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Fulminant myocarditis in a young woman with mixed connective tissue disease: a case report

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Background

Although cardiac involvement is relatively common in mixed connective tissue disease (MCTD), few reports on MCTD-associated fulminant myocarditis are available.

Case summary

A 22-year-old woman diagnosed with MCTD was admitted to our institution for cold-like symptoms and chest pain. Echocardiography revealed that the left ventricular ejection fraction (LVEF) had rapidly decreased from 50 to 20%. Because endomyocardial biopsy revealed no significant lymphocytic infiltration, immunosuppressant drugs were not started initially; however, steroid pulse therapy (methylprednisolone, one 1000 mg/day) was initiated due to prolonged symptoms and unimproved haemodynamics. Despite strong immunosuppressant therapy, the LVEF did not improve, and severe mitral regurgitation appeared. Three days after steroid pulse therapy initiation, she experienced a sudden cardiac arrest; thus, venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pumping (IABP) were initiated. Subsequent immunosuppressant therapy was continued with prednisolone (100 mg/day) and intravenous cyclophosphamide (1000 mg). Six days after steroid therapy initiation, the LVEF improved to 40% and then recovered to near-normal levels. After successful weaning off of VA-ECMO and IABP, she was discharged. Thereafter, a detailed histopathological examination revealed multi-focal signs of ischaemic micro-circulatory injury and diffuse HLA-DR in the vascular endothelium, suggesting an autoimmune inflammatory response.

Discussion

We report a rare case of fulminant myocarditis in a patient with MCTD who recovered with immunosuppressive treatment. Despite the absence of significant lymphocytic infiltration findings on histopathological examination, patients with MCTD may experience a dramatic clinical course. Although it is unclear whether myocarditis is triggered by viral infections, certain autoimmune mechanisms may lead to its development.

Keywords

Myocarditis • Mixed connective tissue disease • Autoimmune diseases • Biopsy • Case reports

ESC Curriculum

6.4 Acute heart failure • 6.2 Heart failure with reduced ejection fraction

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Learning points

- Myocarditis associated with MCTD has often been reported as mild or asymptomatic; however, it may progress to fulminant myocarditis.
- Even in the absence of significant lymphocytic infiltration on conventional histopathological examination, patients with MCTD can follow a drastic clinical course.
- Although it is unclear whether viral infections triggered myocarditis in this case, detailed histopathological findings suggested certain auto-immune mechanisms may be involved in myocarditis development.

Introduction

Mixed connective tissue disease (MCTD) is an autoimmune disorder that is characterized by a combination of clinical features of systemic lupus erythematosus, scleroderma, and polymyositis.¹ The reported prevalence of cardiac involvement (often asymptomatic) in MCTD is 13–65%²; however, only few reports have detailed the rapid development of myocarditis in MCTD. Thus, we aimed to describe a rare case of fulminant myocarditis in a young woman with MCTD and discuss its aetiology.

Timeline

Date	Events
October 2021	The patient was diagnosed with mixed connective tissue disease (MCTD) and treated with non-steroidal anti-inflammatory drugs and sulfasalazine for arthritis
18 December	Onset of fever, chills, sore throat, and cough
19 December	Sudden onset of chest pain
20 December	Presented to a local hospital with prolonged symptoms Echocardiogram revealed a mildly decreased left ventricular ejection fraction (LVEF; 50%) and small pericardial effusion Admitted to a local hospital with a diagnosis of acute myocarditis
21 December	LVEF decreased drastically to 20%. Computed tomography revealed mild pulmonary oedema, systemic lymphadenopathy, and hepatosplenomegaly. Cardiac T2-weighted magnetic resonance imaging revealed a slightly high signal intensity in the mid-to-apical myocardium
22 December	Referred to our institution. Blood tests revealed elevated troponin-I, creatinine kinase, and C-reactive protein levels. Coronary angiography revealed no significant stenosis, while right ventricular endomyocardial biopsy revealed mild inflammatory cell infiltration in the cardiac muscle and an absence of eosinophils, giant cells, and granulomas; these were consistent with myocarditis. However, fulminant myocarditis did not seem likely
24 December	Steroid pulse therapy (1000 mg/day) was initiated because of prolonged fever, chest pain, tachycardia, and new onset of myalgia
25–27 December	LVEF did not improve, and mitral regurgitation became severe. The dobutamine dosage was increased, and diuretics were administered

