NOTE *Pathology*

Cardiac ganglioneuroma in a juvenile pig

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ABSTRACT. A cardiac mass (3 × 5 × 3 cm) was detected at the base between the right auricular wall and right vena cava of a slaughtered 6-month-old female mixed-breed pig during a meat inspection. The tumor comprised infiltrative prominent interweaving fascicles of Schwann cells with Verocay bodies. Moreover, the ganglion cells were scattered or aggregated throughout the neoplastic tissue. The ganglion and Schwann cells had neither cellular atypism nor mitosis. On the basis of the bearing site as well as the morphological and immunohistochemical features, this is the first case of a cardiac ganglioneuroma in a pig.
KEY WORDS: ganglioneuroma, heart, swine

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Neuronal neoplasms are classified into neuroblastoma, ganglioneuroblastoma and ganglioneuroma depending on the degree of differentiation of neoplastic cells. Ganglioneuromas are composed of a mixture of well-differentiated neurons and abundant stroma containing nerve processes and Schwann cells [12]. In domestic animals, ganglioneuroma occurs in various organs, including the intestines [1, 3–5, 8, 13–17], skin [9], adrenal glands [6] and urinary bladder [18]. In the present study, we have reported the histopathological and immunohistochemical findings for a cardiac ganglioneuroma in a juvenile pig.

A mass was detected at the base of the heart of a slaughtered 6-month-old female mixed-breed pig during a meat inspection. The tumor was located between the base of the right auricular wall and the right vena cava and protruded to the area outside of the heart. In addition, it showed infiltrative growth into the auricular wall and, therefore, would have been difficult to remove (Fig. 1A). The tumor was 3 × 5 × 3 cm in diameter with an elastic, solid, glistening cut surface, which was homogenously milky white (Fig. 1A). The pig showed no significant abnormalities in the other organs on clinical and postmortem examinations.

Together, the heart and tumor tissues were fixed in 10% buffered neutral formalin, embedded in paraffin, processed routinely, sectioned and stained with hematoxylin and eosin (H&E) and Nissl stained using cresyl violet. The heat-induced antigen retrieval pretreatment was performed using Target Retrieval Solution (pH 6.0, 121°C for 15 min, Dako, Glostrup, Denmark) prior to immunohistochemical staining. The serial sections were immunohistochemically analyzed using the polymer immunocomplex method (Envision+, Dako). The sections were incubated overnight at 4°C with the following primary antibodies: S-100a (polyclonal, prediluted, Dako), glial fibrillary acidic protein (GFAP, polyclonal, 1:400, Dako), neuron-specific enolase (NSE, polyclonal, 1:10,000, Millipore, Billerica, MA, U.S.A.), neurofilament (monoclonal, 2F11, 1:25, Dako) and class III β-tubulin (5G8, 1:10,000, Promega, Madison, WI, U.S.A.). For visualization, the sections were developed in a 3, 3′-diaminobenzidine (DAB) solution (Liquid DAB+ substrate-chromogen system, Dako) and counterstained with Mayer's hematoxylin.

Histopathologically, the cardiac tumor was poorly demarcated with infiltrative growth encroaching into the auricular wall (Fig. 1B). In addition, it was composed of prominent interweaving fascicles of spindle-shaped mesenchymal cells with elongated, thin and wavy nuclei, which were morphologically identified as Schwann cells. Furthermore, the cardiac tumor revealed an Antoni A pattern, which is characteristic of a schwannoma. Verocay bodies, which are formed by two compact rows of well-aligned nuclei separated by fibrillary cell processes, were also observed in the Antoni A pattern (Fig. 1C). Moreover, the ganglion cells, which varied in size and had a stellate to polygonal shape, pale to eosinophilic cytoplasm and a large vesicular round nucleus with a prominent nucleolus, were scattered or aggregated in the Schwann cell-proliferating area (Fig. 1D). The majority of the scattered ganglion cells showed obvious Nissl substance in the cytoplasm following the cresyl violet staining and were accompanied by satellite cells; therefore, they were mature neurons (Fig. 1E). In contrast, the aggregated ganglion cells, which were not fully mature, lacked satellite cells and Nissl bodies, while the formation of neuropil was not obvious. There was no cellular atypism in the ganglion or Schwann cells, and no mitosis was detected.

