



Successful treatment of extra-pulmonary tuberculosis presenting concomitantly with acute myeloid leukemia

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Abstract

Purpose There were reports of the occurrence of TB during therapy for leukemia with possible complications. In patients with acute leukemia, therapy might be delayed or complicated by the presence of tuberculosis.

Method We present a patient who was diagnosed with acute leukemia and concomitant tuberculosis.

Results The patient's therapy of leukemia had to be delayed and he had relapse of leukemia but was subsequently treated successfully for both diseases despite a prolonged culture positivity for tuberculosis. He required a prolonged course of therapy and additional secondary anti-tuberculosis therapy.

Conclusions The possibility of tuberculosis should be considered in the differential diagnosis of patients with pneumonia, persistent fever, and those with focal signs or symptoms suggestive of tuberculosis. Despite having a sensitive organism, the infection was difficult to treat, even with the addition of two second-line drugs. The standard anti-tuberculosis therapy is usually adequate, but response may be slow, and inadequate even if the organism is sensitive requiring the addition of second-line agents.

Keywords Tuberculosis · TB · AML · Acute myeloid leukemia

Introduction

Tuberculosis (TB) is an ancient human disease and continues to be of global concern. The disease may mimic multiple clinical entities and is of particular concern in immunocompromised patients, such as those with leukemia. In one case report, central nervous system blast crisis secondary to chronic myeloid leukemia was initially misdiagnosed as meningitis secondary to *Mycobacterium tuberculosis* [1]. There are reports of the occurrence of TB during therapy for leukemia with possible complications such as hypercalcemia

and acute pancreatitis [2], cerebral tuberculomas [3], splenic involvements [4], pancreatic mass [5], or prolonged fever [6]. In a series of patients with acute myeloid leukemia (AML), the diagnosis of disseminated tuberculosis was defined as involvement of the blood or bone marrow, the liver or two non-contiguous organs [7]. We present a case of disseminated tuberculosis that was diagnosed simultaneously with the diagnosis of acute myeloid leukemia, thus complicating the course and therapy of both entities.

Case presentation

A 58-year-old male presented with a 2-month history of fever and feeling unwell. Initial laboratory data were as follows: WBC count was $7.4 \times 10^9/L$ with 14% blasts, hemoglobin 7.7 g/dL and platelet count $34 \times 10^9/L$. Investigations revealed acute myeloid leukemia *t*(8;21), blasts of 14% in bone marrow. AML-FISH panel did not identify any other abnormalities. HIV-1 and 2-tests were negative.

Evaluation of fever that was reported for 2 months was done and included CT scan. A CT scan of the chest, abdomen and pelvis showed significant right para-tracheal

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lymphadenopathy (Fig. 1) and there were multiple low attenuation lesions of the spleen. There were also enlarged mediastinal lymph nodes and destructive lesion in the sternum and rib, and low attenuation liver lesions. A mediastinal lymph biopsy could not be done because of severe thrombocytopenia, and platelet count could not be raised adequately by platelet transfusion. He was treated empirically for extra-pulmonary tuberculosis with isoniazid, rifampin, pyrazinamide, and ethambutol. Fever subsided after 10 days of therapy and 2 weeks from presentation, and then he was treated with a standard AML induction regimen with idarubicin 12 mg/m² for 3 days and cytarabine 100 mg/m² for 7 days as a continuous infusion. After recovery of peripheral blood count, a bone marrow examination showed complete remission with resolution of the cytogenetic abnormality by FISH. Follow-up CT showed improvement in mediastinal lymphadenopathy.

Three months from initial presentation and before consolidation chemotherapy and on anti-tuberculous medications, fever recurred. A CT scan showed worsening in lymph nodes (Fig. 2) and there was a development of suprasternal mass. Biopsy of this mass showed caseating granuloma. The tissue was positive for AFB and positive by GeneXpert for *M. tuberculosis* (MTb) and was sensitive to rifampin. Conventional cultures later grew MTb, which was sensitive to isoniazid, streptomycin, rifampin and ethambutol. Consolidation chemotherapy was delayed. He was continued on anti-TB medications and he developed a draining sinus from the sternal biopsy site and culture also grew MTb. Leukemia treatment was delayed because of continuous uncontrolled infection.



