

Carcinoid case presentation and discussion: the American perspective

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Abstract

The rationale underlying an aggressive approach in the management of some carcinoid patients is explained and illustrated by the presented case of a middle-aged man with advanced classic typical midgut carcinoid. The patient exhibited somatostatin receptor scintigraphy-positive massive liver metastases, carcinoid syndrome, severe tricuspid and pulmonic cardiac valve disease with congestive heart failure, ascites and malnutrition. He had been treated for several years with supportive medications and biotherapy including octreotide and alpha interferon but his tumor eventually progressed and his overall condition was markedly deteriorated when he first sought more aggressive treatment. This consisted of prompt replacement of both tricuspid and pulmonic valves, followed by hepatic artery chemoembolus (HACE) injection and then surgical tumor debulking including excision of the primary tumor in the small intestine. In addition, radiofrequency ablation was utilized to reduce the volume of metastases in the liver. Prophylactic cholecystectomy was also performed and a biopsy of tumor was submitted for cell culture drug resistance testing. This was followed by systemic chemotherapy utilizing the drug (docetaxel) which the *in vitro* studies suggested as most likely to be effective. His excellent response to this succession of treatments exemplifies the successful application of aggressive sequential multi-modality therapy.

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Introduction

I have been requested to present a case report to illustrate how carcinoid is treated in the United States. That is easy to do, but it is also difficult since there is no uniformly practiced standard approach being followed in the United States for the management of these patients. Still adhering to the original description of carcinoid as a benign neoplasm, or at least one with extremely slow growth (Oberndorfer 1907), there is a widely prevalent conservative attitude of ‘wait and see’, waiting for the patient to become very symptomatic and/or the tumor to become clearly larger (Öberg 2000), and then to treat as minimally as possible. These tumors vary widely in their aggressiveness and production of symptoms, with many growing very slowly but others having a more malignant course (Jensen 2000). Although this conservative approach works well in many cases it must not be generalized and applied to all since it has become apparent over the past decade that carcinoid is not as completely benign as it was originally thought to be (Modlin *et al.* 2003). At the other end of the management spectrum is the aggressive proactive approach, which is gaining adherence as it becomes noted that properly selected patients fare better with earlier

and sometimes aggressive treatment (Öberg 1998). This observation also applies to many far-advanced cases previously relegated to simple non-interventional palliative care. With this spectrum of management in mind I am presenting a case of very far-advanced metastatic midgut carcinoid with carcinoid syndrome and severe cardiac complications responding very well to aggressive sequential treatment with multiple modalities and exemplifying the benefits of such an approach.

Case report

This 55-year-old Caucasian male postal worker had been in good health, except for mild chronic hypertension, until 1999 when he noted the onset of facial flushing and mild pitting edema of his feet. Physical examination disclosed an enlarged hard nodular non-tender liver. CT scan of the abdomen revealed multiple small nodules and several very large confluent lesions in both lobes of the liver (Fig. 1). Needle biopsy was interpreted as typical carcinoid. A barium contrast study of the small intestine revealed no lesions. Twenty-four hour urinary 5-hydroxyindoleacetic acid (5-HIAA) was

