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Case Series

Pathology Section

Granulomatous Myocarditis as Rare Presentation of *Mycobacterium tuberculosis*: A Series of Four Autopsy Cases

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ABSTRACT

Tuberculosis (TB) is a communicable disease caused by the organism *Mycobacterium tuberculosis*. It has been a leading cause of mortality and a global public health emergency for the last 25 years. Despite being a predominantly pulmonary infection, *Mycobacterium tuberculosis* can affect other organs, such as the nervous system, gastrointestinal system and, rarely, the cardiovascular system. This infection can sometimes present as Tuberculous Myocarditis (TM) in the cardiovascular system, an extremely unusual presentation that can be difficult to diagnose, especially in areas where TB is endemic, like India. Authors report four cases of Granulomatous Myocarditis (GM) across a wide range of age groups, who presented with non specific symptoms of giddiness followed by sudden unconsciousness and death. On gross examination of the hearts received after autopsy, two cases showed left ventricular focal white lesions, while one additionally showed Left Ventricular Hypertrophy (LVH). The hearts in the other two cases were grossly unremarkable. Microscopic examination of the cardiac tissue revealed multiple caseating granulomas composed of necrosis, epithelioid cells and lymphocytes. Three out of four cases also showed disseminated TB. Based on the histopathological examination of the granulomas, *Mycobacterium tuberculosis* aetiology was suspected in all cases. Herein, present series describe the pathological characteristics of this most unusual variant of *Mycobacterium tuberculosis*.

Keywords: Epithelioid cells, Heart, Histopathology, Postmortem, Sudden death

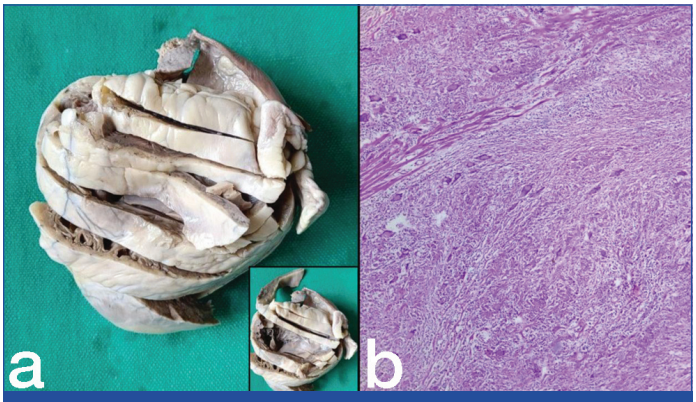
INTRODUCTION

This case series describes in detail the clinical presentation as provided in the autopsy notes, gross examination and histopathological findings in the four autopsy cases of GM at the Dr. RN Cooper Municipal General Hospital, Mumbai, Maharashtra, India, over the past two years (February 2022 - June 2024). It also reviews the available literature to provide insight into this rare entity.

CASE SERIES

Case 1

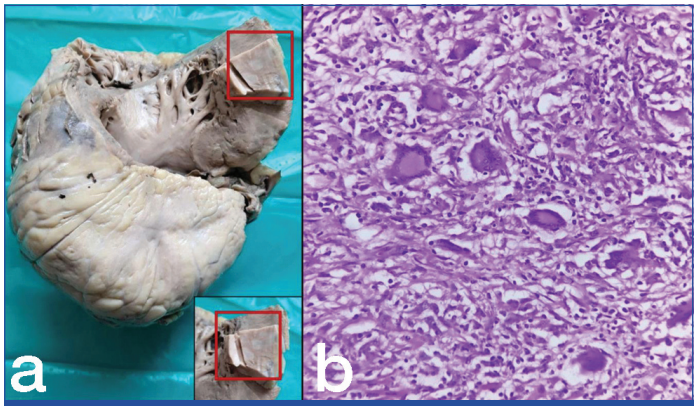
A 27-year-old female student was brought to the emergency department and was declared dead before admission; she had no significant past medical history. She was found unconscious on the bed by her parents. On gross examination, the heart weighed 310 g and measured 14×9×4 cm; the cut surface was unremarkable [Table/Fig-1a]. On microscopy, the heart showed necrotising granulomatous inflammation composed of granulomas, giant cells and lymphocytes [Table/Fig-1b]. Similar findings were noted in the lungs and the liver. The histology was suggestive of disseminated TB involving the lungs, liver and heart.



