

Malignant Retroperitoneal Paraganglioma in a Siberian Tiger

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(Accepted: Oct 05, 2011)

Abstract : A 14 year old female Siberian tiger presented for postmortem examination. A large mass attached to sublumbar area was found to be circumscribing aorta with metastases to mesenteric lymph nodes, uterus, kidney, adrenal gland, lung and thymus. The tumor cells were arranged in clusters or nests separated by well-developed fibrovascular stroma. The individual cells were plump and polygonal with granular eosinophilic cytoplasm and had distinct cell borders. The tumor cells were positive for synaptophysin, chromogranin A and neuron-specific enolase, and negative for cytokeratins, S100 and glial fibrillary acidic protein. The primary tumor was diagnosed as a malignant retroperitoneal paraganglioma.

Key words : Siberian tiger, paraganglioma, chromogranin A, neuron-specific enolase, synaptophysin.

Introduction

Paraganglioma is a rare neuroendocrine tumor usually arising from extra-adrenal paraganglionic cells of autonomic nervous system. Sympathetic and parasympathetic extra-adrenal paraganglia originate embryologically from the neural crest ectoderm and are distributed symmetrically and segmentally along the longitudinal axis of the body (4). Paraganglia may be divided into adrenal and extra-adrenal paraganglia. Extra-adrenal paraganglia are subdivided into branchiomeric, intravagal, aortico-sympathetic and visceral-autonomic paraganglia (4). Most common paraganglioma reported in domestic animals are chemodectoma originated from branchiomeric paraganglia (2,9,12,13,22). In this report, we present the histopathological and immunohistochemical evidence of a malignant extra-adrenal paraganglioma originated from aortico-sympathetic paraganglia in the retroperitoneal region of a Siberian tiger with systemic metastases.

Case

A 14-year-old female Siberian tiger with anorexia and depression died and presented for postmortem examination. At necropsy, large intestinal mesenteric lymph nodes enlarged to 3 to 6 cm with oval-shaped masses and a retroperitoneal solid mass, measuring 13 × 5 cm with irregular shape, was found to be attached longitudinally to the ventral side of lumbar vertebrae (Fig 1A). The masses were moderately firm and encapsulated with fibrous tissues with well developed blood vessels. The mass circumscribed the aorta (Fig 1B). The thymus which enlarged to 7 × 5 cm appeared to be dark red with nodular sur-

faces, and was occupied by large amounts of sanguineous fluid and small nodules in cut surface. Adrenal glands also appeared to be nodular and firm, and heterogenous with hemorrhage in cut surface. In the lung, white variable nodules were scattered throughout the surface of cranial lobe.

Samples of retroperitoneal masses and major organs were collected, fixed in 10% neutral buffered formalin, routinely processed and embedded in paraffin wax. Four-micrometer sections were stained with hematoxylin and eosin (HE) for light microscopic examination.

Histopathologically, the retroperitoneal tumor mass consisted of various sized nests or cords of round to polygonal cells separated by well-developed fibrovascular stroma, which is classically referred to as endocrine, alveolar or Zellballen pattern in human. The tumor cells had distinct borders, abundant eosinophilic granular cytoplasm and round to oval to polygonal shaped centrally or eccentrically located nuclei with finely stippled chromatin and single prominent nucleoli (Fig 2A). Multinucleated cells, mitotic figures and apoptotic tumor cells were occasionally observed at tumor nests circumscribed by fibrovascular stroma. Also, widespread necrosis and hemorrhage were frequently found (Fig 2B). Metastatic cellular foci or mass were

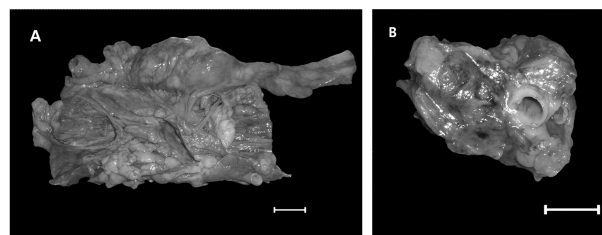


Fig 1. Gross appearance of retroperitoneal masses (bar = 2 cm) (A). An aorta penetrating the mass is noted in the cut surface (bar = 2 cm) (B).

