



NOTE

Pathology

A case of a malignant peripheral nerve sheath tumor in a guinea pig

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81(12): 1859–1862, 2019

doi: 10.1292/jvms.19-0464

Received: 19 August 2019

Accepted: 13 October 2019

Advanced Epub:

24 October 2019

ABSTRACT. Here, we describe the clinical and histopathological characteristics of a malignant peripheral nerve sheath tumor (MPNST) extending from the dorsal subcutis to the periphery of the spine in a female guinea pig aged 3 years 7 months. The patient presented with pleural and blood-like pericardial effusion and died. The tumor had invaded the spine and the surrounding muscles and had grown in hypercellular and hypocellular arrangements of round, broad-spindle, and elongated-spindle cells. We observed a fascicular growth pattern, nuclear palisading, and perivascular accumulations of cells that responded positively to anti-S100, sox10, and CD56 antibodies. This is the first report of a MPNST in a guinea pig.

KEY WORDS: CD56, guinea pig, malignant peripheral nerve sheath tumor, S100, Sox10

The most common soft tissue tumors in guinea pigs are lipomas, with fibrosarcoma, fibrolipoma, and hemangiosarcoma also reported [8, 11, 12]. Soft tissue tumors arising the peripheral nervous system include peripheral nerve sheath tumors (PNSTs) [9], which have been reported in humans, cows, dogs, rats, mice, cats, pigs, goats, and rabbits [6, 9, 10, 17, 18]. In dogs, PNSTs are difficult to distinguish from hemangiopericytomas as the two types of tumor present with nearly identical morphological characteristics and similar immunostaining findings [9]. In rats, PNSTs, naturally occurring in rare cases in the subcutis and trigeminal nerve, are induced at high rates by substances such as nitrosourea and are often malignant; in rare cases, PNSTs also occur naturally in mice [13, 18]. To our knowledge, there are no reports of malignant PNSTs (MPNSTs) in guinea pigs. Therefore, here, we report for the first time the clinical and histopathological characteristics of an MPNST in the dorsal thorax of a guinea pig.

An intact female guinea pig aged 3 years 5 months was examined at another veterinary clinic with chief complaints of lameness and pain in the right hindlimb. Radiography did not reveal any abnormal findings, and the patient was followed up without treatment. At age 3 years 7 months, the patient was brought to our animal hospital with chief complaints of rapid growth of a dorsal subcutaneous tumor, loss of appetite and energy, and abnormal breath sounds. At age 3 years 11 months, radiography revealed severe osteolysis from the 7th to the 12th thoracic vertebra and in the ribs (Supplementary Fig. 1). Two days after admission, the patient presented with abnormal breath sounds and pleural effusion and then died. An autopsy was performed immediately post-mortem.

Tissue specimens were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin wax. Sections (4 μm) were stained with hematoxylin and eosin (HE). Labeled-polymer immunohistochemistry was performed using N-Histofine MAX PO™ (M or R; Nichirei Biosciences, Tokyo, Japan), with anti-smooth muscle actin (SMA; 1 in 200 dilution; mouse monoclonal antibody; Dako, Carpinteria, CA, U.S.A.), anti-cow S100 (1 in 200 dilution; rabbit polyclonal antibody; Dako), anti-PNL2 (1 in 50 dilution; mouse monoclonal antibody; Santa Cruz Biotechnology, Dallas, TX, U.S.A.), anti-CD56/NCAM (1 in 200 dilution; mouse monoclonal antibody; LifeSpan BioSciences, Seattle, WA, U.S.A.), and anti-sox10 (1 in 500 dilution; mouse monoclonal antibody; Santa Cruz) as primary antibodies [4]. As a negative control, mouse or rabbit isotype immunoglobulin diluted to the same concentration was substituted for the primary antibody.

In the autopsy, we observed blood-like pleural and pericardial effusion. The subcutaneous mass in the dorsal thorax was well demarcated on the epidermal side, while the deep portion of the tumor had invaded a wide area spanning the spine and the surrounding muscles and protruded from the right pleural wall into the pleural cavity (Fig. 1A). We could not confirm any abnormalities in any other organs.

