A Canine Case of Mixed Carcinoma of the Sweat Gland in the Footpad

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Abstract: A 9-year-old, castrated male mongrel dog had a mass in the footpad of the left hindlimb. Histologically, the tumor was composed of irregular tubuloacinar structures with desmoplasia, and apocrine secretion was observed on the surface of the neoplastic glands. Several neoplastic foci comprised of the cuboidal to polygonal epithelial cells showing a glandular proliferation and the spindle-shaped neoplastic cells proliferating adjacent to chondroid matrix. The epithelial cells showed a nuclear atypia and frequent mitotic activities. The epithelial cells were immunohistochemically positive for cytokeratin (AE1/AE3 and cytokeratin 8). The spindle-shaped cells showed intense immunoreactivity for vimentin but not for cytokeratins and smooth muscle actin. The tumor was diagnosed as mixed type of adenocarcinoma of sweat gland. Multifocal metastatic masses were observed in the lung 6 months after surgery.

Key words: dog, footpad, mixed tumor, sweat gland

要約：9歳の雄犬，左後肢肉球に腫瘍が認められた。組織学的には，線維形成性に不規則な腺腔構造が増殖し，腺腔内容にはアポクリン分泌が認められた。腫瘍内には，腺腔形成性に増殖する立方形一多角形の上皮性腫瘍細胞の他に，軟骨様基質に接して増殖する紡錘形細胞で構成される結節状病巣も認められた。上皮性腫瘍細胞には異型性が認められ，核分裂像は高頻度に認められた。免疫組織化学的に，上皮性腫瘍細胞は，サイトケラチン（AE1/AE3及びサイトケラチン 8）に陽性を示し，紡錘形腫瘍細胞は，ビメンチンに陽性を示したが，サイトケラチン及び平滑筋アクチンには陰性であった。以上より本例を混合型汗腺腺癌と診断した。腫瘍は摘出後約1ヶ月で肺に転移した。

キーワード：犬，肉球，混合腫瘍，汗腺

Introduction

Among the sweat gland tumors in dogs, malignant neoplasms of apocrine sweat gland represent 2% of canine skin tumors. On the other hand, the eccrine carcinomas in dogs are extremely rare, as the eccrine sweat glands are normally located only in the footpad. Morphological characters of the apocrine carcinoma are similar to those of the eccrine carcinoma; the knowledge of the site of origin is required for the differential diagnosis. Histologically, carcinoma of sweat gland can be subclassified as simple, complex or mixed types. In dogs, mixed carcinoma of the sweat gland is rare. Although the prognosis varies among cases, in the literature, the complex or mixed type of carcinoma of the sweat gland in dogs has been considered to grow slowly and its biological behaviors are less aggressive. Distant metastasis of these carcinomas to the lung rarely occurs. Here, we report a mixed type of carcinoma of the sweat gland in the footpad that metastasized to the lung 6 months after surgery.

Case

A 9-year-old, castrated male mongrel dog was referred with a mass in the footpad of unknown duration. The solitary and firm mass, measuring 2.5 × 2 × 3 cm, was located in the footpad of the left hindlimb (Fig. 1). On the cut section, the mass was divided into many lobules. No significant lesions were observed by the chest x-ray examination. The mass was then removed surgically and submitted for histopathological examination. The dog had been well with no evidence of recurrence and metastasis. However, the dog displayed dyspnea 6 months after surgery; a thoracic x-ray examination revealed multifocal masses in the lung (Fig. 2).

Histopathology and Immunohistochemistry

The tissue sample was fixed in 10% neutral buffered-formalin and embedded in paraffin. The sections of 4 µm-thick were made and stained with hematoxylin and eosin (HE). For immunohistochemistry, some selected sections were incubated with 3% hydrogen peroxidase in methanol for 5 min at room temperature to block endogenous peroxidase activity. The primary antibodies used in the present study were monoclonal antibodies against cytokeratin 8 (Progen Biotechnik GmBH, Heidelberg, Germany, clone Ks 8.7), alpha-smooth muscle actin (SMA; Dako-Japan, Kyoto, Japan; clone 1A4, 1:50), cytokeratin (Dako-Japan; clone AE1/AE3, 1:50) and vimentin (Dako-Japan; clone V9, 1:25). Sections were incubated with these primary antibodies for 60 min at 37°C. Sections were then incubated with peroxidase-conjugated anti-mouse IgG (Histofine Simple Stain MAX-PO (M), Nichirei, Tokyo) for 60 min at 37°C. The immunoreaction was visualized with 3, 3'-diaminobenzidine tetrahydrochloride (DAB, Sigma, St. Louis, MO, USA) and counterstained with Mayer’s hematoxylin.