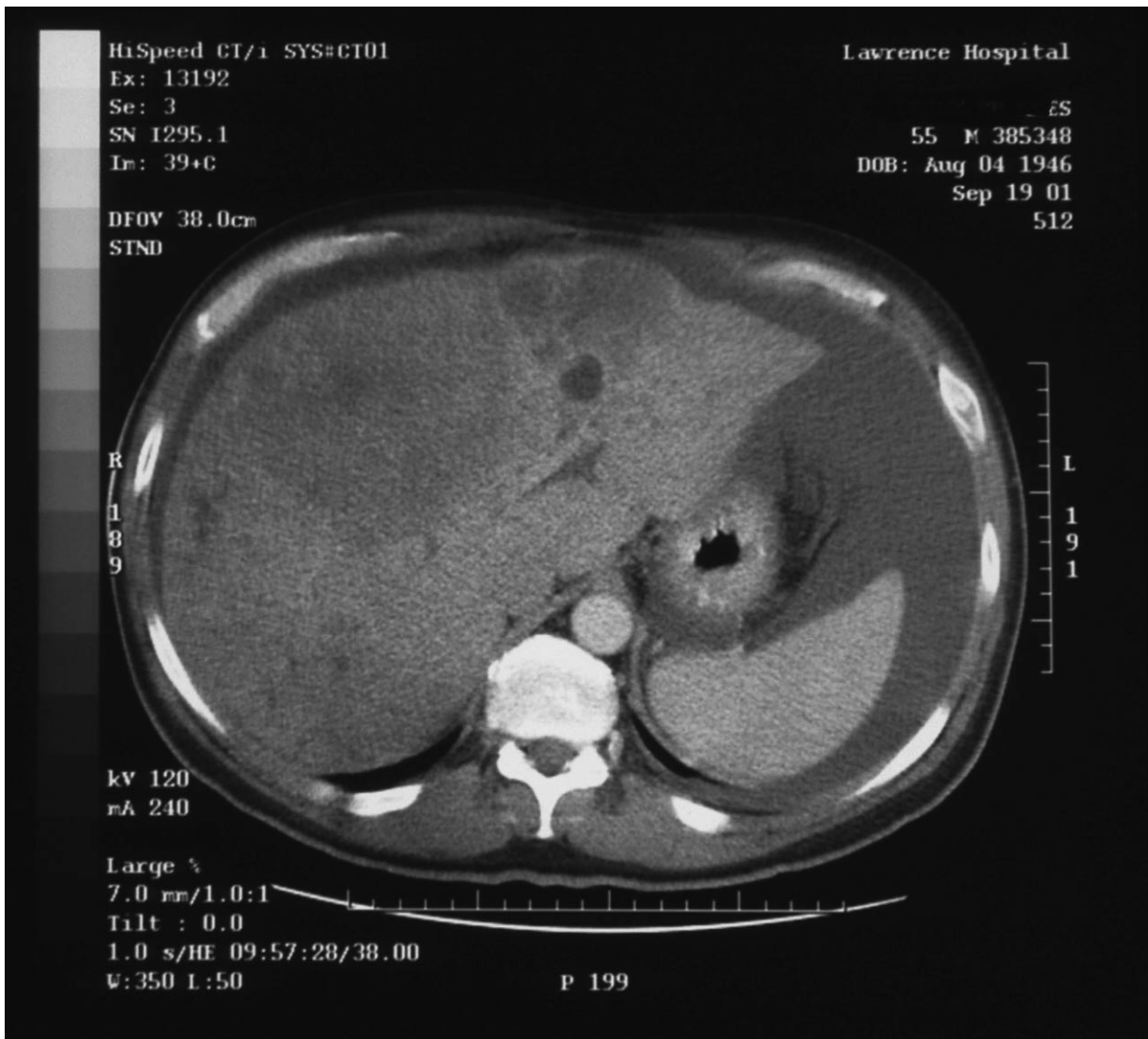


Figure 1 CT scan of abdomen, 2 September 2001; prior to aggressive treatment.

markedly elevated at 230 mg (normal <6). Blood serotonin was also increased with a value of 702 ng/ml (normal <80) (Table 1). An echocardiogram revealed marked tricuspid regurgitation and pulmonic hypertension.

Treatment with s.c. injections of octreotide was started and rapidly switched to monthly i.m. injections of 30 mg of the long-acting formulation. The flushing was relieved. He had been maintained on low-dose chronic diuretic (hydrochlorothiazide). This was increased and spironalactone was added. Additional medications consisted of metoprolol and potassium chloride. Alpha interferon treatment was initiated using 3 million units by s.c. injection three times a week.

His pedal edema cleared and he remained comfortable for approximately 1 year but then ascites and non-productive cough occurred and he required large volume abdominal paracentesis on three occasions. He became progressively weaker and also began to note mild diarrhea. Flushing returned. Therefore in search of additional treatment the patient consulted us on 2 January 2002.

