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HEPATO-BILIARY MIXED NEUROENDOCRINE NON-NEUROENDOCRINE NEOSPLAMS: 3 CASE REPORTS.

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ABSTRACT

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN) are rare tumors defined as the association of at least two morphologically different neoplastic components, including one neuroendocrine, according to the 2019 World Health Organization (WHO) classification. MiNENs usually originate from organs that contain neuroendocrine cells and in which classical neuroendocrine neoplasms (NEN) are known to develop, such as pancreas, appendix, colon, and to a lesser degree small intestine. However, MiNEN can develop in organs initially lacking in neuro-endocrine cells, such as extra and intrahepatic MiNEN, suggesting the existence of different pathological pathways. Due to rarity of hepato-biliary MiNENs, epidemiology, staging, diagnosing and treatment are based on case reports.

In this paper we report the clinical cases of three MiNEN originating from three different sites in the hepatobiliary tract: i) a first patient with a mixed neuroendocrine tumor and a high-grade adenomatous lesion of the ampulla of Vater, ii) a case of a mixed cholangiocarcinoma and NEN of the biliary confluence and iii) an intrahepatic MiNEN combining a hepatocellular carcinoma with small cell neuroendocrine carcinoma.

Conclusions

MiNENs originating from the biliary system (gallbladder, biliary tract, or ampulla of Vater) are extremely rare and have not been discussed in detail. Informations on hepatobiliary MiNENs are exclusively collected from a little number of case reports, raising many interrogations concerning their pathogenesis and their management. Hence, new studies are needed to understand etiology and carcinogenesis of MiNEN leading of novel targeted therapy, mainly in pancreatico-biliary MiNENs, which seem to have the worst prognosis.

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INTRODUCTION

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN) are rare tumors defined by the last World Health Organization (WHO) classification as tumors made up of at least two morphologically different neoplastic components, with one having a neuroendocrine nature.[1] Currently, tumoral components of a MiNEN must represent at least 30% of the whole tumor to be considered as different entities. This threshold was arbitrarily described in 1987, as found being a cut-off value affecting long-term prognosis.[2] Another pathological classification proposed by La Rosa et al. stratifies MiNEN according to three malignancy grades: high grade - mostly dependent on the behavior of the neuroendocrine component - intermediate and low grade, based on the differentiation of the non-neuroendocrine component (Table 1).[3] MiNEN usually originate from organs that contain neuroendocrine cells and in which classical neuroendocrine neoplasms (NEN) are known to develop, such as pancreas, appendix, colon, and less frequently small intestine.[4] However, MiNEN can also develop in organs initially lacking in neuroendocrine cells, such as extra and intrahepatic biliary ducts, suggesting the existence of different pathological pathways.[4] Due to the rarity of hepato-biliary MiNEN, epidemiology, staging, diagnosing, and outcomes are based on few case reports present in literature. To expand this knowledge, this article reports 3 clinical cases of hepato-biliary MiNEN: one derived from the ampulla of Vater, another combining a large cell neuroendocrine tumor with a well-differentiated cholangiocarcinoma component complicated with high-grade dysplasia of the biliary ducts of the biliary confluence and a third case in which a neuroendocrine component was found to be combined with a well to moderately differentiated hepatocellular carcinoma (Figure 1).

Table 1: Classification of MiNEN according to the behavior of the two components.

MiNEN GRADE	NON-NEUROENDOCRINE COMPONENT	NEUROENDOCRINE COMPONENT
LOW grade	Adenoma	Well differentiated neuroendocrine tumor (G1-G2)
INTERMEDIATE grade	Adenocarcinoma/Squamous cell carcinoma/ Acinar cell carcinoma	Well differentiated neuroendocrine tumor (G1-G2)
	Amphicrine carcinoma	
HIGH grade	Adenocarcinoma/Squamous cell carcinoma/ Acinar cell carcinoma	Poorly differentiated carcinoma (G3) of small or large cell type
	Adenoma (villous or tubulo-villous)	

