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Metastasis of carcinoid tumor to the transplanted liver graft: A rare case report

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ABSTRACT

In this study, we present a rare case of gastrointestinal carcinoid tumor that metastasized to a transplanted liver graft. A 14-year-old female patient suffering from cryptogenic cirrhosis had undergone liver transplantation. The liver was received from a deceased donor. She presented to our clinic with complaints of abdominal pain, diarrhea, flushing, fatigue, and syncope four years after transplantation. On multislice computed tomography, multiple masses ranging from 1 cm to 4 cm in size were detected in both lobes of the transplanted liver. Biopsy from both lobes revealed carcinoid tumor. The primary tumor could not be localized, and a colonoscopy was scheduled. As the patient refused an invasive investigation, octreotide therapy was begun. Her symptoms related to the carcinoid tumor diminished following initiation of the octreotide therapy. During the fifth year of octreotide therapy, a whole-body positron emission tomography (PET CT) with 10 mCi F-18 fludeoxyglucose (FDG) showed an increase in the metabolic activity with a SUVmax value of 8 at the localization site, consistent with the ileocecal region. The findings were considered secondary, as the carcinoid tumor originated from the appendix or distal ileum. Again, the patient again refused endoscopic investigations and continued the follow-up visits. To our knowledge, this is the only reported case in the scientific literature of a carcinoid tumor that metastasized to a transplanted liver.

Keywords: Liver transplantation, carcinoid tumor, metastasis, PET-CT

Case Report

INTRODUCTION

Carcinoid tumors (CTs) are neuroendocrine tumors that originate from enterochromaffin cells. These tumors most commonly arise from the gastrointestinal tract (68-80%) and bronchial epithelium (25%) (1-3). Gastrointestinal carcinoid tumor (GCTs) may cause chronic abdominal pain, obstruction, and sometimes perforation and bleeding (2). Some GCTs may cause carcinoid syndrome that is characterized by vasomotor, cardiac, and gastrointestinal symptoms. The clinical signs and symptoms of the carcinoid syndrome are usually seen in patients with liver metastasis. In the majority of the cases, symptoms of carcinoid syndrome may appear well before the signs or symptoms of the primary tumor. Some cases may even show liver metastasis, even though the primary tumor can not be located. Although liver metastases and cases that were approaching metastases of CTs have been reported, cases with GCTs that metastasized to a transplanted liver graft have not been reported so far. In this report, we present the first case of CT with metastases to a transplanted liver graft.

CASE PRESENTATION

A 14-year-old female patient, Child-Pugh Score: 11, suffering from cryptogenic cirrhosis had undergone orthotopic liver transplantation in 2002. The liver was obtained from a deceased donor. The histopathological examination of the recipient's hepatectomy specimen revealed no primary or metastatic tumor disease, except for mixed macro- and micronodular cirrhosis. The patient was administered tacrolimus and steroid therapy for immunosuppression. Four years after the liver transplantation, she presented with abdominal pain, diarrhea, flushing, fatigue, and syncope. The results

