[症例報告]Huge Carcinoid Tumor of the Gallbladder : A Case Report

Huge Carcinoid Tumor of the Gallbladder : A Case Report

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ABSTRACT

A case of a huge carcinoid tumor of the gallbladder in a 68-year-old Japanese woman is reported herein. The patient presented with a huge mass in the right upper quadrant of the abdomen without a carcinoid syndrome. Diagnostic modalities demonstrated a huge tumor suggesting some malignant tumors of the gallbladder. Right hepatectomy with cholecystectomy and regional nodal dissection was carried out. The tumor together with the right hepatic lobe weighed 3,018 gm and the tumor itself measured 23 × 18 × 16 cm in size. Upon bisection, it was solid and well circumscribed, containing gallstones without any spread to the liver and regional lymph nodes.

Microscopically, the tumor was composed of solid or trabecular nests with atypical polygonal cells which were argyrophil positive, expressed by CEA and chromogranin A, but not by NSE. They possessed several dense core neurosecretory granules on electron microscopic examination. Based on these morphological data, this carcinoid tumor was thought to be categorized as an endocrine cell carcinoma of a poorly differentiated carcinoid. The patient expired eight months after surgery with massive hepatic metastases. This case might be the largest carcinoid tumor from this location reported in literature.

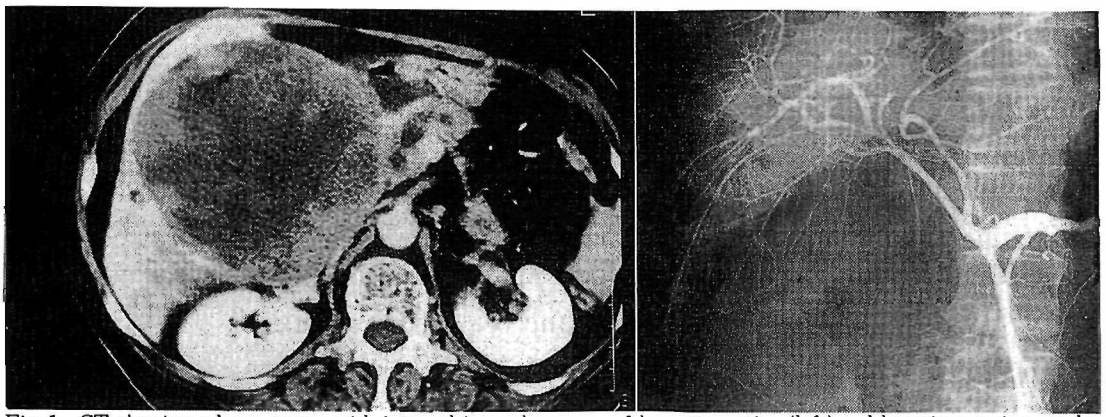

Fig. 1. CT showing a large tumor with internal irregular areas of low attenuation (left) and hepatic arteriogram demonstrating the right hepatic arterial branches being stretched (right).

INTRODUCTION

Carcinoid tumors arising in the gallbladder are smaller than those in the gastrointestinal tract [1-3], and are usually clearly diagnosed on histopathological examination of the resected gallbladders after cholecystectomy [4-8]. On the other hand, some sarcomas such as rhabdomyosarcoma of the gallbladder have been reported frequently to grow to a huge size [9]. However, we have never encountered a huge carcinoma of the gallbladder without massive hepatic metastasis.

The present case is a huge carcinoid tumor which remained confined to the gallbladder without any macroscopic extension to the liver and more distant metastases. This carcinoid tumor might be the largest one from this location reported in literature.

