RESEARCH ARTICLE

A RARE CASE OF CARDIAC TAMPOONADE DUE TO RIFAMPICIN-RESISTANT TUBERCULOSIS: A REAL DIAGNOSTIC AND THERAPEUTIC CHALLENGE

Mohamed El Jamili, Gansé Ismael, Ali Laalou, Safaa Azmoun, Sara Bellabyad, Hayat Idrissi, Elmassraoui Joumana, Phany Issanga, Çamara Mamady, Cornelly Ahouissoussi, Saloua Abassi, Benzarouel Dounia, Fatima-Ezzara Hazmiri, Nabila Soraa, Saloua El Karimi, Mustpha Elhattaoui and Gansé Ismael

1. Departement of Cardiology, Errazi Hospital, Mohammed VI University Teaching Hospital, Marrakech, Morocco.
2. Departement of Anatomopathology, Errazi Hospital, Mohammed VI University Teaching Hospital, Marrakech, Morocco.
3. Departement of Microbiology, Errazi Hospital, Mohammed VI University Teaching Hospital, Marrakech, Morocco.

Abstract

Pericarditis is a rare manifestation of tuberculosis. We report the case of a 35-year-old woman admitted for clinical tamponade. The echocardiogram revealed a pericardial effusion of great circumferential abundance with significant respiratory variations and a bilateral pleural effusion of average abundance on chest X-ray. The patient underwent emergency pericardial drainage. The initial tuberculosis assessment was negative. The culture of the liquid was positive after 8 days Revealing Rifampicin-Resistant tuberculosis (RR-TB). Therefore, examination of the pericardial fluid is useful in the diagnosis of pericarditis due to RR-TB. The patient was put on a special treatment regimen after consensus, which yielded satisfactory clinical improvement. Our findings suggest that though pericardial tuberculosis remains a rare disease, it is important to consider it as an etiological diagnosis, especially in endemic countries because it’s poor therapeutic prognosis. Early diagnosis would allow better management of these cases in order to limit cases of resistance.

Introduction

Globally, in 2018, approximately 10.0 million people were infected with TB. The African region recorded 24% of new cases. In Morocco, an incidence of 36,000 cases was documented the same year according to the WHO (2019).

TB accounts for <5% cases of pericardial disease in developed world, yet is the cause of 50-70% of cases in the developing world (Chhina et al., 2013). Early treatment of pericarditis due to tuberculosis can be life-saving and it requires a fast and accurate diagnosis of disease, but this frequently can be difficult (Johari et al., 2019).

Corresponding Author: Mohamed El Jamili
Address: Departement of Cardiology, Errazi Hospital, Mohammed VI University Teaching Hospital, Marrakech, Morocco.
Multidrug Resistant Tuberculosis (MDR-TB) has spread to most regions of the world and represents a serious threat to the success of the struggle against tuberculosis (Zellweger, 2011).

The existence of Rifampicin-Resistant Tuberculosis (RR-TB) is a serious public health problem with a prevalence of 9-10.3% in Ethiopia and 12.1% Nigeria (Arega et al., 2019).

Here, we report the case of isolated RR pericardial tuberculosis revealed by a pericardial tamponade. This report illustrates the importance of a complete etiological investigation for any case of pericarditis in a region where tuberculosis is endemic, like Morocco.

Case Report:
A 35-year-old woman of low socioeconomic status, with two months history of low grade fever, breathlessness and significant weight loss was admitted to clinical tamponade in the Department of Cardiology of the Mohamed VI University hospital center of Marrakech. There was no past history of diabetes, heart disease or tuberculosis.

He onset of symptoms dated back two weeks with the onset of an atypical chest pain worsening on deep inspiration, without referred pain, associated with NYHA stage II dyspnea occurring during exertion and a productive cough with whitish sputum. The patient reported fever and night shivers.

Upon consulting a general practitioner she was placed on antibiotic treatment and iron supplementation.

The clinical course was marked by the persistence of the same clinical symptomatology with a worsening of the dyspnea which had reached NYHA stage III and eventually, stage IV (shortness of breath on exertion associated with orthopnea).

At admission, the patient was conscious but presented with haemodynamic and respiratory instability with a respiratory rate of 45 cpm and tachycardia with a heart rate of 150 cpm. BP was 110/67 mmHg, O₂ saturation at 96% in ambient conditions and there was no coldness of the extremities.