Continued

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Date	Events
27 December	Sudden cardiac arrest occurred after crying due to emotional distress Venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pumping (IABP) were initiated
28 December	Prednisolone sodium succinate was initiated (100 mg/day)
29 December	Intravenous cyclophosphamide (IVCY) was initiated (1000 mg)
30 December	LVEF suddenly improved to 40%
31 December	LVEF improved to 50–55%. Successful weaning off of VA-ECMO
1 January 2022	Withdrawal of IABP
3 January	Successfully extubated without neurological damage
5–27 January	Oral prednisolone dosage was reduced from 60 to 25 mg per week
27 January	Second course of IVCY (500 mg) was initiated
3 February	She was discharged with full walking ability

Case presentation

A 22-year-old woman with Raynaud’s syndrome, anti-RNP antibody positivity, autoimmune arthritis, and a skin rash was diagnosed with MCTD. Non-steroidal anti-inflammatory drugs and sulfasalazine achieved insufficient disease control. Thus, she was admitted to a local hospital with a 2-day history of fever, chills, sore throat, and cough and a 1-day history of chest pain on inhalation. She had no contact with persons with coronavirus disease 2019 and had tested negative for the causative virus on polymerase chain reaction (PCR) testing. Transthoracic echocardiography (TTE) revealed a mildly decreased left ventricular systolic function, with a left ventricular ejection fraction (LVEF) of 50%, and small pericardial effusion. Blood tests revealed elevated troponin-I, creatinine kinase, and C-reactive protein (CRP) levels. Computed tomography revealed mild pulmonary oedema, systemic lymphadenopathy, and hepatosplenomegaly. Cardiac T2-weighted magnetic resonance imaging revealed a slightly high signal intensity in the mid-to-apical myocardium. The next day, although clinical symptoms did not change significantly, the LVEF decreased drastically from 50 to 20%; thus, fulminant myocarditis was suspected and she was transferred to our institution.

At admission to our institution, her blood pressure, pulse, and body temperature were 102/68 mmHg, 124 b.p.m., and 37.7°C, respectively. Physical examination revealed erythema on the cheeks, painful mild erosion on the hard palate, and sausage-like oedema on the fingertips. No cardiac and pulmonary murmur, jugular venous distention, leg oedema, hair loss, skin hardening, and ulceration were noted. Electrocardiography showed a narrow QRS sinus tachycardia and no

