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PRIMARY NEUROENDOCRINE TUMORS OF THE LIVER AND GALLBLADDER

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To study Clinico-pathological characters of the neuroendocrine tumors of the liver and gallbladder.

Methods

Using histology, immunohistochemistry and electron microscope, 3 cases of liver and gallbladder were investigated. The primary antibodies including anti-chromogranin A, gastrin, serotonin, insulin, somatostatin, gastrin, pancreatic polypeptide, adreno- corticotropic hormone (ACTH), calcitonin, bombesin, β-human chorionic gonadotropin (β-HCG) were employed to identify the property of tumors.

Results

In one cases tumor of neuroendocrine carcinoma. In the other two cases tumor were typical carcinoid. In immunohistochemistry study, the tumor cells showed positive reaction to chromagranin A and contained positive cells of gastrin, serotonin, insulin and pancreatic polypaptide. Electronmicroscopy showed the cytoplasm contained dense round granules.

Conclusion

The Nuroendocrine tumor of liver and gallbladder is a special type neoplasm with character of histology, immunohistochemistry and electron microscopy. Subject headings neuroendocrine tumor gallbladder liver immunohistochemistry and electron microscopy.

Key words: Neuroendocrine tumor, Gallbladder, Liver, Immunohistochemistry, Electron microscopy.

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Neuroendocrine tumor are most commonly found in the gastrointestinal tract, and the primary neuroendocrine tumor of the gallbladder and liver are rare. The first case of carcinoid in the gallbladder was reported by Joel in 1929.[1] In an analysis of 2837 cases of patients with carcinoids by Godwin, the most common sites of carcinoids were the appendix (35%), small intestine (15%) and rectum (12%); none of the carcinoid of liver, one case in the gallbladder and biliary tract was found.[2] Extrahepatic biliary carcinoid are rare neoplasms representing 0.2–2% of the digestive tract carcinoid.[3,4] Review of the world literature has shown a 40 total carcinoid tumors of the gallbladder[5–8] and only 17 cases of the liver.[9–13] The study are report of three cases primary neuroendocrine tumor of liver and gallbladder using histology, immunohistochemistry and ultrastructural analysis.

MATERIALS AND METHODS

Clinical Data

Case 1

A 52-year-old female was admitted to the Naval General Hospital with the complaint of four months of diarrhea. The ultrasonography and CT revealed "hepatomegaly and cystic areas in the left and right lobes of the liver" and pancreas normal. Lung x-ray series was normal. A pathological diagnosis of metastatic small carcinoma of the liver was made on

fine needle aspiration biopsy and right segmentectomy of the liver and cholecystectomy were performed. In operation, gastrointestinal tract was carefully examined and there was not any tumor to be found. Three months later After operation ultrasonography revealed multiple metastatic nodules in the liver and enlargement of lymph nodes of the porta hepatis. The patient was discharged because she refused further treatment.

Case 2

A 58-year-old female presented with 3 month history of recurrent right upper quadrant pain and was admitted because complaints of nausea, vomiting, and that right upper abdominal pain become more severe. Abdominal ultrasonography revealed stones in the gallbladder. A diagnosis of cholelithias is and cholecystitis was made, and a cholecystectomy was performed on June 12, 1990. Five years and 10 months later, she was well without any evidence of recurrence or metastasis.

Case 3

An 83-year-old female was admitted for chronic obstructive pulmonary disease and cor pulmonale. Upon physical examination she was also found to have a large mass in the liver. The mass had a firm, nodular surface, and the lower border was palpated 4 cm below costal margin. Ultrasonographic examination of the liver revealed sparse microwaves and showed that upper border was 1 cm above and the lower border 5 cm below the costal margin. The patient died of secondary pulmonary infection complicated by DIC. An autopsy was performed.

Immunohistochemical Study and Ultrastructural Analysis

The samples were fixed in 10% formalin, embedded in paraffin, and cut into 5 μm sections. The sections were stained with hematoxylin-eosin. Masson-Hamperl method for argentaffin granules and Grimelius and modified Bodian method for argyrophilic granules.

Immunohistochemical study was performed on paraffin embedded sections with overnight exposure at 4 ℃ to the monoclonal antibodies or rabbit antisera with avidin- biotin- peroxidase complex (ABC) method was employed, using a Zimed ABC kit (Zimed Co. USA). Peroxidase was stained with DAB. Appropriate positive and negative controls were employed. Antibodies used are listed in Table 1. Once the nature of the tumor was suspected, electro microscopic samples were obtained from the tumor tissue blocks, which had been fixed in 10% formalin for 1–2 day. They were sliced into 1 mm fragments, postfixed in 1% OsO_4, dehydrated by graded acetone, and embedded in Epon 812 and 815. One μm thick sections were prepared for orientation purposes. Thin sections were cut with an LKB V ultramicrotome, counterstained by uranyl acetate-lead citrate, and examined by a JEOL 100 CX II electron microscope.

