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CASE REPORT

Primary Hepatic Carcinoid in a Renal Transplant Patient

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There seems to be a world-wide increase in the incidence of tumors among immunosuppressed patients. Of 1350 renal allografts transplanted in the past 23 years at the Department of Transplantation and Surgery, 56 cases had malignant tumors. The case of a 58-year-old female patient is reported, with disseminated primary carcinoid in the liver detected 86 days after renal transplantation. According to the literature only 39 patients with primary liver carcinoids have been reported until 1997, but this is the first where the carcinoid developed in an immunosuppressed patient. The rapid progression of the carcinoid could be associated with the immunosuppression. (Pathology Oncology Research Vol 5, No 1, 67–69, 1999)

Key words: renal transplant, hepatic carcinoid

Introduction

The increased incidence of tumors among organ transplant patients is well known, and it is associated with the immunosuppressed state. At our Department, over 1350 renal allograft transplantations were performed in the last 23 years. During this period 56 cases of malignant tumors were detected, 53 related to cadaveric kidney transplantations and 3 to living donations.[21] The carcinoid is a common primary endocrine tumor of the gastrointestinal tract, but it is a rarity in the liver as the primary site[1-3,8-15,17-20,23-25] and has not been published before in an immunosuppressed patient.

Case Report

The 58 years old woman had hypertension since 1960, elevated blood glucose with obesity, osteoporosis since 1976, and left nephrectomy because of coral stone in the kidney. In 1976 she was treated for Cushing's disease. Her diabetes mellitus worsened; Insulin therapy was initiated. In 1994 progressive renal failure was found caused by Kimmelstiel-Wilson syndrome, due to which regular hemodialysis was introduced. In February 1995 the endocrinology control showed normal cortisol and ACTH levels. In December 1995 successful cadaver kidney transplantation was performed. No postoperative complications occurred. Two months later she was admitted again due to wound healing problems and epigastric discomfort. Gastroscopy was performed, which did not show any abnormalities.

As a secondary finding a 10 cm large mass was found in segments 2. and 3. of the liver by ultrasonography. The abdominal CT scan raised the possibility of other masses in the right lobe of the liver. The investigation repeated with contrast material did not verify tumor in the small bowel. Sternal puncture was performed which showed reactive bone marrow. Percutaneous fine needle aspiration biopsy of the liver was performed and cytological examination showed carcinoid. To exclude gastric origin of the tumor, the gastroscopy was repeated but no primary tumor was found. CT scan of the thorax excluded pulmonary progression. In May 1996, 5-hydroxyindolacetylacid (5-HIAA) investigation and percutaneous core biopsy of the liver clearly demonstrated hormonally inactive carcinoid. The tumor was technically inoperable. Octreotid therapy was introduced (with 3x333 micrograms of Sandostatin) and interferon (Intron-A), in addition to cyclosporin-A (blood

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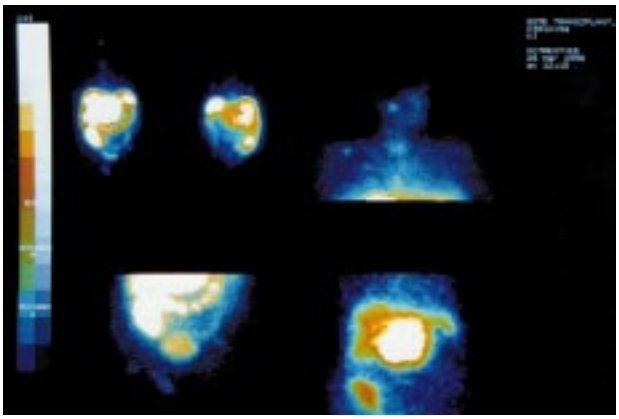

Figure 1. *Octreoscan image of the tumor and metastases. Right-lower: Significantly high somatostatin analog uptake was detected in the left lobe of the liver and on the right iliac fossa, where the transplanted kidney can be visualised (sandostatin clears partly through the kidneys). Left-upper/lower: Anterior and posterior views of the whole body scan. Sandostatin visualized stongly in the graft urinary bladder, kidney, and in the intestines. Right-upper: Multiple somatostatin receptor positive metastases in the bone (skull, ribs, scapula) and bone marrow. (^{111}I labelled Pentetreotide, GE Starcam XRIT 600)*

level: 100-150 ng/l). Two months later, new tumor masses in the right lobe of the liver and enlarged portocaval lymph nodes were detected. Therefore, the initiated interferon-treatment was interrupted to at least preserve renal function. After two months the octreoscan detected more local as well as bone progression of the tumor in the scull and ribs *(Figure 1)*. Octreotid treatment was withdrawn considering no benefit with serious side-effects. Eight months following the diagnosis of carcinoid, opioid pain killer had to be introduced. No primary locus was found, therefore we had to consider the carcinoid to be primary in the liver. The tumor further propagated through the liver, causing vena cava inferior compression, with consecutive crural oedema. Although the renal graft function remained sufficient, the patient's condition worsened and she died 12 months after the kidney transplantation. Autopsy verified a 20 cm large primary carcinoid in the right lobe of the liver with metastases in the left lobe *(Figure 2)*. No other locus was found elsewhere in the body which could be considered primary, and no gastrointestinal, pulmonary adrenal or hypophyseal carcinoid tumors/hyperplasias were detected. Tumor cells identical to the ones seen in the liver carcinoid were detected in the bone lesions and the lymph nodes.

