries; B: Sagittal T1-weighted MRI showing clival involvement (white arrow); C: Axial T2-weighted MRI showing hyperintense central areas suggest cyst degeneration or central necrosis (white arrow) evoking metastasis.

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pattern. the cells were arranged in sheets and clusters surrounded by labyrinths of capillaries. It was extensively haemorrhagic (Figure 2). Immunohistochemically, the tumor cells were noted to show a strong positive reactivity for Synaptophysine, CD56 and Chromogranine. The Pancreatin positivity was weak in this case. Additionally, for a differential

diagnosis with a glial tumor, there was no expression of GFAP, neither of PS100 by the tumor cells (Figures 3 and 4). Post operatively, the patient remained neurologically intact and was discharged in excellent condition. There were no complications during a follow up extended to 32 months.

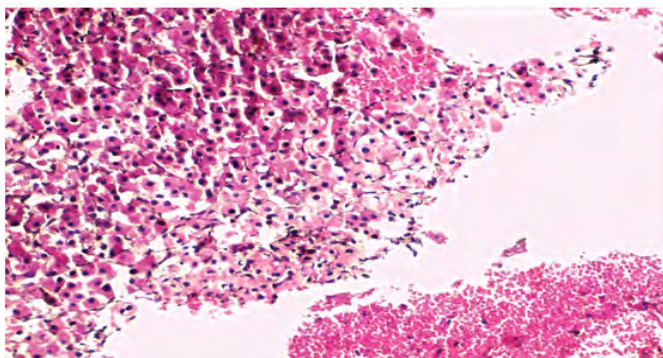


Figure 2: Atypical cells with eosinophilic cytoplasm and hyperchromatic nuclei and diffuse pattern [20x]. The cells were arranged in sheets and clusters surrounded by labyrinths of capillaries with areas of haemorrhage.

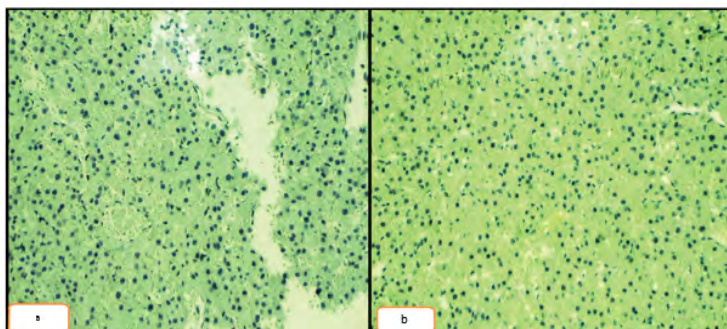


Figure 3: The tumor cells showed no expression of a. GFAP neither of b. PS100 [Magnification power 20x].

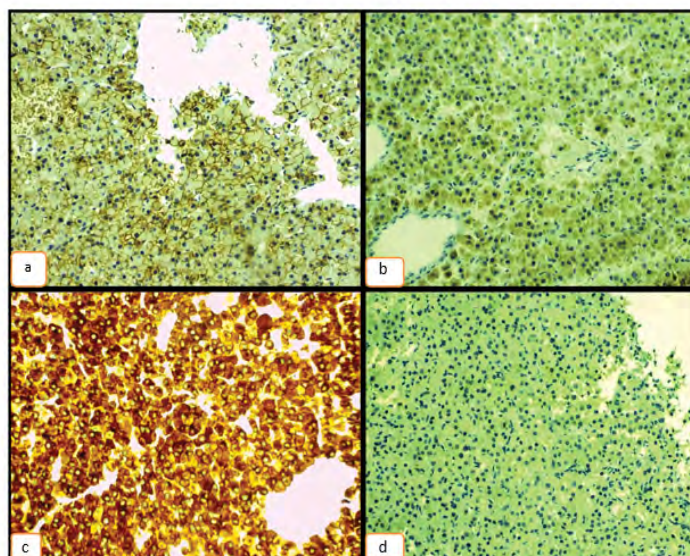


Figure 4: Intense positive staining of tumoral cells by: a: CD56. b: Chromogranin. c: Synaptophysin. d. weak and focal staining of tumoral cells by the CKAE1/AE3.

