A CASE OF MALIGNANT PHEOCHROMOCYTOMA TREATED BY ^{131}I-METAIODOBENZYLGUANIDINE

Sir—Pheochromocytoma is a rare disease with a reported annual incidence of 1.8 cases per million inhabitants in Scandinavia (1, 13). Malignancy is found in about 10 percent of the cases. As in some other well differentiated endocrine tumors malignancy cannot be recognized histologically but has to be defined by metastases usually to bones, lungs and liver or by local invasion in adjacent tissues.

A few reports on chemotherapy with cytotoxic agents for malignant pheochromocytoma have been published (2, 5, 10) but the effect has not been convincing. External radiation therapy can produce palliation in patients with painful bone metastases (10).

Since 1980 scintigraphy with radiolabelled metaiodobenzylguanidine (MIBG) has been performed in several hundreds of patients (3, 11, 15). The agent is taken up by chromaffin cells and the method is quite useful for diagnosis and localization of pheochromocytomas.

Until now about twenty cases of malignant pheochromocytomas treated with ^{131}I-labelled MIBG have been published (4, 6, 8, 9, 12, 14). We now present the first patient treated with ^{131}I-MIBG for malignant pheochromocytoma in Denmark.

Case report. In 1983 a 54-year-old female was hospitalized with severe chest pain. Myocardial infarction was suspected but could not be verified. After admission the patient had 4–6 daily attacks of severe anginal pain. Treatment with nitroglycerine, beta-blockers, calcium-antagonists, diuretics and digoxine was unsuccessful.

Coronary angiography was normal, but chest radiogram showed enlarged pulmonary hili. One year later a thoracotomy was performed with a left lower lobectomy for a palpable tumor. The pathologists suggested a renal adenocarcinoma, and ultrasonography and urography showed a tumor at the upper pole of the left kidney. However, at operation the kidney was normal and the suprarenal gland was grossly enlarged by a tumor invading the surrounding tissues. The tumor was removed and a histological diagnosis of pheochromocytoma was made. The anginal pain disappeared completely after the operation.

The patient was subsequently referred to the Department of Oncology and Radiotherapy. Computerized tomography and conventional radiograms of the lungs as well as ^{123}I-MIBG scintigraphy showed bilateral lung metastases. Urinary excretion of epinephrine and norepinephrine and vanillyl mandelic acid (VMA) was considerably increased.

From March 1985 to January 1986 the patient was treated at intervals of 4–12 weeks, with 7 doses of ^{131}I-MIBG, each administered intravenously in 500 cc of isotonic saline over 90 min. The dose range was 2.07–5.1 GBq with a total of 25.2 GBq. The patient was given potassium iodide 300 mg daily to block the thyroid gland. The woman was taken into hospital for a few days at each treatment and was cardially monitored both during and after administration of ^{131}I-MIBG.

The radiation dose to the pulmonary metastases, liver and whole body was calculated from the retained ^{131}I-MIBG at 24 h and measurements of the effective half-life ($T_{1/2}$). $T_{1/2}$ did not change appreciably from treatment to treatment (25–31 h) and was similar concerning retention in metastases and whole body. The total dose in the metastases was 125 Gy while the liver received 6.6 Gy and the whole body dose was 1.7 Gy.

During and after treatment the blood pressure was regularly measured to about 130/80 and no episodes of hypertension have been demonstrated. The patient has complained of minute-long attacks of headache with moderate sweating. Urinary excretion of hydroxyindolicacetic acid (HIAA) and vanillyl mandelic acid (VMA) was initially slightly elevated but became normal. Urinary excretion of epi- and norepinephrine was pretherapeutically moderately elevated, but decreased and is now only slightly elevated (Figure).

In January 1986 the accumulation of MIBG in the metastases was so low that further treatment was considered futile. CT-scan, chest radiogram and ^{123}I-MIBG scintigraphy showed regression of the lung metastases.

Discussion. Undiagnosed or untreated pheochromocytoma is a lethal condition, usually due to cerebral, renal or myocardial lesions. About 40% of the tumors are not found until autopsy although they were responsible for the lethal course. The radical treatment is surgical removal of the tumor, but in malignant cases this may not be possible. The prognosis is difficult to establish. Some patients have had symptoms for up to 20 years before diagnosis, while patients operated for a supposedly benign pheochromocytoma years later turn out to have metastases (5, 10).

In the presented case the urinary excretion of catecholamines decreased considerably and the metastases were clearly reduced in size after treatment with ^{131}I-MIBG. One year after treatment no regrowth has been observed. Whether the treatment will have any prognostic influence on the patient's survival can of course not be proved. However, the lowering of catecholamine secretion will probably protect the patient from the well-known disastrous effects on heart, brain and kidneys.

For many years well-differentiated metastatic thyroid cancer has been successfully treated with radioactive iodine. Elevated values of thyreoglobulin produced by thyroid cancer cells are often found in patients with metastases even when the cancer cells do not take up iodine (7). This observation may be similar to the situation in our patient in whom the tumor uptake of ^{131}I-MIBG decreased with successive treatments while the catecholamine excretion still was elevated.

