

Geriatric patient with acute respiratory distress syndrome attributed to miliary tuberculosis

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SUMMARY. For the last three decades miliary tuberculosis (MT) has been observed in adolescent and elderly patients with an increasing prevalence. The development of acute respiratory distress syndrome (ARDS) on the background of MT is a complication that may be difficult to recognize as it may not be thought of, even though its frequency is not negligible. The mortality of the syndrome in this situation is very high and negative prognostic factors are hyponatraemia, hypoalbuminaemia, elevated blood levels of transaminases and older age. This report describes the case of an immunocompetent 78 year-old woman who presented with MT and later meningitis. Despite the administration of appropriate antituberculosis treatment the patient's condition deteriorated rapidly, with significant hypoxaemia and development of new opacities on the chest X ray that were consistent with ARDS. *Mycobacterium tuberculosis* was detected in the bronchoalveolar lavage (BAL), gastric contents and cerebrospinal fluid (CSF), which was reported sensitive to all primary antituberculous drugs. The patient's clinical condition worsened and she succumbed two days later from progressive ARDS. The development of ARDS in the setting of MT may have an adverse outcome despite administration of the appropriate treatment. *Pneumon 2013, 26(4):369-373.*

INTRODUCTION

The term "miliary tuberculosis" (MT) was introduced in 1700 to describe the postmortem finding of innumerable, small sized tubercles in patients suffering from disseminated disease¹ and it has been used since then for the description of the disseminated, haematogenous dispersion of tuberculosis in various organs². In such cases, lung involvement exceeds 80%³. According to Matsushima, the term "miliary" should refer to the characteristic presence of nodules of up to a few millimeters on chest X ray or chest computed tomography (CT) scan, in distinction from the term "disseminated" that describes those cases of generalized tuberculosis where miliary shadows are absent⁴.

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Three hundred years after its first description, MT is still considered to be a complicated disease that can be under-diagnosed, even by experienced doctors, and it carries a consistently high mortality. The acute respiratory distress syndrome (ARDS), which is recognized to be a rather rare complication of pulmonary and extrapulmonary tuberculosis⁵, when occurring with underlying MT appears to constitute a lethal combination⁶. For this reason the case of a geriatric patient who developed ARDS in the setting of MT and tuberculous meningitis is presented.

CASE REPORT

A 78 year-old female patient was transferred from a regional hospital to the Department of Pulmonary Medicine, Aristotle University of Thessaloniki, for investigation of a marked nodular pattern on her chest X ray with a history of mild fever and weakness. Her medical history included atrial fibrillation under maintenance therapy, multiple valvular heart disease and a left chest wall injury incurred from an accidental fall one month earlier. The patient was reported to be fully functional prior to the onset of the current symptomatology.

Eight days before her hospital admission, the patient presented with fever of up to 38.5 °C that was initially managed as a community acquired infection by the administration of oral clarithromycin. As the fever persisted, she was admitted to the regional hospital where she remained febrile but haemodynamically stable with normal arterial oxygen saturation. The chest X ray showed a miliary pattern (Figure 1) and the high resolution computed tomography (HRCT) of the chest showed interspersed tiny intrapulmonary nodules with a random distribution, particularly in the upper pulmonary zones (Figure 2). These findings were considered compatible with MT and the patient was transferred to the Department of Pulmonary Medicine for further investigation.

The main clinical and laboratory findings were: bilateral mild decrease in the breath sounds, systolic murmur of the mitral valve, hypoxaemia (arterial blood gas pH: 7.38, pO₂: 58.2 mmHg, pCO₂: 28.9 mmHg, HCO₃: 17 mmol/l with oxygen supply of 2 lt/min), normochromic normocytic anaemia with Hb 11.5 g/dl and Ht 35.6%, mild leukocytosis, white blood cells (WBC): 11,700/mm³, polymorphonuclear leukocytes 93%, Lymphocytes 2%, monocytes 5.2%, hypoalbuminaemia (2.3 g/dl), hyponatraemia (128 mmol/l), erythrocyte sedimentation rate (ESR) 88 mm/1h, C reactive protein (CRP) 11 mg/dl and an increase in ACE (93.1 U/L with a normal range of 23-57 U/L). Screening



