Ultrasound calcifications in gallbladder lesions as a sign of suspected neuroendocrine tumour of the gallbladder

Calcificaciones ecográficas en lesiones vesiculares como criterio de sospecha de tumor neuroendocrino de vesícula biliar

Gallbladder neuroendocrine tumours (GB-NET) are very rare. According to data published in the Surveillance, Epidemiology and End Results (SEER) database, they account for 0.5% of all neuroendocrine tumours (NET) and 2.1% of gallbladder tumours.[1] However, a retrospective analysis of SEER data from 1973 to 2016 shows an increase in their incidence of 7% per year in this period.[2]

These days, GB-NET are usually found by chance in cholecystectomy specimens, and pre-surgical diagnosis is uncommon due to the limitations of tumour markers and imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), which make it difficult to properly diagnose.[3] The main diagnostic technique is therefore immunohistochemistry on the cholecystectomy specimen, with the most specific tests being chromogranin A (CgA), synaptophysin and neuron-specific enolase.[4]

We present a case report of a GB-NET with the finding of calcifications on preoperative ultrasound that led to malignancy being suspected.

This was a 51-year-old woman, former smoker, with a previous history of idiopathic epilepsy. Her family history included her mother, who died of pancreatic cancer, and her father, who died of hepatocellular carcinoma; both having had an alcohol habit. She went to the Accident and Emergency department repeatedly for a year and a half complaining of pain radiating from her right hypochondriac region, nausea and weight loss, with no associated laboratory abnormalities. As a bile duct disorder was suspected, an ultrasound scan was performed, identifying microlithiasis in the gallbladder. In a later magnetic resonance cholangiography scan, only biliary sludge was observed. A second ultrasound revealed a sessile hypoechoic image with an immobile peripheral calcification 13 mm in size, consistent with a polyp (Fig. 1). As malignancy could not be ruled out, a laparoscopic cholecystectomy was performed. The surgical specimen showed a brown polypoid formation in the gallbladder 0.5 × 0.3 cm in size, with free surgical margins, without vascular or lymphatic invasion. Immunohistochemical staining was positive for CK8/18, chromogranin and synaptophysin, and negative for inhibin. It was a G1 well-differentiated GB-NET (Ki-67 = 1%; TNM stage: pT1a). As a staging study, the patient underwent a CT of the chest, abdomen and pelvis, which did not identify distant spread, and somatostatin receptor scintigraphy, without pathological uptake. Successive testing of 5-HIAA and CgA were within the normal ranges. A MEN-1 mutation study was performed, with negative results. The patient is in biochemical and radiological remission, and remains asymptomatic after 6-months follow-up.

GB-NET are more common in females than in males (65.6% versus 34.4%), with a mean age of onset of 65.2 ± 14.3 years. Advanced disease (regional and distant) is found in around 60.3%, meaning they are aggressive tumours.[2]

The origin of GB-NET is unknown, as there are no neuroectodermal cells in this location,[5] but there are several theories as to how they form[3]:

1) Undifferentiated stem cells transform into neoplastic neuroendocrine cells.
2) Degeneration of an adenocarcinoma.
3) Chronic inflammation caused by cholelithiasis and chronic cholecystitis could lead to gastric or intestinal metaplasia with neuroendocrine cells, ultimately generating a GB-NET.

In most reported cases, carcinoid syndrome is anecdotal, with non-specific symptoms being more common (for example, abdominal pain, nausea, vomiting),[3] which, together with low-sensitivity diagnostic tests (tumour markers and imaging tests), makes it difficult to diagnose. Ultrasound only detects alterations in the thickness of the wall, bladder lesions and hypoechoic nodules, while in reported CT and MRI studies, the most common alteration was the greater enhancement of the lesion compared to adenocarcinomas, the main alternative in the differential diagnosis.[6] In adenocarcinomas, the most common ultrasound finding is wall thickening, followed by a space-occupying mass. The presence of calcifications is unusual, except where there is coexistence of cholelithiasis or porcelain gallbladder.[7] The most cost-effective tool for diagnosis is therefore immunohistochemistry on the surgical specimen. Pathology examination also allows them to be classified, according to the rate of tumour proliferation evaluated by the Ki-67 index, as: low grade/differentiated (G1, Ki-67 index <3%); intermediate grade/moderately differentiated (G2, Ki-67 index ≥3% and ≤20%); or high-grade neoplasms (G3, Ki-67 index >20%), which, according to their differentiation, are subdivided into well-differentiated or poorly differentiated (neuroendocrine carcinomas [NEC]).

