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Iodine-131-MIBG Therapy of a Patient with Carcinoid Liver Metastases

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Iodine-131-metaiodobenzylguanidine (MIBG) is highly concentrated by >60% of carcinoid metastases and thus provides a therapeutic oppportunity. **Methods:** A symptomatic patient with carcinoid liver metastases, unresponsive to chemotherapy combined with interferon-alpha, was subsequently treated with ^{131}I-MIBG. **Results:** Radionuclide therapy, which was without significant side effects, resulted in symptomatic improvement and reduced urinary 5-hydroxyindoleacetic acid levels. No new metastases were observed for 15 mo after ^{131}I-MIBG therapy. Gross cystic change occurred in existing liver metastases, presumably as a result of ischemic necrosis. Surgical deroofing and aspiration of cysts led to regeneration of normal liver tissue. **Conclusion:** Iodine-131-MIBG therapy can provide prolonged symptomatic relief and improved quality of life in patients with metastatic carcinoid disease unresponsive to other therapies. The antitumor effect of ^{131}I-MIBG was accompanied by few side effects, suggesting that this therapy should be considered in symptomatic patients with an early stage of disease.

Key Words: iodine-131-metaiodobenzylguanidine; liver carcinoid; pseudocyst

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Carcinoid liver metastases are common but are only rarely amenable to resection. Medical therapy aims to control symptoms and to extend survival by affecting tumor growth. Therapeutic options for symptomatic patients with unresectable disease include chemotherapy, interferon-alpha and octreotide (a somatostatin analog), but response to these treatments is often poor. Hepatic artery ligation or embolization are alternative options and have a better response rate. External beam radiotherapy has been tried in a small number of patients, and a good palliative response has been reported. Iodine-131-metaiodobenzylguanidine (MIBG), a guanethidine analog, is highly concentrated by >60% of carcinoid metastases (*1*) and thus provides an alternative therapeutic opportunity.

CASE REPORT

A 55-yr-old woman presented in November 1993 with a 6-mo history of flushing, diarrhea, abdominal pain and weight loss. Clinical examination was unremarkable. Urinary 5-hydroxyindoleacetic acid (5HIAA) levels were elevated at 596 μmol/24 hr (normal range < 45μmol/24 hr). CT revealed several space-occupying lesions in the liver (Fig. 1A); liver function tests were normal. Liver biopsy revealed monotonous tumor cells staining positive for chromogranin A, indicating metastatic carcinoid tu-

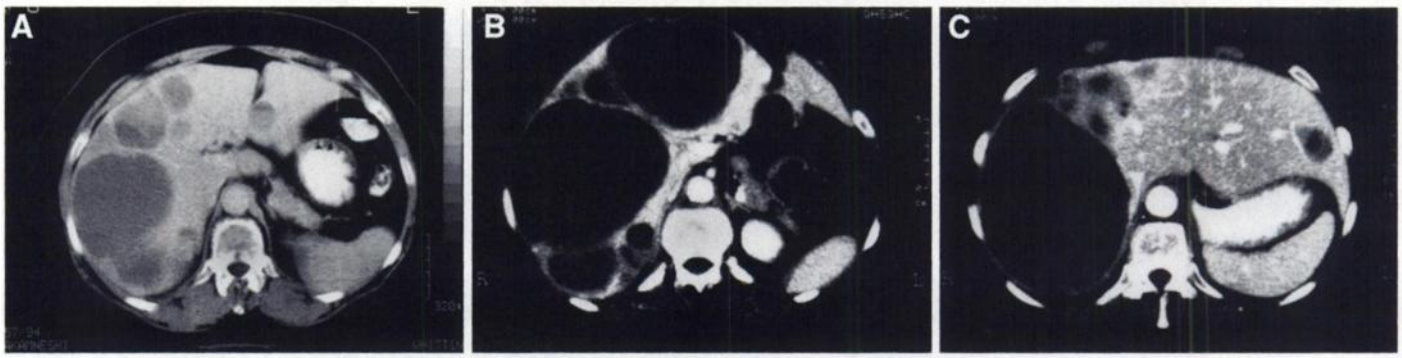

FIGURE 1. (A) Adominal CT scan taken at presentation in November 1993 shows several lesions of variable density within the liver. (B) Abdominal CT scan taken 3 mo after second ^{131}I-MIBG therapy dose in June 1995 shows liver to be largely occupied by several very-low-density (cystic) lesions. (C) Abdominal CT scan taken 3 mo after surgery and two ^{131}I-MIBG therapy doses in October 1995 shows fewer large cystic lesions and significant regeneration of normal liver.

mor. No primary tumor or extrahepatic metastases were discovered. Cyproheptadine was prescribed for diarrhea.

