Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 59; Numer/Number 4/2008
ISSN 0423–104X

Multimodality palliative treatment of ^{111}In-pentetreotide negative/^{123}I-MIBG positive metastatic carcinoid — a case report

Multimodalne leczenie paliatywne chorej z ^{111}In-pentetreotydo-ujemnym/ /^{123}I-MIBG-dodatnim przerzutowym rakowiakiem — opis przypadku

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Abstract

Patients with carcinoid tumours frequently present with metastatic disease. There are only a few therapeutic options for these patients, and the main goal of palliative treatment is to reduce symptoms and thus to improve quality of life. Current therapy includes surgical resection, hepatic artery embolisation, chemotherapy and somatostatin analogue treatment; however, all these options have limitations. It seems probable that therapeutic modalities based on radiopharmaceuticals may provide better therapy, not only in relation to symptom reduction but may also improve patient survival.

In this case report we present a 46-year-old woman with a symptomatic carcinoid, who at the time of diagnosis had liver and abdominal lymph node metastases, the primary tumour being located in the terminal ileum. ^{111}In-pentetreotide scanning was negative, whereas ^{123}I-MIBG scanning showed high avidity in the tumour tissue. After right hemicolectomy, two courses of ^{131}I-MIBG treatment were given (12.95 GBq and 12 GBq, respectively). After the second dose of ^{131}I-MIBG temporary pancytopenia was present. Octreotide therapy was given empirically only for a short time and was stopped because of drug intolerance. The patient underwent tricuspid and pulmonary valve replacement because of her carcinoid heart disease, followed by two courses of embolisation of liver metastases. While ^{131}I-MIBG therapy reduced the patient's symptoms of flushing and diarrhoea, there has not yet been any effect on tumour response or 5-HIAA production. This case illustrates the multimodality and multidisciplinary approach to such patients. **(Pol J Endocrinol 2008; 59 (4): 342–347)**

Key words: *carcinoid, metastatic disease, paliative treatment*

Streszczenie

U chorych z rakowiakiem często występują przerzuty. W takich przypadkach istnieje niewiele opcji terapeutycznych. Głównym celem leczenia paliatywnego jest złagodzenie objawów i poprawienie jakości życia. Dostępne obecnie metody terapii obejmują chirurgiczną resekcję zmian nowotworowych, embolizację tętnicy wątrobowej, chemioterapię i stosowanie analogów somatostatyny. Jednak wszystkie te metody mają ograniczenia. Wydaje się, że stosując techniki radiofarmakologiczne można uzyskać najlepsze rezultaty, nie tylko pod względem zmniejszenia objawów, ale również wydłużenia okresu przeżycia.

W niniejszej pracy autorzy opisują przypadek 46-letniej kobiety z objawowym rakowiakiem, u której w chwili rozpoznania choroby stwierdzono przerzuty do węzłów wątroby oraz brzusznych węzłów chłonnych. Guz pierwotny znajdował się w końcowym odcinku jelita krętego. W badaniu radioizotopowym z użyciem ^{111}In-pentetreotydu nie wykazano gromadzenia radioznacznika, natomiast w scyntygrafii z użyciem ^{123}I-MIBG stwierdzono zwiększony wychwyt znacznika przez tkanki guza. Po wykonaniu prawostronnej hemikolektomii zastosowano dwa cykle terapii ^{131}I-MIBG (odpowiednio: 12,95 i 12 GBq). Po drugiej dawce ^{131}I-MIBG wystąpiła okresowa pancytopenia. Zastosowano empirycznie terapię okreotydem, jednak przerwano ją po krótkim czasie z uwagi na nietolerancję leku. Chora przebyła zabieg wymiany zastawek trójdzielnej i płucnej z powodu rakowiakowej choroby serca, a następnie 2-krotną embolizację przerzutów wątrobowych. Chociaż terapia ^{131}I-MIBG spowodowała złagodzenie objawów, napadowego przekrwienia skóry i biegunki, jednak nie zaobserwowano zmniejszenia guza ani ograniczenia produkcji 5-HIAA. Opisany przypadek jest przykładem multimodalnego i wielodyscyplinarnego leczenia rakowiaka. **(Endokrynol Pol 2008; 59 (4): 342–347)**

