

POORLY DIFFERENTIATED LARGE CELL NEUROENDOCRINE CARCINOMA OF THE GALLBLADDER

Sinaa Mohamed¹, Oukabli Mohamed² and Albouzidi Abderrahmane²

¹Department of pathology, Military Hospital Moulay Ismail, Meknes, Morocco

²Department of pathology, Military Hospital Mohammed V, Rabat, Morocco

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ABSTRACT

Introduction: Neuroendocrine tumors (NET) of the gallbladder are rare. Only 0.2% of all NET of the digestive system are localized in the gallbladder. We report an exceptional case of poorly differentiated large cell neuroendocrine carcinoma of the gallbladder (LCNEC).

Observation: A 54-year-old man, admitted for hepatic colic evolving for 16 months. The ultrasound and the scanner are objectived a vesicular multilithiasic. Cholecystectomy by celoscopy was performed. The pathological study concluded with poorly differentiated a large cell neuroendocrine carcinoma confirmed by the immunohistochemical study.

Discussion: With only eight cases reported in the literature, LCNEC of the gallbladder, part of the NET group, is exceptional. It is probably derived from cells of the diffuse neuroendocrine system (DNES) in a context of chronic inflammation by vesicular lithiasis. The diagnosis of certainty is the pathological and immunohistochemical study. This tumor is often diagnosed fortuitously during cholecystectomy for vesicular lithiasis in the few cases described in the literature. The treatment is essentially surgical. The indication of adjuvant therapy is discussed according to the prognostic factors. The survival at 5 years is 8, 3 %.

Conclusion: Our study give more importance of systematic histological examination of all cholecystectomy specimens. The pathological study remains the only way to confirm the diagnosis, to establish staging and to guide the therapeutic approach.

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INTRODUCTION

Endocrine tumors of the gall bladder are very rare, accounting for less than 1% of gallbladder tumors and 0.2% of endocrine tumors of the digestive tract [1,2]. The poorly differentiated LCNEC, well individualized in the 2010 WHO classification of NET [3,4], is exceptional in the gallbladder and extrahepatic biliary tract with only eight observations described in the literature [5].

Case report

A 54-year-old man, without notable antecedents, had pains in the right hypochondrium evolving for 16 months, without other associated sign. The biological analyse was normal. Ultrasound and abdominal scanner showed a multilithiasic gallbladder with irregular thickened wall [Figure 1]. Cholecystectomy was decided. The macroscopic examination found a gallbladder measuring 12x6x5 cm. At the opening, the presence of multiple lithiasis was noted, the wall was irregularly thickened. The microscopic study showed a proliferation with architecture made of nests, traveled without

glandular formations [Figure 2]. The tumor cells were large, with abundant eosinophilic cytoplasm, reduced nucleocytoplasmic ratio, and an irregular nucleus.



Figure 1 the scanner showing a multilithiasic gallbladder (▲)

The nuclear had a granular chromatin [Figure 3]. The mitoses were estimated at 17 mitoses per ten fields at high magnification. The stroma is endocrinoid. The presence of large foyer of necrosis tumor was observed, without images of vascular embol. The Immunohistochemical complement showed a positivity of the tumors cells to chromogranin A

*Corresponding author: Sinaa Mohamed

Department of pathology, Military Hospital Moulay Ismail, Meknes, Morocco

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[Figure 4] and synaptophysin [Figure 5]. The proliferative index Ki67 was estimated about 40% [Figure 6].

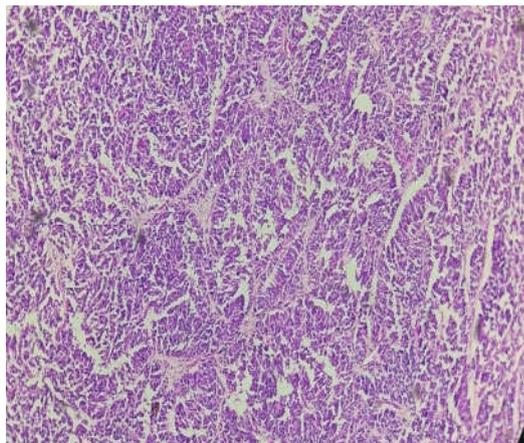


Figure 2 Pathologic findings : The tumor architecture made of nests, traveled without glandular formations (H&E, 200)

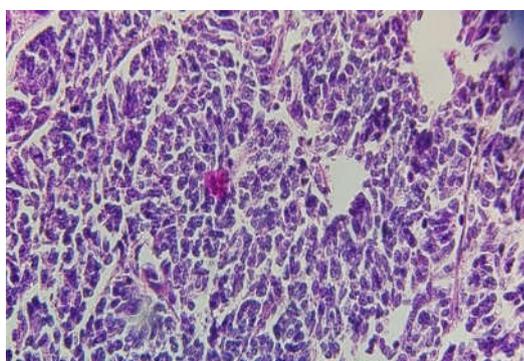


Figure 3 Pathologic findings : Large tumor cells, with an eosinophilic cytoplasm, a reduced nucleocytoplasmic ratio, and an often eccentric nucleus. The nucleus had a granular chromatin (H&E, 400)

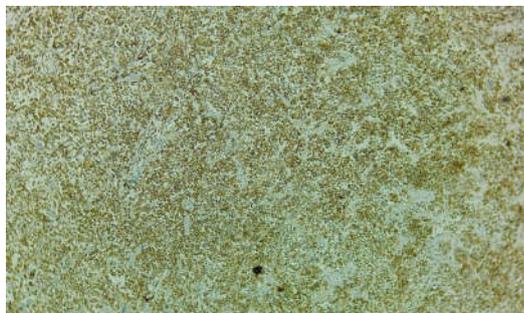


Figure 4 The tumor cells reveal immunopositivity for chromogranin A (x200)

