Liver transplantation for metastatic neuroendocrine tumor: A case report and review of the literature

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Abstract

Neuroendocrine tumors are divided into gastrointestinal carcinoids and pancreatic neuroendocrine tumors. The WHO has updated the classification of these lesions and has abandoned the term “carcinoid”. Both types of tumors are divided into functional and non-functional tumors. They are characterized by slow growth and frequent metastasis to the liver and may be limited to the liver for long periods. The therapeutic approach to hepatic metastases should consider the number and distribution of the liver metastases as well as the severity of symptoms related to hormone production and tumor bulk. Surgery is generally considered as the first line therapy. In patients with unresectable liver metastases, alternative treatments are dependent on the type and the growth rate. Initial treatments consist of long acting somatostatin analogs and/or interferon. Streptozocin-based chemotheraphy is usually reserved for symptomatic patients with rapidly advancing disease, but generally the therapy is poorly tolerated and its effects are short-lived. Locoregional therapy directed such as hepatic-artery embolization and chemoembolization, radiofrequency thermal ablation and cryosurgery, is often used instead of systemic therapy, if the disease is limited to the liver. However, liver transplantation should be considered in patients with neuroendocrine metastases to the liver that are not accessible to curative or cytoreductive surgery and if medical or locoregional treatment has failed and if there are life threatening hormonal symptoms. We report a case of liver transplantation for metastatic neuroendocrine tumor of unknown primary source and provide a detailed review of the world literature on this controversial topic.

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Key words: Liver metastases; Neuroendocrine tumors; Liver transplantation

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INTRODUCTION

Neuroendocrine tumors are divided into gastrointestinal carcinoids and pancreatic neuroendocrine tumors[1]. However, it is suggested that they may be grouped together and be categorized into functional and non-functional tumors[2] to indicate the clinical manifestations of syndromes caused by hypersecretion of neuropeptides and biogenic amines at supraphysiologic levels[2-3]. These tumors are very rare and occur with an incidence of 2 per 100 000/year (with a slight female predominance) for carcinoids[4-6] and 1-1.5 per 100 000/year for pancreatic neuroendocrine tumors[1].

Gastrointestinal carcinoid tumors originate from cells of the diffuse neuroendocrine system, which is composed of amine-and peptide-producing cells[8]. These cells are scattered throughout the body and predominantly occur in the submucosa of the large and small intestine, stomach and larger bronchi[1]. In 85% of all cases they arise in the lung, stomach, ileum, appendix and rectum[1]. Although the majority of these tumors are nonfunctional, certain primary site locations, such as the ileum and bronchi, have a predilection for producing the carcinoid syndrome[1]. This syndrome is characterized by flushing, diarrhea, abdominal pain and less often by wheezing and heart disease and is predominantly caused by the production of serotonin[10]. Other biological substances, produced by carcinoid tumors, such as kalikrein and prostaglandins also take part in the pathogenesis of the carcinoid syndrome[8]. Overall, the carcinoid syndrome develops in only 5% of all carcinoid tumor patients, but this figure rises to approximately 60% in cases with liver metastases[11]. Prior to metastasizing to the liver, carcinoid tumors are usually
silent because their secretory products are inactivated in the liver\textsuperscript{[8,9]}

Pancreatic endocrine tumors arise from pleuropotential stem cells within the pancreas\textsuperscript{[9,10]} and those that are functional produce biologically active peptides such as gastrin, insulin, glucagon, vasoactive intestinal polypeptide, somatostatin, growth hormone releasing factor, and pancreatic polypeptide which are responsible for distinct clinical syndromes\textsuperscript{[11-13]}. Gastrinomas and the insulinomas are the most common functional pancreatic endocrine tumors whereas all others are rare\textsuperscript{[1,11]}. Non-functional pancreatic neuroendocrine tumors (45-50\% of all pancreatic neuroendocrine tumors) exhibit no specific syndromes; such tumors present only with symptoms due to tumor mass\textsuperscript{[13,14]}

