^{131}I-MIBG ON DIAGNOSTIC AND THERAPEUTIC FRONTIERS IN EXTRA-ADRENAL ABDOMINAL PARAGANGLIOMAS: A CASE REPORT WITH MINI REVIEW

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ABSTRACT

Paraganglioma are tumors originating from paraganglial system and may be associated with parasympathetic (head, neck and anterior mediastinum tumors) or sympathetic (adrenal or extraadrenal or posterior mediastinal tumor) system. Majority of sympathetic paraganglioma and minority of parasympathetic tumor are functional and ^{131}I or ^{123}I labeled MIBG (Meta Iodio Benzyl Guanidine) is a well established tool with good sensitivity and exceedingly high specificity. We are presenting a case report of a large extradrenal paraganglioma with extensive bony metastases and raised serum Chromogranin-A level. In this case ^{131}-MIBG was not only helpful in revealing the true burden of functional disease but also showed an overwhelming therapeutic response proven on post-therapy MIBG scan and normalization of serum Chromogranin-A level. This case report is followed by a mini-review about pathology, genetic mutation, diagnosis and treatment of focused on extraadrenal paragangliomas.

Key words: paraganglioma; extraadrenal; MIBG; MIBG therapy; FDG-PET; Somatostatin receptor imaging

Case Report

We present a case of 39 years old male, known diabetic and mildly hypertensive with 8 months history of lower backache. His MRI spine revealed a large retro-peritoneal mass close to left kidney with abnormal signal intensity lesions over T10-11, L1,2,4,5 and both iliac bones with a provisional diagnosis of lymphoma (Fig. 1). A subsequent CT abdomen and Chest with contrast showed a large heterogenous enhancing soft tissue mass with necrosis located medially within left perinephric space displacing renal vein anteriorly, renal artery and ureter posteriorly. The mass lesion was also associated with multiple lytic bony lesions (Fig.2).

There was no evidence of pulmonary or liver metastases. After 3 days a whole body radionuclide bone scan (Techentium-99m Methylene Diphos-phonate) was performed which revealed multiple bony metastases with lateral displacement of left kidney due to clinically known retroperitoneal mass (Fig. 3). A CT guided core biopsy of left sided abdominal mass was done and histopathology revealed paraganglioma. His vanillylmandelic acid level was raised (30 mg; Normal <13.6 mg). He underwent an exploratory laparatomy and retroperitoneal mass was resected with left kidney. Histopathology revealed paraganglioma (Ki-67 proliferative index 15-20%) and no evidence of tumor invasion to left kidney.

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Figure 1: T1 pre and post contrast Sagittal and T2 sagittal images showing a area of abnormal T1 signal with enhancement. Axial post contrast T1 shows the vertebral lesion along with an enhancing mass adjacent to the left kidney.
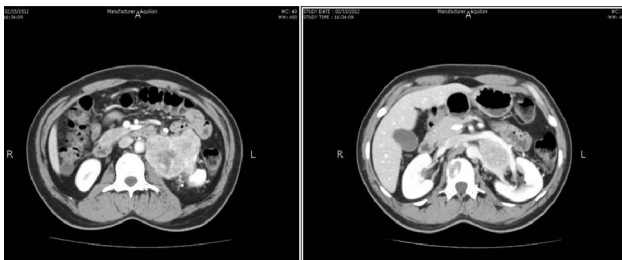

Figure 2: Axial contrast enhanced CT scans through the upper abdomen. There is a heterogeneous enhancing lesion in the left lumbar area lying medial to the left kidney and behind the renal vein. No evidence of vascular invasion. Note the lytic lesion in the adjacent vertebral body consistent with a metastatic deposit.


Figure 3: Tc-99m MDP bone scan showing desne tracer uptake over L1 (right side) and small areas of uptake over right 3rd rib and left 7th rib. Left kidney is displaced laterally (arrow) due to retroperitoneal mass.

