CASE REPORT

A 50 year-old man with a 30-year history of schizophrenia was referred to our hospital from a local clinic in October 2005 for a gastric mass that was found incidentally during an examination. At the local clinic, he underwent an endoscopic biopsy of the stomach and was diagnosed with an adenocarcinoma. In the abdominal computed tomography scan, a small flat mass was noted in the lesser curvature of the gastric antrum, but there were no enlarged lymph nodes or metastases to other organs. Moreover, he did not present with any gastric symptoms. A subtotal gastrectomy and gastroduodenostomy were performed in November 2005 with no indication of a yolk sac tumor. No tumors were found in any other sites, including the testes and pelvic area. Following the gastrectomy, the patient was discharged on the 14th postoperative day without any plan for chemotherapy or radiotherapy. He has not demonstrated any complications or other problems and has been relapse-free, both radiologically and biochemically, for 12 months since the operation.

Histopathology

The stomach specimen demonstrated a superficial-depressed ulcerative mass with elevation surrounding the mucosa in the antrum, measuring 4.5 × 3 cm (Fig. 1). The debris material contained in the gastric lumen was examined as well. The ulcerative lesion was diagnosed as a type IIc early gastric carcinoma, Gastric yolk sac tumors are extremely rare with only a few cases reported in the literature. Here, we present the case of a 50-year-old man with an adenocarcinoma and a yolk sac tumor of the stomach, without metastasis to the lymph nodes. The tumor was an early gastric carcinoma confined to the submucosa. Twelve months post-operation the patient was alive with no complications. The yolk sac tumor showed positive labeling for α-fetoprotein (AFP), α-antitrypsin (α-AT), cytokeratin (CK) and carcinoembryonic antigen (CEA), but was negative for human chorionic gonadotrophin (hCG), placental alkaline phosphatase (PLAP), epithelial membrane antigen (EMA) and p53. The adenocarcinoma was positive for α-AT, CK, EMA, and CEA, but was negative for AFP, hCG, PLAP, and p53. These findings suggest that the yolk sac tumor and the adenocarcinoma components are closely related and may represent distinct phenotypes that arise from a common mucosal epithelial cell.

Yolk sac tumors are rare malignant germ cell tumors that usually originate in the gonads. They rarely arise in extra-gonadal sites, including the mediastinum, sacrococcygeal region, upper respiratory tract, lung, female reproductive tract, and retroperitoneum.

Yolk sac tumors of the stomach are extremely rare, with only 8 cases reported in the English-language medical literature. They can present alone or associated with a conventional adenocarcinoma. This observation is very important to understand the pathogenesis of gastric yolk sac tumors.

We recently encountered a case of a gastric yolk sac tumor of the stomach associated with an adenocarcinoma. We present this case with a review of the literature and describe the close relationship that exists between these two components using immunohistochemistry.

Key Words: Stomach; Yolk sac tumor; Adenocarcinoma; Immunohistochemistry
which was confined to the submucosa.

The tumor demonstrated three histological types (Fig. 2): a yolk sac tumor, transitional area, and moderately differentiated adenocarcinoma. The tumor extended to the submucosa without metastasis to any (of the 9) regional lymph nodes. The debris material within the gastric lumen was diagnosed as components of the yolk sac tumor. The majority of the yolk sac tumor revealed reticular, nests and glands formed by columnar cells with abundant clear cytoplasm and a microcystic pattern lined by cuboid and flattened cells, with a festoon and pseudopapillary pattern (Schiller-Duval body). Periodic acid-Schiff (PAS) positive, diastase-resistant material was observed frequently in the yolk sac tumor (Fig. 3). Other components of germ cell tumors, such as choriocarcinoma, were not observed.

Immunohistochemistry

Immunohistochemically, the yolk sac tumor components showed strong positive cytoplasmic and membranous staining for α-fetoprotein (AFP), α1-antitrypsin (α1-AT), cytokeratin (CK) and carcinoembryonic antigen (CEA), but were negative for human chorionic gonadotrophin (hCG), placental alkaline

Fig. 1. The stomach shows an ulcerofungating mass in the antrum, measuring 4.5 × 3 cm.

Fig. 2. The tumor consists of a yolk sac tumor (A, B), transitional area (C) and adenocarcinoma (D). The yolk sac tumor shows nests and glands formed by columnar cells with abundant clear cytoplasm (A) and microcystic pattern (B).
phosphatase (PLAP), epithelial membrane antigen (EMA), and p53. The conventional intestinal-type adenocarcinoma and the transitional area demonstrated strong cytoplasmic staining for α1-AT, CK, EMA, and CEA, but was negative for AFP, hCG, PLAP, and p53 (Fig. 4, Table 1).

Fig. 3. Schuller-Duval body (A), and numerous PAS-positive hyaline globule in the extracellular and intracytoplasm, (B).

Fig. 4. Immunohistochemically, the yolk sac tumor components show strong positive cytoplasmic and membraneous staining for α-fetoprotein (A, B), cytokeratin (C) and Epithelial membrane antigen (D). Immunoreactivity of α-fetoprotein (B) shows positivity in the yolk sac tumor (left), but negativity in the transitional area of the yolk sac tumor and the adenocarcinoma (right). In contrast to α-fetoprotein, EMA staining shows positive in the adenocarcinoma (right) and negative in the yolk sac tumor (left).
Yolk Sac Tumor of the Stomach

DISCUSSION

Yolk sac tumors of the stomach are extremely rare, with only 8 cases reported in the English-language medical literature (Table 2). In six of the reported cases, the patients were male: four were over the age of 60 years, and the other two were 36 and 56 years old. Two patients were female, aged 72 and 38 years. Most of the reported cases were tumors composed of both yolk sac tumor and adenocarcinoma. However, two cases appeared to be pure yolk sac tumors without adenocarcinoma.

