CASE REPORT

Carcinoid crisis induced by receptor radionuclide therapy with 90Y-DOTATOC in a case of liver metastases from bronchial neuroendocrine tumor (atypical carcinoid)

M.V. Davì[1], L. Bodei[2], G. Francia[1], M. Bartolomei[2], C. Oliani[3], L. Scilanga[1], D. Reghellin[4], M. Falconi[5], G. Paganelli[2] , V. Lo Cascio[1], and M. Ferdeghini[6]

[1]Biomedical and Surgery Science Department; [3]Institute of Oncology; [4]Institute of Pathology; [5]Endocrine Surgery; [6]Morphological and Biochemical Science, University of Verona, Verona; [2]European Institute of Oncology, Milan, Italy

ABSTRACT. SS receptors are overexpressed in many tumors, mainly of neuroendocrine origin, thus enabling the treatment with SS analogs. The clinical experience of receptor radionuclide therapy with the new analog [90Y-DOTA0-Tyr3]-octreotide [90Y-DOTATOC] has been developed over the last decade and is gaining a pivotal role in the therapeutic workout of these tumors. It is well known that some procedures performed in diagnostic and therapeutic management of endocrine tumors, such as agobiopsy and hepatic chemoembolization, can be associated with the occurrence of symptoms related to the release of vasoactive amines and/or hormonal peptides from tumor cell lysis. This is the first report of a severe carcinoid crisis developed after receptor radionuclide therapy with 90Y-DOTATOC administered in a patient affected by liver metastases from bronchial neuroendocrine tumor (atypical carcinoid). Despite protection with H1 receptor antagonists, octreotide and corticosteroids, few days after the therapy the patient complained of persistent flushing of the face and upper trunk, severe labial and periocular oedema, diarrhoea and loss of appetite. These symptoms increased and required new hospitalisation. The patient received iv infusion of octreotide associated with H1 and H2 receptor antagonists and corticosteroid therapy, which induced symptom remission within few days. The case here reported confirms that radionuclide therapy is highly effective in determining early rupture of metastatic tissue and also suggests that pre-medication should be implemented before the radiopeptide administration associated with a close monitoring of the patient in the following days.

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INTRODUCTION

Carcinoid syndrome is due to excessive secretion of serotonin and other vasoactive peptides and usually occurs when an intestinal or bronchial neuroendocrine tumor has spread to the liver. It is characterised by episodic flushing, diarrhoea, wheezing and, eventually, by right-sided valvular heart disease (1). Acute carcinoid crisis has been reported during surgical manipulation of liver metastases and/or anesthesiological induction (2, 3). Moreover many diagnostic or therapeutic procedures leading to cell rupture, such as fine needle agobiopsy, laser broncoscopy, liver chemoembolization may cause massive release of vasoactive substances, thus resulting in acute symptoms. Neuroendocrine tumors often bear SS receptors, particularly the subtype 2, which allow the treatment of tumor hypersecretion and possibly of primary and metastatic lesion growth by octreotide or lanreotide (4-7). SS analogs are effective either in long-term symptom control or in prevention of the acute carcinoid crisis, when administered before and during tumor manipulation or anesthesia. Receptor

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Correspondence: M.V. Davì, Biomedical and Surgery Science Department, University of Verona, Verona, Italy.

E-mail: mariavittoria.davi@azosp.ur.it

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radionuclide therapy with radiolabeled SS analog [90Y-DOTA0-Tyr3]-octreotide [90Y-DOTATOC] is a new treatment for neuroendocrine tumors, that has been developed over the last decade with promising results. 90Y-DOTATOC therapy was used in various phase-I/II trials. In a 10-yr experience, 90Y-DOTATOC has proved to be a safe therapy, with mild toxicity and few side effects. Indeed complete plus partial remissions were reported in 10-30% of patients in most studies (8-11).
Here we report a severe carcinoid crisis occurring after 90Y-DOTATOC therapy in a patient affected by metastasised bronchial neuroendocrine tumor.

