Case Report

Spontaneous Gastric Carcinoid Tumor in a Male B6C3F1 Mouse

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Abstract: A gastric carcinoid was found in the glandular stomach of an untreated male B6C3F1 mouse of 109 weeks old. Neoplastic cells had a hyperchromatic nucleus and scant cytoplasm, and were grouped into lobules by fine connective tissue, a characteristic growth pattern of arrangement of the neuroendocrine organ. The cytoplasmic granules were argyrophilic when stained with Grimelius and Sevier-Munger stain. Immunohistochemically, the neoplastic cells were positive for neuron specific enolase and synaptophysin. In the electron microscopic examination, they contained numerous cytoplasmic granules consistent morphologically with neuroendocrine secretory granules. Metastases were present in the regional lymph nodes. (J Toxicol Pathol 2003; 16: 175–178)

Key words: carcinoid tumor, B6C3F1 mouse, spontaneous

Few spontaneous tumors of the glandular stomach are reported in laboratory animals with the exception of African rodent Praomy (Mastomys) natalensis which is known to develop gastric carcinoid spontaneously at high frequency1. Spontaneous gastric carcinoid is of the tumor type extremely rare in rats and mice, and only 3 cases have been reported in old Sprague-Dawley rats2,3, and 9, 7, and 2 cases in B6C3F1 mice4,5. Striped Field mice6, and CD-1 mice7, respectively. In the present communication, we describe morphological, immunohistochemical and ultrastructural features of a spontaneous gastric carcinoid found in a male B6C3F1 mouse.

The animal served as a control in a 2-year carcinogenicity study, and was kept individually in a suspended wire-mesh cage in a barrier system room maintained at a temperature of 22 ± 2°C and a relative humidity of 55 ± 10% with a 12-hr light cycle. Commercial diet (CE-2, Clea Japan Inc., Japan) and city water were available ad libitum.

The animal showed no unnatural clinical signs over the course of the study, and was euthanized by exsanguination under ether anesthesia at the study termination when it was 109 weeks of age. At necropsy, a large mass measuring 8×9×2 mm was observed at the fundus of the glandular stomach in association with ulceration. The regional lymph nodes were enlarged. All organs and tissues including the mass were fixed in 10% neutrally buffered formalin, processed routinely to paraffin blocks, sectioned at 5 µm, stained with hematoxylin and eosin (HE), and examined histopathologically.

Histopathologically, the mass was confined in most part to the gastric mucosa; however, there were several multiple small foci found beneath the muscularis mucosa (Fig. 1). These lesions were composed primarily of a sheet of small round cells containing a hyperchromatic nucleus and scant cytoplasm with indistinct cell boundary (Fig. 2). These cells were subdivided by fine fibrous septa into small lobules, a characteristic growth pattern of arrangement of neoplastic cells arising from the neuroendocrine tissues (Fig. 3). The neoplastic cells located adjacent to the ulcer were rather arranged in anastomosing cords and had spindle or vacuolar appearance. Mitoses were infrequently noted across the whole mass.

The regional lymph nodes were nearly completely replaced by the neoplastic cells. Unlike in the original gastric mass, the solid, acinar or trabecular form was predominant in these metastatic lesions (Fig. 4). To characterize the cytoplasmic content, Grimelius and Sevier-Munger argyrophil silver stain, Fontana-Masson argentaffin silver stain and periodic acid-Schiff (PAS) reaction techniques were applied. As a result, the cytoplasmic granules were stained in dark-brown by Grimelius and Sevier-Munger stain, whereas they were unstained by the other two, indicating that the neoplastic cells were of the type classified into argyrophilic endocrine cells (Fig. 5).
Fig. 1. Glandular stomach. Neoplastic cells are located within the mucosa and beneath the muscularis mucosa. HE, × 17.

Fig. 2. Neoplastic lesions are composed of small round cells with a hyperchromatic nucleus and scant cytoplasm. HE, × 250.

Fig. 3. Neoplastic cells are grouped into small lobules by the fine connective tissue. Reticulin stain, × 170.

Fig. 4. Metastasis to the regional lymph node. Neoplastic cells are in solid form. HE, × 80.

Fig. 5. Cytoplasmic granules demonstrate strong argyrophilic reaction. Grimelius and Sevier-Munger stain, × 250.

Fig. 6. Cytoplasmic granules are positive to anti-NSE antibody. Anti-NSE immunohistochemistry, × 250.
Amongst immunohistochemical staining performed with an avidin-biotin complex LSAB kit (DAKO Corp., USA) using antibodies against neuron-specific enolase (NSE), chromogranin A, synaptophysin, glucagons, insulin, somatostatin, gastrin and cytokerin (DAKO Japan, Japan), the NSE and synaptophysin showed a strong reactivity in the neoplastic cells of all the cell type (Fig. 6), while the others were uniformly negative.

For further evaluation, ultrathin sections were prepared from formalin-fixed tumor samples, stained with uranyl acetate and lead citrate, and examined with a transmission electron microscope (H-7000, HITACHI Co., Ltd., Japan). The cytoplasm was filled with numerous secretory granules measuring 100–600 nm in diameter (Fig. 7). The granules had a characteristic electron-dense core surrounded by electron-lucent halo. Well developed Golgi complex and mitochondria were another electron microscopic features for the neoplastic cell. All these morphological, behavioral, histochemical and immunohistochemical findings obtained from the gastric mass were well consistent with gastric carcinoid reported in mastomys1, mice4–7 and rats2,3.

Other key lesions found in this male B6C3F1 mouse included hemangiosarcoma in the liver, alveolar-bronchiolar adenoma and preputial gland abscess, all being irrelevant to gastric carcinoid and of the type not uncommon in this strain of mice at this age.

Gastric carcinoids can be induced in rats and mice by treatment with various compounds over a prolonged period of time. They may include H2 receptor antagonists; loxidine8, BL-63419, SKF9347910 and ICI162,84611, and a H+, K+–ATPase inhibitor; omeprazole12. Hypergastrinemia resulting from decreased gastric acid secretion is a common finding, and the sustained hypergastrinemia is thought in turn to stimulate proliferation of enterochromaffin-like cells, leading ultimately to tumor production. On the contrary, spontaneously occurring gastric carcinoids in CD-1 mice were reported not to be associated with hypergastrinemia7. In our case, there were no morphological evidences that could suggest G-cell activation, and therefore, hypergastrinemia was unlikely present. Gastric carcinoids spontaneous in origin and those related to chemical treatment appear to differ from each other with respect to underlying pathogenesis for tumorigenesis.

References