Physical examination revealed him to be a gaunt, wasted, chronically ill-appearing middle-aged white male with a markedly red facial flush. The skin was dry. He was 186 cm in height and weighed 81 kg. Blood pressure was 110/80 and heart rate was 76 beats per minute and was regular. Neck veins were distended and pulsatile. The lungs were clear.

Table 1 Pertinent laboratory tests

Test	Before aggressive treatment (January 2002)	After aggressive treatment (March 2003)
Urine		
5-HIAA	230 mg/24 h (normal <6)	—
Blood		
Serotonin	702 ng/ml (normal <180)	396 ng/ml
Chromogranin-A	716 ng/ml (normal <39)	615 ng/ml
Atrial natriuretic factor	180 pg/ml (normal 20–77)	—
Blood urea nitrogen	24 mg/dl (normal 7–25)	—
Creatinine	0.9 mg/dl (Normal 0.5–1.4)	—
Electrolytes	Normal	—
Total bilirubin	0.77 mg/dl (normal 0.2–1.5)	0.81 mg/dl
Alkaline phosphatase	170 U/l (normal 20–25)	152 U/l
γ -Glutamyltransferase	106 U/l (normal 2–80)	—
Alanine aminotransferase	35 U/l (normal 2–60)	35 U/l
Aspartate aminotransferase	33 U/l (normal 2–50)	35 U/l
Albumin	2.9 g/dl (normal 3.5–4.9)	3.8 g/dl
White blood cells	4600 \times 10 ⁹ cells/l (normal 4.6–11.0)	—
Hematocrit	42.3% (normal 40–52%)	—

A prominent systolic ejection murmur was heard along the left sternal border and the abdomen was soft but markedly distended by ascites. A 3 cm slightly tender nodular mass was felt in the mid-epigastrium. The hands and feet had a dusky cyanotic appearance and one plus pitting edema of both feet was present.

A new CT scan of the abdomen with contrast showed a markedly enlarged liver with large bilobar confluent metastases and multiple small lesions. A new small bowel barium contrast X-ray series showed a filling defect in the distal ileum, which narrowed the lumen of the intestine to approximately 3 mm (Fig. 2). An octreoscan showed multiple foci of isotope concentration in the liver only.

Management

The patient's prior medications were continued and low-dose niacin (25 mg p.o. b.i.d.) was added. Repeat cardiac evaluation was obtained and confirmed the presence of severe tricuspid regurgitation and pulmonic stenosis. The patient was felt to be in marked right heart failure and the urgency of his cardiac disease was considered to supercede any consideration of cytoreductive treatment. Furthermore he was felt to be unable to tolerate any attempt at anti-tumor treatment. Accordingly, on 15 February 2002 he underwent cardiac surgery consisting of replacement of both the tricuspid and pulmonic valves with bovine pericardial prostheses and he also underwent closure of a patent foramen ovale discovered at that surgery.

He experienced a remarkably rapid improvement following this surgery and noted 15 kg weight loss, clearing of his pedal edema and cough, and decrease in his ascites over the

next 3 weeks. However, 1 month following the surgery (15 March 2002) his blood chromogranin-A had risen to 1320 ng/ml and the chromogranin-A content of his residual ascitic fluid was 716 ng/ml. The ratio between the concentration of this marker in each of these fluids was interpreted as indicating the ascites was due to a hemodynamic disturbance rather than to direct tumor exudation. Therefore no additional treatment was given beyond continuation of his diuretics, octreotide and the same pre-operative medications. Over the next 2 months his ascites totally receded.

In September of 2002 he was started on a series of three HACE injection treatments which were carried out monthly. Injected drugs consisted of cisplatin, doxorubicin, mitomycin, X-ray contrast and microspheres (embospheres) which were all injected simultaneously into different segments of the liver on each of the three treatment procedures. He tolerated this very well and in December of 2002 was finally submitted for laparoscopic abdominal surgery. At that time the segment of terminal ileum containing the primary carcinoid was resected and a new biopsy of tumor was obtained for histological studies and also for *in vitro* cell culture drug resistance testing. Also, a prophylactic cholecystectomy was performed along with ultrasonography-guided radiofrequency ablation of a 4 cm metastasis and two smaller adjacent ones in segment 4 of the liver. Supplemental octreotide was administered perioperatively and the patient tolerated the entire procedure very well. He was fully ambulatory and eating a regular diet on his 4th postoperative day.

