

Neuroendocrine tumor of the common bile duct: case report

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SUMMARY: Neuroendocrine tumor of the common bile duct: case report.

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Neuroendocrine tumors (NET) are a very heterogeneous group of neoplasms; in recent years we have seen an increase in their incidence (3.65 /100.000/year).

They can be associated with hereditary endocrine syndromes (MEN, Von Hippel Lindau); they can occur at any age and the incidence is slightly higher in men than women. The aetiology of the neuroendocrine tumors is unclear; in most cases, inflammation of the bile ducts may be the underlying cause and for this reason, the initial patient's evaluation should be focused on the different aspects concerning the oncological one and the possible sequelae of the biliary obstructions that can evolve in biliary sepsis. All neuroendocrine tumors have malignant potential.

The most frequent sites of extrahepatic biliary NETs are the common hepatic duct and the distal common bile duct (19.2%), followed by the middle of the common bile duct (17.9%), the cystic duct (16.7%), and the proximal common bile duct (11.5%). We can divide them into: well-differentiated and poorly differentiated. Considering the clinical features, neuroendocrine tumors can be divided into functional and non-functional. As regards the staging, we distinguish localized, regional and metastatic tumors.

Tumors derived from the bile duct are difficult to diagnose preoperatively, mainly because of its low incidence and difficult diagnostic process. However since cholangiocarcinomas account for about 80% of

all primary biliary tumors, it is important to think about other options despite their low frequency when a patient presents with abnormal characteristics.

The most sensitive immunohistochemical markers are expressing neuron-specific enolase, synaptophysin and chromogranin A.

Liver function tests, alkaline phosphatase and bilirubin are often high. Sometimes an anemia can appear in the presence of a chronic disease or in patients with more advanced disease. It is known that the measurement of chromogranin A is useful for the preoperative diagnosis of neuroendocrine tumors. Chromogranin A is elevated in 90% of neuroendocrine tumors of the intestine, and the levels correlate with tumor burden and the possibility of recurrence and, therefore, chromogranin A can be an effective biological marker for preoperative diagnosis of neuroendocrine tumors. Bile endocrine tumors remain silent until metastasizing or growing into neighboring organs, because of its uncommon diagnosis in early stages due to its low incidence, absence of serum markers and lack of symptoms related to the hormonal pattern.

Preoperative diagnosis of common bile duct carcinoma is extremely difficult, because it is foretold by non-specific symptoms that include pain or discomfort in the right upper quadrant level and weight loss. A 51-year-old woman presented a jaundice and severe bile duct dilatation. The enhanced CT scan showed a mass, approximately 15 mm in diameter, in the distal common biliary duct. The MRI and ERCP confirmed the mass. Chromogranin A value was negative. The diagnosis of well differentiated endocrine tumor of the biliary tract was done after its surgical resection was performed. The postoperative period was uneventful.

Extrahepatic biliary NETs are rare, and extrahepatic bile ducts reportedly account for only 0.32% of primary NET sites.

The prognosis for NET of the bile duct appears to be poor.

KEY WORDS: Neuroendocrine tumor of the common hepatic duct - Chromogranin A.

Introduction

Neuroendocrine tumors (NET) are a very heterogeneous group of neoplasms; in recent years we have

seen an increase in their incidence (3.65 /100.000/year) (1).

They can be associated with hereditary endocrine syndromes (MEN, Von Hippel Lindau); they can occur at any age and the incidence is slightly higher in men than women (2). The aetiology of the neuroendocrine tumors is unclear; in most cases, inflammation of the bile ducts may be the underlying cause and for this reason, the initial patient's evaluation should be focused on the different aspects concerning the oncological one and the possible sequelae of the biliary obstructions

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Tumors derived from the bile duct are difficult to diagnose preoperatively, mainly because of its low incidence and difficult diagnostic process. However since cholangiocarcinomas account for about 80% of all primary biliary tumors, it is important to think about other options despite their low frequency when a patient presents with abnormal characteristics (3).

