Chapter IX

Sudden Death Related to Myocardial Tuberculosis

Valentina Gabbolini*, Anna Laura Santunione and Enrico Silingardi
Department of Legal medicine, University of Modena and Reggio Emilia, Emilia-Romagna, Italy

Abstract

Sudden death is currently described as natural unexpected death occurring within 1h of new symptoms. A frequent cause of sudden death in adults is related to cardiovascular disease. Sudden cardiac death is defined as death due to cardiac causes, and preceded by an abrupt and unexpected loss of consciousness within one hour of the onset of acute symptoms, in an individual who may have or not known pre-existing heart disease. In the young adults, myocarditis is the major cause of sudden unexpected death. Tuberculosis (TB) is still a serious problem for public health, even in highly developed countries. In the latest World Health Organization (WHO) report, TB was responsible for 8.5–9.2 million cases and 1.2–1.5 million deaths (including deaths from TB among HIV-positive people). TB is also more common among men than women, and around 2/3 of cases are estimated to occur among people aged 15–59 years. Tuberculosis has a predilection for the pulmonary system; extrapulmonary manifestation is rare, but around 1-2% of TB patients have cardiovascular involvement (MTB). MTB can present in a miliary or nodular form, occasionally with aneurysm. The infection can reach the myocardium through the blood or the lymphatic system, or as a result of contiguity from pericardium or pulmonary cavity. In the past MTB was hardly ever diagnosed while the person was alive, but now the advancement in cardiac imaging and imaging guided biopsy techniques, lead to a more frequent antemortem diagnosis. Clinically, MTB may be asymptomatic or presenting with different manifestations including intractable ventricular arrhythmias, long QT syndrome, complete heart block and in some rare cases right atrial obstruction, right ventricular outflow tract obstruction, superior vena cava obstruction,

* Correspondence: Valentina Gabbolini, MD, valegabbolini@hotmail.it.
left ventricular aneurysm, aortic regurgitation and heart failure. The MTB average incidence on the total number of autopsies is < 0.3%. A systematic study relative to 13,658 autopsies reported a frequency of 0.14%. MTB represents up to 4% of all TB related deaths and the majority of TB related sudden death. Cases of sudden death from previously undiagnosed MTB have rarely been reported in the literature, and they refer frequently to male subjects. According to the clinical symptoms observed in living patients, the most probable mechanism for sudden cardiac death is cardiac arrhythmias. The autopsy diagnosis of MTB depends largely on the microscopic detection of acid-fast bacilli (AFB) and on mycobacterial culture, but the demonstration of AFB within foci of necrotizing granulomatous inflammation is rare. In recent years, polymerase chain reaction (PCR) amplification for the detection of mycobacterial DNA in formalin-fixed, paraffin-embedded archival tissues has been widely demonstrated in various tissue specimens, including heart, lung, lymph nodes, and other tissues. Differential diagnosis is from other forms of granulomatous inflammations including sarcoidosis and large cell idiopathic granulomatous myocarditis. A proposal of diagnostic criteria may comprise positive TB PCR, positive bacterial culture or acid-fast bacilli isolation from myocardium, since these tests provide definitive diagnosis.

Keywords: Sudden death, tubercular myocarditis, autopsy diagnosis

Introduction

Sudden death is currently described as natural unexpected death occurring within 1h of new symptoms.

In particular sudden cardiac death is defined as death due to cardiac causes, preceded by an abrupt loss of consciousness within one hour of the onset of acute symptoms, in an individual who may have known pre-existing heart disease, but in whom the time and the manner of death are unexpected.

The underlying pathology is usually coronary heart disease in middle-aged and elderly. However, it can also be one of the familial well-defined cardiomyopathies, such as hypertrophic or dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia or long QT syndrome. In the young adults, myocarditis is the major cause of sudden unexpected death. Myocarditis is an inflammatory disease of the myocardium caused by various infections, autoimmune disorders and toxic agents.

Tuberculosis (TB) is still a serious problem for public health, even in highly developed countries. In the latest World Health Organization (WHO) report, TB was responsible for 8.5–9.2 million cases and 1.2–1.5 million deaths (including deaths from TB among HIV-positive people). TB is also more common among men than women, and around 2/3 of cases are estimated to occur among people aged 15–59 years.

The disease is spread in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing. Only few patients infected with Mycobacterium tuberculosis will go on to develop TB disease. The probability of develop TB is much higher among people infected with the human immunodeficiency virus (HIV).

