CASE REPORT
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Miliary tuberculosis presenting with acute respiratory distress syndrome in a patient with Down syndrome

Milijarna tuberkuloza sa akutnim respiracijskim distres sindromom kod bolesnice sa Daunovim sindromom

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Abstract

Introduction. Miliary tuberculosis (TB) is a rare and potentially fatal form of disseminated TB. It is caused by a widespread haematogenous dissemination of *Mycobacterium tuberculosis* from an active caseous focus to different organs. Sometimes it can have an acute presentation with a rapid-onset clinical deterioration and death. Miliary TB complicated with an acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (MV) is rare, even in countries with a high incidence of TB. **Case report.** A 35-year-old woman with Down syndrome (DS) was admitted to the Clinic for Pulmonology, Clinical Centre Kragujevac, due to an evaluation of cough and weight loss during last 2 months. Laboratory findings revealed anaemia, leukocytosis, elevated C-reactive protein (CRP) and hypoalbuminemia. A chest x-ray showed bilateral reticulonodular shadows, predominantly in the mid and lower right lung lobes. A purified protein derivative (PPD) skin test and induced sputum smear for acid-fast bacilli (AFB) were both negative. On the fifth day following admission, her health condition suddenly declined, and after developing a moderate ARDS, she was put on the mechanical ventilation. Due to a high clinical suspicion of miliary TB and the fact that her life was compromised, an empirical anti-tuberculosis therapy was initiated. Despite all therapeutic and supportive measures, the patient expired 3 days later. The diagnosis of miliary TB was established *post-mortem*. **Conclusion.** Miliary TB should be kept in mind in patients with DS due to immunosuppression associated with deficient cell-mediated immunity. The development of ARDS as a complication of miliary TB is difficult to identify due to a low causal association. High clinical suspicion and a chest radiograph with a typical appearance of miliary pattern justify the initiation of empirical anti-tuberculosis treatment in such patients, as an attempt to change poor prognosis.

Key words:
down syndrome; tuberculosis, miliary; respiratory distress syndrome, adult.

Apstrakt

Uvod. Milijarna tuberkuloza (TB) je retka, potencijalno fatalna forma diseminovane TB. Nastaje masivnom hematogenom diseminacijom *Mycobacterium tuberculosis* iz aktivnog kazeoznog fokusa u različite organe. Ponekad može da ima akutnu prezentaciju sa brzim kliničkim pogoršanjem i smrću. Milijarna TB komplikovana akutnim respiratornim distres sindromom (ARDS) koji zahteva mehaničku ventilaciju (MV) je retka čak i u zemljama sa visokom incidencijom TB. **Prikaz bolesnice.** Trideset petogodišnja žena sa Daunovim sindromom (DS) je bila primljena u Kliniku za pulmologiju zbog ispitivanja kašlja i gubitka telesne mase tokom poslednja dva meseca. Laboratorijski nalazi su ukazali na anemiju, leukocitozu, povećanu vrednost C reaktivnog proteina (CRP) i hipoalbuminemiju. Radiografijom grudnog koša su ustanovljene bilateralne retikulonodularne senke, dominantno u srednjem i donjem plućnom polju, desno. Tuberkulinski kožni test (*Purified protein derivative* – PPD test) i razmaz sputuma na acidorezistentne bacile (ARB) su bili negativni. Petog dana od prijema, stanja bolesnice se naglo pogoršalo, razvio se umereni ARDS i bolesnica je stavljena na mehaničku ventilaciju. Zbog visoke kliničke sumnje na milijarnu TB i životno ugrožavajućeg stanja bolesnice uvedena je empirijska terapija antituberkuloticima. Uprkos preduzetih terapijskih i potpornih mera, nakon tri dana došlo je do letalnog ishoda. Dijagnoza milijarne TB je postavljena obdukcionim nalazom. **Zaključak.** Milijarnu TB treba imati na umu kod bolesnika sa DS zbog imunosupresije povezane sa deficitom ćelijski posredovanog imuniteta. Razvoj ARDS, kao komplikacije milijarne TB, težak je za prepoznavanje zbog njihove slabe uzročne povezanosti. Visok stepen kliničke

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sumnje i tipični milijarni uzorak na radiografiji grudnog koša opravdavaju započinjanje empirijske terapije antituberkuloticina kod ovih bolesnika, u pokušaju da se promeni loša prognoza.