Histology of the biopsied tumor was read as typical carcinoid with a low proliferation index (MIB-1 < 1%). Stains for p53 were negative. Cell culture drug resistance testing indicated that *in vitro* the tumor was sensitive to docetaxel.

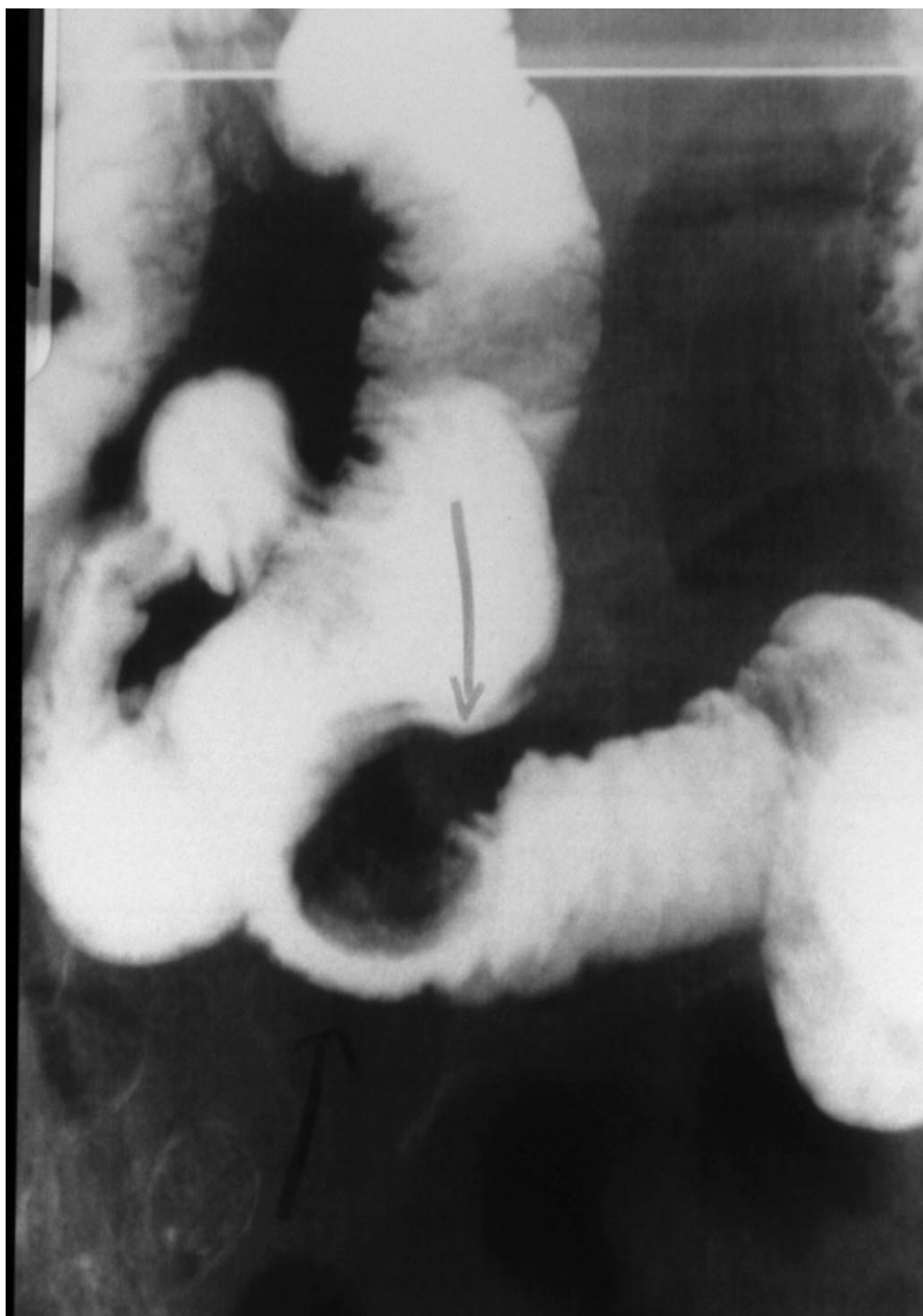


Figure 2 Barium contrast small bowel X-ray study showing marked narrowing of distal ileum lumen by primary carcinoid tumor.