Tuberculosis has the ability to infect any part of the human body, but it has a predilection for the pulmonary system (pulmonary TB); extrapulmonary TB is commonly found in the
pleura, lymph nodes, abdomen and central nervous system. Around 1-2% of TB patients have cardiovascular involvement (MTB).

Cardiac involvement is usually secondary to lesions elsewhere in the body, the pericardium is most commonly involved in cardiac tuberculosis, and according to Rooney et al., tuberculous pericarditis accounts for 11% of all types of pericarditis. Pericardial involvement may result either from direct extension from a mediastinal, pulmonary, or osseous lesion or from retrograde lymphatic spread. Endocardial and coronary artery tuberculosis is exceedingly rare.

Myocardial involvement is rare. The earliest report of myocardial tuberculosis was in 1664 by Maurocordat, a Turkish physician. As late as 1865, Virchow denied the existence of tuberculous nodules in the myocardium. The specific findings of TB in the myocardium are rarely seen and are postulated to be related to a low affinity of M. tuberculosis for the myocardium. The incidence of myocardial tuberculosis in patients died of tuberculosis was <0.3% in a 1935 study and 0.44% in a 1939 study. For the most part, it affects subjects in their youth and it is generally asymptomatic; for this reason, is usually an autopsy diagnosis.

Horn and Saphir described three histological patterns of cardiac TB:

- a nodular type (also known as tuberculoma), varying “from pea to egg size” with central caseation usually affecting the right side of the heart, particularly the right atrium;
- a miliary type of the myocardium complicating generalized miliary disease;
- the uncommon diffuse infiltrative type, usually associated with tuberculous pericarditis, in which the myocardium is diffusely infiltrated by granulation tissue containing giant cells, endothelial cells and lymphocytes.

Three possible routes of spread were postulated: firstly via direct extension from the pericardium or the pulmonary cavity, secondly via lymphatic spread, and thirdly by haematogenous seeding.

The common sites are the right atrium and left ventricle. Right atrial involvement is considered to be related to frequent involvement of the right mediastinal lymph nodes.

The differential diagnosis of myocardial tuberculosis includes granulomatous diseases such as sarcoidosis, idiopathic granulomatous and giant-cell myocarditis, syphilitic gummata, fungal infection, rheumatic fever, rheumatoid arthritis, and metastatic tumors containing giant cells, e.g., Hodgkin disease and osteosarcoma.

### Symptomatology and Diagnosis

The increasing rates of immigration from countries where tuberculosis and multidrug-resistant variants are endemic emphasize the importance of making a prompt diagnosis in cases of tubercular myocarditis.

MTB is hardly ever diagnosed while the person is alive. Clinically, tuberculoma may be asymptomatic or presenting with varied manifestations including intractable ventricular arrhythmias, long QT syndrome, complete heart block, right atrial obstruction, right
ventricular outflow tract obstruction, superior vena cava obstruction, left ventricular aneurysm, aortic regurgitation and heart failure.

Outflow obstruction is an important cause of sudden death in hypertrophic obstructive cardiomyopathy, in particular the obstruction of superior vena cava and the right atrium lead to a progressive deterioration of cardiac function that are detectable with echocardiograms.

The valvular dysfunction tends to present with chronic symptoms such as prostration and dyspnoea and is not been reported to cause sudden cardiac death. Cardiac murmurs may be heard on auscultation. Echocardiograms often demonstrate impaired cardiac output and this usually signifies gradual deterioration of cardiac function.

Although there is an association between pulmonary tuberculosis and venous thromboembolism, in fact deep vein thrombosis and pulmonary emboli have been reported to occur in TB patients without underlying coagulation disorders but the mechanism is not known.

Once the condition is suspected, relevant investigations must be undertaken to exclude viral illnesses, sarcoidosis and malignancies such as lymphoma. Definitive diagnosis of the condition relies on the detection of characteristic histological changes using Ziehl-Nielsen staining.

The cardiac MRI diagnostic imaging is the most important for diagnosis; it is a technique to identify non-invasively and accurately the extension of the interest infarction by this pathology. The myocardial inflammation in fact induces an abnormal signal intensity mode T2 and analysis of sequences late after injection of gadolinium allows to highlight the areas later collection, with localization preferably sub-epicardial or intra-myocardial median. Breton et al. have emphasized the diagnostic importance of MRI in cardiac myocardial TB in the observation of 3 cases. The examination has allowed to highlight a contrast late one or more nodules disseminated without vascular distribution.

