Case Report

Spontaneous Pituitary Carcinoma of the Pars Intermedia in a B6C3F1 Mouse

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Abstract: We encountered one pituitary carcinoma derived from the pars intermedia in an untreated female B6C3F1 mouse in a carcinogenicity study. A white nodule (6 × 5 × 3 mm) was observed in the base of the brain at necropsy. Tumor cells were histologically arranged in a solid sheet or nest-like structures, and had round or oval nuclei and pale eosinophilic granular cytoplasm. Sporadic mitotic figures were seen in the tumor while necrosis was a prominent feature. In addition, distinct infiltration into the brain parenchyma was observed. Immunohistochemically, tumor cells were positive for α-melanocyte stimulating hormone (α-MSH), γ-melanocyte stimulating hormone (γ-MSH), β-endorphin and adenocorticotropic hormone (ACTH), but were negative for prolactin. However, there were no histological abnormalities such as adrenocortical hyperplasia related to the pars intermedia tumor. These results suggest that the tumor cells might not have actively secreted proopiomelanocortin (POMC)-derived peptides. The present report provides additional histopathological evidence of pituitary carcinoma of the pars intermedia in aging mice.

Key words: pituitary carcinoma, pars intermedia, mouse, infiltration, immunohistochemistry

Pituitary tumors of the pars distalis are common neoplasms in aging mice of some strains such as B6C3F1. Pituitary adenomas of the pars distalis occur more often in female than in male mice, and a similar situation exists in rats. For example, the incidences of pars distalis neoplasm in B6C3F1 mice are reported as being approximately 0.2% and 15% for males and females, respectively, in the National Toxicology Program historical control database of the previous 2-year carcinogenicity studies. In contrast, pituitary adenomas of the pars intermedia are uncommon neoplasms, and pituitary carcinomas of the pars intermedia are extremely rare tumors in aging mice. Previous reports have described the criteria for pituitary carcinoma of the pars intermedia as follows: (i) projection into a large cystic space; (ii) abutting against brain or bone without infiltrating brain or bone; (iii) infiltration into the meninges. Another report described the critical points for differential diagnosis between carcinoma and adenoma of the pars intermedia as being distinct infiltration into the brain. In addition, although these tumor cells demonstrated immunoreactivity for adenocorticotropic hormone (ACTH), detailed morphological and immunohistochemical features have remained unclear. Herein, we describe our experience with a single pituitary tumor suspected to be a carcinoma derived from the pars intermedia in an aged mouse at our center. The present report describes the histological and immunohistochemical characteristics of the tumor.

The animal was a female Crj:B6C3F1 (C57BL/6N × C3H/HeN) mouse in the untreated group of a carcinogenicity study. The animal was housed individually in an aluminum cage with a stainless steel wire mesh front and floor, under barrier conditions of 23 ± 3°C room temperature, 55 ± 20% relative humidity, and a 12 hour light-dark cycle. The animal had free access to a standard radiation-sterilized laboratory diet (CRF-1, Oriental Yeast Co. Ltd., Tokyo, Japan) and tap water via an automatic water supply system. All animal care and procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals at the Biosafety Research Center, Foods...
Drugs and Pesticides (An-Pyo Center). The animal was observed for clinical signs twice a day (in the morning and afternoon). The animal showed the clinical sign of emaciation at 64 weeks of age, and piloerection, staggering, swelling of the head and decreased locomotor activity became apparent at 68 weeks of age. Therefore, the animal was euthanatized by exsanguination via the abdominal aorta under ether anesthesia at 68 weeks of age.

At necropsy, a white nodule (6 × 5 × 3 mm) was observed in the base of the brain and the pituitary gland was not recognizable. After gross postmortem examinations, the nodule was fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 3 µm and stained with hematoxylin and eosin (H&E) for routine histopathological
except prolactin and PCNA, are proopiomelanocortin. We chose these antibodies because the relevant hormones, concurrently stained for control of immunohistochemistry. Pituitary adenoma of the pars intermedia in aging mice were analyzed. LSAB2 System-HRP, CA, USA). Tissue sections of typical adenoma of the pars intermedia in aging mice were concurrently stained for control of immunohistochemistry. We chose these antibodies because the relevant hormones, except prolactin and PCNA, are proopiomelanocortin (PCNA, clone: PC10, DAKO, Denmark, dilution 1:50), anti-prolactin (R&D Systems, Inc., MN, USA, dilution 1:10) and anti-proliferating cell nuclear antigen (PCNA, clone: PC10, DAKO, Denmark, dilution 1:50), using a labelled streptavidin-biotin method (DAKO LSAB2 System-HRP, CA, USA). Tissue sections of typical pituitary adenoma of the pars intermedia in aging mice were concurrently stained for control of immunohistochemistry. We chose these antibodies because the relevant hormones, except prolactin and PCNA, are proopiomelanocortin (POMC)-derived peptides9. Furthermore, the intermediate lobe of the pituitary gland is a major part of the POMC system in mice and rats8.

