68Ga-DOTA-NOC PET and Peptide Receptor Radionuclide Therapy in Management of Bilateral Ovarian Metastases from Gastrointestinal Carcinoid

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The management of neuroendocrine tumours is challenging when curative surgery is ruled out because of distant metastases. We report a case of gastrointestinal carcinoid with bilateral ovarian metastases in a 50-year-old female who received octreotide therapy followed by peptide receptor radionuclide therapy and surgery thereafter. Somatostatin receptor expression on neuroendocrine tumours has implications in diagnosis and therapy. 68Ga-DOTA-NOC PET is a recent advancement in the field of somatostatin receptor imaging. The lesions which demonstrate tracer uptake on positron emission tomographic studies can be further planned for treatment with octreotide and 177Lu-DOTA-TATE. The case in discussion responded well to non-invasive treatment options before proceeding to definitive surgical management.

Key words: carcinoid — bilateral ovary — 68Ga-DOTA-NOC PET — 177Lu-DOTA-TATE

INTRODUCTION

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms originating from the gastrointestinal tract and the lung. The great majority are either benign or relatively slow growing (well-differentiated NETs), retaining many multipotent differentiation features. The possession of neuroamine uptake mechanisms and/or specific receptors at the cell membrane, such as somatostatin receptors (SSTRs), can be used for the identification, localization and therapy of NETs. Radiolabelled receptor binding peptides have emerged as a new class of specifically targeting radiopharmaceuticals for tumour diagnosis and therapy. One of the advantages and attractions of peptide receptor scintigraphy is the fact that, in addition to the simple tumour localization, it tells whether or not the tumour expresses a peptide receptor that may be instrumental for a successful long-term therapy with a non-radioactive peptide or, if the density is sufficiently high, for a peptide radiotherapy programme. Till date, no case of carcinoid tumour with metastases to bilateral ovaries diagnosed by 68Ga-DOTA-NOC PET-CT followed by peptide receptor radionuclide therapy (PRRT) has been described in the literature.

CASE REPORT

A 50-year-old woman was referred for management after having been diagnosed with unresectable metastatic disease from gastrointestinal carcinoid. In the past, the patient has had symptoms of recurrent incomplete intestinal obstruction (colicky epigastric pain radiating to lower abdomen, bilious vomiting) for which conventional imaging with contrast-enhanced CAT scan was performed. Concentric mural thickening of terminal ileum measuring ~1.2 cm in length with minimal regional adenopathy was reported on the conventional imaging. With presumptive diagnosis of intestinal tuberculosis which is rampant in India, the patient was put
on three anti-tubercular drugs (rifampicin, isoniazid and ethambutol). However, the symptoms did not abate despite 3 months of intensive treatment and laparotomy was undertaken in November 2006 to confirm the diagnosis. The surgeon excised 9.5 cm long distal ileal segment with regional mesenteric lymph nodes and ileo-ileal re-anastomosis was done. The tissue specimen so obtained yielded the diagnosis of well-differentiated carcinoid of the ileum with metastases to lymph nodes. On re-look laparotomy for curative resection, few grossly visible mesenteric nodules, appendices epiploicae and regional nodes were removed as the surgeon found the peritoneum to be studded with multiple tumour implants and diffuse infiltration of the mesentry by tumour cells. The patient was then started monthly depot administrations of long-acting octreotide (Sandostatin LAR 20 mg) on monthly basis until March 2007. The long-acting octreotide was stopped a month prior to SSTR imaging using 68Ga-DOTA-NOC PET (Fig. 1A). Few subcentimetric peritoneal nodules and occasional mesenteric nodes with increased tracer uptake were observed, which apparently did not correlate well with the tumour burden as estimated by serum chromogranin A (CgA) levels. Since, no other therapeutic options were available at that time, the patient was advised to continue Sandostatin LAR and was kept on close follow-up. The patient was experiencing progressively increasing functional limitations due to severe symptoms of carcinoid syndrome (diarrhoea, flushing, vomiting). The serum CgA levels had escalated from 231.1 to 500.1 ng/ml within a span of 2 months, suggesting biochemical progression. The patient was recruited into PRRT trial at our institution using 177Lu-DOTA-TATE in May 2008. The study was ethically approved by the institution ethical committee and written informed consent was obtained. A repeat SSTR PET study was ordered prior to first administration of 177Lu-DOTA-TATE to ensure the presence of receptors and reassess the disease extent. There was no significant interval change in the scan findings except that the outline of the uterus appeared irregular with bulky bilateral adnexae with minimal tracer uptake (Figs 1B and 2A). No further investigations were done for the pelvic findings attributing the same to benign inflammatory pathology. The patient was administered 800 mCi (29.6 GBq) in five divided cycles over a period of 11 months with co-administration of renoprotective amino acids (Fig. 2B and C). The patient tolerated PRRT well with no serious acute side effects except nausea. There was a favourable response to treatment as there was arrest of otherwise rapidly progressive disease in terms of stabilization of serum CgA levels and significant improvement in the quality of life (Fig. 3). The haemogram (haemoglobin 13 g/dl; total leucocyte count 10 800/cc; platelets 2.8 × 10^3/cc) was normal at baseline and remained unaltered during the course of treatment. The symptoms of subacute intestinal obstruction recurred after the completion of last administration of 177Lu-DOTA-TATE requiring the patient to undergo right hemicolectomy in July 2009. There was a decrease of ~70% in serum CgA and urinary

