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SCIENTIFIC LETTER

Neuroendocrine tumour of the gallbladder☆

Tumor neuroendocrino de la vesícula biliar

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms that originate from neuroendocrine system cells, primarily located in the gastrointestinal tract and the lung.[1]

NETs of the gall bladder (NET-GB) are very uncommon: they account for only 2.1% of all gall bladder tumours and are often an incidental finding during the histopathological examination of the gall bladder following a cholecystectomy.[2,3]

We present two cases of NET-GB and discuss the symptoms, diagnosis and treatment of these uncommon tumours.

Case 1: 51-year-old woman with a history of biliary colic. The ultrasound showed cholelithiasis; the blood tests showed no abnormal values. A scheduled laparoscopic cholecystectomy was performed and she was discharged after 24 h with no complications. The histological study showed low-grade 1.6 × 0.7 cm NET, G1, Ki67 1%, with positive chromogranin and cystic node with no signs of malignancy. The CT of the chest and abdomen showed no signs of distant metastases. The chromogranin A figure was <5 ng/ml. There were no signs of recurrence in the annual follow-up at three years with CT and chromogranin.

Case 2: 50-year-old male with a history of type 2 diabetes mellitus, hepatitis C virus infection and schizophrenia, in whom an ultrasound showed a large 1 cm polyp in the gall bladder; the blood tests showed no abnormal values. A scheduled laparoscopic cholecystectomy was performed and he was discharged after 24 h with no complications. The histopathological study showed low grade NET, G1, microcarcinoid, with polyp-like configuration, measuring 3.5 mm, limited to mucosa, Ki67 1.2%, with positive chromogranin and no involvement of the pericystic lymph node (Fig. 1). The CT of the chest and abdomen showed no signs of distant spread. The chromogranin A figure was 130 ng/ml. There were no signs of recurrence in the annual follow-up at two years with CT and chromogranin.

NET-GB account for 0.5% of all NETs and are more common in women (68%). The age of onset varies from 26 to 79 years.[4]

There are two theories regarding the origin of NET-GB. One postulates that they could originate from multipotent stem cells, ectopic pancreatic tissue or nerve fibres located in the wall of the gallbladder, while the other proposes that they originate from neuroendocrine cells (enterochromaffin or Kulchitsky cells) in the intestinal or gastric metaplasia of the gallbladder epithelium, produced after chronic inflammation caused by cholelithiasis.[3]

Non-functioning NETs are indolent, generally give rise to symptoms derived from the mass effect such as abdominal pain and jaundice. They tend to be diagnosed in advanced stages, with metastasis in approximately 40% of all cases.[1] Functioning NETs can cause a wide range of signs and symptoms due to hormonal hyperactivity. Carcinoid syndrome, characterised by flushing, hypotension, diarrhoea, wheezing and heart disease caused by serotonin, has been reported in less than 1% of cases of NET-GB.[4]

NET-GB is rarely diagnosed pre-operatively. By extrapolation of NETs of the digestive tract and pancreas, for NETs the cancer staging manual (version 3.2018) of the American Joint Committee on Cancer recommends CT or MRI and, as appropriate, images based on somatostatin receptors (preferably PET or scintigraphy), CT of the chest and serum chromogranin or 5-HIAA in urine.[5]

In NET-GB, however, the diagnosis is usually incidental from the histopathological study and the immunohistochemical staining of a surgical specimen taken from a cholecystectomy scheduled due to cholelithiasis or cholecystitis, and only studied by abdominal ultrasound.[1] These two cases were only identified in the histopathological study after cholecystectomies indicated for cholelithiasis. The histological diagnosis should include morphology (large versus small cells and differentiation), staining for chromogranin A and synaptophysin, Ki-67 and mitotic count. This facilitates their classification as: low grade, differentiated (G1, Ki-67 index <3%); intermediate grade, moderately differentiated (G2, Ki-67 index $\geq$3% and $\leq$20%); poorly differentiated high grade neoplasms (G3, Ki-67 index >20%), small or large cell.[1,4]

The most commonly used serum marker is chromogranin A, secreted by neuronal and neuroendocrine cells. It can be elevated in patients with kidney or liver failure and in patients treated with proton pump inhibitors.[5] Chromogranin B, neuron-specific enolase and quantification of 5-HIAA in urine can also be useful.[1] They should only be used to support the diagnosis and as indicators of tumour burden and response to treatment.