Liver metastases develop in 46-93\% of patients with neuroendocrine tumors and can involve large portions of the liver before becoming symptomatic\textsuperscript{[12]}. They exhibit a slow growth despite their multilocular and bilateral occurrence in most cases\textsuperscript{[13]} and may be limited to the liver for long periods\textsuperscript{[14]}. Surgery is generally the first line therapy for patients with liver metastases due to neuroendocrine tumors\textsuperscript{[15-17]}. Potentially curative resection is considered in patients with solitary or unilobar hepatic metastases and without radiological evidence of systemic disease\textsuperscript{[18]}. However, curative resection is possible only in approximately 20\% of patients\textsuperscript{[19]}, because liver metastases frequently diffuse at the time of diagnosis\textsuperscript{[8]}. In patients with bulky disease, preoperative hepatic artery embolization is recommended in order to decrease the blood flow and shrink tumors\textsuperscript{[20]}. In patients with previously resected or resectable primary tumors, regional nodal disease and metastases confined to the liver, cytoreductive surgery is recommended, provided that preoperative imaging confirms that the primary and regional diseases are controlled or controllable and 90\% or more of the bulk of the tumor can be removed\textsuperscript{[14]}. In patients with unresectable liver metastases alternative treatments that can be considered include immunotherapy (somatostatin analogs and/or alpha-interferon) and chemotherapy (usually streptozocin-based). Additional therapy such as hepatic-artery embolization or chemoembolization, radiofrequency ablation and cryosurgery are pursued as needed\textsuperscript{[21-24]}. Some studies report a tumoricidal effect of somatostatin analogs such as octreotide and lanreotide in 36.5-75\% of treated patients lasting for 3-12 months\textsuperscript{[21-24]}. Furthermore, treatment with high-dose somatostatin analogs may induce apoptosis in neuroendocrine tumors\textsuperscript{[25]}. In addition, small liver metastases (diameter less than 1-2 cm) may respond to radiopharmaceutical agents such as Y (90)- and In (131)-labeled octreotide which involve insertion of radiotherapeutic agents directly into the tumor\textsuperscript{[26]}. A recent study suggested that the administration of combinations of Y (90)- and Lu (177)-labeled octreotide in patients with tumors of different sizes may allow wider tumor penetration\textsuperscript{[27]}. In patients with bilobar hepatic tumors, hepatic artery embolization combined with octreotide treatment has also been proposed\textsuperscript{[28]}

Liver transplantation is considered in patients with neuroendocrine metastases to the liver which are not accessible to curative or cytoreductive surgery, tumors which do not respond to medical or interventional treatment and in tumors causing uncontrollable life-threatening hormonal symptoms (severe hypoglycemia, gastrointestinal hemorrhage, severe diarrhea, valvulopathy)\textsuperscript{[29,30]} providing the disease has not extended beyond the liver, although certain hormonal symptoms (e.g. insulinoma) may be less amenable to transplantation than others.

We report herein a case of liver transplantation due to metastatic neuroendocrine tumor of unknown primary source. In addition, we present a comprehensive review of liver transplantation in patients with metastatic neuroendocrine tumors.

CASE REPORT

A 61-year-old white male with a prior history of hypertension and arteriosclerotic heart disease was referred in May 1999 for evaluation of multiple liver metastases from an unclear primary source. In the 4-5 years prior to referral, he described that he had flushing and cough. The flushing was primarily on his face, lasted for about an hour at a time and was precipitated by heat. In the few months prior to referral he developed episodes of fevers, chills and lassitude and had been treated briefly with antibiotics with a good response. The patient had lost about 16 pounds, which was attributed to dieting and anxiety. Physical examination revealed hepatomegaly. Ultrasound of the right upper quadrant and CT scanning of the chest and abdomen revealed multiple metastases in the liver but no other obvious primary tumor (Figure 1A). Laboratory data included a urinalysis which was negative, a serum albumin of 2.9 gm/dL (n.: 3.5-5.0), an elevated alkaline phosphatase of 197 IU/L (n.: 12-41), an ALT of 96 IU/L (n.: 10-60), an AST of 57 IU/L (n.: 10-42), a BUN of 18 mg/dL (n.: 6-20), a normal serum calcium and normal chloride and electrolytes. His total bilirubin was 1.0 mg/dL (n.: 0.2-1.0) and his total protein was 6.7 gm/dL (n.: 6.4-8.2). His CBC was within normal limits.