Older age, spread, histological grade and early surgery are the main prognostic factors; early diagnosis is therefore essential for establishing the right management plan. The main treatment is surgery, aiming for complete resection (R0).[2] Chemotherapy based on regimens of streptozocin, 5-fluorouracil, adriamycin, cisplatin and etoposide is indicated in high-grade/poorly-differentiated GB-NET and NEC in which surgery is not possible, as well as in association with adjuvant radiotherapy of the NEC.[8] As with other NET, somatostatin analogues have been used in low-grade GB-NET.[9] Radionuclide therapies (Lu-177, Y-99) have also been used, as well as locoregional techniques such as ethanol injection and radiofrequency in liver metastatic lesions. Targeted therapies are not yet available.[3]

Detection of calcifications in imaging techniques has been reported in gastrointestinal and bronchial NET[3]; in pancreatic NET, calcifications have also been correlated with a higher histological grade and a more advanced stage,

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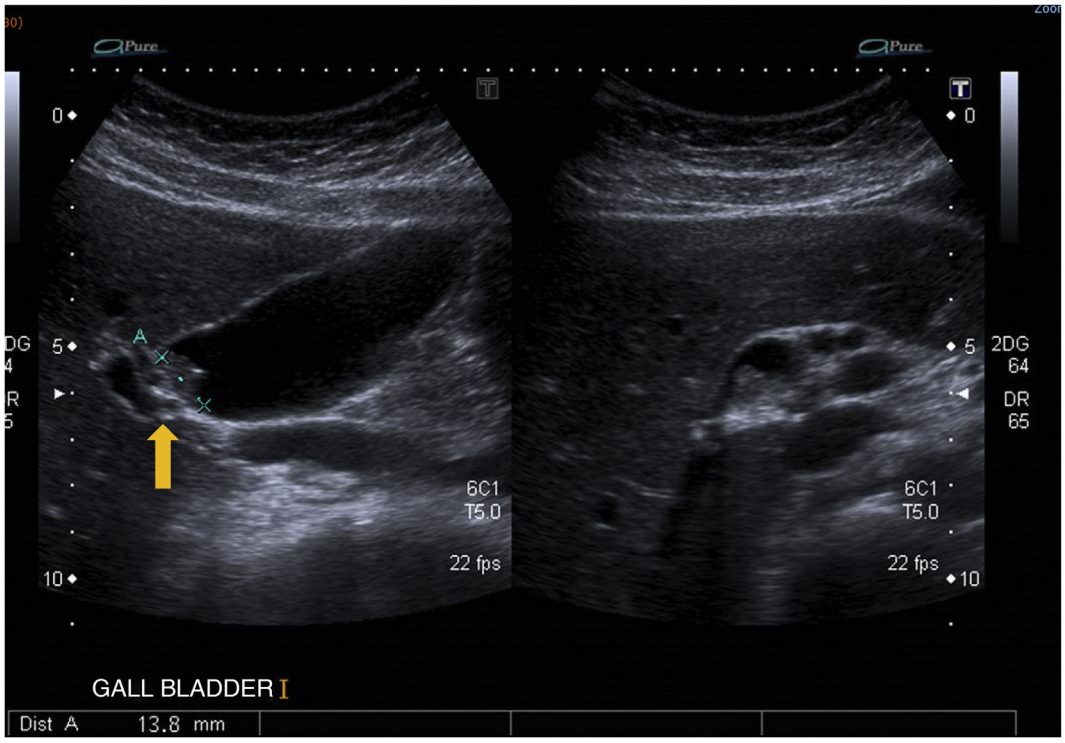

Figure 1 Abdominal ultrasound showing a sessile hypoechoic image in the gallbladder with a peripheral calcification 13 mm in size, consistent with a polyp (indicated by the arrow).

being an independent pre-surgical predictor of lymph node metastasis.[10] However, to our knowledge, there are no published cases, either nationally or internationally, of patients with GB-NET who have visible calcifications on imaging studies. In conclusion, we have presented a case in which the finding of calcifications could establish the basis for suspecting malignancy of possible neuroendocrine origin, given the low frequency of calcifications in other histologies. This would enable early diagnosis, along with the determination of markers such as chromogranin, and earlier treatment, thus improving the prognosis.[2]

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Pendred's syndrome diagnosed in adulthood at the high resolution thyroid clinic

Síndrome de Pendred diagnosticado en la edad adulta en la consulta de alta resolución de patología tiroidea

Congenital deafness affects 1–3/1000 live births. Over 50% of cases can be attributed to genetic causes, among which 30% correspond to syndromic causes.[1] Of these, Pendred syndrome (PS) is one of the most common, accounting for up to 4–10% of cases.[2]

