Cardiovascular Pathology 42 (2019) 10–14

Contents lists available at ScienceDirect

Cardiovascular Pathology

Original Article

An autopsy case of giant cell myocarditis showing shared pathology in the myocardium and skeletal muscles

Keiko Ikarashi [a,b], Kenta Uto [b,c,*], Shunji Kawamura [d], Yuichiro Yamada [a], Shoji Haruta [a], Nobuhisa Hagiwara [b]

[a] Department of Cardiology, Tokyo Women's Medical University, Yachiyo Medical Center, Chiba, Japan
[b] Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan
[c] Department of Pathology, Division of Experimental Pathology, Tokyo Women's Medical University, Tokyo, Japan
[d] Department of Diagnostic Pathology, Tokyo Women's Medical University, Medical Center East, Tokyo, Japan

ARTICLE INFO

Article history:
Received 12 December 2018
Received in revised form 18 April 2019
Accepted 17 May 2019

Keywords:
Fulminant myocarditis
Giant cell myocarditis
Myositis
Cardiogenic shock
Myocardial infarction
Heart failure

1. Introduction

Myocarditis, a lethal disorder in which immune cells are activated by unknown mechanisms, is classified according to the type of infiltrating cells involved and certain histological profiles, including lymphocytic, eosinophilic, giant cell, and granulomatous. Cases of giant cell myocarditis (GCM) are particularly prone to developing fulminant myocarditis. In clinical practice, histological evaluation to determine the diagnosis of myocarditis is undeniably necessary; however, the patient's condition may render endomyocardial biopsy (EMB) infeasible, making a confirmed histological diagnosis of myocarditis difficult. Therefore, severe cases of myocarditis are often diagnosed at autopsy. Here we report a case of fulminant myocarditis that resulted in rapid cardiogenic shock and the death of the patient due to pump failure despite intensive treatment. In the postmortem analysis, GCM was diagnosed histologically, and giant cell myositis of the skeletal muscles was also found.

* Corresponding author at: Department of Pathology, Division of Experimental Pathology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8111; fax: +81 3 5269 7473.
E-mail address: uto.kenta@twmu.ac.jp (K. Uto).

2. Case

2.1. History

A 63-year-old man presented with chest discomfort and cold sweating as chief complaints. Four years before admission, the patient had suffered an acute anterior wall myocardial infarction (MI) and had undergone percutaneous coronary intervention (PCI) for complete obstruction of the left anterior descending artery, along with placement of a stent. Heart wall motion deteriorated rapidly, with a reduced ejection fraction of 35%, but the course after PCI had been uneventful. The patient had a history of diabetes, hypertension, and hyperlipidemia since the age of 40 years, for which he had for several years been taking aspirin, carvedilol, losartan, spironolactone, pitavastatin, glimepiride, and sitagliptin.

Approximately 1 month before death, the patient developed generalized eczema, which was suspected to be viral toxicoderma. The eczema persisted, and 2 weeks before hospitalization, the patient developed intermittent coughing, expectoration, and a high fever (38°C). The patient was prescribed antibiotics, and the symptoms subsequently improved; however, at that time, he developed diarrhea and appetite loss.

On admission, the patient was intelligible, but his blood pressure (BP) was 63/43 mmHg and pulse frequency was irregular (75 bpm). In addition, physical examination revealed massive perspiration with a breathing frequency of 38 breaths/min, indicating cardiogenic shock. Heart sounds were weak, but heart murmur, crackle, and pleural friction rub were not detected. Electrocardiogram showed complete atrioventricular block (CAVB) with an idioventricular rhythm.

A chest radiograph revealed marked cardiomegaly with a cardiothoracic ratio of 58% and pulmonary congestion. Echocardiography showed a dilated left ventricle with poor systolic function, and wall thinning and elevated brightness in the myocardium were also evident at the site of prior MI. Mild pericardial fluid had accumulated around the heart. Biochemical analysis showed inflammation, with a white blood cell count of $19.49\times10^3/\mu l$ (neutrophils: 84.8%, lymphocytes: 7.1%, monocytes: 3.2% and eosinophils: 4.7%, respectively) and a C-reactive protein level of 5.91 mg/dl. Moderate elevation of his creatine phosphokinase (CK: 2104 U/L, MB form CK: 137.3 U/L), brain natriuretic peptide (1271 pg/ml), and troponin I (37.89 μg/ml) levels indicated either heart failure (HF) or degeneration of the myocardium.

https://doi.org/10.1016/j.carpath.2019.05.003

Hypo-oxygenemia was detected by arterial blood gas analysis. In addition, liver and kidney dysfunction was observed. No autoimmune antibodies were identified. The results of viral serology testing revealed a markedly elevated titer of antibody against Coxsackie virus B3; additionally, the titers of antibodies against Coxsackie viruses A3, A4, and B2 and Echovirus 11 were slightly elevated (Table 1), but paired serology testing could not be performed. Neither fungal nor mycobacterial infection was detected by blood culture.

