

Miliary tuberculosis: the role of necropsy studies

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SUMMARY

This case study of generalized miliary tuberculosis in a Brazilian man without AIDS is reported in order to emphasize the role of histopathological study for diagnosis. We comment on a recent Indian study involving 40 cases of surgical and necropsy specimens in which the diagnosis of tuberculosis was made, as well as a previous Brazilian case report. The authors believe

that non-specialists should be better informed about the possibility of miliary tuberculosis, which involves clinical diagnostic challenges. Despite limitations, minimally invasive necropsy may be an alternative to elucidate causes of death in low-income countries.

Keywords: miliary tuberculosis, necropsy.

INTRODUCTION

Tuberculosis (TB) is one of the ten major causes of death worldwide and 1.8 million are estimated to die from this disease, including 0.4 million among individuals with HIV; and over 95% of TB deaths occur in low- and middle-income countries [1]. In 2015, 10.4 million new cases of TB were estimated worldwide - 56% men, 34% women and 10% children; and 11% of the new cases were HIV-positive individuals [1]. India, Indonesia, China, Nigeria, Pakistan and South Africa accounted for 60% of cases [1]. As 30% of the world population is infected and latent TB infection (LTBI) is the source of most future cases of TB in industrialized countries, one must diagnose and treat LTBI [2]. Italia with a 60 million population had a TB incidence including HIV: 3.5 thousand; incidence of HIV-positive: 0.21 thousand; and multi-drug resistant TB (MDR-TB): 12 thousand [1]. Brazil's population is 208 million; HIV-negative TB mortality: 5.5 thousand; HIV-positive TB

mortality: 2.2 thousand; TB incidence: 84 thousand; HIV-positive TB: 13 thousand; and MDR-TB: 2.3 thousand [1]. Difficulties to control tuberculosis in developing countries have increased following the growing number of people with malnutrition and AIDS [1, 3, 4]. Currently, there is no vaccine that is effective in preventing TB disease in adults, either before or after exposure to this very ominous infection [1]. In addition, TB active may show nonspecific clinical manifestations if occurring in the miliary form, which poses additional challenges to clinical diagnosis. Disseminated TB often causes nonspecific changes in laboratory tests, and may not be evident on chest x-ray [3]. Interferon gamma release assays tests have a higher sensitivity and specificity than Mantoux to detect LTBI, but both do not solve challenges of unsuspected active TB [1, 2]. So, miliary TB has been detected by invasive procedures, or necropsy [3, 5, 6].

CASE REPORT

A 56-year-old woman presented with a seven-day history of left pleuritic pain irradiating to dorsum, and progressive dyspnea; as well as two

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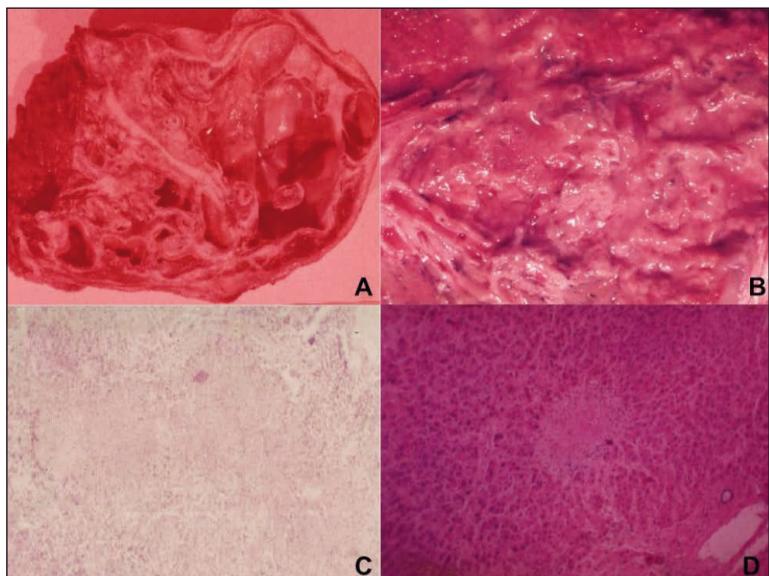
months duration of cough productive of mucoid or clear sputum, which was followed by hemoptysis three days before the admission. Her medical history was significant for tobacco smoking (30 pack-years) and chronic productive cough, in addition to previous contact with a grandmother with diagnosis of TB. Physical examination revealed body mass index: 15 kg/m²; blood pressure: 90/70 mmHg; heart rate: 120 bpm; body temperature: 38.5°C; pale mucosae; cyanosis of extremities; tachypnea; fine and medium crackles at anterolateral upper left chest and in both lung bases; moderate hepatomegaly, discrete splenomegaly; and absence of lymph node enlargement. Chest radiography revealed multiple bilateral foci of parenchymal condensations suggestive of bronchopneumonia more conspicuous at upper third of the left lung and in the lung bases. Laboratory routine showed anemia; neutrophilia with left deviation; elevated erythrocyte sedimentation rate; low albumin; hyperglycemia; hyponatremia; and high levels of liver tests. The search of mycobacteria in sputum, and the cultures of blood and sputum were negative. The Mantoux test, and serological test for HIV, invasive fungi, and syphilis were negative. Her immediate clinical course was characterized by gradual worsening of dyspnea, elevated fever, supraclavicular retraction, and development of irreversible circulatory shock, despite of the intensive care support. The

complete necropsy was performed to detect the cause of death. Worthy of note were the multi organ features classically described in the circulatory event. But the most remarkable findings were observed in the lungs, characterizing the diagnosis of chronic obstructive pulmonary disease (COPD) in association with residual cavity of TB (Figure 1A-B) and acute pneumonia (Figure 1C); in addition to miliary dissemination to the liver (Figure 1D), spleen and adrenals. Furthermore, cultures for *M. tuberculosis* in the specimens of pulmonary tissue were positive. Miliary lesions were not found in the central nervous system, kidneys, and bone marrow. Without a complete or a minimally invasive necropsy (MIN) procedure, the case study herein described of miliary dissemination from the pulmonary source could not be confirmed; moreover, the extra thoracic foci of lymphohematogenous spreading would stay undetected [6].