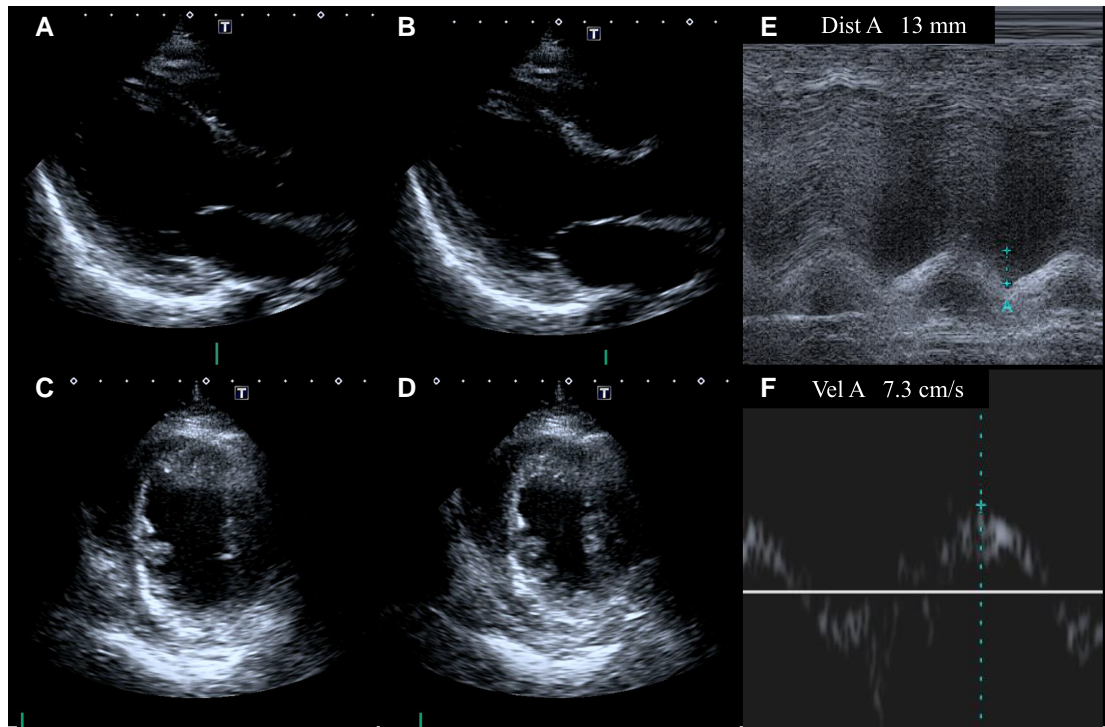


Figure 1 Echocardiographic findings. Transthoracic echocardiography performed at admission to our institution reveals an left ventricular ejection fraction of 26% and end-diastolic left ventricular diameter of 51 mm (A–D). No left ventricular hypertrophy is observed; the interventricular septum is 7.5 mm and the posterior wall thickness is 9.1 mm. (E) The tricuspid annular plane systolic excursion is 13 mm and (F) the tricuspid lateral annular peak systolic wave velocity is 7.3 cm/s. A small pericardial effusion is observed. Dist, distance; Vel, velocity.

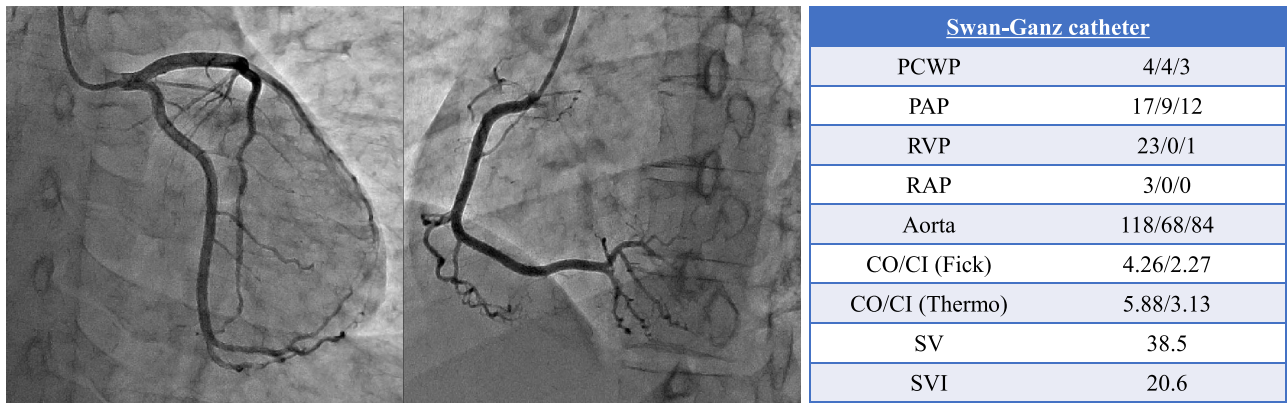


Figure 2 Findings from coronary angiography and Swan-Ganz catheter. Coronary angiography reveals no significant stenosis in the left and right coronary arteries. The Swan-Ganz catheter reveals a mean pulmonary capillary wedge pressure of 3 mmHg, mean pulmonary artery pressure of 12 mmHg, mean right atrial pressure of 0 mmHg, cardiac output of 4.26 L/min, cardiac index of 2.27 L/min/m² (Fick method), and stroke volume of 38.7 mL. PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; RVP, right ventricular pressure; RAP, right atrial pressure; CO, cardiac output; CI, cardiac index; SV, stroke volume; SVI, stroke volume index.