Immunohistochemically, the scattered mature or aggregated immature ganglion cells stained positivey for S-100a, NSE and class III β-tubulin (Fig. 1F), while the Schwann

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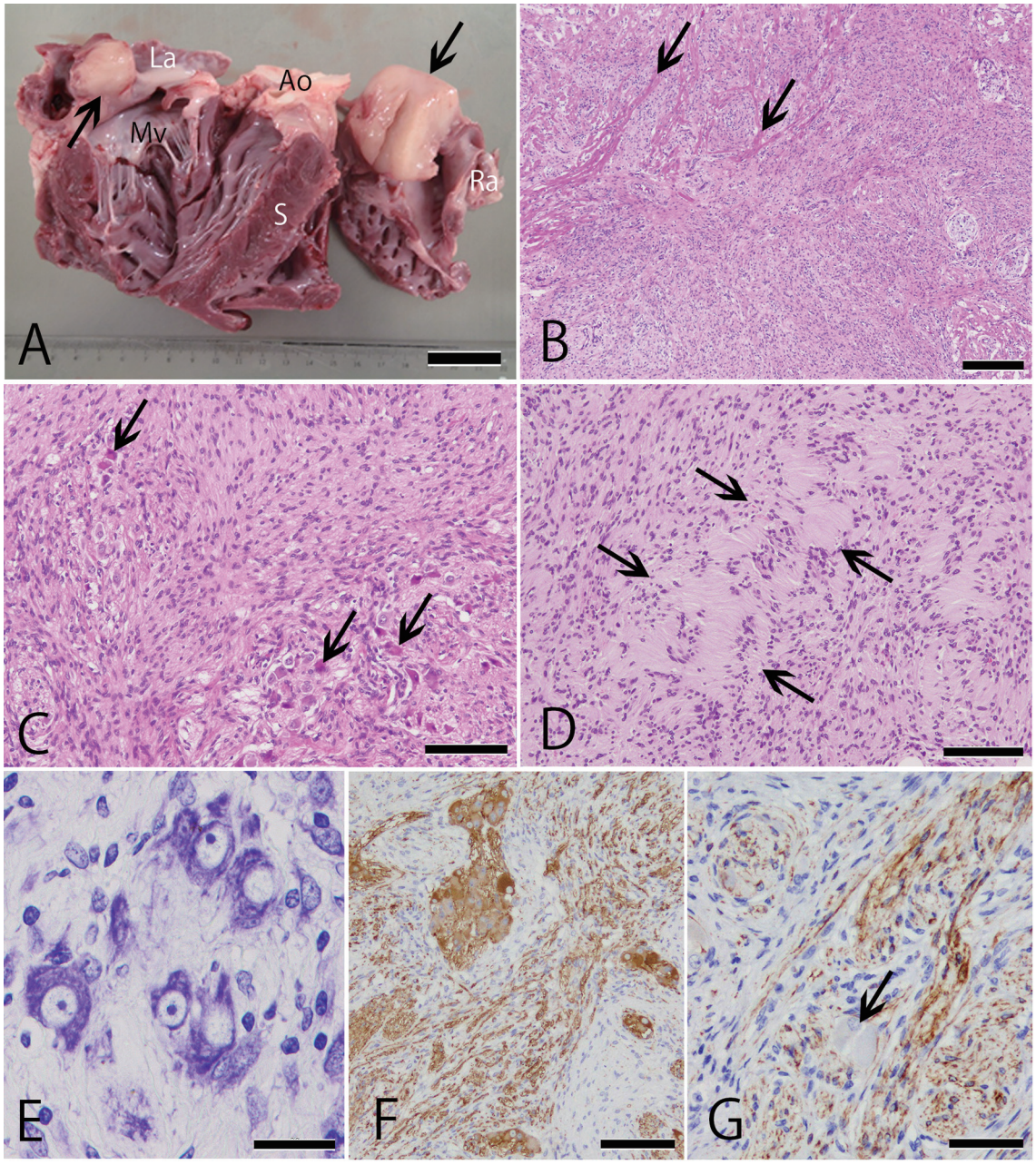