Fig. 1 A CT scan of the chest and abdomen was done on initial presentation and is showing significant right para-tracheal lymphadenopathy (arrow)

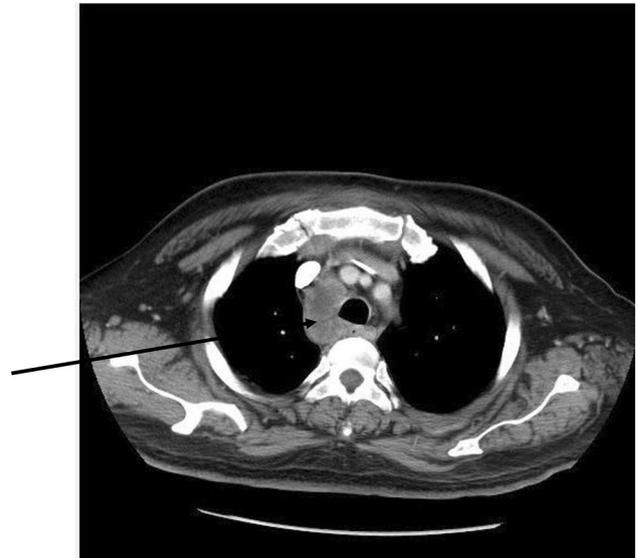


Fig. 2 Three months after presentation, CT scan showed worsening lymph nodes (arrow)

Five months from initial presentation, a follow-up CT scan showed interval worsening in skeletal changes with significant bony destruction and an associated subpleural enhancing collection. In light of worsening radiograph, amikacin and levofloxacin were added.

Seven months from initial presentation, he was clinically well. A follow-up CT showed more hepatic lesions (Fig. 3) and a liver biopsy showed granulomatous inflammation with focal necrosis and cultures were negative. At this point, he



Fig. 3 Seven months after presentation, a follow-up CT scan showed a hepatic lesion (arrow)

was continued on four standard anti-TB medications (INH, rifampin, pyrazinamide and ethambutol) together with amikacin and levofloxacin.

Eight months from presentation, he was admitted for abdominal pain and no fever. On examination, he had a tiny left supraclavicular lymph node and small left axillary lymph node. However, he had evidence of relapse of leukemia. There was new chromosomal abnormalities apart from $t(8;21)$ to indicate clonal evolution. Follow-up CT scan showed mediastinal lymph node slightly smaller and the hepatic and splenic lesions were stable. There was a marked increase in retroperitoneal lymph nodes near the bifurcation of the aorta. A biopsy of the left axillary lymph node showed myelocytic sarcoma. Induction chemotherapy with the same regimen was given with prompt resolution of abdominal pain.

Nine months from initial presentation, bone marrow showed morphologic and cytogenetic remission. Anti-tuberculosis treatment was continued without amikacin and levofloxacin. Subsequently, he received a total of four cycles of high-dose cytarabine (3000 mg/m^2) twice daily every other day for a total of six doses in each cycle. Ethambutol and pyrazinamide were discontinued after 10 months. A follow-up CT scan of the chest, abdomen and pelvis showed decreased mediastinal lymph nodes, hepatic and splenic lesions.

Eleven months from initial presentation, retroperitoneal lymph nodes cleared a month after starting induction chemotherapy, suggesting that they were caused by leukemic infiltrate. Peripheral blood count has been normal.

He was continued on anti-tuberculous medications for a year from his last positive culture (which was 5 months from initial presentation) because of bone involvement. He was turned down for sibling human leukocyte antigen (HLA) matched hemopoietic cell transplantation, because of concern of reactivation of tuberculosis. He was treated for 2 years with decitabine and he stayed in molecular remission in peripheral blood (by quantitative real-time-PCR for AML1/ETO $t(8;21)$) and had remained free of tuberculosis for the follow-up period of 5 years. Table 1 shows the timeline of the clinical course of the patient.

