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NOTE

Surgery

Clinical features and their course of pituitary carcinoma with distant metastasis in a dog

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ABSTRACT. An 11-year-old male toy poodle with neurological symptoms was diagnosed with a macroscopic pituitary tumor, which produced adrenocorticotropic hormone. Radiation therapy with a linear accelerator was performed for the pituitary tumor, and resulted in good local tumor control. However, serum endogenous adrenocorticotropic hormone concentrations were uncontrollable even after the tumor disappeared. Abdominal computed tomography revealed splenic masses, and splenectomy was performed. Histopathological examination of the surgical specimen showed tumor cells with eosinophilic and finely granular cytoplasm suggestive of endocrine origin. Since these cells were positive for adrenocorticotropic hormone, the case was diagnosed as a pituitary carcinoma with distant metastasis. Necropsy revealed multiple metastases to the abdominal organs. This is the first case report describing canine pituitary carcinoma with distant metastasis.

KEY WORDS: adrenocorticotropic hormone, distant metastasis, dog, pituitary carcinoma, spleen

Macroscopic pituitary tumors are common brain tumors in dogs, and compression of the surrounding normal brain tissue leads to various neurological symptoms [8, 13]. To treat these tumors, megavoltage radiation therapy is currently used, and has resulted in a better prognosis [2, 5, 9, 12, 20]. Some macroscopic pituitary tumors are hormonally functional and produce adrenocorticotropic hormone (ACTH), which may present clinically as pituitary-dependent hyperadrenocorticism (PDH). Shorter survival times have been reported in ACTH-active cases compared with those of ACTH-negative cases [5]. To date, the general purpose of treatment for pituitary tumors in dogs has been to achieve local tumor control, and little attention has been paid to distant metastases.

Pituitary tumors are also common in humans; however, pituitary tumors with distant metastases have been reported rarely. These cases are called pituitary carcinomas, and they account for only 0.1−0.2% of all pituitary tumors [6, 16, 18]. Furthermore, human pituitary carcinoma is reported to occur frequently in hormone-secreting tumors, especially in prolactin- and ACTH-secreting tumors [6, 22].

In small animal practice, information on pituitary carcinoma can be found in one veterinary pathology textbook [17], and in one case report [4]; however, the information in these sources is limited to pathological findings, with no clinical information. We experienced a case of a dog with an ACTH-producing pituitary tumor, which metastasized to distant organs, including the spleen and liver. We report the clinical features of the dog, obtained from a treatment period of over 1 year, including clinical symptoms and their course, time-sequential change in ACTH concentration, diagnostic imaging for metastatic lesions and the necropsy findings.

An 11-year-old male toy poodle visited our animal medical center (Day 0) for radiotherapy for the pituitary tumor. The patient was diagnosed previously with a pituitary tumor based on diagnostic imaging to evaluate the neurological symptoms of circling and anorexia. At the first visit, the dog's general condition was stable. Blood examination showed no abnormalities other than mild alkaline phosphatase (ALP) elevation; however, serum endogenous ACTH concentration was 35.9 *p*g/m*l*, which was slightly above the upper limit of the normal range, and in an ACTH stimulation test, post-cortisol concentrations were elevated (34.7 μg/d*l*).

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Brain contrast-enhanced magnetic resonance imaging (MRI) revealed a pituitary mass showing uniform enhancement (Fig. 1A). Abdominal computed tomography (CT) examination also showed bilateral adrenal gland enlargement. These results suggested that this case was an ACTH-producing macroscopic pituitary tumor.

Radiation treatment was performed with a linear accelerator (Elekta Synergy; Canon Medical, Ohtawara, Tochigi, Japan). The tumor was irradiated with a total dose of 42 Gy twice a week for a total of 10 doses. At the end of the radiation therapy (Day 40), the tumor remained visible on MRI, but had almost disappeared 2 months after the end of treatment (Day 98, Fig. 1B). The dog's general condition was well maintained, but serum endogenous ACTH concentrations remained above the upper limit of the normal range even after treatment. Therefore, treatment with oral trilostane was continued. However, serum endogenous ACTH increased gradually to 122 *p*g/m*l* on Day 168 and 319 *p*g/m*l* on Day 231. Blood examination and diagnostic imaging were performed on the suspicion of recurrence of the pituitary tumor. Laboratory blood examination showed a marked increase in liver enzymes (ALP: >35,000 IU/*l*, alanine aminotransferase: 3,005 IU/*l*). MRI showed no recurrence of the tumor in the pituitary region; however, abdominal contrast-enhanced CT revealed multiple lesions in the spleen appearing as ring-shaped enhancement (Fig. 2A). A large thrombus was also found in the lumen of the portal vein branching into the right lobe of the liver, suggesting that the blood flow in the liver was markedly decreased (Fig. 2B).