CASE REPORTS

MiNEN of the ampulla of Vater

We report the case of a 94-year-old woman, whose main antecedents were hypertension, dyslipidemia and a history of pulmonary embolism in 2012 without long-term anticoagulation. She had no pancreato-biliary history before. She was admitted in our unit for asthenia, abdominal pain, fever and jaundice. Her laboratory tests showed cholestasis and cytolysis associated with hyperbilirubinemia (total bilirubin:162 µmol/L, NV <21; direct bilirubin: 133 µmol/L, NV <4,3) and a light biologic inflammatory syndrome (CRP: 35 mg/L, NV <4; leukocytes: 11,68 G/L, NV <10). Tumor markers were within normal ranges. The contrast-enhanced abdominal CT scan showed a uniform dilation of the main bile duct and intrahepatic bile ducts with a 15 mm hypodense periampullary mass. As well, multiple hypodense hepatic lesions were found, suggesting possible metastatic sites. The Endoscopic Ultrasonography (EUS) revealed a hypertrophied, ulcerated major papillae associated with a double duct dilation view due to an ampullary mass infiltrating the major pancreatic duct and common bile duct. A fine needle biopsy (FNB) was

performed. The Endoscopic retrograde cholangiopancreatography (ERCP) allowed the insertion of an uncovered metallic stent of 10 x 40 mm in the common bile duct (Figure 2). Pathological report revealed the association of a giant cell neuroendocrine tumor infiltrating the mucosa with a high-grade adenomatous lesion, in favor of a MiNEN. In immunohistochemistry, neuroendocrine - synaptophysine (clone 27G12) and chromogranine (clone LK2H10) - and non-neuroendocrine - cytokeratine 7 (clone OV-TL 12/30) and Cdx2 (clone EPR2764Y) - markers were both positive (Figures 1 C-D). Moreover, the Ki67 proliferation index of the neuroendocrine component was 90%. After drainage, a regression of the cholestasis was observed. A theoretical indication of systemic chemotherapy based on Carboplatin and Etoposide was proposed at the multidisciplinary consultation meeting but did not fit with patient's age and status. Patient died 3 months from the diagnosis.

Extrahepatic biliary MiNEN

We report the case of a 68-year-old man, whose main antecedents were hypertension, benign prostatic hyperplasia and L2-L3 disc hernia complicated by ductal stenosis. He was admitted in our unit for symptomatic jaundice. He complained of pruritus associated with fluctuating epigastric abdominal pain, reproduced on palpation. His laboratory tests showed cholestasis (alkaline phosphatase: 220 UI/L, NV <117; Gamma GT: 95 UI/L, NV <68) associated with slight cytolysis (SGOT: 64 UI/L, NV <34; SGPT: 49 UI/L, NV <59), hyperbilirubinemia (total bilirubin: 243 µmol/L, NV < 21; direct bilirubin: 192 µmol/L, NV <4,3) and biologic inflammatory syndrome (CRP: 48 mg/L NV < 4; leukocytes: 13,91 G/L, NV <10). Tumor markers were elevated with ACE 8 µg/L (NV <5) and CA 19-9 392,2 kU/L (NV <37). The contrast-enhanced CT scan and the MRI (Figure 3) showed a perihilar infiltrating mass suggestive for a hilar cholangiocarcinoma (Bismuth-Corlette classification IIIA) associated with a bilobar dilation of the intra-hepatic biliary ducts. There was not any sign of portal or arterial invasion. An endoscopic ultrasound was performed and showed a solid nodule developed on the common bile duct in its subhilar portion. A sphincterotomy was performed allowing the realization of a biliary brush cytology, which revealed both large cells of a neuroendocrine carcinoma and a biliary adenocarcinoma, suggesting a MiNEN. He benefits few days after of a percutaneous bilateral hepatic external drainage, after failure of endoscopic drainage. The PET-scan did not reveal any extra-hepatic secondary lesions. After the approval of the multidisciplinary meeting, a portal embolization of the right portal vein was performed to assure a good future liver remnant. The patient underwent a right hepatectomy extended to segment I and IV ten weeks after the portal embolization, associated with a biliary convergence resection and regional lymphadenectomy. Left biliary duct frozen section revealed low-grade dysplasia and a left hepatic-jejunal anastomosis was realized. Anatomopathological report confirmed the presence of two different components, with a diagnosis of high-grade MiNEN combining large cell neuroendocrine tumor with an adenocarcinoma component (Figures 1 E-F). It was classified as pT3N2R0 with an infiltration of five lymph nodes (5/16). The Ki67 proliferation index, concerning the neuroendocrine component was 85%. After multidisciplinary board discussion, he underwent adjuvant chemotherapy by 6 cycles of Carboplatin and Etoposide. A surveillance was proposed after the end of the therapy with a CT scan every three months. At one year from the intervention, CT scan revealed the appearance of 2 hepatic nodules in segment II, confirmed at MRI and PET-scan. Biopsies were positive for intrahepatic metastases of a high-grade MiNEN with a sarcomatoid dedifferentiation. A FOLFIRI-based chemotherapy regimen was administrated with poor tolerance, replaced thus by FOLFOX. Follow-up is ongoing, with no new imaging reassessment.