CASE REPORT

A 68-year-old Japanese woman developed postprandial epigastric discomfort for a few months, and thereafter noticed a large mass in the right upper quadrant of the abdomen. The patient was referred to the Ryukyu University Hospital in August, 1988 with a possible diagnosis of liver cell carcinoma. On admission, she appeared lethargic. A huge tumor mass was palpated below the right costal margin down to the right lower quadrant of the abdomen. Her blood cell count was within normal limits. Liver function tests showed total bilirubin 0.9 mg/dl (0.3-0.8), GOT 54 IU/l (10-32), GPT 38 IU/l (7-36), alkaline phosphatase 389 IU/l (90-265) and LDH 859 IU/l (240-475). HBs-antigen and antibody were negative. AFP (alfa-fetoprotein) was 313.9 ng/ml (lower than 20), CEA (carcinoembryonic antigen) 2.5 ng/ml (lower than 2.5), and CA 19-9 (carbohydrate antigen 19-9) 68.3 U/ml (lower than 37). Serum serotonin was 83 ng/ml (20-200); however, urinary 5-HIAA (5-hydroxy indoleacetic acid) was not examined before surgery. The patient had not previously presented symptoms due to the carcinoid tumor.

Ultrasonography showed a large hypoechoic tumor with several strong internal echoes in the anatomic location of the gallbladder. Computed tomography through the lower portion of the right hepatic lobe demonstrated a well-circumscribed tumor with hypodense internal irregular, large areas. The gallbladder itself was not outlined and identified. Hepatic arteriography disclosed the right hepatic arterial branches being

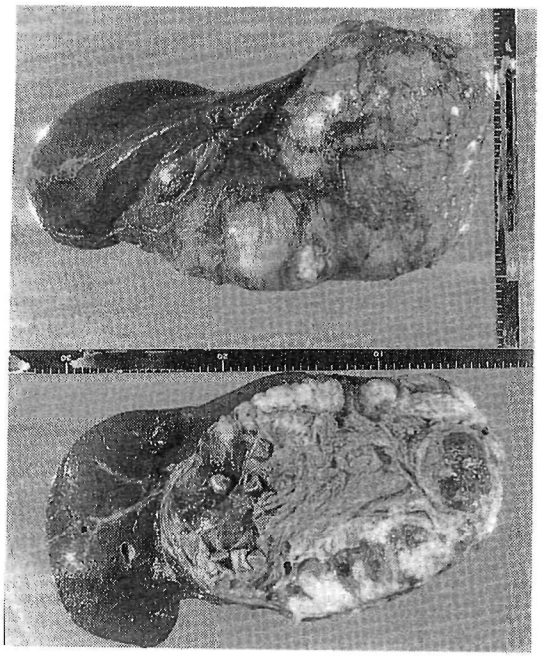

Fig. 2. Macrophotographs of the resected specimen showing a huge tumor of the gallbladder (top) and its cut surface (bottom).

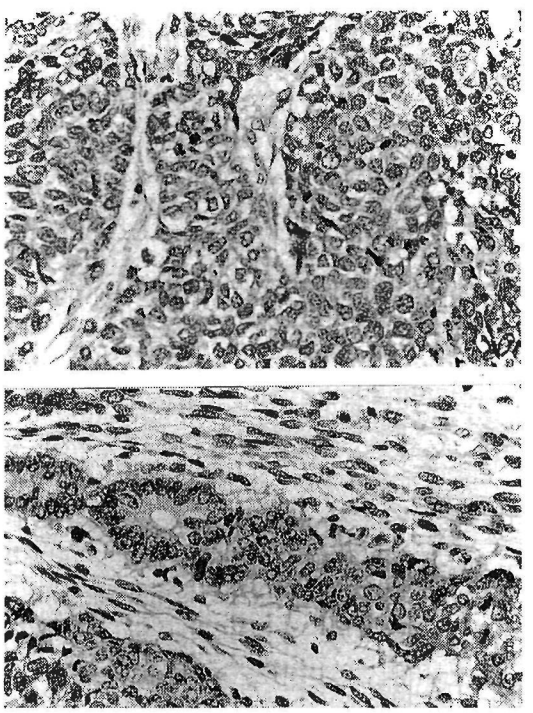

Fig. 3. Microphotographs of the tumor showing solid nests with atypical polygonal cells (top) and pseudoglandular structures in the trabecular nests (bottom) (Hematoxylin and eosin, ×100)

stretched around the large tumor with medial compression of the common hepatic and gastroduodenal arteries (Fig. 1). The cystic artery could not be identified. The venous phase showed it to be a hypovascular tumor.

