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Primary neuroendocrinal tumor of gallbladder: A brief review

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ABSTRACT: Neuroendocrine tumors (NET) are thought to arise from embryonic neural crest cells and may occur anywhere that these cells are found.Most NETs tend to be associated with the gastrointestinal tract and respiratory system; however, primary NETs of the gallbladder are rare. We herein present a primary NETs found in gallbladder of a 60-year-old woman.

NET is frequently seen in gastrointestinal tract especially in appendix, small intestine, rectum and stomach.The normal GB mucosa does not contain neuroendocrine cells.The Neuroendocrinal cells detected at sites of intestinal meta-plasia induced by long standing chronic inflammation, which may be the initial step in development of GB-NET.For pre-invasive and early-detected cancer simple cholecystectomy is probably an adequate therapy.The Prognostic factors for NET include primary tumor site, histological differentiation, tumor size, infiltrative growth, angioinvasion, and production of hormones.

For GB-NETs an increased awareness and understanding of the biological background of this tumor entity is required.

KEYWORDS: Neuroendocrine tumors, Gallbladder, Gastrointestinal tract

INRODUCTION

The primary neuroendocrine tumors of gallbladder (NET-GB) are extremely rare with aggressive behavior, representing 0.5% of all neuroendocrine tumors and 2% of gallbladder cancers. [1] The diagnosis is coincidental in most cases. In the Surveillance, Epidemiology, and End Results (SEER) registry, only 278 cases of NET-GB have been reported between 1973 and 2005. [2] The significant increase in incidence of NET could be attributed to both better imaging techniques and better understanding of the disease. The majority (66%) occur in the gastrointestinal tract. [3] The second most common location is the bronchopulmonary system (31%), followed by less frequent locations including the ovaries, testes, hepatobiliary system, and pancreas.

PRESENTATION OF CASE

A 60 year old female presented with complaints of pain in right hypochodrium and significant weight loss from last 4 months. There was no previous history of medical or surgical illness or including jaundice, sweating or diarrhea. Physical examination revealed tenderness in the right upper quadrant of the abdomen. Abdominal computed tomography scans showed a polypoidal mass with heterogeneous enhancing mass lesion of size 37 X 31mm in the fundal region along with thickening of gall bladder wall. Fat planes of liver were well maintained. (Figure 1) Mild liver function derangement was present. The

patient subsequently underwent cholecystectomy with hepatoduodenal lymphadenectomy. On gross pathological examination, a polypoidal mass was present in the fundus of GB which measured 35 X 30mm. The growth involved full wall thickness of the gallbladder and didn't involve the liver tissue. The cut sections of tumor revealed tan gray hemorrhagic foci. Histopathology features of nested and trabecular pattern of the neoplasm was compatible with a neuroendocrine carcinoma. (Figure 2A) Eight hepatoduodenal lymph nodes were removed and all were normal. So the pathologic stage was pT3N0Mx. Microscopically, the tumor was composed of monomorphic cells that contained small round nuclei that were organized in small nodular, trabecular, and acinar structures. The cells were positive for chromogranin A and synaptophysin, (Figure 2B-C) and a diagnosis of "typical" carcinoid of the gallbladder was made. Other markers were positive like CK 7, CK 20, PCEA and Ki 67 index ranged from 2 to 20%. (Figure 2D-F) The patient was disease-free 12 months after surgical management.