This is the first clinical case reporting a sarcomatoid dedifferentiation of metastases of high grade MiNEN. A similar association was described by Kaneko and al, who reported a case of primary hepatic MiNEN associated with gallbladder carcinosarcoma.[5]

Intra-hepatic MiNEN

We report the case of a 73-year-old man, whose main antecedents are diabetes, hypertension, dyslipidemia, chronic obstructive arterial disease requiring several stentings, COPD and transurethral bladder resection. A hepatic nodule localized in the segment IV was accidentally discovered on an abdominal ultrasound. The abdominal MRI confirmed a 42 mm lesion with an arterial enhancement and a rapid washout, typical for a hepatocellular carcinoma (Figures 4 A-B). There were no secondary lesions on the thoraco-abdominal CT scans and no argument for a chronic liver disease. Percutaneous biopsies confirmed the diagnosis of hepatocellular carcinoma. The patient was asymptomatic. There were no perturbation of the liver function tests and no markers of cirrhosis, with, however, an elevated alpha fetoprotein (51,2 µg/l, NV: <7). A surgical resection was indicated and a segmentectomy IV was performed. Anatomopathological report revealed a MiNEN combining a well to moderately differentiated hepatocellular carcinoma with a small cell neuroendocrine carcinoma (Figures 1 A-B). Surgical sections were in healthy tissues. The Ki67 proliferation

index, concerning the neuroendocrine component, was 70%. The multidisciplinary meeting recommended oncological surveillance without any adjuvant treatment. Six months after the intervention, a left pulmonary small cell neuroendocrine carcinoma with cerebral and mediastinal metastases was diagnosed. He rapidly started a systemic chemotherapy based on Carboplatine, Etoposide and Durvalumab.

DISCUSSION

In this article we reported three different cases of MiNEN developed from the hepato-biliary system. These tumors were first reported in 1924 by Cordier.[6] In 2008, the incidence of MiNEN was below 0.01/100,000 cases per year, according to the surveillance of rare cancers in Europe registry. [7] Even if their description dates back to almost 100 years, few data are available in literature with limited series due to their rarity. For instance, only 30 cases of MiNEN of the ampulla have been reported according to a recent systematic review. [8] Part of their rarity could be explained by a hostile diagnosis during biopsy, as the neuroendocrine component is preferentially located in the deepest layers of the mass.[7] Therefore, these tumors are usually underestimated in case of advanced disease, or, otherwise, it is quite frequent to discover a MiNEN on surgical specimen not suspected on biopsy sample.