■ DISCUSSION

The patient was a moderate tobacco smoker with COPD, two major factors of aberrant inflammatory response and of chronic subclinical infections [2]. Depending on the integrity of immune system, latent TB infection represents a protective condition of host to avoid the spread of the

Figure 1 - (Gross aspects of the lung samples) A: residual anfractuouse cavity and bronchiectasis surrounded by fibrotic sequels at the left upper lobe; and B: presence of parenchymal consolidation related to pneumonia. C: photomicrography of lung specimen showing features of the pneumonia (H & E, low power magnification); and D: photomicrography of liver sample showing a TB granuloma with caseous necrosis, macrophage infiltrate, and a multinuclear giant cell (H & E, medium power magnification).



agent. However, with lower levels of defenses, residual low-viable bacilli can disseminate from the granuloma to the entire organism [2]. Other concern is about identification of *Mycobacterium tuberculosis* after using fluoroquinolones in cases of unsuspected TB, because the agent is sensitive to the drug [4]. Dissemination predominates among patients with AIDS, renal insufficiency, diabetes mellitus, alcoholism, malnutrition, smoking, COPD, hematological disorders, malignancies, immunosuppressive treatments, and individuals of age groups <5 years and >75 years [1-5]. Nutritional status and parameters of acute phase response (APR) were evaluated in 29 adult patients with AIDS [7]. Protein-energy malnutrition (PEM) was characterized by body mass index inferior than 18.5 kg/m², and height-creatinine index lower than 70%. PEM (77.8 vs 40%) and pulmonary TB (44.4 vs 9.5%) were more frequent in the APR-positive group [7]. The HIV-positive patients with acute systemic response to invading pathogens presented worse nutritional status than the group of APR-negative patients [7]. Dos Santos et al. described the necropsy findings of an old Brazilian man with disseminated miliary TB involving the lungs, lymph nodes, liver, pancreas, bone marrow, spleen, adrenals, prostate, and kidneys [3]. There was chronic granulomatous inflammatory process and caseous necrosis, in addition to *M. tuberculosis* [3]. Worthy of note, the chest radiograph showed inflammatory infiltrate in the middle lobe; whereas necropsy revealed scattered miliary nodules in both lungs and pleura; and nodule at the left upper lobe with caseous necrosis, associated with apical adhesions [3]. The HIV-negative old patient was an alcohol abuser and malnourished male with antecedent of COPD, and unsuspected prostate cancer [3]. He presented laboratory changes indicative of APR - hyponatremia, hyperglycemia, hypoalbuminemia, elevated globulins, and accentuated thrombocytopenia and leukopenia [3]. The authors emphasized the important role of the necropsy evaluations to establish the consistent diagnoses of miliary TB [3]. Gupta et al. analyzed the histopathological pattern of pulmonary TB in 33 autopsy cases in which sections from both lungs were submitted and 7 surgically resected cases including 4 lobectomies, 2 pneumonectomies, and one lung tissue for frozen section [5]. The age range of patients was from 20 to 75 years, with a

mean age of 41 years; the majority of them in the third decade (40%), and with high predominance among males (92.5%) [5]. Tubercular consolidation, miliary TB, and empyema were detected in 23 cases; miliary TB was observed in 10 individuals (25% of the cases), and especially in patients presenting with dissemination of disease from the lungs to distant organs [5]. The miliary form is a potentially fatal manifestation due to the lymphohematogenous dissemination; and the diagnosis is very challenging because of variable symptoms as well as nonspecific images of radiographs [5]. Undiagnosed TB represented a very elevated rate of the active cases (87.8%) in necropsy studies; the authors highlighted the previously undetected cases of pulmonary TB that were diagnosed *post mortem*, and of patients with late complications or sequelae of this preventable and curable chronic infectious disease [5]. Castillo et al. evaluated the role of MIN in 30 *post mortem* studies done in Mozambique, and concluded that the samples were adequate for histological and microbiological analysis, characterizing the microorganisms causing the death in a significant number of cases [6]. More than two thirds (63.3%) of patients were HIV positive, and three among these (15.7%) had associated TB; moreover, in two of them the diagnosis of miliary TB was established [6]. The authors emphasized the validity of MIN to detect microbes putatively causing the death. Because infectious diseases constitute a significant proportion of the commonest causes, the procedure might be a good alternative for complete necropsy in the developing countries [6].

■ CONCLUSIONS

The cavity at the left upper lobe was not shown by the plain chest radiography, but could be detected before death on imaging studies by the modern multislice computed tomography. Undiagnosed cases may constitute elevated rate of active tuberculosis diagnosed at necropsy. Histopathological and necropsy studies are more often necessary to confirm cryptic or protean tuberculous infections, mainly in cases of chronic lymphohematogenous miliary spreading. Complete autopsy study is the best diagnostic tool in cases of unclear infectious deaths; however, minimally invasive tissue sampling may be more easily authorized by families.

Further researches should establish the cost-effectiveness of MIN in low income countries.

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

Funding source. There were no sources of funding that could have influenced the outcome of this work.

ACKNOWLEDGEMENTS

The authors would like to thank Almir José Batista, the official photographer of the Armed Forces Hospital, in Brasília-DF, Brazil for the images that illustrate the present case study.

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