significant ST-T changes. TTE revealed a decreased biventricular systolic dysfunction (LVEF, 26%; tricuspid annular plane systolic excursion, 13.0 mm; and tricuspid lateral annular peak systolic wave velocity, 7.3 cm/s), an absence of left ventricular hypertrophy and valvular disease, and a small pericardial effusion (Figure 1; Supplementary material

online, Video S1). Coronary angiography revealed no significant stenosis. Under 3.5γ of dobutamine, Swan-Ganz catheter revealed a pulmonary capillary wedge pressure and cardiac index of 3 mmHg and 2.65 L/min/m², respectively (Figure 2). Right ventricular endomyocardial biopsy revealed mild inflammatory cell infiltration in the cardiac muscle and

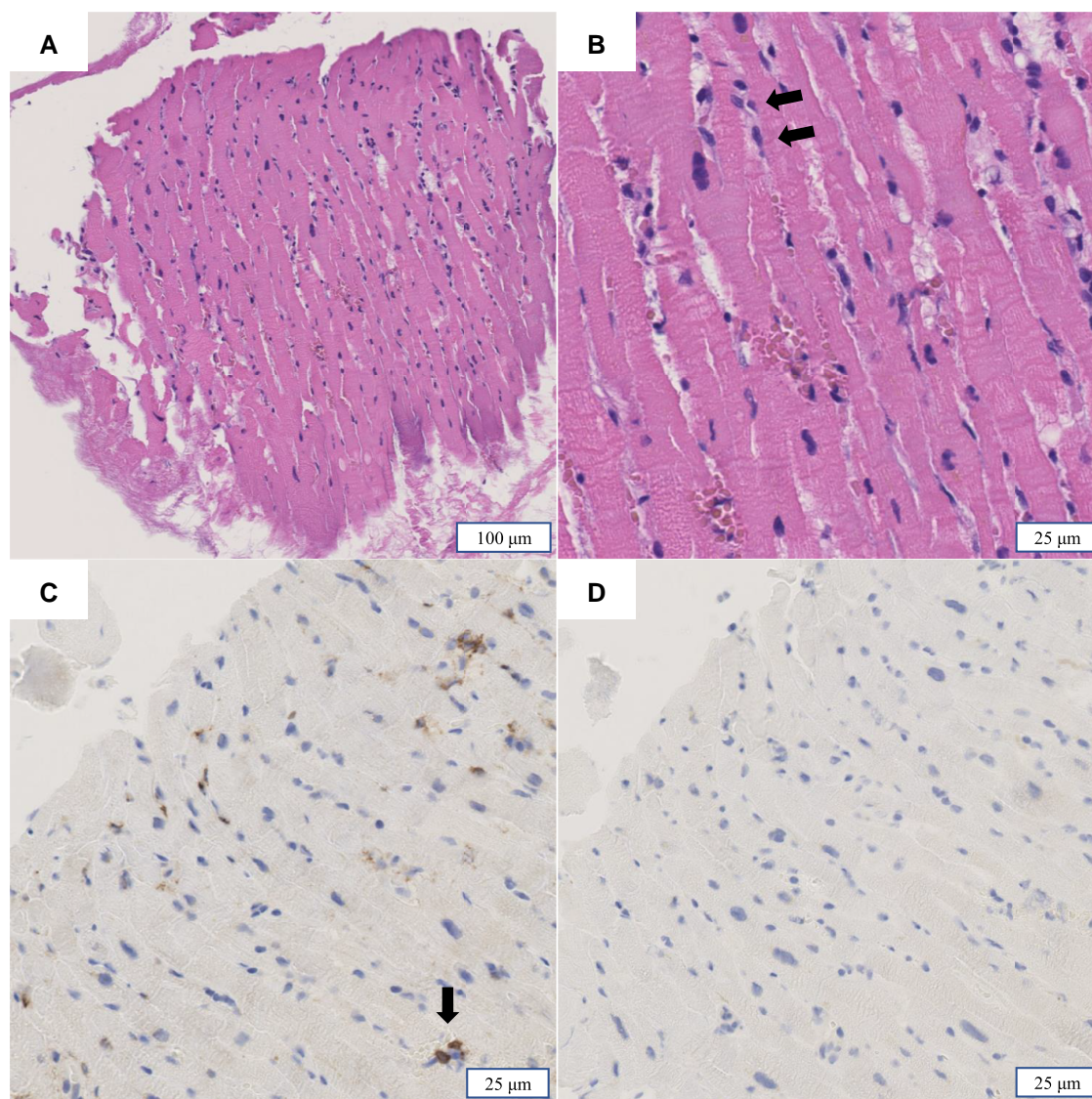


Figure 3 Histopathological findings. (A–D) Histopathological findings of the right ventricular septal biopsy taken on the day of admission to our institute. Some small and large irregularities are observed; however, signs of fibrosis, myocardial fascicle, or fibre disarray are absent. Small numbers of neutrophils (approximately 5/high-power field) and lymphocytes (approximately 15/high-power field) appear to have infiltrated the connective tissue (block arrows). No eosinophils, granulomas, or giant cells are observed (A) haematoxylin and eosin staining, scale bar: 100 µm; (B) haematoxylin and eosin staining, scale bar: 20 µm. (C) Immune staining for CD3 reveals a small number of CD3-positive T-cells (block arrow). (D) Immune staining for CD20 reveals no CD20-positive B-cells. CD, cluster of differentiation; HE, haematoxylin and eosin; HPF, high-power field.

absence of eosinophils, giant cells, and granulomas. These findings, though consistent with myocarditis, were deemed not severe enough for a fulminant myocarditis diagnosis (Figure 3). Laboratory findings revealed increased levels of troponin-I, creatinine kinase, CRP, hepatic enzymes, ferritin, triglyceride, and sIL-2 receptor, with atypical lymphocyte expression. Tests for anti-nuclear and anti-RNP antibodies were positive, while tests for anti-cardiolipin, anti-DNA, and anti-neutrophil cytoplasmic antibodies (C-ANCA and P-ANCA) were negative. Serological tests for viruses, including the Epstein–Barr virus and cytomegalovirus, and PCR test for Respiratory Syncytial Virus, Parvovirus B19, Influenza A and B were also negative (Table 1). Atypical lymphocytes in the peripheral blood suggested a temporary viral infection or a complication of the haemophagocytic syndrome; hence, we initially

