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Rare Site Primary Soft tissue Neuroendocrine Tumour with metastases and near-complete resolution with ^{177}Lu-DOTATATE: documenting a Promising Clinical Application of Peptide Receptor Radionuclide Therapy

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Abstract:

Neuroendocrine tumours(NETs) of the skin or soft tissue are rare tumors (mostly describedas site of metastasis), while primary soft tissue neuroendocrine tumours are extremely rare; they are usually diagnosed at advanced stages with distant metastases due to their indolent nature.We herein describe our experience with two such cases. In the first case, the NET originated in the retroperitoneal soft tissueand the second patient was a middle aged lady with NET arising from soft tissue in the pelvis. Both patients were treated with ^{177}Lu-DOTATATE in view of SSTR expressing metastatic lesions, demonstrating excellent outcome reflected by complete metabolic response and near-complete anatomical response to the administered PRRT.The noteworthy factors of the reported cases were: (i) unusual sites of primary tumourand (ii) near-complete to complete symptomatic, anatomical and metabolic resolution of the recurrent primary tumour and metastatic lesions with PRRT alone. NETs arising from the rare anatomical locations are usually non-functioning with good clinical outcomes and ^{177}Lu-DOTATATE PRRT can be considered a promising therapeutic modality in patients with metastatic oradvanced disease.

Introduction:

Neuroendocrine tumours are rare heterogeneous tumours with incidence ranging from 1 to 5 per 100,000 patients (*1*) and arising from the neural crest cells (Kulchitsky cells), enterochromaffin cells, and enterochromaffin like cells having both neural and endocrine components. They were first known as carcinoid tumours, but the term has been replaced by “NET” in the World Health Organisation (WHO) and European NET Society (ENETS) classification (*2*). Malignancy is not infrequent to encounter and most of them are diagnosed at advanced stages

with distant metastases due to their indolent nature. The most common sites in decreasing order of involvement are: gastroenteropancreatic (GEP) NETs(73.7%) followed by tracheobronchopulmonary NETs (25.1%), while other sites which are seldom affected and include parathyroid, adrenal and pituitary glands and calcitonin producing C-cells of thyroid and still uncommon ones such as cutaneous and soft tissue NETs (*3,4*). NETs found in skin and soft tissues are almost always metastatic from primary of the other more commonly involved organs (*5,6*). Primary cutaneous and soft tissue NETs arising *de novo* are extremely rare and lack description in the published literature, except for the well-documented Merkel Cell carcinoma of the skin (*7-9*). The published account on primary soft tissue NET is sparse and comprises of only a few case studies(*10-13*). This report presents our experience in two such cases of primary soft tissue and their favorable outcome with PRRT. Both these patients of metastatic NET demonstrated an uptake Grade of Krenning score 3 on ^{68}Ga-DOTATATE PET-CT and was considered for PRRT based upon multidisciplinary team discussion, with the patients receiving the therapy following written informed consent.

Case I:

A 42-year-old female with no co-morbidities presented with pain abdomen, vomiting and increased frequency of loose stools in June of 2017. Her baseline haematological examination, renal function, liver function, serum electrolytes and electrocardiograph were all within normal limits. On further evaluation,computed tomography (CT) scan of abdomen and pelvis revealed multiple retroperitoneal nodes with irregular peritoneal thickening with cholelithiasis without active cholecystitis and a sclerotic lesion at the junction of body and pedicle on the right side of D12 vertebra. She underwent open cholecystectomy with diagnostic laparotomy with biopsy of the suspected abdominal nodes in June of 2017. Histopathology of the nodes revealed a well differentiated neuroendocrine tumour (World Health Organisationgrade II, 2010) with immunohistochemistry (IHC) panel showing Chromogranin and Synaptophysinpositivityalong with epithelial markers AE1 and AE3 and Mib 1 index (proliferative index) of 8%. This was further correlated with an increased tumour marker level, serum Chromogranin A of 2910 ng/ml (normal value < 98.1 ng/ml).

Based on the above-mentioned clinical profile, laboratory evaluations, imaging and histopathological evidences diagnosis of Grade II (intermediate grade) Neuroendocrinetumour (NET) of retroperitoneal soft tissue mass with lymph nodal and solitary skeletal metastases was made, and she was evaluated accordingly with functional/molecular imaging and referred for peptide receptor radionuclide therapy (PRRT) at our centre in the August of 2017.