On 2 January 2003 he was started on systemic chemotherapy with docetaxel as well as continuing his prior medications, increasing the i.m. long-acting octreotide to 40 mg each month, and adding pancreatic extract to his treatment regimen.

By March 2003 he exhibited very marked improvement, having achieved a weight of 81 kg with no edema. His strength was very good and he insisted on returning to full-time work, which he was able to perform without difficulty. There was no ascites, pedal edema or facial flushing.

His blood serotonin and chromogranin-A were improved (Table 1) and a new CT scan of the abdomen showed >50% regression of the tumors in the liver (Fig. 3). He was continued on treatment with octreotide, chemotherapy, low-dose niacin, multiple vitamins and other supportive medications.

Discussion

There are three categories of treatment employed in the management of carcinoid tumors and carcinoid syndrome. Many components of each are utilized concurrently or sequentially

with their choice and timing determined by the particular and specific features of each patient's tumor and symptoms. These categories are I, medical supportive; II, surgical; and III, anti-proliferative (Table 2).

The principal component of medical therapy is the use of somatostatin analogues, octreotide or lanreotide. Other conventional and less specifically targeted anti-diarrheal medications and digestion-enhancing agents may also be used along with supportive and nutritional agents.

Although cure can only be accomplished by complete surgical excision of tumor, very prolonged palliation and