Fig. 1. (A) Gross findings in a pig heart with a cardiac ganglioneuroma. A demarcated, solid, homogenous milky white cardiac tumor is located between the right atrium and right vena cava. (Ao, aorta; La, left atrium; Ra, right atrium; S, septum; and Mv, mitral valve; bar=3 cm.) (B) Low magnification of the cardiac ganglioneuroma. The tumor was composed of prominent interweaving fascicles of Schwann cells with infiltrative growth in the auricular wall. Arrows indicate myocardium. (Section stained with H&E, bar=200 μm.) (C) Ganglioneuronal and Schwann cell components of the cardiac ganglioneuroma. Arrows indicate solitary ganglion cells and their aggregations. Interweaving proliferation of Schwann cells can be observed in the center. (H&E staining, bar=100 μm.) (D) Antoni A pattern proliferation of Schwann cells. Verocay bodies (arrows) can be observed in the higher-cellularity area of Schwann cells. (H&E staining, bar=100 μm.) (E) Mature ganglion cells with cytoplasmic Nissl substance. (Cresyl violet staining, bar=20 μm.) (F) Immunohistochemistry of class III β-tubulin. Ganglion cells are strongly positive. (Bar=100 μm.) (G) Immunohistochemistry of GFAP. Schwann and ganglion cells (arrow) are positive and negative, respectively. (Bar=50 μm.)

cells and satellite cells that adhered to the mature ganglion cells stained positive for S-100a, NSE and GFAP (Fig. 1G).

To the best of our knowledge, there are only 2 previously reported cases in which ganglioneuromas developed in the small intestine of swine without any obvious clinical signs and were discovered during a meat inspection [13, 21]. In addition, cardiac ganglioneuromas are very rare, and only three cases have been reported in humans [7, 10, 20]. In the veterinary medical field, only one known case of a feline malignant ganglioneuroma of the heart has been published. In this case, the tumor was considered to have originated from the intramural parasympathetic ganglia in the right atrium [11]. In the present case, the tumor was located between the right atrium and right vena cava, including the right vena cava–right atrial ganglionated plexus [2], where it may have originated.

Ganglioneuroblastoma consists of an admixture of ganglioneuromatous components and a >50% composition of neuroblastomatous components, while neuroblastoma is primarily composed of neuroblastomatous components. In contrast to these 2 tumors, ganglioneuromas are predominantly composed of ganglioneuromatous components and are therefore the most differentiated in all neuronal tumors. In the present case, the ganglion cells stained positive for neurofilament, NSE and class III β-tubulin. Further, the ganglion cells had Nissl substance and satellite cells. Therefore, they were morphologically mature, and neuroblasts were not observed anywhere in the neoplastic tissue. However, aggregations of immature ganglion cells, which lacked satellite cells and Nissl bodies, were scattered in the neoplastic tissue. The existence of immature ganglion cells provides some evidence to suggest that peripheral neuroblastic neoplasms originate from the progenitor cells of neural crest [19]. Additionally, the Schwann cell component was rich in scattered Verocay bodies, which are typically found in the densely packed Antoni A regions of schwannoma [22]. It is necessary to distinguish the present case from another cardiac schwannoma, which involved the intrinsic cardiac ganglia and showed ganglion cells dispersed at varying densities throughout the neoplastic tissue. On this basis, the present case was diagnosed as a ganglioneuroma with a rich Schwann cell component.

In conclusion, the present case is the first report of a cardiac ganglioneuroma that probably originated from the right vena cava–right atrial ganglionated plexus in a swine.

