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Polypoid Neuroendocrine Tumor G1 of Gallbladder

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ABSTRACT

Recently, WHO classification has proposed a uniform classification framework for all neuroendocrine neoplasms (NENs). The classification is the distinction between well-differentiated neuroendocrine tumor (NETs, previously called carcinoids) and poorly differentiated neuroendocrine carcinomas (NECs). We describe histopathological characteristics of a very rare case of the gallbladder polypoid NET. The patient was a 49 year old man with upper abdominal pain. Laparoscopic cholecystectomy was performed and the polypoid tumor was pathologically diagnosed as NET, grade 1 (G1). The polypoid tumor was composed of monotonous proliferation of tumor cells with weakly eosinophilic cytoplasm and oval nuclei. Immunohistochemically, tumor cells were positive for chromogranin A, synaptophysin, CD10 and MUC1. We speculated that the NET G1 had arisen from enterochromaffin cells (also called Kulchitsky cells) because the surrounding mucosa exhibited gastric-type metaplasia including enterochromaffin cells.

Keywords: Neuroendocrine neoplasms, Neuroendocrine tumor, Neuroendocrine carcinomas, Polypoid, Gallbladder

INTRODUCTION

Recently, WHO has classified neuroendocrine neoplasms (NENs) into two distinct groups: well-differentiated neuroendocrine tumor (NET) and poorly differentiated neuroendocrine carcinoma (NEC) [1,2]. Primary NENs of gallbladder are very rare. The majority of the previously reported gallbladder cases were NECs with infiltrative/aggressive growth and poor patient's prognosis [3,4]. On the other hand, NETs have been reported as unusual cases.

Here, we describe histopathological characteristics of a gallbladder polypoid tumor of the well differentiated NET.

CASE PRESENTATION

The patient was a 49 year- old Japanese man with upper abdominal pain, and underwent laparoscopic cholecystectomy under the diagnosis of gallbladder polyp. Macroscopically, the yellowish-white pedunculated polyp was located to the gallbladder body, and measured 17 × 14 × 15 mm in size **(Figure 1)**. Histologically, the polypoid tumor was composed of monotonous proliferation of tumor cells with weakly eosinophilic cytoplasm and oval nuclei **(Figure 2)**. Nuclear atypia is mild in a degree, and mitoses were few. In addition, the surface was covered by the non-neoplastic gallbladder epithelium. The tumor cells are limited within the mucosal polypoid lesion. There were no apparent foci of lymphatic/venous invasion.

Immunohistochemically, tumor cells were positive for chromogranin A, synaptophysin, CD10 and MUC1 **(Figure 3)**; but negative for MUC5, AC, MUC6, MUC2 and p53 **(Table 1)**. Ki-67 index is much less than 1%. The tumor cells did not show any immunoreactivities for insulin, glucagon, somatostatin, serotonin and gastrin. The surrounding non-neoplastic mucosa exhibited biliary phenotype positive for CD10, as well as phenotype of gastric-type metaplasia positive for MUC5AC and MUC6; but negative for intestinal phenotype (MUC2).

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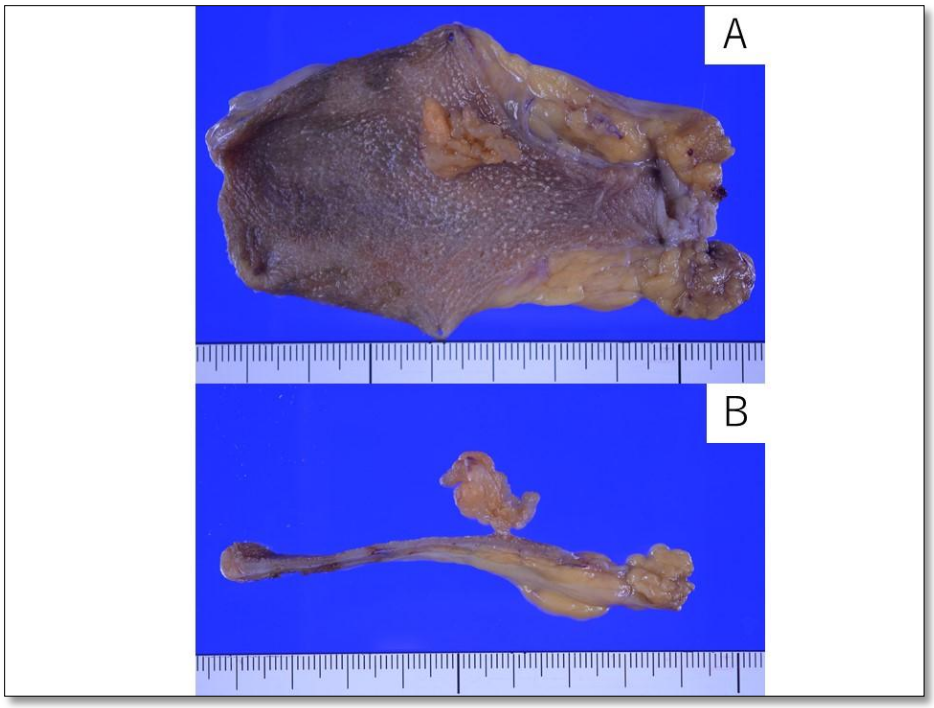

