Fulminant myocarditis with myositis of ocular and respiratory muscles

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ABSTRACT

A 46-year-old Japanese woman visited a nearby hospital because of diplopia after flu-like symptoms. One month later, she presented with blepharoptosis and external ophthalmoplegia. Laboratory tests showed a high creatine kinase concentration (3146 U/L). She underwent intravenous immunoglobulin therapy; however, her symptoms did not improve, prompting transfer to our institute. On admission, transthoracic echocardiography revealed 30% of left ventricular ejection fraction and edema of the left ventricular wall. Coronary angiography showed no significant coronary stenosis. An endomyocardial biopsy resulted in a diagnosis of acute myocarditis. On the following day, she needed a temporary pacemaker because she had complete atrioventricular block and intra-aortic balloon pump because of cardiogenic shock. Intravenous immunoglobulin therapy was again administered and her cardiac function gradually recovered. She was successfully weaned off her temporary pacemaker and intra-aortic balloon pump on Day 5 after improvement in her complete atrioventricular block. Steroid therapy administered from Day 9 was effective in reducing her creatine kinase concentrations. However, contrast-enhanced magnetic resonance imaging revealed inflammation of the scalene, semispinalis cervicis, sternocleidomastoid, and intercostal muscles. On Day 25, her cardiac function had recovered to a left ventricular ejection fraction of 59%. Finally, she was successfully discharged on Day 45 after undergoing rehabilitation.

Keywords: fulminant myocarditis, myositis, ocular muscle, respiratory muscle

Abbreviations:
AChR: acetylcholine receptor
AMA: anti-mitochondrial antibody
CK: creatine kinase
CVAB: complete atrioventricular block
ECG: electrocardiogram
IABP: intra-aortic balloon pump
IVIg: intravenous immunoglobulin
LVEF: left ventricular ejection fraction
MRI: magnetic resonance imaging
MuSK: muscle specific kinase

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INTRODUCTION

Acute myocarditis, an inflammation of cardiac muscle, often leads to decreased cardiac contraction or conduction disturbances. Some patients with acute myocarditis follow a fulminant course and require mechanical circulatory support; fulminant myocarditis remains a fatal disease.\(^1\)\(^-\)\(^5\) The commonest cause of myocarditis is viral infection.\(^6\) In contrast, skeletal myositis occurs in association with several underlying diseases or some virus infections.\(^7\) However, very few previous reports have described patients with simultaneous myocarditis and myositis; accordingly, the characteristics of this combination have not been established. Herein, we report a rare case of fulminant myocarditis with symptomatic myositis of ocular and respiratory muscles that was successfully treated with a circulation assist device, intravenous immunoglobulin, and steroid therapy.

CASE REPORT

A 46-year-old woman visited a nearby general practitioner because of flu-like symptoms. She had no relevant medical history or medications. Although her symptoms had improved one week later, she developed diplopia and revisited her general practitioner. On examination she had a normal conscious state with no neck stiffness or Kernig’s sign. There were no chest rales or murmurs. Abdominal examination was normal and she had no skin rash. Electrocardiogram (ECG) and chest roentgenogram were normal. A neurologist found bilateral ptosis and external ophthalmoplegia. Furthermore, laboratory tests showed that a high creatine kinase (CK) concentration of 3146 U/L. The neurologist suspected Guillain-Barre syndrome or Fisher’s syndrome. Therefore, she was hospitalized and administered intravenous immunoglobulin (IVIg) therapy (1.0 g/kg/day) for 3 days, as a consequence of which her neuromuscular manifestations, including diplopia, ptosis, and external ophthalmoplegia, improved. In addition, her CK concentration decreased to 1396 U/L. She was discharged from that hospital with an improved general condition after 1-month hospitalization.

However, two weeks later, she was hospitalized again because of pain in the neck, shoulders, and back. Blood tests revealed her CK concentration was high again at 8486 U/L. IVIg therapy was administered again together with steroid therapy (prednisolone 500 mg/day for 5 days). Although her CK concentration decreased to 537 U/L, her symptoms returned and she developed dysphagia and hoarseness. Furthermore, her ECG showed ST elevation in leads V1 and V2 and transthoracic echocardiography showed systolic dysfunction with a left ventricular ejection fraction (LVEF) of 10% with hypokinesia in the posterior wall of the left ventricle.

She was transferred to our institute for further investigation and management of her unidentified myositis and myocarditis. On arrival, her blood pressure was 107/82 mmHg, heart rate 118 beats/min, respiratory rate 18/min, body temperature 37.1°C, and oxygen saturation 99% on nasal cannula oxygen of 3 L/min. Physical examination revealed bilateral ptosis and limitation of abduction, adduction, and supraduction of her eyes. In addition, her cervical flexor muscles such as the sternocleidomastoid and scalene muscles were weak with no weakness of the proximal muscles of her extremities.