As no side effects were observed in our patient and no complications have been reported by others, we are considering using higher activities of ^{131}I-MIBG per treatment in the future in order to increase the radiation dose in the tumor.

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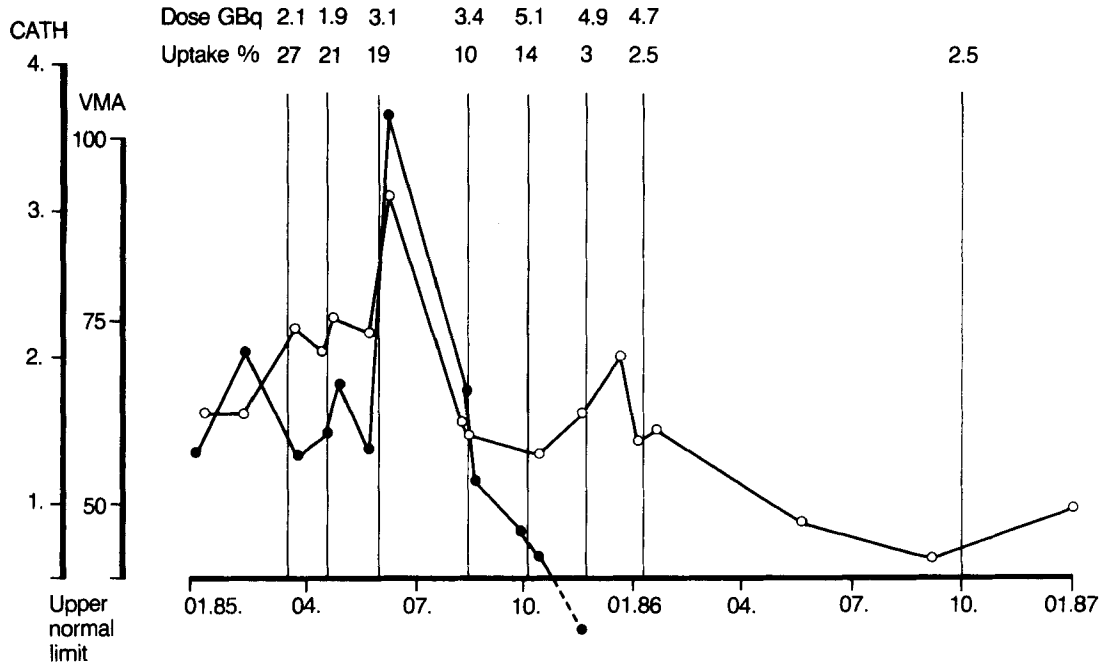

Figure. Urinary excretion of catecholamines (○) (CATH = epinephrines and norepinephrines) micromol/24 h, and vanillyl mandelic acid (●) (VMA) micromol/24 h in a patient treated with ^{131}I-MIBG for 9 months. The doses are given at the top in GBq and the scintimetrically determined uptake in the tumor is given in percentages of the retained dose at 24 h after injection.

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WEEKLY LOW-DOSE DOXORUBICIN WITH OR WITHOUT HIGH-DOSE MEDROXYPROGESTERONE ACETATE AS SECONDARY TREATMENT IN METASTATIC BREAST CANCER—A RANDOMIZED TRIAL

Sir—Bone marrow toxicity is the most important dose limiting factor in second-line chemotherapy. Weekly low-dose doxorubicin has been reported to have less toxic side-effects than standard dose doxorubicin, both being equally effective (2–4, 8, 9, 11). A number of clinical studies has been published showing decreased bone marrow toxicity when medroxyprogesterone acetate given in high doses (HD-MPA) has been added to cytotoxic agents (1, 5, 7, 12).

The present prospective study was designed to evaluate the response rate and toxicity of low-dose doxorubicin randomized with or without HD-MPA as secondary treatment for advanced breast cancer.

Patients. Forty-three women aged 33–78 years (mean 56 years) with metastasized breast cancer were randomly allocated to second-line treatment with doxorubicin as a single agent (n=22) or combined with high-dose medroxyprogesterone acetate (HD-MPA) (n=21). The dose of doxorubicin was 12 mg/m^2 i.v. weekly and that of MPA 500 mg i.m. twice weekly. All patients received the treatment for at least 8 weeks. All patients received postoperative radiotherapy to operation area and regional lymph nodes. Forty patients were previously treated with between 1 and 4 (median 2) hormonal, and 29 patients with 1–3 (median 1) cytotoxic regimens. Twenty-four patients had previously received doxorubicin. In 10 of them the dose reached 750 mg/m^2 during the present trial. This dose limit was not exceeded.

At the start of treatment the patients had metastatic involvement of between 1 and 4 sites (median 2). Pretreatment characteristics and metastatic sites in the 2 groups are shown in Tables 1