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Reverse Attitude and two-step Hepatectomy for Neuroendocrine Bilateral Metastasis

Pr. Berkane[1], Dr. A. Bennani[2]Pr. L. Abid[2], A. Bendjaballah MD[3]
[1]*Bejaia teaching hospital / ALGERIA*
[2]*Bologhine Hospital ALGIERS /ALGERIA*
[3]*Ain Taya Hospital ALGIERS/ALGERIA*

Abstract:*Hepatic metastatic neuroendocrine tumor is a possibility to justify radical surgery when possible. When liver metastases are bilateral and bulky with the possibility of a potentially insufficient remaining liver, the treatment becomes perilous. We report a case of a 38year woman with neuroendocrine tumor with 2 bilateral synchronous liver metastasis. A left hepatectomy was performed as first step. The postoperative course was uneventful. Histological examination with immunohistochemistry was for a low-grade neuroendocrine tumor. To give an enlarged liver and remaining to ensure the absence of tumor scalability, we waited 6 months after the first operation. A second operation was performed and a bi segmentectomy of the VI &VII was performed. The postoperative period was smooth. Third and 4th interventions were carried out after 9 months and 12 months. The pre-sacral tumor was resected on the third intervention and we realized intraperitoneal chemotherapy on fourth intervention (positive cytology examination at the third intervention). The 2 postoperative courses were uneventful. The OSTREOSCANN performed 6 months after showed a normal status. At present, the patient is alive without apparent recurrence at 36 months postoperatively. This case illustrates the possibility of a reverse attitude for bilateral voluminous and metastatic neuroendocrine tumors with complete control tumor sites. Metastatic neuroendocrine tumor can be an avenue to be explored for this attitude because of their slow growing.*

Keywords:*hepatic metastatic- neuroendocrine tumors- rivers attitude- intraperitoneal chemotherapy-complete control tumeurs sites*

I. Introduction

Neuroendocrine tumors (NETs) are a heterogeneous and unusual group of neoplasms, with slow-growing and often indolent evolution. They are characterized by the ability to synthesize, store and secrete hormonal substances and vasoactive amines, which are directly related to clinical manifestations**(1)** The incidence is variable between different studies, involving **1-7** cases / 100,000 individuals**(2)**representing 0.49% of all cancers**(3)**. Over the past 30 years there has been an increased incidence of this tumors at a rate of 6% per year, possibly due to improvement in diagnostic methods and greater awareness of the disease by physicians **(3, 4)**.Although neuroendocrine tumors are generally indolent, slow-growing compared to carcinomas, metastases can occur, making the prognosis poor. Neuroendocrine tumors series show that 17% to 27% haveregional disease, and 17% to 74%, distant metastatic involvement **(1)**. The liver is the organ which is most affected by distant metastases and it is estimated that 75% of patients with small bowel TNE and 30% to 85% of those with TNE of pancreatic origin develop liver metastases, of whom 80% die within five years **(3, 5)**. The liver is often the only organ affected by distant metastases**(6).**The TNE five-year survival in the presence of liver metastases ranges from 13% to 35 %**(5, 7, 9)** and from 77% to 99% in the absence of hepatic involvement**(8)**

Neuroendocrine hepatic metastases represent approximately 10% of all hepatic metastatic neoplasms **(10)**.These metastases occur in 25–90% of patients with neuroendocrine tumors. Metastasis from neuroendocrine tumors are a poor prognostic factor for survival and quality of life **(11)**Although surgical intervention is the current reference standard curative treatment of patients with liver metastases, nonsurgical alternatives also play an important role in controlling tumor growth and the systemic hormonal effects, particularly in nonsurgical candidates. Tumor-directed methods described in the literature are chemotherapy **(12)**biotherapy, including interferon and somatostatin analogs **(13);** and transarterial chemoembolization (TACE). TACE is thought to be an effective symptomatic and antiproliferative treatment in patients with progressive disease **(11).**An important advantage of TACE is that it has been shown to be a safe technique in high-risk patients. Multiple studies have shown that TACE provides symptomatic control in patients with neuroendocrine metastasis **(14)**

II. Case Report

A 38 years old female, with no particular history, admitted for investigation of functional ovarian cyst and 2 liver tumors discovered during routine ultrasound. Physical examination, found a palpable tumor of the upper abdomen, firm, mate, painless and mobile with respiratory and therefore belonging to the liver.