An ECG showed sinus tachycardia with 118 beats/min with right bundle branch block and ST elevation in leads II, III, aVF, and V1–V6 (Figure 1A). A chest roentgenogram showed bilateral perihilar vascular congestion suggestive of pulmonary edema with cardiomegaly (cardio-thoracic...
ratio of 53%) (Figure 1B). Transthoracic echocardiography showed severe left ventricular systolic dysfunction (LVEF of 13%) with Takotsubo cardiomyopathy-like paradoxical wall motion and edema of the left ventricular wall (Figure 1C). There was no evidence of wart-like lesions or valvular regurgitation to suggest infective endomyocarditis.

She was diagnosed as being in cardiogenic shock due to acute decompensated heart failure. Right heart catheterization showed a cardiac index of 2.3 L/min/m² and mean pulmonary capillary wedge pressure 23 mmHg while receiving dobutamine 3 µg/kg/min. After establishment of mechanical ventilation, intra-aortic balloon pump (IABP) was inserted via the femoral vessels. Coronary angiography revealed normal coronary arteries. An endomyocardial biopsy was taken from the right ventricular septum (Figure 2A) after obtaining informed consent for the procedure, which was approved by the Ethics Review Board of our institute based on the Helsinki Declaration. Immunohistostaining of the endomyocardial biopsy specimens showed scattered
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CD3 positive, CD8 positive, or CD20 positive lymphocytes, together with diffuse infiltration of the myocardium with CD4 positive lymphocytes and CD68 positive cells and mild myocardial fibrosis. There were very few eosinophils and no granulomatous lesions with giant cells on any section of the specimens. It was therefore considered that eosinophilic myocarditis and giant cell myocarditis had been excluded and a diagnosis of acute lymphocytic myocarditis was made. Accordingly, active steroid pulse therapy was not administered.

Laboratory findings upon arrival included CK and CK isoenzyme MB concentrations of 6580 U/L and 431 U/L, respectively (Table 1). Troponin T was 6.48 ng/mL. The white blood cell count was 21.3 \( \times 10^3 \) /µL (neutrophils 84.0%, lymphocytes 5.2%, eosinophils 0.1%), hemoglobin 11.4 g/dL, and platelet count 340 \( \times 10^3 \) /µL. As to liver function tests, the serum total bilirubin was 0.6 mg/dL, aspartate aminotransferase 543 U/L, alanine aminotransferase 217 U/L, and lactate dehydrogenase 1879 U/L. Her renal function has normal with a blood urea nitrogen of 14.1 mg/dL, and serum creatinine of 0.30 mg/dL. High-sensitivity C-reactive protein concentration was 14.47 mg/dL. As to anti-autoimmune antibodies; her anti-nuclear antibody concentration was 80-fold normal, rheumatoid factor 3.1 mg/dL, anti-cyclic citrullinated peptide antibody 0.8 U/mL, anti-double stranded DNA antibody 3.6 U/mL, anti-ribonucleoprotein antibody 1.0 U/mL, anti-centromere antibody 5.0 U/mL, and anti-smooth muscle antibody <20 U/mL. As to anti-Jo1, anti-mitochondrial, anti-mitochondrial M2, anti-Kv1.4, anti-signal recognition particle, anti-acetylcholine receptor (AChR), and anti-muscle specific kinase (MuSK) antibodies were negative. Anti-SS-A antibody concentration was 10.8 U/mL, anti-SS-B antibody 0.5 U/mL, myeloperoxidase-antineutrophil cytoplasmic antibody <1.0 U/mL, and proteinase 3-antineutrophil cytoplasmic antibody <1.0 U/mL. The following anti-virus antibodies were investigated: Coxsackie virus A16, B1, B2, B3, B5, and B6, rubella virus, varicella virus, mumps virus, herpes simplex virus, measles virus, Epstein–Barr virus, cytomegalovirus, and parvovirus B19; none of them were significantly increased in paired serum.