On physical examination, the palpebral conjunctiva were pale; on cardiac auscultation, the normal heart sounds were muffled without additional sounds. There was a slight decrease in vocal fremitus at the base of thorax and no signs of right or left heart failure.

A twelve-lead electrocardiogram documented sinus tachycardia, diffuse micro voltage, diffuse negative T waves and signs of electrical alternation.

Transthoracic echocardiography (Fig. 1) was performed and the result revealed a large and abundant pericardial effusion with signs of cardiac tamponade (with RV collapse during diastole and significant respiratory variations); therefore, pericardiocentesis was performed urgently with 500 mL of fluid initially collected and eventually, a total of 3 litres of serohematic fluid with the presence of fibrinous deposits:

1. The initial biological evaluation revealed: normochromic inflammatory anemia at 9.3 g/dl, neutrophile-predominant hyperleukocytosis of 11980 and lymphopenia. C-reactive protein was elevated, 122 mg/L and the sedimentation rate was 63
2. As part of the etiological assessment (Table 1):
3. We’d collected a citrine yellow liquid, lymphocyte-dominant exudate
4. evaluation of tuberculosis: Search for bacilli in the sputum was negative, the Genexpert ® was negative in the sputum and in the fluid. The QuantiFERON-TB Gold In-Tube assay was positive. The Tuberculin skin Test (TCT) was not performed; LDH
5. hepatic, syphilitic and HIV serologies were negative
6. thyroid assay returned negative, phosphocalcic and renal assays were normal, LDH returned to normal
7. In addition, the search for a neoplastic pathology was negative except for the tumor marker ca125 which, in isolation, had no predictive value
8. sputum, urine and stool culture did not reveal any growth of any identified pathogen

Table 1: Result of laboratory test.
Complete blood count Biochemistry Others
| Hemoglobin | 9.3 g/dL | Na | 141 mmol/L | Quantiferon Gold | positif |
| Leucocyte count | 11.9x10⁹ /L | K | 4.1 mmol/L | BK in sputum | negatif |
| Platelet count | 563x10⁹ /L | Cl | 99 mmol/L | |
| Differential WBC count | Urea | 0.13 g/L | Liquid |
| Hemoglobin | 9.3x10⁹ /L | Creatinine | 4.2 mg/L | Pericardial fluid | references value |
| Lymphocytes | 0.63x10⁹ /L | Bilirubin | 5 umol/L | Appearance | clear |
| Monocytes | 0.77x10⁹ /L | ALT | 41 U/L | Color | pale yellow |
| Eosinophils | 0.02x10⁹ /L | AST | 32 U/L | With Blood Cell count | 160 cells/microL |
| Inflammatory markers | ALP | 87 U/L | Red Blood cell count | None |
| ESR | 63 mm | GGT | 54 U/L | Protein | 5.5 g/dL |
| CRP | 122 mg/L | Protein | 59.4 g/L | Cytology | No abnormal cell |
| | | Albumin | 26.1 g/L | Culture | MBT |
| | | Calcium | 64 mg/L | Gram Stain | no |
| | | | | | organisms seen |
| | | | | | Serologie |
| | | | | | TSH | 1.1 mUI/L | Antibiotic sensibility | Rifampicin |
| | | | | | HIV antibody | negatif | |
| | | | | | Hepatic serology | negatif | |
| | | | | | syphilitic serology | negatif | |
| | | | | | Serum iron | 0.18 mg/L | CEA | 1.83 ng/mL |
| | | | | | serum Ferritine | 307 ng/mL | CA 15.3 | 18.5 UI/mL |
| | | | | | Serum iron | 199 UI/L | CA125 | 294 UI/mL |
| | | | | | Serum iron | 199 UI/L | CA19.9 | 7 UI/mL |

CRP: C-reactive Protein; ESR: Erythrocyte Sedimentation Rate; HI: Human Immunodeficiency Virus; WBC: White Blood Cell; CEA: Carcinoembryonic Antigen; CA: Carcinome Antigen; MBT: Mycobacterium Tuberculosis

Fig. 1:- Parasternal long axis ultrasound section showing the anterior and posterior pericardial effusion.
The initial management consisted of an emergency pericardiocentesis which improved the vital prognosis of the patient with a marked clinical improvement of dyspnea and tachycardia.

The patient was initially put on antibiotic therapy based on amoxicillin clavulanic acid 1g three times a day per os.

