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Liver transplantation in metastatic intestinal neuroendocrine tumor: a case report and review

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ABSTRACT

Endocrine tumors of chromaffin cells are most frequent in the gastrointestinal tract. Moreover, they are the ones of best prognosis. Promising results have been recorded for liver transplantations in case of metastatic gastrointestinal neuroendocrine tumors. We exhibit a case report of a patient presenting dyspeptic and carcinoid syndrome, hepatic metastasis diagnosis and primary tumor of the ileum detected through scheduled hepatectomy. Liver transplantation was the chosen therapy given the impossibility of hepatectomy due to hepatic metastatic involvement. Liver transplantation is a healing therapeutic option for patients with gastrointestinal neuroendocrine tumor in case of unresectable hepatic metastases. It assures more than 50% survival within 5 years in case of primary tumors in the small intestine. Survival is longer in case of liver transplantation after primary tumor resection than in usual palliative treatments such as embolization and chemoembolization.

The article points out the importance of the therapeutic management of the neuroendocrine gastrointestinal metastatic tumor, with emphasis on performing liver transplantation as a possible curative treatment.

Introduction

Endocrine tumors of chromaffin cells (ECT) are more often found in the gastrointestinal tract (73%)[1]; the small intestine, the cecal appendix and the rectum are the main organs affected in the digestive tract[2]. Cells of the diffuse neuroendocrine system are the origin of neuroendocrine tumors of the gastrointestinal tract (TNEGI). They represent from 1/3 to 1/2 of all primary neoplasms of the small intestine and have the best prognosis[3,4].

Nowadays, surgery is the standard curative therapy for TNEGI; however, liver transplantation in TNEGI cases with unresectable hepatic metastasis has recorded promising results, as well as survival rates greater than those of usual palliative therapies such as chemoebolization[5].

Case report

White, 58-year-old female patient reported pain in the right hypochondrium, postprandial fullness, diarrhea five times a day and facial flushing for two months after the first consultation. The physical examination showed palpable mass 10 cm from the right costal border and ejection murmur in the pulmonic auscultatory area (2+/6+). Magnetic resonance imaging of the abdomen depicted

hypervascular mass in segments VII and VIII (12x 12.4x 10.8cm), besides nodules with contrast enhancement in segments IVa (1.2cm) and VI (1cm). The hepatic function was preserved and serum-alpha-fetoprotein recorded 2.06 (reference value <6.6 ng/ml). Colonoscopy (up to the cecum) did not show any remake.

The liver biopsy evidenced solid neoplasm with moderate atypia. Immunohistochemistry was positive for chromogranin and synaptophysin and negative for CK20 and CK7, compatible with neuroendocrine carcinoma. Regarding the proliferative index, the tumor is characterized by being well differentiated, with Ki-67 positive in less than 1% of the neoplastic cells (Figures 1-4).

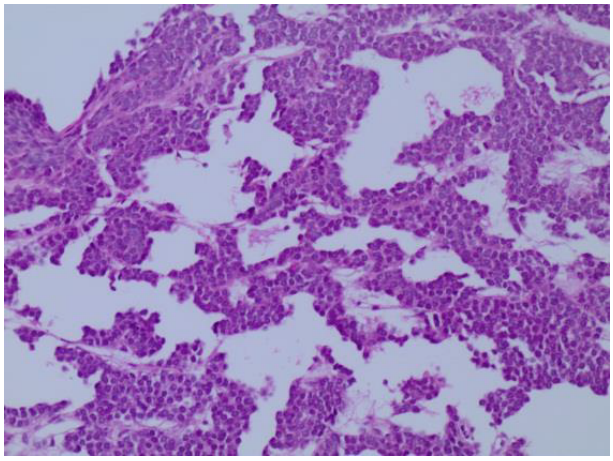

Figure 1. Liver biopsy: solid neoplasm of the liver with moderate atypia, increased nucleus / cytoplasm relation (oval-shaped nucleus) distributed in cell blocks surrounded by free spaces. Immunohistochemistry compatible with neuroendocrine carcinoma. (H&E, 20X).

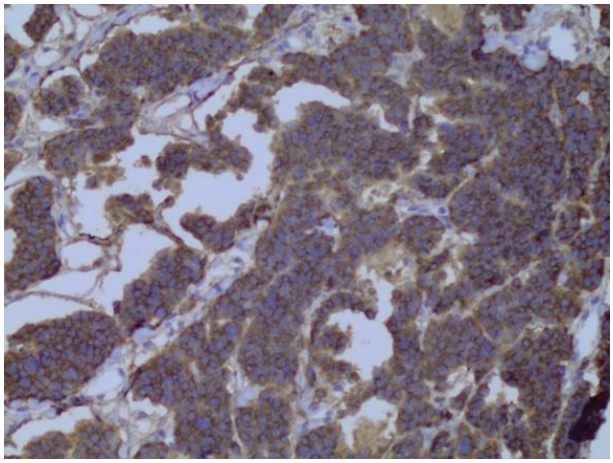

Figure 2. Liver biopsy: solid neoplasm of the liver. Immunohistochemistry compatible with neuroendocrine carcinoma. chromogranin-A (H&E, 200X).