^{68}Ga-DOTATATE Positron Emission Tomography (PET) CT scan of whole body revealed: high grade somatostatin receptor (SSTR) expression in omental thickening with multiple serosal and peritoneal deposits on surface of liver, pelvic organs and bowel loops. SSTR expressing multiple enlarged bilateral pelvic, retroperitoneal, epiphrenic, internal mammary, mediastinal, bilateral supraclavicular and few tiny mesenteric nodes with SSTR expressing right pleural deposits and areas of pleural thickening and SSTR expressing D12 vertebral lesion at the junction of body and pedicle on the right side. A small hypodense lesion was seen in the segment II of liver with no tracer uptake.^{18}F-FDG (Flurodeoxyglucose) PET-CT scan of whole body revealed moderate to high grade metabolism in the almost all of the above mentioned lesions except in subcarinal and right supraclavicular nodes. The segment II liver lesion did not reveal any hypermetabolism.

Renal functional scans as a part of pre therapy work up were done with ^{99m}Tc labelled DTPA (Diethylenetriaminepentaacetic acid) and EC (Ethylenedicysteine), were within normal limits.She underwent first cycle of PRRT with ^{177}Lu-DOTATATE in August of 2017 following standard renoprotective protocol. She tolerated the therapy well and was discharged the next morning with post therapy (PT) scan showing uptake similar to ^{68}Ga-DOTATATE PET CT scan findings.

Similarly she underwent 2 more cycles of PRRT at an interval of 3 to 4 months with a cumulative activity of ~ 600 mCi, last done in June of 2018. She reported in October of 2018 for her fourth cycle work up with complete symptomatic resolution. The^{68}Ga-DOTATATE PET-CT at this time showed physiological tracer distribution with no abnormal tracer uptake (Figure 1). Contrast enhanced CT (CECT) scan revealed: Complete anatomical resolution of omental and serosal deposits, mediastinal, retroperitoneal and pelvic lymph nodes, a small unchanged mildly enhancing solitary lesion in segment II of liver and small sclerotic focus at the junction of body and pedicle on the right side of D12 vertebra. The mesentery, omentumand bowel loops were normal.

The above findings suggested complete anatomical and metabolic resolution and hence no further PRRT was administered and she was decided to be observed on a biannual follow up.

Case II:

A 50-years-old female with history of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) for large uterine fibroid, presented with pain in perianal region and right lower leg for 2 years duration. Systemic examination was essentially normal with no organomegaly or free fluid on per abdominal palpation. Per rectal examination revealed a hard, nodular and fixed mass felt through right lateral rectal wall with intact mucosa at 4 cm from anal verge. Physical inspection of other body parts revealed no significant abnormalities. Contrast enhanced MRI Pelvis revealed an enhancing altered signal intensity mass lesion ~ 6*5.5*4 cm in the right pararectal space with pelvic side wall infiltration and a small locoregional node, inseparable from the lateral aspect of the lower rectum on the right side. Computed Tomographic (CT) scan of thorax and abdomen was also done in an effort to diagnose the primary site which revealed an unremarkable thoracic and abdominal cavities and the contained viscera. USG guided trucut biopsy from the lesion revealed neuroendocrine tumour, grade II.She was taken for exploratory laparotomy where a 5*5 cm fixed mass was found in the right pelvis involving lateral pelvic wall with sacral infiltration and hence deemed inoperable.A follow up contrast enhanced MRI revealed a 6*3cm enhancing mass with irregular borders in the right side of pelvis. Fat planes with rectum, ipsilateralpyriformis, ipsilateral sacrum, right internal iliac vessels, sciatic and sacro-coccygeal nerves were either inconspicuous or lost. There was obvious infiltration of ipsilaterallevatorani and obturatorinternus.She was taken for re-surgery with combined multispeciality team exploratory laparotomy with wide excision with diversion ileostomy was done. Per-operative findings revealed an approximately 5*4 cm hard, irregular growth lying in the pre-sacral plane in front of S2, S3 and S4 towards the right of midline, closely abutting lower rectum, vaginal stump and urinary bladder. S2 nerve was found traversing through the tumour and was removed *en block.* Wide excision was undertaken with removal of pyriformis, sacrospinous ligament and periosteum. There was rectal wall injury in the pelvis which was repaired and a diversion ileostomy was made. In December of 2015, the ileostomy closure was done with side to side approach using staples.