Resection is the primary treatment approach.[5] Cholecystectomy is usually sufficient if the cystic node is negative and there is a free margin; otherwise, the surgery should be extended[1] and more intensive treatment considered, based

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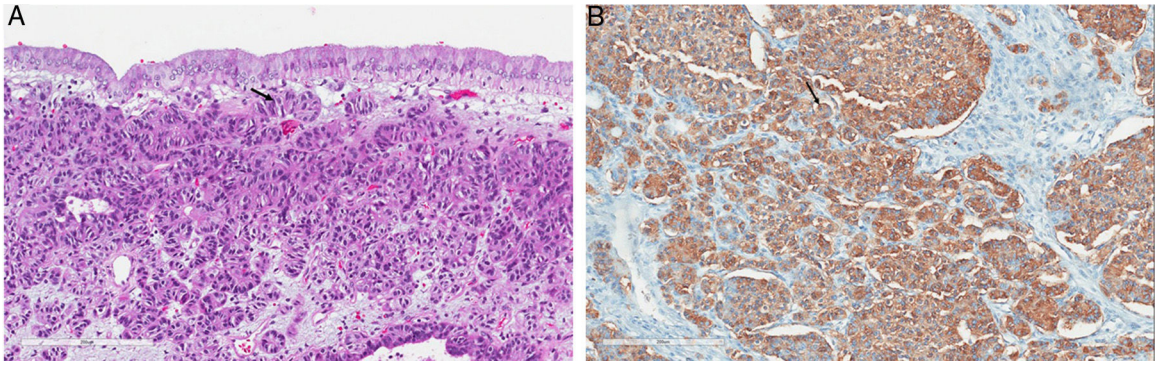

Figure 1 A) The tumour grows beneath the surface epithelium, forming small nests and trabeculae. The cells are of uniform size, with slightly eosinophilic cytoplasm and an ovoid nucleus, with no significant atypia (H&E). B) Immunohistochemical staining for chromogranin: intense cytoplasmic positivity is seen in the neoplastic cells.

on regional lymphadenectomy or IVb-V bisegmentectomy. Adjuvant therapy is recommended in patients with a Ki-67 value of >20–55%, which is more effective for the small cell subtype. Specific prognostic factors have not been identified in NET-GB, but the proliferative index, differentiation and tumour size are global prognostic factors.[1,4]

According to the NCCN Guidelines, serum chromogranin or 5-HIAA in urine should be analysed and a CT or MRI should be performed between three and 12 months post-resection and every 12–24 months.[5]

The five-year survival rates for advanced disease are currently 77–95% when treated with primary tumour resection and adjuvant therapy. However, more aggressive subtypes have been reported, with a fast clinical course in which survival and prognosis are considerably worse.[1]

In conclusion, NET-GB are uncommon and generally non-functioning. They tend to be diagnosed in the histopathological study of the gallbladder after cholecystectomy due to cholelithiasis. The cystic node should be studied to decide whether to use the lymphadenectomy or IVb-V bisegmentectomy approach and adjuvant therapy should be considered based on the proliferative index.

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Endoscopic submucosal dissection for localised gastric amyloidosis mimicking malignancy

Disección submucosa endoscópica para la amiloidosis localizada gástrica que simula una malignidad

Amyloidosis is characterized by the extracellular deposition of insoluble amyloid fibrils, which commonly results in systemic organs dysfunction. A single organ or tissue involved is uncommon, especially regarding the gastric localised amyloidosis. The lesion may manifest as erosions, ulcerations, nodular mucosa or polypoid protrusions. However, the specific treatment for localized amyloidosis has not been established. We present a case of gastric localized amyloidosis mimicking malignancy, in which endoscopic submucosal dissection (ESD) was successfully done with the guidance of multiple endoscopic imaging techniques.

A 54-year-old man presented with occasional postprandial epigastric discomfort for several months. Esopha-