Figure 1. Transaxial images of 68Ga-DOTA-NOC PET-CT fusion images. Serial scans of the patient in discussion from 2007 to 2011. (A) Left tubo-ovarian mass with minimal radiotracer uptake in the year 2007. (B) Multiple nodules on the surface of the uterus with bulky adnexae in the year 2008. (C) Enlargement of bilateral ovaries (left measuring 3.8 × 2.3 cm; right measuring 2.9 × 2.1 cm) with intense radiotracer uptake. Also, there is a small ill-defined nodule on the posterior aspect of surface of the uterus with increased tracer uptake (2009). (D) Decrease in size (left measuring 3.4 × 2.0 cm; right measuring 2.3 × 1.8 cm) as well as uptake of bilateral ovarian masses in 2010 compared with the study in 2009. (E) No abnormality in the pelvis after panhysterectomy in 2011.
5-hydroxy-indole-acetic acid (5-HIAA) from pre-operative value of 572 ng/ml and 24 mg/24 h, respectively. The patient underwent PET scan 3 months later which revealed bilateral enlarged ovaries with few peritoneal nodules with intense radiotracer uptake (Fig. 1C) and serum CgA levels were reported to be 582.5 ng/ml. In view of indirect evidence of SSTR expression by tumour, the patient was restarted on monthly intramuscular depot injection of 20 mg Sandostatin LAR. There was a decrease observed in the serum CgA, urinary 5-HIAA and radiotracer uptake in PET study performed 15 months after hemicolectomy (Fig. 1D). Both the ovaries were found to be enlarged (right ovary 2 × 1.5 × 1.5 cm; left ovary 2.5 × 2 × 1.5 cm) with tumour deposits in panhysterectomy specimen (Fig. 4) which was done in October 2010. There were <2 mitoses per 10 high power fields (10 HPFs) and tumour necrosis was characteristically absent. The serum CgA transiently decreased to 170 ng/ml after surgery which doubled in a month’s duration and tripled in the next month. Recent PET scan in May 2012 revealed the presence of disseminated omental and serosal deposits which corroborated well with serum CgA of 512.3 ng/ml and recurrence of symptoms.