Upon surgery, the tumor was found to originate from the gallbladder. There were no macroscopic spreads to the liver, and the regional lymph nodes were not enlarged. Right hepatectomy together with cholecystectomy, and nodal dissection encompassing the cystic and pericholedochal nodes to the right para-aortic nodes was carried out.

The patient had been doing well for six months after surgery. She expired two months after her readmission due to massive hepatic metastases. However, she had not displayed any symptoms of a carcinoid tumor during this hospitalization period.

PATHOLOGY

Macroscopy

The tumor together with the right hepatic lobe weighed 3,018 gm and the tumor itself was 23 × 18 × 16 cm in size. Upon bisection, it appeared solid, well-circumscribed and replaced the whole gallbladder, which contained several mixed-type cholesterol stones (Fig. 2).

Light microscopy

The resected tumor was fixed in a solution of 10% formalin. Multiple sections were taken for a histologic study, and processed in the routine manner for paraffin embedding. These sections were stained with hematoxylin and eosin and AB-PAS (alcian-blue-PAS). After recognition of the carcinoid tumor, Grimelius' nitrate method and immunohistochemical staining by the PAP method were performed. Antibodies against the following immunoreagents were obtained from a Dako PAP kit (Santa Barbara, CA) : CEA, chromogranin A and NSE (neuron-specific enolase).

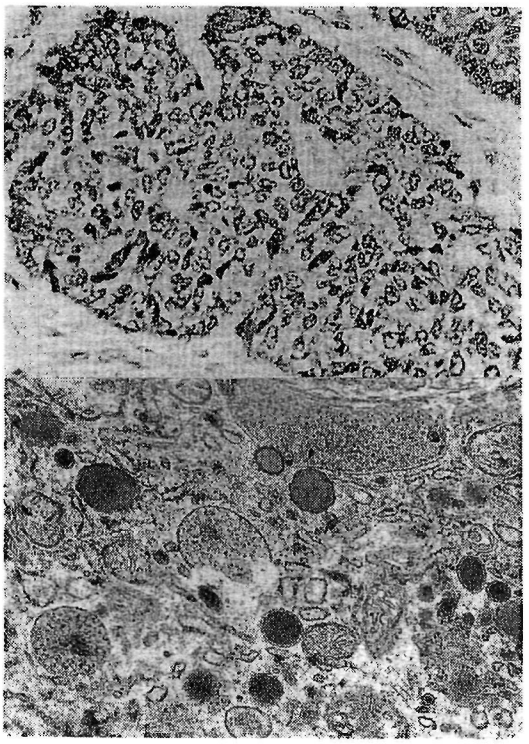

Fig. 4. Microphotograph of argyrophil positive tumor cells (top; Grimerius stain, ×100) and electron micrograph of the tumor cell demonstrating several dense core neurosecretory granules (bottom; magnification, ×20,000).

The tumor was mostly composed of solid or trabecular nests with polygonal cells and delicate fibroconnective tissue. The tumor cells showed pleomorphism with atypical and hyperchromatic nuclei, and had faintly granular cytoplasm. Many mitotic figures were observed throughout the tumor. In some areas, pseudoglandular structures were evident in the trabecular nests mimicking adenocarcinoma (Fig. 3). In a few areas at the periphery of the tumor as in a previously reported case [5], apparent transition between carcinoid and ordinary adenocarcinoma was found. Carcinoid tumor cells showed argyrophilic reaction with negative argentaffin reactivity (Fig. 4). Alcian-blue positive mucin were observed in the pseudoglandular lumen and in the cytoplasm of ordinary adenocarcinoma. The carcinoid tumor cells were expressed

