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DOI: 10.5582/irdr.2026.01022

Fulminant myocarditis and sudden death associated with thymoma-related autoimmunity

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SUMMARY: Fulminant myocarditis (FM) is a severe, rapidly progressive and life-threatening condition of myocarditis associated with infectious or autoimmune etiologies. Here, we present three patients with an invasive thymoma who had FM, which eventually led to sudden death. The most frequent clinical presentations at onset include palpitations, orthopnea, and acute worsening of myasthenia gravis (MG). Highly elevated myocardial biomarkers and positive autoantibodies against cardiac muscle, skeletal muscle, and neuromuscular junctions were detected in serum. The electrocardiograph (ECG) findings progressed to life-threatening ventricular arrhythmias. Although high-dose methylprednisolone or intravenous immunoglobulin was administered along with advanced respiratory support, profound hemodynamic collapse rapidly occurred, and these patients eventually died within days. This case series underscores the importance of rapid recognition of FM associated with thymoma and early aggressive supportive and immunomodulatory interventions, including consideration of mechanical circulatory support when clinically indicated.

Keywords: invasive thymoma, fulminant myocarditis, sudden cardiac death, autoantibody

1. Introduction

Fulminant Myocarditis (FM) is a form or a syndrome of severe myocarditis that presents with sudden-onset acute heart failure, cardiogenic shock, or life-threatening arrhythmia (*1*). Infections, autoimmune diseases, and drug toxicity are the main triggers for the development of FM (*2,3*), among which, viral infection is the most common etiology (*4*). Thymoma-associated immunologic paraneoplastic disorders (PNDs) involve multiple systems, including neuromuscular, central nervous system (CNS), hematologic, endocrine, cutaneous, gastrointestinal, renal, cardiac (*5*), and other systems (*6*). The frequency of myocarditis associated with thymoma is less than 1% (*7*). Pathologically speaking, WHO subtypes B2 and AB are the most prevalent forms associated with thymoma (*7*).

Here, we briefly present 3 cases of FM associated with invasive thymoma and multiple autoantibodies that were treated at a single centre (Huashan Hospital). Written informed consent for publication of this report and the accompanying clinical images was obtained from their legal representatives. We aim to emphasize the need for early diagnosis and aggressive interventions to improve the clinical outcome for this devastating, rare complication.

2. Shared clinical pattern of invasive thymoma-associated fulminant myocarditis

In these patients, the age at diagnosis was 30 to 43 years with invasive thymoma, the pathology of which was WHO B2-B3 and Masaoka staging III-IV. Ocular onset, or generalized onset of myasthenia gravis (MG), the most prevalent form of thymoma-associated autoimmunity, was the initial clinical presentation. All three patients rapidly developed myasthenic crisis (MC), a life-threatening condition with respiratory failure requiring ventilation. Highly elevated titers of anti-Acetylcholine receptor antibody (AChR-Ab), anti-Titin antibody, anti-skeletal muscle antibody, and anti-cardiac muscle antibody were identified. These were

potential culprit antibodies for multisystem involvement, including neuromuscular junction impairment, myositis and myocarditis.

The clinical characteristics and serological antibodies of three cases are presented in Table 1. After admission, progressively decreased blood pressure and malignant arrhythmia occurred (Figure 1). The bedside echocardiography identified motion abnormality in the multi-segmental left ventricular wall. Serum testing identified elevated cardiac biomarkers, such as troponin T (TnT), pro-Brain natriuretic peptide (BNP), and heart-type Fatty Acid-Binding protein (H-FABP). Initially, the electrocardiograph (ECG) revealed sinus tachycardia and ST-segment elevations, which progressed to life-threatening ventricular arrhythmias. Profound hemodynamic collapse rapidly occurred, followed by a gradual loss of consciousness. Despite timely ventilatory support and immunotherapies, resuscitation failed for these patients. The time from cardiac presentations to sudden death was 4 to 5 days.

These cases shared the same clinical patterns, including invasive or advanced thymoma, thymoma-associated myasthenia gravis, myasthenic crisis, high titers of anti-striational or anti-cardiac antibodies, rapid cardiac deterioration, malignant arrhythmia, and sudden death.

