Small Cell Anaplastic Carcinoma of the Lung with Cerebral Metastasis in a Dog
Takashi MORI, Tetsushi YAMAGAMI, Masaki UMEDA, and Masahiro SUGIYAMA
Department of Veterinary Pathology, Nippon Veterinary and Animal Science University, 1-7-1 Kyonan-cho, Musashino, Tokyo 180, Japan
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Primary lung tumors are uncommon in domestic animals in contrast to their high incidence in man. Most of the cases belong to adenocarcinomas, squamous cell carcinomas are occasionally encountered in dogs, and anaplastic carcinomas are uncommon [2, 9-11, 17, 18]. In the canine species, some anaplastic carcinomas of the lung have been described [2, 10, 12, 17]. This report describes the pathological, histochemical and immunohistochemical studies of a small cell anaplastic lung carcinoma with cerebral metastasis in a dog.

A 5-year-old, female Japanese dog (Shiba dog), weighing 20.2-kg was referred to the Nippon Veterinary and Animal Science University for pathological examination. She showed intermittent epilepsy-like symptoms, turning towards the right, and marked respiratory noises with dyspnea until death on the 7th day after onset of symptoms. Therefore, she was euthanized.

At necropsy, multiple tumor masses of various sizes were seen in the left and right lobes of the lung. The largest tumor mass was located in the right caudal lobe, spherical, 5.5 to 6 cm in diameter, well circumscribed, yellowish and soft (Fig. 1). On cut surface, such neoplastic masses varied in size, 2.5 to 6 cm in diameter and were pinkish white or light yellow in color with rather regular borders, compressing the adjacent pulmonary parenchyma. These lesions were spread in the pulmonary parenchyma in close association with the larger bronchi. Cavitations were noted in confluent larger nodules. The largest mass showed severe liquefactive change with congested vessels. There was no adhesion between the tumors and the chest wall, hilum pulmonis or mediastinum including the adjacent lymph nodes.

In the corpus callosum of the left cerebral hemisphere, there was a yellowish round tumor, 1.5 cm in diameter, with liquefaction in the central portion and relatively regular borders. On cross section, the tumor compressed the lateral ventricles of both sides and the mesencephalic aqueduct, resulting in distortion of the midbrain and hippocampus (Fig. 2). No metastasis was noted in the other organs.

Tissue specimens were fixed in 10% neutral buffered formalin solution and routinely embedded in paraffin. Sections were stained with hematoxylin and eosin, or silver stain. Grimmelius stain was performed to evaluate cytoplasmic neuroendocrine granules in the neoplastic cells. Paraffin sections of formalin-fixed tissue were also examined immunohistochemically by the streptavidin-biotin (SAB) technique (Histofine SAB-PO KIT; Seikagaku Kogyo, Tokyo, Japan), using the following primary antibodies against cytokeratin (CK; dilution of 1:400, DAKO, Santa Barbara, CA), neuron specific enolase (NSE; dilution of 1:400, DAKO, Santa Barbara, CA), carcinoembryonic antigen (CEA; dilution of 1:400, DAKO, Santa Barbara, CA), glial fibrillary acidic protein (GFAP; dilution of 1:400, DAKO, Santa Barbara, CA), and S-100 protein (dilution of 1:400, DAKO, Santa Barbara, CA).

Microscopically, almost all the tumor masses were
composed of relatively small tumor cells. The pulmonary parenchyma was atelectatic due probably to continuous pressure by expansive and partially infiltrative growth. Tumor tissues were separated by delicate stroma (Fig. 3). Necrotic changes were frequent and widespread in the larger nodules. Neoplastic cells were clustered in many bronchioles, alveoli and veins. In addition, the neoplastic nests contained a few indistinct keratinized areas indicating a differentiation towards squamous epithelium. In the cerebrum, the parenchyma adjacent to the tumor tissue exhibited moderate spongy degeneration and mild astrocyte reaction. No keratinized areas were noted in the cerebral neoplastic mass.