Discussion

The carcinoid tumor is the most frequent endocrine tumor of the gastrointestinal tract.[1,5,23,25] The majority of primary carcinoids occur in the appendix (40%), followed by the ileal and rectal localizations (12%), while carcinoids are rare in the stomach, duodenum, jejunum, and in the large bowel (1–2%).[1,5] Carcinoids often occur together with other endocrine neoplasia (MEN I).

The majority of carcinoids do not release any mediator substance.[5,8,10,12,13,24] The carcinoid syndrome is caused by hormonally active substances, like 5-hydroxytryptophane, 5-hydroxytryptamine (serotonine), kallikreine, bradykinin, histamine, and prostaglandin E, causing paroxysmal vasomotor disturbances, flush, diarrhoea, tachycardia, salivation, hypotension, tremor.[5] One of the most reliable signs of the carcinoid syndrome is endocardial fibrosis affecting the atria, chambers and valves of the heart. In general the alterations are more serious in the right side of the heart. The urinary excretion of 5-HIAA is essential in the diagnosis. It must exceed 25 mg/24 hours, generally being 50–100 mg/24 hours.

The prognosis of carcinoids is usually good: 10 years survival is not rare, however, it depends on the localization. The 5 years survival rate is 99% in the bronchoalveolar carcinoid, 87% in the rectosigmoid and 83% in the gastric, as well as the ileal location. Carcinoids tend to produce metastases into the liver and pancreas, while bronchial carcinoids usually give bone metastases.[5]

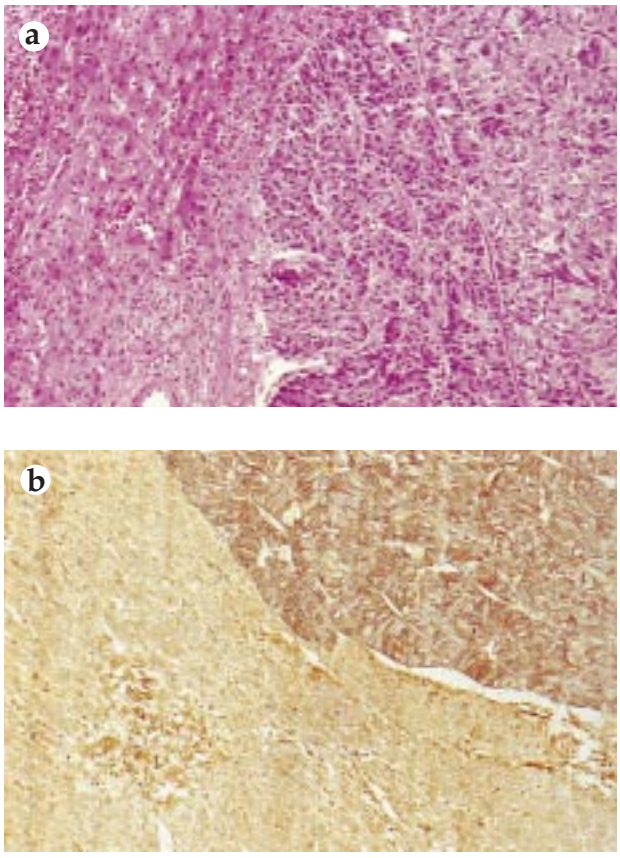

Figure 2. *Hepatic carcinoid by (a) PAS reaction and by (b) Grimelius staining. x250*

In our case the carcinoid tumor was histologically verified. It was detected very early, 86 days after the transplantation, and 15 months after the last (negative) ultrasonography, which suggests that the carcinoid was present at the time of transplantation. The decreased blood glucose tolerance observed in the patient might be an effect of serotonine. It is difficult to differentiate between Cushing's syndrome and ectopic ACTH release. DeGennes et al reported on a patient whose hormonally active carcinoid remained unknown for 20 years.[4] Andreola et al supposed an origin of primary liver carcinoid from pluripotential stem cell.[2] The aforementioned MEN I. consists of (Wermer's syndrome) hyperparathyreosis, hypophysis tumors, pancreas tumors, as well as others, like adrenal hyperplasias/tumors. This might cause Cushing-like symptoms, which could be present prior to transplantation. It is uncommon, however, for carcinoids to progress to death as quickly as our case. At the time of diagnosis the liver mass was already inoperable, and several bone metastases were present. Therefore, the suggested interferon treatment was only temporarily introduced.[22] Investigations during autopsy confirmed primary liver carcinoid.

Until 1997, 39 cases of primary liver carcinoids have been reported. One of them was a child, all others were adults. Holbrook et al reported on a 14-year study of primary liver tumors.[9] Among the 184 liver tumors 46 resections were performed, and only one of them was carcinoid.[9] Pi reported 20 cases of rare hepatic tumors in 20 years.[17] An uncommon locus of carcinoid was presented by Goldblum et al in the kidney,[6] and by Hayashi et al in the thymus.[7] Mauer et al found 29 primary pancreas carcinoids in a 30 years' retrospective study.[16] According to our knowledge no primary liver carcinoids have been reported so far in immunosuppressed patients. Reviewing the case, the primary liver carcinoid was probably present at the time of kidney transplantation, however, in much smaller size than two months later. The rapid growth and progression of the tumor in the following 12 months – causing tumor-related death of the patient – could be associated with immunosuppressive therapy following the kidney transplantation.

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