Some authors, for the patients with intra-cardiac masses, suggest transthoracic and transesophageal echocardiography as a method of choice to perform myocardial guiding biopsy safe and easy, especially if the right atrium wall, the predominant location of tuberculoma is involved. Endomyocardial biopsy is not a procedure without risk. It is therefore appropriate to reserve it in the event that the other diagnostic procedures have been inconclusive.

## Cases Reports of Sudden Death from MTB

There are very few cases described in the literature of sudden cardiac death rate from MTB and the first to describe this association was Behr et al. in 1977.

In the first case the authors described a case of young man (21 years old) physically fit that died after an episode of syncope. The histological sections showed a caseating granulomas of myocardium and mediastinal lymph nodes, while other organs were not involved, specially the lungs. Because the tubercular bacilli were not demonstrated from the granulomas, the authors made the diagnosis of MTB with mediastinal lymph node involvement based on characteristic histological findings. In this case the mechanism of death was not specified. The second case is another young man who died to ventricular fibrillation and the post-mortem examination showed a MTB. This patient was found in ventricular
Sudden Death Related to Myocardial Tuberculosis

...tachycardia, treated with drugs and electrical cardioversions but he developed ventricular fibrillation and asystole. The patient was treated 5 years prior for tuberculous tenosynovitis. Because the cardiac enzymes were raised, was suspected a myocarditis or infarction and the diagnosis was confirmed at autopsy. In fact were observed two large areas of myocardial necrosis, in the left ventricular wall and in the inter-ventricular septum. Also it was found granulomas in the lymph nodes and the porta hepatis. The other organs were not involved, specially lungs and coronary vessels. Though this case was not classify as sudden cardiac death because the cause of death was known and the death was not unexpected, it suggested that ventricular tachycardia (VT) was induced by MTB or myocardial necrosis. Although it was known that a damage of interventricular septum caused the VT, however the authors didn’t specify which of the two foci of necrosis played a more important role. Finally they showed that the MTB is possible without co-morbid pulmonary or miliary TB, which was not thought possible previously.

In 1984 Wallis at al. described a case of 31 years old Asian man who collapsed and died unexpectedly at work. The postmortem examination showed miliary tubercles in the choroid, lungs, liver, kidneys, lymph nodes and heart. In particular the heart was enlarged and the microscopic examination of the interventricular septum revealed an extensive granulomatous infiltration surrounding but not destroying the conducting tissue. For the authors, the MTB was the most likely cause of death for the abrupt onset of death and for the lack of pulmonary symptoms, and the cause of the sudden death was probably a fatal ventricular arrhythmia or a conduction defect due to extensive disease surrounding the conducting tissue of the heart.

Chan and Dickens reported in 1992, a case of 71 years old Chinese male, who died unexpectedly during a recovery for haematuria. The autopsy showed active caseating tuberculosis with intrapulmonary miliary spread, also the liver and the spleen showed multiple whitish miliary nodules. The histology also showed multiple caseating granulomas in the kidneys, in the bone marrow and also in the heart. The abruptness of death and in the excellent premorbid state justified a sudden death. The authors recognized the cause of death in a fatal arrhythmia due to the position of the granulomas in atrial wall near the sino-atrial node.

In 2000 Dada et al. described a 25 years old fit man who died suddenly during a soccer match. The autopsy demonstrated a fibrinous pericarditis with pericardial effusion. The pericardial fluid was rich in neutrophils, protein and gram-positive bacilli, which were considered to have been postmortem contamination. No acid fast bacilli were seen. The heart show a firm, white, well demarcated nodular lesion with the appearance of an infiltrative tumor involving the posterior wall of the left ventricle; no pathological changes were observed in the valves and coronary arteries. The histological examination showed necrotizing granulomatous inflammation involving the myocardium associated with a fibrinous pericarditis; the acid fast bacilli were not demonstrated. The authors demonstrated the presence of TB from the myocardial specimens using a proteinase K ligase chain reaction technique. This was important because it was the second case demonstrating sudden cardiac death secondary to MTB without evidence of miliary TB and it also highlighted the importance of using molecular techniques to detect TB in samples stained negative for acid fast bacilli.

Biedrzychi et al. described in 2006 a case of 20 years old Asian female that getting off a bus and collapsed to the ground and died. The autopsy showed a single area of fibrosis in the myocardium in the anterior wall of the left ventricle. Endocardium, coronary vessels and
Valentina Gabbolini, Anna Laura Santunione and Enrico Silingardi

Cardiac valves are unremarkable. The histologic examination of the myocardium revealed an area of fibrosis with lymphocytic infiltrate and the Ziehl-Nielsen stain confirmed the presence of acid-fast bacilli in the sections from the myocardium. Lungs, kidneys and liver contained multiple noncaseating granulomas confirming the presence of miliary TB. The authors did not comment on the possible mechanism of sudden cardiac death, but they point out that unlike the other cases, the patient was asymptomatic.