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of routine biochemistry tests, tacrolimus blood level, and the complete blood count were all within normal limits. Multislice computed tomography (CT) for screening purposes revealed smooth-contoured, space-occupying lesions in both lobes of the liver. Due to the presence of these lesions, an ultrasonography (US)-guided biopsy was performed. The histopathological examination of the biopsy specimen revealed that the tumor had a characteristic architecture of nests and trabecular patterns of uniform cells with round, regular nuclei and stippled chromatin (Figure 1). There was no cellular atypia or mitotic activity. The tumor cells were immunoreactive for synaptophysin, CD56 (Figure 2), and neuron-specific enolase (NSE) (Figure 3). Immunohistochemically, tumor cells were not stained with HepPar-1, cytokeratin 7, cytokeratin 19, cytokeratin 20, polyclonal carcinoembryonic antigen, and chromogranin A. The 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) was 30 mg/L (normal range: 2-8 mg/L). A colonoscopy was scheduled to detect the primary focus of the carcinoid tumor, but the patient declined. Therefore, administration of subcutaneous octreotide acetate (Sandostatin LAR Depot, Novartis, Basel, Switzerland) once a month was begun. The patient's carcinoid symptoms regressed completely following this treatment. CT scan imaging studies during the 3rd and 4th years of therapy showed an increase in the size of the mass, even though the symptomatic status of the patient remained unchanged (Figure 4). A positron emission tomography (PET-CT) was planned during the 5th year of treatment. A whole-body PET-CT scan with 10 mCi F-18 FDG revealed two pathologic activities with SUVmax values of 5.11 and 5.12 (normal SUVmax value for the liver is 2.71) in the right lobe of the liver and one pathologic activity with an SUVmax value of 7.61 in the left lobe. In addition, an increase in metabolic activity with a SUVmax value of 8 in the ileocecal region was detected. These findings were attributed to a carcinoid tumor originating from the appendix or the distal ileum, and a diagnostic colonoscopy was planned. The patient did not consent to any surgical or endoscopic intervention and was administered follow-up octreotide therapy. The patient continues to live with minimal symptoms during the 6th year of octreotide therapy and the 10th year of liver transplantation. Informed consent was taken from the patient.

DISCUSSION

Carcinoid tumors (CTs) are neuroendocrine tumors that originate from the endoderm of any tissue or organ. These tumors arise from enterochromaffin cells that are a part of the amine precursor uptake and decarboxylation (APUD) system (4,5). CTs were first classified into three groups based on the embryologic region that they originate from: foregut, midgut, and hindgut carcinoid tumors (1-3,5). On the basis of many immunohistochemical parameters, the World Health Organization (WHO) classified CTs into three groups: well-differentiated neuroendocrine tumors (carcinoid, low-grade), well-differentiated neuroendocrinecarcinoma (malignant carcinoid, intermediate-grade), and poorly differentiated neuroendocrine carcinomas (small-cell, high-grade) (2,3,6,7).

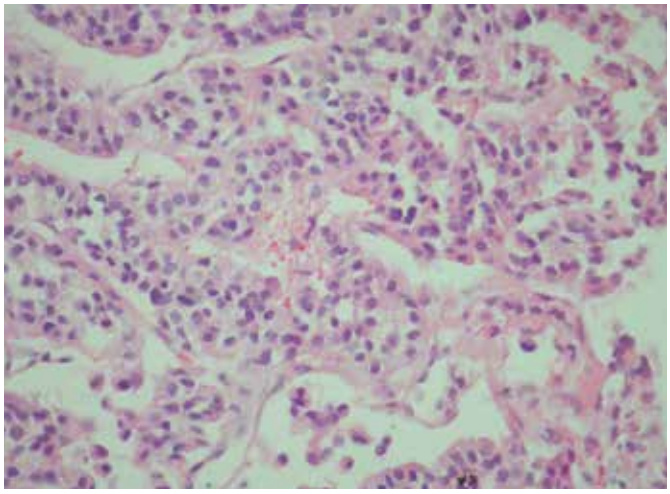

Figure 1. Microscopic analysis shows the presence of uniform cells with regular nuclei in the tumor with a trabecular pattern (H&E X400).

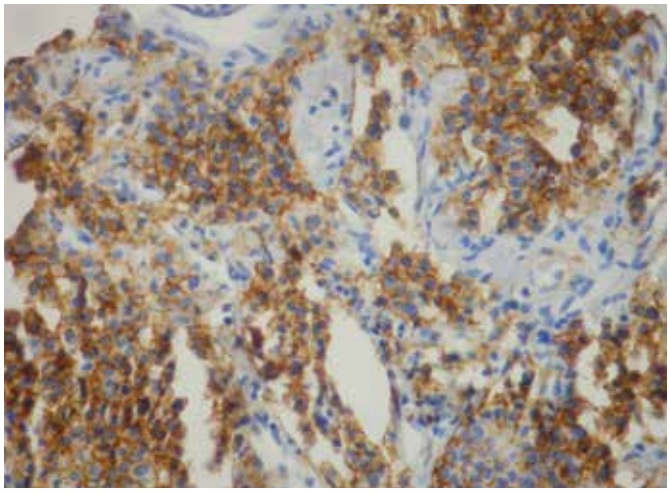

Figure 2. CD56-positive tumor cells (Magnification: 400X).