Ključne reči:
daunov sindrom; tuberkuloza, milijarna; respiratorni distres sindrom kod odraslih.

Introduction

Tuberculosis (TB) is an infectious disease caused by the aerobic bacterium *Mycobacterium tuberculosis*. Despite the available effective therapy, TB is still a global emergency because of its high morbidity and mortality rates (10.4 million new cases and 1.3 million died in 2016) [1]. It is estimated that almost 1/3 of the world population has a latent TB infection (LTBI) and of these, 10% are at risk of developing an active form of the disease during their lifetime [2]. The lungs are usually the first site of TB infection, and they are involved in more than 90% of cases. In case of extrapulmonary TB (EPTB) the most commonly affected sites are lymph nodes, pleura, genitourinary and osteoarticular systems. However, any organ can be affected [3].

Miliary TB is a rare form caused by a widespread hematogenous dissemination of *M. tuberculosis* from an active caseous focus (usually lung) to different organs. The definite diagnosis of miliary TB is established by: 1) microbiological (positive acid-fast bacilli smear and/or culture), 2) radiological [evidence of miliary nodules on the chest radiograph or on a high resolution computed tomography (HRCT)], and 3) histopathological findings. A characteristic histopathological finding in miliary TB is caseous granuloma measuring approximately 2 mm in diameter, in two or more noncontiguous organs [4]. However, even today, miliary TB remains a formidable diagnostic and therapeutic challenge. The diagnostic dilemma is even greater if the disease is presented with complications.

Down syndrome (DS) is the most common cause of intellectual disability of mostly mild or moderate range. Only rare, individual cases of individuals with mosaic DS have severe mental retardation, with IQ ranging 10–30 [5]. Improved living conditions and lifestyle have resulted in an increase of life expectancy of, not only, general population, but also of individuals with DS whose life expectancy is 60 years at present [6].

DS is the most common human chromosomopathy (1 : 600–700 live births) caused by the presence of all or part of a third copy of chromosome 21 [7]. Autoimmune diseases such as primary hypothyroidism [8], coeliac disease [9] and diabetes mellitus [10] as well as haematological malignant diseases, acute lymphoblastic leukaemia and myeloproliferative diseases [11] are more frequent in patients with DS than in people with normal karyotype.

Similarly, there is an increased susceptibility of these patients for recurrent infections, mostly lower respiratory tract infections, characterized by increased severity and a prolonged course of the disease as well as the need for extra or augmented treatment compared to the general population [12]. Anatomical and immunological problems associated with DS are thought to be the reason for this [13].

TB has been occasionally reported in patients with DS. Patients with chromosomal abnormalities such as DS may be at a higher risk of unusual forms of TB, mostly extrapulmonary with rare and serious complications [5, 14–16].

Case report

A 35-year-old female with DS was hospitalized in the Clinic for Pulmonology, Clinical Centre Kragujevac due to cough with scanty expectoration for 2 months. She had on and off night sweats and chills. Body temperature was not measured. Over this time period, she lost 5 kilograms. A few days back, due to frequent diarrhea, she reported more pronounced weakness and fatigue.

The patient had no congenital anomalies of the heart and gastrointestinal tract. Apart from moderate hearing impairment, according to data provided from the father, during childhood the patient did not have any serious respiratory infections requiring hospitalization. She was a non-smoker, and does not take any alcohol. The obtained data on maternal death caused by TB, about 1 year ago, were not supported by medical documentation.

At the examination, the patient had temperature 36.8 °C, pale color of the skin and mucous membranes, pulse rate 120/min, blood pressure 120/75 mmHg and a respiratory rate of 20/min with oxygen saturation of 95% on room air. Auscultatory finding on the lungs registered decreased breathing sound over basal part of the right lung with inspiratory crackles. Cardiovascular system examination revealed tachycardia without any murmurs. Physical examination of the abdomen was normal. There was no lymphadenopathy.

Results of laboratory analyses showed positive biohumoral inflammatory syndrome [erythrocyte sedimentation rate 66 mm/first hour, white blood cell (WBC): 19.5 x 10⁹/L with 91.7% of neutrophils, C-reactive protein (CRP): 121.7 mg/L, normochromic normocytic anaemia with hemoglobin (Hgb) of 88 g/L, hypoalbuminemia of 18 g/L] and there were no significant variations in liver function tests, compounds of nitrogen metabolism, and electrolyte levels. Chest radiograph showed bilateral reticulonodular shadows, predominantly in the middle and lower field of the right lung (Figure 1A). HRCT of the lung was not done because of technical malfunction of the appliance. Antibiotic treatment was initiated (cefrtiaxon and azithromycin combination) under the suspicion of bilateral bronchopneumonia with albumin substitution, probiotic and rehydration.