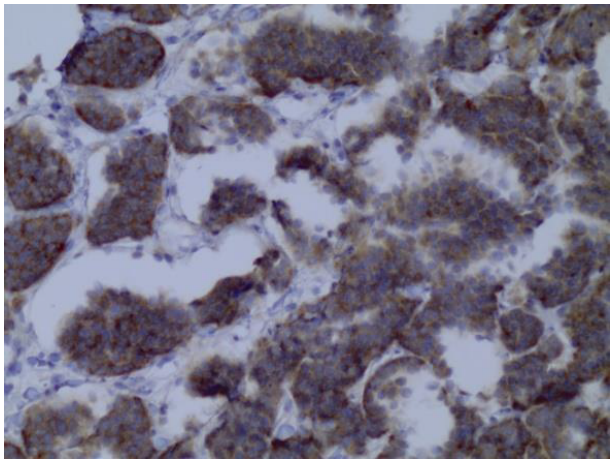

Figure 3. Liver biopsy: solid neoplasm of the liver. Immunohistochemistry compatible with neuroendocrine carcinoma. Synaptophysin (H&E, 200X).

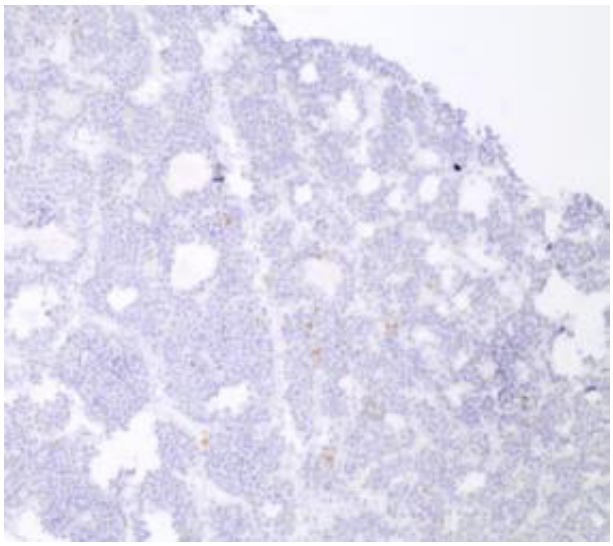

Figure 4. Liver biopsy: Immunohistochemistry for Ki-67 revealing a rate of 1% (H&E, 20X).

Somatostatin receptor scintigraphy did not show primary focus. There was negative staging for lungs and brain.

The patient evolved to dyspnea on exertion. Echocardiogram: atrial septal aneurysms; double lesion in the right valves (severe tricuspid regurgitation). The 5-Hydroxyindoleacetic acid was 119mg/urine 24h (reference value 2-9). Intramuscular administration of octreotide (30mg) in a monthly basis led to partial symptom improvement.

Patient evolved to dyspnea on minimal exertion; cardiac catheterization showed no signs of coronary artery disease. Tumor chemoembolization of the right lobe on segment IV was carried out after the tricuspid and pulmonary valve

was replaced by a biological prosthesis. Also, the interatrial communication was cut. Such procedure improved dyspnea symptoms.

The patient maintained carcinoid syndrome symptoms. The medication was changed to 1 ampoule (120 mg) of lanreotide every 39 days through subcutaneous administration.

Intraoperative ultrasound was performed during the right hepatectomy, and it detected multiple nodules on the left and right lobe. During the intraoperative, a retraction of the distal ileum and of the cecum was identified. A sample was collected and the anatomopathological examination confirmed the primary tumor (Figures 5 and 6).

The patient evolved to tricuspid dysfunction after the ileotiflectomy, and it pointed towards the need of changing the valve after the liver transplantation procedure due to the risk of new cardiac episodes resulting from the active tumor. The patient presented a special condition for transplantation. The magnetic resonance from December 2017 showed a mass in segments VII and VIII (12.8x11.3x11cm) with a central scar after chemoembolization and viable tumor displacing the contiguous intrahepatic vessels. The nodules presented intense arterial enhancement, low T2 sign in segments IVa (1.9cm) and VI (1.7cm) (Figure 7).

