Tuberculosis in African Refugees from the Eastern Sub-Sahara Region

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ABSTRACT: **Background:** The southern region of Israel has recently experienced an influx of African refugees from the Eastern Sub-Sahara desert area. These influxes have led to a significant increase in incidence of tuberculosis (TB) in that region.

Objectives: To review the data of African refugees diagnosed with TB between January 2008 and August 2010 at a tertiary care regional hospital.

Results: Twenty-five TB cases were diagnosed, 22 of which presented with pulmonary TB, 3 with extra-pulmonary TB (EPTB), and 7 with combined pulmonary and EPTB. Only one case had concomitant human immunodeficiency virus (HIV) infection and multidrug-resistant TB. Fifteen patients underwent extensive radiological investigations including chest, abdominal and spine computed tomography, 1 was reviewed by magnetic resonance imaging, and 9 underwent tissue biopsy. Eighteen patients were admitted as suspected TB and 4 as suspected pneumonia or pulmonary infiltrates that could have been defined as suspected TB. All 24 HIV-negative cases were sensitive to first-line drugs for TB, except for one case that was resistant to streptomycin and one to rifampicin. All patients responded well to first-line therapy. The average duration of hospitalization was 8.7 days (range 1–36). Following diagnosis 23 patients were transferred to a quarantine facility.

Conclusions: We identified overutilization of medical resources and invasive procedures. For African refugees from the eastern Sub-Sahara who were HIV-negative and suspected of having TB, a sputum acid-fast smear and culture should have been the primary investigative tools before initiating treatment with four drugs (first-line), and further investigations should have been postponed and reserved for non-responders or for patients for whom the culture was negative. Physicians should maintain a high index of suspicion for EPTB in this population.

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Tuberculosis continues to be a global epidemic. More than two billion people, or approximately a third of the world population, is estimated to be infected with TB [1]. While the global incidence of TB peaked around 2003 it now appears to be gradually declining [2]. The TB burden is divided among countries with very low incidence rates such as Switzerland (4.9/100,000) [2,3] and countries with a very high incidence. Twelve of the 15 countries with the highest estimated incidence of TB are in Africa, where the TB incidence rate is estimated to be 363/100,000 [2]. Poverty, human immunodeficiency virus and drug resistance are major contributors to the global TB epidemic [4,5].

Multidrug-resistant TB (defined as TB resistant to rifampicin and isoniazid), or extensively drug-resistant TB (defined as a MDR-TB with additional resistance to any fluoroquinolones and to at least one of three injectable drugs used for TB treatment) has been reported by the World Health Organization in 25 countries in the European region and has become a growing concern [5]. Eastern European countries are among those with the highest rates of MDR-TB in the world [5,6]. Few studies have been published on the prevalence of MDR and XDR-TB in the Sub-Saharan area of Africa and current viewpoints suggest that MDR-TB is a growing concern in this area [7]. These concerns have caused countries with a low incidence to launch aggressive programs aimed at detecting and treating immigrants in an attempt to control the spread of TB and MDR-TB [3,8,9].

The incidence of TB in Israel has increased from 3.8/100,000 cases in 1989 to 10/100,000 in 1991 and to 11/100,000 in 1998, mostly due to waves of immigration from the former Soviet Union and Ethiopia, and has remained stable at about 5/100,000 cases between 2006 and 2008 [2,10-13]. We previously reported that the incidence of MDR-TB was rising in southern Israel, and has shifted mostly to immigrants from Eastern Europe [10].

In recent years, the southern region of Israel has seen an influx of African refugees crossing the border from Egypt on foot. Most of them came from Eritrea and Sudan, the eastern part of the Sub-Saharan desert area. Israeli Immigration Authorities have initiated a screening program for all African refugees that includes a chest X-ray. Individuals with suspi-

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MDR-TB = multidrug-resistant TB
XDR-TB = extensively drug-resistant TB

cious findings were referred to medical services for further investigation. Soroka University Medical Center, the major tertiary medical center in southern Israel, is the only medical facility with two negative-pressure isolation rooms and the capabilities to identify and treat TB in the southern region of Israel; therefore, all seriously ill African refugees were admitted and investigated at Soroka. The aim of this study was to outline the clinical data on tuberculosis among African refugees in southern Israel.