RESULTS

The Table 2 showed 3 cases of neuroendocrine tumor included two cases primary tumor from gallbladder and one case primary tumor from liver. In the three tumor cases, many cells demonstrated chromogranin A and the positive cells are exceed the 50% of tumor. The case 1 included resected gall-bladder and section of liver. In the gallbladdera polypoid tumor measuring 2.4×2×11.5 cm at the body. Microscopically, the tumor was predominantly in the lamina propria and muscularis. The hyperplastic mucosa adjacent to the tumor. The tumor is consisted of small, uniform, round cells arranged in the solid nests, which were separated by the connective tissue. The tumor cells had a moderate amount of eosino-philic cytoplasm and centrally located nuclei. Several mitoses can been seen. The resected liver specimen measuring 19×12.5×6 cm, contained partially encapsuled brown-pink mass (16×6×4 cm) with clear margin, which included cystic and necrotic areas. Microscopically, the tumor cells were similar in appearance to the neuroendocrine carcinoma in the gallbladder. The immunohistochemistrical staining showed no different from that of gallbladder. A diagnosis of primary neuroendocrine carcinoma of gallbladder with liver metastasis was made. The case 2 showed that tumor measuring 1.8×1×1 cm at fundus confined to the mucosa and a definite capsule was seen. Microscopic examination showed that the tumor consisted of small cuboidal and low columnar cells of uniform size. The cells were arranged in narrow cords. Mitotic figures rare were seen. A diagnosis of primary of carcinoid of gall-bladder was

made. Other findings are shown in Table 2. In the case 3, a tumor measuring approximately 8.5×7×6 cm was found in the right lobe of the liver. No alternative primary source of tumor was found at autopsy despite intensive and careful search, especially in the bile duct, gallbladder, pancreas, gastrointestinal tract, ovary, kidney, adrenal, thyroid, breast, and lung. Light microscopic examination showed the neoplasm was composed of small, uniform, polygonal or cuboidal cells that had distinct cellular borders and grew in broad strands, ribbons and islands arranged in a palisade pattern. There was no significant cytologic atypia or pleomorphism, and mitotic figures were very rare. Neoplastic cells with the same appearance were found in lymph nodes in porta hepatis and small vessels in the lung. A diagnosis of primary neuroendocrine carcinoma of liver was made. Other findings were shown in Table 2.

Table 1 List of antibodies used in the present study

Code	Antigens	Antibody type	Working dilution	Source
M869	Chromogranin A	P	1:400	DAKO
BM0080	Insulin	M	1:100	Sigma
M758	Serotonin	M	1:20	DAKO
A565	Glucagon	P	1:800	DAKO
M566	Somatostatin	P	1:400	DAKO
M686	Gastrin	P	1:300	DAKO
A619	PP	P	1:4000	DAKO
A571	ACTH	P	1:800	DAKO
A576	Calcitonin	P	1:800	DAKO
CA-08210	Bombesin	P	1:20000	Cambridge
A231	β-HCG	P	1:800	DAKO

Table 2 Character of three cases primary neuroendocrine carcinoma of gallbladder and liver

Case no	Age	Sex	Clinical manifestations	Location of tumor	Largest diameter of tumor	Histology	Metastasis	Argentaffin reaction	Argyrophil reaction	Size of electron-granules	Immunoreactive for hormones
1	52	F	Duarrgea	Body of gallbladder	2.4 cm	Neuroendocrine carcinoma	Liver	–	+	100 nm	Serotonin + PP + Gastrin + Insulin +
2	58	F	Cholecystolithiasis	Fondus of gallbladder	1.8 cm	Carcinoid	None	+	+	150 nm	PP + ACTH + Gastrin +
3	83	F	None	Right lobe of liver	8.5 cm	Neuroendocrine carcinoma	LN at porta hepatis and small vessels in lung	–	+	100–200 nm	Gastrin + PP +

LN: lymph nodes.

DISCUSSION

The neuroendocrine tumor are infrequently seen

in the liver and gallbladder.[2-4] While the jejunoileum, appendix and rectum are relatively frequent sites for carcinoids. As far as we can determine, 40 cases of endocrine cell tumor in the gallbladder[5-8] and 17 cases[9-13] in the liver have been reported. We report primary two cases of neuro-endocrine tumors of the gallbladder and primary one case of liver. The liver is the most common location for metastasis from malignant tumors in gastrointestinal tract. However, a thorough search of all the viscera failed to uncover any additional primary or metastatic neoplasm. The tumor in the liver was a large mass with several satellite nodules around it. Thus, based on the autopsy examination and gross inspection, this one is very likely that the tumor was primary.

The three cases neuroendocrine tumors are in keeping with those of the concept introduced by Tahara's classification[5,14] of endocrine tumor. The first cases was diagnosed as neuroendocrine carcinoma. These tumors are as one of malignant epithelium consisting predominantly of neoplastic endocrine cells showing cellular plemorphism, atypia and numerous mitoses, the endocrine cell nature being established by diffuse positive CgA antibody immunostaining. and the presence of dense core granules on electronmicroscopy in our three cases. Tahara's classification included carcinoid, muco-carcinoid and endocrine cell carcinoma. He further subdivides endocrine cell carcinomas into well-differentiated, poorly differentiated and undifferentiated subtypes. The first case belong to the poorly differentiated, the second case is carcinoid, the third case belongs to the well-differentiated endocrine carcinoma. Studies of 5-year survival rates of gastric endocrine cell carcinoma confirmed a higher grade of malignancy as compared with carcinoid tumors. On the basis of this subdivision, the present third case would fit into the category of a well-differentiated endocrine cell carcinoma,[14] the lymph nodes at porta hepatis and small vessels in lung adding support to the increased malignant potential.

The exact histogenesis of neuroendocrine tumor in gallbladder and liver. Some possibilities have been raised: (1) developing from aberrant pancreatic tissue in gallbladder and liver, (2) arising from the cells of neuroectodermal origin scattered in the foregut and its embryologic derivatives, or from primitive cells with multiple potential, (3) deriving from "neuroendocrine programmed ectoblast", and (4) deriving from metaplastic endocrine cell epithelium.[15]

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