REFERENCES

1. Allen, D., Swayne, D. and Belknap, J. K. 1989. Ganglioneuroma as a cause of small intestinal obstruction in the horse: a case report. *Cornell Vet.* **79**: 133–141. [Medline]
2. Arora, R. C., Waldmann, M., Hopkins, D. A. and Armour, J. A. 2003. Porcine intrinsic cardiac ganglia. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* **271**: 249–258. [Medline] [CrossRef]
3. Bemelmans, I., Kury, S., Albaric, O., Hordeaux, J., Bertrand, L., Nguyen, F. and Abadie, J. 2011. Colorectal hamartomatous polyposis and ganglioneuromatosis in a dog. *Vet. Pathol.* **48**: 1012–1015. [Medline] [CrossRef]
4. Cole, D. E., Migaki, G. and Leipold, H. W. 1990. Colonic ganglioneuromatosis in a steer. *Vet. Pathol.* **27**: 461–462. [Medline] [CrossRef]
5. Fairley, R. A. and McEntee, M. F. 1990. Colorectal ganglioneuromatosis in a young female dog (Lhasa Apso). *Vet. Pathol.* **27**: 206–207. [Medline] [CrossRef]
6. Grossi, A. B., Leifsson, P. S., Jensen, H. E., Vainer, B. and Iburg, T. 2013. Histologic and immunohistochemical classification of 41 bovine adrenal gland neoplasms. *Vet. Pathol.* **50**: 534–542. [Medline] [CrossRef]
7. Gupta, S. K. 1958. Ganglioneuroma arising from the superficial cardiac plexus. *Heart Cent. Bull. (Roslyn)* **15**: 29–38. [Medline]
8. Hazell, K. L., Reeves, M. P., Swift, I. M. and Sullivan, N. 2011. Small intestinal ganglioneuromatosis in a dog. *Aust. Vet. J.* **89**: 15–18. [Medline] [CrossRef]
9. Hermeyer, K., Kuhn, M., Kuchelmeister, K., Laik, C., Baumgartner, W. and Wohlsein, P. 2007. Multiple cutaneous ganglioneuromas in a dog. *Vet. Dermatol.* **18**: 360–364. [Medline] [CrossRef]
10. Jozsa, L., Steczik, A. and Lusztig, G. 1963. On primary ganglioneuroma of the heart. *Zentralbl. Allg. Pathol.* **104**: 257–260. [Medline]
11. Kobayashi, R., Ohsaki, Y., Yasuno, K., Ogihara, K., Kasai, T., Chambers, J. K., Uchida, K., Saegusa, S., Kamiie, J. and Shirota, K. 2012. A malignant and metastasizing feline cardiac ganglioneuroma. *J. Vet. Diagn. Invest.* **24**: 412–417. [Medline] [CrossRef]
12. Koestner, A., Bilzer, T., Fatzer, R., Schulman, F. Y., Summer, B. A. and Van Winkle, T. J. 1999. Histological classification of tumors of the nervous system of domestic animals, 2nd ser., vol. 5. Armed Forces Institute of Pathology, Washington, D. C.
13. Murakami, M., Sakai, H., Mizutani, K. and Yanai, T. 2011. Ganglioneuroma in the small intestine of a juvenile pig. *J. Vet. Med. Sci.* **73**: 1501–1504. [Medline] [CrossRef]
14. Paris, J. K., McCandlish, I. A., Schwarz, T., Simpson, J. W. and Smith, S. H. 2013. Small intestinal ganglioneuromatosis in a dog. *J. Comp. Pathol.* **148**: 323–328. [Medline] [CrossRef]
15. Porter, B. F., Storts, R. W., Payne, H. R. and Edwards, J. F. 2007. Colonic ganglioneuromatosis in a horse. *Vet. Pathol.* **44**: 207–210. [Medline] [CrossRef]
16. Reimer, M. E., Leib, M. S., Reimer, M. S., Saunders, G. K. and Johnston, S. A. 1999. Rectal ganglioneuroma in a dog. *J. Am. Anim. Hosp. Assoc.* **35**: 107–110. [Medline] [CrossRef]
17. Ribas, J. L., Kwapien, R. P. and Pope, E. R. 1990. Immunohistochemistry and ultrastructure of intestinal ganglioneuroma in a dog. *Vet. Pathol.* **27**: 376–379. [Medline] [CrossRef]
18. Sakai, H., Yonemaru, K., Takeda, M., Niimi, K., Murakami, M., Hirata, A. and Yanai, T. 2011. Ganglioneuroma in the urinary bladder of a dog. *J. Vet. Med. Sci.* **73**: 801–803. [Medline] [CrossRef]
19. Shimada, H., Ambros, I. M., Dehner, L. P., Hata, J., Joshi, V. V. and Roald, B. 1999. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. *Cancer* **86**: 349–363. [Medline] [CrossRef]
20. Tiraspol'Skaia, M. M. 1961. Ganglioneuroma of the heart. *Arkh. Patol.* **23**: 72–74. [Medline]
21. Une, Y., Iwama, K., Yoshida, H., Shirota, K., Nomura, Y. and Saito, Y. 1984. Multiple ganglioneuroma derived from intramural plexus of jejunum in a sow. *Jpn. J. Vet. Sci.* **46**: 247–250. [Medline] [CrossRef]
22. Wippold, F. J., Lammle, M., Anatelli, F., Lennerz, J. and Perry, A. 2006. Neuropathology for the neuroradiologist: palisades and pseudopalisades. *AJNR Am. J. Neuroradiol.* **27**: 2037–2041. [Medline]