avoided steroid treatment to prevent interference with the patient's condition. However, the bone marrow test was negative for the haemophagocytic syndrome; furthermore, there was little improvement in the fever, chest pain, and tachycardia, and myalgia occurred 2 days after admission. Hence, steroid pulse therapy (methylprednisolone, 1000 mg/day) was started.

Despite a 3-day steroid pulse therapy, the LVEF did not improve, and mitral regurgitation became severe. We increased the dobutamine dosage and started diuretics; however, pulmonary congestion progressed, although there was no need for mechanical ventilatory support or oxygenation. On the 6th post-admission day, profuse crying due to stress from the prolonged hospital stay induced a sudden cardiac arrest without ventricular fibrillation or tachycardia. Despite

Table 1 Laboratory findings and results of comprehensive viral testing

Laboratory parameters	Observed values	Reference range	
On admission			
WBC	4100	3300–8600	/μL
Neutrophil	61.0	40.0–71.0	%
Lymphocyte	22.0	26.0–47.0	%
Eosinophil	0.0		%
Atypical lymphocyte	11.0	0.0–0.0	%
Hb	12.3	11.6–14.8	g/dL
Ht	37.2	35.1–44.4	%
Plt	11.7	15.8–34.8	×10 ⁴ /μL
APTT	42.3	26.0–38.0	s
PT-INR	1.11	0.85–1.15	
D-dimer	5.7	<1.0	μg/mL
AST	154	13–30	U/L
ALT	72	7–23	U/L
LDH	973	124–222	U/L
ALP	50	38–113	U/L
γ-GTP	68	9–32	U/L
T-bil	0.5	0.4–1.5	mg/dL
TP	6.2	6.6–8.1	g/dL
Alb	2.6	4.1–5.1	g/dL
BUN	13.4	8–20	mg/dL
Cr	0.64	0.46–0.79	mg/dL
eGFR	96.2	≥60	mL/min/ 1.73 m ²
Na	133	138–145	mmol/L
K	3.9	3.6–4.8	mmol/L
Cl	104	101–108	mmol/L
CK	1283	41–153	U/L
CK-MB	14	≤12	U/L
Glucose	93	73–109	mg/dL
CRP	8.4	≤0.14	mg/dL
TG	554	28–149	mg/dL
Ferritin	2355	5–152	mg/mL
sIL-2R	2209.7	156.6–474.5	U/mL
Troponin-I	3418	≤24	pg/mL
BNP	200.2	≤18.4	pg/mL
RF	23	<15	IU/mL
C3	87	73–138	mg/dL
C4	27.2	11–31	mg/dL
CH50	51.2	25–51	U/mL
Anti-nuclear antibody	>2560, Sp	<40	
Anti-dsDNA antibody	(–)	(–)	
Anti-DNA antibody	(–)	(–)	
Anti-Sm antibody	(–)	(–)	
Anti-RNP antibody	>550	<10	IU/mL
Anti-SS-A antibody	(–)	(–)	
Anti-cardiolipin antibody	(–)	(–)	
Lupus anticoagulant	(–)	(–)	
Coombs test	(–)	(–)	
C-ANCA	(–)	(–)	