Słowa kluczowe: *rakowiak, choroba przerzutowa, leczenie paliatywne*

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Introduction

Gastro-enteric neuroendocrine tumours (NETs), formerly known as carcinoids, appear to have increased in overall incidence over the past 30 years. In spite of improved diagnostic technology and increased awareness, patients with such tumours still frequently present with metastatic disease [1, 2]. In addition, carcinoid heart disease (CHD) appears in more than half of the patients with the carcinoid syndrome, and remains a major cause of morbidity and mortality among these patients [3, 4].

There are relatively few therapeutic options for widely metastatic carcinoids, and the main aim of this treatment is to reduce the symptoms related to hormone excess and to prolong survival. Palliative therapy includes surgical resection, hepatic artery embolisation, immunomodulatory therapy (principally interferon) and octreotide treatment; chemotherapy plays only a limited role. It is apparent that new therapeutic modalities based on radiopharmaceuticals *e.g.* ^{131}I-MIBG (Iodine-131 metaiodobenzylguanidine) and radolabelled octreotide may provide better therapeutic possibilities in selected patients with metastatic carcinoid, not only in relation to symptom reduction but also long-term survival [5].

In this case report, we present a patient with a symptomatic carcinoid who was initially diagnosed with metastatic disease with primary localisation in the terminal ileum, complicated by carcinoid heart disease, who underwent complex treatment including right hemicolectomy, ^{131}I-MIBG therapy, embolisation of liver metastases, and tricuspid and pulmonary valve replacement. We demonstrate the modern multimodality treatment of this difficult condition, and the fact that ^{131}I-MIBG therapy has appeared to reduce the patient's symptoms, although with little effect on tumour bulk so far.

Case report

A 47-year-old dental nurse was first seen in the Department of Endocrinology, St. Bartholomew's Hospital in London, in January 2006. Her previous medical history started in 2003, when she suffered night sweats and flushing; she disregarded these symptoms believing that they were related to her imminent menopause. Her family and social history was unremarkable, she had three healthy children, never drank alcohol and had never smoked.

In 2004 she had visited her General Practitioner (GP) for a routine cervical smear, which showed mild dysplasia. In 2005 she returned to GP for a repeat smear test. During routine examination her blood pressure was found to be elevated (196/103 mm Hg), and she was started on anti-hypertensive medications. Despite different treatment combinations, her blood pressure control was not satisfactory (234/122, 218/166 mm Hg). She developed intermittent diarrhoea, which was attributed at that time to treatment side effects. She was referred to a specialist in hypertension, who investigated her secondary causes of hypertension. Her renal magnetic resonance angiography showed normal renal arteries but her right kidney was displaced by an enlarged liver with multiple focal masses, present in both lobes. Because her initial blood tests had revealed hypokalaemia (3.2 mmol/L) and an elevated aldosterone/renin ratio (50.7 and 79 ng/mu, normal range 0–25 ng/mu), she was referred for further specialist endocrine investigation.

Subsequent blood tests showed elevated serum chromogranin A (> 1000 pmol/L, normal range: 0––60 pmol/L) and 24-urine 5-HIAA (5-hydroxyindoleacetic acid) excretion (876 μmol/24 h, normal range: 9-31 μmol/ /24 h). An abdominal CT scan with contrast showed multiple focal masses throughout the liver with normal adrenal glands, a 3cm mass high and anterior in the left abdomen, and an eccentric lesion in a loop of small bowel below the right kidney. CT-guided biopsy of the liver lesion established a diagnosis of metastatic neuroendocrine tumour (immunohistochemistry showed positive chromogranin, CD56, neuron-specific enolase and Cam 5.2 staining). In December 2005 she was referred to our Department.