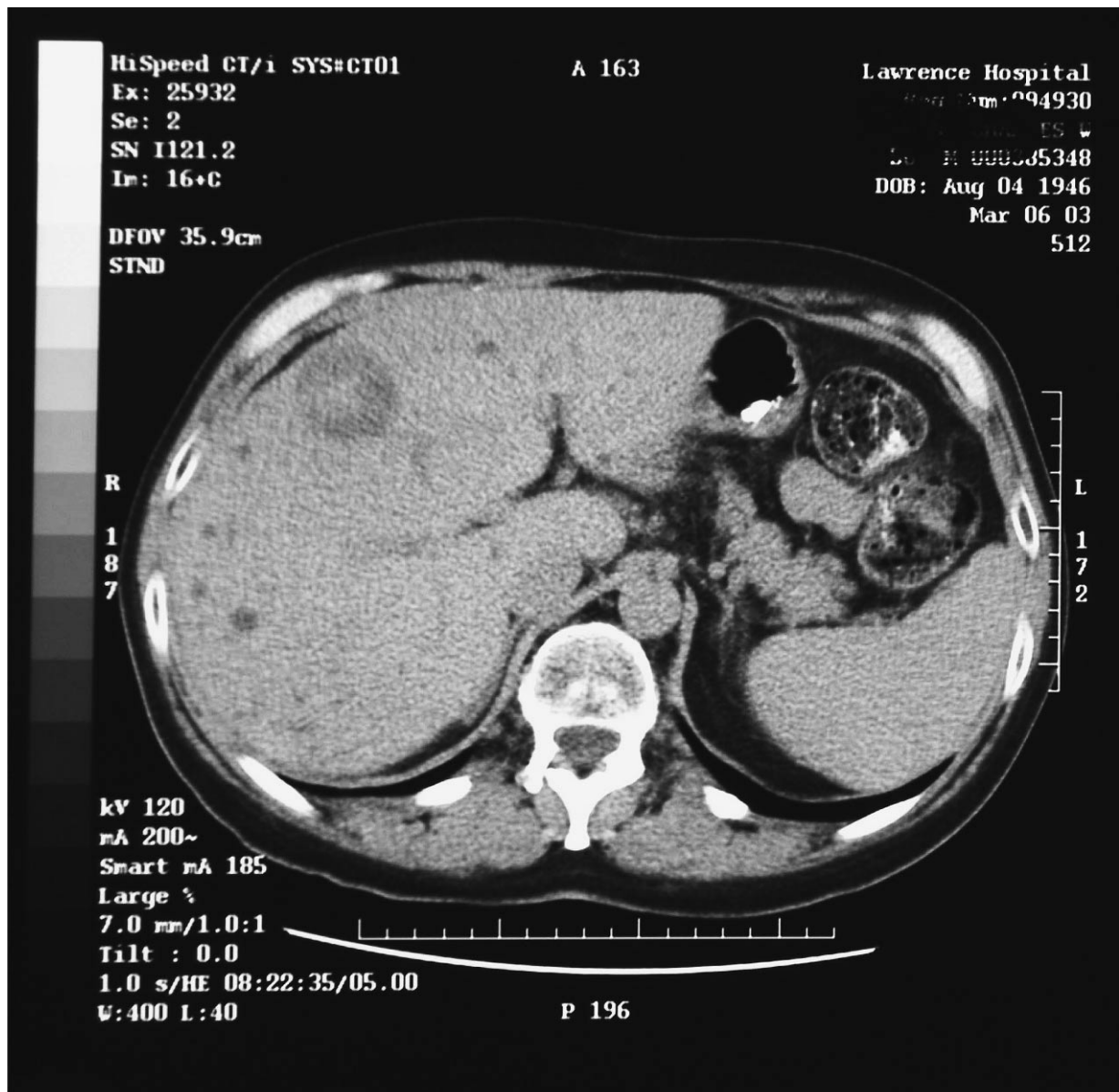


Figure 3 CT scan of abdomen following chemotherapy showing >50% reduction in metastatic tumors in the liver.

Table 2 Treatment of carcinoid

I. Medical supportive treatment
Anti-diarrhea drugs
Octreotide, lanreotide
Opiates, diphenoxylate, loperamide
Cyproheptadine
Cholestyramine
Pancreatic extract
Nutritional factors
Diet, supplements
Niacin
Hematinics
Electrolytes
Anti-ulcer medications
Antifibrosis
Fish oil
II. Surgery
Biopsy
Total resection with curative intent
Control bleeding; relieve obstruction, resect ischemic bowel
Debulk tumor by resection, radiofrequency ablation, cryoablation, embolus or chemoembolus injection
Heart valve replacement
Relieve ascites – tap, shunt
Stent placement for biliary or vascular obstruction
Liver transplant
III. Anti-proliferative treatment
Biotherapy
Somatostatin analogues
Alpha interferon
Radiotherapy
External beam
Internal: ¹³¹ I-MIBG, ¹¹¹ In, ⁹⁰ Y, ¹⁷⁷ Lu
Chemotherapy

survival can result from early and aggressive surgery, even when cure is not possible (Makridis *et al.* 1990, Norton 1994, Que *et al.* 1995, Chen *et al.* 1998, Frilling *et al.* 1998, Shebani *et al.* 1999, Chamberlain *et al.* 2000, Hellman *et al.* 2002). This often consists of removal of primary tumor and debulking metastases. Various other cytoreductive techniques are also often useful and include radiofrequency ablation (Wessels & Schell 2001), cryoablation (Seifert *et al.* 1998), biological modulation (octreoscan, lanreotide, alpha interferon) (Frank *et al.* 1999, Öberg 2001), HACE injection (Mitty *et al.* 1985, Rusniewski *et al.* 1993, Diaco *et al.* 1995, Yao *et al.* 2001, Soulen 2002) and internal and external radiotherapy and chemotherapy (Pelley & Bukowski 1999, Jensen 2000, Öberg 2001).