**At 8 days of hospitalization:**
The clinical evolution was marked by a persistence of NYHA stage II dyspnea and on the lab tests, inflammatory assessment remained positive and on the ultrasound a pericardial effusion which was reconstituted. A small thoracotomy to create a pleuro-pericardial window was performed in the operating room under general anesthesia. At the opening, we noted the presence of microadenopathies along the mediastinal chain and a biopsy of the pericardium was performed (Fig. 2). A pathology study revealed the presence of giganto-epithelioid follicles with signs of necrosis thus confirming the diagnosis of pericardial tuberculosis (Fig. 3).

The culture on Lowenstein Jensen medium showed rough and buff colonies evoking Mycobacterium tuberculosis (M. tuberculosis) after 8 days of incubation and was confirmed by rapid acid staining and biochemical tests revealing a strain resistant to rifampicin. After the advice of pulmonologists and infectiologists, the patient was first put on ERIPK4 (= ethambutol/isoniazid/pyrazinamide/rifampicin) 1 tablet/day. A discussion was conducted with the doctor responsible for the national tuberculosis control center so that the patient could be followed up in a center close to her place of residence with the molecules ERI-PK4 + Cycloserine. The patient was also placed on a steroid regimen, oral prednisolone 60 mg once per day.
Fig. 3: Patient's chest and abdominal CT scan after pericardial puncture showing thickening of the pericardium reflecting pericardial constriction.

Fig. 4: Granuloma composed of giant Langhan cells, histiocytes, epithelioid cells (HEX20).
Discussion:

For most of recorded history, tuberculosis has been a problem of enormous dimensions worldwide—and it still is. Extrapulmonary tuberculosis presents more of a diagnostic and therapeutic problem than does pulmonary tuberculosis (Hopewell et al., 2016).

Pericardial Tuberculosis (TB) is a rare presentation of extrapulmonary TB. Extrapulmonary tuberculosis usually develops in 20% of patients with TB infection. It has been estimated that around 1-4% incidence of TB pericarditis commonly occurs via dissemination of lung, spine, sternum, mediastinal lymph node, as well as during milliary infection (Khandaker et al., 2010).

Tuberculous pericarditis is a serious form of extrapulmonary TB associated with substantial morbidity (i.e., cardiac tamponade and constrictive pericarditis) and death during treatment for TB. Tuberculosis is said to be the most frequent cause of constrictive pericarditis in Africa and Asia (Mayosi, 2009).

Tuberculous pericarditis is estimated to occur in 1% to 2% of instances of pulmonary tuberculosis (Fowler, 1991).

In developed countries, TB-related pericardial disease is uncommon (<1% of extrapulmonary TB) and cases complicated by life-threatening cardiac tamponade are extremely rare (Houston and Macallan, 2014).

The clinical manifestations of tuberculous pericarditis are wide-ranging and varied. While chest pain, cough and dyspnea are common, non-specific constitutional symptoms, including fevers, night sweats, weight loss and fatigue, may also arise (Mayosi et al., 2005). In some cases, it can be presented with chronic cardiac compression mimicking heart failure or may be presented acutely with cardiac tamponade (Wallrauch et al., 2010). This patient was admitted with symptoms mimicking heart failure. The patient complained of a progressive aggravation of her dyspnea evolving since one month admitted for cardiac tamponade requiring an emergency pericardiocentesis.

Active pulmonary tuberculosis and pleural effusion can be observed in 30% of cases of tuberculous pericarditis while 90% of the cases present characteristics of active pulmonary tuberculosis (Mayosi et al., 2005).

Our patient presented a pleural effusion syndrome clinically which was confirmed by radiological explorations.

The incidence of tuberculous pericarditis is increasing with the advent of the AIDS pandemic. Tuberculosis accounts for up to 4% of acute pericarditis and 7% of cardiac tamponade. The mortality rate of tuberculosis still ranges from 14-40% (Prasad et al., 2018). Tuberculous pericarditis is a potentially lethal condition. The pericardial effusion is mainly due to hypersensitivity to tubercular protein (Wanjari et al., 2009).

The emergence and spread of Multidrug-Resistant Tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) are a major medical and public problem threatening the global health.
MDR-TB is ubiquitous and the number of cases appears to be gradually increasing. Globally in 2018, approximately 3.4% of new cases and 18% previously treated cases had MDR-TB/RR (WHO, 2019). MDR-TB, defined as tuberculosis caused by strains of Mycobacterium tuberculosis (MTB) resistant to the two most important antituberculous drugs – isoniazid and rifampicin – carries a poor prognosis, a high mortality rate and treatment success rates as low as 65% (Weiss et al., 2014).