FIGURE 1. 78 year-old female with military tuberculosis: Chest X ray on admission.

for connective tissue diseases was negative and urine calcium (on the grounds of possible sarcoidosis), was within normal limits. The Tuberculin skin test was negative and fundoscopic examination (for possible presence of tubercles on the retina) revealed no abnormal findings. Because of the patient's inability to expectorate, gastric fluid and bronchoalveolar lavage (BAL) were obtained and tested for the presence of acid-fast bacteria (AFB) and common microbial pathogens and molecular probing for *Mycobacterium tuberculosis* (AMTD, Gen-Probe) was performed. On the fourth day after admission, and although the direct staining of both gastric fluid and BAL was negative, quadruple antituberculous therapy with isoniazid, rifampicin, ethambutol and pyrazinamide was initiated. The patient showed an initial favorable response and the fever resolved. Five days later, however, the fever recurred, and in addition the patient developed behavioural derangement with intense agitation, a decline in the level of consciousness and deterioration of hypoxaemia (ABGs pH: 7.39, pO₂ 69.32 mmHg, pCO₂ 31.9 mmHg, HCO₃ 19.3 mmol/l, FiO₂:50% - Venturi mask). The pathological findings on the chest X ray were noticeably aggravated (Figure 3). Brain CT showed diffuse ischaemic encephalopathy, but no focal lesions. Echocardiography performed one day after the chest X ray showed mild left ventricular hypertrophy without wall hypokinesia, normal injection fraction and mild mitral and aortic valve regurgitation. CPAP pressure of 7 cm H₂O was applied, which led to temporary increase in pO₂. The patient's family refused intubation and transfer to the intensive care unit (ICU). In the context of a possible hospital acquired pneumonia