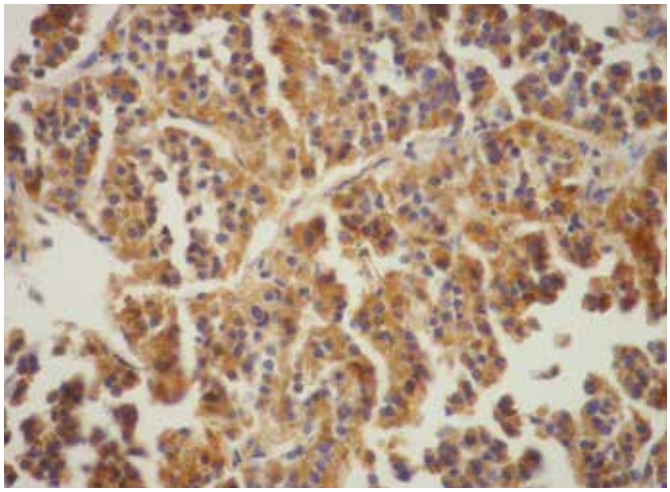

Figure 3. Tumor cells stained for neuron-specific enolase (NSE) (Magnification: 400X).

Most CTs develop from the gastrointestinal system, and 90% of gastrointestinal carcinoid tumors are formed in the small intestine, appendix, and the rectum. More than half of the carci-

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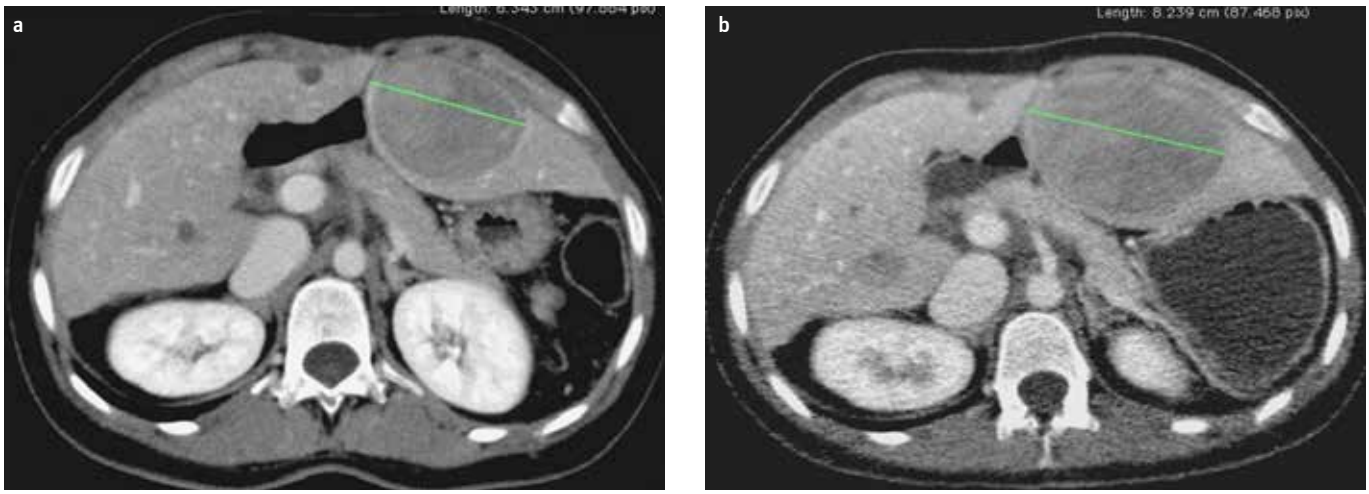

Figure 4. a, b. Axial contrast-enhanced CT images 7 years after transplantation **(a)** and 8 years after transplantation from the same level demonstrate increase in the number and size of the lesions in both lobes **(b)**. Biopsied lesion in left lobe increased from 6.3 cm to 8.2 cm in one year.

noids located in the small intestine are found in the distal ileum (2,6). The appendiceal carcinoid tumor is considered the most common type of primary appendiceal malignant lesion and accounts for almost 60% of all appendiceal tumors (8).

