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Case Report Open Access

Exceptional Therapeutic Outcome of Metastatic Neuroendocrine Tumor with Peptide Receptor Radionuclide Therapy with Brief Review of Literature

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Abstract

NETs are rare, heterogeneous group of neoplasm presented as chronic oncologic disease. Somatostatin analogue is the standard first line systemic therapy for mainly hormone control. No standard second line systemic treatment is available except everolimus which has no reported complete response. PRRT is an innovative molecular targeted treatment based on theragnostic concept for well differentiated NETs.

We presented here a 63-year-old lady with grade 1 NET of rectum with lymphnodal and liver metastasis. She underwent sigmoid colostomy for bowel symptoms and started on sandostatin LAR. After progression, patient was treated with 4 cycles of 7.4GBq of 177Lu-DOTATATE at 10 weeks interval. No hematological and renal toxicity were noticed. Patient showed complete response in liver lesions & lymphnodes and partial response in rectal lesion on 68Ga-DOTANOC PET-CT. After multispecialty clinic board discussion, patient underwent curative surgery for residual rectal lesion and colostomy closer later on.

Our case highlights a common presentation of NETs but an uncommon outcome with currently approved drugs. With this potential of disease cure in metastasis, PRRT may also be offered for locally advance disease as an adjuvant treatment for down staging.

Keywords: Neuroendocrine tumor; Peptide receptor radionuclide therapy; Theragnostic; 177Lu-DOTATATE; Complete response

Introduction

Neuroendocrine tumors (NETs) are relatively slow growing with 80% of patients presenting in stage IV and 5 year survival of 35%-55% [1]. Somatostatin analogue is the standard first line systemic therapy for inoperable locally advanced or metastatic patient for both control of hormone secretion and tumor growth [2]. No standard second line systemic treatment option is available except everolimus. Peptide receptor radionuclide therapy (PRRT) is a promising targeted treatment for well differentiated (grade 1&2) NETs using radiolabelled somatostatin analogue to deliver cytotoxic radiation at cellular level [3]. We presented here a successful treatment outcome of an inoperable metastatic NET case to disease free state following PRRT.

Case Report

A 63-year-old lady was presented with difficult defecation and occasional red coloured stool since 2 years. Triple phase contrast enhanced computed tomography whole abdomen (TP-CECT WA) showed upper 1/3rd rectal lesion with perirectal, paraaortic lymphadenopathy and liver lesions. Colonoscopy revealed rectal growth and biopsy of which showed grade 1 (Ki-67<2%) NET. 68Gallium-DOTA1-NaI3-octreotide (68Ga-DOTANOC) Positron Emission Tomography- Computed tomography (PET-CT) showed strong (more than spleen) somatostatin receptor expression in all sites. Initial Chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) were 312.2ng/ml and 5.4 ng/24 hours urine respectively. Sigmoid loop colostomy was done due to inoperable rectal lesion and she was started on sandostatin LAR (long acting release) 30 mg 4 weekly. 5 months later, she was re-evaluated with 68Ga-DOTANOC PET-CT with TP-CECT WA which revealed progressive disease. Case was discussed in multispecialty clinic (MSC) board and PRRT was advised. She was treated with 4 cycles of 200 mCi (7.4GBq) 177Lutetium-DOTA0-Tyr3-octretate (177Lu-DOTATATE) at 10 weeks interval with renal protection protocol (2 litres Aminoven 10% 500ml at 1 hour+500 ml Gelofusine 100 ml/one hour) started 30 minutes before radiopharmaceutical infusion. Biochemical tests at 1, 4, and 8 weeks intervals after each cycle for complete blood count, kidney function test and liver function test were done which showed no toxicity. CgA at 8 weeks interval of each cycle showed decreasing trends (354.2 ng/ml at base line and 105.9 ng/ml after 4 cycles of PRRT). 99mTc-DTPA glomerular filtration rate (GFR) at 8 weeks interval of each cycle showed no derangement (109.6 ml/min GFR at base line and 101.5 ml/ml after 4 cycles of PRRT). 68Ga-DOTANOC PET-CT with TP-CECT WA scan was done at 8 weeks interval for response evaluation which showed serially decrease in tracer intensity and size in all disease sites (Figure 1). Lymphnodes and liver lesions showed complete response (CR) after 4 cycles of PRRT. Residual rectal lesion after 4 cycles of PRRT was surgically removed (Lower anterior resection with side to end colorectal anastomosis with covering transverse loop colostomy) after MSC board decision. Histopathology was residual rectal NET grade 1 (Figure 2) with 1/6 perirectal

lymphnodes positive (ypT3N1). 6 months post-surgery 68Ga-DOTANOC PET-CT with TP-CECT WA scan and colonoscopy were normal. CgA was 52.5 ng/ml. Colostomy reversal done and patient was in disease free state since last 8 months of follow-up.