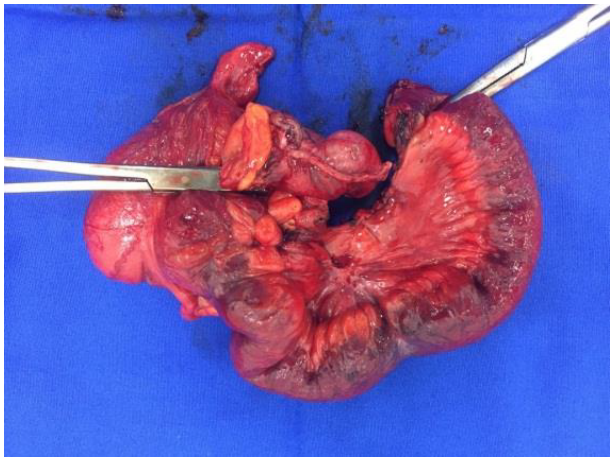

Figure 5. Ileotiflectomy: ileum and cecum showing stenosis area due to neoplasm.

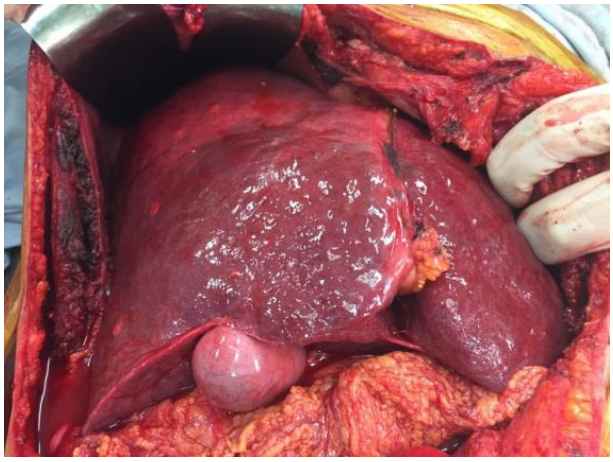

Figure 6. Laparotomy: *aspect of intraoperative hepatic lesions.*

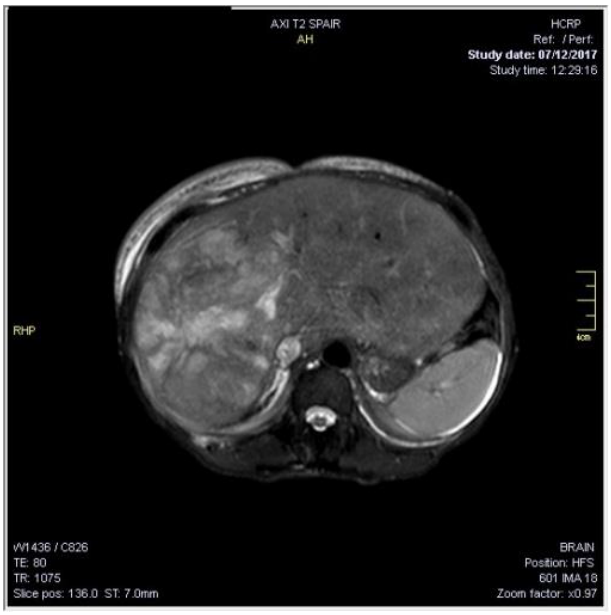

Figure 7. Magnetic resonance of the abdomen*: T2*-weighted axial cut. Hyperintense mass in the hepatic segments VII and VIII.

Discussion

Among the neuroendocrine tumor (NETs), gastrointestinal-origin NETs are relatively rare; however their incidence has been rising in recent decades[6].

The carcinoid tumor remains undiagnosed for long periods-of-time due to its slow growth. It is often found by accident when it presents itself by a mass effect or produces bioactive amines[7].

The case in study raised suspicion of a neuroendocrine tumor due to carcinoid syndrome, but the diagnosis of the primary tumor, during a laparotomy, only occured two years after the onset of symptoms. In addition, the ileocolonoscopy examination, fundamental exam to identify the primary tumor, did not contemplate visualization of the ileum and was performed only once at the beginning of the investigation, when the neoplasm was probably at an early stage, difficult to identified.

The most common NETs, usually arise from the small bowel, lung, and bronchus, occurring less often in the apêndix and pâncreas[8].

Neuroendocrine tumors, despite slow growth, tend

to develop distant metastasis with a certain frequency, especially at the liver, leading to a reduction in survival. Currently, surgical resection is the only potentially curative treatment[9,10].

Patients with hepatic metastasis subjected to palliative treatments (embolization and chemoembolization) show clear benefits in response to the symptoms, although it have a low impact on survival. Transarterial chemoembolization (TACE) is a non curative option for bridging-therapy or downstage for transplantation[11,12].