Preoperative laboratory tests are normal. The liver functions are normal. ACE and CA19.9 were also normal. Abdominal ultrasound showed liver seat 2 hyperechoic tumors of 117mmx71mm. CT scan showed heterodense appearance of a tumor, taking contrast in the arterial phase and localized in the left liver. It measures 146X77mm. There is another tumor confinedto IV and VII segments having the same characteristics as the first tumor. It measured 102X82mm. MRI described two left and right hepatic formations whose dimensions are respectively 141X85mm and 88X85mm. They look and take tissue contrast. There is a small diameter 30mm formation next to the first sacral vertebra hypodense and taking contrast homogeneously. In front of this aspect of bilateral tumors, we decide to carry out a resection of this tumors of the liver in 2 times (left hepatectomy followed by a right hepatectomy segmental atypical, separate from 5 to 6 months and lumpectomy last time). First intervention was started by bi-subcostal incision. Exploration showed: existence of a large irregular surface tumor, firm in places and purplish red color. The dimensions of this tumor are of 160mmx140mm. Peritoneal fluid sample for routine cytology study was taken routinely. A left hepatectomy was realized under pedicle clamping discontinuous 2x20minutes. A bleeding during surgery was 980cc without transfusion. No incident was noted. The patient passed a smooth post-operative period and she was discharged at the 10th postoperative day. Histological findings noted that it was a neuroendocrine tumor of low-grade confirmed by immunohistochemical study. The cytology of peritoneal fluid is in favor of a benign cytology. The nodes resected at the hepatic pedicle and the common hepatic artery are not infiltrated. The second operation was carried out after 5 months and a half. The second look is performed after ascertaining the liver hypertrophy and normalization of all liver functions. Under general anesthesia and bi-subcostal iterative incision. A sampling peritoneal fluid for routine cytological study was done. Conducting a lumpectomy atypical liver in the right pedicle clamping discontinuous 2x15minutes. Intraoperative incident occurred as cardiovascular collapse because of a great hemorrhage. The bleeding was estimated by 3800cc and patient received transfusion of 8 PRBCs and 5 fresh frozen plasma. The postoperative period was smooth and patient was discharged on the 15th postoperative day. The histological results were as the first tumor with immunohistochemical confirmation. The cytology is in favor of a benign cytology. The OSTREOSCAN scintigraphy was performed just after the second intervention, and confirmed the pre-sacral tumor as a single neuroendocrine tumor site. Three months and a half, the presacral tumor resection is performed under midline laparotomy. This intervention was successful and the postoperative course was uneventful. She was discharged on the 8th postoperative day. Histological study confirmed the same kind for liver metastases from pre-sacral tumor. Cytological study was in favor of a malignant cytology. The 4th action is scheduled to perform intraperitoneal chemotherapy. An appendectomy was performed in combination with intraperitoneal chemotherapy for 5 days.

