CASE REPORT

Malignant neuroendocrine tumour of the gallbladder with elevated carcinoembryonic antigen: case report and literature review

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SUMMARY

A 58-year-old woman presented to a tertiary care centre with signs and symptoms of acute cholecystitis, cholelithiasis and diagnoses of a high-grade neuroendocrine tumour of the gallbladder primarily with peritoneal and liver metastases. She had a liver abscess secondary to *Salmonella* and *Enterococcus fecalis* that was drained and treated with appropriate antibiotics. Interestingly, the serum chromogranin A levels were within normal limits, but carcinoembryonic antigen was elevated, which helped evaluate responses and pick progression. She was treated with 10 cycles of palliative chemotherapy when malignancy associated complications started to recur, that is, cholangitis, worsening pain, cachexia, intestinal obstruction, etc leading to chemotherapy delays. Her disease progressed during these times with rapid deterioration of performance status. She died of septic complications postlaparotomy for intestinal obstruction. Her progression-free survival remained for 8 months with subjective and objective improvements, and her overall survival remained at 13 months. We describe the course of her illness and give a brief review of the literature.

BACKGROUND

Neuroendocrine tumours (NET) are complex neoplasms that originate from a heterogeneous diffuse endocrine system and are composed of highly specialised cells of endodermal origin. These provide the richest source of regulatory peptides outside the brain. The precursor cells 'enterochromaffin cells' are distributed throughout the GIT, bronchus, endocrine glands and skin, etc. The neoplasm arising may be relatively benign 'typical carcinoids' or a highly aggressive malignant counterpart like a 'small-cell or large-cell NET'. Only rarely are these associated with secretion of neuropeptide hormones and carcinoid syndrome (~1%).¹ The incidence of gallbladder carcinoids and malignant NET is exceedingly low (0.5% of all NET).¹ Tumour markers, including serum chromogranin A and quantitative urinary 5 hydroxyindoleacetic acid (5HIAA),² are measured to assess response to therapy and for predicting recurrence or progression. Elevation of serum carcinoembryonic antigen (CEA) is uncommon, which remains a specific marker for adenocarcinoma, for example, colorectal cancer, thyroid medullary carcinoma, etc. Elevated CEA may also be seen with liver disease, peritoneal involvement and cholecystolithiasis.³ We describe the first case of malignant NET of the

gallbladder with elevated CEA and normal chromogranin A, which was managed at Sultan Qaboos University Hospital in Muscat (SQUH), Sultanate of Oman.

CASE PRESENTATION

A 58-year-old housewife presented to the surgery department of SQUH in August 2011 with right-upper quadrant abdominal pain radiating to the right shoulder, anorexia and weight loss. On examination, she was found to have an Eastern Cooperative Oncology Group performance status 2, pallor, right-upper abdominal drain with pussy discharge (20 ml), tender hepatomegaly, and coarse right-basal crepitations. The impression was acute on chronic cholecystitis with cholelithiasis. White cell count was high with absolute neutrophilia. Liver functions were mildly deranged but urea electrolytes were within normal limits. The accompanying CT images of the abdomen revealed fatty infiltration of the liver, a thick-walled gallbladder containing multiple stones and a hypoechoic mass in the region of the gallbladder. An attempted laparoscopic cholecystectomy was carried out elsewhere in June 2011, and the per-operative findings were: contracted gallbladder containing stones and associated mass, multiple liver and peritoneal nodules. The procedure was abandoned because of unresectability, and biopsies were taken from the mass and peritoneal nodules.

INVESTIGATIONS

The histology was consistent with malignant tumour with necrosis. The slides review at our hospital confirmed the diagnosis: a tumour composed of solid sheets of pleomorphic cells, with hyperchromatic nuclei and irregular nuclear membrane with focal areas of necrosis. The malignant cells were positive for CD 56, PGP 9.5, synaptophysin and background staining with NSE (figure 1A,B) but negative for CK, vimentin, CD 99, bcl 2, desmin and LCA. The results were consistent with high-grade NET, that is, small-cell carcinoma of a quite likely gallbladder origin.

The patient was referred to the Oncology section of SQUH, where a repeat staging CT revealed a small proximal gallbladder mass, multiple stones with hepatic metastatic lesions in segments 4 and 5 with reduction in the segment 6 lesion and intrahepatic and extrahepatic biliary dilation (figure 2A).

There was significant peri-portal, peri-pancreatic, aortocaval and para-aortic lymphadenopathy. Bone

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Figure 1 (A) H&E stained section at ×40 magnification. (B) Synaptophysin IHC stain.

scintigraphy was unremarkable and the baseline CEA was 723 µg/l, while the baseline and serial serum chromogranin A levels were within normal limits.

TREATMENT

The patient was started on standard palliative chemotherapy, that is, carboplatin/etoposide, in September 2011. She tolerated 10 cycles of the same regimen without any grade 3 or 4 side effects and with marked subjective and objective responses. Her pain intensity scores regressed with reduction in opiate demand, and interval imaging revealed a nearly 30–40% reduction in the metastatic liver lesions and a further reduction in biliary dilation (figure 2B). CEA levels declined on serial measurements (figure 3).

