

Metastatic Paraganglioma: A rare Endocrine Tumor with an atypical presentation

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ABSTRACT

Background: Paraganglioma, rare endocrine tumors, are considered like pheochromocytomas but they arise from the autonomic ganglia outside the adrenal medulla. We report a case of a male with paraganglioma who presented with paraplegia and with an extensive metastatic disease at presentation.

Case presentation: A 48-year-old male presented with paraplegia for one week in neurosurgery clinic. He had a history of weight loss and intermittent hypertension for 1 year which was not associated with any headache, sweating or palpitation. His history of note was a hypertensive spell during his cholecystectomy three years ago, but it was not worked up further. His MRI spine showed multiple lytic lesions in the thoracic and lumbar spine with a paraspinal mass and multiple enlarged lymph nodes in the para-spinal and para-aortic location. His PET scan showed extensive disease with very high SUVs. A CT guided biopsy of Left paraspinal mass suggested paraganglioma. At this stage he was referred to the Endocrinology clinic. His plasma metanephrines levels were done which showed metanephrines 5840pg/ml (ref. range 0-190). Since the neurosurgeon decided for surgery, he was started on alpha blockers (Doxazocin 4 mg twice daily) followed by Beta blockers (Atenolol 75 mg once daily) to control blood pressure and prevent any Hypertensive crisis during surgery. He underwent D4 laminectomy and spinal decompression. After surgery his paraplegia improved to some extent. His I131 MIBG (Metaiodobenzylguanidine) scan was negative so this could not be a possible therapeutic option. His presentation suggests a very high possibility of SDHB mutation of paragangliomas. We have discussed the option of genetic testing with the family, but this is not available in Pakistan, so it could not be done till now. The three siblings of the patients were screened with the urine metanephrines, and all came out to be negative. The patient has been started on Chemotherapy with a VAD (Vincristine, Adriamycin, Doxorubicin) regimen and has experienced a slight improvement in his clinical condition.

Conclusion: Any patient with an increased pressor response to surgery or a diagnostic procedure must be screened for paraganglioma pheochromocytoma syndrome.

KEY WORDS: Paragangliomas, Pheochromocytoma, Paraplegia, Hypertension.

INTRODUCTION

Paragangliomas are infrequently seen, slow growing tumors arising from the sympathetic or parasympathetic ganglia, commonly in the head and neck region. Their presentation varies considerably. They may present as an asymptomatic mass, with symptoms caused by

compression of surrounding structures or by production and secretion of catecholamines. About 1% of tumors are functional and 2-10% of the paragangliomas are malignant. Metastasis to distant body sites is the only clue to their malignant nature.¹

We are presenting a case of an atypical appearance of a metastatic secretory paraganglioma, which is quite

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rare. This case also signifies the importance of timely diagnosis of this condition before the metastatic spread of disease. Although family history is negative in this case, genetic testing for hereditary paraganglioma/pheochromocytoma syndrome should be done in this patient, along with genetic screening of family members to diagnose the asymptomatic paraganglioma at an early stage.

CASE SUMMARY

A 48-year-old male married, non-smoker having no known co-morbid presented to the neurosurgery clinic with bilateral lower limb numbness and weakness. The weakness started gradually one week before presentation and progressively increased to the extent that he was unable to walk without support and presented to the neurosurgery clinic on a wheelchair. He also complained of a dull backache, constipation and urinary hesitancy since a month. There was no preceding history of fall or trauma. He had experienced significant weight loss over the previous 6 months. History was significant for an episode of hypertension documented at the time of laparoscopic cholecystectomy 2 years prior to presentation for which he required anti-hypertensives and was told that the blood pressure was very difficult to control at that time. He was prescribed anti-hypertensive medication at the time of discharge, but his home blood pressure monitoring was normal, so he stopped this. There was no history of episodic headache, palpitations, diarrhea or sweating. He has 5 brothers, and all are Hypertensive.

On examination, his weight was 60kg with a BMI of 20.33 kg/m² (normal range for Asians 18.5-23). He had a blood pressure of 150/90 and a spastic paraparesis with a sensory level at T5-T6. He was unable to stand. Rest of the examination was normal.