His serum gastrin level was 38 pg/mL (n.: 0-100), serum chromogranin A level was 275 ng/mL (n.<50) and serum pancreatic polypeptide was 258 pg/mL (n.<312). 24-h urine analysis for 5-hydroxyindolacetic acid was normal. A transcutaneous liver biopsy was positive for neuroendocrine tumor. The tumor was strongly positive for neuron specific enolase, synaptophysin, insulin, S100 and chromogranin. An OctreoScan showed liver and midline abdominal foci of increased radiotracer uptake compatible with neuroendocrine lesions. There were no neuroendocrine lesions within the lungs and mediastinum. His small bowel enema was normal. An upper endoscopy revealed a few small prepyloric ulcers with no evidence of Helicobacter pylori. In addition, there was evidence of extrinsic antral compression from the left lobe of the liver. An echocardiogram was performed which showed a thickened and calcified aortic valve and mitral valve with mild mitral regurgitation. A diagnosis of metastatic...
Neuroendocrine tumors represent an unusual group of rare tumors due to their slow growth and ability to produce and secrete a multitude of peptide hormones and amines. These substances give rise to different clinical syndromes related to the peptide production, such as the carcinoid syndrome, insulinoma syndrome, Zollinger-Ellison syndrome, glucagonoma syndrome, WDHA syndrome and somatostatinoma syndrome. However, as in this case, many patients have nonfunctional tumors and present with hepatic metastases. In most cases neuroendocrine metastases to the liver are located in both lobes. Gastrointestinal carcinoid tumors, especially those located in the small intestine or ascending colon, are the most common neuroendocrine tumors presenting with liver metastases. Gastrointestinal carcinoids and pancreatic neuroendocrine tumors have different degrees of malignant potential and frequency of liver metastases.

The therapeutic approach to hepatic metastases should consider the natural history of the disease and the progression and severity of symptoms caused by both hormone production and tumor mass. In contrast to nonendocrine tumors, therapy for hepatic metastases from neuroendocrine tumors with liver transplantation is reasonable because the disease may be confined to the liver for extended periods and the growth is slow. The presence of liver metastases from neuroendocrine tumors is a very important prognostic factor for decreased survival. The 5-year survival rate in untreated patients is approximately 30%, and chemotherapy only prolongs life by a mean of 12-24 mo.

There have been several single-center (Table 1) retrospective analyses and three multicenter retrospective studies of liver transplantation in patients with liver metastases from neuroendocrine tumors. They are summarized in Table 1. However, closer review of these reports reveals that some of the patients were part of more than one publication. Several tumor and patient characteristics influence the outcome following liver transplantation. A large retrospective study of 637 patients who underwent OLT between 1968 and 1991, observed that 67% of patients with carcinoid tumors had recurrence. The authors concluded that patients with slowly growing metastatic neuroendocrine tumors might be suitable candidates for liver transplantation.
Table 1  Liver transplantation for metastatic neuroendocrine tumors

