Survival : a rare outcome in large cell neuroendocrine carcinoma of the gallbladder

E. Shapera[1], C. Bitting[2]

(1) Department of Surgery, Sunrise Consortium ; (2) Department of Pathology, University of New Mexico.

Abstract

Large cell neuroendocrine carcinoma of the gallbladder is extremely rare. We present a case report and review of literature. We report the rare outcome of survival at 19 month follow-up and hope to raise awareness about this lesion, its treatment modalities and lend credence to the proposed mechanism of its pathogenesis. (Acta gastroenterol. belg., **2019**, 82, **433-436**).

Introduction

Large cell neuroendocrine gallbladder carcinoma is rare with poor prognosis. Its pathogenesis is a topic of debate as the gallbladder is not a known source of neuroendocrine cells. Most reported cases result in mortality. We present a case of survival with 19 months follow up and a hypothesis of its pathogenesis

Case Report

A 65 year old female with 10 months of epigastric pain unrelated to meals presented to an outside hospital. Her past medical history was remarkable for hypertension, hyperlipidemia and diabetes mellitus type II. She had undergone a lumpectomy, hysterectomy and bladder repair (all benign). The patient smoked 1 cigarette per night, drank 1-2 alcoholic drinks per day, had no asbestos exposure, but did report a chemical exposure of unknown type while working with aircraft electrical equipment. On physical exam she was obese. An abdominal ultrasound

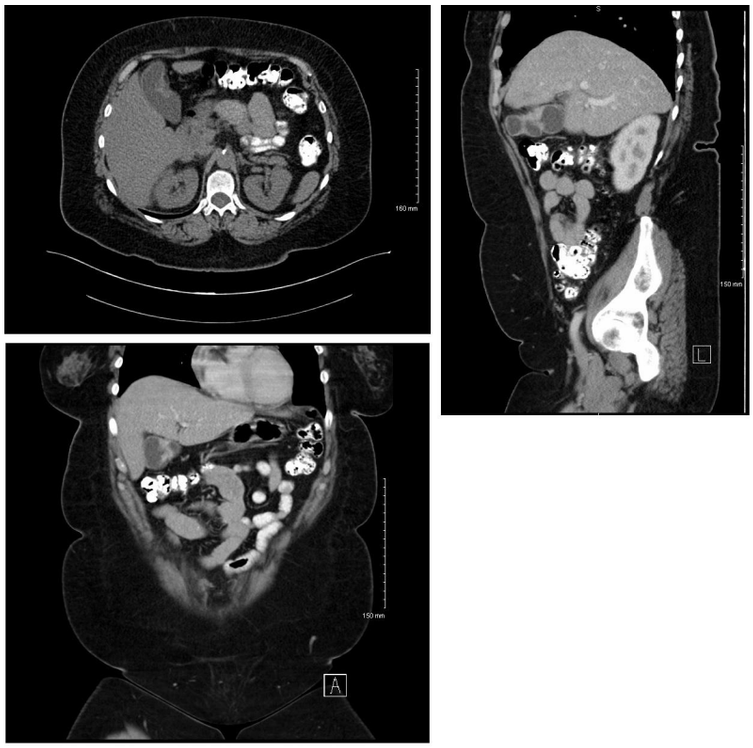

Figure 1. — From top-left clockwise: Gallbladder architectural distortion with Axial slice (a), Sagittal slice (b) and Coronal slice (c).

Correspondence to : Emanuel Shapera, 2880 North Tenaya Way, 2nd Floor, Las Vegas, Nevada 89128. Phone : 619 274 6255.
E-mail : emanuelshapera@gmail.com