3. Clinical implications for early recognition and aggressive intervention

Thymomas are associated with a variety of autoimmune disorders. Pathophysiological mechanisms are complex and include decreased expression of autoimmune regulator (AIRE), MHC Class II, and T regulatory cells (Tregs) (*6*). The above mechanisms cause production of organ-specific autoantibodies, including those against the myocardium. Pathogenic antibodies detected in FM associated with thymoma are anti-heart antibodies (AHA), which are present in up to 60% of patients with inflammatory cardiomyopathy and their relatives (*8*). These autoantibodies probably target cardiac autoantigens, particularly cardiac α-myosin heavy chain (also known as myosin 6) and β-myosin heavy chain (also known as myosin 7) isoforms (*9*). Diagnostic value of AHA as compared with myocardial biopsy was highlighted in a previous study (*10*). The role of AHA has been repeatedly shown in development of inflammatory and autoimmune diseases of the myocardium and pericardium, as well as in progression of genetically determined cardiomyopathy (*11*).

Due to the high mortality rate of FM, early identification and intervention are of critical importance. Once a healthy individual or a non-cardiac disease patient shows rapid heart failure, it is very important to consider the possibility of FM. When a suspected patient is admitted, routine tests including physical examinations, blood chemistry, ECG, and emergency echocardiography should be conducted (*12*). In certain patients with a history of thymoma and MG, clinical presentation of arrhythmia warrants immediate cardiac evaluations and early intervention. More specifically, immunotherapies using large doses of glucocorticoids and intravenous immunoglobulin (IVIG) are necessary. Plasma or blood

Table 1. The clinical characteristics and serological antibodies of three cases

Characteristics	Case 1	Case 2	Case 3
Sex	Male	Female	Male
Age	30	43	40
Thymoma Pathology (WHO)	B2	B2	B3
Thymoma Pathology (Masaoka)	IIIB	III	IV
Resection status for thymoma	One resection	No resection, only biopsy	Two resections
Antibody profiles:			
AChR-Ab (nmol/L)	36.2	42.96	11.51
anti-Titin antibody	+++	+++	+++
anti-skeletal muscle antibody	1:320	1:320	1:1000
anti-cardiac muscle antibody	1:320	1:320	1:1000
Cardiac manifestations	blood pressure rapidly dropped, motion abnormality in the multi-segmental left ventricular wall, ventricular arrhythmia, cardiac biomarkers elevated	heart failure and malignant arrhythmia, cardiac biomarkers elevated	difficulty in breathing, cardiac biomarkers elevated
Myasthenia Gravis (MG) or other autoimmunity	Ocular onset of MG	Generalized onset of MG	Generalized onset of MG
Interventions and Therapies	non-invasive mechanical ventilation, plasmapheresis, IVIG and IVMP	endotracheal intubation, plasmapheresis and IVMP	non-invasive mechanical ventilation, plasmapheresis, IVIG and IVMP
Time from cardiac presentation to sudden death	5 days	4 days	5 days

Abbreviations: AChR, acetylcholine receptor; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone.

