CASE REPORT

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Granulomatous Myocarditis Caused by Candida Spp Infection in a Spontaneously Diabetic Torii Rat

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ABSTRACT

Background: Myocarditis refers to myocardial inflammation with necrosis caused by non-infectious of infectious agents such as bacteria, fungi, or drugs. Candida is known to cause myocarditis in healthy and immunocompromised individuals. Diabetes mellitus causes chronic hyperglycemia due to impaired secretion or hypofunction of insulin, induces a compromised state, and increases the risk of contracting various infections. **Objective:** We report a case of granulomatous myocarditis caused by Candida in a Spontaneously Diabetic Torii rat, a non-obese diabetic model. **Case report:** A male SDT rat, 61 weeks of age, was housed in conventional environment. The rat was provided a commercial diet and tap water ad libitum. The heart was sampled and prepared the specimen of hematoxylin-and-eosin-, Sirius-red-, Giemsa-, Grocott-stain. Histologically, formation of large granulation tissue was observed in the left ventricular wall. A center of the foci showed necrosis. Moreover, inflammatory cells infiltration and fibrous component were increased surrounding the foci and between myocardial cells. A Grocott and Giemsa staining-positive cell masses occasionally appearing in the foci were considered to be Candida because of their characteristic form. **Conclusion:** The development and progression of myocarditis were potentially related to a diabetes-induced compromised state.

Keywords: Malignant Triton Tumor, peripheral nerve sheath tumors.

1. BACKGROUND

Myocarditis is the term used to refer to myocardial inflammation with necrosis caused by infectious agents, cardiotoxic substances, or autoimmunity to them. In cases involving infections, the causal agents are viruses, bacteria, fungi, and parasites (1). Candida spp is a resident fungus in the human body. Diabetes mellitus leads to chronic hyperglycemia due to impaired secretion or hypofunction of insulin, and hyperglycemia is responsible for various complications such as retinopathy, nephropathy, peripheral neuropathy, and myocardial infarction. Moreover, hyperglycemia induces a compromised state and increases the risk of various infections (2). Spontaneously Diabetic Torii (SDT) rats have been developed as a non-obese diabetic model and are produced from Sprague–Dawley (SD) rats with polydipsia and polyuria. In male SDT rats, the cumulative incidence of diabetes is 100% at 40-week. And the plasma glucose significantly increases at 16-week compared to SD rat (3).

2. OBJECTIVE

In this study, we report the findings in a case of granulomatous myocarditis caused by Candida spp in a diabetes mellitus model rat.

3. CASE PRESENTATION

A male SDT rat was purchased from CLEA Japan Inc. (Tokyo, Japan) and housed at an average temperature of 20-26° under air-controlled conditions in colony cages with a 12-h light/12-h dark cycle. The rat was provided a commercial diet (CRF-1; ORIENTAL YEAST CO., LTD., Tokyo, Japan) and tap water ad libitum. The rat kept to 61 weeks of age in conventional environment. It showed no obvious changes throughout the rearing period, and was euthanized by exsanguination under isoflurane anesthesia. Necropsy revealed a white mass focus on the surface of the heart (Fig. 1). The

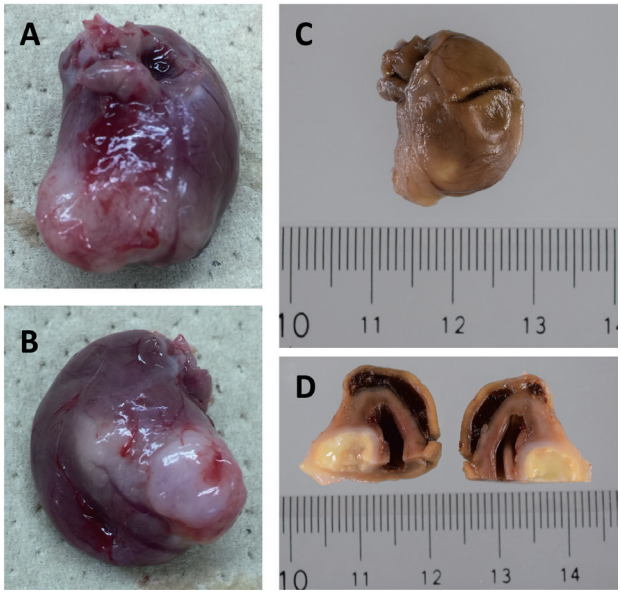

Figure 1. Gross pathology. Images (A) and (B) were obtained before fixation, (C) and (D) were obtained after fixation in 10% neutral-buffered formalin.