Results

Histopathology revealed that the subcutis of the footpad was extensively disrupted by irregular tubuloacinar
Structures, lined by mono- or several layers of cuboidal to polygonal tumor cells with abundant eosinophilic cytoplasm (Fig. 3). The nuclei of these tumor cells were irregular in shape and size, and had prominent nucleoli. Small number of the neoplastic cells had irregular vacuoles in the cytoplasm. The neoplastic cells sometimes exhibited distinct decapitation secretion on the surface of the neoplastic glands (Fig. 3). Mitoses were frequently detected in the epithelia neoplastic cells. Occasionally, there were multifocal cholesterin depositions with a severe infiltrate of macrophages and neutrophils in the stroma. Immunohistochemically, the epithelial cells were intensely positive for cytokeratin (AE1/AE3 and cytokeratin 8) (Figs. 5 and 6). The proliferating spindle-
shaped neoplastic cells adjacent to the chondroid matrix showed intense immunoreactivity for vimentin but not for cytokeratins and SMA.

**Discussion**

In cats, pulmonary adenocarcinoma sometimes metastasizes to the footpad\(^4\) associated with digital swelling\(^5\). In the present study, thoracic radiographs showed masses in the lung; however, they were multifocal and occurred after surgery, suggesting that the multifocal pulmonary masses might be metastatic lesions from the footpad. In addition, the neoplastic cells were immunohistochemically positive for cytokeratin 8 that is specific to simple epithelial cytokeratins. Hence, it is suggested that the tumor is originated from sweat gland in the footpad.

As the tumors occurred in the footpad, mixed type of eccrine carcinoma might be considered as a differential diagnosis\(^5\). In comparison with the sweat gland tumors in humans, the eccrine gland tumor in dogs is rare because the distribution of the eccrine gland in dogs is limited in the footpad\(^4\)\(^–\)\(^5\). It is extremely difficult to differentiate the apocrine carcinoma from the eccrine carcinoma due to the similarity of the morphological features\(^5\)\(^–\)\(^8\).

Apocrine sweat gland, which develops embryologically from primary hair germ, is characterized by the secretion process of apical blebs. In contrary, eccrine sweat gland, derived from embryonal epidermis, is able to secrete their substances not only by eccrine secretion but also by microapocrine blebbing, which may lead the controversy that decapitation secretion is enough to convince that the neoplastic cells are derived from apocrine sweat gland.

In humans, immunohistochemistry is available for the differentiation; B72.3, which is a tumor-associated glycoprotein observed in a wide variety of human adenocarcinomas, is expressed in the apocrine sweat gland rather than in the eccrine gland\(^14\). Although carcinoembryonic antigen and growth cystic disease fluid protein-15 were also used to identify the apocrine sweat gland, those markers are not specific to the apocrine sweat gland\(^11\)\(^–\)\(^13\). In dogs, to our knowledge, B72.3 is used to distinguish the apocrine sweat gland from the eccrine sweat gland in few reports. Thus, it seems that routine histopathologic methods are not useful for the differentiation of canine sweat gland tumors in the footpad\(^9\). Therefore, the present case was diagnosed as a mixed carcinoma of sweat gland. Despite the controversy, in the literature, identifying the secretion pattern is suggested to be a key to make a diagnosis of the sweat gland tumor\(^9\). Aumuller et al.\(^1\) reported that the apocrine secretion process might not be an artifact. Therefore, the tumor in the present study might be derived from apocrine sweat gland because of the apocrine secretion observed in the neoplastic foci.

The mesenchymal component with the formation of chondroid matrix was observed in this case. It is well known that the metaplasia can be seen in canine mammary gland tumors\(^10\); myoepithelial cells, which show immunoreactivity for cytokeratin and SMA, have been suggested to be involved in the formation of bone or cartilage in the benign mixed tumors\(^10\). However, it is also suggested that undifferentiated mesenchymal cells in the tumor tissue might play roles in the metaplasia in the mixed tumors\(^9\). Gulbahar et al.\(^6\) reported a case of mixed apocrine sweat gland tumor in a cow in which the mesenchymal elements were not immunopositive for SMA, suggesting that the metaplastic bone or cartilage might be derived from the undifferentiated stem cells rather than myoepithelial cells. In the present study, the spindle-shaped neoplastic cells adjacent to the chondroid matrix were not positive for SMA, suggesting that undifferentiated mesenchymal cells might be involved in the formation of chondroid matrix in this case.

In summary, the sweat gland tumor in the footpad showed an aggressive behavior and metastasized to the lung after surgery, which is rarely observed in dogs. As there are no distinct evidences that the tumor is originated from apocrine sweat gland, the diagnosis of mixed carcinoma of sweat gland seems to be appropriate for this case.

**References**