III. Discussion

Neuroendocrine tumors, although considered slow growing tumors and mildly aggressive, tend to develop distant metastatic disease with relative frequency, and the liver is the most affected organ. The development of liver metastasis results in a significant reduction in survival and quality of life of patients. There is some doubt in the management of patients with liver metastases from neuroendocrine tumors. The goals of treatment when there is metastatic disease are improved quality of life by relieving symptoms and increased survival. Surgical resection is the only potentially curative treatment. Other forms of treatment have been employed with intra-arterial chemoembolization and systemic treatment, with results poorer than resection**(15)**. Due to the indolent behavior and less aggressive evolution when compared with other metastatic diseases to the liver, patients with liver metastases deemed unresectable have undergone livertransplantation **(16).** The result of the transplant for this group of patients was very heterogeneous, with five-year survival ranging from 14 to 90%, being much better for patients with non-pancreatic tumor metastasis[3]. For patients with restricted but unresectable liver disease, transplantation appears to be the best therapeutic alternative**(17).**Neuroendocrine hepatic metastases represent approximately 10% of all hepatic metastatic neoplasms **(18).** These metastases occur in 25–90% of patients with neuroendocrine tumors. Metastases from neuroendocrine tumors are a poor prognostic factor for survival and quality of life **(19).** Although surgical intervention is the current reference standard curative treatment of patients with liver metastases, nonsurgical alternatives also play an important role in controlling tumor growth and the systemic hormonal effects, particularly in nonsurgical candidates. Tumor-directed methods described in the literature are chemotherapy **(20)** biotherapy, including interferon and somatostatin analogs **(21)** and transarterial chemoembolization (TACE). TACE is thought to be an effective symptomatic and antiproliferative treatment in patients with progressive disease **(19).** An important advantage of TACE is that it has been shown to be a safe technique in high-risk patients. Multiple studies have shown that TACE provides symptomatic control in patients withneuroendocrine metastasis **(22).**Because of the rarity of these neoplasms, most studies are retrospective and composed of small case series, ranging between 13 and 47 patients, especially when only analyzing patients who underwent surgical treatment of metastases **(23, 24, 25)**.

In our case the attitude consist of double reverse liver metastases from neuroendocrine tumors and which required two separate hepatectomy of 5 months and a half. A resection of the primary tumor after 9

months and an appendectomy associated with intraperitoneal chemotherapy 12 months after the first hepatectomy. This is a reverse attitude which required 12 months for its completion and incorporated the time of liver regeneration, simplifying the surgery for the safety of the patient and verification of the absence of new tumor sites. To our knowledge this is the third case reported in the literature. The first was reported by Marchesi et al on 2006 **(26).** It concerned a woman who had benefited from right hepatectomy for neuroendocrine metastasis originating from primitive tumor of the pancreas. Six Months after the hepatectomy with Whipple procedure was done and it was successful. A second case was reported by Moriyama et al 2016**(27)**. A 77-year-old woman benefited from by hepatectomy in stage one and low-rectal resection for rectal neuroendocrine tumor.

After surgery, treatment with an octreotide LAR was initiated. The patient remained disease-free for 1 year 8 months after surgery. As our patient, these two cases reported by these authors respond to the criteria which are the following: patient with good state, resectable lesions even for the primitive tumor and liver and tumor with a slow growth**.** The slow evolution of neuroendocrine tumors allows a reverse attitude and spread over time. This iterative and scheduled surgery allows the treatment of a number of patients in a safe and secure manner. Mentha G. and al **(28)** have reported study their series about colorectal metastatis cancer on 2008. As the surgery of liver metastases is more complex than the resection of the primitive neuroendocrine tumor in the majority of cases, (except cephalic pancreatic location) it can be performed by step to more than 2 liver metastases. We can well imagine the use of other methods such as the radio frequency for example with conventional surgery. Our case is unique by the fact that we performed two stages of hepatectomy followed by the resection of the primitive tumor. We waitedsixmonths between the stages of the hepatectomy to allow the remnant liver to reach an acceptable hypertrophy. This method is possible because this kind of tumor neuroendocrine tumor has a relatively slow evolution. The treatment is surgical. Surgical resection of liver metastases of neuroendocrine tumors even if multiple is possible **(29)**.

The number of metastatic lymph nodes showed significant influence on disease-free survival; patients with a number higher than or equal to ten metastatic nodules had lower disease-free survival. The presence of symptoms at diagnosis also had a significant influence on disease-free survival, and symptomatic patients had lower disease-free survival.In the past, liver resections were considered highly complex operations. Nevertheless, with the development of surgical and anesthetic techniques and perioperative management, these operations have become safer, especially if performed in specialized centers. In the analysis of predictive factors for the occurrence of postoperative complications, the highlights were the performance of multiple hepatectomies and other procedures associated with the liver resections. Likewise, SØreide et al.demonstrated that patients who submitted to aggressive surgical treatment, including the re-hepatectomy and operations in two stages, had gain in overall survival, but displayed high complications (33%) and mortality (9%)**(30).**