Microbiological analysis of the induced sputum, including anaerobes, and fungi, did not isolate any potential pathogenes. Tuberculin skin test was negative, and 3 sputum specimens were negative for acid-fast bacillus (AFB). Serological analysis for *Mycoplasma pneumoniae* infection, enzyme-linked immunosorbent assay (ELISA) for human immunode-

ficiency virus (HIV) antibodies, anti hepatitis C virus (HCV) antibody and hepatitis B surface antigen (HBsAg) were negative. Immunology parameters did not show any significant disturbances. Coproculture did not isolate any pathogen (bacteria or parasites), including *Clostridium difficile*. The patient was afebrile, hemodynamically stable, active, although diarrhea persisted.

On the fifth day of hospitalization, in the evening, sudden appearance of high fever of 40°C was noted, with a sharp deterioration in the general condition of the patient with progressive dyspnea, tachycardia (138/min) and mental confusion with decrease of oxygen saturation to 70% on room air. Auscultatory finding in the lungs registered mass of inspiratory crackles in the lower and middle areas of both lungs. Arterial blood gas analysis on room air [fraction inspired oxygen (FiO_2) 21%] showed severe hypoxemia, partial arterial oxygen pressure (PaO_2) – 4.8 kPa, [partial pressure of arterial carbon dioxide ($PaCO_2$) – 4.0 kPa; pH-7.46 and bicarbonate-25.3 mmol/L]. On oxygen by face mask, the calculated PaO2/FiO2 ratio was 151 mmHg.

Chest X-ray showed a distinct radiographic progression with confluent nodular infiltrates bilaterally, diffuse reduction of parenchymal transparency, without changes in the size and configuration of the cardiac silhouette (Figure 1B). The patient was transferred to the intensive care unit (ICU), intubated electively and put on mechanical ventilation (MV).

On the basis of clinical, PaO2/FiO2 and radiological findings, working diagnosis of ARDS was set. Due to the high index of suspicion of milliary TB (the fulminant course of the disease, despite antibiotic therapy, medical history data about maternal death of TB and DS as a primary disease) after intubation the patients was started on antituberculosis medications: rifampicin (RIF), isoniazid (INH), pyrazinamide (PYZ) and ethambutol (EMB). Despite therapy and MV, the patient died on the 8th day of admission. Because of unexplained etiology of fulminant course of the disease, clinical autopsy and post mortem lung biopsy were performed.

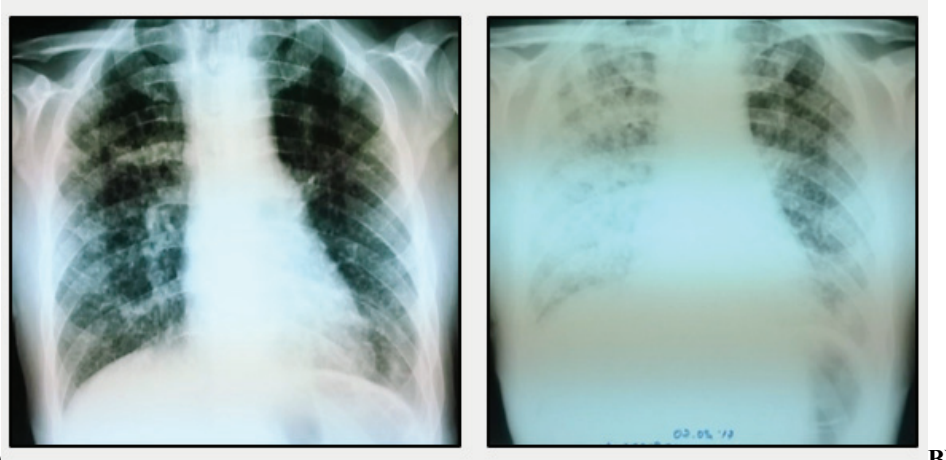
Autopsy showed multiple whitish nodules, individual and plums, present in the lungs (Figure 2A). Miliary seeding of lymph nodes were detected in the small intestine mesentery (Figure 2B). On the cross section of the kidney, there were cystic formation filled with greyish-white, mucoid material (Figure 2C). Histopathological findings of the lung tissue showed numerous granulomas composed of epithelioid multinuclear cells, gigantic cells of Langhans type and lymphocytes, with caseous necrosis within the center (Figure 3). Histopathological findings of the small intestine mesentery and kidney biopsy were identical. This confirmed the diagnosis of miliary TB.