During investigations, magnetic resonance imaging (MRI) spine was done which showed a destructive compression fracture at C7 vertebral body. Multi-level lytic lesions were present with fracture and destruction

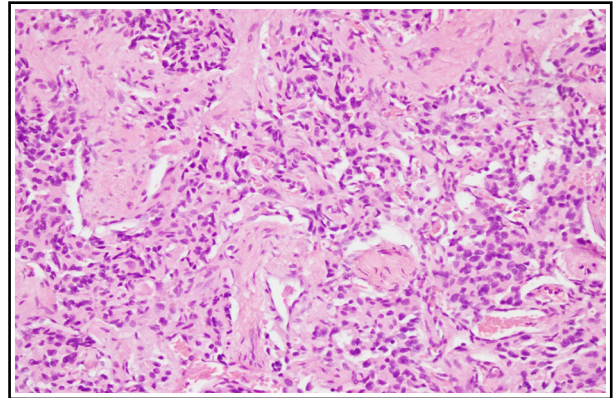


Fig.A: Tumor composed of small nests of polygonal cells with granular eosinophilic cytoplasm and rounded vesicular nuclei. Nucleoli are occasionally evident. These nests are surrounded by elongated sustentacular cells. No mitosis or necrosis is seen.

of posterior pedicle and spinous process, more marked at level of T4, T12 and L3. A lytic lesion with superior end-plate fracture was also present at T11 vertebrae. There was a left paraspinal mass with calcifications measuring approximately 38 x 56.2 mm. There was another soft tissue mass at left superior pubic ramus measuring approximately 54.8 x 43.2. Multiple enlarged lymph nodes were also noted in left para-spinal location largest one measuring 11mm in short axis. Few enlarged lymph nodes were present in left para-aortic location, largest one measuring 23mm in short axis. These findings were in favor of a metastatic disease involving the spine at multiple levels. A subsequent 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scan showed an extensive metastatic disease of high standardized uptake value (SUVs), maximum of 24 at the para-aortic nodal mass.

Computed tomography (CT) guided biopsy of left paraspinal mass was done, which was suggestive of paraganglioma. He had another hypertensive episode

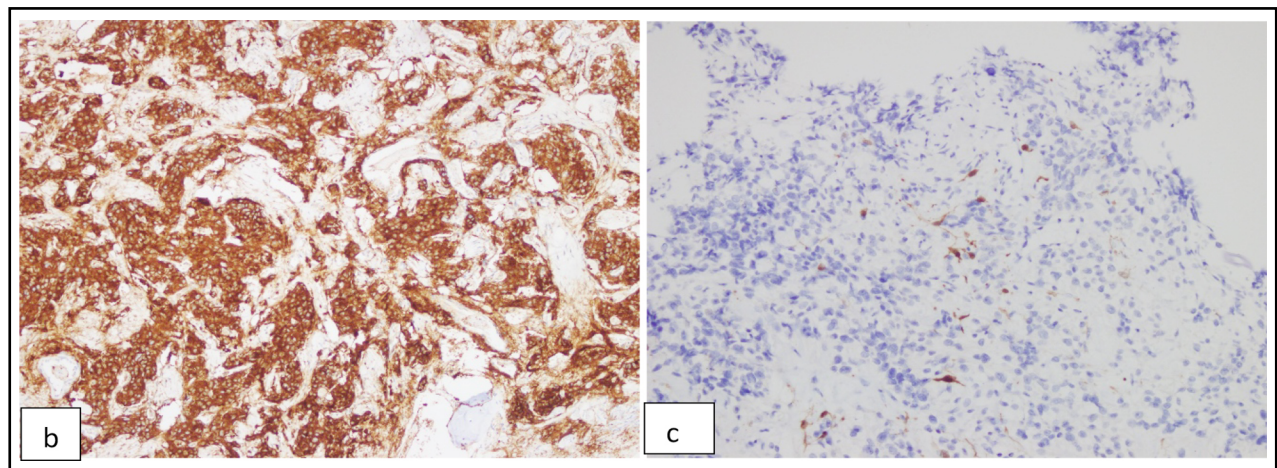


Fig.B & C: Immunohistochemistry was strongly positive for synaptophysin and S-100.

during this procedure. He was then referred to the endocrine clinic for further workup. Plasma free metanephrines and nor-metanephrines were advised, results shown below:

Plasma metanephrines	104.73 pg/ml (0-90)
Plasma nor-metanephrines	5840 pg/ml (0-190)

Since the neurosurgeon decided for surgery, he was started on an Alpha blocker (Doxazocin 4mg twice daily) followed by a Beta blocker (Tenormin 75mg once daily) to control his blood pressure and to

prevent any hypertensive crisis during surgery. He underwent D4 laminectomy and spinal decompression surgery, and his symptoms improved to some extent after that. Histopathology report also supported the diagnosis of paraganglioma. Immunohistochemistry was strongly positive for synaptophysin, and S-100 focally highlights sustentacular cells (Fig.A). It was also positive for Chromogranin A and Ki-67 score was low (Fig.B & C).

MIBG scan was performed after surgery, which was negative, so it could not be used as a possible therapeutic option. The presentation of this patient and negative MIBG scan suggest a likely possibility of SDHB mutation of paraganglioma. We have discussed the option of genetic testing with the family, but it's not available in Pakistan.



Fig.D: PET CT showing extensive metastatic disease and a paraaortic mass.

