Abstract: Spontaneous nonneoplastic proliferative lesions of the cardiac hemangioendothelium are extremely rare in humans and animals. Here, we describe a spontaneous hemangioendothelial cell hyperplasia in the heart of a 9-week-old male ICR mouse. The lesion was observed focally in the interventricular septum, with no compression of the surrounding tissues. In the lesion, a single layer of hemangioendothelial cells that had a polygonal shape with enlarged nuclei and plump cytoplasm closely lined surrounding widened capillary vascular spaces and cardiac muscles. There was little cellular atypia, and there were no multilayered endothelial cells. Immunohistochemical staining revealed that these cells were partly positive for factor VIII and CD31, hemangioendothelial cell markers, and negative for Ki-67. These features were consistent with those in aged female B6C3F1 mice in the only report in mice of spontaneous cardiac hemangioendothelial cell hyperplasia. Therefore, this is the first report of spontaneous hemangioendothelial cell hyperplasia in the heart of a young mouse. (DOI: 10.1293/tox.2019-0008; J Toxicol Pathol 2019; 32: 289–292)

Key words: hemangioendothelial cell hyperplasia, young mouse, Crl:CD1(ICR), heart, spontaneous

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was observed focally, and its maximal diameter was approximately 0.5 mm. The lesion was not continuous with the epicardium or endocardium. A single layer of the cells in the lesion closely lined surrounding widened capillary vascular spaces and cardiac muscles (Fig. 1A). In the lesion, most cells were polygonal-shaped cells with enlarged nuclei and plump cytoplasm, and some cells had spindle-shaped nuclei and scant cytoplasm similar to normal endothelial cells. Although these cells in the lesion that were similar to normal endothelial cells were positive for factor VIII and CD31, a hemangioendothelial cell marker, the polygonal-shaped cells in the lesion were negative for these markers (Fig. 2A and B). The cells in the lesion were also negative for Ki-67, a proliferating cell marker; F4/80, a macrophage marker; α-SMA, a smooth muscle cell marker; and desmin, a muscle cell marker (Fig. 2C and F). Hemangioendothelial cell hyperplasia is diagnosed on the basis of a proliferation of small vessel endothelial cells with luminal dilation, which indicates that the lesion is hemangioendothelial hyperplasia. In a previous report regarding spontaneous hemangioendothelial cell hyperplasia of the heart in aged female B6C3F1 mice, the cells in the lesion were focally positive for both factor VIII and CD31 and negative for proliferating cell nuclear antigen (PCNA). In the current case, the cells in the lesion were partly positive for both factor VIII and CD31 and negative for Ki-67 (Fig. 2), which is consistent with the previous report of spontaneous hemangioendothelial cell hyperplasia.

In the differential diagnosis, hemangioma and hemangiosarcoma were considered from among the other proliferative lesions of the hemangioendothelial cell. Hemangioma is diagnosed on the basis of a moderate compression of the surrounding tissues and a single layer of prominent uniform endothelial cells without atypia. In the current case, there was no compression of the surrounding tissues, and polygonal-shaped cells and normal endothelial-like cells closely lined the wide capillary vascular space in a single layer. These findings suggest that the present case does not match hemangioma. Hemangiosarcoma is diagnosed on the basis of cellular atypia and an obvious proliferation with multilayered or clustered endothelial cells. In the current case, there was little cellular atypia, and there were no multilayered endothelial cells, and the lesion was focal, indicating that the lesion was not a hemangiosarcoma. There-
fore, we concluded that the present case was a case of he-
mangioendothelial cell hyperplasia.

Some of the polygonal-shaped cells were more enlarged
than other cells in the lesion and included eosinophilic drop-
lets in the cytoplasm, which were positive for PAS staining
(Fig. 1B and C). Hemangioendothelial cells have a highly
developed system of cell membrane vesicles to transport macromolecules, such as albumin, from the bloodstream
to tissue spaces. These vesicles accumulate and fuse in
hypertrophied endothelial cells in vascular diseases such as
cardiac hypertrophy, dyslipidemia, and hyperglycemia. Eosinophilic globules are a commonly seen histological fea-
ture in pyogenic granuloma, granulation tissue, and various
hemangioendothelial tumors such as glomeruloid hemangi-
oma, papillary hemangioma, and Kaposi’s sarcoma. One
hypothesis for this is that eosinophilic globules are formed
due to an impaired lysosomal degradation process in injured
cells demonstrating membrane blebbing, increased influx of
plasma proteins, and increased autophagocytic activity. There-
fore, the eosinophilic droplets may have resulted from
the accumulation and fusion of cell membrane vesicles.

Spontaneous cardiac endothelial cell hyperplasia is
associated with thrombi of the atrium and ventricle in hu-
mans. In aged mice with adenocarcinomas of the mam-
mary gland, spontaneous cardiac endothelial cell hyperpla-
sia is diffusely observed with little mitosis at 86 to 109 weeks
old and is considered to be related to female sex hormones
and humoral endothelial cell growth factors produced by
mammary tumors. On the other hand, chemically-induced
cardiac endothelial cell hyperplasia is observed at earlier
ages, and it has a more focal/multifocal distribution pat-
tern and shows prominent mitoses. In the current case,
the lesion was focally observed at 9 weeks old without high
proliferation activity such as increases in mitosis and cells
positive for Ki-67 immunohistochemical staining, suggest-
ing that the current case cannot be categorized according
to previous reports. We could not determine the patho-
genesis of the hyperplasia because no other lesions were ob-
served in the heart or other organs.

In conclusion, we found spontaneous endothelial cell
hyperplasia of capillaries in the heart of a 9-week-old male
ICR mouse. The observations reported here may be useful
for evaluating cardiac proliferative lesions in carcinogenic-
ity and/or general toxicity studies.

Disclosure of Potential Conflicts of Interest: The authors
have no conflicts of interest in connection with this paper.

Fig. 2. Immunohistochemistry in the heart of a young ICR mouse. Hemangioendothelial cells in the lesion were partly positive for CD31 (A, arrows) and factor VIII (B, arrowheads) and negative for Ki-67 (C), α-SMA (D), desmin (E), and F4/80 (F). Bar: 50 µm.
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