In view of multiple bony metastases, I-131 labelled MetaIodo Benzyl Guanidine (MIBG) therapy was considered and a diagnostic whole body scan with 1 mCi of ^{131}I-MIBG was performed to assess extent and avidity of functioning metastases for MIBG. This scan showed widespread MIBG-avid bony metastases involving predominantly axial skeleton (Fig. 4). His serum Chromogranin-A (CgA) level was >600 ugm/liter (Normal : <36.4 ugm/liter). In June and October 2012 he received 400 mCi of ^{131}I-MIBG (200 mCi per session) and in December 2012 his CgA level came down to <6 ugm/liter (below normal limits). In January 2013, his follow up diagnostic whole body ^{131}I-MIBG (1 mCi) revealed complete resolution of metastatic foci with very subtle uptake over L1 and L4 consistent with complete response to radionuclide therapy (Fig. 5).
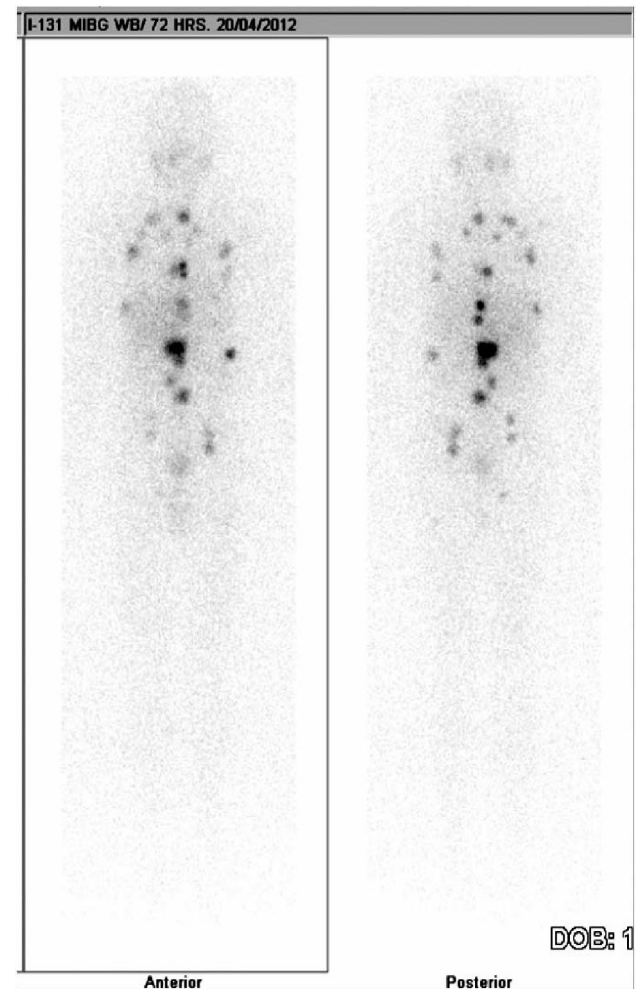
Figure 4: ^{131}I-MIBG diagnostic scan (72 hours; post-operative but pre-MIBG therapy) showing more extensive functioning bony metastases as compared to 99mTc-MDP bone scan.