Submission date : 10/07/2016
Acceptance date : 29/12/2017

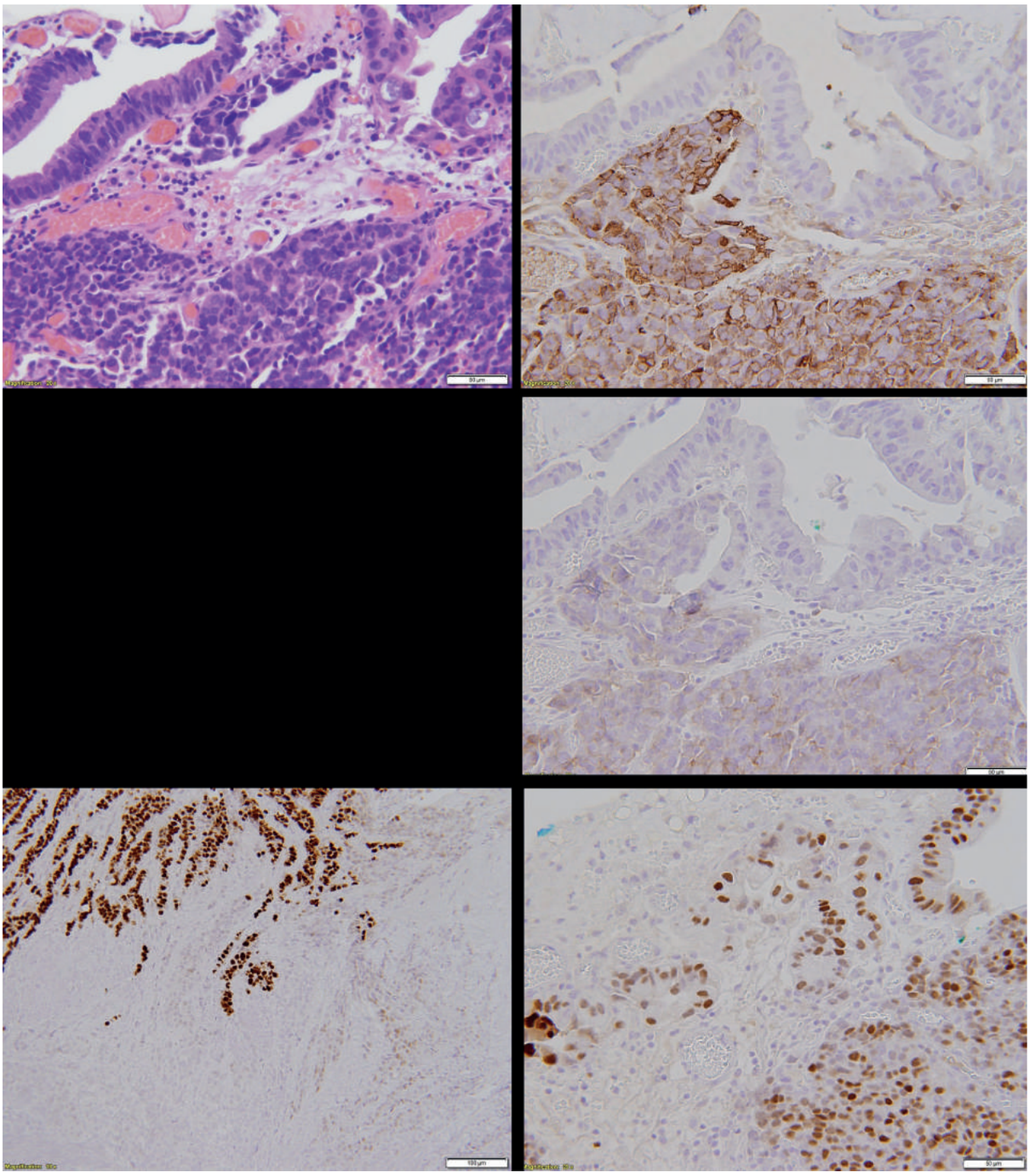

Figure 2. — From top-left clockwise: Tumor architecture shows a solid and nested pattern of cells with scant cytoplasm and rounded nuclei with finely dispersed chromatin (a). Tumor cells are positive for chromagranin A (b), synaptophysin (not shown) and CD56 (c). CDX-2 is expressed in the areas of intestinal metaplasia and dysplasia as well as in more superficial areas of the tumor (d). CDX2 expression was lost in more deeply infiltrative tumor cells (e).

revealed a small gallstone, incidental renal cyst and possible sludge versus mass in the gallbladder. To clarify the renal cyst she underwent a CT of the abdomen and pelvis with intravenous contrast, revealing focal gallbladder wall thickening with hyper enhancement and architectural distortion which had not been present on a CT scan 3 years earlier (Figure 1A, 1B, 1C). She agreed to undergo laparoscopic cholecystectomy for symptomatic resolution and did well post-operatively. Pathology revealed a 2.5 cm tumor within the body and fundus, away from the hepatic bed, extending transmurally into the subserosal connective tissue to within 0.1 cm of