The most sensitive immunohistochemical markers are expressing neuron-specific enolase, synaptophysin and chromogranin A.

Liver function tests, alkaline phosphatase and bilirubin are often altered. Sometimes an anemia can appear in the presence of a chronic disease or in patients with more advanced disease. It is known that the measurement of chromogranin A is useful for the preoperative diagnosis of neuroendocrine tumors. Chromogranin A is elevated in 90% of neuroendocrine tumors of the intestine, and the levels correlate with tumor burden and the possibility of recurrence and, therefore, chromogranin A can be an effective biological

marker for preoperative diagnosis of neuroendocrine tumors. Bile endocrine tumors remain silent until metastasize or invade neighboring organs, because of its uncommon diagnosis in early stages due to its low incidence, absence of serum markers and lack of symptoms related to the hormonal pattern (4).

Preoperative diagnosis of common bile duct carcinoma is extremely difficult, because it is foretold by non-specific symptoms that include pain or discomfort in the right upper quadrant level and weight loss.

Extrahepatic biliary NETs are rare, and extrahepatic bile ducts reportedly account for only 0.32% of primary NET sites.

The prognosis for NET of the bile duct appears to be poor (5).

Case report

A 51-year-old woman was found to have a marked dilatation of the intrahepatic bile duct during an ultrasonography performed, as part of a medical examination, and was admitted to hospital for further investigation (Figure 1). The patient showed: jaundiced skin, itching all over the body, issuance of dark urine and feces hypocholic; the laboratory tests it was found increase of direct bilirubin values, GGT and alkaline phosphatase.

An abdominal ultrasonography examination, together with a contrast-enhanced abdominal computed tomography scan, showed a mild dilation of the biliary tree and a solid hypoechoic mass, approximately 15 mm in



Fig. 1 - Ultrasonography examination: marked dilatation of the intrahepatic bile duct.



Fig. 2 - Contrast-enhanced abdominal computed tomography scan: mild dilation of the biliary tree and a solid hypoechoic mass, approximately 15 mm in diameter, in the distal common bile duct.

diameter, in the distal common bile duct (Figure 2).

The common bile duct, in his proximal segment, presents a distinctly hyperdense tissue in the arterial phase occupying entirely the lumen for a 1.5 cm longitudinal extension and 1.2 cm transverse. Respect to the possibility of a classic common bile duct carcinoma, it showed an atypical post contrastographic behaviour, placing the suspect for a neuroendocrine tumor of the same (0.2 % of the common bile duct tumors).

MRI showed dilatation of the intrahepatic bile

ducts, more evident in the left sections, with a maximum caliber at the left hepatic duct (9 mm). Dilatation of the common bile duct (DT Max 11 mm) presenting empty signal, not univocal interpretation (Figure 3).

ERCP showed a lesion protruding into the lumen, at the level of the common hepatic duct, about 0.3 cm, irregularly oval, approximately 12 x 8 mm. The intrahepatic biliary ducts were moderately dilated and the gallbladder was not displayed. An endoscopic Papillotomomy (PTE) and brushing of the lesion was made



Fig. 3 - MRI: dilatation of the intrahepatic bile ducts, more evident in the left sections, with a maximum caliber at the left hepatic duct (9 mm). Dilatation of the common bile duct (DT Max 11 mm).



Fig. 4 - ERCP: a lesion protruding into the lumen, at the level of the common hepatic duct, about 0.3 cm, irregularly oval, approximately 12 x 8 mm. The intrahepatic biliary ducts are moderately dilated and the gallbladder is not displayed.

and it was positioned a 7 Fr nose-biliary drainage into the distal end of the right hepatic duct (Figure 4).

Furthermore, it was found a negative result to the pre-operative dosage of chromogranin A.