Study	Sex	Adrenal PCC laterality, age at resection (y) or discovered on autopsy	Intracranial PCC					Other
			Age (y) at diagnosis	Presentation	Location	Surgery	Immunohistochemistry	
Meningeal								
Epidural								
Boettcher [9]	M	Unilateral biopsy	24	Headaches, elevated systolic blood pressure, extremely elevated blood pressure on mild exertion, and elevated urine catecholamine	Right parietal mass	GTR Follow up 12 weeks	Synaptophysin chromogranin	SDHB mutation Death several weeks later
Epidural/Subdural								
Mercuri et al. [10]	F	Unilateral, 23	46	Headaches, vomiting, hypertension	Right temporoparietal extra-axial lesion with inner table skull infiltration. Epidural and subdural involvement without parenchymal infiltration	GTR, 6-year follow-up, no evidence of disease	Neuron-specific enolase, chromogranin A, synaptophysin	Authors labeled the tumor a multiple primary benign PCC
Cerebral								
Pallini R et al. [20]	F	Unilateral, 23	31	Partial motor crisis	Right frontal lesion	GTR, 4-year follow-up, no evidence of disease	Neuron-specific enolase, S100 protein and chromogranin; negative for anti-calcitonin antibodies	MEN type 2a (medullary thyroid carcinoma at age 9)
Ross et al. [14]	M	Unilateral, 41	49	NS	NS	NS	NS	Additional lung, lymph node metastases. Deceased 8 years after intracranial metastasis
Gruber et al. [3]	M	Bilateral, autopsy	47	Progressive Cognitive deterioration	Multiple lesions in Frontal, parietal, temporal and occipital lobes and cerebellum	None	NS	Death 22 days after presentation
Spatt and Ghayzel. [11]	F	Bilateral, autopsy	51	Headaches, falls, and memory loss	Multiple lesions in peduncles, cerebellum, pons, medulla and cerebrum	Right subtemporal decompression	NS	Death 8 days after presentation
Melicow [18]	M	Unilateral, autopsy	61	Headaches, convulsions, diaphoresis, palpitations, and hypertension	NS	None	NS	Death 6 weeks after presentation. Additional liver metastasis and carcinoid of ileum
Present case	M		59	Progressive drug-resistant headache	Clival bone (posterior fossa)		Chromogranin Synaptophysin CD56 S100 GFAP	The patient is well doing

PCC: Pheochromocytoma; NS: Not Specified; GTR: Gross-Total Resection; y: Years; MEN: Multiple Endocrine Neoplasia; SDHB: Succinate Dehydrogenase Subunit B

Table 1: Reported cases of primary and metastatic meningeal and cerebral pheochromocytoma.

Discussion

Pheochromocytomas are neuroendocrine tumors deriving from chromaffin cells. The reported incidence in literature is 0.9 per 100000 person years [1,2]. The only wide admitted criterion of malignancy remains the presence of metastases at distant sites that lack chromaffin tissue, other histological criteria of malignancy being inadequate alone to differentiate between benign and malignant forms [3-6]. The most common sites of metastases are bones, liver, kidney, lung and lymph nodes [3,7]. Intracranial involvement of pheochromocytoma is exceedingly rare, as only one case of primary meningeal disease and as few as five cases of metastatic cerebral disease have been reported previously Table 1 [8-10]. The current case of pheochromocytoma is unusual because the malignant character was diagnosed on the basis of a confirmed metastatic intracranial tumor in the clival bone. There are

34 reported cases of clivus metastases in the literature which did not include pheochromocytoma [11-25]. This is by far the first case of PCC metastases to the clival bone. The most frequent lesions of this region are Chordomas (accounting for 40%). Solitary non chordomatous lesions are exceedingly rare, particularly metastases [25]. The differential diagnosis can be challenging since they may appear clinically and radiologically similar to chordomas. Headache and diplopia are signs of the sixth nerve palsy by compression and are not specific (seen also in Chordomas) [25]. Histopathological study remains mandatory to make the accurate diagnosis, even if MRI aspect can be suggestive of metastases. In our case, there were no specific symptoms allowing to the diagnosis. The neurosurgeon thought first to a glial tumor, and the data concerning the primary adrenal tumor were also missing.