According to the Moroccan Ministry of Public Health, in 2015, there were 160 MDR-TB cases out of 30,636 tuberculosis cases registered, therefore 0.52%. A diagnosis of tuberculous pericarditis requires analysis of pericardial fluid or tissue. Therefore, routine testing of all patients with TB is widely recognized as the most appropriate surveillance approach for monitoring trends in drug resistant TB (Snider et al., 1985). The development of molecular techniques, in particular GeneXpert, has not only made it possible to make a much faster diagnosis, with relatively good sensitivity and specificity and dependent on the type of sample, but also to rapidly detect any resistance to rifampicin and to isoniazid (Prasad, 2010). After eight days of liquid culture, the laboratory confirmed the presence of mycobacterium tuberculosis with a strain resistant to rifampicin.

The GenoType MTBDR plus (Hain Lifescience GmbH, Nehren, Germany) is a molecular line probe assay containing probes specific for M. tuberculosis complex, as well as probes for common Rifampin (RIF) resistance-conferring mutations and a subset of the mutations conferring resistance to Isoniazid (INH) (Ling et al., 2008).

We were unable to perform this specific molecular test, but a sensitivity test to the 4 first-line anti-tuberculosis drugs, whose rifampicin showed resistance to rifampicin.

Note that only the QUANTIFERON-GOLD test was positive outside the culture of the pericardial fluid. No other etiological evaluation guided us with certainty towards pericardial tuberculosis. The diagnosis is therefore purely etiological.

Treating resistant TB is difficult, complicated and requires experience and skill. Treatment can be standardized or individualized. Conventional regimen takes up to 24 months but recently shorter regimen of up to 12 months was introduced in specific subset of MDR-TB/RR-TB patients (Prasad et al., 2018).

In the absence of universal accessibility to early diagnostic tests characterizing the nature of drug resistance, the addition of drugs such as cycloserine or linezolid to a diet including aminoglycosides, fluoroquinolones, ethionamide and clofazimine is recommended for the empirical treatment of MDR-TB, either suspected or proven by an Xpert MTB/RIF test (Mullerpattan et al., 2017).

We therefore opted for our patient to add cycloserine to the first line of treatment, including (ERIPK4 = ethambutol/isoniazid/pyrazinamide/rifampicin).

A few reviews on the use of corticosteroids have shown that it reduced the mortality rate and re-accumulation of fluid after 18-24 months of follow-up. However, the drawback of the reviews is that, the small sample size renders the results to be inconclusive (Ntsekhe et al., 2003).

The short-term clinical status of our patient is marked by the recurrence of pericardial effusions with the onset of pericardial constriction which required a pleuropapercardial window and the introduction of low-dose corticosteroids. The patient was reviewed as part of her follow-up with two episodes of dyspnea linked to effusion of pericardial fluid in the pleura of low to medium abundance. She was referred to pulmonologists for follow-up with a good clinical prognosis.

**Conclusion:**

Tuberculosis remains an endemic disease in Morocco. Pericardial effusions are well documented, but cases of cardiac tamponade are rare. Even if the etiological evaluation of any pericardial effusion includes the systematic search for tuberculosis, emphasis must also be placed on the sensitivity of the strains and strict adherence to treatment in order to avoid cases of resistance to treatment since the treatment of RR-TB is extremely complex. The case described here reminds us that the presence of rifampicin resistance is a serious challenge. It is important to consider it as an etiological diagnosis, especially in endemic countries because it has a poor therapeutic prognosis. Early diagnosis would allow better management of these cases in order to limit cases of resistance. To prevent the
development of highly drug-resistant TB, the approach should go in the direction of finding contextualized solutions to limit the impact and spread of MDR/RR TB.

Conflict of Interests:
There are no conflicts of interests for the development of this publication.

Ethical Standards:
Informed consent was obtained from the patient’s parents for the publication of this case.