We present the case of a 20-year-old woman referred to our Department's high-definition thyroid disease clinic after an ultrasound thyroid scan had been performed on her at another centre for goitre detected in an occupational health check-up. The patient reported having had a non-compressive goitre with no symptoms of thyroid dysfunction for 2 years. As history of interest, she was suffering from moderate-to-severe sensorineural deafness diagnosed 2 years earlier. An ear CT at the age of 8 showed a vestibular aqueduct dilation associated with mild cochlear dysplasia and a deficiency in the modiolus. She had a history of thyroid carcinoma in a maternal aunt and primary autoimmune hypothyroidism in a paternal grandparent, without being able to obtain further data owing to lack of contact with them. She was taking no medication, nor was she consuming any goitrogens.

Upon physical examination, she presented an irregular class III goitre. The ultrasound showed an enlarged thyroid, with 3 nodules on the left thyroid lobe (N1: 1.67 × 3.13 × 2.48 cm; N2: 1.2 × 1.34 × 1.84 cm and N3: 1.34 × 1.34 × 1.96 cm) and 2 on the right lobe (N4: 0.7 × 1.64 × 2.06 cm and N5: 0.92 × 1.96 × 1.82 cm). All of them were well delimited, with hypoechogenic halo, spongiform aspect, except for N2 which was solid and isoechogenic, and with peripheral vascularisation in N2 and mixed vascularisation in the remaining nodules (Fig. 1).

The blood chemistry showed a TSH of 3.94 μIU/mL (NV: 0.35–4.95 μIU/mL), free thyroxine of 0.75 ng/dl (NV: 0.70–1.48 ng/dl), serum thyroglobulin 1,926.00 ng/mL (NV: 3.50–77.00 ng/ml), 24 -h urinary iodine h of 208.1 μg/l (NV: 100.00–199.00 μg/l) and negative anti-thyroid peroxidase and anti-thyroglubulin antibodies.

In light of the suspicion of PS owing to the coexistence of sensorineural hearing loss and goitre, a genetic study was requested, which was positive, with 2 variants being found (c.1198delT and c.1226 G > A) in biallelic expression (compound heterozygosity) in the SLC26A4 gene.

PS is an autosomal recessive disorder characterised by sensorineural hearing loss, goitre, and a partial iodide organification defect. The mutation arises in the SLC26A4 gene at the 7q22.3 locus, responsible for codifying pendrine, a glycoprotein located in the apical membrane of the thyrocytes, where it acts as an iodide transporter, which gives rise to a disruption in thyroid hormone synthesis. Pendrine is also expressed in the kidney and inner ear.[2] The molecular analysis of the SLC26A4 gene is currently considered the gold standard for establishing the diagnosis of PS, owing to the lack of standardisation, and on occasion availability, for performing the perchlorate discharge test

Sensorineural Deafness is a consistent finding in PS, while goitre may be absent in certain cases.[3–5] The predominant thyroidal involvement in PS is goitre, which is present in 50–83% of cases, starting in late infancy and adolescence, diffuse, increasing in size until the appearance of nodules in adulthood. The size of the goitre is variable, depending on iodine intake, reaching large goitres with endothoracic extension. The treatment of rapid-growth compressive goitre with suspicious or malignant nodules is surgery. Up to 30–50% of cases require surgery, which must be a total thyroidectomy, since if a sub-total thyroidectomy is performed, growth over time in the remainder is observed owing to the persistence of pathogenic factors.[5,6]

Thyroid function is variable, depending on iodine intake. Thyroid dysfunction does not usually appear if there is sufficient iodine intake in the diet. 50% of cases present normal thyroidal function, and 30–50% subclinical or clin-

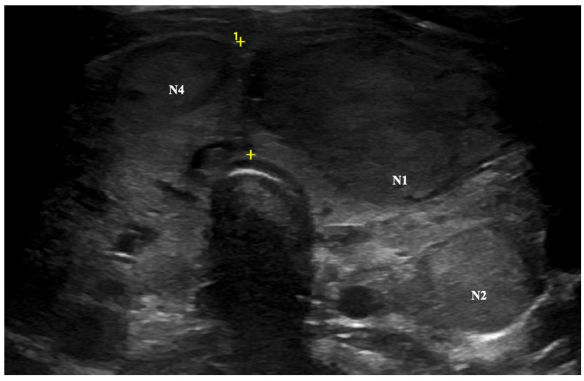

Figure 1 The patient's thyroid ultrasound scan. In this cross section, N1, N2 and N4 can be seen.

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