CASE REPORT

The patient, a 65-yr-old-male, underwent surgery for the removal of 2 liver metastases in July 1998 and right bilobectomy for the bronchial primary neuroendocrine tumor in September 1998. According to the last World Health Organization (WHO) classification the histological tumor type is a well-differentiated, functionally, endocrine carcinoma of the lung, classified as an atypical carcinoid on the basis of the histological pattern, the Ki-67 value (10%) and the number of mitoses (4/mm^2). Although the patient was asymptomatic, serotonin was 1.95 µmol/l (n.v. 0.45-1.2) and 5-hydroxyindoleacetic acid (5-HIAA) was 17.6 mg/24 h (n.v. 2-8 mg/24 h) at surgery. Abdomen and chest computed tomography (CT) scan, performed 6 months later, was negative. In August 1999 the OctreoScan, bone scintigraphy and CT scan showed bone metastases of the right iliac horn and occipito-parietal region of the skull. The patient was treated with LAR octreotide 20 mg monthly and subsequently also in combination with α-interferon 2b (3 MU x 3/week sc) from March to July 2001 for 4 months. Nevertheless, the disease progressed with multiple liver metastases on CT scan performed in July 2001. Therefore, α-interferon 2b was withdrawn, while LAR octreotide was continued.
From August 2001 to July 2003 the patient received additional chemotherapy, based on the combination 5- fluorouracil (400 mg/m^2) plus streptozotocin (1000 mg/m^2) for one day, every 3 weeks. In June 2002 an abdomen CT showed a partial response of the liver lesions and the value of chromogranin A (CgA) decreased from 158 to 68 ng/ml (n.v.19-98 ng/ml). The disease remained stationary till July 2003, when an abdomen magnetic resonance (MR) (Fig. 1) showed an increase in the number of liver metastases, so the chemotherapy was stopped. The OctreoScan showed high uptake to the liver and bone metastases, whereas a whole-body 18F-FDG-PET was negative. Serum CgA increased to 162 ng/ml. In September 2003, the patient received the first cycle of 90Y-DOTATOC therapy (2.1 GBq). Neither acute (such as bronchospasm, laryngospasm, allergy) nor delayed side effects, particularly renal and bone marrow toxicity, were observed after the therapy. The scintigraphic control performed 18 h after the therapy revealed a good uptake to the liver and bone lesions (Fig. 2).

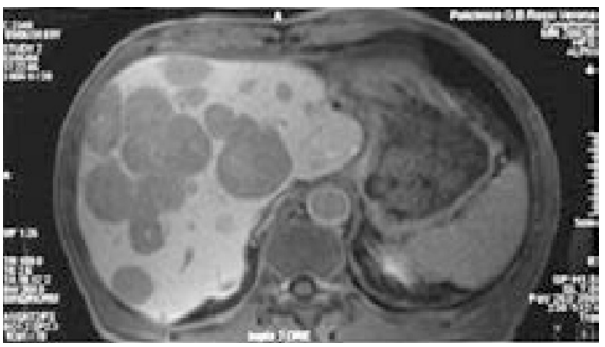

Fig. 1 - *Abdominal magnetic resonance (MR) showing multiple hypervascularised liver lesions.*

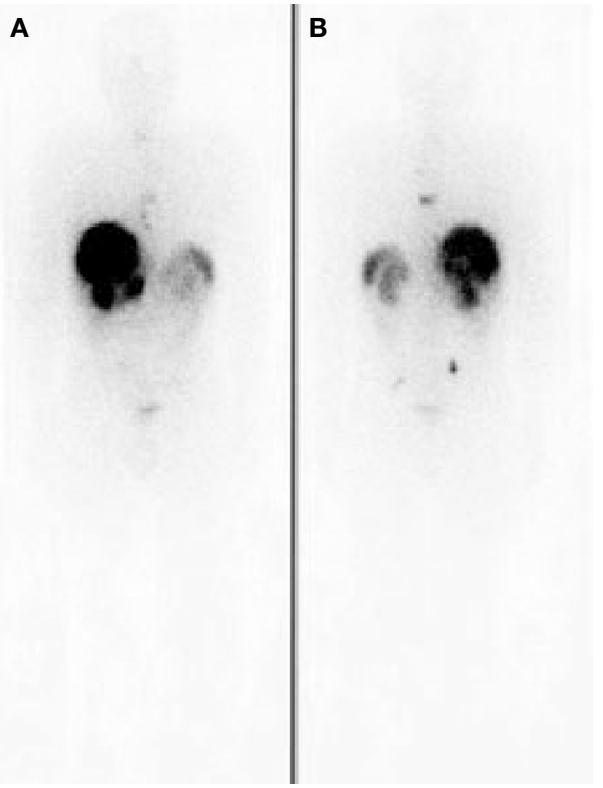

Fig. 2 - *OctreoScan performed after the first cycle of 90Y-DOTATOC therapy showing a good uptake to the liver and bone lesions (A: anterior, B: posterior).*

