Minute Squamous Cell Carcinoma of the Gallbladder: a Case Report
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Following a simple cholecystectomy, a 63-year-old woman with gallstones was histologically diagnosed as having minute squamous cell carcinoma of the gallbladder. A laparotomy revealed a small, firm nodule that appeared to be an adenoma, which was palpated in the fundus of the gallbladder. The resected gallbladder contained 37 small stones and a small and firm mass (0.4 × 0.4 × 0.3 cm in size) on the mucosal side. Histologically, a pure type of well-differentiated squamous cell carcinoma of the gallbladder was diagnosed. To our knowledge, this is the first case of a minute and pure type of squamous cell carcinoma in the gallbladder. This case may have implications for the histogenesis of squamous cell carcinoma of the gallbladder.

Key words: gallbladder – squamous cell carcinoma – minute carcinoma

INTRODUCTION
The most common type of gallbladder cancer is adenocarcinoma. Squamous cell carcinoma accounts for only 0–12.7% of all gallbladder tumors (1). In the Surveillance, Epidemiology and End Results Program of the National Cancer Institute, only 45 (1.7%) of 3038 patients with gallbladder cancer were recorded as squamous cell carcinoma (2). Since squamous cell carcinoma of the gallbladder grows very rapidly, it is usually detected as a large carcinoma (1). This paper describes a very rare case of minute squamous cell carcinoma (0.4 × 0.4 × 0.3 cm) of the gallbladder, which was associated with multiple gallstones.

CASE REPORT
A 63-year-old woman was suspected of having cholecystolithiasis on the basis of an abdominal ultrasonogram (US) performed at a community clinic where she was receiving outpatient treatment for hypertension. In October 1989, she was admitted to the National Numata Hospital for a cholecystectomy. Upon admission, her height was 160 cm and her weight was 50 kg. She had neither conjunctival anemia nor jaundice. No abnormalities were detected in her abdominal examination. Laboratory tests revealed no abnormalities except for an elevation of alkaline phosphatase (308 IU/l). Serum levels of α-fetoprotein and carcinoembryonic antigen were normal. US showed many small strong echoes with acoustic shadows. Endoscopic retrograde cholangiopancreatography (ERCP) also showed many small radiolucent areas in the gallbladder. We diagnosed cholecystolithiasis and performed an operation. At laparotomy, no obvious inflammation of the gallbladder was observed, but a small and hard nodule was palpated in the fundus. Since this nodule was thought to be an adenoma, a simple cholecystectomy was performed. A total of 37 gallstones were contained in the resected specimen and a firm tumor, which was 0.4 × 0.4 × 0.3 cm in size, was noted at the base of the gallbladder (Fig. 1).

Histologically, the mass consisted of cords or sheets of malignant keratinized squamous cells separated by a fibrous stroma. Prominent keratinization with cancer pearl formation and intercellular bridge structure was evident. The cancer cells had invaded to the subserosal layer. However, no lymphatic or vascular permeation was observed (Figs 2 and 3). Both PAS and Alcian Blue staining were negative. Mucin production and tubular structure were not detected even on serial tissue section. The diagnosis of pure squamous cell carcinoma was made after examination of multiple tissue sections. Moderate dysplastic changes were observed in the surrounding gallbladder mucosa with chronic cholecystitis, but neither a metaplastic squamous epithelium nor a heterotopic squamous epithelium was observed. Nine years and eight months after the operation, the patient continues to be free from recurrence.
DISCUSSION

It is extremely difficult to detect squamous cell carcinoma of the gallbladder in the very early stage when the carcinoma is still minute. Squamous cell carcinoma accounts for only 0–12.7% of all cases of gallbladder cancer (1). The wide variation of the reported occurrence is probably due to the fact that in many of the series, adenosquamous carcinoma or mucoepidermoid carcinoma was also included as squamous carcinomas or in other series a poorly differentiated adenocarcinoma or an anaplastic carcinoma was misdiagnosed as squamous carcinoma (1,3). It is not rare to find portions of a squamous cell carcinoma in cases other than the usual adenocarcinoma of the gallbladder (4). These must be differentiated from the pure squamous cell carcinoma of the gallbladder (3). Excluding such cases, the incidence of pure squamous cell carcinoma is 0–3.3% (2,3,5,6). There is evidence of squamous epithelial differentiation characterized by keratinization or intercellular bridge formation without any tubular formation or mucin production. It has been suggested that rapid growth and metastasis and wide infiltration and dissemination are the characteristics of squamous cell carcinoma (7–9). This is probably due to including adenosquamous cell carcinoma with pure squamous cell carcinoma. Pure squamous cell carcinoma is characterized by a well-localized growth, no visceral metastasis and a rarity or lack of lymph node metastasis even when the tumor has grown to large size locally (1,3). However, a minute and pure squamous cell carcinoma in the gallbladder has never been reported. Regarding the etiology of squamous cell carcinoma of the gallbladder, various hypotheses have been proposed, including (i) malignant transformation of heterotopic squamous epithelium, (ii) malignant transformation of metaplastic squamous epithelium and (iii) squamous metaplasia of adenocarcinoma (1,7). However, there has been no report documenting the presence of congenital heterotopic squamous epithelium. Most authors now believe that the squamous cells seen in the squamous cell carcinoma of the gallbladder arise from squamous metaplasia or squamous differentiation of pre-existing adenocarcinoma (10). Muto et al. (11) histologically examined the resected gallbladders of 1,000 patients and found no evidence of squamous metaplasia. Most squamous cell carcinomas are found deep beneath an adenocarcinoma at the mucosal surface and a transitional
histological picture is observed between the adenocarcinoma and squamous carcinoma regions. Therefore, the hypothesis of squamous metaplasia of adenocarcinoma is very plausible (11). According to this hypothesis, squamous cell carcinoma develops as follows: an initial adenocarcinoma undergoes squamous metaplasia to produce an adenosquamous carcinoma, and a metaplastic carcinoma then grows rapidly and replaces the adenocarcinoma component to form a pure squamous cell carcinoma.

Since minute carcinomas possess the early features of carcinogenesis, these lesions may have important implications for the investigation of the histogenesis of all types of carcinoma. In the present case, a minute squamous cell carcinoma infiltrated the subserosal layer from the mucosal surface and it was found not to contain either a part of an adenocarcinoma or the transitional cells of an adenocarcinoma in conversion to squamous cell carcinoma. In addition, the cancer cells were negative for PAS and Alcian Blue staining and neither a metaplastic squamous epithelium nor heterotopic squamous epithelium was observed in the surrounding gallbladder mucosa. Mucin production and tubular structure were not detected even on serial tissue section. Therefore, the present squamous cell carcinoma appears to have histological features which differ from those in any of the proposed hypotheses. This case, therefore, merits consideration in future research into the histogenesis of squamous cell carcinoma of the gallbladder.

References