Discussion

The annual incidence of tuberculosis in Saudi Arabia was cited as 3.5–11.1 per 100,000 population in one study [8]. Patients with AML are at increased risk of infection with possibly increased morbidity and mortality. Febrile neutropenia and the development of blood stream infections are common among patients with neutropenia [9]. There is a potential for intersection between TB and AML, although typically during treatment of the malignancy. The reported

TB rate in acute leukemia varies from 28 per 1000 to 69 per 1000 in Western countries and India, respectively [10]. One study found that TB is more common among AML than acute lymphoblastic leukemia (ALL) patients despite the wider use of steroid in the latter group [10]. The rate of TB among AML patients in Saudi Arabia was 4 (3.1%) out of 128 patients [11]. The initial symptoms of tuberculosis might be undifferentiated from those of other infections in patients with AML. We presented a patient who had a concomitant TB and AML necessitating therapy initially for TB and subsequent delay of AML therapy to allow adequate TB treatment. The incidence of tuberculosis among AML patients was 6.3% in a study of 95 patients [12]. In a previous study of 12 AML patients, the median interval between TB and AML diagnosis was 13 weeks [7]. The majority (57.1%) of these patients developed TB during the induction phase of chemotherapy. One of the unique features of the present case is the prolonged febrile illness prior to the concomitant diagnosis of acute leukemia. Prolonged fever is one of the key presentation of TB among leukemia and non-leukemic patients. In a previous case report, prolonged febrile illness led to the diagnosis of disseminated TB in a patient who had three cycles of chemotherapy for childhood leukemia [6]. The present patient had a disseminated TB and it was cited that 8 (27.6%) of 26 leukemic patients had disseminated TB [7]. In a case report, an AML patient had a hemophagocytosis in the bone marrow, supraclavicular lymphadenopathy, and mediastinal and nodular pulmonary infiltrate [13] and one case had also disseminated tuberculosis [14]. The presentation of tuberculosis in general is usually classified as pulmonary and extra-pulmonary tuberculosis with variable proportions [8]. The current patient had a disseminated TB disease. One of the fears of the development of TB during acute leukemia is the potential delay in therapy of leukemia. In one study, no such delay was observed [10]. The proposed mechanism for the development of TB in patients with leukemia is a reduction in the CD4+ cells and the CD4+:CD8+ ratio in patient with acute lymphoblastic leukemia and those undergoing hemopoietic stem cell transplantation [15, 16]. The risk of TB among chronic myelogenous leukemia (CML) patients was 3.76 times those without CML [17].

The usual therapy of tuberculosis relies on the use of four anti-tuberculosis medications in areas where isoniazid resistance is high. The available data show that the rate of isoniazid resistance in Saudi Arabia is variable and ranges from 8.13 to 12.11% [8, 18, 19]. Thus, a four-drug therapy should be used initially in these patients pending final susceptibility pattern. The outcome of tuberculosis in AML patients was reported to be excellent utilizing the recommended therapy [7, 10, 12] with no alteration in the duration of the course of TB treatment in previously reported cases. However, the current patient had concomitant tuberculosis and AML at