[Table/Fig-1]: a) Heart with unremarkable myocardium; b) Destruction of myocardial muscle fibres with granulomas (H&E stain, 10x magnification).

Case 2

A 63-year-old male security guard was on duty and apparently all right before he experienced sudden giddiness followed by loss of consciousness. He was declared dead upon arrival at the emergency services. At gross examination, the heart weighed 340 g, measured 14×11×7 cm, and on cut section showed LVH with a focal white lesion measuring 2×1 cm [Table/Fig-2a]. On histology, the myocardium showed necrotising granulomatous inflammation with areas of necrosis, epithelioid cell granulomas, neutrophils, lymphoplasmacytic infiltrate and a few Langhans giant cells [Table/Fig-2b].

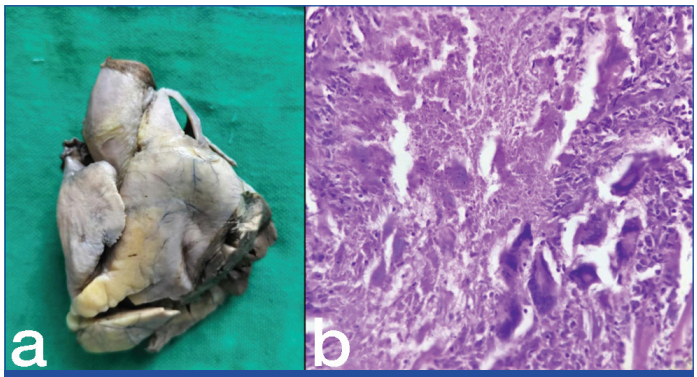


[Table/Fig-2]: a) Heart showing myocardium with grey-white lesions; b) Granulomas composed of langhans giant cells, epithelioid cells and lymphocytes (H&E stain, 40x magnification).

Case 3

A 48-year-old alcoholic male was admitted to the hospital due to complaints of abdominal pain for one month. He was receiving treatment for the same and succumbed eight days post-admission. The cause of death was suspected to be liver failure. According to the postmortem notes, forensic examination revealed that both lungs showed evidence of lobar pneumonia and pleural effusion; however, the final opinion was reserved for histopathological examination. Only a part of the heart was received, which weighed

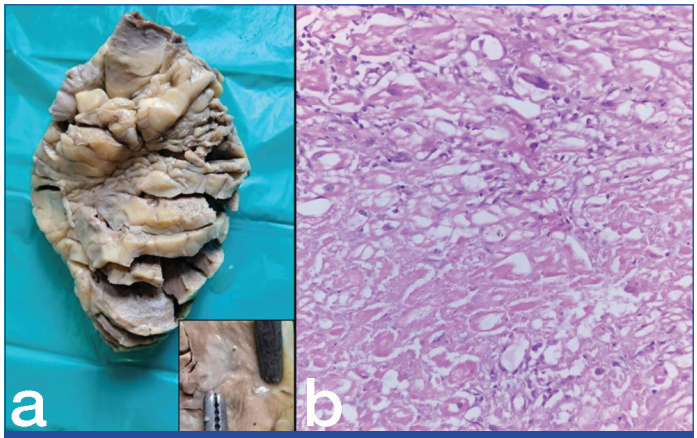
125 g, measured 5×4×3.5 cm, and was unremarkable on gross examination [Table/Fig-3a]. The lungs showed features of miliary TB, and the liver exhibited a tuberculous abscess. On histology, the myocardium showed necrotising granulomatous inflammation composed of epithelioid cell granulomas and Langhans giant cells [Table/Fig-3b]. The liver, spleen, kidneys and lungs exhibited similar histological features.



[Table/Fig-3]: a) Part of heart showing unremarkable myocardium; b) Granulomas showing large areas of necrosis and langhans giant cells (H&E stain, 40x magnification).

Case 4

A 31-year-old male experienced hiccups while traveling by auto. This was followed by sudden unconsciousness, and he was brought to the casualty department, where he was declared dead. According to the autopsy notes, forensic examination revealed bilateral lung pneumonic consolidation. On gross examination, the heart weighed 300 g and measured 15×10×3 cm. It was unremarkable externally but showed a grey-white focus [Table/Fig-4a] on the internal surface of the left ventricle, measuring 1×0.5 cm. On microscopy, the myocardium showed necrotising granulomatous inflammation composed of large areas of necrosis [Table/Fig-4b], surrounded by lymphocytes, histiocytes, plasma cells and eosinophils, along with Langhans giant cells. The liver and lungs also demonstrated features of miliary TB.