The white nodule grossly resembled a tumor arising from the brain because the nodule adhered to and merged into the brain tissue. Histologically, the tumor was considered to have been derived from the pars intermedia of the pituitary gland because the pars distalis was separated from the tumor mass and compressed at the base of the brain. The tumor of the pars intermedia had grown expansively, and showed infiltrative growth into the brain parenchyma (Fig. 1). Clinical signs including swelling of the head were considered to be attributable to compression of and damage to the base of the brain, including the hypothalamus by the pituitary tumor. The tumor consisted of polygonal or elongated cells, and tumor cells were arranged in a solid sheet or nest-like structures intermingled with fibrovascular stroma. Tumor cells had round or oval nuclei and pale eosinophilic granular cytoplasm (Fig. 2), and showed slight cellular pleomorphism. Sporadic mitotic figures were seen in the tumor while necrosis was a prominent feature. A large number of PCNA-positive nuclei was observed in the tumor compared with adenoma of the pars intermedia (Fig. 3). In addition, distinct infiltration into the brain parenchyma was observed in some areas (Fig. 4). However, distant metastases were not observed.

Immunohistochemically, tumor cells were positive for α-MSH (Fig. 5), γ-MSH (Fig. 6), β-endorphin (Fig. 7) and ACTH (Fig. 8), but negative for prolactin. However, there were no histological abnormalities such as adrenocortical hyperplasia related to this pars intermedia tumor. As in the case of this animal, it was reported that mice and rats with paras intermedia adenomas had no endocrinological abnormalities in the other organs including the adrenal glands6. On the other hand, there are interesting reports of paras intermedia adenoma affecting other organs and causing functional changes in horses and dogs. Pituitary adenomas of the pars intermedia in horses immunohistochemically express POMC, α-MSH, β-endorphin and ACTH10. High levels of plasma ACTH and/or adrenocortical hyperplasia have been reported in some horses with pituitary adenomas11,12. In the pars intermedia of dogs, most cells demonstrated immunoreactivity to either ACTH or α-MSH13. Adenomas of the pars intermedia in dogs were endocrinologically inactive and associated with varying degrees of hypopituitarism and diabetes insipidus, or were endocrinologically active and secreted excessive amounts of ACTH, leading to bilateral adrenocortical hyperplasia and a syndrome of cortisol excess14. Our histopathological and immunohistochemical results suggest that the tumor cells might not have actively secreted POMC-derived peptides, though we have no data on the serum concentrations of these hormones in this animal. In conclusion, the mouse described above was found to have a pituitary carcinoma of the pars intermedia. The present report provides additional histopathological evidence of pituitary carcinoma of the pars intermedia in aging mice.

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Fig. 1. Low-power magnification of the pituitary tumor of the pars intermedia. The tumor shows expansive growth and infiltrative growth into the brain parenchyma (arrows). Necrosis (asterisks) is a prominent feature of the tumor. PT: pituitary tumor, A: Ammon’s horn, C: cerebral cortex, H&E. Bar = 1 mm.

Fig. 2. High-power magnification of the pituitary tumor of the pars intermedia. The tumor consists of polygonal or elongated cells, and tumor cells are arranged in a solid sheet or nest-like structures intermingled with fibrovascular stroma. Tumor cells have round or oval nuclei and pale eosinophilic granular cytoplasm. H&E. Bar = 50 μm.

Fig. 3. A large number of PCNA-positive nuclei is observed in the tumor. Inset: the number of PCNA-positive nuclei in adenoma is far fewer than the present case. Bar = 100 μm.

Fig. 4. High-power magnification of the pituitary tumor of the pars intermedia. Note the distinct infiltration into the brain parenchyma. H&E. Bar = 50 μm.

Fig. 5. Tumor cells are positive for α-MSH by immunohistochemical staining. Bar = 50 μm.

Fig. 6. Tumor cells are positive for γ-MSH by immunohistochemical staining. Bar = 50 μm.

Fig. 7. Tumor cells are positive for β-endorphin by immunohistochemical staining. Bar = 50 μm.

Fig. 8. Tumor cells are positive for ACTH by immunohistochemical staining. Bar = 50 μm.
References