| Author | Year | Number of patients | Actuarial survival (%) | Comments | Ref. no |
|--------|------|---------------------|------------------------|----------|---------|
|        |      |                     | no 1 (yr) 2 (yr) 3 (yr) 4 (yr) 5 (yr) |          |         |
| O'Grady | 1987 | 2 nr nr nr nr nr | 2 carcinoids, 1 death at 7 mo, 1 symptom free at 12 mo after LT | 53       |
| Makowka | 1989 | 5 nr nr nr nr nr | 3 alive 7, 16 and 34 mo after LT | 35       |
| Arnold  | 1989 | 4 nr nr nr nr nr | 2 no recurrence 20, 38 moths after LT, 2 deaths 7, 8 mo (chronic rejection) | 54       |
| Bramley | 1990 | 1 nr nr nr nr nr | VIP-oma, no tumor 12 mo after LT | 55       |
| Alsina  | 1990 | 2 nr nr nr nr nr | 1 carcinoid and 1 PNT no symptoms 5, 13 mo after LT | 56       |
| Penn   | 1991 | 13 nr nr nr nr nr | 9 carcinoids, 4PNT; 67% recurrence for carcinoids | 42       |
| Bechstein | 1994 | 30 52 52 52 52 nr nr | multicenter study at the time of report: 57% alive, 43% dead, 30% recurrence, 70% no evidence of disease | 43       |
| Allessiani | 1995 | 14 nr nr nr nr nr | cluster transplantation, recurrence rate 45.5% | 44       |
| Routley  | 1995 | 11 82 nr nr nr nr | 7 carcinoids, 2 PNT, 2 ET-primary unknown; 6 alive (2 carcinoids) 8-106 mo after LT; 5 deaths (3 carcinoids) in 8-67 mo after LT | 45       |
| Curtiss | 1995 | 3 nr nr nr nr nr | 3 alive 12, 20, 30 mo after LT | 57       |
| Anthuber | 1996 | 4 nr nr nr nr nr | 4 deaths 10 days and 4, 8, 33 mo after LT | 58       |
| Doussset | 1996 | 9 nr nr nr nr nr | 4 carcinoids, 5 PNT; 3 (carcinoid) alive 15, 24, 62 mo after LT, 6 deaths 6, 7, 12, 83 days and 7, 8 mo after LT | 59       |
| Le Treut | 1997 | 31 58 51 47 36 36 | multicenter study, 11 centers in Europe; disease free survival: 45% at 1 yr, 29% at 3 yr, 17% at 5 yr after LT; higher survival for carcinoids (69% at 5 yr) than for non-carcinoids (8% at 4 yr) | 46       |
| Le Treut | 1997 | 37 66 56 46 46 46 | literature review, 14 centers, higher survival for non-carcinoids (83% at 2 yr) than carcinoids (34% at 2 yr) | 46       |
| Lang  | 1997 | 12 nr nr nr nr nr | 9 alive-median survival 55 mo (4 no recurrence 2, 57, 58, 103.5 mo after LT) | 47       |
| Lehnert | 1998 | 103 68 60 53 47 47 | multicenter study; disease-free survival: 60% at 1 yr, 48% at 2 yr, 42% at 3 yr, 32% at 4 yr, 24% at 5 yr; favorable prognostic factors: age>50 yr, limited operation (survival 65% at 5 yr) | 48       |
| Pilchmayr | 1998 | 15 nr nr nr nr nr | 11 alive, 4 with no recurrence, the longest survival 10 yr after LT | 49       |
| Gottwald  | 1998 | 1 nr nr nr nr nr | Gastrinoma, alive with good liver function after LT | 60       |
| Frilling | 1998 | 4 nr nr nr nr nr | 3 carcinoids (2 alive, 1 dead 32 d after LT), IPNT (death 4 days after LT); 1 recurrence-free | 61       |
| Pascher | 2000 | 4 nr nr nr nr nr | 4 carcinoids; 2 deaths 14, 42 mo after LT, 2 alive 36, 76 mo after LT | 62       |
| Claude | 2000 | 1 nr nr nr nr nr | 1 carcinoid | 63       |
| Coppa | 2001 | 9 100 100 100 70 70 | Disease-free survival 53% at 5 yr | 19       |
| Ringe | 2001 | 5 nr nr nr nr nr | 4 alive (2 tumor-free survivals 4-25 mo after LT); 1 death 0.2 month after LT | 64       |
| Olausson | 2002 | 9 89 nr nr nr nr | 5 PNT, 4 carcinoids; 7 OLT, 2 MVT; 8 alive, 6 no evidence of disease, 4 recurrent tumors 9-36 mo after LT | 29       |
| Rosenau | 2002 | 19 89 nr nr nr nr | Survival at 10 yr 50%; recurrence free survival 56% at 1 yr, 21% at 5 and 10 yr; survival 100% at 7 yr with Ki67<5% and regular E-cadherin staining; survival 0% at 7 yr with Ki67>5% and E-cadherin aberrant staining | 50       |
| Fernandez | 2003 | 5 nr nr nr nr nr | 2 alive and recurrence free 3, 6 yr after LT; 3 deaths 4, 10, 17 mo after LT | 65       |
| Amarapurkar | 2003 | 14 nr nr nr nr nr | MIB-1 index >5%: recurrence at median 11 mo, survival median 13 mo MIB-1 index <5%: recurrence at median 69 mo, survival median 80.5 mo | 66       |
| Cahlin | 2003 | 10 nr 80 nr nr nr | 7 OLT, 3 MVT; 2 yr survival 100% for carcinoids; 67% for PNT; 2 yr disease-free survival 75% for carcinoids and 33% for PNT | 51       |
| Florman | 2004 | 11 73 nr nr nr nr | 1 patients disease-free at 5 yr after LT | 52       |
| Ahlman | 2004 | 12 nr nr nr nr nr | 8 after OLT alive at time of study, 2 after MVT died 4 mo after LT; other 2 after MVT with no recurrence at 8, 36 mo. | 14       |