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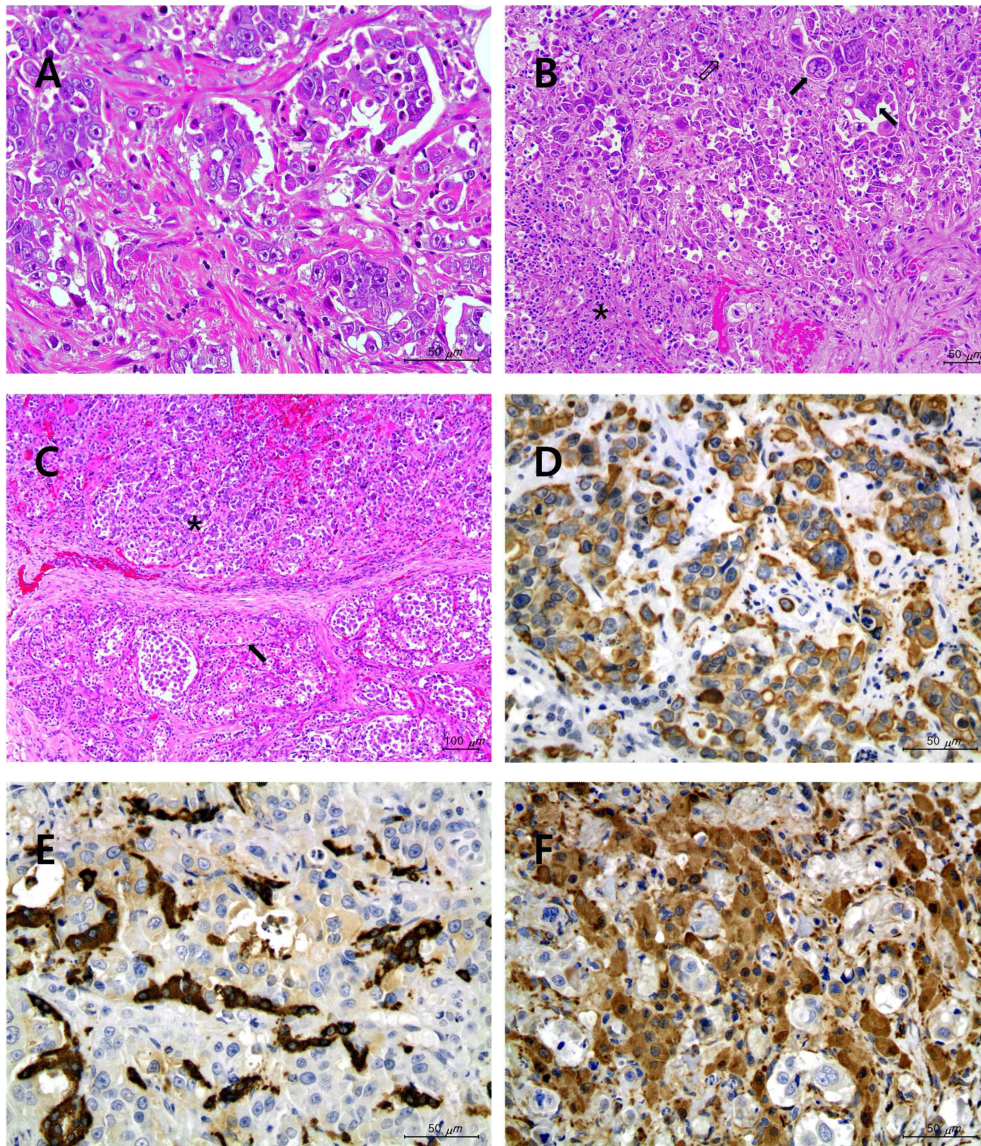


Fig 2. Microscopical appearance of the tumor. (A) Tumor cells are arranged in nests or cords and separated by fibrous stroma. Oval to polygonal tumor cells have abundant eosinophilic granular cytoplasm and vesicular nuclei with prominent nucleoli. (B) Occasionally multinucleated cells (arrows) and mitotic figures (empty arrow) are seen. Areas of necrosis (asterisk) and hemorrhage with well-developed fibrous tissues are frequently noted. (C) Metastatic cancer cells are arranged in nests in sinusoids of adrenal gland (asterisk). Note the normal cortical cells (arrow). (D-F) Immunohistochemical expression of synaptophysin (D), chromogranin A (E) and neuron-specific enolase (F).

observed in lungs, thymus, uterus, kidney and adrenal glands (Fig 2C). Immunohistochemistry was performed to define the diagnosis with avidin-biotin peroxidase complex kit (VETASTAIN; Vector Laboratories, Burlingame, CA, USA). The primary antibodies utilized were monoclonal anti-human synaptophysin (SYN, 1:20, Abcam, Cambridge, UK), chromogranin A (CGA, 1:500, Enzo, New York, USA), neuron-specific enolase (NSE, 1:200, Dako A/S, Glostrup, Denmark), cytokeratin clone 34 β E12 (1:20, Dako A/S), pan cytokeratin AE1/AE3 (1:10, Abcam), rabbit anti-S100 (1:50, Dako A/S) and glial fibrillary acidic protein (GFAP, 1:250, Dako A/S). Negative controls included staining reactions in which the primary

antibodies were eliminated. SYN was intensively expressed in most tumor cells (Fig 2D), whereas CGA (Fig 2E) and NSE (Fig 2F) showed positive reaction in some tumor cells. Reactions against other antibodies were all negative. Based on the histopathology, anatomical location and immunohistochemistry, the final diagnosis was made to malignant retroperitoneal paraganglioma.