She was running fever and having increasing right hypochondrial pain and mild jaundice with impression of cholangitis in May 2012. Ultrasound imaging confirmed CBD stone leading to aggravation in her symptoms. Palliative chemotherapy was withheld; a sphincterotomy was done with successful removal of a solitary stone through endoscopic retrograde cholangiopancreatography (ERCP) and the patient was discharged in a stable condition. Unfortunately, she presented back through emergency after 1 week with similar complaints. At repeat ERCP, the scope failed to pass through the sphincter of oddi due to the presence of a tight stricture from a tumour invading the duodenum at D2 from the outside, which was subsequently dilated to 15 mm. The patient was managed conservatively with intravenous

Figure 2 Pre-chemo CT image, 8 July 2011: a diffuse infiltrative lesion involving the anterior aspect of the right lobe of the liver measuring approximately 10 cm in the longest dimension with another mainly degenerated lesion seen posteriorly located in the right lobe of the liver involving segment VI and segment VII measuring 7.5 cm in the longest dimension. Multiple upper abdominal lymphadenopathies are seen especially around the origin of the superior mesenteric.

Figure 3 Carcinoembryonic antigen graph.

infusion morphine and antibiotics. A biochemical failure was seen with CEA rising to 102.6 µg/l. Repeat CT imaging was suggestive of frank disease progression in the retroperitoneal lymph nodes and liver and the appearance of new metastatic deposits in the peritoneum and spleen (figure 2C,D). Her performance status declined to 4, with anorexia, marked weight loss and cachexia, and was managed with best supportive care and discharged in June. The progression-free survival was 8 months.

OUTCOME AND FOLLOW-UP

She returned through the emergency SQUH to the surgery department in July 2012, with increasing abdominal girth and pain after recent exploratory laparotomy in the UAE, for gastric perforation due to ulcer, which was managed with Graham patch repair and placement of an IVC filter. On examination, wound dehiscence was found with acute abdominal obstruction, as well as evidence of air under the diaphragm. Her abdomen was re-explored and closed. Per-operatively massive gastric dilation (atonia) with pneumatosis gastricus was found with extensive small peritoneal seedlings from the tumour. Her postoperative recovery was complicated by pneumonia, overwhelming sepsis, DIC and electrolyte imbalance leading to SVT. She breathed her last on 13 September 2012 with an overall survival of 13 months.

DISCUSSION

We report the first case of a malignant NET of the gallbladder in Oman with elevated CEA levels. NET of the gallbladder is an extremely rare neoplasm,⁴ thought initially to be derived from cells which migrated from the neural crest, but are now considered to be arising from the enterochromaffin cells of the diffuse endocrine system present throughout the GIT and confined to the neck of the gallbladder. The first carcinoid tumour reported in the literature was way back in 1929.⁵ NET usually involves the gastrointestinal tract (67.5%) of which the appendix, small gut (41.8%), rectum (27.4%), stomach (8.7%), pancreas (1%), colon, etc, remain the common sites. These may also involve the bronchopulmonary (25.3%) or thymic epithelium, the endocrine glands such as the pituitary, parathyroid, thyroid, adrenal, prostate glands and the skin. The gallbladder mucosa in the fundus and body is devoid of neuroendocrine cells, which may appear after intestinal metaplasia⁶ due to chronic inflammation, for example, gallstones, and helicobacter pylori⁷ or congenital anomalies, for example, anomalous union of the pancreaticobiliary duct, or heterotopic gastric mucosa of the gallbladder.⁸ Only 1–4% are reported to be functional tumours associated

with the carcinoid syndrome and the symptoms are usually secondary to the tumour mass. Unfortunately, the gallbladder was not removed in this case.

The malignant transformation is thought to be due to the activation of oncogenes or the inactivation of tumour suppressor genes leading to the inhibition of apoptotic pathways.⁹ Downstream cell signal transduction pathways including PI3k, pTEN and mTOR, etc through the activation of VEGF, EGF and IGF receptors are implicated in carcinogenesis.¹⁰ NETs may occur either sporadically or as part of familial syndromes, MEN 1 and MEN 2 syndromes. Other genetic and epigenetic changes may also occur involving the VHL and NF1 genes and ret proto-oncogene, etc. NET possess specific receptors at the cell membrane, that is, somatostatin receptors, which help in identifying and localising these tumours and provide targets for octreotide and radiolabelled therapy.