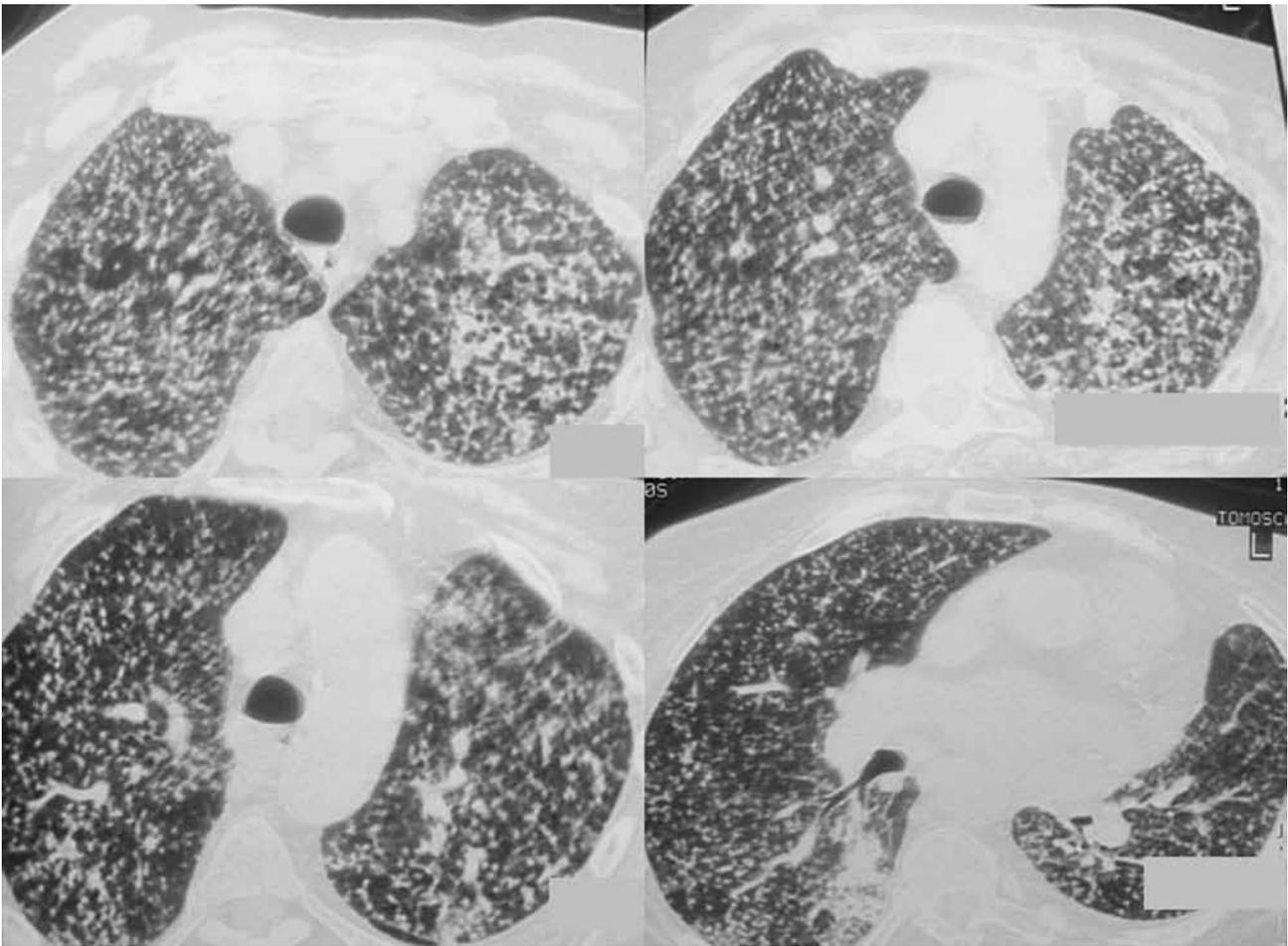


FIGURE 2. 78 year-old female with military tuberculosis: computed tomography (CT) scan on admission.



FIGURE 3. 78 year-old female with military tuberculosis and acute respiratory distress syndrome: Chest X ray at the time of deterioration.

(HAP), and even though the WBC was normal, the patient was administered levofloxacin and meropenem. Because of the CNS symptoms the patient underwent lumbar puncture and the cerebrospinal fluid (CSF) examination showed 20 cells/mm³ with a lymphocytic predominance, glucose 42 mg/dl (blood glucose 133 mg/dl), and albumin 79 mg/dl. Although more cells, lower glucose levels and higher protein levels would be expected, these findings were regarded as compatible with tuberculous meningitis, since the patient was already under antitubercular treatment when the lumbar puncture was performed. Adenosine deaminase (ADA) testing was not available at that time. The CSF direct stain was positive for *M. tuberculosis*. With the conclusive diagnosis of tuberculous meningitis, treatment with dexamethasone (12 mg daily) was initiated, but the patient's condition remained critical and she died two days later from respiratory insufficiency. After death, RNA molecular analyses for *M. tuberculosis*

was reported positive for the gastric fluid (551.501 RLU) and the CSF (1.585.587 RLU) but was not diagnostic in the BAL. Lowenstein-Jensen cultures were positive for both gastric fluid and BAL but negative for the CSF. The drug sensitivity test revealed *M. tuberculosis* sensitive to all first-line anti-tuberculosis drugs.

DISCUSSION

MT usually follows primary infection but may also occur later, due to reactivation of latent tuberculosis. The time-honoured assumption that MT is almost exclusively a childhood disease has been revised because during the past three decades the diagnosis of MT in adult patients has been not uncommon. The incidence of MT is estimated to be as high as 2% of TB cases in immunocompetent adults^{2,7,8}, peaking in adolescence and in advanced age^{7,8}. This change in epidemiology is probably due to a number of factors, including the wide spread of Human Immunodeficiency Virus (HIV) infection, the increasing number of conditions leading to immunosuppression (such as the administration of biological agents and immunosuppressive drugs to patients with connective tissue diseases and following organ transplantation) and the increase in subjects on chronic haemodialysis⁷. Several articles have documented the fact that 25-60% of patients with MT have an identifiable underlying disease^{2,9,10}, unlike the present case where, with the exception of her advanced age, no other risk factor was evident. The correlation between tuberculous meningitis and MT is widely accepted¹¹⁻¹³, as meningitis is described in 10-30% of adults with MT^{7,14}. The role of MT in the pathogenesis of meningitis involves bacteraemia, which leads to the development of tuberculous foci, called Rich foci, in the meninges or the cerebral cortex^{15,16}.