Seventy percent of GCTs are asymptomatic, and the majority is detected incidentally. The symptoms mostly develop due to the mass effect of the tumor, fibrosis, and the released bioactive products (5,6). The CTs can cause carcinoid syndrome by producing bioactive substances, such as serotonin, histamine, kallikrein, bradykinin, and prostaglandin (1). Carcinoid syndrome is a constellation of symptoms that result from liver metastasis or conditions when the venous drainage of the tumor occurs directly into systemic circulation, as in ovarian, testicular, and lung tumors. The most common symptoms are flushing of the face, arms, and legs; diarrhea; hypotension; palpitations; and bronchospasm (1). This syndrome develops in 10-30% of gastrointestinal carcinoids (1,3).

The diagnosis is made by the combined evaluation of biochemical, radiologic, and histopathologic examinations. Increased levels of 5 HIAA, serum chromogranin A, and platelet serotonin in the 24-hour urine sample are of diagnostic importance (3,6). US, CT, and angiography are important modalities in localization of the tumor and the metastases (1-3,6). Somatostatin receptor scintigraphy and metaiodobenzylguanidine (MIBG) scintigraphy alone and in combination detect tumor presence with a sensitivity of 95%. PET-CT is very effective in localizing tumors that are not detected by somatostatin receptor scintigraphy (2,3,6). Recently, studies with 11C-5-hydroxy-tryptophan PET-CT have shown promising results (9). However, biopsy materials that are sampled endoscopically or percutaneously and evaluated histopathologically are required for definite diagnosis.

The malignancy potential of CTs is dependent on whether the metastatic disease has developed. The malignancy potential of CTs depends on tumor localization, size, invasion depth, and growth pattern. Thirty-five percent of ileal carcinoids metastasize, whereas only 3% of appendix carcinoids do so. Two percent of carcinoids with a tumor diameter less than 1 cm are associated with metastasis, whereas the rate increases to 50% in tumors with a diameter of 1-2 cm and 80-90% in those with a size ≥2 cm.

Treatment approaches vary depending on the location, size, and metastatic status of the tumor. Tumors show markedly diffuse extension into both lobes of the liver in cases with liver metastases, and 90% of these patients experience carcinoid symptoms. Symptoms of carcinoid syndrome can be controlled in 70% of the cases with somatostatin analogs or interferon treatment (3). Furthermore, medical therapy can stabilize symptoms in nearly half of the patients. Liver metastases suitable for resection can be operated for curative therapy. Radiofrequency ablation, transcatheter arterial chemo-embolization, or intraarterial chemotherapy may be performed in patients in whom curative surgery is not an option (3,10). In the last 25 years, successful liver transplantation has been reported for patients with liver metastases of neuroendocrine tumors (2,4,7,10). Cases of successful liver transplantation have been reported in unresectable tumors, tumors that occupy a large space in both lobes of the liver, and refractory carcinoid cases. However, no data exist in the literature about cases with a carcinoid tumor that metastasizes to a transplanted liver graft. Thus, there is no consensus regarding the approach to such cases. In our opinion, after elimination of the primary tumor focus, liver metastasis should be assessed. The general condition of the patient, the tumor's histopathology, and the medical center's experience should be thoroughly evaluated to select from the options of medical therapy, re-transplantation, or tumor resection.

In the case presented in this study, no carcinoid tumor had been detected in routine investigations prior to liver transplan-

tation or in the recipient's hepatectomy specimen. It is very important to note that this tumor had advanced enough to metastasize to the liver after four years since transplantation. The patients are followed up with a routine biannual examination that includes ultrasonography and an annual tomography. Progression of the tumor transition into a symptomatic phase during the interval between the two controls can be explained by either aggravation of the biological behavior of the tumor due to concomitant immunosuppression therapy or standard progression of the tumor that was overlooked. Based on previous studies on cancer development following organ transplantation, it is more likely that a tumor was present prior to transplantation.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

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