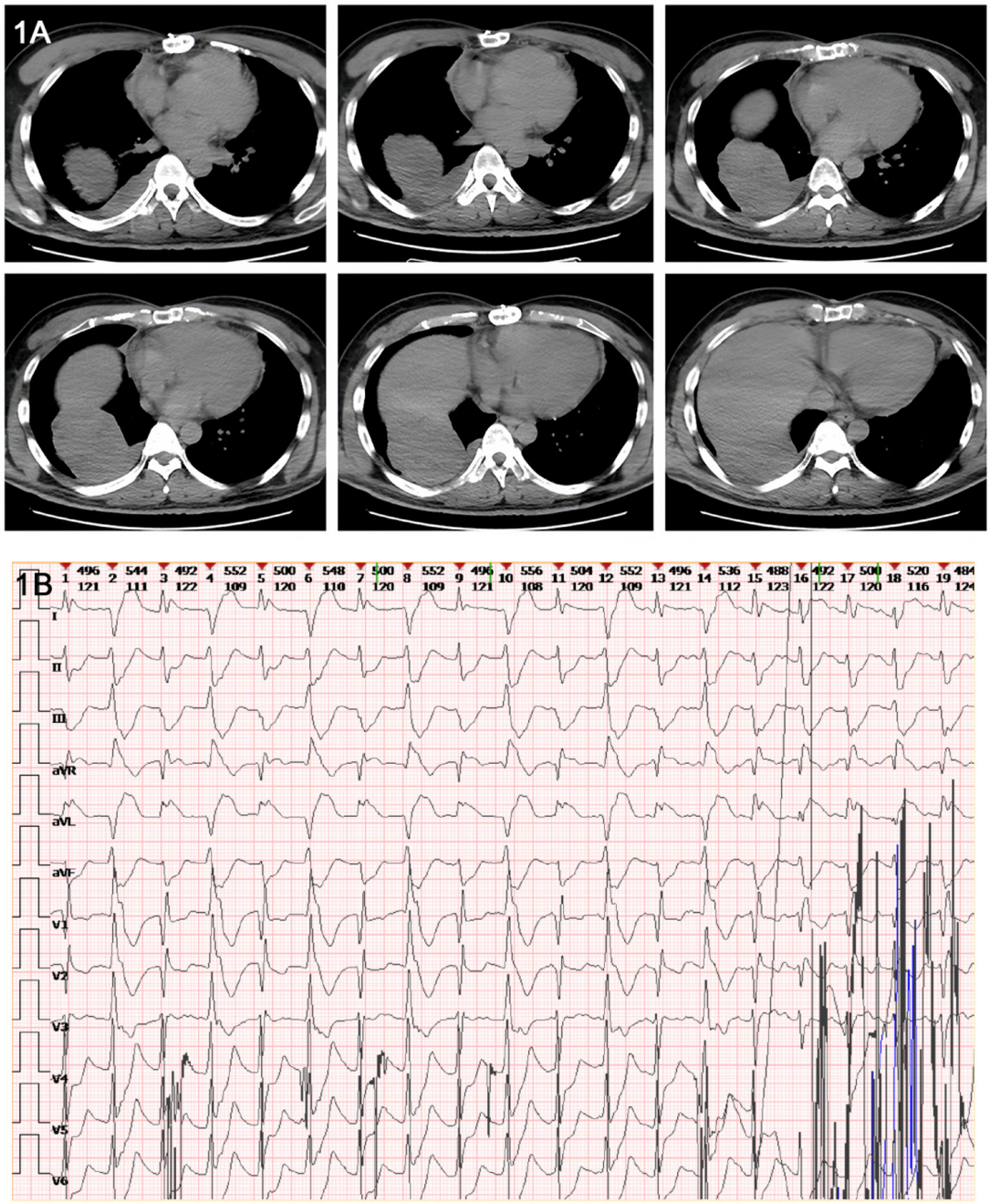

Figure 1. Representative radiological and electrocardiographic findings in Case 1. (A) Chest CT scan showing a large thoracic mass and pleural effusion; **(B)** ECG showing ventricular arrhythmia and ST-segment changes.

purification and life-support techniques, including intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), assisted mechanical ventilation, and temporary pacemaker implantation if necessary, should be employed if needed (*2*). Despite timely initiation of immunotherapies, all our cases failed treatment. This failure may be due to an excessively high tumour burden, which involves the pericardium. More aggressive intervention, such as ECMO, should be initiated early for these cases.

In conclusion, FM is a rare and fatal complication associated with invasive thymoma. These cases highlight that patients with invasive or recurrent thymoma who develop worsening myasthenic symptoms and new cardiac manifestations, such as dyspnea, palpitations, hypotension, arrhythmia, or elevated cardiac biomarkers, may rapidly progress to fatal fulminant myocarditis and therefore require immediate cardiac evaluation and aggressive early intervention.

Funding: This study is supported by financial grants from the National Natural Science Foundation of China (82571592 and 82471426), and the National Clinical Collaboration Project for Major and Difficult Diseases with Integrated Traditional Chinese and Western Medicine (No.ZDYN-2024-A-076).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received March 6, 2026; Revised June 28, 2026; Accepted July 7, 2026.

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Released online in J-STAGE as advance publication July 15, 2026.