LT: liver transplantation; OLT: orthotopic liver transplantation; MVT: multivisceral transplantation; PNT: pancreatic endocrine tumors, nr: results not reported
These data were further supported by another experience on 30 patients from 14 centers who underwent OLT for metastatic neuroendocrine tumors. It was noted that the actuarial survival, often combined with other upper abdominal resective procedures, for the entire group of patients was 52% after 1 year and remained stable for another 24 mo. Overall, mortality during the first year after transplantation due to recurrent tumor was 17%.

The longest survival, 42 mo, was in a patient who died from recurrent carcinoid tumor. Overall, at the time of this study 57% of patients were alive, 30% had developed recurrence, 43% had died and 70% did not have evidence of disease recurrence. Based on their observations they proposed that extrapancreatic primary neuroendocrine tumors be treated with radical hepatic resection followed by medical therapy and that the tumor response should be evaluated before considering liver transplantation. Even the primary pancreatic primary tumors with slow growth that do not respond to medical therapy can be considered for liver transplantation but with a combination of a pancreatic resection procedure.

The role of abdominal cluster transplantation was best described in 57 patients presenting with primary or metastatic liver tumors. Abdominal cluster transplantation for metastatic neuroendocrine liver tumors had a better 3-year survival rate (64%) than for patients who underwent this procedure due to sarcoma (44%), hepatocellular carcinoma (25%), cholangiocarcinoma (20%) and other adenocarcinomas (20%). OLT was found to be effective in controlling symptoms that were caused by carcinoid metastases to the liver. The tumor recurrence was not necessarily associated with early recurrence of symptoms. The patients with non-carcinoid tumors were found to have a higher likelihood of prolonged disease-free survival than those with carcinoid tumors. On the other hand Le Treut et al. found significantly higher survival in patients with metastatic carcinoid tumors (80% after 1 year and 69% after 5 years) than in patients with non-carcinoid neuroendocrine tumors who underwent OLT (38% after 1 year and 8% after 4 years). However additional analysis of 37 cases of OLT for metastatic neuroendocrine tumors presented in the literature revealed significantly higher survival rates in patients with non carcinoid apudomas (83% after 2 years) than in patients with carcinoids (34% after 2 years).

When liver transplantation was done only in cases with unresectable liver tumor, untreatable hormonal symptoms or massive tumor bulk and without extrahepatic tumors at the time of transplantation, patients were observed to derive benefit from OLT. A characteristic of the patients who did not have recurrence during follow up was that they had less than 40–50% tumor bulk in the explant. Thus, it has been suggested that OLT may be also regarded as curative treatment in some patients with neuroendocrine metastases who have relatively low tumor burden. In contrast, Florman found only 1 rare case of 5-year disease free survival among 11 transplanted patients. Moreover, it was claimed that due to only few reports in the literature of 5-year disease free survival (4.6%), OLT cannot be considered as a curative procedure.