DISCUSSION

NET is frequently seen in gastrointestinal tract especially in appendix, small intestine, rectum and stomach but primary GB-NET is rare. More recent investigations have confirmed that NE cells are usually not present in normal gallbladder mucosa, while gallbladder mucosa undergoing intestinal or gastric metaplasia expresses a variety of different NE cells, including histamine, serotonin, gastrin, somatostatin, and glucagon containing cells. [2] The neuroendocrinal cells detected at sites of intestinal metaplasia are induced by long standing chronic inflammation, which may be the initial step in the development of GB-NET. [4] So the NET cells derive from local multipotent gastrointestinal stem cells rather than, as initially guessed, by migration by the neural crest cells. [5] [6] Heterotopic pancreatic tissue in the GB is an exceedingly rare condition (<50 reported cases) with potential relevance for gall bladder neoplasia. The ectopic pancreatic tissue demonstrates typical islet peptide immunoreactive cells scattered within an active exocrine parenchyma, and the condition may result in acute pancreatitis and secondary cholecystitis. It has been hypothesized that the amylase/trypsin leakage damages the gallbladder mucosa may lead to precancerous lesions and eventually neoplasia.It is also possible that NETs may arise in ectopic pancreatic tissue in a same way as the Meckel's diverticuli. [2]

The age at presentation of GB NETs ranges from 38 to 81 years, and there is a markedly higher incidence in women. [5] The carcinoid syndrome is very rare (<1%), and most GB carcinoids are incidentally diagnosed during histological examination of GB specimens during autopsy, after cholecystectomy for acute or chronic cholecystitis, or after surgery for another suspected biliary pathology. [7] The prognostic factors for NET include primary tumor site, histological differentiation, tumor size, angio-invasion, infiltrative growth, and production of hormones. [8] The presence of a mucinous or adenocarcinoma phenotype and elevated Ki67 and high mitotic index are likely to be predictive of worse prognosis. Invasion of adjacent structures is also an important negative predictor of outcome, whereas if the tumor is localized to the gallbladder wall, the prognosis is better. [9] The surgical treatment of gallbladder NETs varies widely, with the goal of complete resection, is the gold standard for typical carcinoids of the GB. For pre-invasive and early-detected cancer simple cholecystectomy is probably an adequate therapy. For advanced lesions, a more aggressive radical surgery, including radical cholecystectomy and regional lymphadenectomy combined with a hepatic resection in order to obtain adequate free margins, is

needed. [10]

For NETs- GB, an increased awareness and understanding of the biological background of this tumor entity is required. In order to improve survival of NETs-GB aggressive surgical management appears to be the only effective at this time and the tumors should be considered as highly malignant and comparable to the more common gall bladder adenocarcinoma.

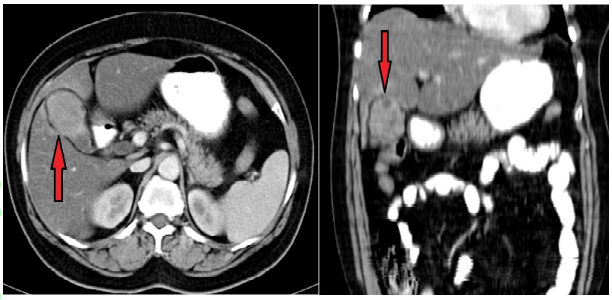

Figure 1: (A) Transverse and (B) Coronal view of upper abdomen showing gall bladder mass lesion in fundal region with wall thickening and showing fat planes with liver are well maintained

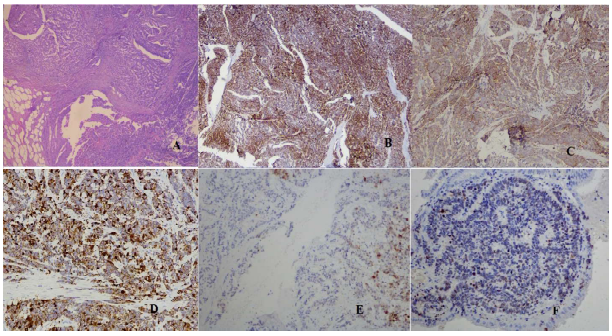

Figure 2: showing (A) HP specimen showing nested and trabecular pattern, (B-F) showing IHC marker positivity as chromogranin, synaptophysin, CK7, CK20 and Ki-67 index range from 2-20% respectively.

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