[Table/Fig-4]: a) Heart showing myocardium with grey-white lesions; b) Large areas of necrosis with scattered epithelioid cells and langhans giant cells (H&E stain, 20x magnification).

The [Table/Fig-5] summarises the causes of death, along with the gross and histopathological features of the four cases of GM.

Case no.	Age (years)/ Sex	Clinical presentation	Gross	Microscopy	Other organs
Case 1	27/F	Sudden unconsciousness	Heart-UNR	Granulomas, langhans giant cells, and lymphocytes	Liver, Lung-miliary TB
Case 2	63/M	Giddiness and sudden unconsciousness	Heart LV-LVH and focal whitish lesion	Epithelioid cell granulomas, areas of necrosis with neutrophils, lymphoplasmacytic infiltrate and a few langhans giant cells	NAD
Case 3	48/M	Abdominal pain	Heart LV-UNR	Epithelioid cell granulomas, langhansgiant cells, and areas of necrosis	Lung, Spleen, Kidney-miliary TB
Case 4	31/M	Hiccoughs and sudden unconsciousness	Heart-focal whitish lesion	Necrotising granulomas, large areas of necrosis surrounded by lymphocytes, plasma cells, histiocytes, eosinophils, and langhans giant cells	Lungs, Liver-miliary TB

[Table/Fig-5]: Summary of findings of the four autopsy cases.
UNR: Unremarkable; LVH: Left ventricular hypertrophy; NAD: No abnormality detected; TB: Tuberculosis

DISCUSSION

The TB is a highly transmissible disease caused by *Mycobacterium tuberculosis* and is the most common cause of infectious agent-related mortality, as well as a major source of morbidity globally [1]. Despite being curable, TB remains one of the top 10 infectious diseases with high mortality worldwide, accounting for more deaths than malaria and HIV combined. According to the World Health Organisation, there are 1.3 million TB-related fatalities and 10.6 million new cases of TB each year, with 95% of mortality occurring in underdeveloped and less-developed nations [2].

Although any organ in the body can contract TB and present with variable symptoms that can pose diagnostic difficulties, some organs, such as the heart, thyroid and skeletal muscles, are rarely affected. TM is one of the uncommon manifestations of extrapulmonary TB and is usually seen secondary to lesions elsewhere in the body. It affects 1-2% of all TB patients, claiming less than 0.3% of lives lost to the disease [2].

Research indicates that the lactic acid generated during physical exertion, due to the constant movement of the myocardium, shields the heart muscle from tubercle bacilli, preventing the lodging of tubercular bacilli in the myocardium [3,4]. However, direct pericardial lesions, lymphatic dissemination from mediastinal lymph nodes, or haematogenous spread from a distant site are potential causes that could lead to myocardial infiltration by TB [3-5].

There are very few occurrences of TM documented in the literature, making it an uncommon illness [6,7]. TM is rare and often presents with unusual clinical symptoms; however, it is a recognised cause of sudden death [8]. The intensity and affected site of the disease are usually related to the clinical presentation of TM, which can range from asymptomatic to cardiac failure. Presentations may include pericarditis, arrhythmias, myocardial infarction, valve dysfunction, ventricular outflow tract obstruction, cardiac rupture, coronary occlusion, decreased myocardial contractility, ventricular fibrillation, heart failure, sudden cardiac arrest, long QT syndrome and dilated cardiomyopathy, all of which could potentially lead to sudden cardiac death [2,5,9,10].

According to published studies, the majority of cases of sudden death associated with TB between 1966 and 2000 were due to tuberculous bronchopneumonia (64%) and extensive haemoptysis (30%), with TM being one of the minor causes of death. Due to its subtle onset and varied non specific symptoms, along with a low incidence rate, TM frequently goes undetected antemortem [2]. The antemortem diagnosis of this entity is challenging because it is difficult to collect a sample for Acid Fast Bacilli (AFB) staining or cardiac culture; many patients remain asymptomatic, and it is rarely suspected clinically. Consequently, the majority of *Mycobacterium tuberculosis* cases are discovered incidentally during autopsy [11]. The current series emphasises that there were no specific antemortem cardiac symptoms in all four patients.