During her first admission in our Department in January 2006, she was reported to be suffering from diarrhoea and flushing. Investigations at this time revealed normal plasma neuroendocrine peptide concentrations and normal 24-urine catecholamine collections. Her 24-urine 5-HIAA was elevated and even higher than in 2005 (2132 μmol/24 h; Figure 1). An ^{111}In-pentetreotide scan

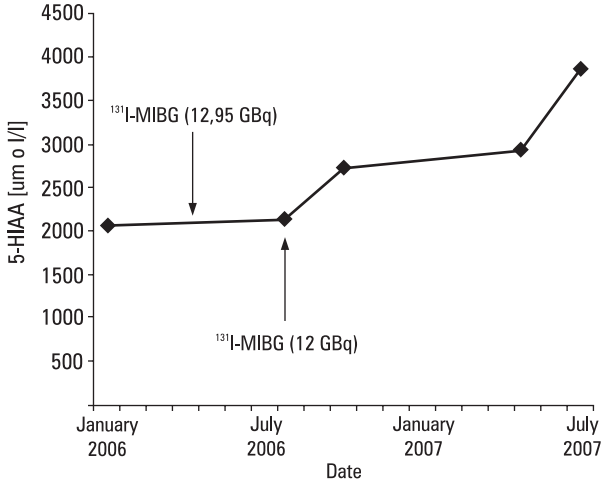

Figure 1. *Urine 5-HIAA 24-hour measurements performed between January 2006 and May 2007 in Barts and the London Hospital*

Rycina 1. *Oznaczenie zawartości 5-HIAA w dobowej zbiórce moczu. Badania wykonano w* Barts and the London Hospital *w okresie od stycznia 2006 do maja 2007 roku*

Table I. *Neuroendocrine markers results*
Tabela I. *Stężenia markerów neuroendokrynnych*

	Jan 2006	Jul 2006	Normal range	Unit
Plasma				
Gastrin	14	8	0–40	pmol/L
VIP	< 4	3	0–30	pmol/L
PP	22	30	0–300	pmol/L
Glucagon	6	< 5	0–50	pmol/L
Somatostatin	30	36	0–150	pmol/L
Neurotensin	56	22	0–100	pmol/L
Chromogranin A		> 1000	0–60	pmol/L
Chromogranin B		156	0–150	pmol/L
Urine				
Adrenaline	< 30	< 30	0–560	nmol/24 h
Noradrenaline	212	205	0–560	nmol/24 h
Dopamine	928	941	0–3194	nmol/24 h
5-HIAA	2049	2162	0–50	umol/24 h

(OctreoScan™) showed no evidence of somatostatin receptor expression; however, ^{123}I-MIBG showed multiple ^{123}I-MIBG avid in both lobes of the liver and in the mass in the left upper abdomen. Echocardiography (ECHO) demonstrated very mild tricuspid regurgitation (TR). Isotope bone scan was normal.

The patient was discussed at a multi-disciplinary team meeting and it was decided to remove the ileac primary lesion. In February 2006 right hemicolectomy was performed. A carcinoid tumour in the terminal ileum was resected, histologically showing vascular and perineural invasion, and with multiple mesenteric lymph nodes (6 of 21 examined showed tumour) and liver metastases.

In April 2006 she was admitted for the first dose of ^{131}I-MIBG treatment (12.95 GBq; 350 mCi). Treatment with ^{131}I-MIBG was performed on an inpatient basis. Before ^{131}I-MIBG, the patient was given potassium iodide to block thyroid accumulation of radioiodine. A repeated echocardiogram reported progression in the tricuspid regurgitation with borderline right ventricle systolic pressure overload (RVSP — 37 mm Hg).

