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Autopsy case of Rosai–Dorfman disease presenting as fibrinous pericarditis

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Abstract

Rosai–Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis that is characterized histopathologically by accumulation of CD68-positive, S100-positive, and CD1a-negative histiocytes. Cardiac involvement of RDD is rare. We report here an autopsy case of cardiac involvement of RDD presenting as fibrinous pericarditis. A 14-year-old Japanese boy complained of loss of appetite and breathing difficulty when lying down. He was found dead on his back in his bedroom. One year before his death, he was diagnosed with RDD after skin biopsy. At autopsy, the deceased was 153 cm in height and weighed 38 kg with systemic edema. He had flat pigmented light-brown spots, as well as many pale reddish-brown papules on the abdomen and both thighs. Cervical and mediastinal lymphadenopathy was observed. A large amount of pleural and ascitic fluid was observed. The spleen weighed 381.9 g and showed splenomegaly. The heart weighed 620 g and showed acute fibrinous pericarditis with adhesion. Abundant fibrin was observed on the epicardial surface. The infiltrating cells were CD68-positive, S100-positive, and CD1a-negative histiocytes. The skin and spleen showed histiocytic involvement. Systemic edema, large amounts of pleural and ascitic fluid, a high brain natriuretic peptide level in blood, and hemosiderin-laden macrophages in the lungs suggested chronic heart failure. We speculate that the cause of death was extranodal cardiac involvement of RDD with chronic heart failure. This case highlights the need for forensic pathologists to perform a complete autopsy to determine the cause of sudden death when cardiac involvement of RDD is present.

Keywords: Rosai–Dorfman disease, histiocyte, cardiac involvement, pericarditis, forensic pathology, congestive heart failure

1. Introduction

Rosai–Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis that is characterized histopathologically by accumulation of CD68-positive, S100-positive, and CD1a-negative histiocytes [1,2] with variable frequency of emperipolesis [3] (intact lymphocytes and red blood cells entrapped within the cytoplasm). RDD was first described in 1965 in four children and young adults with lymphadenopathy by Destombes [4], and was called "adenitis with lipid excess". Four years later, in 1969, Rosai and Dorfman reported a separate series of four patients with massive cervical lymphadenopathy with specific histopathological features, and called this condition "sinus histiocytosis with massive lymphadenopathy" [5]. Since the original description of RDD, further reports, including a summary of 423 cases from an international registry in 1990, described nodal and extranodal manifestations of RDD [6]. Among extranodal manifestations, cardiac involvement is rare. We report an autopsy case of cardiac involvement of RDD presenting as fibrinous pericarditis.

2. Case report

A 14-year-old Japanese boy complained of loss of appetite and breathing difficulty when lying down. During the summer 3 years before his death, his entire lower limbs and trunk developed asymptomatic red papules. In autumn, he developed bilateral eye inflammation and was diagnosed with iritis by a nearby physician. In another hospital, he was diagnosed with anterior uveitis of both eyes and was under observation after steroid eye drops were applied. During a follow-up physical examination 1 year before

his death, numerous millet- to grain-sized red-to-brown papules were observed on his trunk, as well as grain-sized localized red papules scattered on his thighs. After a skin biopsy, he was diagnosed with RDD. Furthermore, he was found to have slightly enlarged axillary lymph nodes and hepatosplenomegaly. For symptomatic treatment, steroid eye drops and topical steroids were administered for the uveitis and skin lesions, respectively. At 23:00 hours on the day before his death, his father came home, and they had a conversation. The boy then went to bed at 24:00 hours. At 05:00 am the next day, his father went to see him and found him in cardiopulmonary arrest on his back in his bedroom. He was transported to the emergency room but was not resuscitated. To identify the cause of death, a medicolegal autopsy was performed on the same day at 12 hours postmortem.

