Fatal paradoxical cryptic miliary tuberculosis and immune reconstitution disease in a young non-HIV immunocompromised male patient: case report with autopsy findings

MILENA ADINA MAN1), OANA CRISTINA ARGHIR2), SORIN MAN1), COSTIN TEODOR STREBA3), MIHAI OLTEANU3), MIMI NIŢU3)

1) "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
2) Faculty of Medicine, "Ovidius" University, Constanta, Romania
3) Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

Abstract
Non-HIV immunocompromised patients may develop immune reconstitution inflammatory syndrome (IRIS) as an abnormal response to invading microorganisms, such as Mycobacterium tuberculosis (MTB). IRIS consists in a sudden change in the dominant T-helper responses to inflammation, which is not balanced by anti-inflammatory response, playing a critical role in microbial pathogenesis. A patient with restoration of host immunity during anti-tuberculosis treatment can become gravely ill with a paradoxical severe form of tuberculosis (TB) disease named TB immune reconstitution disease (IRD). The diagnosis of acute cryptic miliary TB is difficult and requires an accurate histopathology. We report a fatal association between a generalized lymphadenitis tuberculosis and IRD in a 34-year-old male patient, non-smoker, non-HIV immunocompromised, but with a previously co-morbid diabetes mellitus (DM) type I. The purpose of this report is to describe an unusual and rare case of a progressive extrapulmonary TB disease to a liver involvement, mimicking a hepatotoxicity secondary to anti-tuberculosis therapy. The diagnosis of disseminated miliary TB with cryptic pulmonary was confirmed later after performing necropsy. Formalin-fixed paraffin-embedded pulmonary and extrapulmonary miliary foci were processed for histology and stained with Hematoxylin and Eosin. This rare entity of cryptic miliary involvement of the lungs is described more in elderly than in young individuals. In the reported case, IRD induced a paradoxical progressive dissemination of TB lesions leading to death in a patient with an apparent uncomplicated form of lymphadenitis TB.

Keywords: tuberculosis lymphadenitis, immune reconstitution inflammatory syndrome, cryptic miliary, non-HIV immunocompromised, diabetes mellitus.

Introduction
The World Health Organization estimated about 10% of TB disease cases globally are linked to diabetes mellitus (DM) [1]. TB infected individuals with DM may have a weak immune system because of chronic diseases, particularly such as type I, and are at a higher risk (2–6-fold) of progressing to active TB disease which is late, under- or misdiagnosed [1, 2]. At the same time, Mycobacterium tuberculosis (MTB) is the best known common pathogen associated with the immune reconstitution disease (IRD) in immunocompromised hosts, mostly HIV-infected [3].

Before the HIV epidemic era, IRD had been reported in non-HIV persons as a paradoxical reaction (PR) following anti-tuberculosis treatment, by Chloremis even since 1955 [4]. PR is frequently reported as related with lymph node, cerebral TB disease in non-HIV (30%) [4–7], and disseminated TB disease in HIV immunocompromised persons [3]. The phenomenon of PR during tuberculosis treatment is related with a documented clinical worsening of TB and reflects a restoration of pathogen-specific cellular immune response influenced by the overall mycobacterial load [4, 8].

Although PR is rarely reported in diabetic patients with treated TB disease, clinical deterioration of TB-related DM has been observed for more than 2000 years [9], and rates of TB failure, relapse, and death are higher in diabetic patients [1, 2]. TB is more common in insulin-dependent diabetics, and the risk of TB disease and death increases as complications of diabetes increase. Before the discovery of insulin, diabetes occurrence represented a death sentence with a mean survival time of less than five years and the usual cause of death was TB [9]. Before the era of TB treatment, in 1883, Bouchardat observed in several autopsies that “every case of diabetes had tubercles in the lung” [9]. The link between TB and DM is still strong nowadays, and the risk of death is five times greater among treated patients [2, 10] and the impact of IRD has not been defined yet.