Unlike typical carcinoids, which in 50% of cases are localised to the gallbladder, the malignant counterparts are aggressive, metastasise early and associated with poorer outcome like in our case. The median survival with metastases from the gallbladder small-cell carcinoma is 5 months and 5-year survival is 0–5%.¹¹ Prognoses of the NET varies with tumour size, differentiation, site, secretion of hormones and stage.¹² The current nomenclature and classification system for NET are well described,^{13 14} and divide NET according to the grade of differentiation, tumour size, presence of vascular invasion, or invasion of muscularis propria, Ki67 (cancer cell proliferative index) and metastases. Well differentiated or grade 1 tumours have <2 mitoses/10 HPF and Ki 67<2% (typical carcinoids); intermediate or grade 2 tumours have mitoses between 2 and 20/HPF and Ki67 of 3–20% (atypical carcinoids). High-grade tumours or grade 3 have mitoses >20% and Ki67>20% (small-cell carcinoma and large-cell NET). Our patient was a case of small-cell NET on immunostains. The age of our patient was 58 years, which is well within the range of 38–81 years,¹⁵ with a female preponderance¹⁶ described in the literature. The common mode of presentation is non-specific vague abdominal pain more on the right, so typical of cholelithiasis,¹⁷ and our patient typically presented like this with pain radiating to the right shoulder. Carcinoid syndrome (exceedingly rare and usually from the foregut primary) presents with malar flush, loose motions, bronchospasm, retroperitoneal and cardiac fibrosis due to ectopic hormonal secretions. High-grade NETs are usually non-functional like this case. Imaging cannot identify NET, but NETs usually have elevated serum chromogranin A and quantitative urinary 5HIAA levels (>15 mg/24 h). These markers have 100% specificity but low sensitivity.

Interestingly, there is limited information on serum CEA,¹⁸ which was found to be elevated in our case and was serially followed for response evaluation and predicted progression, which were subsequently confirmed by imaging. Carcinoids may secrete a number of other peptides and hormones including: serotonin, NSE, pancreatic polypeptide, calcitonin, substance P, neurokinin A, prostaglandin A, E and D, histamine and pancreastatin, etc. Medullary thyroid carcinoma may also present with carcinoid-like syndrome producing calcitonin, CEA and prostaglandins, while certain pituitary tumours secrete prolactin.

In practice ultrasonography, CT imaging of the hepatobiliary area and MRCP are highly sensitive in identifying and estimating the extent of disease in the regional lymph nodes, liver and soft tissue, etc. Bone scintigraphy has a high sensitivity to pick bone metastases. Novel imaging techniques including [18F]-fluorodeoxyglucose positron emission tomography/CT (PET/CT) and gallium dotatate scintigraphy can be helpful in

staging and response evaluation in some patients in all categories of NETs.¹⁹ Tumours can also be imaged using octreoscan²⁰ and if lights up can be effectively palliated with octreotide. Our patient did not have a functional tumour and was already metastasised to the regional lymph nodes, liver and peritoneum but not to the bones. The most common sites of metastases in high-grade NETs are regional lymph nodes, liver and bones. The brain remains a sanctuary site. Localised tumours (T1) undergo surgery with negative margins (R0 resection) using laparoscopic or open cholecystectomy, while extended cholecystectomy is reserved for higher stages. The G1–2 tumours are slow-growing tumours that typically do not respond to chemotherapy or radiotherapy, and therefore adjuvant therapy is not warranted.²¹ In a metastatic setting, octreotide LAR²² and/or mTOR inhibitors, for example, everolimus,²³ may be used effectively where the latter is associated with ~5 months improvement in the PFS. By virtue of the presence of somatostatin receptors, radiolabelled somatostatin may also be used for palliation and disease control, as these may be visualised by octreoscan or Ga68 Dotate PET/CT. Patients with inoperable carcinoid tumours that are growing, or whose symptoms are not well managed by somatostatin analogues, can also be effectively treated with radiolabelled therapy. At least three radiopeptides are available: Indium111,²⁴ Yttrium90²⁵ and Lutetium177 destroy carcinoids after selective uptake by emitting β or γ rays. High-grade NETs are aggressive counterparts but rarely functional like in our case. Localised disease is best managed with or without surgery using definitive treatment in line of small-cell lung carcinoma including chemotherapy comprising etoposide cisplatin or carboplatin.

The response rates to chemotherapy vary between 40% and 70%,²⁶ while topotecan, irinotecan, taxanes, gemcitabine, etc are reserved for salvage. Chemotherapy remains the treatment of choice for metastatic diseases like ours, using the same drug combinations. Local irradiation is reserved for consolidation, palliation of pain due to bone metastases, cord compression and prophylactic radiation to prevent an impending fracture. Liver metastases may be palliated using surgery, radiofrequency ablation, transarterial chemoembolisation, transarterial-radioablation or cryoablation. The median survival had been reported to be 9.8 months in 278 gallbladder NETs reported in SEER, while a 5-year survival rate for small-cell cancer remains dismal (0%) in one report.

Learning point

High-grade neuroendocrine tumours (NETs) are aggressive neoplasms associated with median survival of less than a year. The data on gallbladder NETs are scarce and treatment is crafted from case series or reports from small-cell lung cancers. Chemotherapy in advanced stage disease provides effective palliation, but the disease remains a therapeutic challenge for researchers in the oncology community.

Competing interests None.

Patient consent Obtained.

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