2.1 Autopsy findings (macroscopic)

The deceased was 153 cm in height and weighed 38 kg with no significant trauma noted. Flat pigmented light-brown spots on the abdomen and both thighs, as well as many pale reddish-brown papules (2–4 mm in diameter), were observed (Fig. 1E). Edema was observed on both lower limbs. No eye lesions were found. The sternum was deformed. In addition to cervical lymphadenopathy, mediastinal (including paraaortic and subcarinal) lymphadenopathy was observed (Fig. 1D). The left and right pleural cavities contained 650 and 310 mL, respectively, of reddish effusion. The peritoneal cavity contained 250 mL of red ascites.

The heart weighed 620 g, contained dark red blood with fluidity, and showed acute fibrinous pericarditis with adhesion (cor villosum). Abundant red fibrin was observed on the epicardial surface (Fig. 1A, B). The endocardial surface was white and thickened. White areas were scattered on the myocardial cut surface (Fig. 1C). The coronary arteries were smooth without atherosclerosis or stenosis. The left and right lungs weighed 291.4 g and 397.6 g, respectively. The spleen weighed 381.9 g and showed splenomegaly (Fig. 1F). The liver weighed 1479.8 g and no macroscopic lesions were found. The brain weighed 1328.4 g and did not show any macroscopic lesions.

2.2 Autopsy findings (microscopic)

Abundant red fibrin was observed on the thickened epicardium with histiocytic infiltration (Fig. 2A). Eosinophilic cells with a plump cytoplasm, which suggested histiocytes, infiltrated from the pericardium to the endocardium (Fig. 2B, C). Histiocytic infiltration was also observed in the cardiac conduction system (Fig. 2B inset). Myocarditis was not observed (Fig. 2B inset). On an immunohistochemical examination, the cells were positive for CD68 (Fig. 2F), S100, and CD163, and were negative for CD1 and langerin, and showed a non-Langerhans cell immunophenotype. Fibrotic areas were found. No myocardial hypertrophy was observed.

In paraaortic lymph nodes, histiocytic infiltration with marked dilatation of the sinuses was observed (Fig. 2D). Plasmacytic infiltration was unremarkable and only a small number of immunoglobulin G4 (IgG4)-positive cells were found. Occasionally,

several lymphocytes and red blood cells were incorporated into the histiocytic cells (emperipolesis, Fig. 2).

The skin and spleen showed histiocytic involvement (Supplementary Figure), but the liver had no histiocytic infiltration. No involvement of histiocytes was observed in the pulmonary parenchyma, although subcarinal lymph nodes were involved. Edematous fluid was shown in the alveoli and hemosiderin-laden macrophages were identified by Berlin blue staining. The brain showed no microscopic lesions.

2.3 Postmortem laboratory studies

A venous blood test at the emergency room showed that the brain natriuretic peptide (BNP) level was high (130.9 pg/mL; normal value, <18.4 pg/mL). A venous blood test at autopsy showed that the IgG level was 1770 mg/dL (normal value, <1700 mg/dL) and the IgG4 level was 115 mg/dL (normal value, <121 mg/dL). Alcohol was not detected in the blood. Drug screening with Instant-View M-1™ (Alfa Scientific Designs Inc., Poway, CA, USA) was negative.

2.4 Virological testing (human herpesvirus 6 and Epstein–Barr virus)

Immunohistochemically, paraaortic lymph node tissue was negative for human herpesvirus 6 (HHV-6) using a rabbit polyclonal antibody against HHV-6 immediate early-A protein [7]. Genomic DNA was extracted and purified from

unstained paraffin-embedded sections of paraaortic lymph node tissue using a commercially available kit (QIAamp® DNA FFPE Tissue Kit; Qiagen K. K., Tokyo, Japan). A genetic assay to detect HHV-6-specific DNA with real-time PCR was conducted using a primer and probe set as previously reported [8]. Beta-actin gene expression was analyzed as an endogenous control [9]. The real-time PCR assay showed no copy of *HHV-6* genes.