In the case presented it was apparent that severe carcinoid heart disease with congestive heart failure required urgent correction in order to salvage this patient, and before any anti-tumor treatment could be considered. Connelly (2001) points out that cardiac disease occurs in more than 50% of carcinoid syndrome patients and is the single main cause of death in carcinoid syndrome. She further notes that

surgery is the only effective treatment for carcinoid valvular disease. Optimum timing for such surgery is uncertain but the presence of right heart failure in a patient with demonstrated marked carcinoid valve disease clearly indicates a need for prompt valve replacement. The observation that carcinoid syndrome patients with valve disease in general have higher serotonin levels than do those without cardiac valve disease suggests that treatment to maintain lower serotonin levels may be protective against the development of carcinoid valve disease (Denney *et al.* 1998, Meijer *et al.* 2002). The direct effect of serotonin on the valve surface appears to be the cause of the fibrous plaques that characterize this condition. This is another reason for the liberal use of octreotide in a patient with high serotonin blood levels, even in the absence of symptoms of carcinoid syndrome.

An *in vitro* study has demonstrated that fish oil, eicosapentaenoic acid, prevents fibroblast proliferation (a process involved in the development of carcinoid valve disease) by blocking the local effects of serotonin (Pakala & Benedict 1995). This study has prompted me to prescribe this dietary supplement to carcinoid patients with very elevated blood serotonin levels.

Niacin supplements were included among the presented patient's medications in order to treat and prevent subclinical pellagra, a known but not generally recognized, complication of carcinoid syndrome (Fleischmajer & Hyman 1961, Castiello & Lynch 1972).

The persistence of moderate ascites at 1 month after cardiac surgery raised the question of whether this was being produced by peritoneal tumor exudate, lymphatic obstruction by tumor or lingering of right-sided heart failure. The finding of chromogranin-A concentration in the ascitic fluid approximately one-half that in the patient's peripheral venous blood was interpreted to indicate the persistence of a cardiac hemodynamic mechanism, rather than direct tumor exudation as the cause (Warner *et al.* 2002). This conclusion seems to have been borne out by complete subsidence of the ascites over the following 2 months with continued diuretic medication.

Thereafter the patient's general condition was improved enough to allow cytoreductive treatment. Since almost all of his demonstrated tumor was in the liver, HACE injection treatment was undertaken. We strongly favor HACE rather than bland embolus injection since even though a few studies suggest no added benefit by including injection of chemotherapy along with embolic material (Carrasco *et al.* 1986, Marlink *et al.* 1990, Kim *et al.* 1999), the preponderance of recent evidence supports HACE as producing a longer palliative effect as well as prolongation of survival (Mitty *et al.* 1985, Diaco *et al.* 1995, Soulen 2002, Warner *et al.* 2003). Following completion of this therapy it was considered likely that its beneficial effect could be enhanced by further tumor debulking via surgical resection and radiofrequency ablation. The survival benefit of carcinoid tumor debulking has been

well established. Furthermore the primary tumor discovered in the ileum could be resected at this surgery along with a prophylactic cholecystectomy to avoid future cholelithiasis – a well-known risk in a patient chronically treated with octreotide. This surgery would also provide the opportunity for obtaining a new biopsy of tumor of sufficient size to submit for cell culture drug resistance testing. The laparoscopic accomplishment of this surgery minimized the risk and made the procedure more tolerable for the patient.

Cell culture drug resistance testing is a relatively old technique (Weisenthal & Nygren 2002) that has not fulfilled its initial promise for clinical benefit in managing most common malignancies but it is often useful for neuroendocrine tumors, particularly midgut carcinoids, which are usually unresponsive to most chemotherapy protocols. In this instance, based on the *in vitro* finding of sensitivity to a drug (docetaxel) not commonly used for carcinoid, docetaxel was administered to the patient and his tumor responded very well.

Summary and conclusions

The carcinoid syndrome case presented is an example of modest temporary benefit from conservative management, followed eventually by severe deterioration which almost precluded aggressive treatment. However, continued application of supportive measures and careful choice and timing of aggressive sequential surgery and other invasive treatment followed by chemotherapy effected marked tumor regression and rehabilitation of the patient. Although this good a response to vigorous treatment does not occur in all advanced metastatic carcinoid patients, we feel that it can occur in a significant percentage of such cases. Therefore consideration should be more often given to altering the traditional conservative treatment of metastatic carcinoid towards a more proactive aggressive approach.

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