Case Report

Spontaneous hemangioendothelial cell hyperplasia of the heart in a young ICR mouse

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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

Hemangioendothelial cell hyperplasia, a nonneoplastic proliferative lesion, is induced by chemicals such as 1,3-butadiene1–3, captofol4, and PPAR agonist5. However, this lesion rarely occurs spontaneously in humans6–11 and animals12–14. In the mouse heart, there is only one report of a hemangioendothelial cell hyperplasia, a report in aged female B6C3F1 mice with mammary adenocarcinomas14. Here, we describe the pathological features of spontaneous hemangioendothelial cell hyperplasia in the heart of a young male ICR mouse.

The animal was a 9-week-old male ICR [Crl:CD1(ICR)] mouse (Charles River Laboratories Japan, Inc., Kanagawa, Japan) orally treated with water for 14 days in the control group of a toxicity study. The mouse was housed in a plastic cage with softwood chip bedding under controlled conditions (12 h light/dark cycle, 40–70% humidity at 21–25°C) and fed a standard diet (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water ad libitum. This study was reviewed and approved by the head of the test facility and performed in accordance with the Guidelines for Animal Experiments, Research & Development Division, Toray Industries, Inc.

The animal had no abnormalities in clinical signs, body weight, hematology, blood chemistry, organ weight, or necropsy findings. The histopathological lesion was only observed in the heart; it was not observed in any other organs in this animal. The heart of the animal was routinely fixed in 10% neutral buffered formalin, trimmed longitudinally, embedded in paraffin, and sectioned. Sections were stained with hematoxylin and cosin (HE) and periodic acid Schiff (PAS). For immunohistochemical staining, a rabbit anti-human factor VIII polyclonal antibody (Biocare Medical, LLC, Concord, CA, USA)15, a rat anti-mouse CD31 monoclonal antibody (Abcam K.K., Tokyo, Japan)16, a rabbit anti-mouse Ki-67 polyclonal antibody (Novus Biologicals, LLC, Littleton, CO, USA)17, a rat anti-mouse F4/80 monoclonal antibody (AbD Serotec. Ltd., Kidlington, UK)18, a goat anti-human alpha smooth muscle actin (α-SMA) polyclonal antibody (Abcam K.K.), and a rabbit anti-human desmin monoclonal antibody (Abcam K.K.)19 were used. For antigen retrieval, heat treatment of the sections was performed for Ki-67 and α-SMA immunohistochemical staining, and sections were treated with protease for factor VIII, CD31, and F4/80 immunohistochemical staining. The proliferative lesion was observed in the heart of only one animal, and there was no similar lesion in the remainder of the animals examined in this study.

In the interventricular septum, the proliferative lesion
Cardiac Hemangioendothelial Hyperplasia in a Young Mouse 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 hyperplasia20. 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)14. 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 hyperplasia14.

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 atypia20, 21. 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 cells20, 21. 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-
Therefore, we concluded that the present case was a case of hemangioendothelial cell hyperplasia.

Some of the polygonal-shaped cells were more enlarged than other cells in the lesion and included eosinophilic droplets 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 spaces22–24. These vesicles accumulate and fuse in hypertrophied endothelial cells in vascular diseases such as cardiac hypertrophy, dyslipidemia, and hyperglycemia25, 26. Eosinophilic globules are a commonly seen histological feature in pyogenic granuloma, granulation tissue, and various hemangioendothelial tumors such as glomeruloid hemangiomma, papillary hemangiomma, and Kaposi’s sarcoma27–29. 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 activity27, 28. Therefore, 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 humans9, 10. In aged mice with adenocarcinomas of the mammary gland, spontaneous cardiac endothelial cell hyperplasia 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 tumors14. On the other hand, chemically-induced cardiac endothelial cell hyperplasia is observed at earlier ages, and it has a more focal/multifocal distribution pattern and shows prominent mitoses1–5, 14. 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, suggesting that the current case cannot be categorized according to previous reports1–5, 14. We could not determine the pathogenesis of the hyperplasia because no other lesions were observed 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 carcinogenicity 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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