Epstein–Barr virus-encoded RNA (EBER) was examined with *in situ* hybridization using the BOND EBER Probe (Leica Biosystems, Nussloch, Germany). Paraaortic lymph node tissue was negative for EBER.

2.5 Genetic testing for *KRAS, NRAS*, and *BRAF* genes.

We used the RASKET Kit (MBL, Nagoya, Japan) for detecting mutations of *KRAS* and *NRAS*, and *BRAF* genes from formalin-fixed paraffin-embedded paraaortic lymph node tissues. However, owing to DNA denaturation, gene amplification could not be obtained.

2.6 Conclusions from autopsy findings

On the basis of the above-mentioned autopsy results, the cause of death was determined to be extranodal cardiac involvement of RDD with chronic heart failure.

3. Discussion

The etiology of RDD is not well defined and is likely not uniform across the spectrum of phenotypes [1]. Historically, clonality studies suggested that lesional RDD cells were polyclonal, reactive, and non-neoplastic. Previous studies have associated RDD with viral infections, such as HHV-6, Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus, although a clear link has not been proven [1]. However, recent studies identified *NRAS*, *KRAS*, *MAP2K1*, and *ARAF* mutations in patients with features of RDD, which indicated the possibility of a clonal origin in some forms of RDD [1]. Furthermore, germ line mutations in *SLC29A3* have been reported in patients with familial RDD [10].

Some forms of extranodal RDD are associated with an increased number of IgG4-positive plasma cells [11,12]. However, some studies have shown a low number of IgG4-positive plasma cells and a low IgG4/IgG ratio (<40%) compared with IgG4-related disease samples [13]. No clear evidence has suggested that these two disorders share the same pathogenesis [1]. Because only a small number of IgG4-positive cells were found in our case, our case is unlikely to have been associated with IgG4-related diseases.

Although in most cases RDD can be observed or treated with local therapies, some patients with refractory or multifocal disease experience morbidity and mortality [1, 14]. The mortality rate of RDD was reported as 7% [13]. With regard to treatment, no uniform approach has been delineated for RDD, and treatment is best tailored to the individual clinical circumstances [1]. Treatment for RDD includes observation, surgery,

corticosteroids, chemotherapy, sirolimus, radiotherapy, and immunomodulatory therapy [1].

For classic nodal RDD, the prognosis has been found to correlate with the number of nodal groups involved by RDD [1]. For extranodal RDD, the prognosis is correlated with the number of extranodal systems involved [1].

The present case had nodal (cervical and mediastinal) and extranodal (heart, skin, and spleen) involvement, and cardiac involvement led to death. RDD was previously diagnosed as a nodal condition in 95% of cases [2], while currently, it is generally regarded as an extranodal disorder, with classical nodal presentation accounting for only 8% of cases [2]. Frequent extranodal sites of RDD in decreasing order are as follows: skin and soft tissue; the nasal cavity and paranasal sinuses; the eyes, orbit, and ocular adnexa; bone; salivary glands; central nervous system; oral cavity; kidneys and genitourinary tract; respiratory tract; liver; tonsils; breast; gastrointestinal tract; and heart [14].

Involvement of the heart in RDD is rare. Lesions may arise in any cardiac site. A total of 29 cases of cardiac involvement of RDD have been reported [2,16-26]. Among those, six cases had pericardial involvement [2,16-18]. Epicardial thickening or mass, hydropericardium, and large pericardial effusion leading to cardiac tamponade have been reported in RDD [2,16-18]. Fibrinous pericarditis as found in our case has not been reported.

With regard to other lesions that could have been extranodal lesions, our case was diagnosed with uveitis and bone deformity before death. Ophthalmic manifestations

occur in 11% of RDD cases, manifesting as a mass in the orbital soft tissue, eyelids, lacrimal glands, conjunctiva, or cornea, and as uveitis or compressive optic neuropathy [1,27]. Bone involvement in RDD occurs in <5% to 10% of cases and skeletal lesions are usually multifocal [15]. In our case, deformity of the sternum may have been bone involvement, although bone tissue was not examined histologically.