In early 2017, she presented with pain in the right pelvic region and was found to have recurrence of the mass at the surgical site. Contrast enhanced CT scan revealed a 9*7*6 cm soft tissue mass in the right pelvis adjacent to the urinary bladder and infiltrating pelvic wall muscles and sacrum posteriorly with resultant widening of the second sacral neural foramina and extension of soft tissue through it. There was evidence of metastatic lesions in liver (segments VI and VII of right lobe), lesser sac above pancreas and multiple bilateral lung nodules. A Somatostatin Receptor (SSTR) imaging Positron Emission Tomography Computed Tomography (PET-CT) scan revealed SSTR expression noted in the above described pelvic pre-sacral soft tissue mass and lung nodules. No abnormal SSTR expression was seen in hepatic lesions and lesser sac deposits.The baseline serum chromogranin A was 86.8ng/ml and 24 hrs urinary 5HIAA was 2.56 mg.

In view of above findings, she was referred to our department for PRRT. She underwent 4 cycles of PRRT with ^{177}Lu-DOTATATE between May 2017 and December 2018 with a cumulative activity of ~ 700 mCi according to standard renoprotective protocol, as in the first case. Follow up ^{68}Ga-DOTATATE and ^{18}F-FDG whole body PET CT scans revealed progressive decrease in the size and metabolic activity of the tumour with normal tumour marker levels; serum chromogranin A was 54.9ng/ml and 24 hrs urinary 5HIAA was 2.52mg. The follow-up scans done after 4 cycles of PRRT, in October of 2018 showed complete anatomical and metabolic resolution of the right pelvic soft tissue mass and the lung nodules. Although a subcentimeter sized right internal iliac node with minimal SSTR expression was persisting, it showed significant decrease in size; also mild uptake was seen in the sacro-coccygeal region, but no abnormal soft tissue mass was noted (Figure 2). None of the lesions showed abnormal increased FDG uptake suggesting no abnormal metabolic activity and hence favourable prognosis.

In view of the favourable outcome reflected by complete metabolic response and near complete anatomical response, further PRRT was withheld for her and was put on biannual follow up.

Discussion:

Neuroendocrine tumours are rare tumours and are classified according to their various attributes viz., [a] embryological origin into foregut, midgut and hindgut derivatives, [b] functional and non-functionaltumours

depending upon synthesis and release of biologically active amines and peptides, and [c] grades I, II and III, depending upon proliferation index and mitotic figures and also as [d] neuroendocrine tumours (NET) or neuroendocrine carcinoma (NEC).

The differential diagnosis of the soft tissue tumours in our patients included metastatic deposits from primary GIT, malignant transformation of nerve sheath tumours and spindle cell neoplasm. Metastatic origin was nearly ruled out in view of negative imaging and other clinico-pathological examinations which failed to find any substantial evidence towards a second primary tumour. Hence a diagnosis of primary soft tissue neuroendocrine tumour was made. The incidence of primary soft tissue NET is extremely rare and most of the soft tissue involvement in NET is metastases from a more common primary in GIT and lungs. Till date, only eight publications are available that reported soft tissue primary NET. In most of these, the primary tumour was detected in breast, thigh or axilla (*11-18*). Inthis regard, the peculiarity of our cases lied in their unusual locations i.e., in retroperitoneal soft tissue in the first case and the pelvic soft tissue in the second case.

Diagnosing NET could be challenging at times due to their widespread location, small size and indolent nature. Functional tumours are diagnosed earlier than non-functional ones. Trans abdominal USG, endoscopic examination of GIT and tracheo-bronchial tree and MRI along with SSTR and GLUT receptor based PET imaging fused to CT or MRI has been widely used to diagnose the small and inconspicuous lesions with increasing confidence. The primary tumour highlighted by these modalities are then amenable to tissue diagnosis and IHCs, thus increasing the sensitivity, specificity and yield (*19-23*). Treatment and follow up strategies are then devised based on metastatic involvement and proliferation index/grade of the tumour. Both of our cases were grade II tumours and hence carried better prognosis as compared to grade III tumours or the neuroendocrine carcinoma (NEC) (*8*).