In the same year Silingardi et al. reported a case of sudden cardiac death in a 33 years old Italian woman, in good health, that died suddenly at home. At autopsy the surface of incision of the left ventricular myocardium showed nodules, localized throughout the antero-septal wall and posterior wall and they extended longitudinally from the atrio-ventricular groove toward the apex. Nothing was found in endocardium, valves, coronary tree and pericardium. Also lymph nodes and spleen are infiltrated by nodular formations and pale nodules of small dimension were observed on the surface of the liver. The histological exams of the myocardium showed large cell granulomas, epithelial cells and lymphocytes immersed in a wide context of dense fibrous replacement tissue. The nodules at the hepato-splenic and lymphonodal level showed similar aspects. Some microscopic granulomas were observed in the lungs and the remaining organs were negative. The test for alcohol-acid resistant bacilli was negative. Given the probable tubercular nature of the granulomatous inflammation, the mycobacterial DNA was examined using the nested polymerase chain reaction method that carried out with specific oligonucleotides and was positive for Mycobacterium avium in all samples examined and also for tubercular complex in left ventricle, liver, spleen and kidneys. We postulated that ventricular arrhythmia was the underlying mechanism leading to sudden cardiac death. This was supported by the rapid onset of death and the extensive TB infiltration of the septal conduction system and also by the absence of coronary and valvular pathologies.

In 2009, Amonkar et al. described a case of a 65 years old woman, who was admitted to hospital for diabetic foot and oliguria and died suddenly after 48 h. At autopsy the heart showed multiple lesions measuring 2x2 cm in the postero-septal wall of both ventricles; also the liver showed tiny whitish lesions, the other organs were unremarkable. Histological analysis demonstrated extensive necrosis of the myocardium with surrounding lymphocytes, macrophages and multinucleate giant cells of both Langhans type and also pericardial mononuclear infiltrations and caseating granulomas in the liver. Stains for acid-fast bacilli and fungi were negative; however the authors diagnosed MTB based on the characteristic histological appearance.

The final report was by Kanchan et al. in 2010. They reported a case of a 58 years old diabetic Indian man, who developed sudden onset of chest pain and died on the way to hospital. The internal examination didn’t show lesions of the organs, but the histopathology of the heart revealed a single granuloma of the left ventricular apex. It comprised a central area of caseous necrosis surrounded by epithelioid cells, lymphocytes, plasma cells and Langhans giant cells. Sections from the ascending aorta showed grade III atherosclerosis with narrowing of the coronary ostia. Acid fast bacilli were not demonstrated. The other organs did not show any significant histopathology, and no primary site of infection was demonstrated. The authors excluded the possibility of cardiac sarcoidosis based on the absence of systemic involvement and a non-necrotic granuloma. Also other conditions were excluded based on the medical history. Based on the histopathological findings, the authors postulated that the cause of death could be ventricular arrhythmia originating from either the apical granuloma or from the underlying coronary artery disease.
Pathogenetic Mechanisms

The causes of death resulting from MTB include arrhythmias, cardiac rupture, coronary occlusion, obstruction to pulmonary blood flow leading to fatal hemorrhage, heart failure and impaired myocardial contractility.

Heart failure, an important cause of sudden cardiac death, is most commonly caused by hypertension or ischemic heart disease and frequently occurs in patients with congestive heart failure and dilated cardiomyopathy. For this reason these are possible causes of sudden cardiac death in MTB. However, the link between ischemic heart disease and TB related sudden cardiac death is not clear. In all reported cases the coronary arteries were intact but a minor coronary inflammation or spasms are possible causes of ischemic heart disease.

The most probable mechanism for sudden cardiac death is cardiac arrhythmias because MTB may causes heart blocks and ventricular tachyarrhythmias. Ventricular arrhythmias capable to causing cardiac death are broadly divided into ventricular tachycardia or ventricular fibrillation, which can be caused by asystole. Case reports which demonstrated extensive septal involvements of MTB indicate aberrant conduction as the cause of ventricular tachycardia. Other cases showing ventricular wall necrosis suggest electromechanical uncoupling as the source of ventricular tachycardia.