Due to their rarity and their heterogeneity, their nature is not well known and represents today a challenge for both pathologists and clinicians. Morphologically, MiNEN can be classified into three entities: collision, composite, and amphicrine tumors.[9] Collision MiNEN corresponds to a juxtaposition of two malignant cell populations that do not have a common precursor. Conversely, composite MiNEN involve two malignant cell populations that coexist in an intermingled group. Amphicrine MiNEN is composed of a single cell population that displays the phenotypes of at least two neoplasms.[10] The latter suggests a common origin and precursor, which seems to be less evident for collision or composite MiNEN. Most hepato-biliary MiNEN reported in case reports are combined forms, as confirmed in a recent systematic review based on cases arising from the hepatobiliary system.[11] These phenotypes suggest cito-histologic differences as well as tumoral origin. Three theories have been proposed to clarify the histogenesis of MiNEN.[8] The first one suggests that both neuroendocrine and non-neuroendocrine components arise independently from distinct precursor cells. The second theory supports that the two components derive from a common pluripotent stem cell, able to acquire two different phenotypes during carcinogenesis and the third one postulates a common monoclonal origin of the two components. All of these theories are plausible without any possible confirmation given the considerable lack of clinical data and preclinical models. In the same way, many alterations involving frequent cancer gene drivers or their protein products such as TP53 (tumor protein p53), RB1 (retinoblastoma tumor corepressor 1), PTEN (phosphatase and tensin homolog), APC (adenomatous polyposis coli), PI3KCA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), KRAS (Kirsten rat sarcoma viral oncogene homolog), BRAF (v-raf murine sarcoma viral oncogene homolog B), and MYC (v-myc avian myelocytomatosis viral oncogene homolog) seem to play an essential role in the carcinogenesis of MiNEN.[7] Other well-known repair genes can be deficient, as shown by Lou and al, where the immunohistochemical expression of MMR proteins was lacking in 38,6% of their series, demonstrated to be correlated with a better prognosis.[12] Furthermore, Yeo and al. showed that the neuroendocrine component generally carried 1,5 times more genes mutations than the non-neuroendocrine component, which may be a part of the explication of the worst prognosis of the neuroendocrine component.[13]As their pathogenesis remains controversial, the demonstration of these mutations could allow to the development of new targeted therapies.

Today, the European Neuroendocrine Tumor Society (ENETS) clinical practice guidelines recommend that the management of MiNEN should follow treatment algorithms based on pure neuroendocrine carcinomas, as this component is most poorly differentiated and predominant, both in the primary location and in distant metastatic sites.[14] The first-intent treatment of an advanced disease should include systemic chemotherapy combining etoposide and a platinum salt [8], which was respected in our 2 first case reports given the metastastic dissemination and the high risk of recurrency, respectively. Alternatively, when the exocrine component is the preponderant and/or most aggressive histology, some clinicians choose to apply the standard of care of adenocarcinomas from the same site of origin.[15] Both practices are based on principles of histological analogy but are not supported by evidence from prospective randomized trials. In case of localized MiNEN, surgery should be considered when an R0 resection is possible, achieving good long-term results as shown by Pommergaard and al.[16] Nevertheless, given the low quality of the evidence collected, it is impossible to formulate recommendations on the best management of patients with MiNENs.

The two cases of intra and hilar MiNEN described in this article benefited of a R0 resection, although a regional

lymphadenectomy was not performed in the third case given the presumed diagnosis of HCC. Follow-up showed a rapid recurrence for the patient with hilar MiNEN while the mixed neuroendocrine-HCC presented a metastatic synchronous NET, raising the problem of the effectiveness of current treatments and of its dismal prognosis.

A systematic review addressing all types of MiNEN recently described a median overall survival of 35 months in 69 patients, [7] whereas prognosis seems less favorable in those rising from the biliary tract, with reported OS between 21 and 23 months. [11] Compared to patients with pure NEC of the small intestine and appendix, Shi and al showed a worse prognosis in patients with MiNEN of the same location, whereas there was no significant survival difference in other sites of the gastro-intestinal system, including liver and biliary tracts.[17] Recently, it has been demonstrated that MiNEN with a neuroendocrine major component have a worse clinical outcome than those with an inferior neuroendocrine proportion.[13] Concerning ampullary MiNEN, half of them have an intermediate grade of malignancy, combining well-differentiated G1-G2 NEN with adenocarcinoma components that generally have an intestinal phenotype and a better prognosis rather than bilio-pancreatic adenocarcinoma variants.[18-19]

CONCLUSION

MiNEN originating from the biliary system are extremely rare and recommendations on their management come from a limited number of case reports, with a consequent low quality of evidence. Hence, new studies are needed to understand their etiology and carcinogenesis and, at the same time, refine the standard of care towards these entities.

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