WholeBody(96 HRS) 19/01/2013

2567361 Anterior   Posterior

DOB: 1
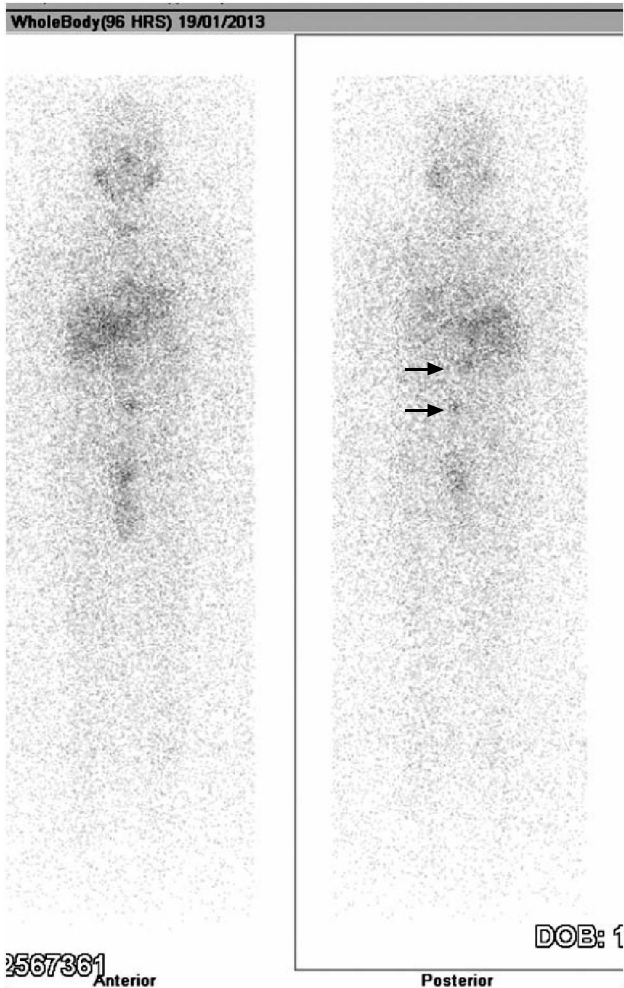
Figure 5: ^{131}I-MIBG diagnostic scan (96 hours; post-MIBG therapy – 400 mCi) showing complete resolution of functioning bony metastases with subtle uptake over L1 and L4 (arrows).

Introduction

Pragangliomas are tumors that originate from neural crest stem cells and may arise anywhere along the paraganglial system and can be associated with parasympathetic or sympathetic nervous system. The parasympathetic paragangliomas develop from endocrine cells in branchiomeric paraganglial (chemo-receptors) and primarily located in head, neck and anterior mediastinum.[1] The sympathetic para-gangliomas are derived from chromaffin cells of adrenal medulla (pheochromocytoma as per WHO's 2004 classification), the organ of Zuckerkandl, and less commonly in urinary bladder (trigone) and gall bladder.[2] Majority of sympathetic paragangliomas are functioning with raised plasma and urinary levels

of catecholamines (epinephrine, norepinephrine and dopamine) while majority of parasympathetic PG (5-10%) are non-functioning.[3]

Extraadrenal paragangliomas (EAP) of abdomen are usually retroperitoneal and arise primarily from the organ of Zuckerkandl and affect predominantly adult in 4th and 5th decade with no gender biasness.[4] Most paragangliomas are solitary and arise sporadically but about 25% are hereditary with a propensity for multifocal disease.[5] Due to this high incidence of hereditary syndrome, it has been proposed that all patients diagnosed with a pheochromocytoma or paraganglioma should consider genetic testing.[6] Majority of EAPG are functional and secrete cathe-cholamines and related classical presentation like headache, palpitation and sweating.[7,8] While less commonly EAPG are non-functional and presented with a palpable mass or pain and other local symptoms due to retroperitoneal mass.[9] Approximately 10% of EAPG are non-functioning and detected incidentally (incidentaloma) during imaging for other clinical problem.[10] So far 10 susceptibility genes have been identified for paragangliomic tumors including succinate dehydrogenase (SDH-B, SDH-C, SDH-D), Von Hippel-Lindau disease (VHL), RET (REarranged during Transfection) in Multiple Endocrine Neoplasia type 2 (MEN2) and type-1 neurofibromatosis.[2] Most EAPG are highly vascular, rubbery, firm with well demarcated and expansile borders, ranging in diameter from few centimeters to 20 cm. Micros-copically they are composed mainly of chief cells in a trabecular pattern with bands of highly vascular fibrous bands. No welldefined criteria for malignant paraganglioma exist for histaopatho-logically[11] except the presence of documented metastases to regional lymph nodes, bone, liver and lung. The incidence of malignant paragangliomas, varies from 2% to 36%[12,13] for sporadic cases and >50% for patients with SDHB mutations.[14]

