

Tubulopapillary Carcinoma with Spindle Cell Metaplasia of the Mammary Gland in a Cat

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ABSTRACT. Sarcomatous proliferation of spindle cells was present in the mammary gland and many metastatic sites in a 10-year-old female domestic cat with tubulopapillary carcinoma in the mammary gland. Transition from neoplastic tubular structures to spindle cells in the primary site and fascicular proliferation of the spindle cells with or without coexistence of tubulopapillary carcinoma in the primary and metastatic sites were observed. Most of spindle cells were positive for cytokeratin CAM5.2 as well as the normal luminal epithelium but not the myoepithelium. From these results, this case was diagnosed as tubulopapillary carcinoma with spindle cell metaplasia and it was clarified that neoplastic luminal epithelial cells can transform to sarcomatous appearance.

KEY WORDS: feline, mammary tumor, spindle cell.

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The mammary gland is composed of three major cell populations: luminal epithelial cells, basal epithelial (myoepithelial) cells, and interstitial cells; and mammary neoplasms can show wide histological variations according to the cell types involved [3, 7, 8]. Spindle cell proliferation in the mammary gland can be derived from myoepithelial, glandular epithelial, smooth muscle, fibroblastic or myofibroblastic cells [3, 7, 8]. In this report, we describe a feline case of mammary carcinoma with prominent spindle cell components in primary and metastatic sites, and discussed the nature of the spindle cells.

A ten-year-old female domestic cat was presented to the Rakuno Gakuen University Veterinary Teaching Hospital (RGUVTH) from the local veterinary clinic with a subcutaneous mass, 3.0 × 2.5 × 2.5 cm in size, at the right third mammary gland and pulmonary metastases detected by radiographs. The mammary mass had been diagnosed as tubulopapillary carcinoma via punch biopsy, and radiation therapy was performed thereafter according to the owner's wish. The subcutaneous mass had shown a slight decrease in size, but thoracic X-rays revealed deterioration of pulmonary lesions. Three months after the first presentation at RGUVTH, she died of respiratory failure during anesthesia for an X-ray examination.

Grossly, there was a white solid neoplastic mass, 2.5 × 1.5 × 1.0 cm in size, at the right third mammary gland and white and black nodules, 0.4 and 0.2 cm in diameter, respectively, between the left first and second nipples. The right superficial inguinal lymph node was displaced with white solid tissue and had enlarged to 1.0 × 0.7 × 0.7 cm in size. In the lungs, white nodules, up to 1.5 cm in a diameter, were disseminated and residual pulmonary tissue showed

atelectasis. Similar nodules were also presented in the mediastinum and the cortex of the left kidney. The left ventricular wall presented mild hypertrophy.

Histopathologically, the subcutaneous mass at the right third mammary gland was composed of several well- or ill-defined nests of neoplastic growth and abundant collagenous tissue between and around the nests. In the nests, epithelial neoplastic cells formed solid to tubular structures and partial papillary projections (Fig. 1). The nuclei were vesiculated, round to oval, and mitotic figures were often observed. This epithelial cell proliferation was consistent with tubulopapillary carcinoma as preexamined in biopsy specimens. Neoplastic cells showed infiltrative growth into the surrounding collagenous tissue and formed small nests and tubules, and transformed to spindle-shaped cells (Fig. 2). In addition, spindle cells arranged in interlacing bundles were also present (Fig. 3). The spindle cells had elongate nuclei without apparent nucleolei or mitotic figures. Nodules between the left first and second nipples comprised lobular hyperplasia with partial nuclear atypia, and macroscopically-detected black coloring was likely due to melanin-like brown pigments in the cytoplasm of glandular epithelial cells.

In the lungs, there was multifocal proliferation of spindle cells arranged in interlacing bundles showing sarcomatous appearance. These lesions were accompanied with variable amounts of collagenous stroma, and included extensive necrosis and hemorrhage. Partially, alveolar structures with broad interstitial spindle cell proliferation showed a cribriform appearance. The proliferation extended into the lamina propria of the bronchi, resulting in stenosis and atresia of the bronchial lumina. Boundaries of the spindle cell lesions from the residual pulmonary tissue were indistinct. In the residual tissue, alveolar epithelium was largely displaced by type II pneumocytes. The alveolar spaces were filled with a number of macrophages, neutrophils, and cell debris. Spin-