Although prior research has indicated that the majority of TB involvement is limited to the pericardium and that the frequency of myocardial TB is approximately 0.14% at autopsy, there are

currently no reliable statistics available regarding its incidence [2]. Various layers of the heart can be involved in TB. A study by Chan ACL and Dickens P, covering cases recorded between 1955 and 2020, revealed that pericarditis accounted for 2-5% of all cases of cardiac involvement in TB, with myocarditis accounting for 0.14-2% of cases and aortitis for 0.3% of all cases [5,12].

Four pathological stages of tuberculous pericarditis are recognised: (1) fibrinous exudation rich in neutrophils, early granuloma formation, and abundance of mycobacteria; (2) serosanguineous effusion with numerous mononuclear cells; (3) absorption of effusion with multiple caseating granulomas, which later leads to thickening of the pericardium and ultimately fibrosis; and (4) constrictive pericarditis due to fibrous scar formation around the heart, encasing it and reducing diastolic filling [1]. Three different ways of myocardial involvement in TB have been described pathologically: caseating nodular (characterised by central caseation), miliary (due to systemic haematogenous spread), and diffuse infiltrative (characterised microscopically by the presence of giant cells and lymphocytes) [5]. In present series, four autopsy cases primarily involved caseating nodular histology. Grossly, these lesions appeared as firm, white nodular masses, giving the impression of an infiltrative tumour [9,13]. Only two out of the four cases in this series showed a gray-white lesion in the myocardial wall. Microscopically, TM is characterised by caseating granulomas exhibiting massive caseation necrosis, surrounded by lymphocytes, epithelioid cells and Langhans giant cells [9,13,14]. Similarly, all the cases in the present series showed TM with caseating granulomas.

The possible differential diagnosis of GM include sarcoidosis, rheumatic fever, Systemic Lupus Erythematosus (SLE), syphilis and fungal infections. However, the current cases did not show naked granulomas as seen in sarcoidosis; no Aschoff bodies associated with rheumatic fever were observed; interstitial mononuclear cell infiltrates with myocardial fibrosis, as well as Libman-Sacks endocarditis of SLE, were not present; special stains were negative for fungi; and the immune status of the cases could not be commented upon as the autopsy notes did not provide that information. Three out of the four cases in the current series exhibited features of dissemination [1,9].

The diagnosis of TM can be very challenging due to the lack of a particular diagnostic approach. The low incidence, late diagnosis, and underreporting have created a knowledge gap among healthcare workers over time [6]. Histopathological findings are the mainstay for diagnosing TM [3,4]. Other techniques may include Ziehl-Neelsen (ZN) staining; however, the positive rate of this stain is only between 20-40% with the current staining methodology [3,5]. Similar findings were reported by Zhang L et al., where out of 44 cases of TM diagnosed following sudden death, only 12 (27%) were positive for ZN staining [3]. The sensitivity of ZN staining is influenced by numerous factors, such as the prevalence and severity of mycobacterial disease in a geographic area, the type of specimen (as tissue containing necrotising granulomas shows a higher positive rate for ZN staining compared to non necrotising granulomas), the number of mycobacteria present in the specimen and the staining technique used [6,7]. In the current study, all four cases were tested for ZN staining, but all were negative for AFB.

Molecular testing via Polymerase Chain Reaction (PCR) techniques can be utilised for diagnostic purposes; however, the sensitivity of PCR techniques stands at only 15-20% [3,8]. Therefore, a negative PCR result cannot rule out TB infection [1,13]. Thus, despite negative PCR results, TM can be corroborated by histomorphology [3,9]. PCR tests for the current autopsy cases could not be performed as the samples were received in formalin. Newer research suggests the use of Endomyocardial Biopsy (EMB) and Cardiovascular Magnetic Resonance Imaging (CMRI) for suspected TM diagnosed in antemortem cases [3].

CONCLUSION(S)

TM is one of the causes of GM, which is uncommon and often fatal, typically presenting with non specific symptoms. In the absence of a clear understanding of diagnostic criteria for cardiac TB, histopathological evaluation remains the primary method for diagnosing TM lesions.

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