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Atypical Fibrosarcomas Derived from Cutaneous Ganglion Cell-Like Cells in 2 Domestic Djungarian Hamsters (*Phodopus sungorus*)

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Androgen-dependent atypical fibromas are benign tumors derived from ganglion-cell-like cells that are particular to Djungarian hamsters (*Phodopus sungorus*). Masses excised from 2 hamsters were composed of pleomorphic ganglion cell-like cells supported by small to moderate amounts of collagenous matrix. Intracytoplasmic fibrils were present in silver-stained sections, and immunohistochemistry showed that the cells expressed vimentin, androgen receptor, and, in one case, estrogen receptor α. In contrast to previously reported atypical fibromas, these tumors had features of anaplasia and were locally invasive. We diagnosed the tumors as atypical fibrosarcomas and consider them an unusual malignant counterpart of atypical fibroma.

Abbreviation: GL cells, ganglion cell-like cells.

Djungarian hamsters (*Phodopus sungorus*), also known as a Siberian, Russian, and dwarf hamsters, originate from Siberia, northern Kazakhstan, and Mongolia. They are popular domestic pets and have been used as laboratory animals. In laboratory settings, tumors of the mammary gland, skin, and lungs are most common,[5,6] whereas domestic Djungarian hamsters predominantly develop integumental tumors, especially atypical fibromas, mammary tumors, and papillomas.[3] Various subtypes of mammary tumors have been reported.[4,7]

Atypical fibromas are benign tumors consisting of large ganglion cell-like (GL) cells supported by variable amounts of collagen fibers. The tumors increase in occurrence with age and are thought to be androgen-dependent because GL cells express androgen receptor.[1,2] The origin of GL cells is still unclear, but they have been hypothesized to arise from peculiar undifferentiated mesenchymal cells in the skin.[2] Occurrence of these neoplasms has not been reported in species other than Djungarian hamsters. In the current report, we describe 2 Djungarian hamsters with tumors that we consider to be unusual malignant counterparts of atypical fibromas.

Case Reports

Case histories. ***Case 1.*** A 22-mo-old, male Djungarian hamster weighing 43 g presented with a cutaneous mass that had progressively enlarged over a month and was surgically excised. The hemispherical mass elevated the skin on the craniodorsal trunk (Figure 1). The skin overlying the mass had moderate erythema and alopecia. The mass was firm and measured 1 cm in diameter. The cut surface of the mass was homogenous and light tan, with multifocal small areas of hemorrhage. There was no radiographic evidence of distant metastasis.

Case 2. A 12-mo-old, female Djungarian hamster weighing 30 g had a history of acutely painful swelling of soft tissue surrounding the left carpus. The initial differential diagnoses of the left carpal mass included traumatic inflammation, arthritis, and neoplasm. Radiographically, a lytic lesion was evident in the left carpal bones, and the limb was amputated. There was no radiographic evidence of distant metastasis.

Both hamsters had been purchased at a pet store, housed in a wire cage, and fed a commercial seed mix, with free access to water.

The masses excised from the 2 hamsters were fixed in 10% neutral buffered formalin, routinely processed into paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin. Additional special stains included Masson trichrome and Watanabe silver stain. Immunohistochemistry was performed (EnVision System, Dako, Tokyo, Japan). Heat-induced antigen retrieval was performed by using commercially available retrieval solution (Target Retrieval Solution, Dako). Primary antibodies included vimentin (expression in mesenchymal cells; clone V9, Dako), S100 protein (rabbit polyclonal, expression in neurogenic cells; Dako), neurofilament (expression in neurogenic cells; clone 2F11, Dako), glial fibrillary acidic protein (expression in neurogenic and glial cells; clone 6F2, Dako), synaptophysin (expression in neuroendocrine cells; clone SY38, Dako), desmin (expression in myogenic cells; clone D33, Dako), α-smooth muscle actin (expression in smooth muscle; clone 1A4, Dako), androgen receptor (rabbit polyclonal, Ylem SRL, Rome, Italy), and estrogen receptor α (rabbit polyclonal, Abcam, Tokyo, Japan). Antigen–antibody complexes were visualized with 3, 3′-diaminobenzidine as substrate, and tissue sections were counterstained with Mayer hematoxylin. Skin (dermis, peripheral nerves, and blood vessels), skeletal muscle, pancreas, mammary glands, and testis were used as positive controls.