In January 2004, an abdomen US showed stability of liver metastases, whereas a bone scintigraphy showed lower uptake of the right hip joint. In March 2004, he received the second cycle of 90Y-DOTATOC therapy (2.59 GBq). At the hospital admission blood cell count, renal function and electrolytes were all within the normal range. During the radiopeptide administration the patient developed an intense flushing, controlled by administration of anti-H1-receptor antagonists (prometazine 50 mg im) and desametasone (4 mg in 100 ml saline iv). Due to the persistence of symptoms related to carcinoid syndrome, the patient was subsequently treated with desametasone 4 mg daily, octreotide 0.5 mg sc bid and oxatomide 30 mg bid, starting from the day after the therapy up to the discharge. The patient was discharged from the hospital with a home therapy consisting in oxatomide 30 mg bid and octreotide. Nevertheless, at home the patient presented severe carcinoid symptoms, including persistent flushing of the face and upper trunk, important labial and periocular oedema (Fig. 4), diarrhoea and nausea, so that he was readmitted to the hospital. Laboratory assessment showed hypokaliemia (2.4 mEq/l), high creatinine (1.53 mg/dl) and BUN (51.4 mg/dl), sharp increase of CgA (1108 ng/ml), 5-HIAA (280 mg/24 h) and serotonin (5-HT 43 µg/dl). Intensive treatment was therefore carried out with iv infusion of octreotide (50 µg/h), H1 (chlorpheniramine maleate 10 mg td) and H2 receptor antagonist (ranitidine 50 mg every 6 h) and corticosteroid therapy (betamethasone sodium phosphate 4 mg tid) which induced symptom regression within few days.
At the 3 month-follow-up, both clinical status and tumor markers (CgA 588 ng/ml, 5-HIAA 210 mg/24 h) were improved. The patient was subsequently scheduled for the continuation of the receptor radionuclide therapy. In August 2004, the patient received the third cycle of therapy with a lower activity (1.63 GBq), together with anti-H1 and anti-H2, and corticosteroid protection, starting before treatment administration, and the addition of cold octreotide, starting from the day after. Despite a transitory flushing arising immediately after the infusion, no prolonged acute carcinoid crisis occurred (Figure 3 shows the course of CgA and 5-HIAA before and after each radionuclide cycle).

PROTOCOL OF RECEPTOR RADIONUCLIDE THERAPY WITH 90Y-DOTATOC

The SS analog DOTATOC (DOTA: 1,4,7,10-tetra-azacyclododecane-N, N', N'', N'''-tetraacetic acid) was synthesized at the Division of Radiological Chemistry University Hospital, Basel according to a described procedure. 90Y-chloride was purchased from MDS Nordion (Ottawa, Ontario, Canada). DOTATOC was radiolabeled according to a previously published procedure (12-14). Prior to initiation of therapy, the patient underwent physical examination, routine biochemical profile with determination of serum CgA, and imaging-based (CT) evaluation of the disease. 90Y-DOTATOC was injected iv over 20 min in 100 ml of physiological saline. Repeated administrations were performed with at least a 6-8-week interval. A typical administration consisted in 80 µg of DOTATOC labeled with 2.96 GBq of 90Y. According to current concerns for renal protection, the patient received an infusion of positively charged amino acids, namely lysine and/or arginine, immediately before and after therapy.

DISCUSSION

We described a case of severe carcinoid crisis induced by amine release due to receptor radionuclide treat-