Figure 1. Gross findings of polypoid neuroendocrine tumor (NET) G1 of gallbladder (A, top). The yellowish-white pedunculated tumor measures 17 × 14 × 15 mm in size. Cut section of the NET G1 (B, bottom) shows a thin stalk of the polypoid tumor.

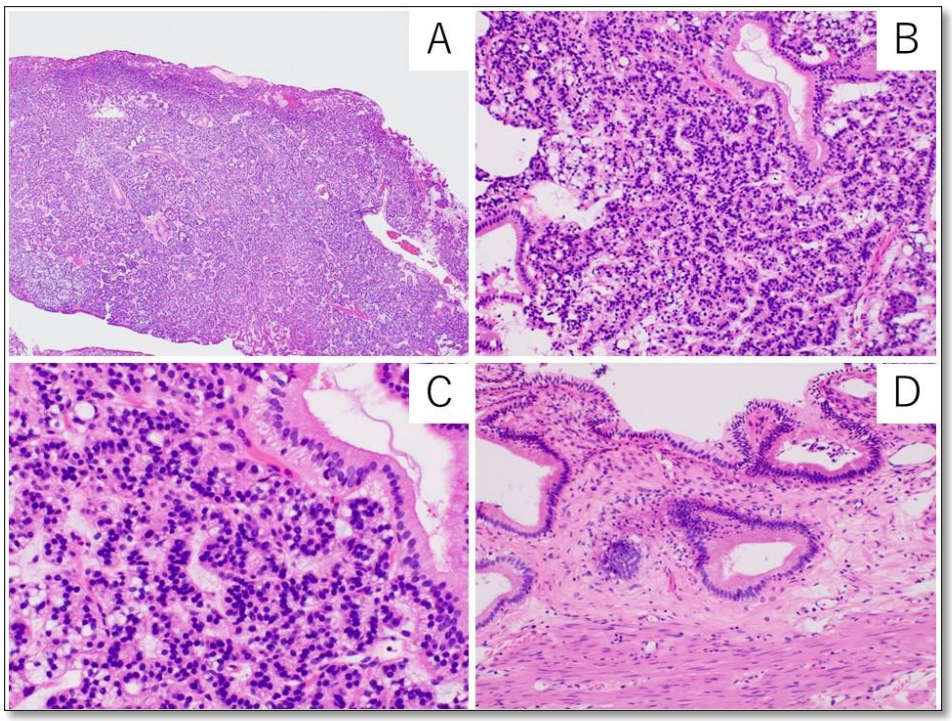

Figure 2. Histopathological findings of polypoid neuroendocrine tumor (NET) G1 of gallbladder (A, x4 objective lens). The polypoid tumor is composed of monotonous proliferation of tumor cells (B, x20 objective lens). The tumor cells have weakly eosinophilic cytoplasm and oval nuclei. Non-neoplastic biliary epithelium is seen in the right upper corner (C, x40 objective lens). The surrounding non-neoplastic mucosa shows surface mucous metaplasia (gastric-type phenotype) of the epithelium (D, x20 objective lens).

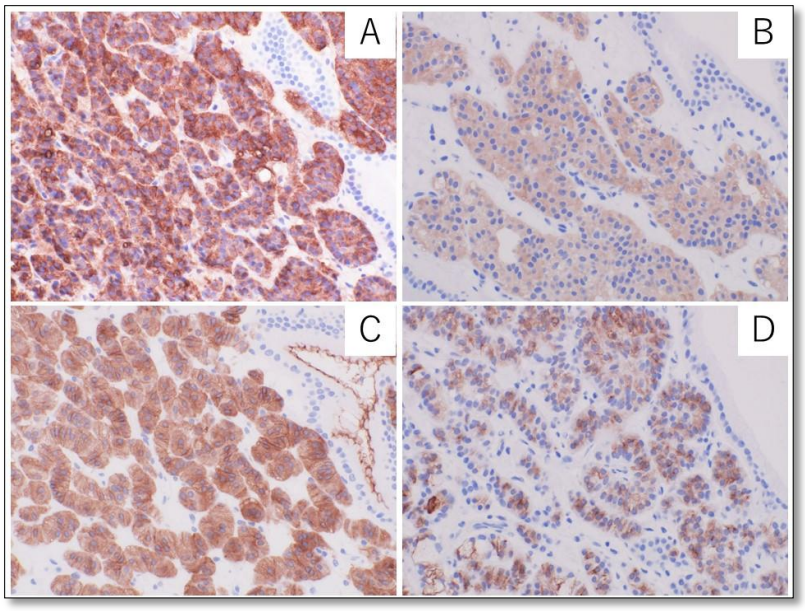

Figure 3. Immunohistochemical findings of polypoid neuroendocrine tumor (NET) G1 of gallbladder. The tumor cells are diffusely positive for chromogranin A (A, x40 objective lens), synaptophysin (B, x40), CD10 (C, x40) and MUC1 (D, x40).