PATIENTS AND METHODS

The medical records of hospitalized African refugees at Soroka University Medical Center diagnosed with TB between January 2008 and August 2010 were identified and evaluated. Relevant data including demographic characteristics, clinical and laboratory findings, radiological workup and treatment regimens were obtained. Statistical analysis was performed using Excel (Microsoft 2003). Permission for the study was obtained from the Institutional Ethics Review Board.

RESULTS

Between January 2008 and August 2010, 25 patients were identified, 23 (92%) of whom were male, with an age range of 19–52 years (mean 26). Twelve had migrated from Eritrea, 10 from Sudan, 1 from Ethiopia, 1 from Nigeria and 1 from an unknown origin [Table 1]. All patients but one were HIV-negative.

Symptoms and laboratory and radiological data upon admission are presented in Table 2. The reasons for admission were suspected TB in 18 patients, fever and pulmonary findings such as pulmonary infiltrates and pneumonia in 4 patients, and 3 other patients were admitted for other reasons such as rhabdomyolysis, backache and a neck mass.

Of the 25 patients, 22 were diagnosed with pulmonary TB. Of these, 15 were considered as well-defined pulmonary TB, while 7 cases were considered as combined pulmonary and extra-pulmonary infection. Three additional patients were diagnosed with extra-pulmonary TB: 1 with mediastinal mass and pleural effusion, but no pulmonary lesions, 1 with psoas abscess and diskitis and 1 with isolated pleural effusion.

All patients in the cohort underwent sputum or gastric fluid acid-fast staining and culture. Of the 25 cases studied, 22 were identified with pulmonary TB based on the following: positive sputum smear and culture in 12/22 (54.5%), and negative smears but subsequent positive cultures in 9/22 (41%); one patient (4.5%) had a positive sputum smear but failed to grow TB colonies in culture. Of the three remaining cases with EPTB, in two cases the diagnosis was confirmed when MTB grew from pleural fluid while the third grew MTB from psoas abscess and in disk biopsy. Culture results of the seven patients with combined pulmonary and EPTB are shown in Table 3.

Fifteen patients underwent extensive radiological investigations: Nine had a chest computed tomography scan, five had an abdominal CT and one had spine CT and magnetic resonance imaging. Biopsies of identified lesions were performed in nine patients; two who underwent trans-bronchial biopsy and pleural biopsy could have been diagnosed as having pulmonary TB without biopsy if the treating physician would have waited for the outcome of the sputum culture, which subsequently grew MTB colonies..

The patient with HIV who presented with pulmonary TB grew an isoniazid-resistant strain of TB, whereas sensitivity to rifampicin and streptomycin fulfilled the criteria for MDR-TB. All other cultures were sensitive to isoniazid, one was resistant to streptomycin, and one was resistant to rifampicin. Treatment for TB was initiated in 14 cases (56%) after a positive acid-fast smear and prior to culture results. Of the 11 cases with negative acid-fast smear, in 5 cases treatment was

Table 1. Demographic characteristics of the population and length of stay in Israel prior to admission

	No. (%) (n=25)
Average age (yrs, range)	26 (19–52)
Gender: Male	23 (92%)
Country of origin	
Eritrea	13 (52%)
Sudan	9 (36%)
Ethiopia	1 (4%)
Nigeria	1 (4%)
Eastern Sub-Sahara, exact origin unknown	1 (4%)
Length of stay in Israel prior to admission	
0–1 month	11 (44%)
1–3 months	6 (24%)
3–6 months	5 (20%)
› 1 year	1 (4%)
Unknown	2 (8%)

Table 2. Symptoms, laboratory and radiological findings upon admission

	No. (%) (n=25)
Symptom	
Fever › 38.2°C	15 (60%)
Cough	20 (80%)
Sputum production	16 (64%)
Weight loss	11 (44%)
Dyspnea	4 (16%)
Chest pain	3 (12%)
Hemoptysis	2 (8%)
Back pain	2 (8%)
Laboratory findings	
Anemia (hemoglobin ‹ 12 g/dl)	14 (56%)
Thrombocytosis (platelets › 400,000/µl)	11 (44%)
Radiologic findings on chest X-ray	
Cavitary lesions	9 (36%)
Infiltrates	10 (40%)
Nodular lesions	3 (12%)
Pleural effusion	9 (36%)
Mediastinal widening	3 (12%)