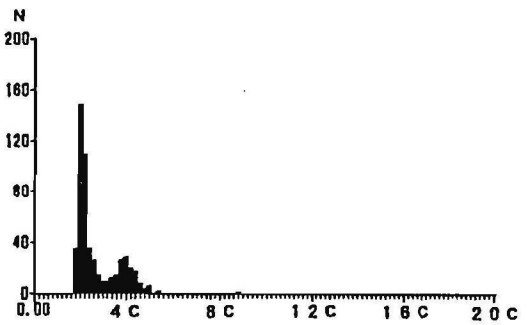

Fig. 5. DNA histogram of the tumor showing aneuploid tumor.

by CEA and chromogranin A, but not by NSE. Sections of the liver adjacent to the gallbladder showed no tumor tissue and regional lymph nodes revealed no metastatic foci.

Electron microscopy

For this study, formalin-fixed tissue was washed in water, postfixed in 1% osmium tetraoxide, and embedded in Quetol 812. Sections were stained with uranyl acetate and lead nitrate, and were examined with a Hitachi 200 CX electron microscope.

Structures of the tumor cells were distorted, and several dense core neurosecretory granules were observed (Fig. 4).

Nuclear DNA analysis

100-micron thick sections were made from paraffin-embedded tissue for isolated cell smears. Nuclear DNA content was measured by the static cytofluorometry method [10,11]. In DNA analysis, if the main peak of the DNA histogram centers around the 2C region and the overall DNA distribution is similar to that of normal lymphocytes, the tumor is classified as "diploid." By contrast, DNA histograms with an anomalous position of the first major peak or presence of one or more anomalous peaks not assignable to that of diploidy are considered as "aneuploid". The DNA histogram of our carcinoid tumor showed the aneuploid pattern (Fig. 5).

DISCUSSION

Carcinoid tumors were originally considered to be benign, but were later divided into benign and malignant categories following the appearance of malignant variants. At present, it is generally accepted that all carcinoid tumors are potentially malignant [12,13].

The wide clinicopathological spectrum of carcinoid tumors has given rise to a number of new terms for carcinoid tumors based on the controversial theories of the origin of the gastrointestinal endocrine cells[13,18]. In recent years, the term "endocrine cell carcinoma" has been proposed for a variety of carcinoid tumors (classical carcinoid, mucocarcinoid and endocrine cell carcinoma) [13]. An endocrine cell carcinoma is defined as a malignant epithelial tumor consisting predominantly of neoplastic endocrine cells with pleomorphism, atypism and many mitoses. This type of carcinoma could be morphologically similar or the same as the atypical or poorly differentiated carcinoids described in the literature [12,13]. The tumor in our case appears to be histologically identical to an endocrine cell carcinoma.

Gallbladder carcinoid tumors are very rare, mostly asymptomatic and small in size, and are often discovered incidentally at cholecystectomy for gallbladder diseases [18]. The present patient had not previously presented any clinical symptoms of a carcinoid syndrome and coexistent gallstones until she developed the large mass in the right upper quadrant of the abdomen. Functional carcinoids are found most frequently in those originating in the foregut and midgut. The gallbladder is the foregut derivative, nevertheless the carcinoid tumors of the gallbladder are commonly silent [18]. A carcinoid syndrome usually develops when the tumor is bulky and extensively involves the liver, which results in failure to activate the normal peptides [19]. The tumor in our patient was extraordinarily bulky, but confined to the gallbladder. Furthermore, a carcinoid syndrome is described to be not usually associated with poorly differentiated carcinoids [12]. Considering these facts and the data described in literature, it should be natural that our patient did not develop a carcinoid syndrome. Unfortunately, in our patient, the hormonal peptides were not examined because of lack of knowledge of the carcinoid tumor before and at surgery.

Morphologically, the silver affinity of carcinoid tumors is an accurate diagnostic procedure, but it is variable and depends on the anatomic location of the tumors. In general, the foregut carcinoid tumors are argyrophilic positive but argentaffin negative [20]. As mentioned before, the tumor in our patient was argyrophil positive, but argentaffin negative.