Table 1. Immunohistochemical results of NET G1 of gallbladder.

	NET G1[a]	Surrounding mucosa
Chromogranin A[b]	+ (diffuse)	-
Synaptophysin[b]	+ (diffuse)	-
CD10[c]	+ (diffuse)	+
MUC1[d]	+	-
MUC5AC[e]	-	+
MUC6[e]	-	+
MUC2[f]	-	-
p53	-	-

[a] *NET G1, neuroendocrine tumor, grade 1*
[b] *Markers of endocrine differentiation*
[c] *Marker of proper biliary epithelial phenotype*
[d] *Marker of pancreato-biliary phenotype*
[e] *Markers of gastric-type metaplasia*
[f] *Marker of intestinal-type metaplasia*

Based on the above findings, the gallbladder tumor was diagnosed as NET, grade 1 (G1).

DISCUSSION

We describe a rare case of polypoid NET G1 of gallbladder. Primary NETs of gallbladder are extremely rare, estimated to account for 0.2% of all NETs [5,6]. NENs arise in most epithelial organs with widely differing clinical features and histopathological findings [2]. Previously, NENs were frequently called carcinoids including different clinicopathological findings. The majority of the previously reported cases, called "carcinoids or atypical carcinoids", were diagnosed as NECs with infiltrative/aggressive growth and poor patient's prognosis [3,4].

Since 2010, WHO classifications have proposed a uniform classification framework for all NENs. The key feature of the classification is the distinction between well-differentiated NETs and poorly differentiated NECs, while the term "carcinoid" is not recommended **(Table 2)**. Therefore, many of the recent reports have distinguished two

histological types: NETs and NECs, according to the WHO classification [3,4,7-9]. In the gallbladder cases, the majority of the NEC cases are mixed neuroendocrine carcinomas; i.e., mixed tumors of neuroendocrine carcinoma and non-neuroendocrine component. In the previous reports, the non-neuroendocrine components were diagnosed as adenocarcinomas (mixed adenocarcinoma-neuroendocrine carcinoma, MANEC). We have speculated the NEC components arose through the phenotypical transformation of the adenocarcinomas, because the adenocarcinoma components were frequently located to the mucosal/superficial parts and the NEC components were usually seen in the invasive/advanced areas.

Table 2. Neuroendocrine neoplasms (NENs) of gallbladder.

	Grade	Mitotic rate (mitoses/2 mm^2)	Ki-67 index
NET and NEC			
NET G1	Low	<2	<3%
NET G2	Intermediate	2-20	3-20%
NET G3	High	> 20	>20%
NEC (SCNEC/LCNEC)	High	> 20	>20%
MiNEN			
MANEC	High	> 20	>20%

Modified table, based on references [1,2]
NET: Neuroendocrine Tumor; NEC: Neuroendocrine Carcinoma; SCNEC: Small Cell Neuroendocrine Carcinoma; LCNEC: Lmall Cell Neuroendocrine Carcinoma; MiNEN: Mixed Neuroendocrine Neoplasm; MANEC: Mixed Adenocarcinoma-Neuroendocrine Carcinoma

In the gallbladder, the NET cases are fewer than the NEC cases [2]. Therefore, histogenesis of gallbladder NET is still poorly understood. Normal gallbladder mucosa lacks enterochromaffin cells, while a few enterochromaffin cells are present in the mucous glands of the gallbladder neck. On the other hand, gallbladder mucosa with chronic cholecystitis frequently exhibits metaplastic changes, such as gastric-type and/or intestinal-type metaplasia [11,12]. The metaplastic mucosa sporadically has enterochromaffin cells (also called Kulchitsky cells, non-neoplastic endocrine cells). In the present case, the surrounding gallbladder mucosa exhibited gastric-type metaplasia positive for MUC5AC and MUC6. Therefore, we speculated that anyone of the enterochromaffin cells (Kulchitsky cells) in the metaplastic mucosa showed neoplastic changes and progressed to the NET G1.

In conclusion, we demonstrate a rare case of polypoid NET G1 of gallbladder. Here, polypoid NET G1 should be added as one of the differential diagnoses of gallbladder polyps.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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