Other prognostic indicators that have been suggested include a limited operation and age of <50 years. Patients with such features had an overall 5-year survival of 65% and median survival of more than 8 years. On the other hand, patients who underwent extended operations including upper abdominal exenteration or Whipple’s operation had 1-year survival of 50% and 5-year survival of 31%. Therefore, an extended operation (Whipple’s operation, abdominal exenteration) and age ≥ 50 years were considered as independent indicators of poor outcome and thus extensive surgery does not translate into better outcomes perhaps because of the high rate of post operative morbidity and mortality (10 of 11 patients with such features died after a median of 7 mo). Interestingly, location of the primary tumor, tumor histology and treatment with somatostatin were not found to be prognostic factors, although patients with primary tumors located in the pancreas or gastrinoma seemed to have poorer outcomes. The outcome of liver transplantation showed a highly significant survival difference between patients with metastases from neuroendocrine tumors and other tumors such as colorectal carcinoma, melanoma, choriocarcinoma or pancreatic carcinoma. The 5-year survival was 86.7% in patients with neuroendocrine metastases and 0% in patients with other malignancies.

Little is known about tumor markers as prognostic factors. It has been demonstrated that low tumor expression of the immunohistochemical marker, Ki67 (<5%), and the adhesion molecule, E-cadherin, might be associated with a favorable outcome after liver transplantation for metastatic neuroendocrine tumors. Patients (n = 12) with an increased expression of the markers (Ki67 ≥ 5% positive cells and/or E-cadherin staining) showed decreased survival (median 46 mo) whereas patients (n = 5) with low expression of these markers showed increased survival (median 90 mo). It was also suggested that the combination of these two markers had an excellent specificity and sensitivity to predict a survival of 7 years after liver transplantation. Further study showed that liver transplantation for metastatic well-differentiated neuroendocrine tumors with a low expression of protein Ki67 (Ki67 < 10%) resulted in relief of hormonal symptoms and long disease-free periods. Another study suggested that MIB-1 antibody expression might have prognostic value in patients undergoing liver transplantation for metastatic carcinoid tumors. The authors assessed the cell proliferative activity by MIB-1 antibody labeling in 14 patients with metastatic neuroendocrine liver tumors (7 carcinoids, 7 non-carcinoids) who underwent liver transplantation. In this group, two patients remained alive and disease-free at 96 and 192 mo after liver transplantation. MIB-1 index was calculated by dividing the number of tumor cells with positive staining for MIB-1 antibody by the total number of tumor cells. It was shown that patients with a MIB-1 index of greater than 5% showed early tumor recurrence (median 11 mo) and shorter survival (median 13 mo).
whereas patients with a MIB-1 index of less than 5% showed late tumor recurrence (median 69 mo) and longer survival (median 80.5 mo). The low MIB-1 index (<5%) was found to have a sensitivity of 71% and a specificity of 83% for predicting survival of greater than 2 years.

Current knowledge about the role of liver transplantation for patients with neuroendocrine liver metastases indicates that liver transplantation should be considered only in selected individuals. Coppa et al. proposed that selection of patients with non-resectable metastatic neuroendocrine tumors for liver transplantation should be based on the Milan criteria: young patients (less than 50 years) with carcinoids confirmed by histology, with less than 50% of the liver replaced by metastases, with a primary tumor (originating from the gastrointestinal tract) drained by the portal venous system, an absence of extrahepatic disease and stable disease during the pretransplantation period. In a group of nine patients who underwent liver transplantation based on these criteria the 5-year survival was 70% and the 5-year disease-free survival was 53%. On the other hand, in the group of 20 patients who were treated by liver resection due to less advanced liver metastases, the 5-year survival was 67% and the 5 year disease-free survival was 29%. Our patient had a 27 mo survival and the less than ideal outcome may have been because of some of the poor prognostic factors of age>50, tumor bulk exceeding 50%, and regional metastasis. Furthermore, whether immunosuppression after OLT has any effect on the rate of tumor recurrence or not is pure speculation. Thus, given the shortage of donor organs and the high rate of tumor recurrence, we currently believe that OLT should only be undertaken, when other therapeutic approaches including combinations of regional or systemic chemotherapy and hormone inhibitors together with partial hepatectomy have failed.

There is a need for prospective studies in large numbers of patients to fully evaluate the role of liver transplantation in patients with metastatic neuroendocrine tumors who may gain many years of effective palliation with careful selection. However, suboptimal outcomes may occur if case selection is compromised.

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