2.2. Clinical course

Initially, the patient was thought to have low cardiac output due to both previous MI and CAVB, which resulted in cardiogenic shock. Therefore, an intra-aortic balloon pump (IABP) was inserted. Cardiac catheterization was performed, and coronary angiography showed that neither significant stenosis nor intrastent restenosis was present. EMB was not possible due to the patient's condition. After IABP insertion, BP recovered to 90/40 mmHg, and both oxygenation and consciousness were maintained; however, BP subsequently declined. In addition, repeated ventricular fibrillation was found, and thus, intravenous amiodarone was administered. Six hours after arrival at the hospital, hemodynamic breakdown occurred, and the patient was intubated and ventilated. In addition, a percutaneous cardiopulmonary support system and continuous hemodiafiltration were also induced. Based on the clinical course, including acute-onset HF with lethal arrhythmias and rapidly deteriorating hemodynamics after admission, fulminant myocarditis was strongly suspected. Although the cause of HF was unknown, immunosuppressive therapy was applied immediately due to worsening heart function. Corticosteroid pulse therapy together with high-dose immunoglobulin was given; however, these treatments were unsuccessful. The patient's hemodynamics deteriorated further prior to cardiac arrest and death. Subsequently, a postmortem examination was performed.

2.3. Autopsy findings

The heart weighed 465 g and was edematous and extremely soft (Fig. 1A) with a massive accumulation of pericardial fluid. Cross sections revealed marked enlargement of bilateral ventricles (Fig. 1B). The septum, anterior wall, lateral walls, and apex exhibited myocardial loss and fibrosis. In addition, there was obvious thinning of the septum on the anterior wall side compared with the posterior wall side (Fig. 1B). Histopathological findings revealed severe inflammation with patchy necrosis in the myocardium; in addition, numerous giant cells with bizarre nuclei accompanied by mononuclear cells were present (Fig. 1C). An immunohistochemical analysis was performed to confirm the origin and type of infiltrating cells. The giant cells were positive for CD68 (Fig. 1D), representing a monocyte/macrophage origin, but negative for desmin (Fig. 1E), representing a cardiomyocyte origin. In contrast, the majority of the other infiltrating mononuclear cells were CD3-positive T lymphocytes (Fig. 1F), representing total T lymphocytes, and CD8-positive cells, representing cytotoxic T-cells, rather than CD4-positive cells, representing helper T cells (Fig. 1G and H); thus, a reverse CD4:CD8 ratio was present in the histology. Furthermore, CD20-positive cells, representative of B lymphocytes, were scarcely detected (data not shown). Eosinophil infiltration was not predominant. Interestingly, severe inflammatory infiltrates, including lymphocytes and giant cells, were observed in the throat muscle, diaphragm, and iliopsoas muscle (Fig. 2A–C). This inflammation was focal and limited within each muscle. The giant cells were positive for CD68 and negative for desmin (Fig. 2D–F), and the majority of infiltrating mononuclear cells were CD3-positive T lymphocytes (Fig. 2G–I); a reverse CD4:CD8 histology ratio was also observed (Fig. 2J–O). CD20-positive cells were scarcely detected (data not shown). Congestive and edematous changes were obvious in the lungs, liver, kidneys, and small intestine but were unremarkable in other organs. Staining for fungi and mycobacteria yielded negative results in all of the organs examined. Based on these findings, a pathological diagnosis of GCM and polymyositis involving giant cells was made, which subsequently led to cardiogenic shock and death.