In July 2006 she was admitted for re-assessment. She now complained of increasing breathlessness, principally on exertion but without associated chest pain, and also persistent peripheral oedema; she had developed gradual deterioration in her exercise tolerance. However, her flushing and diarrhoea following the first dose of ^{131}I-MIBG therapy were well controlled. Her routine blood investigations and 24-urine 5-HIAA collection were stable (Table 1; Figure 1). A CT of the chest and abdomen/pelvis showed multiple liver metastases with a small amount of free fluid in the abdomen and pelvis, which was thought to represent peritoneal disease, but the size of the lesions appeared stable. She received a second course of ^{131}I-MIBG (12 GBq; 324 mCi). A repeat ^{131}I-MIBG post-therapy scan showed ^{131}I-MIBG uptake in the liver and in the upper abdomen (Figure 2). Compared to the previous scan, there appeared to be some increased activity in the upper mild abdomen, but without any clear evidence of disease progression.

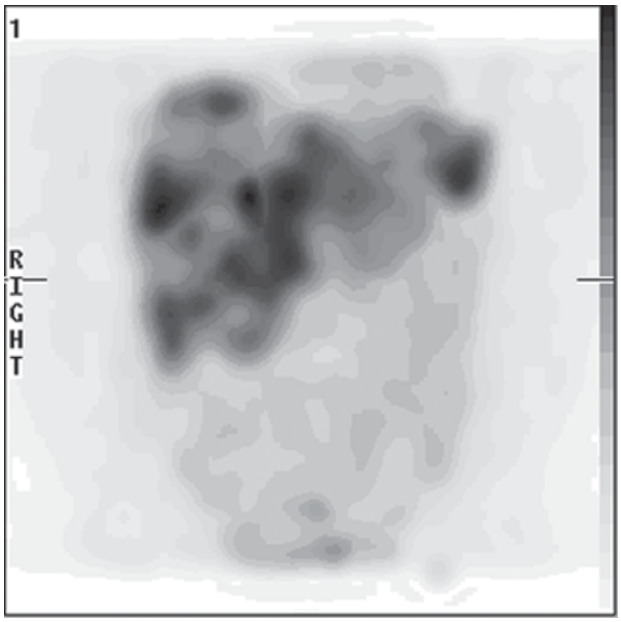

Figure 2. *A repeated ^{131}I-MIBG post-therapy scan*
Rycina 2. *Powtórna scyntygrafia po terapii ^{131}I-MIBG*

In July 2006, in spite of a negative octreotide scintiscan, octreotide therapy was started (100 μg twice a day), but this was poorly tolerated and stopped.

A repeat echocardiogram performed in July 2006 showed severe tricuspid regurgitation: the right ventricle was moderately dilated with a mild reduction in systolic function; the right atrium was also moderately dilated. In a right ventricular angiogram, ventricular, atrial and pulmonary artery pressures were 37/15, 24 and 30/11 mm Hg, respectively. In view of the progression of echocardiographic abnormalities and increasing symptoms, the patient was now considered suitable for appropriate valve replacement. However, at this point (August 2006) the procedure was postponed because of sever pancytopenia, occurring four weeks after the second course of ^{131}I-MIBG (Figure 3). The patient required repeated platelet and blood transfusions, but by January 2007 her haematological parameters had improved sufficiently for her to undergo tricuspid and pulmonary valve replacement. Two tissue grafts were inserted (in order to obviate the need for anti-coagulation), and she rapidly noted an improvement in her exercise tolerance.

Over the next few months she remained well, but due to a persisting very high level of 5-HIAA, which was not improved by ^{131}I-MIBG therapy, further therapeutic options for liver metastases were discussed. In May 2007 she had embolisation of liver metastases, complicated by a transient right unilateral hemianopia. Magnetic resonance of the brain did not show any alteration; she was started on 75 mg of aspirin and discharged home in a good general condition. She has remained well, but in view of the stable but elevated level of urinary 5-HIAA she underwent a second hepatic artery embolisation in February 2008.

She continues to be well with good exercise tolerance and no further flushing or diarrhoea. She is currently taking amiloride, bisoprolol, valsartan, furosemide and codeine phosphate.