On Day 243, an exploratory laparotomy was performed, and the spleen was surgically and routinely removed. A large number of macroscopic white nodules were found in the removed spleen (Fig. 3A and 3B) consisting of cuboidal to polyhedral neoplastic epithelial cells arranged in cords and nests. The tumor cells had eosinophilic and finely granular cytoplasm suggestive of endocrine origin. The tumor cell nuclei showed moderate to high atypia and a high mitotic rate. As the tumor cells were positive for ACTH (Primary antibody: Rabbit polyclonal; ZYMED, San Francisco, CA, USA), the masses were diagnosed as metastatic lesions from the pituitary tumor to the spleen (Fig. 3C and 3D). The liver was ischemic on gross appearance; however, no nodular lesions were observed. On the day after surgery, the serum endogenous ACTH concentration was 81.6 *p*g/m*l*, which was sharply decreased to approximately 1/6th of the preoperative value of 526 *p*g/m*l*. Postoperatively, medical treatment with oral trilostane and thrombolysis was continued. However, serum endogenous ACTH concentrations increased again to 526 *p*g/m*l* on Day 314 and 1,244 *p*g/m*l* on Day 342. CT examination performed on Day 314 revealed multiple masses in the liver, with no detectable lesions

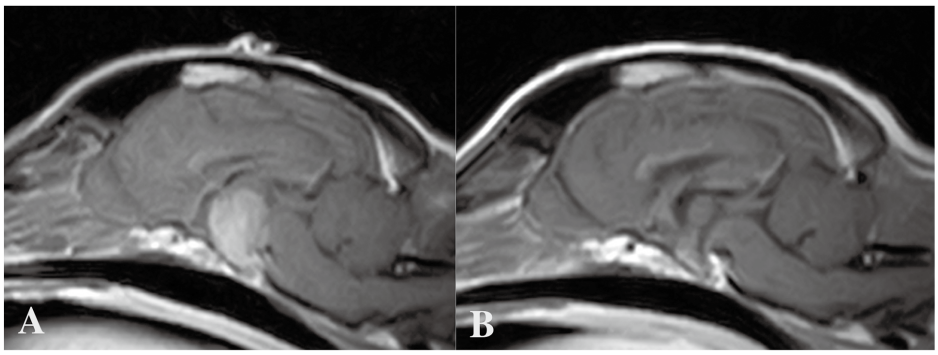

Fig. 1. T1-weighted sagittal contrast-enhanced magnetic resonance (MR) images in the dog in this case. A: at first admission, B: on Day 98. The pituitary tumor disappeared after radiation therapy.

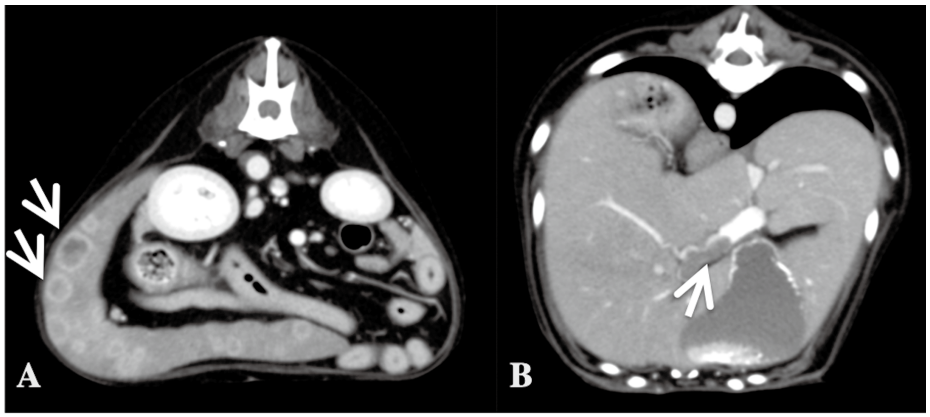

Fig. 2. Computed tomography (CT) findings in the dog on Day 231. A: Multiple lesions with ring-shaped contrast enhancement were observed in the spleen (arrows). B: A large thrombus was found in the lumen of the right branch of the portal vein (arrow).

