sion in the early dynamic phase of both the 99mTc-ECD and 201Tl-Cl studies. The 99mTc-ECD study showed relatively homogeneous accumulation throughout the tumor on static images but 201Tl-Cl showed more localized and eccentricentric accumulation than 99mTc-ECD on the early and delayed views. Thallium-201-Cl uptake is believed to reflect viable tumor tissue and the degree of 201Tl-Cl retention to represent tumor malignancy. We cannot explain why there was a big difference between 99mTc-ECD and 201Tl-Cl uptake. We thought that 99mTc-ECD was a simple lipophilic chelating agent and that increased extraction efficiencies could account for its increased uptake in brain tissue. If 99mTc-ECD bound itself to nonspecific, high capacity binding sites in brain tumors, we could expect that the 99mTc-ECD CBF study would show increased accumulation in brain tumors more often than it did. In our experience, almost all of the brain tumors showed decreased uptake or filling defect on 99mTc-ECD study. Therefore, it is difficult to explain this tumor accumulation by increased blood perfusion, increased extraction efficiency and nonspecific binding sites. Some specific binding sites or mechanism could be considered in such a rare case of increased uptake of 99mTc-ECD.

CONCLUSION
Although 99mTc-ECD appears to be a promising agent for the noninvasive evaluation of cerebral blood perfusion, further work is needed to assess pharmacokinetic properties of 99mTc-ECD accumulation in brain tumors. There is also a potential limitation to evaluate recurrent or residual brain tumor because of background interference from normal brain uptake.

REFERENCES

Left Ventricular Myocardial Uptake of a Labeled Somatostatin Analog in Carcinoid Syndrome

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We report a case of left ventricular (LV) myocardial uptake of a labeled somatostatin analog in a patient with a carcinoid tumor of the small bowel. The patient developed liver metastases and a carcinoid syndrome, including right carcinoid heart disease, without right-to-left shunt on contrast ultrasonography or left ventricular myocardial metastases. The basis for visualization of the LV myocardium is probable somatostatin receptor upregulation.

Key Words: carcinoid; indium-111-pentetreotide; myocardial uptake


Various neuroendocrine tumors, including carcinoid tumors, express many high-affinity somatostatin receptors, a property exploited for in vivo imaging by somatostatin analog scintigraphy with 111In-pentetreotide. The presence of somatostatin receptors in carcinoid tumors can be used to detect primary tumors and metastases and may be predictive of the efficacy of somatostatin analog therapy. We report myocardial uptake during somatostatin receptor scintigraphy in a patient with a carcinoid tumor and carcinoid heart disease.

CASE REPORT
In May 1988, a 65-yr-old woman was admitted for investigation of gastric polyposis. The initial exploration, including abdominal ultrasound, colonoscopy and a small-intestinal series, was normal. Biopsy of the gastric polyps suggested benign glandular cystic polyposis.

Three years later, she was admitted for acute pain in the right upper abdomen and weight loss. Ultrasound, CT and MRI detected a liver mass 6 cm in diameter in segment IV, with a slight compression of the liver pedicle. Biopsy showed that the lesion was a metastasis of a carcinoid tumor. The primary tumor was not discovered despite complete exploration. The plasma serotonin was elevated (450 mg/liter, normal <300). During exploratory surgery, the liver metastasis was removed and a 1-cm diameter tumor in the terminal ileum was discovered and also removed. Histological examination confirmed the diagnosis of a carcinoid tumor. After surgery, the serotonin level continued to rise (1593 mg/liter 1 yr later).