Moreover, the clinical presentation of pheochromocytoma can be varied: Hypertension, palpitations, headaches, sweating,

weakness, lethargy, pallor, anxiety and depression have all been reported as presenting symptoms [12-14]. Thus, the diagnostic may be very challenging; most patients show high levels of circulating catecholamine. Paroxysmal hypertension is seen in 40% of cases, it is the most common features [2-12], and it is frequently associated with episodes of the former symptoms [12,13]. However, our patient had no typical cardiac symptoms and maintained catecholamine levels within the normal range during the course of the case study. In some rare cases PCC are non-functional tumors (do not synthesise or release any catecholamines). Authors report that estimated diagnosis during life is less than half of the patients in whom it is formed at autopsy [15]. In an 18 year-review in Hongkong, undiagnosed tumor formed 17% of cases [16,17], and up to 75% in a series from the Mayo clinic: These tumors are likely to be underdiagnosed. According to the Mayo Clinic Autopsy study, conducted over a 50-year period, only 13 (24%) of 54 PCCs had been correctly diagnosed before death. It was also noted that 54% of the remaining 41 individuals reportedly experienced hypertension in their lifetime [5]. In a review by Melicow [18,19], only 17 of 100 cases of pheochromocytoma displayed no clinical symptoms suggestive of the disease, ten cases remained unrecognised until autopsy, and seven diagnoses were made during the exploratory surgery for the complaint. In no case was clinically silent pheochromocytoma diagnosed on the basis of distant metastasis. Scott and et al. [20] found an evidence of local distant metastasis in 8 of 64 patients with pheochromocytoma. Six of these patients initially showed the "typical" clinical features of pheochromocytoma.

Although metastases are reported in approximately 13% of cases of pheochromocytoma [1-20]. Distant metastasis occur less frequently. Among 72 patients described by Modlin et al. [21], 70 were diagnosed during life or at autopsy. In the series of Scott et al. [20], only two patients had histological confirmation of skull metastasis at any point during the course of their disease, and neither patient was direct intracranial extension of the pheochromocytoma demonstrated radiologically or at autopsy. Only few radiological descriptions of intracranial metastasis of PCC have been reported. James et al. [23] described, for 33 years, the roentgenological aspects of malignant PCC in 16 diagnosed patients during this period. In order of decreasing frequency, the most common sites of metastatic lesions were bone, lymph nodes, liver and lung. Two patients with skull lesions were described. In one patient, an osteolytic defect of the patient bone, which proved at surgery to extent to the dura as well as to the soft tissues of the scalp.

There is an association with the susceptibility gene (mutation of SDHB) with malignant pheochromocytoma [9]. Tumors due to SDHB gene mutation are often subclinical poorly differentiated, contain low amounts of catecholamines and are usually malignant at diagnosis [24]. The literature suggests that genetic alteration may be associated with cerebral metastasis in malignant PCCs. In certain patient groups with a mutation in the Succinate Dehydrogenase (SDH) gene, malignancy is reported to occur in as many as 83% of patients [24]. In the malignant PCC with brain metastasis case reported in 2010, deletion of chromosome 18 q is unique characteristics compared to the malignant process [24]. In our case, neither the patient, nor any member of his family, have a hereditary syndrome that will predispose to the development of PCC (like VHL, MEN type-2, Neurofibromatosis type I). Nowadays, no defined trustworthy predictors exist (neither clinical nor histological or molecular) of metastatic potential of PCC, in spite of that criteria supporting malignant disposition have been suggested [9].

The time of metastasis with pheochromocytoma is markedly variable and can occur as synchronous presentation with the primary

tumor [9] to over 15 years after benign presentation with complete absence of symptomatic malignant disease in the intervening period. MERCURI et al. [10] have reported a meningeal pheochromocytoma that was discovered 23 years after the initial resection of the adrenal primary tumor. In our case, the malignant character have been revealed ten years after the surgical cure of the adrenal tumor, by a distant confirmed intracranial-clival-bone metastasis which join the results reported by most authors. As far as our knowledge, the current case is the seventh case of intracranial metastasis of pheochromocytoma reported in the literature, and the first clival bone localisation metastatic site of pheochromocytoma being reported. This case is also illustrating the highly unpredictable behaviour of a completely excised adrenal pheochromocytoma a long period after excision.

Conclusion

In conclusion, there is always a definite risk of metachronous metastasis of pheochromocytoma, and a periodical screening with whole body imaging must be the rule during the follow up of patient with excised pheochromocytoma, even with normal abdominal imaging.

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