Discussion

Clinical appearances of extra-adrenal retroperitoneal paraganglioma are dependent on its functional or nonfunctional activ-

ity. Main symptoms of functional paraganglioma are episodic hypertension, palpitation, headache and sweating due to excess catecholamine production (14). Nonfunctional paraganglioma, nonsecretory type, is asymptomatic and discovered during image examination for other reasons (3). Complete surgical excision is the mainstay of the treatment. However, long-term follow-up is required because metastasis has been reported years after surgical excision in humans (1).

Literatures about human cases describe the histological features of Zellballen pattern which cellular nests are composed of chief cells (19), nuclear pleomorphism, karyomegaly, multinucleated cells, and necrosis in both benign and malignant tumors (8,11), as is the present case.

The extra-adrenal paraganglia are composed of two specialized cell types, namely, chief cells (type 1) and sustentacular cells (type 2) (4,18). Chief cells originated from neuroectoderm contain neurosecretory granules and may secrete catecholamines in both normal and tumorous condition. Sustentacular cells surrounding the clusters of chief cells are closely related to satellite cells of autonomic ganglia which lack neurosecretory granules (16,18). In human paraganglioma, chief cells are positively stained for SYN, CGA, NSE, whereas sustentacular cells are positive for S100 and GFAP (18). Neuroendocrine tumors are divided into neural neuroendocrine tumor (NNT) and epithelial neuroendocrine tumor (ENT), and only ENT is positive for cytokeratin and desmoplakin (5). SYN is considered to be a novel and specific marker for neuroendocrine tumors (and chief cells) because it is not detected in non-neuroendocrine cells or neoplasms (5). CGA is thought to be the most specific and reliable marker used to distinguish paraganglioma from non-endocrine tumors or tumors of the adrenal cortex (21). NSE is proposed to be the most sensitive marker for chief cells, the predominant cell type in extra-adrenal paraganglia (11). In the present case, positive staining for SYN, CGA and NSE and negative staining for cytokeratins indicate that this tumor is an NNT originated from chief cells of extra-adrenal paraganglia. In view of the anatomical location of the tumor mass, the primary proliferation of this tumor may have occurred at the aortico-sympathetic ganglion in the retroperitoneum. From the histopathology, immunohistochemical evidence, and anatomical location, the tumor was finally diagnosed as a malignant extra-adrenal retroperitoneal paraganglioma. In animals, retroperitoneal paraganglioma is extremely rare. Until now, aortico-sympathetic paraganglioma cases were reported in a cat (17), three dogs (20), two horses (6,10), a cow (15) and a tiger (7). This case would have a great value to report as a rare paraganglioma case being occurred in the retroperitoneum and represents the first description of an aortico-sympathetic paraganglioma with systemic metastasis in a tiger.

Acknowledgment

This work was supported by Priority Research Centers Programs through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology

(2009-0094035).

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시베리아 호랑이에서 발생한 악성후복막부신경절종 증례

신상경 · 박병민 · 염소영 · 김태왕 · 나기정 · 안병우¹

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요 약 : 조직병리소견과 면역염색결과를 바탕으로 14년령 암컷 시베리아 호랑이의 복막뒤공간에서 발생한 악성부신경절종을 보고하였다. 부신경절종은 동물에서 드물게 발생하는 신경내분비종양으로 주로 자율신경계의 부신외신경절 세포로부터 발생한다. 원발종괴는 복막뒤공간에 요추의 배쪽면을 따라 장방향으로 부착되어 있었고, 장간막림프절, 신장, 자궁, 부신, 폐, 흉선으로 전이되었다. 종양세포는 다각형의 통통한 형태에 과립상의 호산성 세포질을 갖고 있었으며, 섬유혈관 기질에 의해 구획되어 집락(cluster) 또는 둥지(nest) 모양으로 배열된 전형적인 Zell-ballen 형태를 나타냈다. 면역염색에서 synaptophysin, chromogranin A, neuron-specific enolase에 특이적인 양성반응을 보였다. 본 증례는 시베리아 호랑이에서 발생한 악성후복막부신경절종이 전신으로 전이된 최초보고이다.

주요어 : 시베리아호랑이, 부신경절종, chromogranin A, neuron-specific enolase, synaptophysin