Histologic and immunohistochemical findings. In case 1, the dermis and subcutaneous tissue were expanded by an unencapsulated, poorly demarcated, densely cellular invasive mass. The mass was composed of randomly interlacing bundles of polygonal to angular to spindle shaped cells in moderate amounts of small bundles of collagenous matrix

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Figure 1. Cutaneous mass; Djungarian hamster, case 1. The hemispherical mass elevates the skin on the craniodorsal trunk. The skin overlying the mass shows erythema and alopecia.

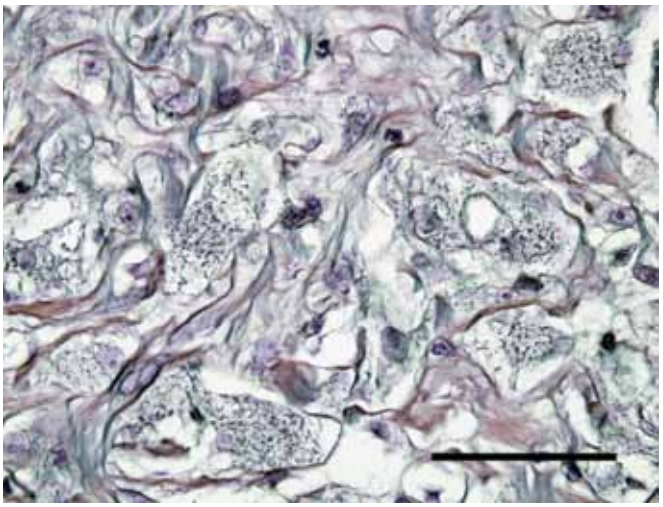

Figure 3. Cutaneous mass; Djungarian hamster, case 1. Moderate numbers of delicate intracytoplasmic fibrils stain black. Collagen fibers are dark purple. Watanabe silver stain; bar, 40 µm.

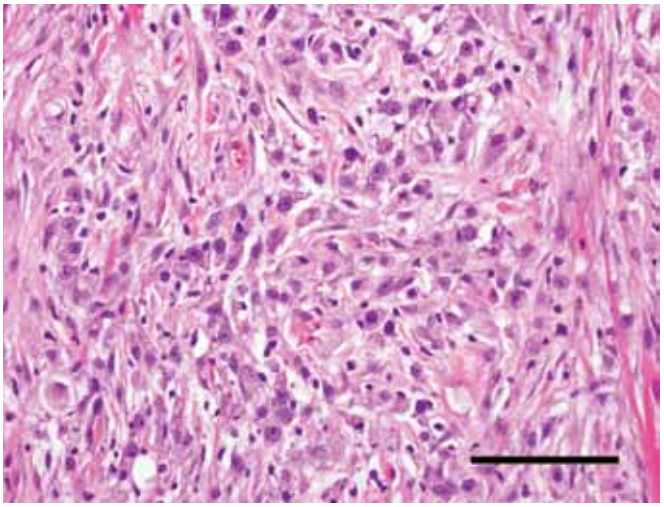

Figure 2. Cutaneous mass; Djungarian hamster, case 1. Randomly interlacing bundles of polygonal to angular to spindle-shaped cells in moderate amounts of small bundles of collagenous matrix. Hematoxylin and eosin stain; bar, 100 µm.