Discussion

Miliary TB is a potentially fatal form of disseminated TB. If not diagnosed and treated early, death is imminent. It can be a manifestation of a primary progressive infection or the result of a latent TB focus reactivation. Large amounts of bacillemia in miliary TB mostly involve organs with high blood supply including lungs, liver, spleen, lymph nodes, meninges, bone marrow and adrenals [17, 18].

In various clinical studies, among immunocompetent adults, miliary TB accounts for less than 2% of all TB cases. It has been reported that immunocompromised states such as advanced age, malnutrition, terminal stage of renal disease, organ transplantation, poorly controlled diabetes, immunosuppressive and cytotoxic therapy (including biologic agents antitumour necrosis factor – anti-TNF), malignant diseases, corticosteroids, smoking, alcoholism, as well as infection such as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) as the most important among them, are associated with a significantly increased susceptibility to TB [17, 18].

There is a very small number of studies dealing with immunological parameters in adults with DS, especially in patients with both DS and tuberculosis. In view of the fact that the aetiology of immunodeficiency is still not clear, the immune system in DS remains the subject of numerous studies. Possible abnormalities of the immune system include: mild to moderately reduced T and B lymphocyte subpopulation with a marked decrease of naive lymphocytes, impaired mitogen-induced T cell proliferation, defects of neutrophil chemotaxis role and reduced specific antibody responses to immunizations. These abnormalities contribute to an increased susceptibility to infections and inflammatory processes [13].



A) **B)**

Fig. 1 – A) Chest x-ray on admission showing bilateral reticulo-nodulare shadows, predominantly right; B) Chest x-ray at the 6th day of hospitalization showing bilateral infiltrates (an acute respiratory distress syndrome – ARDS).