Patient and Methods
We report a case of a young diabetic patient, 34-year-old, white, single, non-smoker, diagnosed with diabetes mellitus type I in 1991. The patient was admitted to the Hematology Clinical Hospital, Cluj-Napoca, Romania, on September 9, 2008, after a three months history of continuous low-grade fever, malaise, fatigability, 15 kg loss in weight, and progressive generalized adenopathy.
with enlarged lymph nodes cervical, axillary and inguinal location. On physical examination, the bilateral soft enlarged lymph nodes measuring up to 3 cm in diameter appeared moderately firm and lymphoma was suspected. One month and a half previously, a Mantoux test with only 4 mm of dermal induration was interpreted as a negative tuberculin skin test (TST). The chest X-ray was normal, the HIV screening was negative, and the smear were also negative for Acid Fast Stains (AFS). An enlarged inguinal lymph node excision and biopsy were performed, and lymphadenitis TB diagnosed. The patient was transferred to “Leon Daniello” Clinical Pulmonology Hospital, Cluj-Napoca, on September 25, 2008, for initiating the anti-tuberculosis first regimen of treatment. The routine physical examination of the chest and abdomen was normal. Body mass index was 18 kg/m². A chest X-ray was performed on September 25, 2008.

Laboratory studies disclosed abnormal values for hematological and chemical constituents of the serum (hemoglobin 8.8 g/dL, white blood cells count 9400/mm³, hematological and chemical constituents of the serum on September 25, 2008. Neutrophils 6300/mm³ erythrocytes 4.1×10⁶/mm³), an inflammatory syndrome with high erythrocyte sedimentation rate (42 mm) in the first hour, CRP 8.22 mg/L (normal under 5 mg/L), mild hyperglycemia (160 mg/dL), proteinuria 1 g/L, elevated serum creatinine to 1.6 mg/dL.

The bacteriological exam of sputum revealed negative smears for acid-fast bacilli and negative cultures for bacterial and fungal germs. Under therapy, an initial clinical improvement was observed in the first seven days, with a TST conversion to a positive reaction of 14 mm. Later, biochemical abnormalities consist in hyperbilirubinemia of 3 mg/dL, the 5-fold elevation of alkaline phosphatase, alanine transaminase (ALT) and aspartate transaminase (AST), correlated with the occurrence of jaundice and nausea, determined the discontinuation of TB therapy.

The death of the patient occurred two weeks later, a necropsy was performed and multi-organ involvement was noticed. The macroscopic and microscopic assessments of the lung, heart, liver, spleen, kidneys, brain, lymph node samples of tissue were done by using standard procedures in the Department of Clinical Anatomopathology, “Leon Daniello” Hospital, Cluj-Napoca. Tissue samples of all involved organs were cut into slices and paraffin embedded, sections of 5 μm thick were stained with routine morphologic methods of staining including Hematoxylin and Eosin (HE). Anatomical diagnosis pointed to disseminated miliary TB complicated with fulminant hepatic failure, anasarca, severe anemia, complicated type I diabetes mellitus.

**Results**

We report a late disseminated miliary TB case with a 3-month history of low-grade febrile generalized peripheral adenopathy, mimicking a lymphoma, in a young male diabetic, HIV-uninfected, non-obese, treated in the last 14 years with insulin replacement therapy. His insulin-dependent juvenile diabetes complicated in the last five years with diabetic retinopathy and nephropathy with secondary chronic renal failure. The chest X-ray performed on September 25, 2008, revealed a small pleural effusion in the right costodiaphragmatic sulcus (Figure 1).

Apparently, the involvement of the peripheral lymph nodes over a period of three months with a delayed histological evidence of necrotizing granulomatous inguinal lymphadenitis (Figure 2a), associated with a small right pleural effusion were considered to be suggestive for a limited form of extrapulmonary TB and directly observed therapy (DOT) was initiated. The patient denied cough and his chest radiography showed no evidence of pulmonary TB and/or mediastinal adenopathy. High resolution CT scan was not recommended. One week after the initiation of the TB therapy, the patient’s condition improved with the absence of fever, gain in weight of 2 kg, good tolerance of drugs, TST conversion, stable small right pleural effusion. At the end of the second week of DOT, he developed a progressive clinical worsening of the symptoms with cyclic high fever (39–40°C), chills, anorexia, nausea, jaundice, hepatosplenomegaly with abnormal liver function tests. Considering an adverse toxic reaction to TB drugs, therapy was interrupted. Cough with dyspnea, night sweats, edema of the lower limbs and ascites and polyserosititis developed after TB therapy was discontinued. The medical condition of the patient worsened more and more, hypotension, metabolic acidosis, coma developed and, in the third week after DOT initiating, death occurred. The anatomical findings of the autopsy consist in cryptic disseminated miliary TB complicated with fulminant hepatic failure, anasarca, severe anemia, diabetes mellitus, renal failure. The expansion of the lymph nodes to other sites was observed in intra-abdominal and intra-thoracic areas through enlarged lymph nodes in prevascular and right paratracheal areas, pericardial effusion, intracranial tuberculosis, meningitis, ascites, small pericardial effusion, bilateral small to moderate pleural fluid collection, and right visceral pleural calcification. Each focus of miliary pulmonary dissemination results in small, up to 4 mm, multiple granulomas some of them with a central caseous necrosis surrounded by epithelioid histiocytes and fibrous tissue stained with Hematoxylin and Eosin (HE) (Figure 2b). The liver and the spleen contained white nodules of millet-seed, sized up to 5 mm (Figure 2, c and d). Necrotic tuberculous foci were found even in pancreatic, adrenal glands and kidneys. Superficial erosions of tracheal, esophageal and gastric mucosa were discovered. A diffuse hemorrhagic pneumonia was also diagnosed, considered an expression of acute respiratory distress syndrome.
Figure 2 – Histopathology of HE staining reveals TB necrotizing granulomatous lesions showing the caseous center, surrounded by lymphocytes, histiocytes, irregular-shaped and large multinuclear Langhans giant cells: lung (a, ×100; b, ×200), inguinal lymph node (c, ×200; d, ×400), spleen (e, ×200; f, ×400) and liver (g, ×200; h, ×400).
Discussion

