NOTE

Internal Medicine

Suspected eccrine adenocarcinoma on footpad of the right hindlimb in a dog

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ABSTRACT. A 12-year-old, male miniature dachshund has an ulcer on the footpad of the right hind limb. Despite treatment for longer than 6 months, the ulcer did not heal. Biopsy of the lesion was done to make a definitive diagnosis. Histologically, there were lumens containing weakly eosinophilic fluid surrounded by tumor cells with a similar circular pale nucleus and distinct nucleoli that showed some variation in size. Immunohistochemically, the tumor cells were positive for cytokeratin (AE1/AE3) and vimentin, were negative for S100 and p63. A poorly differentiated eccrine adenocarcinoma was diagnosed. Treatment was started with toceranib, an anti-angiogenic agent, and enlargement of the lesion was not observed during the administration period.

KEY WORDS: dog, eccrine adenocarcinoma, toceranib

Eccrine adenocarcinoma is an extremely rare tumor in dogs, because eccrine glands only exist in the footpads of these animals. Distinguishing between eccrine and apocrine glands is often impossible by light microscopy and immunohistochemistry. Although the anatomical distribution and the presence or absence of decapitation secretion are used as indicators, there is no specific method for distinguishing between eccrine and apocrine glands. In dogs, eccrine adenocarcinoma presents with swelling of the footpad and ulceration. According to past reports, eccrine adenocarcinoma is an aggressive tumor showing metastasis to lymph nodes [1]. However, there have been few reports concerning this malignancy in dogs, so the pathology, pathogenesis, diagnosis, and treatment are largely unclear. Here, we report a case of suspected eccrine adenocarcinoma in a dog.

A 12-year-old, male miniature dachshund was referred to a private veterinary hospital with an ulcer on the metatarsal pad of the right hind limb that had persisted for longer than 6 months. Treatment for the ulcer was provided, but the lesion did not heal. Therefore, the dog was referred to the Veterinary Teaching Hospital at Iwate University for further evaluation. At the time of referral, no bacteria and no abscess were observed and there was no injury of the other footpads (Fig. 1A). All laboratory test results were in the reference range and an X-ray examination of the right hind limb revealed no surgical diseases such as fracture because there was no difference in the shape of the bones of the left and right hind limbs. Until day 36, the area of the ulcer was reduced by treatment for trauma using chlorhexidine gluconate, but the lesion did not heal. On day 36, another ulcer developed on the same footpad (right hind limb), while there were no lesions on the other limbs. Since it seemed temporarily small but did not heal completely after about one year, skin biopsy was performed on day 134. Because we challenged to perform biopsy on all lesions but the second ulcer was difficult to perform, skin biopsy was only done for original lesion. At the time of skin biopsy, there were no changes of the blood test including CBC and biochemical examinations or X-ray findings.

The sample was fixed in 10%-neutral-buffered formalin solution, routinely processed, and embedded in paraffin. Tissue sections of 4-µm-thickness were stained with hematoxylin and eosin for microscopic examination. Most of the epidermis of the sample was ulcerated. The dermis was replaced by numerous minute tortuous ducts, which were lined by pleomorphic (flattened, cuboidal, polyhedral) neoplastic epithelial cells with distinct cell boundaries. The ducts contained a small amount of pale eosinophilic fluid that was negative for periodic acid-Schiff (PAS) stain. No blebs of secretory material (so-called decapitation secretion) were noticed on the apical surface of the tumor cell. The tumor cell had a moderate amount of eosinophilic cytoplasm, slightly anisokaryotic ovoid hypochromatic nuclei, and distinct nucleoli. Four mitotic figures were observed in ten representative fields, using a high-power (40x) objective with a field number of 22 mm. The polarity of the tumor cell was slightly irregular. The tumor interstitium was composed of abundant fibrovascular tissue with mild pleocellular inflammatory infiltrates. The eccrine glands in

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doi: 10.1292/jvms.18-0286

the deep dermis and subcutis were hyperplastic without cellular/nuclear atypia. Vascular invasion by the tumor cell was not noticed in the specimen. Infectious agents (extracellular bacteria, acid-fast intrahistiocytic bacteria, fungi, and mites) were not detected on tissue sections stained with hematoxylin and eosin, Gram, Ziehl-Neelsen, Grocott, or PAS solution.

Immunohistochemistry (IHC) was performed to further characterize the tumor cells using anti-cytokeratin AE1/AE3, anti-vimentin, anti-p63, and anti-S100 antibodies. Non-neoplastic eccrine glands in the tissue samples were simultaneously evaluated for immunoreactivity to each marker as an internal control. The results of IHC are summarized in Table 1 and shown in Fig. 1. Briefly, the tumor cells strongly reacted to anti-cytokeratin AE1/AE3 and anti-vimentin antibodies, while non-neoplastic eccrine glandular epithelial cells reacted only to anti-cytokeratin AE1/AE3 antibody. A positive reaction to the p63 marker was observed only in myoepithelial cells of non-neoplastic eccrine glands. Neither the tumor cells nor non-neoplastic eccrine glandular epithelial cells showed a positive reaction to the S100 marker.