Diagnosis

A. Biochemical Markers:

As majority of EAPG are functional and secrete catecholamines which are metabolized within chromaffin cells tometanephrines (norepinephrine to normetanephrine and epinephrine to metanephrine,

respectively), and this intratumoral process occurs independently of catecholamine release. According to current recommendations, initial testing for paragangliomas must include measurements of fractionated metanephrines in plasma, urine, or both, as available.[15] Blood sampling must be performed in supine posture after approximately 15 to 20 minutes of intravenous catheter insertion. Raised plasma metanephrines level more than 4-fold above the upper reference limit is associated with around 100% probability of the tumor.[16] However, if plasma metanephrinevalues are above the upper but less than 4 fold reference limit, clonidine suppression test combined with measurements of plasma catecholamines and normetanephrine may prove useful.[15]

B. Imaging
B1. Anatomical imaging:
Cross sectional anatomical imaging: like computed tomography (CT) or magnetic resonance imaging (MRI) is recommended for initial tumor localization, preferably MRI in children and pregnant or lactating women because of concerns regarding radiation exposure. On contrast-enhanced CT scans, these tumors appear as para-aortic soft-tissue masses with either homogeneous enhancement or central areas of low attenuation (Fig 6). Smaller tumors are more likely to be homogeneous in attenuation and sharply marginated as compared with larger ones. Punctate calcification or focalareas of high attenuation caused by acute hemorrhage may be seen in some tumors.
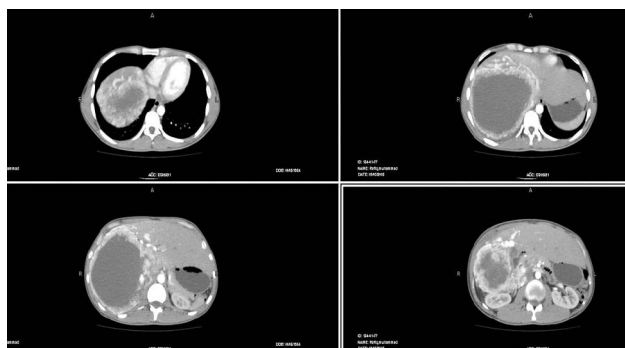

Figure 6: Post Contrast Axial CT of the upper abdomen showing a large, highly vascular lesion with central necrosis in the right lobe of the liver.

CT can be performed safely with intravenous nonionic contrast material as no elevation of serum catecholamine levels have been found in recently

studies.[17] On MRI these tumors are usually hypo-intense or isointense compared with the liver parenchyma on T1-weighted images and are markedly hyperintense on T2-weighted images[18] (Fig. 1). CT and MRI,unlike MIBG scintigraphy, are not useful in differentiating functioning from nonfunctioning-paragangliomas. Even though MRI and CT have excellent sensitivity (90-100%), the ability of CT and MRI alone to specify a paraganglioma is 70-80%.[19]