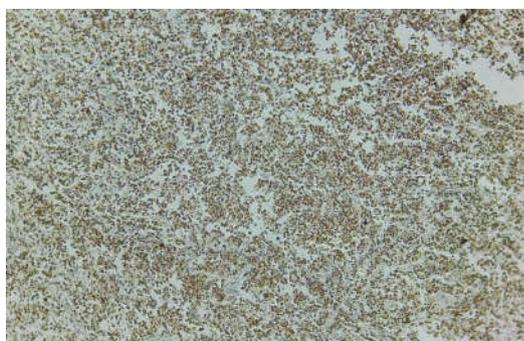


Figure 5 The tumor cells reveal immunopositivity for synaptophysin (x200)

The diagnosis of poorly differentiated neuroendocrine carcinoma with large cells of the gallbladder was retained.

The tumor infiltrated the muscularis. There was no evidence of ganglion at the vesicular collar. The section of surgical section was healthy. The tumor was classified T2N0.

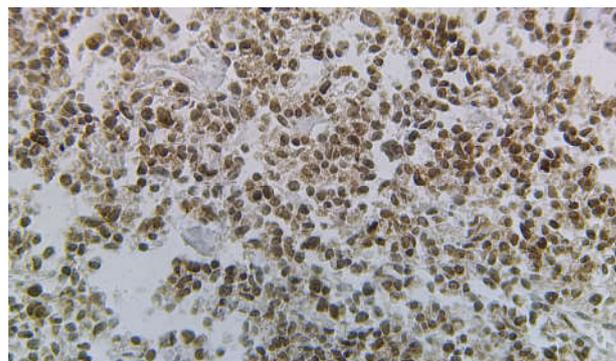


Figure 6 The Ki67 is estimated at 40% (x400)

The Thoracic-Abdominal-Pelvic Magnetic resonance imaging was didn't show any other associated lesion.

The patient didn't receive any adjuvant treatment because the localized stage of the disease, the absence of lymph node, distal metastasis, or vascular embol. Clinical and radiological monitoring for 12 months didn't show any relapse or the occurrence of any secondary lesions.

DISCUSSION

In the gastrointestinal tract, neuroendocrine tumors (NET) are very rare and very heterogeneous, accounting for less than 7% of all digestive system tumors. The most frequent localizations are small intestine and appendix. The localization in the gallbladder accounts for less than 1% of all NET in the digestive system. The WHO classification 2010 distinguished three types of endocrine tumors: neuroendocrine tumors low grade-high grade, neuroendocrine carcinomas (small cell and large cell) and adeno-neuroendocrine carcinoma. The histopathological and immunohistochemical characteristics of these tumors are well defined despite their rarity [2,6,7].

The tumor described in this observation meets the diagnostic criteria for poorly differentiated large cell neuroendocrine carcinoma as described in the 2010 classification of NET [4], a tumor architecture show an endocrine differentiation with a disposition of cells in nests, trabeculae, or palisades, without glandular formation. The cells are large with a low nucleocytoplasmic ratio, granular chromatin, and a nucleus often nucleolated. The mitotic index is more than ten mitoses in ten fields at high magnification. Presence of areas of necrosis in the tumor. The major diagnostic criterion is the expression of two markers of the three neuroendocrine markers: chromogranin A, synaptophysin and CD56. This tumor is easily distinguished from well differentiated large cell neuroendocrine carcinomas by a mitotic index more than ten mitoses in ten fields, by more pronounced cellular atypias and by extensive tumor necrosis [8,9,10]. Small cell carcinomas have the same characteristics as their large cell counterparts and are distinguished by the small cell size (smaller than the diameter of three lymphocytes), a high nucleocytoplasmic ratio, finely granular chromatin without nucleolus and frequent crushing artifacts [1,2,4].

The histogenesis of LCNEC is controversial [11]. Disseminated endocrine cells of the DNES are present in the normal state in the biliary epithelium [8]. They are more

numerous in a context of chronic inflammation by lithiasis [1, 8].

Clinically, like any neuroendocrine tumor, the gallbladder may be secreting or non-secreting [10]. The circumstances of the discovery of neuroendocrine tumors are extremely varied and may be related to the local effect of the tumor if the tumor is non-secreting: right hypochondrium pain, with a large gallbladder. They can be discovered on a piece of cholecystectomy for simple cholecystitis or after surgical treatment of a gallbladder suspected of malignancy. For secreting tumors, the symptoms vary depending on the nature of the secreted peptide [7, 11].

Due to the rarity of this tumor and the lack of knowledge of predictive factors for prognosis, there is no standard protocol for treatment. The latter is essentially surgical with surveillance for localized tumors. Chemotherapy combining cisplatin, etoposide and CPT-11 is indicated for advanced disease, metastatic lymph nodul or vascular embol. The place of radiotherapy is not known. The survival at 5 years is 8, 3 %.

CONCLUSION

We reported the ninth case of a poorly differentiated large cells neuroendocrine carcinoma of the gallbladder. The symptomatology is not specific. The pathological study remains the only way to make the diagnosis, to establish the histo-prognostic factors, and to orient the therapeutic approach. Our study draws attention to a very rare entity and the importance of histological examination of any cholecystectomy for diagnosis of this tumor at an early stage.

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