Based on these findings, a diagnosis of the distal common bile duct tumor was made, and the patient underwent a bile duct resection with the additional dissection of lymph nodes along the common bile duct, hepatic artery, and portal vein. The postoperative course was regular, the postoperative ileus resolved in 3rd postoperative day, no complications were observed during the course and the patient was discharged in the 10th postoperative day.

Histologic examination showed a well differentiated neuroendocrine tumor of the common hepatic duct (G1); with a maximum diameter of 1.8 cm, infiltrating the muscle layer; mitotic count index (10 HPF) <2, proliferative fraction (Ki67) ≤ 2% (IHC: CK7; CK20; CEA; chromogranin; synaptophysin; NSE, ki67; p53; EMA; S100; CD56; CK8-18).

The patient made an uneventful recovery even three weeks after the discharge.

Discussion and conclusion

The patient had a negative pre-operative result of chromogranin A and only after the histological examination a diagnosis of NET of common hepatic duct was made; in fact in this case a correct pre-operative diagnosis was more difficult, so it must be considered very rare.

Generally, the NET are diagnosed in the metastatic

phase; their capability to metastasize is dependent on the site of occurrence of the primary tumor and the histological type. In particular, the most common site of metastasis is the liver (40-93%) followed by bone (12-20%) and lung (10.8%). It is estimated that approximately in 40% of patients with NET are present hepatic metastases at diagnosis.

NETs represent a very heterogeneous group of diseases, and for this reason it is not possible to define a unique treatment strategy. Also, being a quite rare tumor, it is imperative to consult a highly specialized center in which you can define a personalized therapy with a multidisciplinary medical approach. Among the different possible therapeutic options, surgery is the most used in potentially curative purpose: if the tumor is removed entirely, the surgery is on the whole the main step of the treatment and allows in many cases to cure it completely (6). For some neuroendocrine tumors it is possible to use local-regional therapies such as chemoembolization and the alcoholization (for metastases located in the liver areas difficult to reach by surgery) or cryosurgery and the high-frequency thermal ablation. The traditional radiotherapy is little used for the real cure of the tumor, but it is possible to use it with the aim of reducing the symptoms in more advanced stages. The adjuvant treatment should take into consideration the implications of the neuroendocrine system, especially the hypothalamic-pituitary-adrenal axis. In this perspective, the treatment with immunomodulators should be proposed in the future, similarly to other neoplastic as well as non-neoplastic diseases (7, 8). Targeted radiotherapy is based on the ability of some neuroendocrine tumors

to concentrate in themselves radioactive substances. An example is the 131I-MIBG therapy. It is also possible to use octreotide, a somatostatin analogue.

In summary, neuroendocrine tumors are complex diseases and are an example of how a multidisciplinary approach has a favorable impact on diagnosis, treatment and control.

The appearance of a well-circumscribed hypervascular tumor during the arterial phase may help to differentiate NETs from other biliary neoplasms. The computed tomography images in the present case might be typical of biliary NET. The surgical treatment plays an important role in the treatment of NET, when to have healing purposes by excision a primary non metastatic lesion, both when the surgery interpreters the role of palliation in advanced disease. General criteria are needed for correct surgical approach to the disease; it's necessary a radiological research of the primary tumor and a study of any metastases. When the primary tumor has no metastases, radical removal of the lesion appears as curative treatment. Surgical exploration, also with the aid of US intraoperative for digestive NET, has the task of locating the precise location of them. When the primary tumor is resectable, but coexist synchronous metastatic lesions, it is necessary to plan the type of treatment in the number, size and location of secondary localizations. In case of liver multifocal lesions, chemoembolization constitutes the best treatment; but if metastasis are confined to one of the two hepatic lobes may be taken into account the removal of one or more liver segments, after evaluation of anesthetic risk. Regarding debulking, we can use it for functional neoplasia, in order to reduce the amount of secreting tissue and then to control the symptoms of the disease, ensuring the patient a better quality of life but not a longer survival.

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