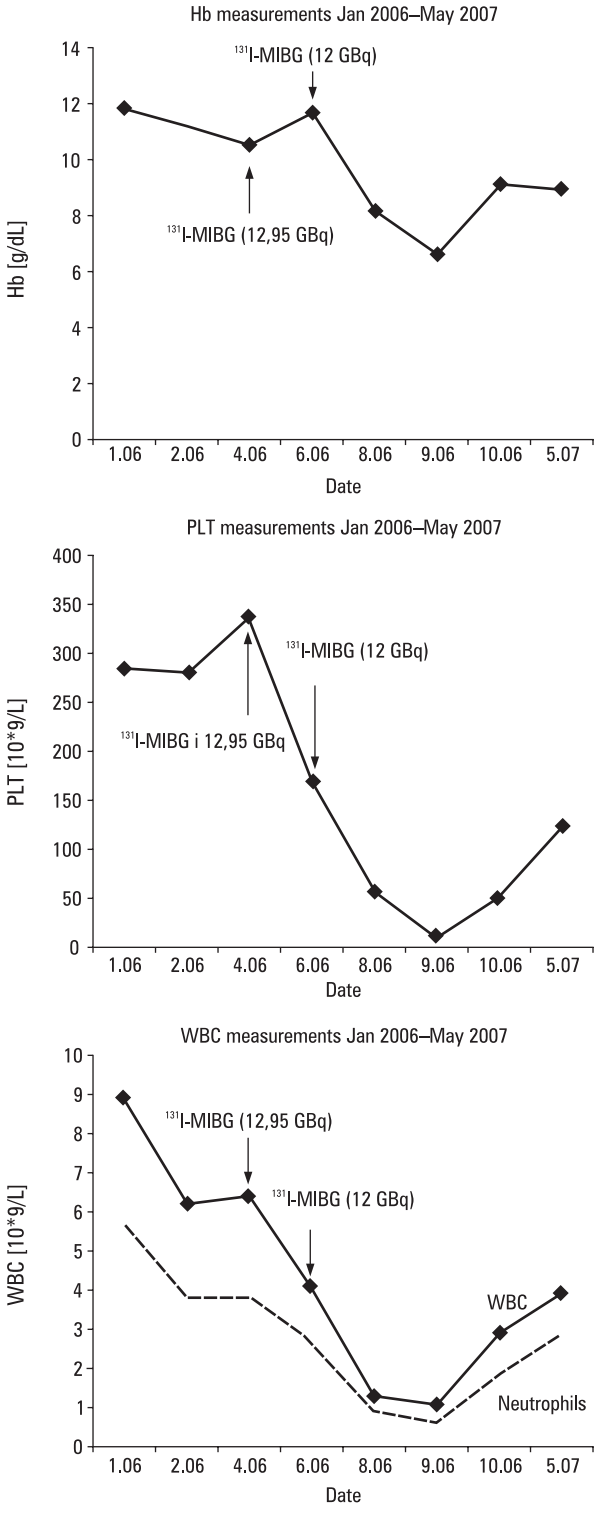

Figure 3. *Blood account assessed between January 2006 and May 2007 in Barts and the London Hospital*

Rycina 3. *Wyniki badania krwi wykonane w* Barts and the London Hospital *w okresie od stycznia 2006 do maja 2007*

Discussion

Carcinoid tumours represent an unusual and complex disease spectrum with protean clinical manifestations [2]. Because many of the symptoms are relatively non-specific, the diagnosis of this disease remains problematic, and many carcinoids are diagnosed late with metastatic complications. Within the gastrointestinal tract, most carcinoid tumours originate in the small intestine (41.8%), but also derive from the rectum (27.4%) and stomach (8.7%). The highest percentages of non-localised lesions are noted for caecal (81.5–83.2%) and pancreatic (71.9–81.3%) carcinoids, whereas the highest percentage of localised disease is found among rectal (81.7%), gastric (67.5%), and bronchopulmonary (65.4%) carcinoids [2].