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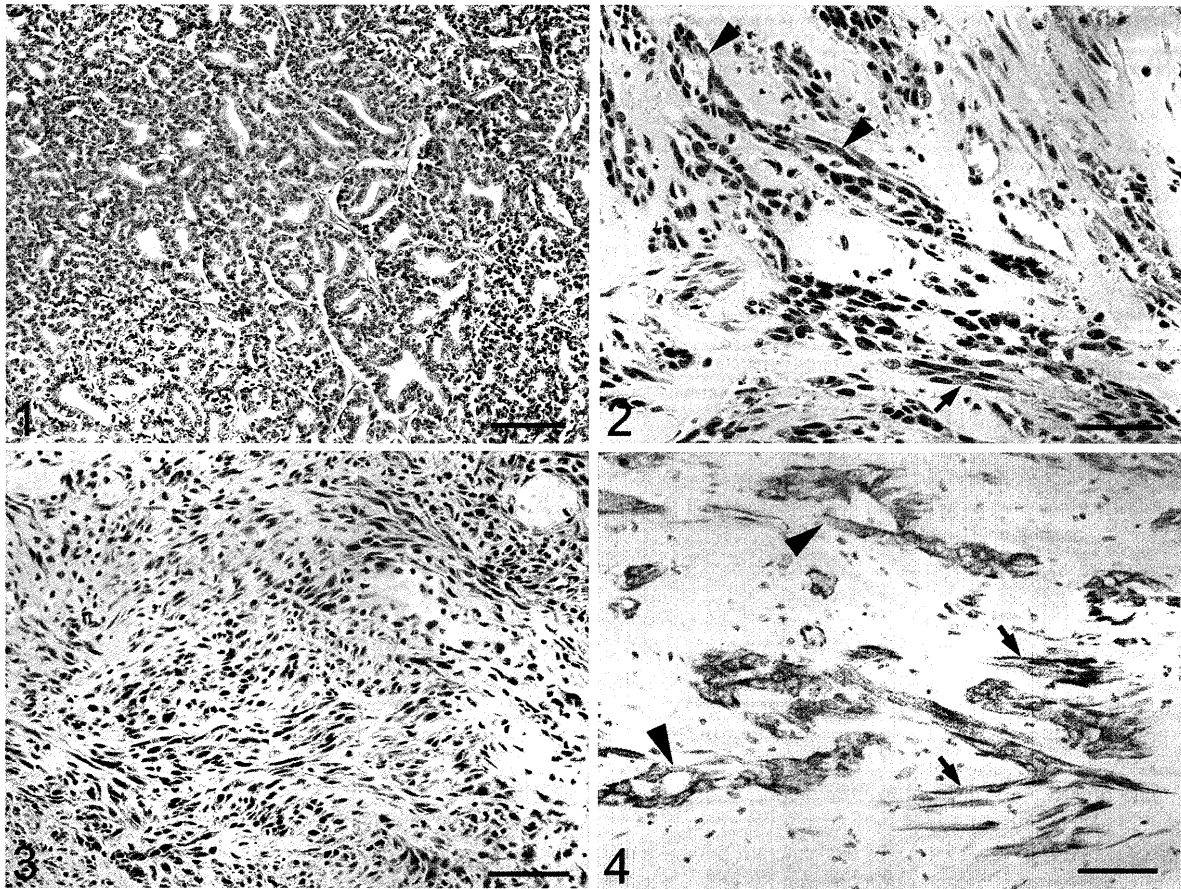


Fig. 1. Tubulopapillary carcinoma in the right third mammary gland. Hematoxylin and eosin (HE) stain. Bar=100 μ m.

Fig. 2. Transition from neoplastic tubules (arrowheads) to spindle cells (arrow) in collagenous stroma in the right third mammary gland. HE stain. Bar=50 μ m.

Fig. 3. Spindle cell proliferation in a fascicular fashion in the right third mammary gland. HE stain. Bar=50 μ m.

Fig. 4. Expression of cytokeratin CAM5.2 in neoplastic cells transforming from tubular structures (arrowheads) to spindle cells (arrows) in the right third mammary gland. Immunohistochemistry for cytokeratin CAM5.2 counterstained with hematoxylin. Bar=50 μ m.

dle cell proliferations similar to those in the lungs were also observed in the mediastinum, mediastinal lymph nodes, tracheobronchial lymph node, endocardium and myocardium of the left atrium, pericardium, right superficial inguinal lymph node, and cortex of the left kidney. In the right superficial inguinal and mediastinal lymph nodes, tubular structures coexisted with the spindle cell proliferation. From the histopathological findings of tubulopapillary proliferation with transition to the spindle cells in the mammary gland and sarcomatous proliferation of spindle cells with or without tubular structures in the metastatic sites, this case was diagnosed as tubulopapillary carcinoma of the mammary gland with spindle cell metaplasia. There were no significant lesions in the other organs examined except for congestion of the liver and multifocal chronic tubulointerstitial nephritis.