Systemic edema, large amounts of pleural and ascitic fluid, a high BNP level in the blood, and hemosiderin-laden macrophages in the lungs suggested chronic heart failure in the current case. We speculate that the cause of death was extranodal cardiac involvement of RDD with chronic congestive heart failure. Myocardial infiltration caused by RDD can be the trigger for arrhythmia [24]. Histiocytic infiltration was observed in the cardiac conduction system and fatal arrhythmia may have contributed to death in the present case.

This case highlights the need for forensic pathologists to perform a complete autopsy to determine the cause of sudden death when cardiac involvement of RDD is present.

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Figure legends

Figure 1 Macroscopic images of the heart (A–C), paraaortic lymph nodes (D), skin (E), and spleen (F).

A, B: Acute fibrinous pericarditis with adhesion (cor villosum) is observed. Abundant red fibrin is observed on the epicardial surface. C: White areas are scattered in the myocardial cut surface. The endocardial surface is white and thickened. D: Fused paraaortic lymph node swelling. E: Flat pigmented light-brown spots, as well as many pale reddish-brown papules, is observed. F: The spleen weighed 381.9 g and showed splenomegaly.

Figure 2 Histological images of cardiac (A–C, E, F) and paraaortic involvement (D).

A: Hematoxylin and eosin staining shows abundant red fibrin in thickened epicardium with histiocytic infiltration. B: Hematoxylin and eosin staining shows histiocytes infiltrating the myocardium. Inset a: Histiocytic infiltration was observed in the cardiac conduction system. Inset b: Myocarditis was not observed. C: Hematoxylin and eosin staining shows infiltrating eosinophilic cells with a plump cytoplasm in the pericardium. D: Hematoxylin and eosin staining shows a paraaortic lymph node. Histiocytic infiltration with marked dilatation of sinuses is observed. E: emperipolesis (lymphocytes and red blood cells incorporated into the histiocytic cytoplasm, arrows). F: Immunohistochemically, histiocytic cells are positive for CD68.

Supplementary Figure

A: Myocardial cut surface after fixation. B: Histological images of the skin.