Table 1
Results of viral serologic panel on admission

Serum virus	Method	Titer	Normal range
Coxsackie A3 virus	NT	32	<4
Coxsackie A4 virus	NT	64	<4
Coxsackie A16 virus	NT	8	<4
Coxsackie B1 virus	NT	<4	<4
Coxsackie B2 virus	NT	128	<4
Coxsackie B3 virus	NT	512	<4
Coxsackie B4 virus	NT	16	<4
Coxsackie B5 virus	NT	16	<4
Coxsackie B6 virus	NT	<4	<4
Echovirus 9	NT	32	<8
Echovirus 11	NT	128	<8
Echovirus 14	NT	16	<8
Echovirus 16	NT	<8	<8
Echovirus 22	NT	32	<8
Adenovirus 1	NT	16	<4
Parbovirus B19 IgM	EIA	<0.80	<0.80
Herpes simplex virus	CF	16	<4
Cytomegalovirus	CF	8	<4
Influenza A virus	HI	10	<10
Influenza B virus	HI	<10	<10

NT: Neutralization test
EIA: Enzyme-linked immunosorbent assay method
CF: Complement fixation test
HI: Hemagglutination-inhibition assay method

3. Discussion

GCM is a rare and lethal disorder, and its etiology is still unknown. GCM is diagnosed histologically based on findings of widespread or multifocal serpiginous necrosis with a mixed inflammatory infiltrate composed of lymphocytes and histiocytes [1]. Infiltrating giant cells are usually located at the edge of the inflammatory lesions and are frequently associated with eosinophils [2]. Histopathological characteristics and differential diagnosis of GCM include primarily granulomatous myocarditis, such as cardiac sarcoidosis, tuberculosis, and rheumatic myocarditis. The findings of sarcoidosis include noncaseating epithelioid granulomas, but in GCM, the granulomas are poorly formed and diffuse myocyte necrosis is frequently recognized. The majority of the infiltrating lymphocytes into the myocardium were CD3-positive T lymphocytes. In this case, CD8-positive cells (cytotoxic T cells) were predominant; thus, they were susceptible to myocardial destruction. Although a low CD4:CD8 ratio is considered a marker of immune senescence in the general population [3], there are few reports of this ratio in myocarditis histological samples.

GCM is associated with thymoma [4], drug hypersensitivity [5], and other inflammatory or autoimmune disorders [6]. In this case, neither thymoma nor autoimmune disease was detected. Although several drugs were prescribed to this patient, there was no evidence of adverse reactions. Moreover, his skin symptoms preceded use of antibiotics, so they are unlikely to be responsible for the GCM. In contrast, high titers of Coxsackie virus B3 antibody were found, and viral infection was subsequently suspected. Lee et al. showed a relationship between GCM and Coxsackie virus infection using immunohistochemical and VP1-RNA analyses, but the pathophysiology of this association is not fully elucidated [7].

In this case, a postmortem analysis showed extensive inflammation involving giant-cell infiltration of the myocardium, with diffuse myocyte necrosis. Giant-cell infiltration of some skeletal muscles was also observed, but granulomas were not detected. Therefore, the patient was diagnosed with GCM and polymyositis involving giant cells. Many cases of GCM with polymyositis in thymoma and myasthenia gravis