It is not uncommon for patients with neuroendocrine tumors to have large-volume metastatic disease predominantly within the liver. The therapeutic options for palliation of their illness are limited. The development of radionuclide therapy performed with somatostatin analogs to carry a β emitter has been a substantial advance during the past 5 years. The problem with administering this type of treatment intravenously to patients with large-volume liver disease is that a substantial proportion of the dose is dissipated within the systemic circulation such that a reduced dose of the agent reaches the target. Hence, for such patients, administering the dose intraarterially directly to the liver metastasis should enable a higher concentration of the therapeutic dose to reach the tumor. However, in this study we did not perform uptake comparisons **.**

Despite the great heterogeneity and clinical presentation of TNE, it is clear that surgical treatment represent a main an important solutionfor these patients. It is worth noting that, in symptomatic patients with multiple nodules, surgical treatment in isolation is not able to provide cure.. Efforts should be oriented for the selection of patients in the hunt for surgical treatment and new therapeutic approaches.

IV. Conclusion

There are a lot of surgical options offered for the treatment of NETs liver metastases. The choice of management depends on the symptoms, the metastasesdistribution, and the histological types of the tumor. However, there is no evidence-based data comparing surgery versus other liver-directed treatment options such as embolization, thermal ablation techniques, and somatostatin analogues in the treatment of patients with metastatic NETs. The future for this entity appears more promising with variable treatment options. Although aggressive surgical resection remains the gold standard for management, the laparoscopic approach by experienced laparoscopic liver surgeons can be safe and provides earlier recovery and less complications. Nevertheless, patients should be managed under the supervision of a multidisciplinary team to guarantee that all treatment options are explored both at diagnosis and follow-upto ensure proper management for this kind of tumors.

Photo 1: showing CT scan of the liver prior first surgery

Photo 2: showing a Perioperative view of left sided tumor of the liver

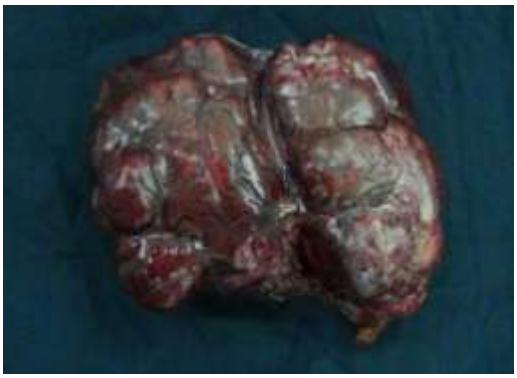

Photo 3 showing a Resected tumor of first surgery

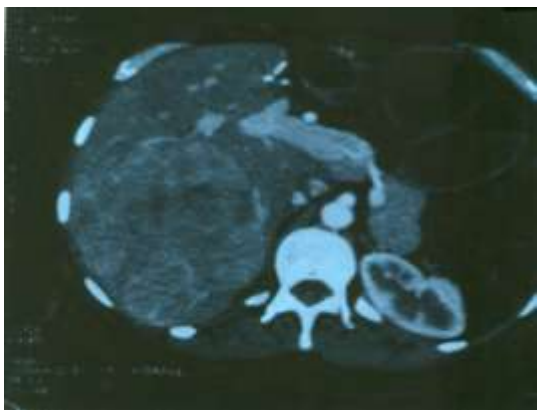

Photo 4: showing CT scan before second surgery

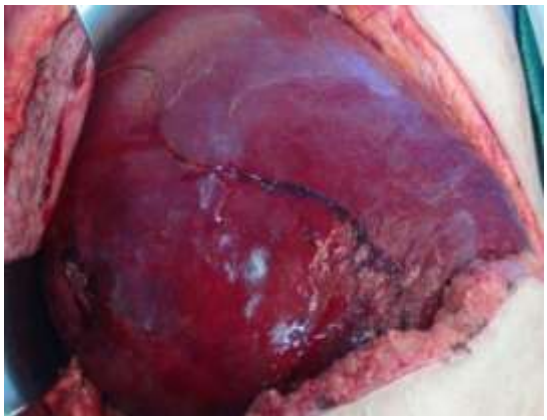

Photo 5: showing a preoperative lesion at second surgery

Photo 6 showing a Resected tumor of second step of surgery

Photo 7: MRI showing Presacral tumor.

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