Two years later, the patient developed symptoms of carcinoid syndrome, including cutaneous flushing, weight loss, leg swelling...
and dyspnea. Physical examination revealed right heart failure with a blowing holosystolic murmur at the lower left sternal border on auscultation. The heart rate was between 76 to 84 bpm and the blood pressure was normal. The liver was enlarged and painful to the touch. The ECG was normal and the chest radiograph revealed a small right pleural effusion. Both the 5-HIAA (294 mmol/liter, normal: <40) and serotonin levels (918 mg/liter, normal <300) were elevated. Echocardiography confirmed the diagnosis of carcinoid heart disease affecting the tricuspid valve leaflets. Two-dimensional echocardiography demonstrated enlargement of the right ventricular and atrial cavities with a thick right endocardium. The tricuspid leaflets were thickened, shortened, retracted and fixed in a semi-open position (Fig. 1A). Severe tricuspid regurgitation was seen on Doppler echocardiography (Fig. 1B). Pulmonary valve stenosis was not seen but regurgitation was present. There was no left valve involvement, myocardial or pericardial masses or right-to-left intracardiac shunt. Left ventricular thickness and function were normal. The thoracic CT was also normal.

Endoscopic biopsy of the diffuse fundus polyposis unexpectedly revealed a microscopic carcinoid tumor inside the polyp chorion. A doubtful pancreatic image was also seen during duodenal ultrasound endoscopy. Abdominal ultrasound showed a liver mass of 9 mm diameter in segment II. A bone scan revealed widespread bone metastases (Fig. 2A, B). The patient received diuretics, steroids and somatostatin (200 mg/24 hr) to relieve symptoms. She did not receive betablockers.

To complete the evaluation of tumor extension, 111In-pentetreotide imaging was performed. Planar images of the head, neck, chest and abdomen (10 min per view) 4, 24 hr and 30 hr after intravenous injection of 120 MBq 111In-pentetreotide were acquired with a circular field of view gamma camera equipped with a medium-energy, parallel-hole collimator. Hot spots were seen over the spine and pelvis and in the proximal humerus, suggesting bone marrow involvement (Fig. 3B, D). This was less clear on HMPD bone scintigraphy. Gastrointestinal sites of uptake were seen in the upper abdomen (corresponding to a lesion of the pancreas or left liver) (Fig. 3A, C). Uptake was also observed in the left supraclavicular area, corresponding to the lymph nodes (Fig. 4). In particular, heterogeneous but significant left ventricular myocardial uptake was seen on 24-hr chest images (Fig. 4).

**DISCUSSION**

Indium-111-pentetreotide is a new radiopharmaceutical with great potential for visualization of various somatostatin receptor-positive tumors, such as neuroendocrine tumors. There is a close correlation between the presence of somatostatin receptors on in vitro autoradiography and tumor visualization by pentetreotide scintigraphy. Carcinoid tumors contain numerous somatostatin receptors that bind octreotide with high affinity. This allows visualization of carcinoid tumors, their metastases and other gastroenteropancreatic tumors (1–6). Somatostatin receptors are also expressed in other diseases, such as granulomas, autoimmune diseases and malignant lymphomas, in which activated leukocytes are involved.

Normal accumulation of 111In-pentetreotide is observed after intravenous administration in the human pituitary and thyroid glands, spleen, liver, breasts, kidneys and urinary bladder. The amount of intestinal radioactivity (mainly in the colon at 24 hr) strongly depends on the simultaneous use of laxatives. We have studied more than 100 patients with neuroendocrine gastroen-
teropancreatic tumors without observing myocardial radioactivity in delayed imaging modalities.

In this case, the upper abdominal, bone and left supraclavicular uptake confirmed the value of this tracer for the evaluation of somatostatin receptor-positive tumors. Myocardial uptake could not have resulted from the circulating pool of radioactivity, because images were obtained 24 hr after intravenous tracer injection. Myocardial uptake was diffuse, heterogeneous and involved the whole left ventricular myocardium but not the right ventricle.

Carcinoid syndromes occur in fewer than 10% of patients with carcinoid tumors but are especially common in patients with tumors of the ileum and jejunum with widespread metastases. Extensive liver invasion by the tumor is present, the only exceptions being primary bronchial and ovarian tumors. The carcinoid syndrome affects several organ systems and is related to the production of pharmacologically active agents by the tumor itself (e.g., serotonin, histamine, bradykinin and prostanoids). The main clinical features are flushes (75–95% of cases), diarrhea (65–80%), bronchiolar obstruction (40–50%) and carcinoid heart disease (40–50%) (7–12).