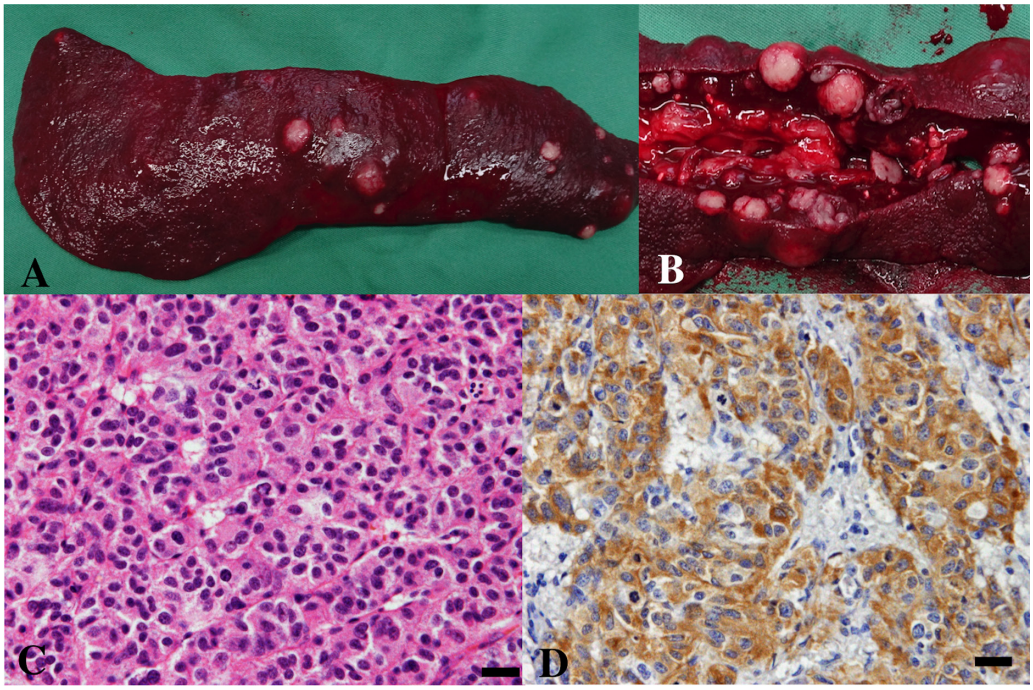

Fig. 3. A and B: Gross findings (A) and cross section (B) of the removed spleen. Multiple white masses are visible. C: Microscopic findings in the splenic mass. The tumor cells had eosinophilic and finely granular cytoplasm suggestive of endocrine origin. D: The tumor cells in the spleen were positive for adrenocorticotropic hormone (Primary antibody: Rabbit polyclonal; ZYMED, San Francisco, CA, USA) (bar=25 μm).

in other locations, including in the pituitary region.

The dog died at home on Day 418, and necropsy was performed the same day. Most of the anterior lobe of the pituitary gland was replaced by fibrous connective tissue accompanied by infiltration of inflammatory cells such as lymphocytes and hemosiderin-laden macrophages. A small number of normal pituitary gland cells remained, but no tumor cells were observed microscopically in the pituitary area and the surrounding brain tissue. The intermediate and posterior lobes showed no obvious pathological lesions. There were multiple nodules in the liver, with a maximum diameter of approximately 4 cm (Fig. 4A), and ACTH-positive tumor cells were observed in these nodules (Fig. 4B). Moreover, many thrombi containing tumor cells were observed in the small blood vessels of the liver (Fig. 4C). In addition, microscopic tumor metastases were observed in the kidney, adrenal glands, and abdominal lymph nodes.

In human medicine, pituitary carcinoma is defined by the presence of metastatic lesions, namely intrathecal dissemination and/or distant metastases. Such cases are considered extremely uncommon even in human medicine, and they account for only 0.1−0.2% of all human pituitary tumors [6, 16, 18].

Information on pituitary carcinoma in dogs is quite limited. Three reports have described pituitary carcinoma [10, 14, 15]; however, two of the reports used the term “pituitary carcinoma” because of the histopathological grade. In another case, the term “pituitary carcinoma” was used because invasion into the surrounding normal brain tissue was observed [14]. No information on distant metastases or intrathecal dissemination was mentioned in these three reports. Another case report describing a canine pituitary carcinoma with intrathecal dissemination was published by Sheehan *et al*. in 2017 [19], which closely matched the definition of human pituitary carcinoma. In another case report, pituitary carcinoma of a young dog with metastases to the spleen, kidneys, and stomach was reported [4]. However, this report focused on the histopathological findings. Since the dog was euthanized 6 days after the onset of clinical symptoms, no clinical aspects were described. In our case, distant metastatic lesions in the spleen, liver and other visceral organs were observed. This case report is considered the first in the veterinary field to describe the detailed clinical course of pituitary carcinoma in a dog with distant metastases, and its necropsy findings.