Neuroendocrine tumours (NETs) may express active amine precursor uptake-1 mechanisms and/or specific receptors at the cell membrane, and therefore can be detected and treated with the use of radiopharmaceuticals reliant upon these specific mechanism [6]. Radiolabelled octreotide, an analogue of somatostatin, is used *in vivo* to demonstrate tumours that have somatostatin receptors on their surface, which is important both diagnostically as well as therapeutically. ^{111}In-pentetreotide remains the principal radiodiagnostic somatostatin analogue [6, 7], although other novel analogues are currently under trial. On the other hand, ^{123}I-MIBG is an alkyl-guanidine derivative that is similar to noradrenaline and is accumulated by tissues thought to arise from neural crest cells; ^{123}I-MIBG has been shown to be highly sensitive for detecting tumours arising from the adrenal medulla but may be also taken up by non-adrenomedullary NETs [6, 7]. A direct comparison of ^{111}In-pentetreotide and ^{123}I-MIBG scintigraphy performed in the same group of advanced NET patients showed that octreotide scanning was more sensitive in detecting metastatic lesions (as demonstrated on computer tomography and/or magnetic resonance) than ^{123}I-MIBG for carcinoid tumours, pancreatic islet cell tumours and medullary thyroid carcinomas, whereas ^{123}I-MIBG was superior to ^{111}In-pentetreotide for phaeochromocytomas and paragangliomas [6].

In our case of metastatic carcinoid, ^{111}In-pentetreotide was negative while ^{123}I-MIBG showed high avidity for tumour tissue. It has been reported that ^{111}In-pentetreotide was positive more frequently than ^{123}I-MIBG scanning in the group of 24 patients with carcinoids (67% *vs.* 50%, respectively), with few patients showing uptake with ^{123}I-MIBG not present with radiolabelled octreotide. However, there were also exceptions to this, since two cases were found to be ^{111}In-pentetreotide-negative and ^{123}I-MIBG positive, and our patient confirms that this pattern can occur and be therapeutically relevant [6].

The therapeutic modalities for advanced carcinoids include palliative surgery, hepatic artery embolisation, chemotherapy, immunomodulatory therapy and/or somatostatin analogue treatment, and more recently radiopharmaceutical therapy.

Our patient underwent right hemicolectomy and removal of the apparent primary tumor, which allowed full histological assessment. While in some more malignant diseases such removal of the primary in the presence of metastases is contraindicated, for many NETs this tumour debulking may be useful in its own right, in terms of tumour bulk reduction to increase the effectiveness of other adjuvant therapies, as well as decreasing the likelihood of intestinal obstruction. Further therapy with ^{131}I-MIBG treatment was chosen based on high ^{123}I-MIBG tumour avidity: the patient received two courses of ^{131}I-MIBG therapy, the doses being based on a dose-finding study to assess maximal marrow tolerability, with a cumulative dose of 24.95 GBq (~ 680 mCi). Pancytopenia related to the second dose of ^{131}I-MIBG precluded further ^{131}I-MIBG treatment, and led to a delay in the replacement of her cardiac valves. However, recent studies have suggested that small numbers of high doses of ^{131}I-MIBG are the most likely to lead to clinical improvement.