Treatment with chemotherapy (5-fluorouracil/folinic acid) and interferon-alpha began in March 1994, when CT and urinary 5HIAA levels showed disease progression. After 12 wk of treatment, the patient's symptoms were unresolved, urinary 5HIAA levels rose to 952 μmol/24 hr and new hepatic lesions were seen on CT. Iodine-123-MIBG scans obtained in July 1994 showed avid uptake (tumor-to-background ratio 2.5:1) of tracer in sulfur colloid photon deficient areas of the liver. A therapeutic dose (7725 MBq) of ^{131}I-MIBG was given in August 1994 with no significant side effects and minimal bone marrow toxicity. Images 3 days after therapy showed ^{131}I-MIBG uptake in approximately 70% of the liver (Fig. 2). A worsening of carcinoid symptoms after therapy was reflected by a rise in urinary 5HIAA levels to 1449 μmol/24 hr at 6 wk.

Iodine-123-MIBG scanning 3 mo after therapy suggested stable disease. CT showed mild cystic change within some existing lesions and no new ones; for the first time, the liver was palpable below the costal margin. Urinary 5HIAA levels were stable at 1008 μmol/24 hr, and the patient's symptoms improved.

A second therapeutic dose (8470 MBq) of ^{131}I-MIBG was given in January 1995. The patient experienced mild nausea, but it was attributed to the potassium iodate, which was used to block the thyroid. After March 1995, the patient complained of malaise, weight loss and right hypochondrial pain; the liver was palpable to the umbilicus. By June 1995, the hemoglobin level had fallen from its pretherapy level of 11.2 g/dl to 8.9 g/dl; and liver function tests were deranged [alkaline phosphatase, 576 IU/liter (normal range 100–280 IU/liter); bilirubin, 26 μmol/liter (normal range 3–17 μmol/liter); and aspartate transaminase, 142 IU/liter (normal range 11–55 IU/liter)]. White cell and platelet counts were normal. CT showed marked enlargement and gross cystic change within existing hepatic lesions but no new ones (Fig. 1B); the right lobe of the liver was almost completely replaced by cystic tumor. Urinary 5HIAA excretion had increased to 1409 μmol/24 hr.

A spiral CT scan showed that the hepatic lesions were poorly vascularized. Palliative aspiration under ultrasound control was abandoned when heavily blood-stained fluid was obtained. In July 1995, after a blood transfusion, the patient underwent laparotomy for persisting symptoms. Deroofing three large cystic masses in the right lobe, aspiration of several additional smaller cysts and hepatic artery ligation were performed. Histologic examination of biopsy specimens confirmed necrotic carcinoid tumor. Urinary 5HIAA could not be measured from cyst fluid because of hemolysis.

Three months after surgery the patient's abdominal pain had mostly subsided, and she was gaining weight. The patient's liver was just palpable, and liver function tests were normal. Spiral CT showed three fewer cystic masses than previously and regeneration of normal liver tissue (Fig. 1C). Urinary 5HIAA excretion was 492 μmol/24 hr in October 1995 and fell to 338 μmol/24 hr in January 1996.

In October 1996, the patient again became symptomatic with a recurrence of diarrhea and flushing. The liver was enlarged, and CT showed progression of hepatic disease. Urinary 5HIAA excretion rose to 2202 μmol/24 hr by January 1997. In April 1997, the patient received a third therapeutic dose (11,000 MBq) of ^{131}I-MIBG that