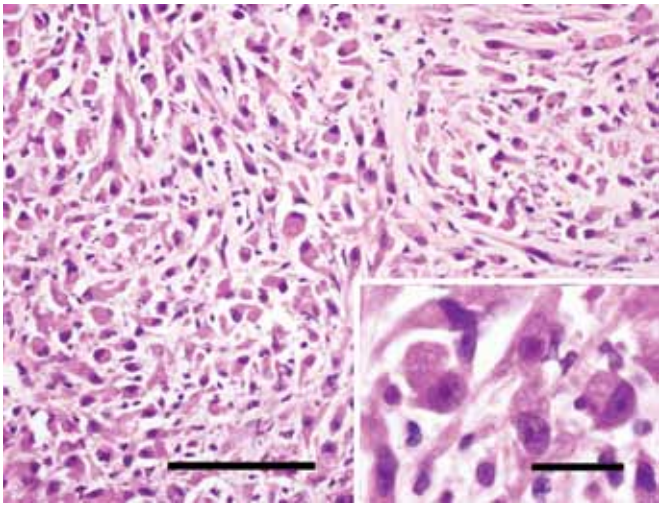

Figure 4. Left carpal mass; Djungarian hamster, case 2. The neoplastic parenchyma is edematous. The neoplastic cells had scant amounts of collagenous matrix. Hematoxylin and eosin stain; bar, 100 µm. Inset: Left carpal mass; Djungarian hamster, case 2. Bizarre mononuclear giant cells that have large nuclei and large amounts of amphophilic cytoplasm. Hematoxylin and eosin stain; bar, 25 µm.

that stained blue with Masson trichrome stain (Figure 2). The cells were medium to large, with moderate to large amounts of amphophilic cytoplasm. Silver staining revealed moderate numbers of delicate black fibrils in the cytoplasm (Figure 3). Nuclei were medium-sized and oval to elongate, with coarsely stippled chromatin and 1 to 3 amphophilic, distinct nucleoli. Anisocytosis and anisokaryosis were moderate. There were 5 mitoses per 10 high-power (400×) fields. The cells invaded the skeletal muscle, and individual myofibers were atrophic and necrotic. Multifocal areas of hemorrhage were observed. Small numbers of neutrophils were scattered throughout the mass.

In case 2, the histologic findings were generally similar to those of case 1. The skin overlying the mass was multifocally ulcerated and covered with a crust composed of debris of degenerative and necrotic epithelial cells and neutrophils. The superficial neoplastic parenchyma was edematous and infiltrated by large numbers of neutrophils. The tumor had less collagenous matrix than that of case 1 (Figure 4). Small numbers of binucleated cells and bizarre mononuclear giant cells were scattered throughout the mass (Figure 4 inset). The skeletal muscle and cortex and bony trabeculae of the carpus were effaced by the neoplastic cells.

Immunohistochemically, the cells of both cases were positive for vimentin and androgen receptor (Figures 5 and 6). Positive reactivity for estrogen receptor α was present only in case 1 (Figure 6 inset). The cells were negative for other antibodies including S100 protein, neurofilament, glial fibrillary acidic protein, synaptophysin, desmin, and α-smooth muscle actin. All positive-control tissues had specific staining for each respective antibody.

Discussion

The histologic and immunohistochemical characteristics of the masses excised from our 2 Djungarian hamsters were generally consistent with those of previous reports of atypical fibromas. However, in contrast to previously described benign atypical fibromas, the masses in these 2 cases had malignant features, including cellular pleomorphism, nuclear atypia, large

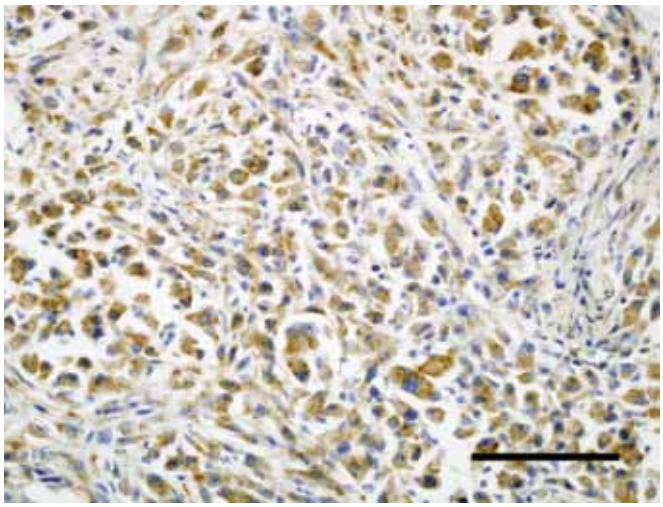

Figure 5. Left carpal mass; Djungarian hamster, case 2. The cytoplasm of the neoplastic cells is diffusely positive for vimentin. Immunohistochemistry for vimentin counterstained with Mayer hematoxylin; bar, 100 µm.