Immunohistochemically, yolk sac tumors demonstrate reactivity to AFP, α-AT, CK, CEA, hCG, PLAP, p53, and EMA. All except one case reported positive immunostaining for AFP in the yolk sac tumor component. The strong reactivity of the yolk sac components to AFP is particularly important, as adenocarcinoma components do not show AFP immunoreactivity.

In our case, the yolk sac components were positive for AFP, α-AT, CK, and CEA, whereas the adenocarcinoma and the transitional area were negative for AFP. AFP is a tumor marker that is usually expected to be observed in hepatocellular carcinomas and germ cell tumors, and is detected in the serum of patients. Up to 10% of gastrointestinal adenocarcinomas demonstrate no morphological features of germ cell tumors, yet they may stain positive for AFP. AFP-producing gastric carcinomas are rare neoplasms that comprise about 2-6% of all gastric carcinomas, and are mostly hepatoid adenocarcinomas.
However, some AFP-positive gastric tumors are gastric yolk sac tumors, and EMA can differentiate these, as hepatoid adenocarcinomas, but not yolk sac tumors, stain positive for EMA.\textsuperscript{9,10,21} The yolk sac component of the present case was negative for EMA. AFP-producing tumors are of particular interest to both clinicians and pathologists because they are highly malignant,\textsuperscript{6,22} and serum levels of AFP are useful in clinical management. Unfortunately, in this case, the serum AFP level was not measured because the clinicians were not suspicious of a yolk sac tumor. In any case, the serum AFP level is a useful clinical marker of the clinical course in patients with gastric yolk sac tumors as well as other AFP-producing tumors.\textsuperscript{10}

All types of gonadal and extragonadal germ cell tumors stain positive for PLAP.\textsuperscript{23} However, in the series of Biermann et al.,\textsuperscript{24} 2 of 30 germ cell tumor cases did not express PLAP as in the present case.

The exact origin of gastric yolk sac tumors, as well as other extra-gonadal yolk sac tumors, is not clear. Pure yolk sac tumors are thought to arise from migrating germ cells sequestered in the mid-line during embryogenesis,\textsuperscript{11} because no adenocarcinomatous components are observed.\textsuperscript{14} Another theory is that during carcinogenesis, somatic cells undergo dedifferentiation resulting in the appearance of a phenotype that is not intrinsic to the host organ, which is also called retrodifferentiation. In other words, germ cell differentiation resulted in somatic cells dedifferentiation during carcinogenesis.\textsuperscript{7,12} Retrodifferentiation of adenocarcinomas may result in the development of gastric yolk sac tumors since most of them are accompanied by adenocarcinomatous components, as in the present case.\textsuperscript{7,9-12,14} The same pattern of p53 mutations in the adenocarcinoma and yolk sac tumor components, as demonstrated by immunohistochemical and molecular techniques, such as PCR/SSCP analysis of p53 mutation and DNA sequencing, also supports this hypothesis.\textsuperscript{11} Both tumor components could have originated from the same cell clone, which supports the hypothesis that both tumor components represented a heterogeneous differentiation of the same tumor.\textsuperscript{11} In the present case, the mutant p53 expression in the adenocarcinoma and yolk sac tumor components was not identified.

AFP-producing gastric carcinomas can be differentiated from fetal intestines.\textsuperscript{12,25} However, most authors have emphasized the theory of retrodifferentiation to explain how tumors that contain germ cell components can arise in the stomach.\textsuperscript{25,26} The theory assumes that since the stomach arises from the foregut and that all cells contain complete genetic material, the tumor cells may dedifferentiate to form the yolk sac phenotype. In our case, a transitional area was observed between the adenocarcinoma and yolk sac tumor. Therefore, the yolk sac tumor may have therefore arisen from multipotent, neoplastic, mucosal epithelial cells rather than from displaced germ cells de novo.

The prognosis of gastric yolk sac tumors is poor. Patients with gastric yolk sac tumors often have widespread metastases at the time of diagnosis and a grave clinical course (Table 2). Response to chemotherapy and radiotherapy is generally poor, with a brief initial response that is followed by the development of resistance to chemotherapy.\textsuperscript{10,12} According to the literature, there is no survival benefit from postoperative radiotherapy or chemotherapy for gastric yolk sac tumors.\textsuperscript{17} Various treatments including chemotherapy, radiotherapy, and surgery have failed to improve the prognosis of this aggressive disease.\textsuperscript{7,9-12,14} In two cases,\textsuperscript{8,13} the patients survived for approximately 3 years after the diagnosis, but no other patients survived for more than 1 year after the diagnosis, despite various treatments. In the present case, no evidence of metastasis was detected by preoperative laboratory examination, including abdominal CT, intraoperative findings, and pathological examination. The patient remains alive and relapse-free 12 months after the operation.

In the present case, the patient was diagnosed as having an adenocarcinoma before the operation. Similarly, in seven of the eight previously reported cases,\textsuperscript{7-11,13,14} the diagnosis of a gastric yolk sac tumor was made after surgery or autopsy. One case\textsuperscript{22} was diagnosed by excisional biopsy of the lymph nodes. Thus, gastric yolk sac tumors are difficult to diagnose without precise histological examination.

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