Continued

Table 1 Continued

Laboratory parameters	Observed values	Reference range	
P-ANCA	(–)	(–)	
TSH	5.1	0.61–4.23	mIU/L
FT3	1.4	2.3–4.0	pg/mL
FT4	1.1	0.9–1.7	ng/dL
IgG	1887	861–1747	mg/dL
IgA	99	93–393	mg/dL
IgM	55	50–269	mg/dL
COVID-19 PCR	(–)	(–)	
Influenza A PCR	(–)	(–)	
Influenza B PCR	(–)	(–)	
VCA-IgG	40		Fold
VCA-IgA	<10		Fold
EBNA	(–)	(–)	
CMV-IgG	(–)	(–)	
CMV-IgM	(–)	(–)	
Coxsackie A9	<4	<4	Fold
Coxsackie B1	<4	<4	Fold
Coxsackie B2	<4	<4	Fold
Coxsackie B3	<4	<4	Fold
Coxsackie B4	<4	<4	Fold
Coxsackie B5	<4	<4	Fold
Coxsackie B6	<4	<4	Fold
Echo 6	8	<4	Fold
Echo 9	<4	<4	Fold
Echo 16	<4	<4	Fold
Echo 30	<4	<4	Fold
Parvovirus B19	(–)	(–)	
Rubella-IgG	12.5		EIA
Rubella-IgM	<0.80		Index
Adenovirus	<4	<4	Fold
RS virus	<4	<4	Fold
Parainfluenza 1	<10	<4	Fold
Parainfluenza 2	<10	<4	Fold
Parainfluenza 3	40	<4	Fold
Two months later			
VCA-IgG	40		Fold
VCA-IgA	<10		Fold
EBNA	(–)	(–)	
Echo 6	4	<4	Fold
Parainfluenza 3	40	<4	Fold

(+) means positive test; (–) means negative test.

WBC, white blood cell; Hb, haemoglobin; Ht, haematocrit; Plt, platelet; APTT, activated partial thromboplastin time; PT-INR, prothrombin time and international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; T-bil, total bilirubin; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; Na, sodium; K, potassium; Cl, chloride; CK, creatinine kinase; CK-MB, creatinine kinase myocardial band; CRP, C-reactive protein; TG, triglyceride; sIL-2R, soluble interleukin-2 receptor; BNP, brain natriuretic peptide; RF, rheumatoid factor; C-ANCA, cytoplasmic-anti-neutrophil cytoplasmic antibody; P-ANCA, perinuclear-anti-neutrophil cytoplasmic antibody; TSH, thyroid stimulating hormone; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; VCA, virus capsid antigen; Ig, immunoglobulin; EBNA, Epstein-Barr virus nuclear antigen; CMV, cytomegalovirus; EIA, enzyme immunoassay.