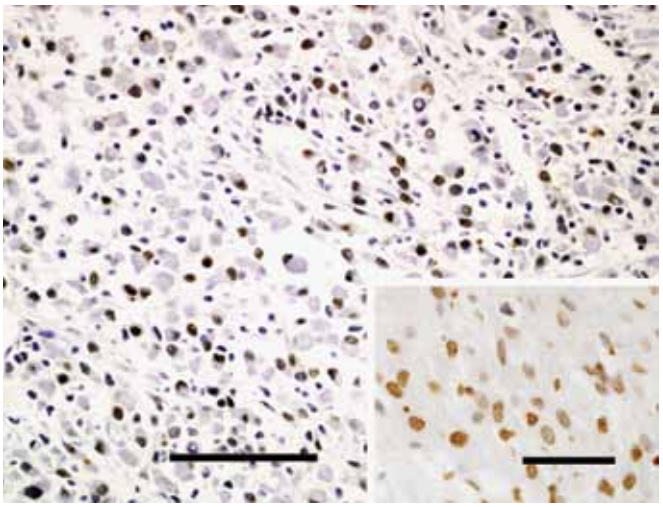

Figure 6. Left carpal mass; Djungarian hamster, case 2. The nuclei of the neoplastic cells are positive for androgen receptor. Immunohistochemistry for androgen receptor counterstained with Mayer hematoxylin; bar, 100 µm. Inset: Cutaneous mass; Djungarian hamster, case 1. The nuclei of the cells are positive for estrogen receptor α. Immunohistochemistry for estrogen receptor α lightly counterstained with Mayer hematoxylin; bar, 50 µm.

nucleoli, binucleated giant cells, and invasion into the adjacent stroma, bone, and skeletal muscle. In atypical fibromas, androgen receptor staining is common. However, the mass from case 1 was positive for both androgen and α-estrogen receptors, a finding that has not been reported for atypical fibromas. We diagnosed these masses as atypical fibrosarcomas and consider them to be malignant counterparts of atypical fibroma.

These tumors are thought to arise from GL cells normally present in the dermis and subcutaneous tissue of Djungarian hamsters. These cells are most common on the ventrum, forelimbs, and hindlimbs; less so on the dorsal areas of the trunk and forelimb; and absent in the skin of the head.[2] The number of GL cells increases with age and is influenced by serum androgen concentration.[1] Therefore, the number of the GL cells in the skin is significantly increased in older male Djungarian hamsters. In contrast, older female hamsters, in which atypical fibromas are rare, have few GL cells.[1,2] The distribution of atypical fibromas appears to correlate with that of GL cells. Almost all atypical fibromas reported have occurred in males older than 7 mo, therefore corresponding to the onset of sexual maturity and suggesting that atypical fibromas are androgen-dependent.[1,2,3]

The pathogenesis of the atypical fibrosarcomas described in the current report may differ from that of atypical fibromas, inasmuch as the tumor in case 1 was on the back, an unusual site for atypical fibroma, and the tumor in case 2 was on the left forelimb of a 12-mo-old female, which was a typical site but rare sex for atypical fibroma. In addition, the tumor in case 1 was positive for both androgen and α-estrogen hormone receptors.

Both atypical fibroma and its malignant counterpart we describe here are neoplasms unique to Djungarian hamsters. Because of the relative obscurity of this entity, misdiagnosis is possible. Understanding the cellular origin and pathogenic potential is crucial in diagnosing tumors in this popular domestic pet.

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