A temporary pacemaker was inserted on Day 2 because she was found to have complete atrioventricular block (CVAB) (Figure 2B). IVlg therapy (1.0 g/kg/day) was administered for 2 days. Her cardiac function gradually improved and she was successfully weaned off the temporary pacemaker and IABP on Day 5 because her CAVB had improved sufficiently. Her CK concentration was 6580 U/L on admission and decreased to 906 U/L on Day 4 as a consequence

| Day | 1 | 2 | 3 | 4 | 8 | 16 | 18 | 19 | 31 | 45 |
|-----|---|---|---|---|---|----|----|----|----|----|
| WBC (\( \times 10^9 \) /µL) | 21.3 | 18.4 | 12.4 | 5.3 | 8.7 | 8.3 | 8.8 | 9.7 | 9.0 | 10.9 |
| Neutrophil (%) | 84.0 | 81.9 | 77.6 | 63.4 | 72.9 | 54.6 | 57.2 | 67.8 | 58.8 | 83.2 |
| Lymphocyte (%) | 2.5 | 9.0 | 11.2 | 21.5 | 16.0 | 32.0 | 31.3 | 19.2 | 26.5 | 13.1 |
| Eosinophil (%) | 0.1 | 0.6 | | | | | | | 0.4 | |
| Hb (g/dL) | 11.4 | 10.5 | 8.9 | 8.3 | 12.6 | 11.6 | 10.6 | 10.3 | 9.8 | 10.7 |
| PLT (\( \times 10^9 \) /µL) | 348 | 324 | 208 | 175 | 183 | 333 | 304 | 440 | 402 | 393 |
| T-Bil (mg/dL) | 0.6 | 0.4 | 0.4 | 0.3 | 0.4 | 0.3 | 0.3 | 0.3 | 0.2 | 0.3 |
| AST (U/L) | 543 | 371 | 323 | 121 | 246 | 143 | 49 | 111 | 81 | 11 |
| ALT (U/L) | 217 | 188 | 364 | 236 | 166 | 200 | 80 | 70 | 64 | 18 |
| LDH (U/L) | 1979 | 1773 | 1356 | 888 | 862 | 599 | 383 | 479 | 358 | 118 |
| CK (U/L) | 6580 | 3613 | 1253 | 908 | 4697 | 646 | 374 | 3533 | 925 | 50 |
| CKMB (U/L) | 431 | 242 | 81 | 52 | 339 | | | | | |
| TnT (ng/mL) | 6.48 | 5.34 | 2.42 | 0.438 | | | | | | |
| BUN (mg/dL) | 14.1 | 18.5 | 29.8 | 28.8 | 12.6 | 21.2 | 15.8 | 10.3 | 10.4 | 12.2 |
| Cr (mg/dL) | 0.30 | 0.34 | 0.44 | 0.37 | 0.28 | 0.40 | 0.45 | 0.45 | 0.44 | 0.80 |
| hs-CRP (mg/L) | 14.47 | 15.64 | 11.6 | 6.65 | 0.92 | 0.34 | 0.17 | 0.51 | 0.44 | 0.01 |
| BNP (pg/mL) | 613.4 | 365.8 | 323.9 | 664.0 | | | | | | |

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; CK: creatine kinase; CKMB: creatine kinase isoenzyme MB; Cr: creatinine; Hb: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; IVlg: intravenous immunoglobulin; LDH: lactate dehydrogenase; PLT: platelet; T-Bil: total bilirubin; TnT: troponin T; WBC: white blood cell.
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However, it had increased to 4697 U/L by Day 8. From Day 9, steroid therapy was administered as oral prednisolone 20 mg/day, after which her CK concentration decreased.

Fig. 2 Images of endomyocardial biopsy, electrocardiography, scintigraphy, and MRI

Fig. 2A: Photomicrographs of endomyocardial biopsy. HE, Hematoxylin–eosin; PSR, Picrosirius Red. Scale bar, 50 µm.

Fig. 2B: Lead II of twelve-lead electrocardiogram on Day 2. This shows complete atrioventricular block.

Fig. 2C: Gallium-67 scintigraphy. There is no evidence of inflammation of the proximal muscles of the extremities.

Fig. 2D: Contrast-enhanced MRI. The yellow arrows show contrast-enhanced areas indicating inflammation of scalene muscle (upper-left panel), sternocleidomastoid muscle (lower-left panel), semispinalis cervicis muscle (upper-right panel), and intercostal muscle (lower-right panel).
markedly to 374 U/L by Day 16.

On Day 18, steroid therapy was ceased because of improvement in her diplopia, neck pain, and back pain. However, on the following day, double vision, ptosis, and cervical and dorsal ache worsened and her CK concentration had again increased to 3533 U/L. There was no evidence of inflammation of the appendicular proximal muscles on Gallium-67 scintigraphy (Figure 2C). However, contrast-enhanced magnetic resonance imaging (MRI) revealed inflammation of the scalene, semispinalis cervicis, sternocleidomastoid, and intercostal muscles (Figure 2D). Prednisolone was restarted at 20 mg/day on Day 20, after which her eye symptoms and muscle pain improved and the CK concentration re-decreased to 925 U/L by Day 21 and 474 U/L by Day 23 (Figure 3).