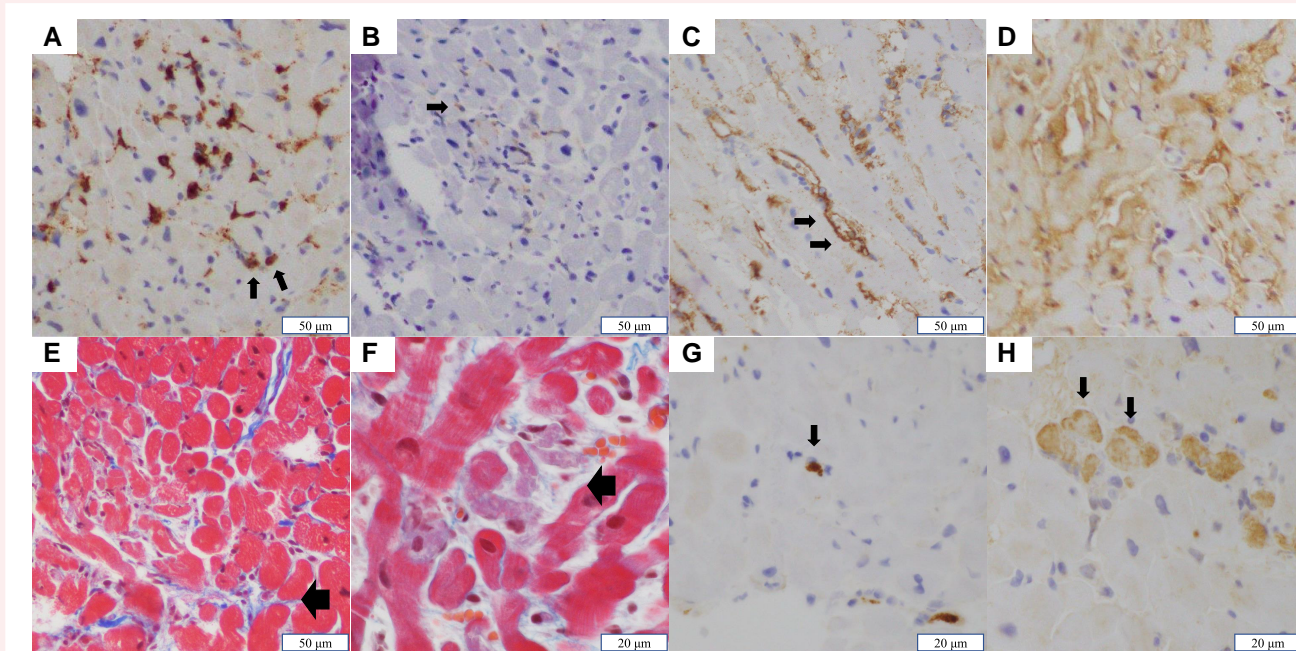


Figure 4 Detailed histopathological findings. (A) Relatively small number of CD3-positive T-cells (block arrows) are observed. (B) Small number of CD68-positive macrophages (block arrow) are observed. (C) human leucocyte antigen-DR-positive staining in the vascular endothelium (block arrows). (D) Diffuse IgG-positive staining in the interstitium. (E, F) Masson's trichrome staining: cardiomyocytes showing microvasculature ischaemic injury (block arrows). (G) CD61-positive micro-thrombi within interstitial micro-vessels (block arrows). (H) C4d staining of a small population of cardiomyocytes (block arrows). CD, cluster of differentiation.

cardiopulmonary resuscitation, spontaneous circulation could not be restored; hence, venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pumping (IABP) were started immediately, followed by normothermia management. There were no signs of mechanical complications of myocardial rupture. Considering the autoimmune pathophysiology of myocarditis, we decided to continue the steroid therapy (prednisolone sodium succinate, 100 mg/day), and started intravenous cyclophosphamide (IVCY; 1000 mg) to restore the cardiac function. Although the LVEF decreased to 5% after the cardiac arrest (Supplementary material online, Video S2), it suddenly improved to 40% after 3 days. Thus, the patient was weaned off of VA-ECMO and IABP. Eight days after the cardiac arrest, the patient was successfully extubated without neurological damage. The steroid dose was reduced early because of steroid-induced psychosis symptoms. A second IVCY course (500 mg) was administered 4 weeks after the first course. Pancytopenia and febrile neutropenia occurred temporarily and were treated successfully with antibiotics and the granulocyte-colony stimulating factor. Although the CRP level was approximately 8 mg/dL on admission, it normalized at discharge. Rehabilitation was continued with assistance from a liaison team; 42 days after admission, she was discharged from the hospital with full walking ability. She has been maintained on mycophenolate mofetil, prednisolone, and beta-blocker, and remains on follow-up with repeat TTE without worsening cardiac function (Supplementary material online, Video S3).