Our case was similar in many respects to human pituitary carcinoma. Human pituitary carcinoma occurs in hormonally-active pituitary tumors, and most often in prolactin- and ACTH-secreting tumors [6, 22]. Our case and the case reported by Gestier *et al.* in 2012 [4] were also ACTH- secreting tumors. Therefore, we should keep in mind that macroscopic hormone-secreting tumors in dogs may cause distant metastasis. Although this might be very rare, it seems important to perform an abdominal CT examination periodically to detect a metastatic lesion in ACTH-producing pituitary tumors. It is unclear whether the ring-shaped enhancement seen in the spleen of this case is unique to this disease; further study of the diagnostic imaging features of metastatic lesions is required. In addition, because an increase in ACTH concentrations preceded detection of metastases, it was considered important to monitor the ACTH concentration in the affected animal. Furthermore, the liver is considered one of the most common organs of distant metastasis in human pituitary carcinoma [22], and in our case, extensive distant metastasis to the liver was observed,

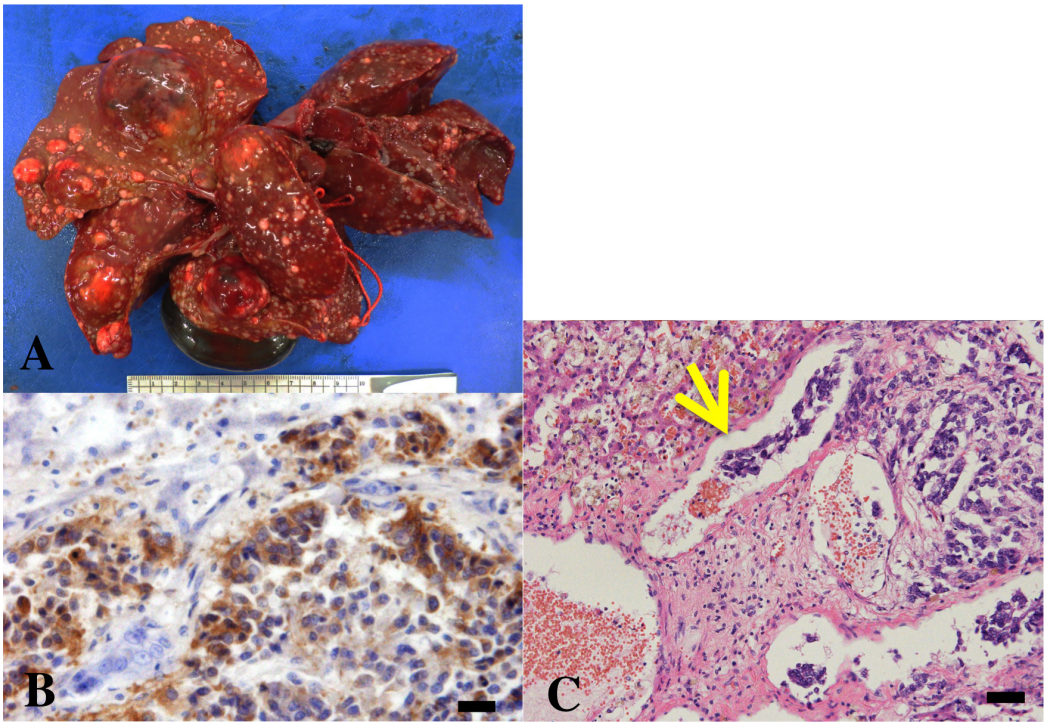

Fig. 4. Necropsy findings in the dog. A: Gross findings in the liver. Extensive metastatic lesions were observed. B: The tumor cells in the liver were positive for adrenocorticotropic hormone (bar=25 μm). C: Thrombi including tumor cells were observed in the small vessels of the liver (arrow, bar=50 μm).

although the spleen was the first metastasized organ. According to Rosol *et al*., the organs predisposed to distant metastasis of canine pituitary carcinoma are the spleen, liver and kidney [17]. In our case, metastasis to the spleen was observed first, followed by the liver and other abdominal organs. Histopathological examination after death also confirmed renal lesions. The findings in our case showed good agreement with previous descriptions.

In this case, a thrombus was found in the portal vein. Since PDH is well known to induce coagulopathy, a possible cause of the thrombosis was the effect of PDH on the systemic blood coagulation system. However, post-mortem histopathological examination revealed a tumor cell thrombus. Since Rosol *et al*. stated that vascular invasion with formation of tumor cell thrombi was a criterion for the diagnosis of pituitary carcinoma [17], it is possible that circulating tumor cells were involved in the formation of the thrombus in our case. However, the detailed cause is unknown.

In treating human pituitary carcinoma, the preferred choice is systemic chemotherapy using an alkylating agent such as temozolomide [11, 21]. Recently, temozolomide has been clinically tested for veterinary neoplastic diseases such as glioma, lymphoma, and malignant melanoma [1, 3, 7]. The drug may be indicated for cases of pituitary carcinoma in dogs, but its usefulness is currently unknown.

CONFLICT OF INTEREST. None of the authors of this article has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

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