Gastric Adenocarcinoma Producing Neuron-Specific Enolase

NOBUO ISHIWATA, MD, TAKAAKI IKEDA, MD, KIKO TOKUSHIMA, MD, SHINICHI TOZUKA, MD, SHIGEMI SAKAMOTO, MD, FUMIAKI MARUMO, MD, SHINSUKE AIDA, MD, and CHIFUMI SATO, MD

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Enolases (2-phospho-D-glycerate hydro-lyase, EC 4.2.1.11) are glycolytic enzymes that convert 2-phosphoglycerate to phosphoenolpyruvate. They are dimers composed of three immunologically distinct subunits α, β, and γ (1, 2). The γγ- and αγ-enolases are expressed preferentially in neurons and neuroendocrine cells (3, 4), and neuron-specific enolase (NSE) has often been used to refer to the γγ-enolase or γ-subunit itself (5).

Tumors with neuroendocrine characteristics, including small cell carcinoma of the lung and neuroblastoma contain high concentrations of NSE (6, 7). A majority of patients bearing such tumors have high serum NSE levels (8–10). Although neuroendocrine granules were often demonstrable ultrastructurally in gastric endocrine tumors (11–14) and a part of “solid carcinoma” of the stomach (15), gastric adenocarcinoma with high serum NSE levels has not been reported. Described in this article is an autopsy case of gastric adenocarcinoma with high serum NSE levels. NSE was detected in the carcinoma cells by immunohistochemistry, which was considered to result in elevated serum NSE levels.

CASE REPORT

Clinical Course. A 69-year-old man with a history of hypertension was admitted to our hospital on March 23, 1995, because of appetite loss and general fatigue. He had felt these symptoms since the beginning of February. Physical examination showed anemia and marked hepatomegaly. The liver was elastic, firm, and palpable three finger-widths below the right costal margin.

Laboratory examinations showed anemia (hemoglobin 9.5 g/dl), increased serum activity of lactate dehydrogenase (7962 units/liter), γ-glutamyltransferase (885 units/liter), alkaline phosphatase (1337 units/liter), aspartate amino-transferase (329 units/liter), and alanine aminotransferase (147 units/liter). Serum carcinoembryonic antigen (CEA) measured by an enzyme immunoassay kit (Dainabot Co. Ltd., Tokyo, Japan) was increased (4230 ng/dl). The assay for NSE was carried out with a commercially available NSE-radioimmunoassy kit (Eiken Co. Ltd., Tokyo, Japan). He had an extremely high level of serum NSE (65.1 ng/dl, reference range: <10 ng/dl). Abdominal ultrasonography and computed tomography revealed marked hepatomegaly and diffuse and multiple space occupying lesions, from 10 to 30 mm in diameter, in both lobes of the liver. Gastrofiberscopy showed Borrman type 2 gastric carcinoma. He was diagnosed as having well differentiated tubular adenocarcinoma of the stomach with multiple liver metastases by gastrofiberscopic biopsy and ultrasound-guided needle biopsy of the liver.

Chemotherapy with oral administration of tegafur (750 mg/day) had little effect, and he died of hepatic coma on April 19. Autopsy was performed 14 hr after death.

Pathological Findings. The autopsy examination disclosed an approx. 5-× 4-cm Borrman type 2 gastric carcinoma in the posterior wall of the gastric angle. Numerous liver metastases, up to 8 cm in diameter, approx. 5-mm metastasis in the right lung, and paragastic lymph node metastases were also found. No other primary tumors except the gastric carcinoma were detected. Microscopically, the gastric carcinoma and its metastases were tubular adenocarcinoma showing a mixed pattern of well- and poorly differentiated components (Figure 1a and b). Intraluminal surface cell membranes in the well-differentiated part and intracytoplasmic microglands in the poorly differentiated part of the tumor retained mucin, an exocrine marker, as proven by alcian blue–PAS stain.

Immunohistochemical Findings. The immunohistochemical staining was performed on formalin-fixed paraffin sections using the streptavidin–biotinylated peroxidase com-
plex method. The antibodies used in this study were polyclonal rabbit anti-NSE antibodies, monoclonal mouse anti-chromogranin-A, anti-CEA antibodies, and biotinylated second antibodies of LSAB kit (Dakopatts, Tokyo, Japan). The poorly differentiated part of the carcinoma was positive for NSE (Figure 2a), and the well-differentiated part was negative for NSE (Figure 2b). Chromogranin A, an endocrine granule marker (16), was negative in both well-differentiated and poorly differentiated parts, while CEA was positive in both parts.

**DISCUSSION**

NSE was originally extracted from bovine brain (17) and was later found in endocrine cells of the central and peripheral divisions of the diffuse neuroendocrine system (18). Therefore, NSE has been considered a marker for neuroendocrine tumors (7, 10).

Fig 1. Photomicrograph of the gastric carcinoma: (a) well-differentiated part of the tumor showing tubular structure consisted of high columnar tumor cells; (b) poorly differentiated part consisted of irregular-shaped tumor cells with intracytoplasmic microglands.