After discharge, a detailed histopathological examination of the biopsy specimen (Figure 4) revealed a small number of CD3-positive T-cells and CD68-positive macrophages in the cardiac tissue; contrastingly, IgG and diffuse HLA-DR were observed in the interstitium and vascular endothelium, respectively. Mild interstitial and perivascular fibrosis, multiple CD61-positive micro-thrombi within the intramural

coronary arteries, and C4d were found in the adjacent cardiomyocytes, suggesting multi-focal ischaemic micro-circulatory injury.

Discussion

We report a case of possible autoimmunity-induced myocarditis in a patient with MCTD. This diagnosis was considered due to the histopathological findings and the marked improvement in cardiac function after steroid therapy.

Initially, fulminant myocarditis was not considered because of the minimal myocardial oedema, pericardial effusion, atrioventricular conduction defect, and significant lymphocytic infiltration in the myocardium. However, the patient's condition turned serious due to the sudden cardiac arrest. MCTD-associated myocarditis is often mild and asymptomatic^{3,4}; hence, a dramatic course (such as in this case) is very rare. The sudden cardiac arrest was possibly caused by circulatory collapse secondary to decreased preload and increased afterload; this in turn was due to a crying-induced increase in the intra-thoracic pressure in a condition of fairly low LVEF and severe mitral regurgitation.

Sporadic lymphocytic and polymorphonuclear leucocyte infiltration are usually seen in the perivascular space surrounding the intramural coronary arteries and in the adjacent myocardium in MCTD-associated myocarditis; however, these are not specific to MCTD.³ Thus, making a definitive diagnosis of MCTD-associated myocarditis is difficult.

In this case, two pathological findings aided our final diagnosis. First, there were signs of multi-focal ischaemic micro-circulatory injury. C4d staining has been proposed as a marker for antibody-mediated rejection, an immune reaction caused by humoral immunity during heart transplantation, and an ischaemic injury.⁵ Herein, perivascular fibrosis, multiple CD61-positive micro-thrombi within interstitial micro-vessels,

and C4d staining of the myocardium suggested ischaemic micro-circulatory injury. The association between micro-circulatory injury and MCTD-associated myocarditis has not been proven; nonetheless, myocardial micro-circulatory ischaemia could possibly be related to myocarditis given that the Raynaud's syndrome is attributed to extremity microvascular ischaemia.⁶

Second, HLA-DR-positive staining was observed in endothelial cells. Major histocompatibility complexes (MHC) are molecules that play an important role in presenting antigens, such as viral particles, to the immune system. Increased expression of MHC antigen presentation has been demonstrated in human tissues undergoing autoimmune injury, allograft rejection, and other inflammatory states.⁷ MHC class II (HLA-DR) antigens are useful markers of autoimmune inflammatory responses in patients with inflammatory myocardial disease.^{7,8} Additionally, HLA-DR antigens improve the sensitivity of autoimmune myocarditis diagnosis because the inflammatory cell infiltration is often focal and sporadic in distribution, while HLA-DR antigens are distributed throughout the myocardium.⁸

Conclusions

This rare case of fulminant myocarditis in a patient with MCTD demonstrated that, although it is unclear whether viral infections trigger myocarditis, certain autoimmune mechanisms may lead to myocarditis. Notably, even in the absence of significant lymphocytic infiltration on conventional histopathological examination, patients with MCTD can follow a drastic clinical course.

Lead author biography



Tomoyo Hamana, MD, is currently working as an interventional cardiologist in the Division of Cardiovascular Medicine, Kobe University Hospital, Kobe, Japan. Her main academic interests include ischaemic heart disease, coronary intervention, and cardiovascular imaging, and heart failure.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

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Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with the Committee on Publication Ethics guidelines.

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Conflict of interest: None declared.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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