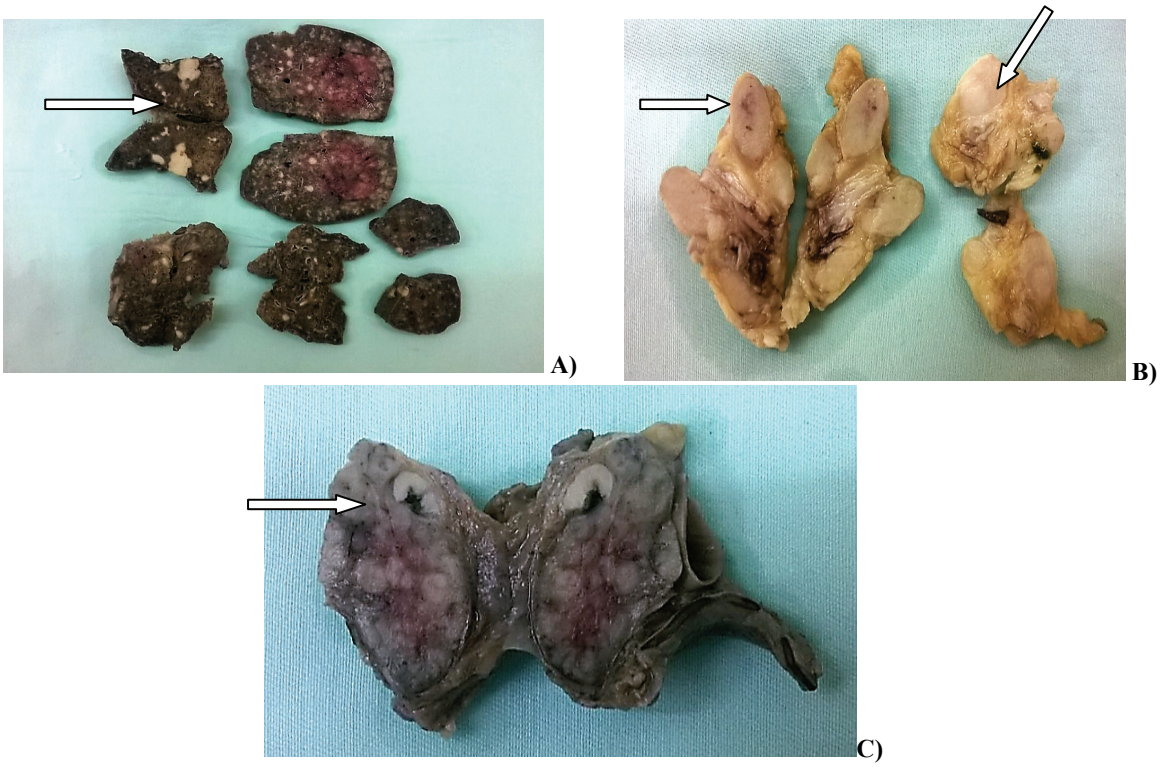


Fig. 2 – A) Miliary seeding of the lungs; B) Miliary seeding of the mesentery and lymph nodes; C) Cut section of the kidney with white cystic lesions and mucoid material.

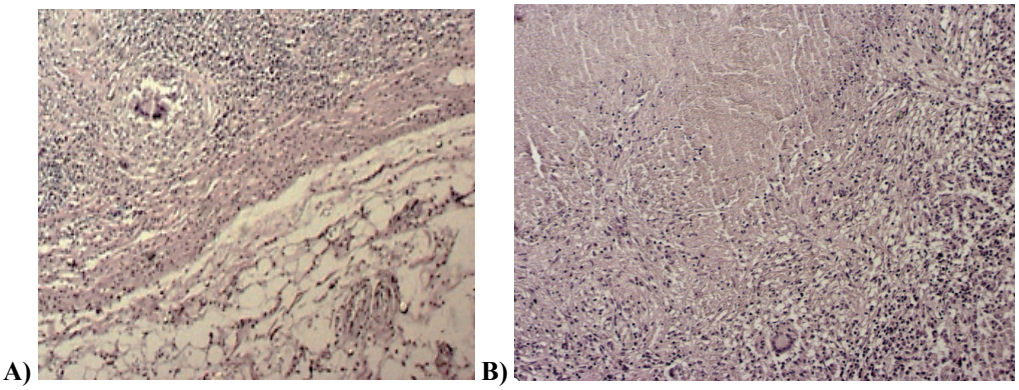


Fig. 3 – A) Histopathological examination of the lung showing features of tuberculosis with granulomas, caseous necrosis, and multinucleated, gigant cells of Langhan's type;
B) Mesenteric lymph nodes showing tuberculous lymphadenitis.

While there is ample evidence of dysfunction or dysregulation of almost every arm of the immune system in DS, the most significant one is the impairment of both the number and activity of T lymphocytes (CD4+ and CD8 suppressor) and natural killer (NK) cells. Thus, DS is associated with T cells dysfunction [19, 20]. This immune dysfunction contributes to recurrent infections and poor microbial clearance [19, 21]. Patients with DS are at a 12-fold increased risk of infectious diseases, especially pneumonia because of their impaired cellular immunity [5]. Although it is justifiable to expect a higher incidence of TB in DS, no data till date has commented about any change in prevalence of tuberculosis in such patients [5]. Therefore this paradoxical finding calls for more research and study.

In the case of our patient, a high risk of future disease was due to a positive family history, namely as a result of the direct contact with her mother who was diagnosed with active TB, resulting in an progressive infection. Approximately 5% of infected individuals get sick within 12–24 months of being infected [2]. As no other members of the family were ill, immunological dysfunction of our patient was a likely factor that contributed to the development of the disease. Although the patient was HIV negative and presented with normal immunoglobulin levels, unknown phagocytic dysfunction in DS could have increased her susceptibility to the disease. Immunocompromised status of the patient, contributed to disseminated TB infection in the lung, intestinal lymph nodes and kidney, which was confirmed by the autopsy report.

Despite a high level of clinical suspicion and a characteristic radiological finding, the diagnosis of miliary TB in our patient was difficult to reach, due to the absence of a microbiological findings and the inability to perform HRCT as a more sensitive method than chest radiography.