Autopsy Diagnostic

The diagnosis of MTB depends largely on the microscopic demonstration of acid-fast bacilli (AFB) and on mycobacterial culture, but the demonstration of AFB within foci of necrotizing granulomatous inflammation is rare. Methods for the diagnosis of MTB have improved in recent years, and several molecular techniques have been introduced for clinical use. Of these, polymerase chain reaction (PCR) amplification for the detection of TB in formalin-fixed, paraffin-embedded archival tissues has been widely demonstrated in various tissue specimens, including lung, lymph nodes, and other tissues.

The histopathological diagnosis of TB is defined as ‘a chronic granulomatous inflammation, suggestive of tuberculosis’, but histopathologic features of chronic granulomatous inflammation can be found in various conditions and diseases other than TB, such as foreign body reaction, fungal infection, sarcoidosis, leprosy and brucellosis. For this reason AFB stain, TB tissue culture and TB-PCR should be performed to enable a definitive diagnosis of TB.

In terms of the speed of diagnosis, the TB-PCR method is advantageous because sensitivity of the Ziehl-Nielsen stain for AFB is low and bacterial culture for TB is protracted.

A Proposal of Diagnostic Criteria

In the diagnosis of myocarditis, a big step forward was made with the advent of the Dallas criteria in 1986 that the demonstration of lymphocyte or monocyte infiltrates with or without necrosis of myocytes would be sufficient to make the diagnosis of myocarditis, there
isn’t equally consent for the diagnosis of tuberculosis myocarditis. For this reason it is important defined a common set of criteria in order to make diagnosis of MTB. Liu et al. have recently proposed a system of diagnostic criteria, divided into major and minor, as is showed in the following table.

**Table 1.**

<table>
<thead>
<tr>
<th>MAJOR CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR identification of tuberculous DNA extracts from myocardial samples</td>
</tr>
<tr>
<td>Positive tuberculous culture from myocardial samples</td>
</tr>
<tr>
<td>Positive acid-fast bacilli from myocardial samples</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MINOR CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive inflammatory cell infiltrates or necrosis in myocardial samples</td>
</tr>
<tr>
<td>Positive granulomas in myocardial samples</td>
</tr>
<tr>
<td>Military tuberculosis in one or more extra-cardiac organs</td>
</tr>
<tr>
<td>Imaging evidence of myocardial tuberculosis, e.g cardiac magnetic resonance</td>
</tr>
</tbody>
</table>

Modified from Liu et al.

Major criteria would comprise of positive TB PCR, positive TB culture or acid-fast bacilli isolation from myocardium, since these tests provide definitive diagnosis. The presence of any one of these criteria would demonstrate the presence of TB in the myocardium thus suggest definitive diagnosis. Minor criteria may include inflammatory cell infiltration and granuloma within the myocardium, each of these is suggestive but non diagnostic of TB myocardium.

The importance of MRI has recently been pointed out by Khurana et al. However, although CMR is a useful tool at demonstrating evidence of myocardial inflammation, this is not specific to TB myocardium, and for this reason, CMR imaging of myocardial inflammation is a suitable minor criterion.

**Conclusion**

Although there are only a few cases reported in the literature, MTB is associated with sudden cardiac death. The majority of patients were asymptomatic before death.

MTB can present in a miliary or a nodular forma, occasionally with aneurysm and the infection can reach the myocardium thorough the blood or the lymphatic system, or as a result of contiguity with mediastinic lymph nodes.

The diagnosis of TB is favored by the histologic demonstration of central caseation, evidence of typical tuberculous lesions in other organs and, infrequently presence of acid-fast bacilli. This emphasizes the role of applying molecular biology techniques to diagnose MTB. In particular, DNA amplification (PCR) on formalin-fixed paraffin-embedded histological samples is currently considered a more sensitive and specific method.
The underlying mechanism of these sudden cardiac deaths was probably cardiac arrhythmias. The absence of coronary and valvular pathologies and the typical circumstances of death in the cases reported, supported this diagnosis.

The diagnosis antemortem of MTB is difficult and rare but it should be suspected in patients presenting with arrhythmias who could have been exposed to tuberculosis.

If the clinical suspicion is strong and the adjunctive imaging, such as a serial late gadolinium-enhanced cardiac magnetic resonance imaging, is suggestive, an early endomyocardial biopsy is indicated. Some authors suggest a transesophageal echocardiography can be a superior method to make biopsy safe and easy, especially if the right atrial wall (the predominant location of tuberculoma) is involved.

References


WHO report 2011, Global tuberculosis control.