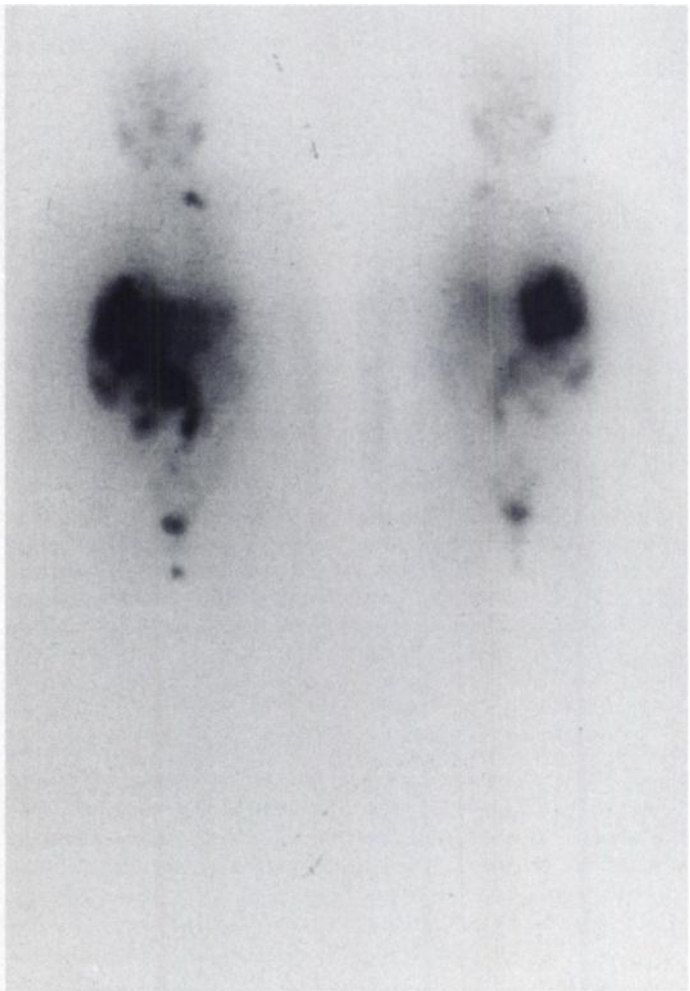

FIGURE 2. Anterior (left) and posterior (right) ^{131}I-MIBG images. There is intense tracer uptake within several liver metastases, and less-marked uptake is seen in left supraclavicular region (possible tracer retention within Hickman line). Normal biodistribution of ^{131}I-MIBG to the gastrointestinal tract, salivary glands, nasal mucosa and bladder is seen.

caused transient nausea. Symptomatic improvement followed, however, and was sustained over 6 mo until the present. Iodine-131-MIBG scanning showed that some previously ^{131}I-MIBG avid lesions were now photon deficient, corresponding to the known cystic sites. However, some fresh lesions were noted in the left lobe of the liver.

DISCUSSION

The total number of patients with metastatic carcinoid treated with ^{131}I-MIBG is still relatively small because the disease is rare and there are many competing treatments. In addition, ^{131}I-MIBG therapy is often reserved for patients with advanced disease and disabling symptoms in whom other treatments have failed. Cumulative data show a partial response in 20% of patients and a palliative response in >50% of patients with end-stage disease (*2–5*). Iodine-131-MIBG therapy targets metabolically active metastases that cause symptoms, and positive scintigraphy results predict a good palliative response to therapy. In this patient, in whom approximately 70% of liver metastases were ^{131}I-MIBG avid, radionuclide therapy reduced hormonal secretion and improved symptoms. It is possible that unlabeled MIBG could have had a similar effect (*5*), but there is insufficient evidence to support this hypothesis. Iodine-131-MIBG therapy was unlikely to be curative in this patient, because the tumor volume was large and a proportion of metastases did not concentrate this radiopharmaceutical.

Nevertheless, ^{131}I-MIBG therapy seems to have caused tumor necrosis in this patient. Gross cystic change was observed in liver metastases after therapy, and the histology of cystic masses deroofed during surgery showed necrotic carcinoid tumor. Furthermore, after two therapeutic doses of ^{131}I-MIBG and surgery, there was a sustained decrease in levels of secreted hormone.

There are five previous reports of pseudocystic carcinoid liver metastases, but all metastases were evident at presentation and did not result from therapy (*5–9*). Most carcinoid liver metastases are not highly vascular, and pseudocyst formation is thought to result from ischemic necrosis of tumor nodules (*8*). In this patient, it seems likely that ^{131}I-MIBG therapy caused infarction and liquefaction necrosis of carcinoid liver metastases.

Although patients undergoing ^{131}I-MIBG therapy require temporary isolation, they are medication free between doses and side effects are generally limited to temporary myelosuppression. This compares favorably with the side effects of other treatments such as chemotherapy, interferon-alpha and octreotide, the last two require frequent subcutaneous injections, which our patient was not keen on. Furthermore, octreotide, which was given to our patient, has no significant antitumor effect.

CONCLUSION

Iodine-131-MIBG therapy provided prolonged symptomatic relief and improved quality of life in, a patient with metastatic carcinoid disease that was unresponsive to other treatment therapies. The favorable side effects profile and antitumor effect of ^{131}I-MIBG suggest that its use should be considered in symptomatic patients with early disease and in patients with advanced disease unresponsive to other therapies.

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