the overlying serosal surface. The cystic duct margin, adherent liver parenchyma (soft tissue margin), and cystic duct lymph node were all negative for tumor (pathologic stage pT2, per WHO classification). Tumor architecture showed solid and nested cell pattern with scant cytoplasm, rounded nuclei and finely dispersed chromatin. There were areas of necrosis, brisk mitotic activity (> 40 mitoses/ 10 HPF), with both perineural and lymphovascular invasion. Epithelium overlying tumor contained intestinal metaplasia with both low and high grade dysplasia, but no component of carcinoma in situ or invasive adenocarcinoma (Figure 2A). Immunohistochemical stains for chromogranin A (Figure 2B), synaptophysin, and CD56 (Figure 2C) were positive in tumor cells. CDX2 was expressed in areas of intestinal metaplasia and dysplasia as well as in more superficial areas of tumor (Figure 2D), but was lost in more deeply infiltrative tumor cells (Figure 2E). Diagnosis was large cell neuroendocrine carcinoma, grade 3. An extensive work up for metastatic disease followed including a Chest CT with IV contrast, Brain MRI and Whole Body PET/CT revealing no evidence of metastases. She was transferred to a tertiary center for higher level of care and after a pre-operative work up consented to completion radical cholecystectomy 2 months from presentation. Pathology revealed no residual tumor in additionally submitted tissue, including Falciform Ligament, lymph nodes and liver parenchyma. She tolerated the procedure well and was discharged. Post-operatively she developed a superficial wound seroma which was treated with drainage and antibiotics. Adjuvant Etoposide and Cisplatin were administered 5 months from original surgery. From that time she underwent 5 cycles of chemotherapy, refusing her 6th cycle. Multiple follow up PET & regular CT scans at 10, 12 and 16 months from her original procedure confirmed no further disease burden. At her last visit 19 months from her original cholecystectomy, patient was doing well with a well healing wound and no evidence of recurrence.

Discussion

Large Cell Carcinomas account for 0.5% of all Neuroendocrine (NE) and 2.1% of all gallbladder cancer.

Patients are usually female and over 60 years of age (1)(2)(3).

There are no cells of neuroendocrine origin in the gallbladder. *Eltawil et al* proposed that NE carcinoma either arise from pluripotent stem cells that become NE cells, or in a background of intestinal metaplasia (4). *Saavedra et al* proposed that gallstones induce endodermal stem cells to undergo gastric and colonic metaplasia in the gallbladder mucosa, followed by carcinoma (5). Our patient had both intestinal metaplasia and severe dysplasia of the gallbladder, adding credence to this hypothesis. The cells in our specimen tested positive for Chromogranin A (6) and Synatophysin (7), both markers of neuroendocrine expression, and variably for CDX2, a homeobox gene expressed in the nuclei of intestinal epithelial cells; this has been implicated in the development of esophageal intestinal metaplasia (Barrett's Esophagus) (8).

Diagnosing this carcinoma is confounded by non-specific signs found with commoner diseases of the gallbladder, such as post-prandial pain in the right to mid upper quadrant. Symptoms resulting from hormonal production is rare (<1%). Diagnosis is often aposteriori with completion radical cholecystectomy mandated in potentially resectable cases. Ultrasound sensitivity is unknown for NE carcinoma, but *Hederstrom* & *Forsberg* noted a sensitivity of 44% for adenocarcinomas of the gallbladder in 25 females (9). Naturally, no large retrospective series exist about CT detection of these lesions. In our patient, the diagnosis was incidentally discovered after a CT scan had been obtained for a renal cyst, highlighting the chance nature of diagnosis, unfortunate given that early detection is crucial to a good prognosis.

The standard regimen for large NE carcinoma of the gallbladder is based on that for small cell NE carcinoma (10) namely a Platinum based agent and Etoposide. In small cell carcinoma, it confers survival benefit in metastatic disease compared to no chemotherapy, but there is no difference in survival between different regimens. In large cell carcinoma, sensitivity is poor, side effects debilitating, and outcomes worse with less differentiated lesions. Nonetheless, *Shimono et al* published a case of a 64 year old female with a T4 unresectable carcinoma who underwent successful neo-adjuvant therapy with radiation and intra-arterial infusion of Cisplatin and Etoposide. This was followed with a radical resection and right trisegmentectomy (11). Metastatic intra-cranial lesions were managed with cerebrellectomy, systemic chemotherapy and gamma-knife irradiation. The patient lived for 69 months with 36 month freedom from recurrence, but eventually succumbed.

Our patient was offered Cisplatin and Etoposide and tolerated this well. She refused to complete the last cycle of her regimen. Although it has only been 19 months since her original surgical procedure she remains free from disease and alive, a substantial feat by the patient given the poor reported outcomes in this disease. Her pathology suggests malignant transformation of a stem cell in an inflamed environment (as evidence by the dysplasia), but the pathogenesis remains to be defined.

Concluding, large cell neuroendocrine carcinoma of the gallbladder is exceedingly rare. Early detection of smaller, resectable & potentially curable lesions is confounded by its non-specific presentation. Multi-modality therapy centered upon the elimination of all anatomical disease burden should be considered in select cases. Data should be pooled for a retrospective analysis of risk factors that can determine treatment course and prognosis.

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