To clarify the nature of the spindle cells observed in the mammary gland and other organs, we performed immunohistochemical examinations by the avidin-biotin-peroxidase

complex method with single antibody and by the indirect immunofluorescent technique with double antibodies. Primary antibodies used were mouse monoclonal antibodies to cytokeratin AE1/AE3 (CKa, Nichirei Bioscience, Tokyo), cytokeratin CAM5.2 (CKc, BD Biosciences, San Jose, CA, U.S.A.), alpha-smooth muscle actin (α SMA, Dako Cytomation, Glostrup, Denmark), and rabbit polyclonal to cytokeratin 14 (CK14, Lab Vision, Fremont, CA). Non-neoplastic mammary glands of this animal were used as normal controls.

In the normal mammary glands, luminal epithelial cells were intensely positive for CKa and CKc, and myoepithelial cells were strongly stained for α SMA and weakly for CKa (Table 1). Some cuboidal cells aligning innermost in the tubules as well as myoepithelial cells expressed CK14. In the tubulopapillary carcinoma of the mammary gland, neoplastic epithelial cells were diffusely positive for CKa and CKc. A single layer of spindle cells located at the periphery of some neoplastic nests were stained for α SMA and CK14.

Table 1. Immunohistochemical results in normal and neoplastic mammary glands

Antigen	Normal			Tumor		
	Luminal epithelium	Myoepithelium	Interstitial cells	Tubular epithelium	Spindle cells	Stromal cells
CKa ^{a)}	+ ^{e)}	+	-	+	+	-
CKc ^{b)}	+	-	-	+	+	-
α SMA ^{c)}	-	+	-/+	-/+ ^{f)}	-/+ ^{g)}	-/+
CK14 ^{d)}	-/+	+	-	-/+ ^{f)}	-/+ ^{h)}	-

a) CKa, cytokeratin AE1/AE3. b) CKc, cytokeratin CAM5.2. c) α SMA, alpha-smooth muscle actin. d) CK14, cytokeratin 14. e) +, positive; -/+ , partially positive; -, negative. f) positive cells at the periphery of some nests. g) some positive cells without CKa or CK14 expression. h) some positive cells without α SMA expression.

The spindle cells proliferating in the mammary gland and other organs were broadly positive for CKa, CKc (Fig. 4) and partially for α SMA. A few spindle cells expressing CK14 were also present. Double immunostains with antibodies to CKa and α SMA, or CK14 and α SMA, respectively, revealed the presence of cells positive for either antigen and double-negative cells, and absence of double-positive cells. In summary, spindle cell components were comprised of several cell phenotypes: those positive for CKa and CKc, those positive for CK14 but negative for α SMA, those positive for α SMA but negative for cytokeratins, and those negative for cytokeratins and α SMA.

Luminal epithelial cells were selectively positive for CKc in the normal mammary glands of this animal and this antigen is expressed in human mammary spindle cell carcinomas of glandular not myoepithelial origin [3]. Therefore spindle cells expressing CKc were considered to be luminal epithelial origin. In human and canine mammary glands, normal and neoplastic myoepithelial cells specifically express CK14 and α SMA [1, 2, 4], and CK14 is also localized in the myoepithelial cells in the normal feline mammary gland [5]. We recognized an immunoreaction to CK14 in a few morphologically glandular epithelial cells in addition to myoepithelial cells in the non-neoplastic glands as reported in dogs [4]. Moreover CK14-expressing spindle cells were negative for α SMA. From these findings, although there was a possibility of presence of cells derived from myoepithelium, we could not clarify it. Spindle cells positive for α SMA but negative for cytokeratins, and those negative for both antigens were considered to be reactive myofibroblasts and fibroblasts, respectively [4]. Single layers of spindle cells reactive to α SMA at the periphery of the neoplastic nests in the tubulopapillary carcinoma were considered to be residual non-neoplastic myoepithelial cells [6]. These immunohistochemical observations confirmed the histopathological diagnosis, tubulopapillary carcinoma with spindle cell metaplasia, and revealed the metaplastic spindle cells to be luminal epithelial origin.

In the classification of the human tumors, this case corresponds to spindle cell carcinoma of the mammary gland, a variant of metaplastic carcinomas (adenocarcinoma with spindle cell metaplasia), defined as a tumor with glandular

epithelial immunophenotype [3]. However the precise classification corresponding to this case was not described in the veterinary pathology [7, 8]. The diagnosis as spindle cell carcinoma, a special type of carcinoma, should be applied to the neoplasm purely composed of spindle cells and was not preferable for this case.

In many metastatic sites in this cat including the lungs, mediastinum, heart, kidney and lymph nodes, neoplastic growth were purely comprised of spindle cells. Hereafter we should perform histopathological examinations more carefully keeping in mind that feline mammary tumor derived from the luminal epithelium can show sarcomatous appearance without tubular structures.

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