B2. Functional Imaging
i) Meta IodoBenzyl Guanidine (MIBG), labelled with either [123]I (pure gamma emitter) or [131]I (beta particle and gamma rays emitter), is a norepinephrine analogue taken up from the circulation by adrenergic tissues via norepinephrine transporter (NET) [type-I uptake]. MIBG scintigraphy provides useful functional information and can be used for the detection of multipleprimary tumors, tumors outside the usual locations, or metastases (Fig. 7 and 8). MIBG scanning offers very good specificity (95–100%) but suffers
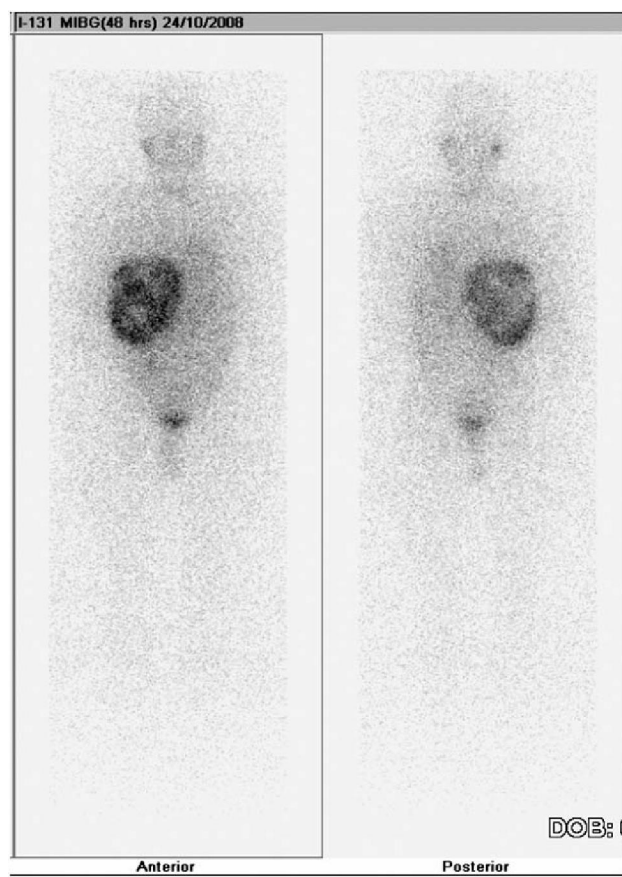
Figure 7: ^{131}I-MIBG diagnostic scan (48 hours; pre-operative) showing a huge biopsy proven paraganglioma occupying the almost whole of right hepatic lobe but no distant metastasis.
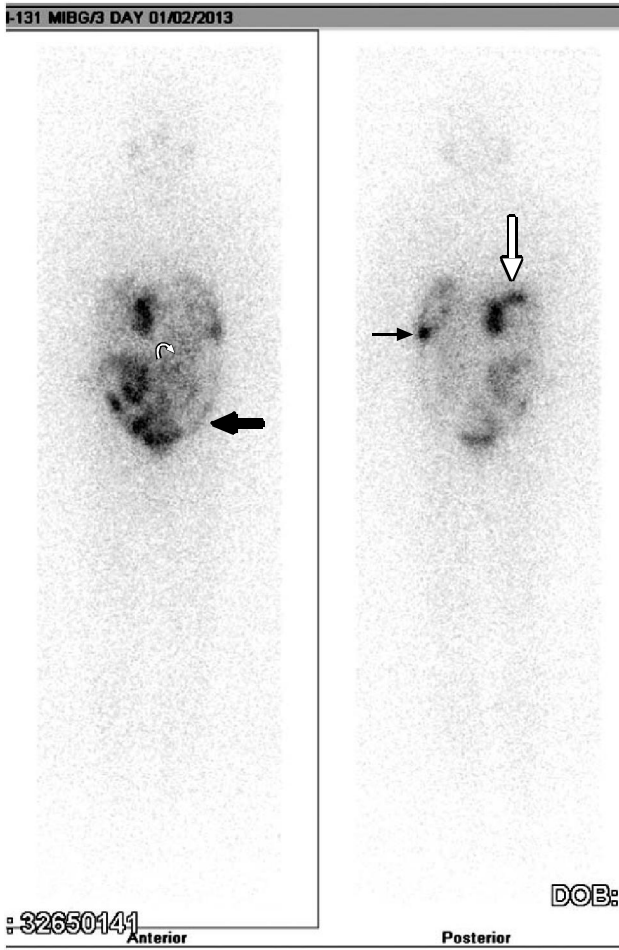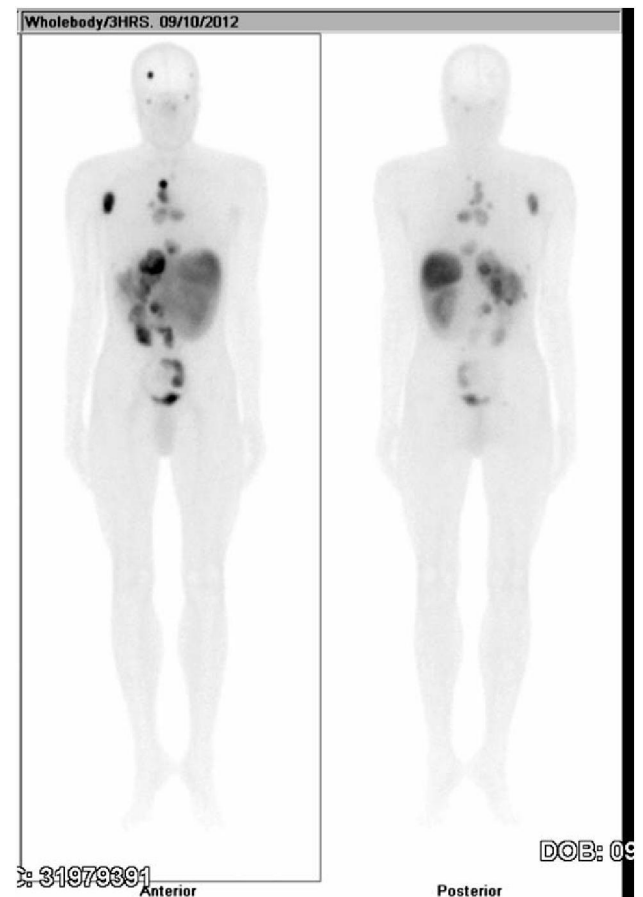
Figure 8: A case recurrent right sided pheochromocytoma (open arrow) with extensive omental (curved arrow), splenic (black arrow) and intestinal deposits (thick black arrow).