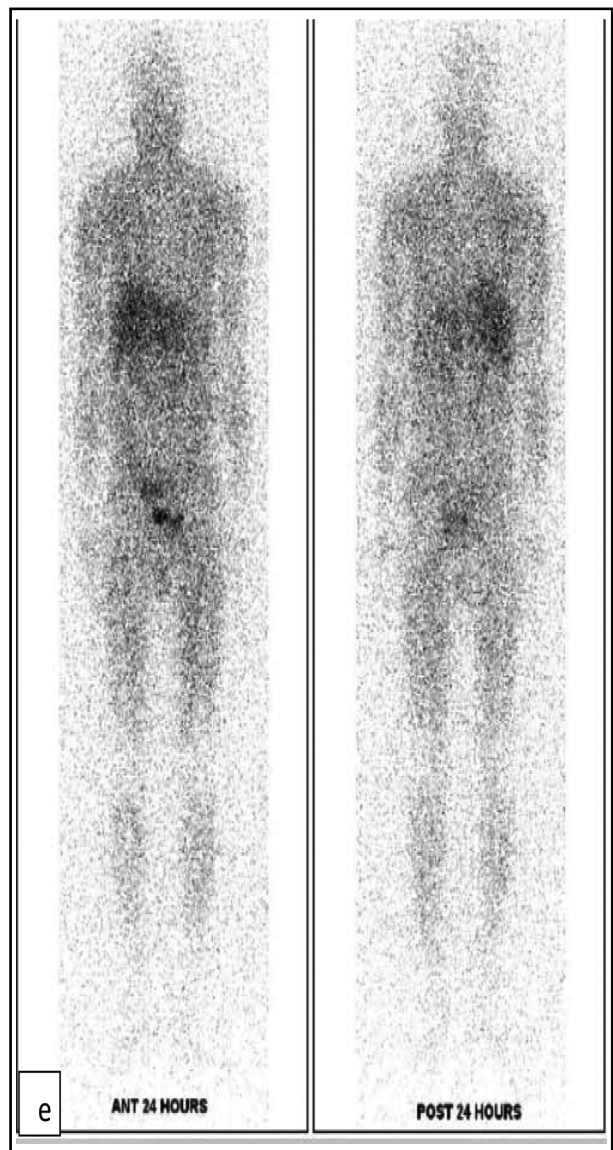


Fig.E: I-131 MIBG Scan with no uptake at primary or metastatic tumor sites

The patient has been started on chemotherapy with VAD (Vincristine, Adriamycin, Doxorubicin) regimen and has experienced a slight improvement in his clinical condition and is now able to walk with support.

DISCUSSION

The word Paraganglioma was first coined by Kohn in 1900. These are rare neuroendocrine tumors arising from autonomic paraganglia.¹ Paragangliomas are considered related to Pheochromocytomas, which arise from the chromaffin cells of the adrenal medulla and are, in turn, sometimes referred to as intra adrenal paragangliomas. In 2004, World Health Organization (WHO) developed a classification of the neuroendocrine tumors and according to this, the tumors confined to adrenal gland are termed as pheochromocytomas and those outside the adrenals arising from the autonomic ganglia are known as extra adrenal paragangliomas.²

Paragangliomas are found in only 0.05-0.1% of individuals who present with hypertension.³ They have been studied most of the times with pheochromocytomas, so individual prevalence/incidence is difficult to determine. In combination, these two are found in about 500-1500 cases/year in the United States(US).⁴ Majority of them are benign, while malignant paragangliomas are reported as 15-25% of total PPGL cases.⁵

Paraganglioma is a neoplasm of adults appearing in their 5th or 6th decade of life and found equally in both genders. Majority of these are sporadic while 10-50% may be familial associated with syndromes like Von Hippel-Lindau disease (VHL), neurofibromatosis 1 (NF1), multiple endocrine neoplasia 2 (MEN2) or secondary to mutations in genes coding for the enzyme Succinate Dehydrogenase (SDH) subunits i.e. A, B, C, and D. Depending upon the gene involved, they are classified as PGL1, PGL2, PGL3, PGL4 and PGL5.⁶ In our case, we have not been able to get genetic testing of this patient yet as this is not available in Pakistan. His presentation is likely suggestive of a mutation in the SDHB gene (PGL4). This mutation is most linked with abdominal/thoracic extra adrenal pheochromocytoma/paraganglioma syndrome which present at a young age, are multiple and more aggressive with higher chances of metastasis at presentation, features correlating with our patient. On the other hand, metastasis is rarely observed in patients with VHL, NF1 and SDHD mutation related disease.⁷ The immunohistochemistry staining can also help to differentiate between SDH subunits but unfortunately this too is not available in our setup.