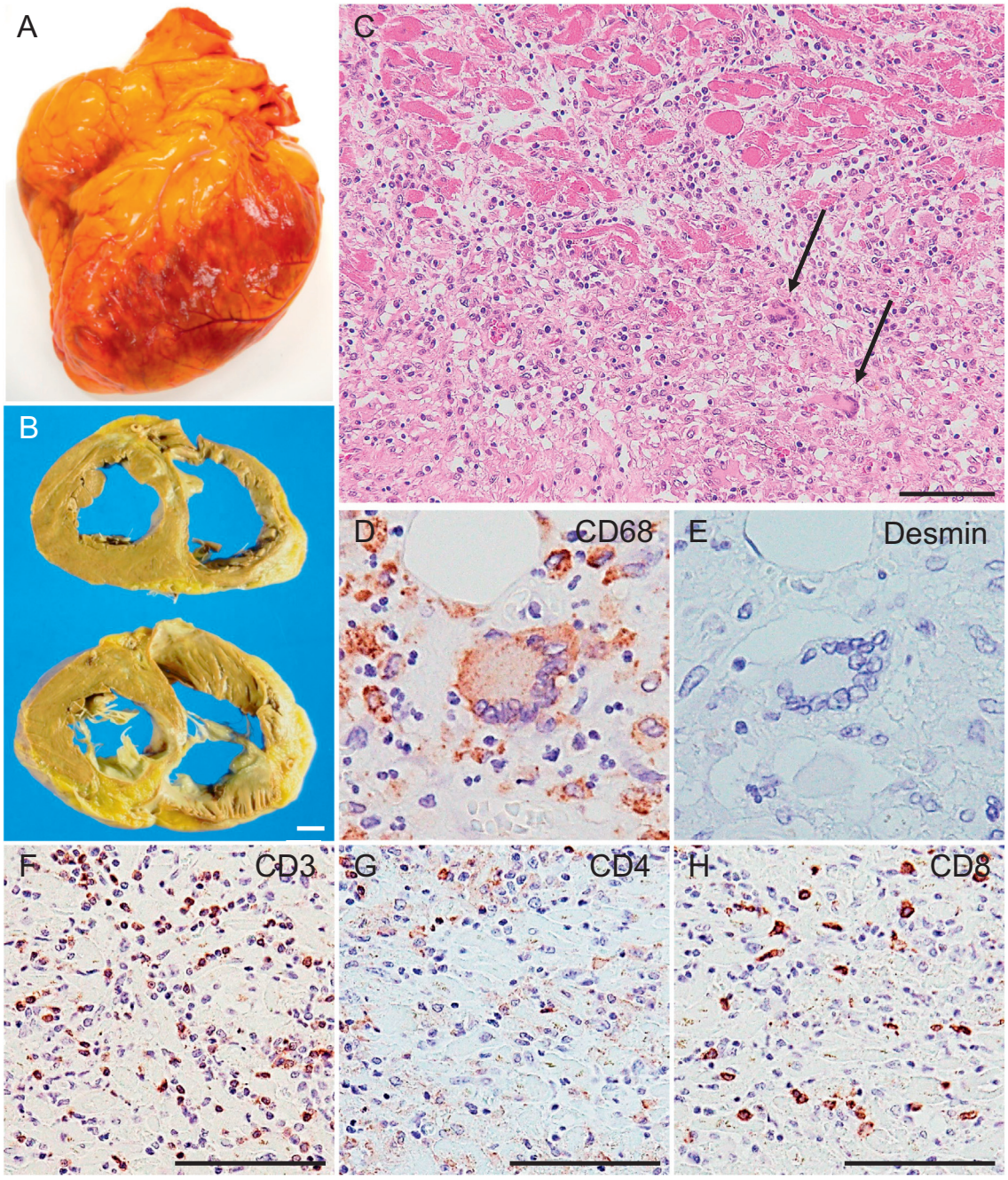

Fig. 1. Findings of the heart. A. Gross appearance: the heart was swollen, congestive, and edematous. B. Sagittal appearance (fixed): the left anterior septal wall shows thinning and fibrosis, and the inferior and posterior walls show swelling. Both ventricles were markedly enlarged. Scale bar: 10 mm. C–H. Histological and immunohistological findings in cardiac muscle. C. Severe inflammation of the myocardium together with giant-cell infiltration (H&E staining). Both lymphocytes and polynuclear giant cells (arrows) had infiltrated the myocardium. Scale bar: 100 μm. D, E. Polynuclear giant cells. The indicated cells were positive for CD68 (D), representing a monocyte/macrophage origin, but negative for desmin (E), representing a cardiomyocyte origin. F–H. Immunohistochemical findings in the infiltrate. The inflammatory cells were positive for CD3 (F), CD4 (G), and CD8 (H). CD3-positive cells, representing total T lymphocytes, were abundant, and CD8-positive cells, representing cytotoxic T-cells, predominated rather than CD4-positive cells, representing helper T-cells (G, H). Scale bar: 100 μm.

(MG) have been reported [8–12]. Priemer et al. described thymoma-associated GCM with polymyositis involving giant cells [12]. Morrissey et al. reported a sporadic case of GCM with polymyositis [13]. The polymyositis in Morrissey's case was histologically proven; nonetheless, giant-cell involvement was not observed. To our knowledge, GCM with polymyositis not associated with thymoma but involving giant cell myositis is uncommon. However, because systemic muscle tissues are not typically examined in the absence of myopathy, latent giant cell myositis could be more common than reported.

Giant cells are commonly found in other viral infections, but in our case, acute and/or chronic activation of immunoreactivity may have resulted in inflammation involving cardiac and skeletal muscles. Suzuki et al. reported on the prevalence of myopathy in patients with MG and its relationship with antistriational antibodies as autoimmune targets in the heart and skeletal musles [11]. In our case, there was no evidence of thymoma or autoantibodies, but myocardial injury caused by a prior MI was present; the relationship between the prior infarction and GCM is unknown. In contrast, although his CK level was only mildly elevated, the patient's clinical phase may have been advanced at the time of hospitalization.