Recent advances in immunohistochemical studies have brought about a clearer understanding of carcinoid tumors. Although NSE was first introduced as the universal marker for these endocrine cell tumors, it has been now found not to be reliable in excluding carcinomas [19]. Chromogranin, a marker of the endocrine cell granule matrix, has been shown to be positive in many carcinoids even when the tumor cells contain a small number of secretory granules [19]. The tumor cells in our case were not expressed by NSE, but by chromogranin A. Thus, histological and immunohistochemical diagnostic modalities are not always reliable in making a definitive diagnosis of carcinoid tumors. Therefore, the demonstration of dense core neuros-ecretory granules by electron microscopy remains the most accurate form of diagnosis of carcinoid tumors, especially of the atypical and poorly differentiated carcinoids like that in our case.

On ultrastructural examination, the carcinoid tumor cells are characterized by dense core neurosecretory granules. The granules in our case were sparsely observed, and this sparsity

of the granules was thought to be secondary to inadequate tissue preparation. However, the less-differentiated and undifferentiated carcinoids have been reported to show increasing sparsity and immaturity of neurosecretory granules [17-19]. This makes interpretation difficult since this sparsity of the granules hampers accurate diagnosis.

As mentioned before, an accurate definition of the atypical and undifferentiated carcinoids or endocrine cell carcinoma is required for proper clinical management. At present, there is wide variation in the diagnosis of these tumors because of lack of uniform diagnostic criteria. In recent years, static cytometry and flow cytometry have proved to be a means of morphologic prognostic evaluation of all neoplasms which are objective and reproducible [10,11,21,22]. In nuclear DNA analysis, human tumors can be divided into two major groups based on the DNA histogram: diploid and aneuploid. Generally, the diploid tumors have a more favorable prognosis in comparison to the aneuploid tumors. Furthermore, the diagnostic and prognostic significance of DNA ploidy patterns depends upon the primary site to origin of a given tumor and its histologic type [22].

Regarding carcinoid tumors, only a few studies on nuclear DNA analysis have been reported [23-25]. It has been suggested that the diploid pattern on the DNA histogram is a general characteristic of the neuroendocrine tumors and that the DNA ploidy patterns could facilitate the discrimination of carcinoid tumors from small cell carcinoma of the lung. Therefore, the diagnostic and prognostic value of DNA ploidy patterns remains unsettled [23].

The DNA ploidy pattern in our case was classified as aneuploid, and the patient had a poor prognosis. At present, large series are needed to establish the prognostic significance of DNA ploidy in all carcinoid tumors, especially in the atypical and poorly differentiated carcinoids.

REFERENCES

1) Godwin, D. J.: Carcinoid tumors. An analysis of 2837 cases. Cancer 36 : 560-569, 1975.

2) Burke, M., Shepherd, N., and Mann, C.V. : Carcinoid tumor of the rectum and anus. Br. J. Surg. 74 : 358-361, 1987.

3) Andarker, L., Lamke, L., and Smeds, S. : Follow-up of 102 patients operated on for gastrointestinal carcinoid. Acta. Chir. Scand. 151 : 569-573, 1985.

4) Schiffman, M. A., and Juler, G. : Carcinoid of the biliary tract. Arch. Surg. 89 : 1113-1125, 1964.

5) Muto, Y., Okamoto, K., and Uchimura, M. : Composite tumor (ordinary adenocarcinoma, typical carcinoid and goblet cell adenocarcinoid) of the gallbladder : A variety of composite tumor. Am. J. Gastroenterol. 79: 645-649, 1984.

6) Wada, A., Ishiguro, S., Takeishi, R., Ishikawa, O., and Matsui, Y.: Carcinoid tumor of the gallbladder associated with adenocarcinoma. Cancer 51 : 1911-1917, 1983.

7) Yamamoto, M., Nakajo, S., Miyoshi, N., Nakai, S., and Tahara, E.: Endocrine cell carcinoma (carcinoid) of the gallbladder. Am. J. Surg. Pathol. 13 : 292-302, 1989.