^{131}I-MIBG treatment was found to be a good palliative therapeutic option for metastatic carcinoid, with response rates of 40–60% [8–10]. In a retrospective analysis performed by Safford and colleges, the results of ^{131}I-MIBG therapy were analysed in a group of 98 patients with metastatic carcinomas, whose ^{123}I-MIBG scans performed before treatment showed abnormal accumulation in the site of known disease. In this study, the endpoints examined included the World Health Organization criteria for treatment response: symptoms, 5-HIAA production, and clinical tumour response. 69, 20 and 4 patients received one, two or three dose of ^{131}I-MIBG, respectively, the mean dose of ^{131}I-MIBG being 401 ± ± 202 mCi. They found that patients who experienced a symptomatic response after ^{131}I-MIBG also showed improved survival (5.76 years *vs.* 2.09 years, $P < 0.01$), but neither the reduction in 5-HIAA levels nor radiographic tumour response after ^{131}I-MIBG treatment predicted survival. Survival improvement was related to ^{131}I-MIBG dose because patients who received an initial ^{131}I-MIBG dose > 400 mCi lived longer than patients who received < 400 mCi (4.69 years *vs.* 1.86 years; $P = 0.05$) [5]. It is well established that ^{131}I-MIBG therapy might be associated with several complications, of which bone marrow suppression (including pancytopenia or thrombocytopenia) remains the most frequent, occurring in 13% of patients [5]. Other toxicities include nausea and emesis. It appears that such complications are not related to the dose level or the number of doses of ^{131}I-MIBG [5].

A short course of octreotide was given, in spite of ^{111}In-pentetreotide-scan negativity, but this was stopped due to poor tolerance. While the ^{131}I-MIBG therapy was not associated with any clear fall in urinary 5-HIAA secretion or tumor regression, the patient did show an improvement in her symptoms. She was finally treated with hepatic embolisation with microspheres on two occasions, and this was well tolerated. It was decided not to use chemo-embolisation as this has not been clearly shown to be superior to simple embolisation alone, and the patient's bone marrow had already been compromised by the radiolabelled therapy.

As yet we have not utilized systemic chemotherapy. Chemotherapy in NETs can be associated with symptomatic and hormonal improvement and, very

occasionally, tumour regression or stabilization; however, long-term survival remains poor. The current role of chemotherapy seems to be for well-differentiated carcinoids and particularly islet-cell tumours showing progression of the disease after treatment with somatostatin analogues or radiopharmaceuticals [11].

Another challenge in carcinoid patient care is related to carcinoid heart disease (CHD) management. CHD is a relatively rare form of valvular heart disease; however, it appears in more than half of patients with carcinoid syndrome [12]. It typically occurs when tumour progression results in the formation of hepatic metastases which allow vasoactive substances to reach the heart without being metabolized in the liver. The only exception in which CHD was not related to liver involvement has been reported in patients with primary ovarian carcinoid tumours [13]. The concentration of circulating serotonin and the urinary excretion of 5-HIAA have been shown to be higher among patients with CHD than among patients without cardiac involvement [14]. Furthermore, urinary 5-HIAA levels have been associated with progression of CHD [15].

Cardiac surgery has been recognised as the only effective treatment option in the group of patients with severe cardiac involvement and well-controlled systemic disease [16]. The current indications for cardiac valve replacement include symptoms of right ventricular failure with progressive fatigue, significantly impaired exercise capacity, progressive right ventricular enlargement and decline in right ventricular systolic function. Valve replacement surgery may not only be beneficial in terms of symptom relief, but may contribute to the improved survival. It seems that early diagnosis and early surgical treatment in appropriately selected patients may provide the best results [12].

Our patient underwent successful tricuspid and pulmonary valve replacement, which improved right ventricular failure and exercise tolerance. Because ^{131}I-MIBG therapy did not stop or even decrease high 5-HIAA secretion, she underwent embolisation of liver metastases in order to avoid further cardiac problems related to exposure to vasoactive substances produced by the carcinoid tumour. In the future, further evidence of progression will lead to consideration of more experimental therapies, such as the chemotherapy agent temozolomide and the 'mTOR' inhibitor everolimus (RAD001, Novartis).

In conclusion, we have presented a case in which a metastatic NET has been aggressively treated with surgery, ^{131}I-MIBG therapy and hepatic artery embolisation, as well as with surgical replacement of the tricuspid and pulmonary vales with tissue grafts. This case emphasizes the importance of assessing such patients with a multi-disciplinary team, and the importance of the availability of multimodality therapies both to improve survival, where possible, and to increase the quality of life in patients with indolent disease.

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