Table 1 A summary of the course of the patient and key factual findings

Months relative to presentation	Clinical symptoms	Routine labs	CT scans	AML status including biopsy results	AML therapy	TB status including biopsy and culture results	TB treatment
-2	Fever and unwell	Normal	-	-	-	-	-
0 (initial presentation)	Fever and unwell	WBC count was $7.4 \times 10^9/L$; 14% blasts; hemoglobin 7.7 g/dL and platelet count $34 \times 10^9/L$	Significant right para-tracheal lymphadenopathy and mediastinal lymph nodes, multiple low attenuation lesions of the spleen, and low attenuation liver lesions and destructive lesion in the sternum and rib	Acute myeloid leukemia t(8;21), blasts 14% in bone marrow	-	Presumed tuberculosis	Empirical therapy with isoniazid, rifampin, pyrazinamide, and ethambutol
0.5	No fever	-	-	AML	Induction regimen with idarubicin 12 mg/m^2 for 3 days and cytarabine 100 mg/m^2 for 7 days	-	Isoniazid, rifampin, pyrazinamide, and ethambutol
3	Fever recurs	-	Worsening in lymph nodes with development of suprasternal mass	Remission	-	Suprasternal mass biopsy showed caseating granuloma, positive for AFB smear and positive GeneXpert for <i>M. tuberculosis</i> , and sensitive to Rifampin	Isoniazid, rifampin, pyrazinamide, and ethambutol
5	No fever	-	Interval worsening in skeletal changes with significant bony destruction and subpleural enhancing collection	Remission	Leukemia treatment was delayed due to continuous uncontrolled infection	Last positive culture for <i>M. tuberculosis</i>	Isoniazid, rifampin, pyrazinamide, and ethambutol Amikacin and levofloxacin were added
7	No fever	-	More hepatic lesions	Remission	-	Liver biopsy: granulomatous inflammation with focal necrosis and cultures were negative for <i>M. tuberculosis</i>	Isoniazid, rifampin, pyrazinamide, and ethambutol, amikacin and levofloxacin

Table 1 (continued)

Months relative to presentation	Clinical symptoms	Routine labs	CT scans	AML status including biopsy results	AML therapy	TB status including biopsy and culture results	TB treatment
8	Abdominal pain and no fever	WBC count was 3.3 x 10 ⁹ /L; 16% blasts; hemoglobin 9.9 g/dL and platelet count 44 x 10 ⁹ /L	Mediastinal lymph node slightly smaller and the hepatic and splenic lesions were stable, marked increase in retroperitoneal lymph nodes	Relapse of leukemia, a biopsy of the left axillary lymph node showed myelocytic sarcoma	Induction regimen with idarubicin 12 mg/m ² for 3 days and cytarabine 100 mg/m ² for 7 days	–	Isoniazid, rifampin, pyrazinamide, and ethambutol, amikacin and levofloxacin
9	No fever and no abdominal pain	–	–	Bone marrow biopsy: morphologic and cytogenetic remission	–	–	Isoniazid, rifampin, pyrazinamide, and ethambutol Amikacin and levofloxacin were discontinued
10	No fever	–	Decreased mediastinal lymph nodes, and hepatic and splenic lesions	–	Four cycles of high-dose cytarabine (3000 mg/m ²) twice daily every other day for a total of six doses in each cycle	–	Isoniazid and rifampin. pyrazinamide, and ethambutol were discontinued
11	Clinically well	Normal CBC	Retroperitoneal lymph nodes cleared	Remission	–	–	Isoniazid and rifampin
17	Clinically well	Normal CBC	–	Remission	For 2 years with decitabine	Cured	Isoniazid and rifampin were discontinued
60	Clinically well	Normal CBC	–	Complete Remission	–	Cured	–

presentation which complicated the course of both diseases. TB infection demonstrated a slow response despite the presence of a sensitive organism and treatment with 4 drugs for 5 months and then 6 drugs for another 4 months before gradual tapering of the regimen and eventually discontinuing therapy after a total of 17 months of treatment. AML went into remission but consolidation therapy was held due to unresolved TB infection and unfortunately AML relapsed at 8 months. Induction therapy was again successful and was followed by maintenance treatment. At final follow-up at 60 months, the patient was in remission of AML and had no evidence of active TB infection. In conclusion, the possibility of tuberculosis should be considered in the differential diagnosis of patients with pneumonia, persistent fever, and those with focal signs or symptoms suggestive of tuberculosis. Standard anti-tuberculosis therapy is usually sufficient, but response may be slow, even if the organism is sensitive, and may require the addition of second-line medications.

Compliance with ethical standards

Conflict of interest The authors have no conflicts to disclose.

Ethical approval The study was approved by the IRB of Johns Hopkins Aramco healthcare.

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