The tuberculosis of the lymph node is one of the most common forms of extrapulmonary TB and, in non-HIV immunocompromised patients, it is considered a self-limited TB. Adult tuberculous cervical lymphadenitis is rarely isolated. A third of these cases are accompanied by pulmonary TB lesions [11].

The inguinal lymph node tissue biopsy and histology were useful in our reported case for the confirmation of tuberculosis etiology versus lymphoma. Miliary dissemination may occur sometimes when an extrapulmonary site reactivates and discharges massive numbers of tubercle bacilli into the stream of blood. Atypical presentation of a limited extrapulmonary TB may often delay and block the disseminated miliary intravitam diagnosis.

Proudfoot et al. coined the term “cryptic” to describe the subtey of a peculiar presentation of miliary tuberculosis [12]. The absence of typical features, the generalized debility induced by a complicated juvenile diabetes mellitus could be the causes of the progression of TB symptoms to severe illness and death. The clinical deterioration is frequently reported in cryptic forms of TB disease and positive diagnosis is usually made only at necropsy in many instances. Cryptic miliary TB, which was often diagnosed only at autopsy, is now being increasingly diagnosed by high resolution CT (HRCT). HRCT could be useful in determining miliary determinants in patients with normal chest X-ray.

The pattern of all additional sites of extrapulmonary TB is essential in earlier diagnosis of disseminated miliary. The occurrence of the hepatic invasion is described in tuberculosis [13]. Cinque et al. suggested that tubercle bacilli may reach the liver via the portal vein or hepatic artery [14]. Involvement of the liver was described among TB patients since 1836 and was commonly found at autopsy [13]. Since the turn of the 20th century, many reports mentioned the usefulness of needle biopsy of the liver in providing histological confirmation, especially in cases of cryptic miliary tuberculosis [13]. The importance of the differential diagnosis between hepatobiliary TB and a drug-induced hepatitis is sometimes vital. Jaundice is rare in TB and it is usually associated with the hepatotoxicity to the anti-tuberculosis therapy [13]. Obstructive jaundice related TB is extremely rare and can be caused by adenitis, pancreatic head determination, biliary TB, a lymph node tuberculosis therapy [13]. Obstructive jaundice related TB is very rare and can be caused by adenitis, pancreatic head determination, biliary TB, a lymph node tuberculosis therapy (6–25%) and the timing of IRD can occur from a few days to many months after the initiation of therapy, but the duration and the severity of reaction are unpredictable [4]. Sometimes, they are self-limiting, at other times, they are accompanied by respiratory failure and death, mainly miliary and pulmonary disease [4]. Diabetes itself represents a risk factor of death among tuberculosis patients.

Conclusions

The differential diagnosis from anti-tuberculosis chemotherapy adverse effects, unmasking disseminated subclinical TB or another newly acquired febrile infection is difficult to perform in a diabetic young male patient. The severity of a complicated juvenile type I diabetes mellitus, hepatic dysfunction and an obstructive jaundice as paradoxical reaction to anti-tuberculosis therapy contributed to a fatal outcome and a late diagnosis of a cryptic form of disseminated miliary TB.

Author contribution

All authors contributed equally to preparing this manuscript.

References


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Corresponding author
Mimi Nițu, Associate Professor of Pulmonology, MD, PhD. University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Romania; Phone +40722–491 034, e-mail: dr_nitumimi@yahoo.com

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