8) Noda, M., Miwa, A., and Kitagawa, M.: Carcinoid tumors of the gallbladder with adenocarcinomatous differentiation : A morphologic and immunohistochemical study. Am. J. Gastroenterol. 84 : 953-957, 1989.

9) Ruymann, R. B., Rany, R. B. Jr., Crist, W. M., Lawrence, W. Jr., Lidberg, R. D., and Soule, E. H. : Rhabdomyosarcoma of the biliary tree in childhood; A case report from the Intergroup Rhabdomyosarcoma Study. Cancer 56 : 575-581, 1985.

10) Hamada, S., Itoh, R., and Fujita, S. : DNA

distribution pattern of so-called severe dysplasia and small carcinoma of the colon and rectum and its possible significance in the tumor progression. Cancer 61 : 1555-1562, 1988.

11) Deguchi, S., Kurihara, K., Tamaki, S., Isa, T., Hokama, A., Muto, Y., and Toda, T. : Alternations of nuclear DNA content in thyroid papillary carcinoma, follicular adenoma and Basedows disease. Endocr. Surg. 6 : 311-316, 1989 (in Japanese with English abstract).

12) Lewin, K. : Carcinoid tumors and the mixed (composite) glandularendocrine cell carcinomas. Am. J. Surg. Pathol. 11 (Suppl.) : 71-86,1988.

13) Tahara, E. : Endocrine tumors of the gastrointestinal tract : Classification, function and biological behavior. Digest. Dis. Pathol. 1 : 121-147, 1988.

14) Andrew, A. : Further evidence that enterochromaffin cells are not derived from the neural crest. J. Embryo. Exp. Morphol. 31 : 589-598, 1974.

15) Bolande, R. D. : The neurocristopathies. A unifying concept of disease arising in neural crest maldevelopment. Hum. Pathol. 5 : 409-429, 1974.

16) Pearse, A.G.E. : The APUD cell concept and its implication in pathology. Pathol. Ann. 9 : 27-41, 1974.

17) Chejfec, G., and Gould, V.G. : Malignant gastric endocrinomas. Ultrastructural and biochemical characterization of their secretory activity. Hum.Pathol.8:433-440, 1977.

18) Sweeny, E.C., and McDonnel, L. : Atypical gastric carciniods. Histopathology 4 : 215-224, 1980.

19) Solcia, E., Capella, C., and Buffa, R. : Cytology and biology of gut endocrine tumours. In Bloom, S.R., and Polak, J.M. ed., Gut hormones, 2nd ed., Edinbrugh, Churchill Livingstone, 1981, pp. 541-546.

20) Soga, J., and Tazawa, K. : Pathologic analysis of carcinoids. Histologic reevaluation of 62 cases. Cancer 28 : 990-998, 1971.

21) Auer, G., Askensten, U., and Ahrens, Q. : Cytophotometry. Hum. Pathol. 20 : 518-527, 1989.

22) Koss, L.G., Czerniak, B., Herz, F., and Wersto, P.R. : Flow cytometric measurement of DNA and other cell components in human tumors: A critical appraisal. Hum. Pathol. 20 : 528-548, 1989.

23) Wilander, E., Bengtsson, A., Lindren, P. G., Lundqvist, M., Norheim, I., and Oeberg, K. : Nuclear DNA in intestinal carcinoid tumors. A study before and after cytotoxin (Streptozocin and 5-fluorouracil) treatment. Cancer 56 : 793-796, 1985.

24) Thunnissen, F.B.J.M., Eijk, J.V., and Baak, J.P.A. : Bronchopulmonary carcinoids and regional lymph node metastases. A quantitative pathologic investigation. Am. J. Pathol. 132 : 119-122, 1988.

25) Kujari, H., Joensuu, H., Klemi, P., Asola, P., and Nordman, E. : A flow cytometric analysis of 23 carcinoid tumors. Cancer 61 : 2517-2520, 1988.