imaging isuseful for identifying malignant / metastatic-pheochromocytomas or EAPG with sensitivity approaching 90%[19] (Fig. 9).

Figure 9: 99mTc-HYNIC Octerotide scan in a patient with recurrent hepatic paraganglioma with extensive nodal and bony metastases.

from relatively imperfect sensitivity (85%).[20] However, MIBG scintigraphy coupled with CT imaging ensures better sensitivity (80%–90%) and specificity (95%–100%).[19] Functional imaging is probably not necessary in the preoperative work-up of patients with negative genetic testing and a small para-ganglioma. However, in absence of genetic status before surgery, MIBG imaging is employed for detection of multifocal or metastatic disease. If there is no family history, theneed to exclude multiple lesions is particularly important in younger patients (≤40 y) and patients with a larger paraganglioma (>5.0 cm).[21]

ii) Somatostatin receptor imaging is a non-specific functional imaging. Both pheochromocytomas and paragangliomas express somatostatin receptors. Indium-111 or Technetium-99m labeled octreotide

iii) Positron Emission Tomography (PET): Flourine-18 labeled deoxyglucose (^{18}FDG) PET has shown uptake of FDG in most pheochromocytomas and recently it has been demonstrated to be a superior tool in the evaluation of metastatic SDHB-associated adult pheochromocytoma and paraganglioma.[14] Newer PET compounds such ^{18}F-fluorodopamine (^{18}F-FDA) and ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA) have emerged with superiority over MIBG for diagnosis of malignant paraganglioma and pheochromocytomas, although ^{18}F-FDOPA has been reported limited sensitivity for metastatic disease.[14]

Treatment

The mainstay of treatment of EAPG is surgical resection, either exploration or laproscopically with

strict pre and per-operative pharmacological blockade using alpha and beta blockers. Preoperative arterial embolization of paraganglioma may be performed to minimize blood loss and adequate resection.After resection, close follow up is necessary as reported recurrence rate for EAPG is 0-7%.[22] The recommended treatment options for recurrent or metastatic paraganglioma is surgical removal and debulking or palliative embolization, radiotherapy, and chemotherapy (cyclophosphamide, vincristine, dacarbazine) when surgery is not a viable option. Radionuclide treatment with high doses of 131 I-MIBG is also a good option with overall initial improvement in symptoms (75%) but only 30% partial tumor remission and <5% of patients demonstrating a complete response.[22]

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