On Day 25, her cardiac function recovered with LVEF of 59% and 74% on Day 42. She was discharged on Day 45 after undergoing rehabilitation. The CK concentration was 50 U/L and troponin T was 0.045 ng/mL at discharge. After discharge, her oral dosage of prednisolone was tapered to 5 mg/day; her symptoms such as diplopia, blepharoptosis, external ophthalmoplegia, neck pain, and backache have not recurred.

DISCUSSION

This is an atypical case of fulminant myocarditis combined with myositis of the ocular and
respiratory muscles. Our initial differential diagnosis included myasthenia gravis. There have been previous reports of myasthenia gravis complicated by thymoma, giant cell myocarditis, and multiple myositis. In addition, particularly in patients with both myocarditis and myositis, anti-Kv 1.4 antibody, an anti-striated muscle antibody, is often positive. Furthermore, about 60% of patients with myasthenia gravis and anti-Kv1.4 antibody positivity have ECG abnormalities including fatal arrhythmias such as ventricular tachycardia, sick sinus syndrome, and CAVB. Our patient had no evidence of thymoma on computed tomography or MRI, no giant cells in the endomyocardial biopsy specimens, and no proximal muscle weakness or pain which is distinctive of multiple myositis. As for laboratory findings, anti-Kv 1.4 antibody, anti-AChR antibody, and anti-MuSK antibody were negative. The tension test was also negative. Thus, the findings were not consistent with myocarditis with myasthenia gravis.

Another different possible diagnosis was anti-mitochondrial antibody (AMA)-positive myositis. The following characteristics of AMA positive myositis have been reported: 1) high prevalence in middle-aged women; 2) arrhythmia or LV systolic dysfunction or respiratory muscle failure; 3) improvement in symptoms with steroid therapy; 4) proximal muscle weakness; 5) AMA or anti-mitochondrial M2 antibody positivity; and 6) chronic myogenic change or granulomatous lesions with CD4 predominant lymphocyte infiltration. Our patient had characteristics 1), 2), and 3), but not 4), 5), and 6). Thus, it is unlikely that she had myocarditis with AMA-positive myositis.

The detailed pathophysiology of the present patient remain unclear. As to her skeletal muscles, the mechanism of site-specific inflammation in the eye and respiratory muscles is unexplained. There have recently been reports of patients in whom the use of immune checkpoint inhibitors was associated with development of both myocarditis and myositis; steroids, immunoglobulins, and immunosuppressive agents have been shown to be effective treatments. Given that steroid and immunoglobulin therapy were also effective in our patient, we postulate involvement of an autoimmune mechanism. Myocardium and skeletal muscle are both striated muscles, and may involve unknown antigenicity or autoantibodies common to myocardium, ocular muscles, and respiratory muscles. As to the possibility of viral infection, the positive predictive value of the measurements of anti-viral antibody titers in paired sera is only about 10%, and we did not perform a skeletal muscle biopsy or viral polymerase chain reaction. Thus, there was no clear evidence of any causative virus. However, it is undeniable that a viral infection may have triggered her myocarditis and myositis, considering the flu-like symptoms that preceded the other manifestations. It is possible that a para-infectious autoimmune mechanism was triggered by some primary viral infection. A previous report revealed that some antibodies against epitopes of cardiomyocyte membrane were cross-reactive to enteroviral proteins, indicating that enteroviral infection may be the etiological trigger of an autoreactive myocarditis. Therefore, antigenic cross-reactivity may exist among myocardium, skeletal muscle, and pathogens, as one of the mechanisms that disrupts immune tolerance. It is expected that similar cases will be collected and the molecular mechanism will be elucidated in the future.

In our patient, even after cardiac function had improved, serum troponin T concentration did not decrease to within the normal range, possibly indicating prolonged inflammation of the myocardium and myocardial damage associated with an autoimmune response. We did not administer steroid pulse therapy because her biopsy findings excluded eosinophilic or giant cell myocarditis. However, we did administer IVIg therapy at an early stage and also prescribed continuous steroid therapy. Both of these interventions may have facilitated decreases in her serum troponin T concentrations, resulting in improved LVEF. At the time of ceasing steroid use, the serum CK, but not troponin T, concentration had re-increased, possibly indicating that the degree of inflammation and responsiveness to steroid treatment in her cardiac and skeletal...
muscle were different.

CONCLUSIONS

We here present a rare case of fulminant myocarditis and myositis with a unique combination of affected muscles: ocular and respiratory muscles. IVIg therapy at an early stage and ongoing steroid therapy can be effective against myocarditis and myositis, suggesting that the pathophysiology includes autoimmune mechanisms that are common to myocardium and skeletal muscle.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest associated with this manuscript.

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