TACE is the recommended treatment modality for symptomatic, large or multifocal HCC without macrovascular invasion. Conventional transarterial chemoembolization (cTACE) using a mixture of a chemotherapeutic agent (e.g. doxorubicin or cisplatin) and lipiodol. Absolute contraindications for TACE includes extensive tumour involving the entirety of both lobes of the liver, malignant portal vein thrombosis, untreatable arteriovenous fistula, creatinine ≥2 mg/dl or creatinine clearance < 30 ml/min. One of the great problems of TACE is the huge heterogeneity of techniques and schedules used in world wide clinical practice[11,12].

Another therapeutic option are the thermal ablative therapies, which are classified as either hyper-thermic treatments (heating of tissue at 60-100^{0}C) – including radiofrequency ablation (RAF), microwave ablation (MWA), and laser ablation – or cryoablation (freezing of tissue at -20^{0}C and -60^{0}C). Most procedures are performed using a percutaneous approach[13].

Thermal ablation with RAF is the standard care for patients with tumor less than 3 cm not suitable for surgery. It is an alternative to surgical resection based on technical factors (location of the tumor), hepatic and extrahepatic patient conditions[13,14].

Important centers have advocated that liver transplantation tend to be a better therapeutic strategy in unresectable metastases than palliative treatment. The metastatic TNEGI has the potential to be ruled out through liver transplantation combined with primary tumor resection, since it is less aggressive biologically compared to other secondary metastases[15,16].

In Brazil, liver transplantation in TNEGI cases corresponds to special situations when it comes to treating unresectable metastases, according to the standard technical norm[17].

In a study with 81 patients subjected to embolization and chemoembolization, the response duration (free from progression) was 17 months, and the survival rates were 75%, 35% and 11% within 1, 2 and 3 years[18]. Compared to multicentric studies recorded 80%, 65% and 52% global survival rate within 1, 3 and 5 years, in patients subjected to liver transplant[19,20].

Mazzaferro et al. identified criteria related to a better prognosis before transplantation: low-grade functioning or non-functioning NET; primary tumor drained by the portal system and removed with a curative resection preceding the transplant; ≤50% of metastatic involvement of the liver; good response or stable disease for a minimum period of 6 months before transplantation and age ≤50 years[21].

The prognostic relevance of Ki-67 and E-cadherin, a marker of cell proliferation and metastatic tumor potential, has also been considered by researchers as positive criteria for better results. Patients transplanted with expression of Ki-67 ≥5% and/or aberrant E- cadherin have a survival rate significantly decreased compared to those with reduced Ki-67 expression and regular E-cadherin staining results (survival at 7 years of 0% vs. 100%, respectively)[22].

The results of the studies have shown better survival after liver transplantation in patients with localized hepatic disease and metastases of non-pancreatic tumors. In a more recent multicentric report from France analysing 85 patients, the 5-year survival rate was 68% in patients with limited hepatic disease and non-duodenopancreatic tumours. In this study the survival rate dropped to 12% in the case of hepatomegaly and primary tumour localized within the duodenum or pancreas[23].

Nonfunctioning pancreatic neuroendocrine tumors (PNETs) comprise the largest group of PNETs and do not produce syndromes of hormonal excess; rather, they cause morbidity and mortality by invading normal tissue and metastasizing. Although the optimal clinical management of PNETs involves a multidisciplinary approach, surgery remains the only curative treatment for early-stage disease. Surgery may also have a role in patients with advanced-stage disease, including those with hepatic metastases[24].

Alternative therapeutic approaches applied to PNETs, including chemotherapy, radiofrequency ablation and transarterial chemoembolization, have failed to demonstrate a long-term survival benefit. Radiotherapy (RT) is recommended in limited cases of postoperative aim along with chemotherapy after surgery or unresectable locoregional disease. In unresectable locoregional disease, RT is recommended with concurrent or sequential chemotherapy.Surgery remains the primary therapeutic option for patients with PNETs[25].

Despite the positive results, the option for liver transplantation is not consensus in most of the treatment centers. The NET, being a rare tumor, presents a small number of patients eligible for transplantation, leading to a scarcity of data that allows the universal acceptance of the transplantation as a viable therapy. Some authors advocated that only the primary tumor resection should be taken into account, even for metastatic tumors, since tumor permanence is linked to increased mortality rates[3,26,27]. A

critical review of the data reveals the importance of further prospective studies.

Conclusion

The present case report calls attention to the need of conducting more comparative studies, and data analysis, for choosing different therapeutic methods in cases of carcinoid tumor. Transplant centers still avoid performing transplantation in TNEGI cases due to data scarcity in the literature.

Data presented shows that the type and location of the tumor, the cell proliferation and extension of the metastasis are some of the important criteria to develop a better understanding of success rates. Since the NET grows slowly, with lower impact on survival than other tumors, prospective studies should be done to define which treatment will lead to better survival rates and lower risks for the patient.

Conflicts of interest

The authors declare no conflict of interests. This paper was not supported by external funding.

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