Histopathologically, the mass was a malignant tumor that grew invasively in repeated hypercellular and hypocellular arrangements of round, broad-spindle, and elongated-spindle tumor cells (Fig. 1B). The mass was diverse, including regions in which cells formed bundles with collagen fibers with a fascicular growth pattern, regions in which cells were highly dense and

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(Supplementary materials: refer to PMC <https://www.ncbi.nlm.nih.gov/pmc/journals/2350/>)

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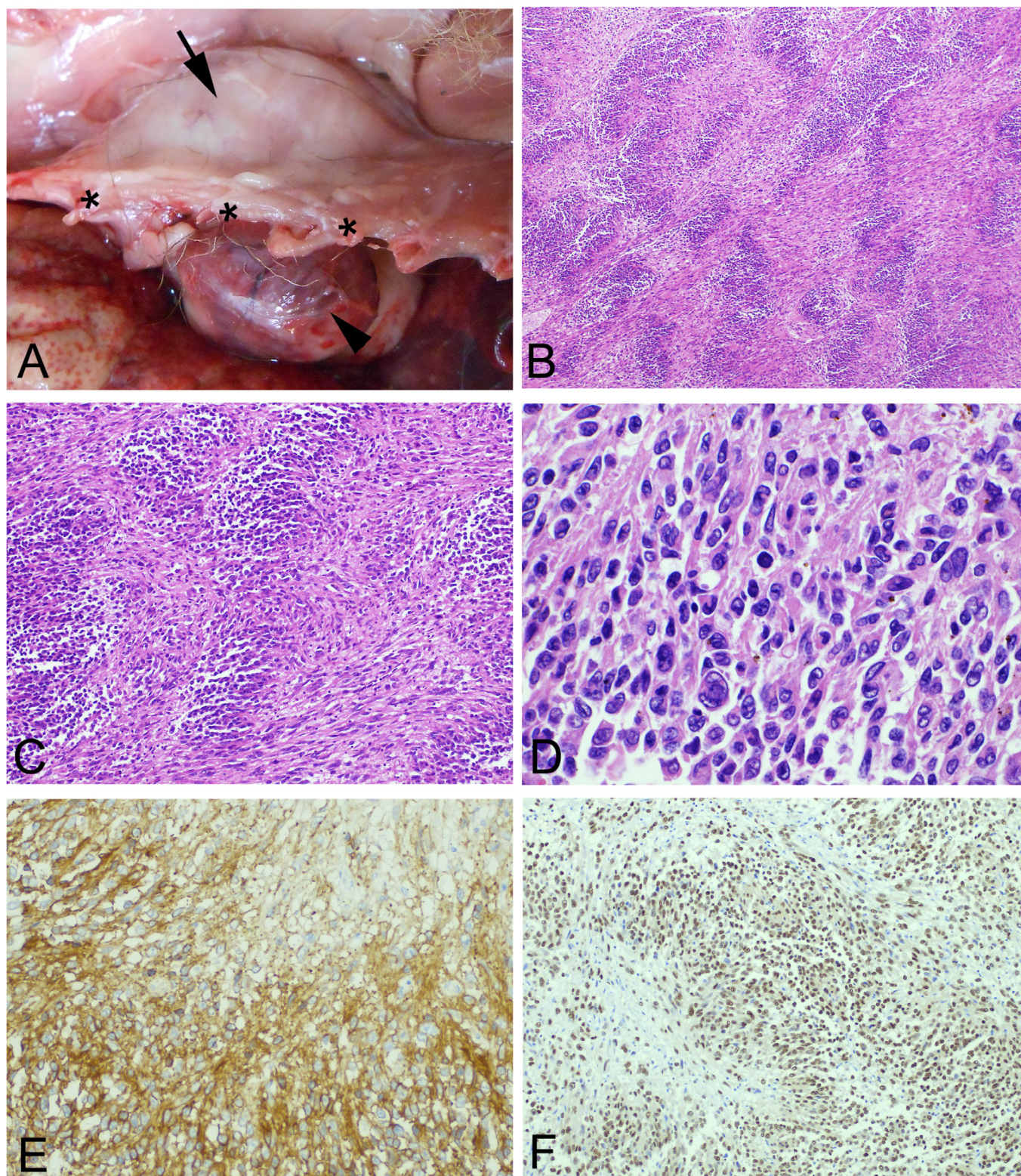


Fig. 1. Malignant peripheral nerve sheath tumor in a guinea pig. (A) The subcutaneous mass in the dorsal thorax was well defined on the epidermal side (arrow) and protruded from the pleural wall (*) into the pleural cavity (arrowhead). (B) The tumor was arranged in repeated regions of high cell density and low cell density; hematoxylin and eosin (HE). (C) In high cell density regions, round and pleomorphic cells grew in a solid fashion, while in low-density regions, spindle cells grew a fascicular growth pattern; HE. (D) Cell morphology was diverse, and nuclear atypia was clear; HE. (E) The cytoplasm was CD56-positive in most cells. (F) The nuclei were Sox10-positive in most cells. HE: hematoxylin and eosin.