Cytologically, almost all the neoplastic cells were polygonal or spindle in shape, with an uneven and discernible outline. The nuclei, intermediate in size, had clumped chromatin and multiple distinct nucleoli (Fig. 4). Mitotic figures were frequent. The cells of the largest tumor mass showed marked atypia, necrotic changes, infiltrative growth and many mitotic figures. In some clusters of these neoplastic cells, there were seen small, round or ovoid tumor cells with indistinct cytoplasm and darkly stained basophilic nuclei. These resembled so-called oat cell.

By Grimelius stain, some neoplastic cells of both the lung and cerebrum disclosed diffusely dark, fine granules in the cytoplasm (Fig. 5).

Immunohistochemical studies using CK disclosed positive immunoreactions in some intermediate sized pulmonary neoplastic cells and also in the keratinized areas (Fig. 6). In the cerebrum, only a small number of intermediate sized neoplastic cells had positive immunoreactions. In comparison to the reaction with CK, a weaker positive immunoreaction of neoplastic cells to NSE was observed in the tumor tissues of both the lung and cerebrum. These cells resembled the positively immunoreactive cells to CK in both size and shape. No positive immunoreactions with CEA, GFAP, or S-100 protein were observed in neoplastic cells in the lung and cerebrum.

The present case had the characteristic features of the polygonal type of small cell anaplastic carcinoma of the lung, according to the WHO classification of tumors of domestic animals [18]. Furthermore, the neoplastic cells in the lung and cerebral lesions had the same features, implicating metastasis from the primary lung lesion.

Several immunohistochemical studies on small cell anaplastic carcinoma of the lung in man [1, 3, 15, 16] have noted that some neoplastic cells had varied degrees of positive immunoreactions to CK, NSE, and CEA. Immunohistochemistry was helpful for diagnosis, since the present case had a positive immunoreaction with CK and NSE in partial agreement with the human cases.

The presence of a few keratinized areas in the neoplastic masses are explained as heterogeneity. Previous reports have described the occurrence of dissimilar tissue and cells occasionally in the same neoplastic tissue of the lung [9, 18]. This heterogeneity tends to occur in the lung, because the bronchial alveolar system is composed of

Fig. 3. A neoplastic mass of right caudal lobe of lung. Relatively small-sized tumor cells are expensively growing supported by delicate stroma. HE stain. ×100.

Fig. 4. Neoplastic cells of lung. Most cells are polygonal or spindle. The nuclei are intermediate in size with clumped chromatin and multiple nucleoli. HE stain. ×600.

Fig. 5. Neoplastic cells of lung. There are diffusely distributed dark, fine cytoplasmic granules in the cytoplasm. Grimelius stain. ×600.
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 Fig. 6. Neoplastic cells of lung. There is positive reaction in intermediate sized neoplastic cells (arrows) and keratinized areas (arrowhead). Immunohistochemical stain to CK. \*200.

many types of epithelial cells [13].

The largest tumor mass of the lung in the present case was evaluated as the primary growth, basis of the following pathological findings; the growth was in close association with the larger bronchi and there were severe necrotic changes and atypia.

Recently, small cell anaplastic carcinomas have been described as an undifferentiated neuroendocrine neoplasm, because neuroendocrine granules were discovered in the cytoplasm of the neoplastic cells [14]. This neoplasm occurs not only in the lung, but also in the thymus, esophagus, pancreas, neck, prostate, and stomach [5]. The origin of these neoplasms is believed to be solitary neuroendocrine cells or organized neuroepithelial bodies which are principally located in the tracheobronchial tree including the bronchi, mucous glands, and bronchioles [1, 4].

The neoplastic cells in the present case, identified as argentaffin cells by Grimelius stain, were supposed to have a similar origin.

This neoplasm frequently invades the lymphatics, blood vessels, alveoli and stroma at an early stage [1, 9]. The common sites of metastasis of lung carcinoma are the regional lymph nodes, spleen, heart, pericardium, pleura, kidney, skeleton, and skeletal muscles [2, 7, 9–12, 17–19].

Metastasis to the adrenal glands and brain is rare in domestic animals [6, 7, 19]. Although some metastases to the central nervous system have been described in primary lung carcinomas in domestic animals [8, 12, 17], no previous reports have documented the metastasis of this tumor to the cerebrum.

REFERENCES