GCM is a life-threatening disorder that, in most cases, fails to respond to intensive treatment. Some combination therapies using

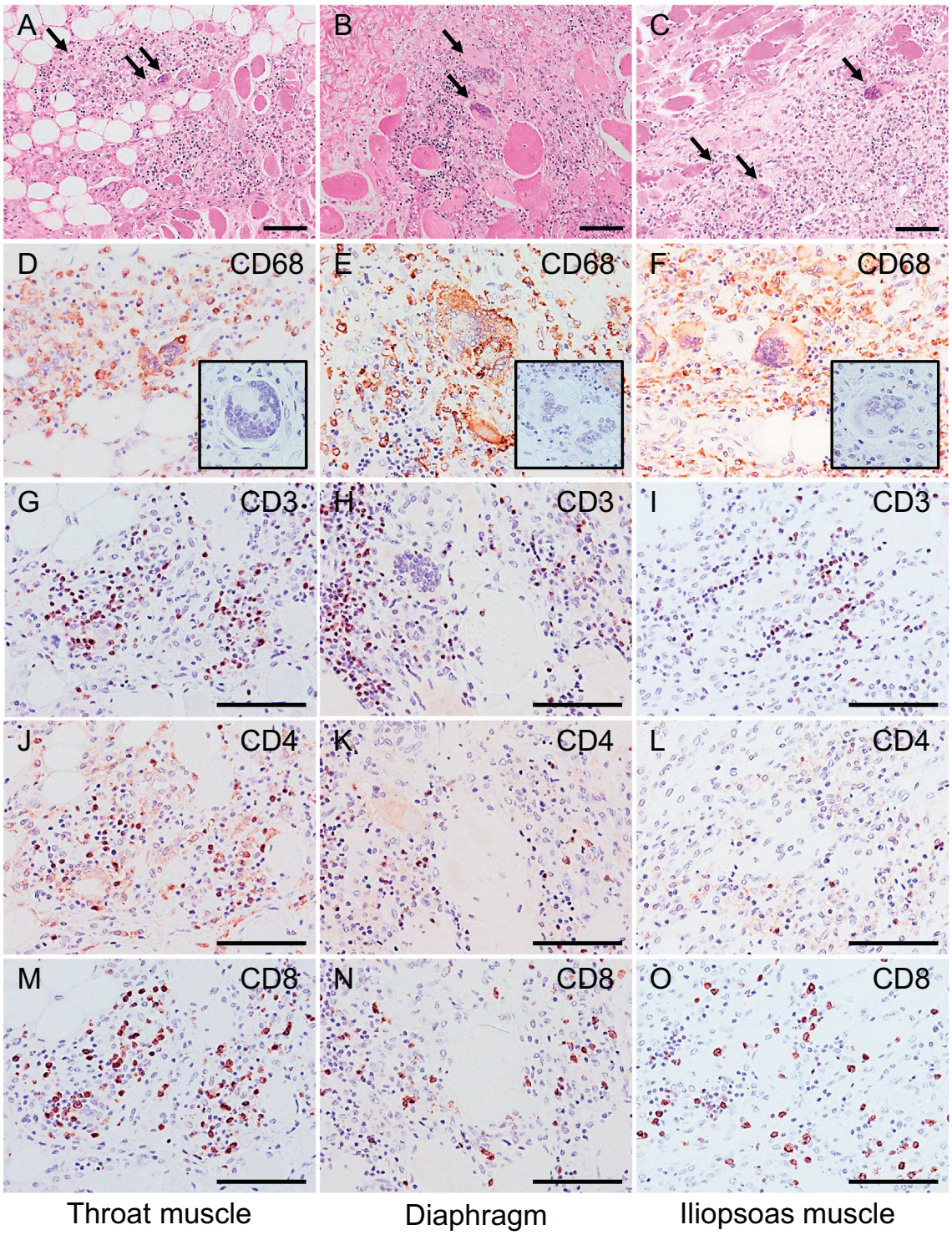

Fig. 2. Findings in skeletal muscles. Throat muscle (A, D, G, J, and M), diaphragm (B, E, H, K, and N), and iliopsoas muscles (C, F, I, L, and O). (A–C) Histopathological findings: severe inflammation of the myocardium together with giant-cell infiltration (H&E staining). Both lymphocytes and polynuclear giant cells (arrows) had infiltrated each sample. Scale bar: 100 μm. (D–F) Polynuclear giant cells. The indicated cells were positive for CD68 and negative for desmin (square). (G–O) The inflammatory cells. CD3-positive cells were abundant (G–I), and CD8-positive cells predominated rather than CD4-positive cells (J–O). Scale bar: 100 μm.