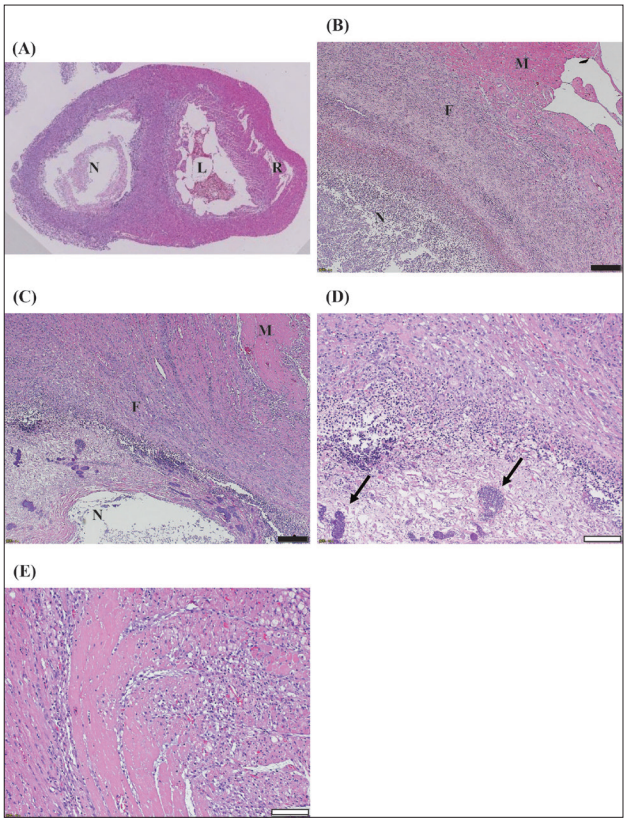

Figure 2. Histopathology of the lesion. HE stains. (A) Axial section of heart. R is the right-ventricle; L is the left-ventricle; and N is caseous necrosis. (B, C) F is fibrotic area; M is myocardium. (D) Enlarged image of C. The arrow indicates the fungal mass. (E) Degeneration of the myocardium, inflammation, and fibrosis between myocardial cells. The black bar is 200 μm, and the white is 100 μm.

organs fixed in 10% neutral-buffered formalin, embedded in paraffin, and sliced into 4-μm slices. The sections were stained with hematoxylin-and-eosin-, Sirius red-, Giemsa-, Grocott-stains.

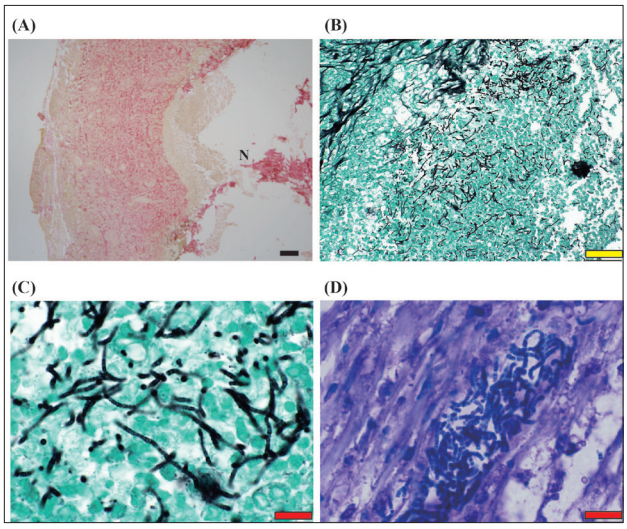

Figure 3. Histopathology of the lesion. (A) Sirius-red-staining. N is caseous necrosis. (B) Grocott-staining. (C) Enlarged image of B. (D) Giemsa-staining. The black bar is 200μm; the yellow is 50 μm; and the red is 10 μm.

The lesion was located in the left-ventricular wall, the center was demonstrated yellowish and creamy (Fig. 1). Histologically, large granulation tissue was observed, myocardial tissue demonstrated necrosis with structural decayed and cavitation (Fig. 2A). There were numerous inflammatory cells, mainly neutrophil and macrophage around the cavity, and a pale acidophilic-component as like as fiber surrounding foci and between myocardial cells (Fig. 2B-2E). A part of myocardium cells was degeneration (Fig. 2E). The cell mass was scattered in the foci. (Fig. 2C, 2D). The other organs, including the liver, spleen, kidneys, and lungs, did not show any notable findings.

The fibrous component showed positive for Sirius red-staining (Fig. 3A). The cell mass was composed of round and hypha-like cells. It was considered to be fungal because it showed positive results in Grocott- (Fig. 3B, 3C), and Giemsa-staining (Fig. 3D). Consequently, this lesion was a granulomatous myocarditis caused by fungus. Based on the Grocott- and Giemsa-staining reactions and the morphological features, the pathogen was considered to be Candida spp (4).

4. DISCUSSION

Candidiasis development has been attributed to a diabetes-induced compromised state (2). The progression factors were assumed to be decreased neutrophil phagocytosis and immune response due to hyperglycemia. Moreover, the infection was presumed to cause cytokine production, which also attenuated the insulin effect, resulting in the exacerbation of inflammation due to hyperglycemia. Mycosis are classified into deep or superficial, and many cases have been reported in rats and mice (5-7). In a case of myocarditis in the canary, Candida albicans induced granulomatous lesions; necrotic core, inflammatory cells infiltration and fibrous capsule (8). The hyperglycemia reported to effect to immune response including function of immune cells and regulation of cytokines (9). Indeed, myocarditis

has been reported to be caused by Candida albicans in a diabetes patient (10). This rat was considered to have been hyperglycemia over the long term. Therefore, we conjectured that granulomatous myocarditis was caused by immunodeficiency against Candida spp in the present case. However, Candida albicans could not be identified by immunohistochemical stained and in situ hybridization due to inadequate sample fixation and storage condition. The infection route could not be revealed in this analysis because did not show findings at the other organs. The route supposed that the Candida spp invaded the heart via blood from oral or skin in the decline of immune function due to hyperglycemia.

5. CONCLUSION

We report the findings for granulomatous myocarditis caused by Candida spp infection in SDT rat. These findings were attributed to background lesion of hyperglycemia. The myocarditis was considered to be related to a compromised state due to diabetes, and the results highlight the importance of controlling for a compromised state.

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- **Author Contributions**:: KU and KM gave substantial contribution to the conception of the work. KU, TSH and KS gave substantial contribution of data. KU and KM gave substantial contribution to the acquisition, analysis, or interpretation of data for the work. KU, NS-K, TO and KM had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors contributed equally to the research, writing, and review of this manuscript. Final proofreading was made by the first author.
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