The treatment of choice in a case of NET is surgical excision (*24*), but many a times, surgery is not possible due to widespread metastases, vascular encasement, high risk for morbidity and mortality due to pre-existing diseases or conditions. In such group of patients where surgery could not be undertaken there are a battery of therapeutic options to choose from, ranging from chemotherapy (with mTOR inhibitors, platinum based compounds, capecitabine, etc), interferon-alpha, somatostatin analogues, localised radiotherapy, ablation therapy

and PRRT (*25,26*). Recently PRRT targeting the somatostatin receptors have gained popularity due to good symptomatic response, favourable toxicity profile and its administration as convenient 3-monthly cycles.

The noteworthy factors of our cases lies in the fact that (i) we encountered unusual site of primary tumour involving the retroperitoneal and pelvic soft tissue (to our knowledge, this has not been reported in the literature) and (ii) near complete to complete symptomatic, anatomical and metabolic resolution of the primary tumour and metastatic lesions with PRRT alone.

Conclusion:

Primary soft tissue NETs are extremely rare entity and surgical resection are potentially curative. However adjuvant therapy with PRRT targeting the somatostatin receptors are effective and safe adjuncts to surgery or in cases of metastatic disease, unresectable primary tumour or patients not deemed fit for surgery. As described above and seen in both of our cases,in patients with favorable histopathologyof the tumour (with low-intermediate proliferation and mitotic profile), PRRT canproduce gratifying tumor regression even in the presence of extensive metastasis.

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Figures:

Figure 1: (a) Maximum Intensity Projection (MIP) images of ^{68}Ga-DOTATATE PET CT scan comparing baseline and post 3 cycles PRRT studies showing complete metabolic resolution of the uptake. (b) & (c) Trans-axial slices comparing fused PET-CT images of ^{68}Ga-DOTATATE PET CT studies done at baseline and post 3 cycles of PRRT showing complete metabolic and anatomical resolution of the lesions seen at baseline.

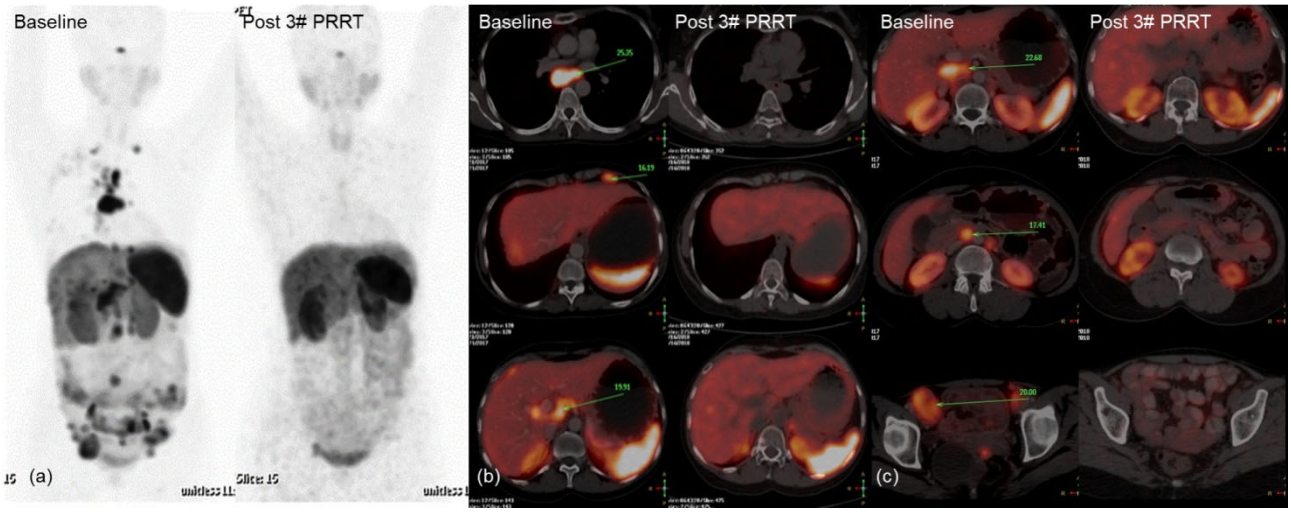

Figure 2: (a) Maximum Intensity Projection (MIP) images of ^{68}Ga-DOTATATE PET-CT comparing baseline and post 4 cycles PRRT studies showing near complete metabolic resolution of the uptake. (b) Trans-axial slices comparative fused PET-CT images of ^{68}Ga-DOTATATE PET-CT done at baseline and post 4 cycles of PRRT showing near complete metabolic and anatomical resolution of the lesions seen at baseline.