In this case, the diagnosis was suspected eccrine adenocarcinoma because the lesion was on the footpad and showed malignant features with no decapitation secretion. It is difficult to distinguish eccrine glands from apocrine glands by histopathological examination and immunohistochemical staining. In dogs and cats, eccrine glands are only distributed in the footpads. These glands have ducts that open at the epidermis directly and the cells secrete sweat into the ducts rather than releasing it into vesicles. In contrast,
apocrine glands are distributed throughout the epidermis. These glands communicate with the hair follicles via an excretory duct and the gland cells release secretion vesicles that undergo degradation in the duct lumen. Thus, the anatomical distribution and method of secretion are important distinguishing features. In humans, immunostaining can be useful for making this distinction. While several proteins are helpful for identification of apocrine glands, they are not specific. It has been reported that eccrine glands in the human dermis are positive for S100 by immunohistochemistry [3], but there have been few reports concerning immunostaining of sweat glands in dogs. In this case, we investigated S100 immunostaining of eccrine glands in the dermis, but we found that even normal eccrine glands were not stained by S100. Therefore, we could not specifically identify eccrine glands in the dermis.

Based on histopathology and immunohistochemistry [4], the tumor in this dog was found to be a poorly differentiated adenocarcinoma. Metastasis was not observed when skin biopsy was done, although the history was quite long. There is a previous report [1] of eccrine adenocarcinoma showing metastasis to local lymph nodes and invading muscles in affected limbs. The stage of this disease at which metastasis occurs is unclear. In the present case, metastasis was suggested by histopathology, so the prognosis of this tumor should be observed carefully.

In cats, eccrine adenocarcinoma should be included in the differential diagnosis when a middle-aged to elderly cat develops claudication and pain in multiple digits [2]. In contrast, it was reported that eccrine adenocarcinoma is solitary in dogs [1]. However, there were two lesions on the same hind limb in the present case. While we are not certain that the other lesion was the same tumor because we did not perform biopsy, it is possible that dogs also develop multiple eccrine adenocarcinomas. Therefore, it may be reasonable to biopsy all such lesions, but it is necessary to accumulate more cases of canine eccrine adenocarcinoma in the future.

Although the dog had pain, Toceranib (Palladia®, Zoetis Inc., New York, NY, U.S.A.) was selected for treatment because the dog owner refused amputation. The treatment of eccrine adenocarcinoma has not been well described. In past reports, dogs and cats with this tumor were euthanized because of the painfullness of the affected area. Broad-spectrum drugs, like carboplatin or toceranib, would be recommended. We offered treatment with carboplatin or toceranib. Carboplatin is a platinum complex synthesized for the purpose of alleviating side effects without weakening the antitumor activity of cisplatin. The administration method is intravenous administration every 3 weeks. The side effects are accumulating myelosuppression, and gastrointestinal disorders have been reported. Toceranib is a receptor tyrosine kinase inhibitor that is used in the treatment of canine mast cell tumors and it may also have an anti-angiogenic effect. The administration method is oral administration every 2 days. The side effects include loss of appetite and diarrhea. The dog owner selected Toceranib because it was difficult to go to the animal hospital for frequent intravenous administration. Toceranib (2.3 mg/kg) was administered orally every other day from day 152 to day 189. During this period, the lesions did not become larger and swelling of local lymph nodes were not noticed. On day 189, the owner called the hospital because he had no time to bring the dog to our hospital. He offered to stop administration of Toceranib because appetite and activity of the dog decreased. After 2 months off treatment, the general condition of the dog improved, but the administration of toceranib was not resumed. During that period, the lesions showed no changes.

In our experience, we could not perform enough examinations to detect the therapeutic effects of toceranib against eccrine adenocarcinoma; however, it was suggested that toceranib might be useful because no enlargement or metastasis of the lesion was observed during administration of the medication. Further research will be required to clarify the efficacy of toceranib for canine eccrine adenocarcinoma, including an examination of the degree of side effects.

In this case, early diagnosis was not achieved as biopsy was performed nine months after the onset. Although footpad injuries are generally difficult to heal, our experience suggests that proactive investigation should be recommended for footpad lesions that have not improved after a long period of treatment. Eccrine adenocarcinoma is an active tumor that recurs locally or rapidly metastasizes to subcutaneous tissues of local lymph nodes and affected limbs. Metastasis to the ipsilateral internal lymph nodes were also reported in a dog. In this case, there was no change in local lymph nodes or the affected limb, although we could not perform enough examinations because the owner did not bring the dog to our hospital. In the future, we hope that the pathology, pathogenesis, diagnosis, and treatment of canine eccrine adenocarcinoma will be clarified by investigations and reports of more cases of this tumor.

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