One of the most interesting findings in this patient was the presence of *M. tuberculosis* in three different samples, gastric fluid, BAL and CSF. Positive staining for AFB in gastric fluid samples or specimens from the respiratory system is elicited in 23-43% of cases of MT, while the rate of specific culture is much higher^{10,14}. Concerning the CSF, the sensitivity of the direct stain may be very low, even below 10%, but the culture sensitivity ranges between 25% and 75%^{10,17}. Apart from its role in tuberculous pleurisy¹⁸ ADA testing is particularly useful in the diagnosis of tuberculous meningitis, as its sensitivity in the CSF is higher than that of the molecular diagnostic methods, reaching 79%¹⁹. Despite the inability to perform ADA testing in this case, it is of note that the first confirmation

of tuberculosis was the positive direct stain on the CSF. The negative CSF culture, in spite of the positive staining, and the detection of RNA of *M. tuberculosis* could be attributed to the fact that the patient had already been under anti-tuberculosis treatment for 7 days. In contrast, the BAL and gastric fluid, which had been collected before the start of the treatment, were culture-positive.

The appearance of ARDS in the setting of MT has been recognized for many years, but most citations are either case reports or very small series^{6,20,21}. As is clear from the few larger series of patients, the incidence of ARDS in patients with tuberculosis is small but not negligible²²⁻²⁴ since ARDS has been observed in 1% of patients, and most often in the context of MT²⁵. MT, prolonged disease, a poor general condition, hypoalbuminaemia, hyponatraemia, lymphopenia, thrombocytopenia, anaemia and elevated blood levels of transaminases are risk factors for the occurrence and dismal prognosis of ARDS²²⁻²⁵. In a recent study²⁴ the incidence of ARDS was higher in patients aged over 70 years. The mortality due to ARDS in the setting of MT is extremely high, ranging from 40% to 60%²³⁻²⁵. The occurrence of ARDS increases the mortality rate in MT, which varies between 15-20% in children and 25-30% in adult patients, even those without ARDS, and despite appropriate treatment⁷.

The diagnosis of ARDS in this patient was made without the confirmation of low pulmonary wedge pressure by pulmonary artery catheterization, although based on the clinical picture and the echocardiographic findings, left-sided heart failure could not be established. The Berlin definition of ARDS²⁶ designates that the risk factor occurrence has to precede the syndrome by a maximum of 7 days. The occurrence of ARDS after the initiation of anti-tuberculous treatment has been documented even in patients who had already been treated for more than 30 days²⁴. Although no pathogen other than *M. tuberculosis* was isolated, broad spectrum antibiotics were administered to the patient to cover the probability of HAP; this is a practice followed in 70% of patients with MT and ARDS²⁴.

The administration of corticosteroids is of questionable efficacy for the treatment of ARDS due to MT²⁴. Nearly 40% of patients receive methylprednisolone at a dose of 1mg/kg, corresponding to the dose proposed for the management of the immune reconstitution inflammatory syndrome (IRIS)²⁷. It is of particular interest that ARDS may occur either in the setting of the multiorgan dysfunction syndrome (MODS) or IRIS^{7,28}. IRIS may involve relapse of fever, deterioration of pulmonary infiltrates,

central nervous system manifestations and meningitis^{27,29}. The exact underlying pathophysiology in our patient was not clear, but with the suspicion of IRIS the administration of steroids at doses higher than those allocated to treat meningitis might have been justified.

In conclusion, MT should not be considered to be an exclusively paediatric disease, but it is a condition that can evolve in all age groups and particularly in the elderly. The development of ARDS on the background of tuberculosis, and more often with the haematogenous spread of the disease, is a complication that may be difficult to recognize and not usually thought of, that may have a dismal outcome, in spite of administration of the appropriate anti-tuberculous treatment.

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