DISCUSSION

The pathological findings of carcinoid tumour cell rests in the ovary may be primary in origin or secondaries from
other sites. Ovarian metastases of carcinoid tumour are a rare phenomenon with no more than 80 cases (1–5) reported till date, whereas at least 200 primary ovarian carcinoid tumours have been reported (6). Primary ovarian carcinoid tumours often arise in the setting of dermoid cysts in up to 90% cases and are considered to be of germ cell origin (7). The source of ovarian NET metastases invariably is the gastrointestinal tract, usually ileal carcinoid tumours; however, other primary tumour sites reported include the jejunum, cecum, pancreas and appendix (8). Intestinal carcinoids >1 cm in size are more likely to be associated with ovarian metastases (4,9). The median age of presentation is usually 57 years (4,5). There is tendency of metastases to both ovaries in metastatic cases from ileal carcinoids in 88–94% cases compared with unilaterality of disease in ∼90% cases of primary carcinoid tumour of the ovary (10). The typical histology in such tissue specimens consist of well-differentiated carcinoid tumours featuring monomorphic tumours cells with <2 mitoses per 10 high power fields (10 HPFs) and absence of tumour necrosis. Such patients have advanced disease at the time of presentation with multiple metachronous metastases and peritoneal seeding is a feature in 28–35% cases. The identification and characterization of ovarian metastases is better possible with ultrasound or magnetic resonance imaging and are incidentally picked up in SSTR scintigraphy (11). Almost all cases may demonstrate indirect evidence of SSTR expression as a result of abnormal radiotracer uptake on 111In-Pentreotide study. The tumour-specific markers (5-HIAA and serum Serotonin) tend to be elevated in all cases of carcinoid tumours with ovarian metastases and average 24-h urine 5-HIAA peak level may be as much as 60 mg. The symptoms of carcinoid syndrome were gradual in onset in our case and correlated well with the increase in urinary 5-HIAA levels. Ambrosini et al. (12) assessed the impact of 68Ga-DOTA-NOC PET/CT in comparison with CT on the clinical management of 90 patients with pathological confirmation of NET. PET/CT affected either stage or therapy in 50 of the 90 (55.5%) patients. The most frequent impact on management (27 patients) was the initiation or continuance of PRRT, followed by the initiation or continuance of somatostatin analogue medical treatment (7 patients) and referral to surgery (6 patients). Gabriel et al. (13) compared the imaging results of 68Ga-DOTA-TOC PET with 99mTc-labelled hydrazinonicotinyl-Tyr3-octreotide (99mTc-HYNIC-TOC) and 111In-DOTA-TOC SPECT in 84 patients. Of all 116 PET-positive lesions, SPECT delineated 84 (72.5%) lesions and CT delineated only 58 lesions (50%). 68Ga-DOTA-TOC PET showed a significantly higher detection rate compared with conventional SSTR scintigraphy and diagnostic CT with clinical impact in a considerable number of patients. The serial ultrasounds of the abdomen in our case did not show any significant genital tract abnormalities and there was a temporal correlation between the detection of ovarian metastases on ultrasound and 68Ga-DOTA-TOC PET in our case.

Treatment with radiolabelled somatostatin analogues is a promising new tool in the management of patients with inoperable or metastasized NETs. Symptomatic improvement may occur with all 111In-, 90Y- or 177Lu-labelled somatostatin analogues that have been used for PRRT. The objective tumour response rates of this treatment have been reported to be 32.6–46% with the median overall survival between 36 and 46 months in different studies (14,15). 177Lu-DOTA-TATE therapy has been shown to significantly improve the global health/QoL and several function and symptom scales in patients with metastasized gastrointestinal-pancreatic tumours, especially in those patients with proven tumour regression (16,17). In our case, stabilization of tumour markers and symptomatic improvement of rapidly progressive gastrointestinal carcinoid tumour with bilateral ovarian metastases was possible with PRRT using 177Lu-DOTA-TATE as well as long-acting octreotide. The surgical outcome was better than medical treatment as a significant decrease in tumour markers, although for a brief duration was observed. The patient in discussion became symptomatic in 2005 and is alive till date on follow-up at our clinic.

CONCLUSION

Stabilization of otherwise rapidly progressive disease is possible with PRRT and long-acting octreotide. Surgical resection/debulking, however, is the mainstay of treatment in NETs with both typical and atypical presentations. SSTR scintigraphy using 68Ga-DOTA-NOC PET plays an important role in identifying metastases of carcinoid tumours and follow-up after invasive/non-invasive therapies. The semiquantitative parameter SUVmax may correlate well with serum CgA and other tumour-specific marker like 5-HIAA indirectly reflecting the tumour burden in certain cases.
Conflict of interest statement

None declared.

References