corticosteroids and immunosuppressive therapies are recommended, but despite these treatments, the prognosis of GCM is poor [1,14]. Furthermore, a prompt and accurate diagnosis is necessary in patients with fulminant myocarditis, and distinguishing GCM from lymphocytic myocarditis is clinically important because the prognosis may differ [1]. Differential myocardial gene expression profiling may be useful for improving clinical diagnosis [15] but is not routinely available. Therefore, skeletal muscle biopsy could be helpful in the diagnosis of patients who cannot undergo EMB due to a serious condition.

In summary, we report a unique case of GCM with latent polymyositis involving giant cells, which was not associated with thymoma. The cause of death was cardiogenic shock; in addition, there were prior MI and suspected viral infection. The reason for the shared pathology of the heart and skeletal muscles is unknown.

Acknowledgments

The authors thank Dr. Hideaki Oda (Department of Pathology, Division of Experimental Pathology, Tokyo Women's Medical University), Dr. Yoji Nagashima (Department of Surgical Pathology, Tokyo Women's Medical University Hospital), and Dr. Kenzo Hiroshima (Department of Diagnostic Pathology, Tokyo Women's Medical University, Yachiyo Medical Center) for providing technical advice that greatly improved the manuscript.

References

[1] Cooper LT, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators N Eng J Med 1997;336:1860–6.
[2] Cooper LT. Giant cell myocarditis: diagnosis and treatment. Herz 2000;25:291–8.
[3] Bruno G, Saracino A, Monno L, Angarano G. The revival of an “old” marker: CD4/CD8 ratio. AIDS Rev 2017;19:81–8.
[4] Kilgallen CM, Jackson E, Bankoff M, Salomon RN, Surks HK. A case of giant cell myocarditis and malignant thymoma: a postmortem diagnosis by needle biopsy. Clin Cardiol 1998;21:48–51.
[5] Daniels PR, Berry GJ, Tazelaar HD, Cooper LT. Giant cell myocarditis as a manifestation of drug hypersensitivity. Cardiovasc Pathol 2000;9:287–91.
[6] Rosenstein ED, Zucker MJ, Kramer N. Giant cell myocarditis: most fatal of autoimmune diseases. Semin Arthritis Rheum 2000;30:1–16.
[7] Lee M, Kwon GY, Kim JS, Jeon ES. Giant cell myocarditis associated with Coxsackievirus infection. J Am Coll Cardiol 2010;56:e19.
[8] Namba T, Brunner NG, Grob D. Idiopathic giant cell polymyositis. Arch Neurol 1974;31:27–30.
[9] Kon T, Mori F, Tanji K, Miki Y, Kimura T, Wakabayashi K. Giant cell polymyositis and myocarditis associated with myasthenia gravis and thymoma. Neuropathology 2013;33:281–7.
[10] Tanahashi N, Sato H, Nogawa S, Satoh T, Kawamura M, Shimoda M. A case report of giant cell myocarditis and myositis observed during the clinical course of invasive thymoma associated with myasthenia gravis. Keio J Med 2004;53:30–42.
[11] Suzuki S, Utsugisawa K, Yoshikawa H, Motomura M, Matsubara S, Yokoyama K, et al. Autoimmune targets of heart and skeletal muscles in myasthenia gravis. Arch Neurol 2009;66:1334–8.
[12] Priemer DS, Davidson DD, Loehrer PJ, Badve SS. Giant cell polymyositis and myocarditis in a patient with thymoma and myasthenia gravis: a postviral autoimmune process? J Neuropathol Exp Neurol 2018;77:661–4.
[13] Morrissey RP, Rana JS, Luthringer DJ, Cheng V, Czer LS, Philip K, et al. Case of fulminant giant-cell myocarditis associated with polymyositis, treated with a biventricular assist device and subsequent heart transplantation. Heart Lung 2011;40:340–5.
[14] Cooper LT, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, et al. Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol 2008;102:1535–9.
[15] Lassner D, Kühl U, Siegismund CS, Rohde M, Elezkurtaj S, Escher F, et al. Improved diagnosis of idiopathic giant cell myocarditis and cardiac sarcoidosis by myocardial gene expression profiling. Eur Heart J 2014;35:2186–95.