Carcinoid heart lesions consist of plaque-like or diffuse endocardial thickening (up to 2 mm). They are almost invariably found on the right side of the heart, being located on the mural and valvular endocardium. The microscopic appearance of carcinoid lesions is uniform. They are superimposed on the normal endocardium and covered by a single layer of endothelium. Carcinoid heart lesions are mainly composed of a stroma rich in acid mucopolysaccharides (MPS), reticulum fibers and collagen but are typically devoid of elastic components. The cells involved (myofibroblasts) are few in number and proliferate slowly (13). The exact pathogenesis of carcinoid plaque is unknown. One hypothesis is that the release of a product by hepatic metastases (serotonin, bradykinin, or an undiscovered irritant) directly leads to the formation of carcinoid plaque (14). A more recent explanation involves transforming growth factor beta (TGF-β), which influences cell growth and differentiation and stimulates fibroblasts to produce extracellular matrix components, particularly in severe fibroproliferative processes. The exact mechanisms of TGF-β activation are not known (15).

Involvement of the left cardiac valves is rare. It occurs only when there is a foramen ovale with a right-to-left shunt demonstrated on contrast ultrasonography or when the tumor is located in the lung, inducing absence of activation of the chemical mediators in the lung (16). This was not the case of the patient described here: left ventricular echocardiography was normal, without right-to-left shunt or thickening of the aortic and mitral valves. Moreover, right carcinoid heart lesions, which are cell-poor and rich in MPS and collagen fibers, should not express somatostatin receptors.

Myocardial uptake could also be explained by the presence of metastases, but these are uncommon [only 4% of patients, as reported by Pellika et al. (17)]; heart uptake in the present case, which involved the whole left ventricle, was too diffuse to correspond to metastases that were not seen on echocardiography or computed tomography.

A third hypothesis involves upregulation of left ventricular somatostatin receptor expression in response to sympathetic overstimulation by adrenergic-like agents secreted by the tumor. Indeed, positive inotropic and chronotropic effects in the human heart can be mediated by receptor systems acting through accumulation of intracellular cAMP (such as S-HT₁, like, H₂ histamine and vasoactive intestinal peptide). By coupling to stimulatory Gs proteins, these receptors stimulate adenylate cyclase activity. On the other hand, at least three receptor systems inhibiting cAMP formation (Gi protein-coupled receptors) exist in the human heart: m-cholinergic, A₁-adenosine and somatostatin receptors (18–23). Activation of m-cholinergic and A₁-adenosine receptors has negative inotropic effects in the nonfailing human heart. The anti-adrenergic effect of muscarinic agonists has been demonstrated on isolated cardiac preparations, as well as on the human ventricle in vivo, and is more potent than that of adenosine (24). The effects of somatostatin receptors on the human ventricle remain to be elucidated (23). It has been speculated that these mediators may play a physiologic role as a feedback inhibitor of myocardial contractility by protecting the heart from excessive beta-adrenergic overstimulation (24–26).

Up to now, myocardial beta-adrenergic and muscarinic receptors could be visualized by PET (27–29) and catecholamine active uptake-1 (MIβG) by SPECT (30). Peripheral somatostatin receptors have been quantified by means of PET with ⁶⁸Ga-(DFO)-octreotide (31). This case shows that myocardial somatostatin receptors can be visualized with ¹¹¹In-pentetreotide scintigraphy. For ethical reasons, we
did not carry out direct binding studies, autoradiography of surgical specimens or PET receptor studies. Such studies are, however, underway in animals.

CONCLUSION
The most probable explanation for left ventricular myocardial uptake of a somatostatin receptor analog in a patient with a carcinoid syndrome is somatostatin receptor upregulation induced by adrenergic stimulation, but this hypothesis remains to be confirmed.

REFERENCES