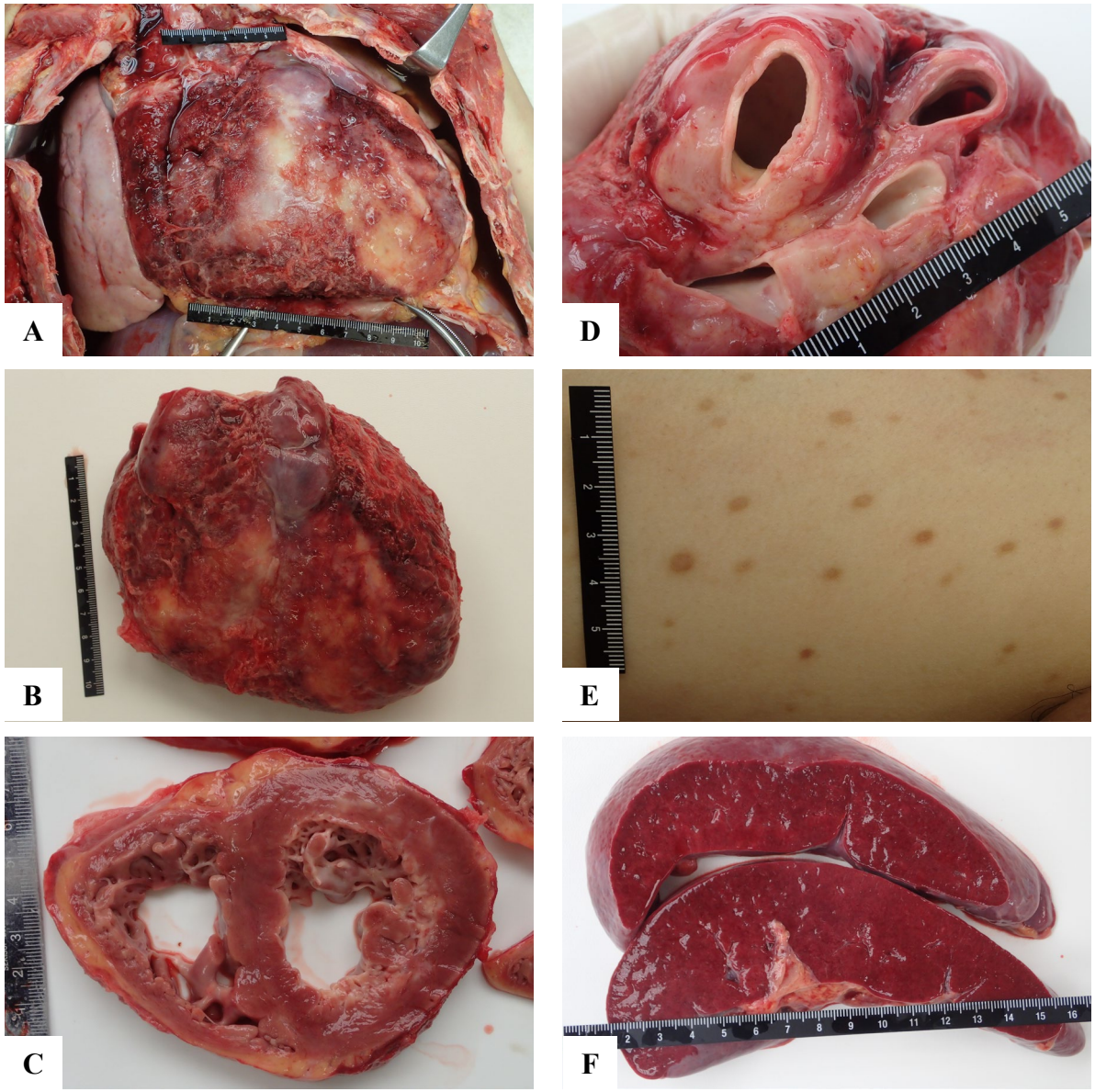


Fig. 1

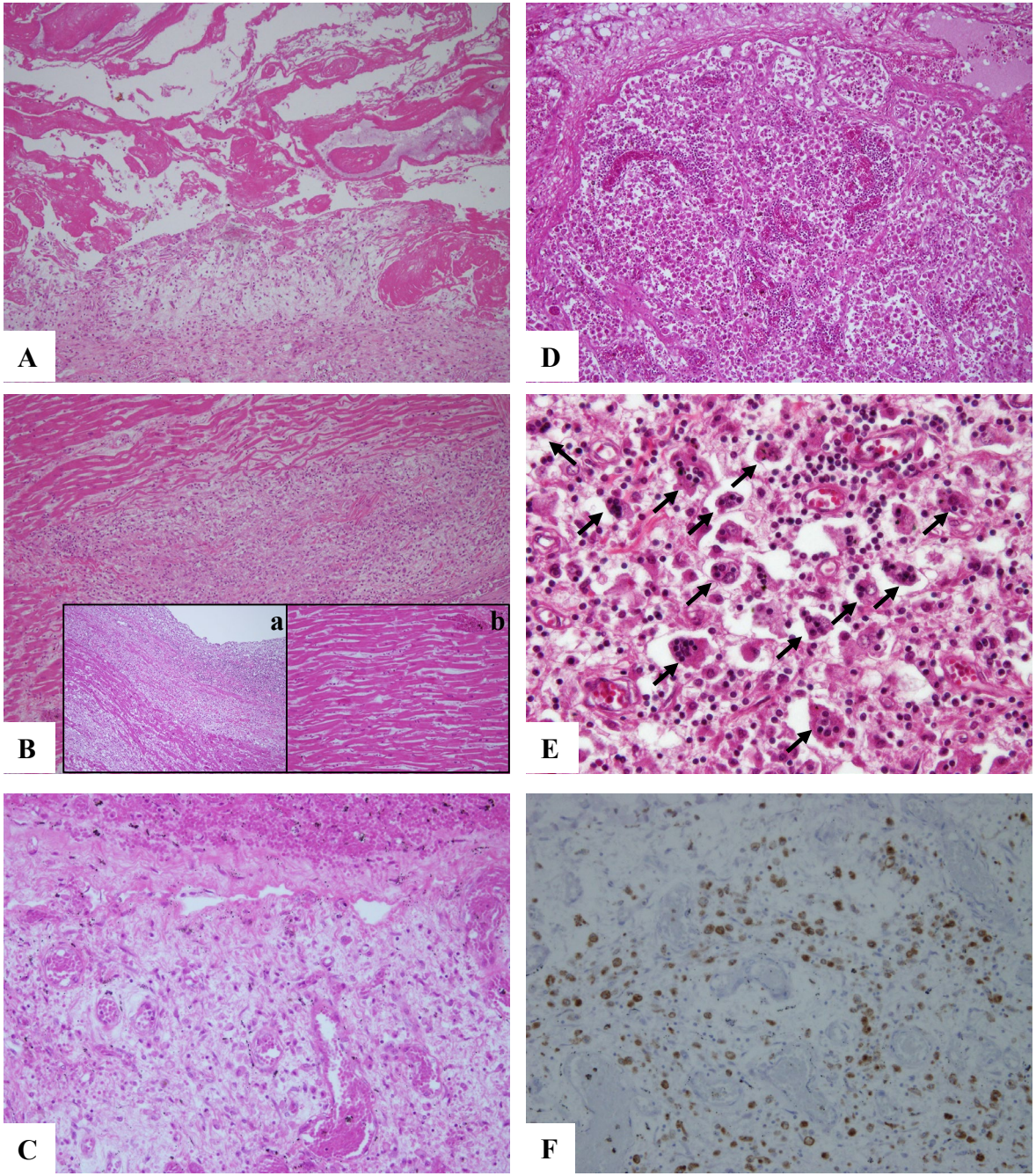
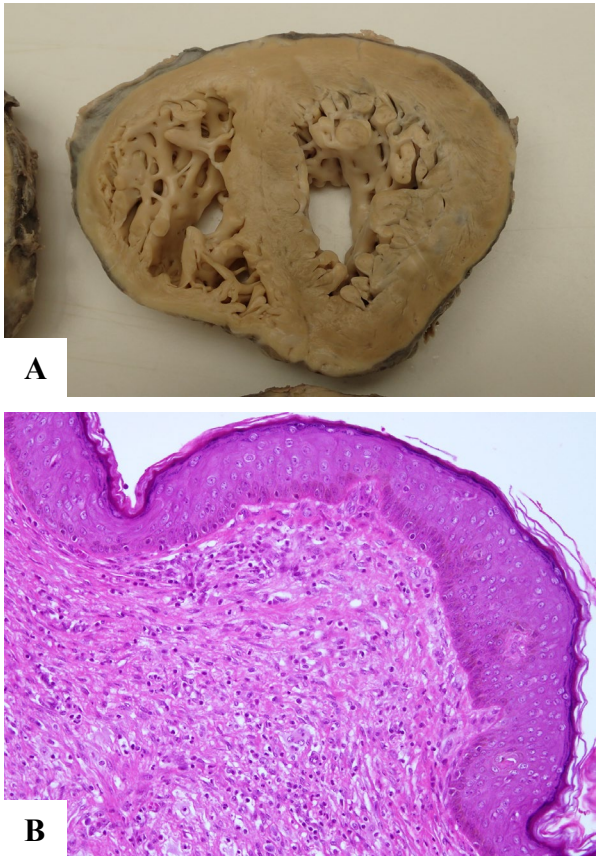


Fig. 2



Supplementary Figure

A: Myocardial cut surface after fixation. B: Histological images of the skin.