propagated with nuclei arranged in palisades, and regions in which cells accumulated around blood vessels; in addition, the mass was frequently associated with necrosis (Fig. 1C). The tumor cell nuclei were diverse, found in round, oval, spindle, elongated-spindle, and wave shapes, and nuclear atypia was clear (Fig. 1D). The cytoplasm was somewhat unclear and was in low quantity in many cells, although ganglion cell-like large cytoplasm was sometimes observed. The mitotic rate was 5 cells for 10 high power fields (400×, 0.237 mm²). The tumor had invaded the vertebrae, spinal cavity, ribs, and surrounding skeletal muscle; however, it had not metastasized to other body organs. Immunohistologically, the tumor showed positive responses to the anti-S100, anti-CD56/NCAM (Fig. 1E), and anti-Sox10 (Fig. 1F) antibodies, but a negative response to the anti-SMA and PNL2 antibodies; thus, it was diagnosed as an MPNST. Aside from the tumor, in the heart, there was infiltration of lymphocytes and heterophils from the epicardium to the myocardium, as well as edema, fibrosis, osseous metaplasia in the epicardium, and bleeding. The most pronounced inflammatory lesion was in the right atrial wall, from which we observed bleeding into the pericardial cavity. There was congestive edema in the lungs.

There are two types of PNSTs, those in clear continuity with the nerve plexus, spinal nerve roots, and peripheral nerves and those which originate in soft tissue and are not in clear continuity with the nerves [9, 10]. In the present case, the tumor originated peripheral to the thoracic vertebrae but did not show clear continuity with the nerve; therefore, to establish a differential diagnosis, we needed to prove histologically that the tumor was derived from the peripheral nervous system. When PNSTs are poorly differentiated, they are difficult to distinguish from other spindle cell tumors with histological analysis alone; therefore, differentiation of PNSTs also requires immunohistological analysis [6, 9]. The histopathological characteristics of PNSTs consist of hypercellular and hypocellular arrangements, cellular and nuclear palisading, pseudocysts, perivascular pseudorosettes, and widespread necrosis; the patient in the present case presented with nearly all of the above [6, 9]. While cell morphology was diverse, the tumor was mainly composed of spindle cells; we did not observe the smooth cigar-shaped nuclei characteristic of leiomyosarcoma and we observed frequent interspersions of round cells, which are rarely observed in fibrosarcoma. Based on these findings, we were able to differentiate the tumor in the present case from leiomyosarcoma and fibrosarcoma [6, 9]. Additionally, the present immunostaining results (positive for S100, SOX10, and CD56 and negative for SMA and PNL2) were able to differentiate the tumor from amelanotic melanoma. The histological and immunohistochemical characteristics of this tumor were consistent with those of PNST in humans, dogs, and rats [2, 5, 7, 9, 14, 15, 18]. In addition to these findings, the pronounced invasiveness in combination with the bone destruction enabled us to confirm that the present tumor was an MPNST. In “Tumors in Domestic Animals,” PNST is not classified as benign or malignant but by grade [9]. However, because there are no previous reports of PNST in guinea pigs, we could not grade the tumor in the present case. We determined the tumor to be highly invasive and malignant, and we diagnosed it as an MPNST.

In dogs, PNSTs that develop near the spinal nerves initially present with no symptoms other than mild lameness and thus early diagnosis is difficult. When the tumor involves the nerve root, palpation often results in pain in the affected limb or the axilla on the affected side, which is typically chronic and gradually worsens [1]. If the tumor invades the spinal canal, symptoms on the affected side become more pronounced [1]. In the present case, the patient initially presented only with lameness and pain, as seen in dogs. Neither palpation nor radiography revealed evident tumor formation. The tumor was recognized 2 months after symptom onset; at 4 months, radiography showed that tumor invasion had progressed to thoracic vertebra destruction and disappearance of the thoracic spinal cord. Although the tumor did not show evident continuity with the nerve in gross or histological examination, the clinical course was similar to that of PNST originating near the spinal nerve in dogs; therefore, we inferred that the tumor originated in a nerve near the spine, gradually progressed, infiltrated the spinal canal, and protruded on the dorsal side. Regarding the metastasis of PNSTs, primary nervous system MPNSTs in dogs are highly expansive and invasive along the course of the nerve, but distant metastasis is reportedly rare [1, 3]. Similarly, distant metastasis does not occur in feline MPNST [16]. Conversely, rodent MPNST has diverse neural origins, its growth ranges from expansive to invasive, and metastasis is observed in highly malignant tumors [13]. In the guinea pig in the present case, the MPNST was highly invasive but there was no distant metastasis. The guinea pig's death was not tumor-related; instead, the cause of death was pleural and blood-like pericardial effusion, which is also observed in dogs and cats.

In conclusion, this is the first report on the clinical and pathological characteristics of an MPNST in a guinea pig. Although the tumor exhibited intense local invasion of the spine and surrounding muscles, there was no distant metastasis. Differentiation of MPNSTs from other rapidly-expanding tumors in the dorsal thorax requires suitable immunohistological testing, accurate pathologic diagnosis, and accumulation of additional cases.

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