References:
1. Arega, B., F. Menbere and Y. Getachew, 2019. Prevalence of rifampicin resistant Mycobacterium tuberculosis among presumptive tuberculosis patients in selected governmental hospitals in Addis Ababa, Ethiopia. BMC Infect. Dis., 19: 307-307. DOI: 10.1186/s12879-019-3943-1
2. Chhina, D., R. Gupta and B. Mohan, 2013. Early diagnosis in an unusual presentation of tubercular pericarditis- A case report. Asian Pacific J. Tropical Dis., 3: 161-163. DOI: 10.1016/S2222-1808(13)60063-8
3. Fowler, N.O., 1991. Tuberculous pericarditis. JAMA, 266: 99-103. DOI: 10.1001/jama.1991.03470010103039
4. Hopewell, P.C., M. Kato-Maeda and J.D. Ernst, 2016. Tuberculosis. In: Murray and Nadel’s Textbook of Respiratory Medicine, Broaddus, V.C., R.J. Mason, J.D. Ernst, T.E. King, Jr. and S.C. Lazarus (Eds.), Elsevier, pp: 593-628.e20.
5. Houston, A. and D.C. Macallan, 2014. Extrapulmonary tuberculosis. Medicine, 42: 18-22. DOI: 10.1016/j.mpmed.2013.10.008
6. Johari, M.I., A.W. Ramli, F.M. Lawi, M.A.H. Bin Fouzi and K.P.S. Suardi, 2019. A rare case of purulent pericardial TB. Cureus, 9:e5356-e5356. DOI: 10.7759/cureus.5356
7. Khandaker, M.H., R.E. Espinosa, R.A. Nishimura, L.J. Sinak and S.N. Hayes et al, 2010. Pericardial disease: Diagnosis and management. Mayo Clinic Proc., 85: 572-593. DOI: 10.4065/mcp.2010.0046
8. Ling, D.I., A.A. Zwerling and M. Pai, 2008. GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: A meta-analysis. Eur. Respiratory J., 32: 1165-1174. DOI: 10.1183/09031936.00061808
9. Mayosi, B., 2009. Tuberculous Pericarditis and Myocarditis in Adults and Children. In: Tuberculosis, Schaaf, H.S., A.I. Zumla, J.M. Grange, M.C. Raviglione and W.W. Yew et al (Eds.), Elsevier, pp: 351-60.
10. Mayosi, B.M., L.J. Burgess and A.F. Doubell, 2005. Tuberculous pericarditis. Circulation, 112: 3608-3616. DOI: 10.1161/CIRCULATIONAHA.105.543066
11. Mullerpattan, J.B., C. Nikam, U. Sharma, C. Rodrigues and L.M. Pinto, 2017. Rifampicin-resistant tuberculosis: what is the best initial empiric regimen in Mumbai, India? Eur. Respir. J., 50: 1602182-1602182. DOI: 10.1183/13993003.02182-2016
12. Ntsekhe, M., C. Wiysonge, J.A. Volmink, P.J. Commerford and B.M. Mayosi, 2003. Adjuvant corticosteroids for tubercular pericarditis: Promising, but not proven. QJM, 96: 593-599. DOI: 10.1093/qjmed/hcg100
13. Prasad, R., 2010. Multidrug and Extensively Drug-Resistant TB (M/XDR-TB): Problems and solutions. Indian J. Tuberc., 57: 180-191.
14. Prasad, R., N. Gupta and A. Banka, 2018. Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis:Principles of management. Lung India, 35: 78-81. DOI: 10.4103/lungindia.lungindia_98_17
15. Snider, D.E., G.D. Kelly, G.M. Cauthen, N.J. Thompson and J.O. Kilburn, 1985. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. Am. Rev. Respir. Dis., 132: 125-132.
16. Wallrauch, C., E. Brunetti, T. Heller and R.J. Lessells, 2010. Tuberculosis pericarditis with cardiac tamponade: Management in the resource-limited setting. Am. J. Tropical Med. Hygiene, 83: 1311-1314. DOI: 10.4269/ajtmh.2010.10-0271
17. Wanjari, K., V. Baradkar, M. Mathur and S. Kumar, 2009. A case of tuberculous pericardial effusion. Indian J. Med. Microbiol., 27: 75-77. DOI: /10.4103/0255-0857.53216
18. Weiss, P., W. Chen, V.J. Cook and J.C. Johnston, 2014. Treatment outcomes from community-based drug resistant tuberculosis treatment programs: A systematic review and meta-analysis. BMC Infect. Dis., 14: 333-333. DOI: 10.1186/1471-2334-14-333
19. WHO, 2019. Global tuberculosis report. World Health Organization.
20. Zellweger, J.P., 2011. La tuberculose multirésistante: Extension, menace et solutions. Revue Maladies Respiratoires, 28: 1025-1033.