As per location, paragangliomas can arise from sympathetic ganglia or parasympathetic ganglia and these are either secretory/functional or non-secretory/non-functional depending upon catecholamine secretion. Parasympathetic paraganglioma arise from the neck and base of the skull in the majority of cases mainly along carotid body, glossopharyngeal or vagal nerves or their branches.⁸ About 80-90 of these parasympathetic paraganglia are non-secretory and present with compression of surrounding structures.⁹ Sympathetic

paraganglia originate from sympathetic ganglia and 75% are present in the abdomen while 10% are in thorax. They have the ability to secrete catecholamines (norepinephrine and epinephrine) or in some cases dopamine.¹⁰ As extra adrenal paragangliomas are deficient in the enzyme phenyl ethanolamine N-methyltransferase (PNMT) which is responsible for the conversion of norepinephrine to epinephrine, they mainly secrete norepinephrine or its metabolite normetanephrines.⁸

Our patient had functional paraganglioma which was secreting normetanephrines in excessive amounts. Although he did not present with the typical history of paroxysmal headache, diaphoresis or palpitation, he did have episodic hypertension documented at the time of laparoscopic cholecystectomy which was difficult to control. This remained undiagnosed and he later presented with metastatic disease leading to compression of spinal cord and paraparesis. This points to the fact that young patients with hypertension should be evaluated for secondary causes of hypertension⁸ even if the patient does not display classic symptoms of paroxysmal headache, palpitation or sweating. Initial evaluation for pheochromocytoma/paraganglioma requires measurement of plasma or urinary fractionated metanephrines. Once confirmed biochemically, localization of tumor is required by radiological assessment either by CT or MRI. Both modalities are good with sensitivity of CT scan ranges 95-100% and specificity of 67% while the sensitivity of MRI is 98-100% and specificity is 70%.¹¹

Another imaging modality is I¹²³/I¹³¹ Metaiodobenzylguanidine (MIBG) scan. MIBG is similar to norepinephrine and gets accumulated into the adrenergic tissue in body thus, can be used as diagnostic as well as therapeutic purposes. It has sensitivity and specificity of 77% and 100% respectively. But the sensitivity falls to 57% in the presence of metastasis and SDHB mutation, for which FDG PET is more helpful.^{12,13} Our patient had a large burden of disease on PET scan with high SUVs, likely indicating MIBG negative disease. The MIBG scan had been requested by a neurologist prior to consulting with the endocrinology team and it came out negative, as expected. The studies have shown that almost 15% of paragangliomas are metastatic but in MIBG negative cases the rate rises to 77%.¹⁴ The patients with SDHB mutation and MIBG negative disease have shorter life expectancy and higher chances of malignant /metastatic disease. In MIBG avid cases, this agent can also be of therapeutic use for inoperable cases.¹⁵

In all patients with paraganglioma, genetic testing should be advocated, especially if the disease is diagnosed at a young age, as in the case of our patient. Absence of family history is not enough, and all family members should be screened.⁶

From management perspective, surgical removal of the tumor is the mainstay of treatment. In cases of metastatic disease, surgical debulking is done to reduce the disease burden, as adopted in our patient.¹² Before going for surgery, it is important to control blood pressure and initiate alpha blocker, followed by beta blockade, to

prevent the hypertensive crisis during surgery. Another point of note is that the patient had another episode of hypertension at the time of CT guided biopsy of the paraspinal mass, as he had not been prepared with alpha and beta blockade prior to this procedure. Although his blood pressure was not elevated at the start of the procedure, such stressful manipulations can precipitate a hypertensive crisis that can be fatal. Other than surgery, treatment options include adjuvant radiation therapy and combination chemotherapy with chemotherapeutic agents which include cyclophosphamide, dacarbazine and vincristine.¹² Such patients require long-term follow up to monitor for residual or recurrence of disease.

In collaboration with an oncologist, we have started this patient on chemotherapy with VAD (Vincristine, Adriamycin, and Doxorubicin) and he is tolerating it well. He has improvement in his symptoms to some extent and he can now walk with support.

CONCLUSION

Careful evaluation for secondary causes of hypertension should be considered in young patients, even in the absence of typical symptoms. Paranglioma/pheochromocytoma syndrome can have varied clinical presentation and clinicians should have a low threshold to screen for these. This is important for timely detection of the disease process at an early stage and initiation of appropriate management accordingly. Another important point is the pre-operative management of these patients, which requires good blood pressure control with alpha blockers and beta blockers. This patient had CT guided biopsy of paraspinal mass without first controlling the blood pressure and this led to a hypertensive spell during the procedure. This could be fatal for such patients. Similarly, patients with a presser response to surgery or a diagnostic procedure should also be screened for secondary hypertension. This patient could have been diagnosed earlier if work up had been done at the time of his first surgery (cholecystectomy) many years earlier.

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Authors Contribution:

Sumerah batool and aisha Shaikh both managed the case and contributed to the literature search and manuscript writing.

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