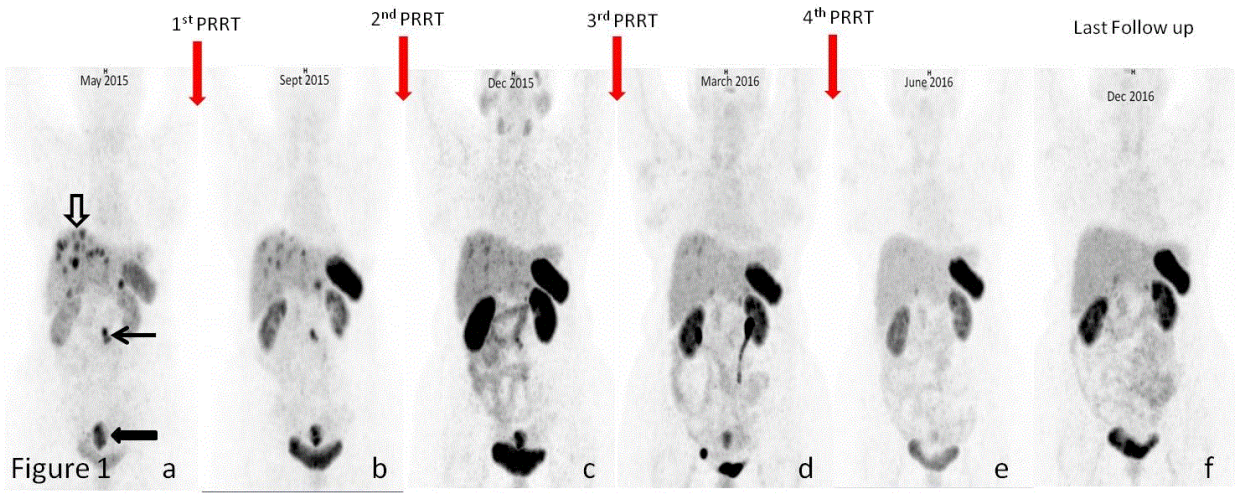

Figure 1: Serial 68Ga-DOTANOC PET-CT Maximum intensity projection images (a-f): Image (a) showed strong (more than spleen) somatostatin receptors (SSTRs) expressing rectal lesion (black block arrow), retroperitoneal lymphnodes (black arrow) and liver lesions (empty block arrow). Serial images (b to e) after each peptide receptor radionuclide therapy (PRRT) showed response in liver lesions and retroperitoneal lymphnodes. Last follow-up image (f) showed no abnormal SSTRs expressing lesion in the body.

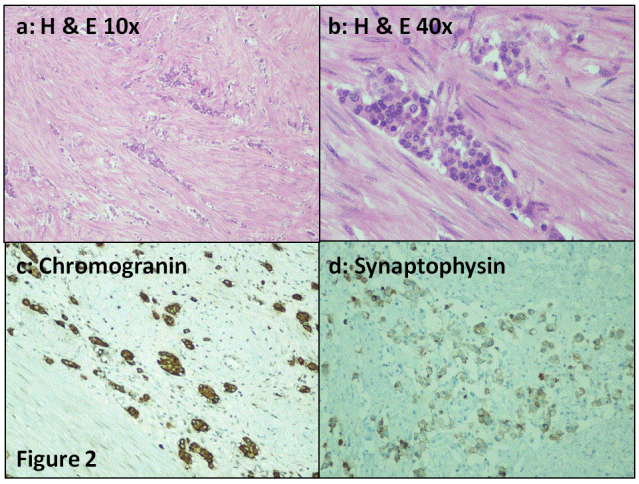

Figure 2: H&E images (2a: 10X; 2b: 40X) shows rectal wall infiltrated by solid nests of tumor cells. IHC images show immunopositivity for chromogranin (2c) and synaptophysin (2d).

Discussion

NETs are rare, heterogeneous group of neoplasm presented as chronic oncologic disease. Incidence has increased over last two decades due to technical improvements in diagnosis with prevalence of 35 cases per 100,000 inhabitants [4]. However no systemic treatment is available with meaningful objective response rate for these patients. The first choice of treatment 'Sandostatin LAR' has median PFS of 14.3 months with <3% partial response (PR) and no CR (PROMID study). In RADIANT-3 trial [5], everolimus an oral mammalian target of rapamycin (mTOR) inhibitor has showed median PFS of 11 months with 5% objective response rate (all PR).

PRRT is a molecular targeted treatment based on 'Theragnostic' concept [6]. In this concept, a specific antigen expression is investigated by an imaging agent and if present same antigen is being targeted by a therapeutic radiopharmaceutical. PRRT exploits the somatostatin receptors (SSTRs) over expression in grade 1 and 2 NETs (Ki67 index ≤ 20%). 68Ga-DOTANOC PET-CT is used for imaging while 177Lu-DOATATE for subsequent treatment. 68Ga is a positron emitting radionuclide with a half-life of 68 minutes and 177Lu is a β and γ emitting radionuclide with half-life of 6.7 days and 2mm maximum particle range. In a single group study of gastroenteropancreatic NETs (N=310) treated with 177Lu-DOTATATE showed 2% CR, 28% PR and median PFS of 33months [7]. A recent phase 3 trial (NETTER-1) of 177Lu-DOTATATE in mid gut NETs showed 18% objective response rate (1% CR+17% PR) with 65.2% median PFS at 20 months [8].

Our case highlights a common presentation of NETs but an uncommon outcome. More disturbing was sigmoid colostomy to our patient which was an inconvenience and restricting her social activities. After 4 cycles of PRRT she not only underwent curative surgery but colostomy reversal later on hence improved her quality of life.

Conclusion

We conclude NETs are rare but chronic oncological disease with rarest chance of cure in metastatic case as of now. PRRT is an innovative molecular targeted treatment with a potential of disease cure. It may also be offered for locally advance disease as an adjuvant treatment for down staging. With the growing literature on PRRT it may become one of the choice treatments in near future.

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