An additional problem in reaching the diagnosis of miliary TB in individuals with DS is that in order to get adequate material for bacteriological analyses and depending on the level of their intellectual disability, diagnostic procedures have to be adjusted. In one documented case, an extremely poor general condition of a DS patient made it impossible for a sputum sample to be collected, so *M. tuberculosis* was isolated from oral mucosa brushing instead [16]. She was found to have negative AFB in induced sputum smear. Even though AFB smear was negative, TB could not be ruled out, since the positive AFB [4] was reported only in 20%–40% of patients with miliary TB. On the other hand, there is a case report of a positive AFB sputum result of a boy with DS and miliary TB [22]. The finding was associated with a very high bacterial load in immunocompromised state in DS, which increases the chance for isolation of AFB in sputum.

On the fifth day of hospitalization, our patient developed ARDS, and given that her life was compromised, an empirical antituberculosis treatment was initiated. However, due to advanced stage of a TB infection, she expired on the 8th day of admission.

ARDS is a syndrome of acute respiratory failure, clinically presented as appearance of acute bilateral pulmonary infiltrates on chest radiograph and severe hypoxemia, refractory to oxygen therapy. According to a new definition, ARDS is classified into 3 groups by the degree of hypoxemia, defined as PaO2/FiO2 ratio: mild, moderate and severe [23].

Miliary TB is a rare cause of ARDS, with estimated comorbidity rates of 1%–2% [24]. A possible pathophysiology for the development of ARDS in patients with miliary TB may be a strong pro-inflammatory response to *Mycobacterium tuberculosis* infection – leading to inflammatory cells accumulation in alveolar spaces, following a release of granular enzymes and oxidants, and resulting in damage to the alveolar-capillary membrane. Damage to the alveolar-capillary membrane allows an increase in cellular permeability, which aggravates oxygen dysfunction and consequently causes ARDS [25].

Aside from immunocompromised status, other independent predictors of ARDS development in patients with miliary TB include: diabetes mellitus as general condition, alanine aminotransferase-ALT(> 70–100 U/L), aspartate aminotransferase-AST (> 94 U/L), D-dimer (>1,6 mg/L), Hgb (< 90 g/L) and albumin (< 25 g/L) [26]. In our case study, a patient had decreased haemoglobin and hypoalbuminemia, which could present additional risk factors for the development of ARDS due to miliary TB. Hypoalbuminemia accelerates fluid exudation, promotes alveolar oedema and contributes to ventilation-perfusion ratio mismatch. Hypoalbuminemia and weight loss in our patient suggested malnutrition, which was clinically presented as well. It is well known that malnutrition affects cell-mediated immunological processes and is a risk factor of developing TB [26]. Anaemia caused by chronic infections, including TB, is the result of the effect of cytokines mediating the inflammatory response. Considering that the severity of anaemia is mainly determined by Hgb level, it is assumed that the decrease of Hgb is a result of inflammation itself, which, in turn, can explain the relationship between low haemoglobin levels and ARDS [26].

Compared with miliary TB alone or other causes of ARDS, miliary TB with ARDS portends a higher mortality of 33%–90% [24]. In the study Deng et al. [26] of 471 patients with miliary TB, 85 had the diagnostic criteria for ARDS, with a mortality rate of 47.1%. In the study Lee et al. [27] of 67 patients with adult respiratory distress syndrome caused by milliary TB, mortality rate was also very high 61.2%. The main reasons for such a high mortality rate should be attributed to the fact that diagnosing and subsequent treatment of miliary TB is delayed and often missed, as well as to a low causal association of miliary TB and ARDS [26]. The duration of symptoms before clinical worsening of miliary TB to ARDS is usually gradual, ranging from 5 to 90 days. However, sometimes the onset of symptoms may be unpredictably rapid. In many reported cases the diagnosis was established *post-mortem*, as was the case of our patient [28].

Conclusion

Miliary TB should be kept in mind in patients with DS due to immunosuppression associated with deficient cell-mediated immunity. The development of ARDS as a complication of miliary TB is difficult to identify due to a low causal association. High clinical suspicion and a chest radiograph with a typical appearance of miliary pattern justify the initiation of empirical anti-tuberculosis treatment in such patients, as an attempt to change poor prognosis.

Careful monitoring of patients is crucial for early detection of ARDScomplication, and laboratory findings, such as anaemia, hypoalbuminemia and high levels of alanine aminotransferase can be of help in identifying such patients. Treatment of miliary TB in advanced disease stages has a poor outcome, due to the development of ARDS and a mortality rate can be predicted according to a relation: PaO_2/FiO_2, in line with the updated "Berlin definition".

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