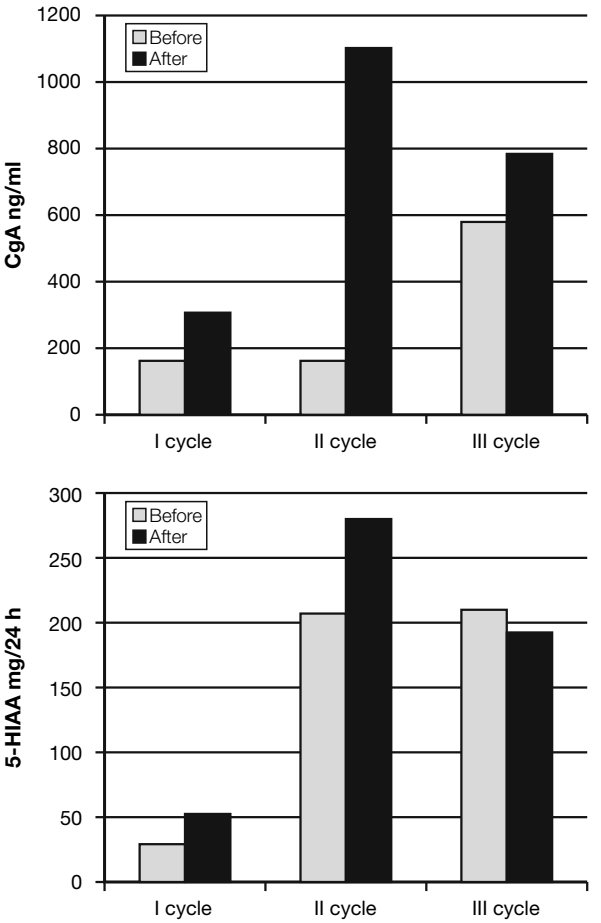

Fig. 3 - *The course of chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are shown before and after each radionuclide cycle.*

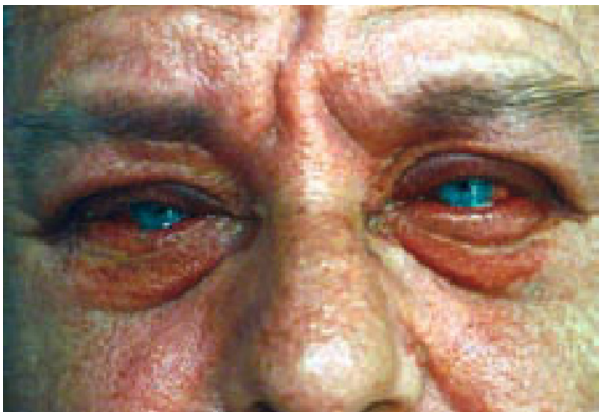

Fig. 4 - *Acute phase of facial flushing with severe periocular oedema.*

ment in a patient affected by liver metastases from atypical carcinoid of the lung. This therapeutic option had been chosen after the failure of biologic therapy with octreotide and interferon, and chemotherapy.
The severity of the diarrhoea and the high levels of serotonine and its metabolite 5-HIAA were consistent with the typical form of carcinoid crisis. Nevertheless the co-secretion of histamine could not be excluded since ocular oedema and lacrimation occurred, although only after the second cycle of radiometabolic therapy, so that antihistaminic treatment was also implemented. Unfortunately histamine concentration is not assessed in our laboratory.
The causal relationship between the radionuclide therapy and the carcinoid crisis was strongly supported by the sharp increase in serum serotonin, released by damaged cells, its urinary metabolite and serum CgA.
One pathogenetic mechanism that could be implicated in the development of the radionuclide-induced carcinoid crisis, is the cell rupture due to acute radiation effect of 90Y-DOTATOC with secondary massive release of vasoactive peptide and hormones.
A 90Y-DOTATOC dose dependent effect in inducing the carcinoid crisis is possible, because the event occurred after the second cycle, performed with the highest dose, but it is not certain. In fact, the difference between the first and second cycle dose is small (2.59 *vs* 2.1 GBq) and the third cycle, with the lowest dose (1.62 GBq), was carried out under protection of anti-H1 and anti H2 drugs.
Carcinoid crisis has been reported after invasive procedures aimed at removing or destroying functional carcinoid metastases (liver metastases resection, chemoembolisation) but to our knowledge, it has never been described after receptor radionuclide treatment up to now.
Our observation seems to provide further evidence of the effectiveness of this treatment in delivering high irradiation doses to neuroendocrine tumors. Nevertheless, the occurrence of a severe carcinoid crisis, like the one we observed, stresses the need for a careful coverage with anti-serotonin and anti-histamine drugs, particularly when high amounts of radioactivity are delivered, in order to prevent and/or attenuate the subsequent carcinoid crisis.
Since SS analogs could interfere with the therapeutic effect of the labelled octreotide, due to the competition for the same receptor, antiserotonin agents and histamine H1-H2 receptor antagonists, combined with corticosteroids, should be preferred before the procedure is started. On the other hand, SS analogs can be added later, starting the day after the radiopeptide infusion. Although in our experience these measures proved to be effective, clinical consequences from massive release of amines and/or vasoactive peptides, after receptor radionuclide therapy, could be unpredictable, depending on the extension and functional activity of neuroendocrine tissue, as well as the coexistence of other pathologies. Therefore, lower activities per cycle should be administered and a careful surveillance of these patients is mandatory soon after the procedure and in the following days.

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