HIV = human immunodeficiency virus
EPTB = extra=pulmonary TB

Table 3. Culture results of patients with combined pulmonary and extra-pulmonary TB

Sputum			Tissue			
Acid-fast smear	Culture	Location of biopsy	Acid-fast staining	Culture	Necrosis	Granuloma
–	+	Neck lymph node	–	+	+	+
–	+	Omental biopsy	–	+	+	–
–	+	Intraabdominal lymph node	–	+	+	+
–	+	Pleural biopsy	–	+	+	–
–	+	Neck mass/abscess	–	+	–	+
+	–	Pleural fluid	–	+	NA*	NA*
–	+	Pleural biopsy	–	+	–	–

Patients (n=7)
*NA = not applicable

initiated as soon as the smears came back negative due to a high index of suspicion for TB. Five additional patients with negative acid-fast smear began treatment following pathological data that demonstrated caseating granulomas. Only one patient was discharged without treatment, whereas treatment was initiated in the outpatient clinic as soon as a positive culture result was reported. All patients responded promptly to an appropriate anti-TB treatment.

The average length of hospitalization for the cohort was 8.7 days (range 1–36 days). Following the diagnosis of TB, 23 patients were transferred to a designated quarantine facility in central Israel, while two cases with negative sputum acid-fast smear were discharged and referred to directly observed treatment.

DISCUSSION

An ongoing refugee influx from TB-suspected global regions should prompt consideration for an appropriate screening protocol designed to identify and treat TB patients for the safety of the harboring community. In the southern regions of Israel an influx of refugees from high TB-burden countries raised the incidence of TB considerably since we identified 25 new cases during a short period. Furthermore, it is safe to assume that there were many more who did not approach medical services and were not screened or identified, thus increasing the risk of TB infection in the region.

All African refugee cases diagnosed and treated in this study contracted a sensitive variant of TB that responded well to first-line drugs except for one patient with HIV diagnosed as having MDR-TB. Treating physicians were concerned for possible MDR-TB and elected to initiate treatment in some of the patients with multidrug regimens of five drug combinations. In other cases TB drug therapy was delayed pending a definite diagnosis. In retrospect, this unnecessarily extended the length of hospitalization and in some cases delayed the initiation of anti-TB treatment.

Of the 25 cases in this study, 18 were admitted as suspected TB cases, either as a result of chest X-ray findings on screening or following classical symptoms combined with chest X-ray findings. Four other patients were admitted with fever, pleural effusions or were initially considered as pneumonia cases. In retrospect, all 22 could have been diagnosed as suspected TB, had a clear guideline been available. Therefore, 22 patients (88%) could have been diagnosed as suspected TB upon admission. Thus, it is felt that significant unnecessary medical resources were used in order to secure a definite diagnosis prior to initiating treatment. Some of these were costly, such as CT and MRI workups, tissue biopsies using invasive procedures and extended periods of hospitalization. One reason for these excessive investigations could have been their availability in the institute, while the other likely dominating factor was that our region was previously exposed to immigrants from Eastern European countries where MDR-TB and XDR-TB were prevalent, while data on the status of TB sensitivity in eastern Sub-Saharan African countries were not available, leading to longer time and additional resources invested to secure the diagnosis. Cohort data in this study imply that for any African refugee who presents to the medical services with classic TB symptoms combined with a radiological finding consistent with TB, the primary investigations needed to initiate treatment with four drugs (first-line) are HIV status, a sputum acid-fast smear and culture, while further investigations may be postponed and reserved for non-responders or for patients presenting with negative TB cultures.

In this small series we saw an unusually large number of patients who were HIV-negative but presented with EPTB upon biopsy. All cases in this category had negative acid-fast staining but TB diagnosis was established based on pathological data or on data from tissue culture. It appears that relying on acid-fast staining was not useful in these cases. The implication of the high percentage of EPTB is unclear, but it should alert clinicians to be aware of the possibility of EPTB in this population and to raise suspicion.

CONCLUSIONS

African refugees from the eastern part of the Sub-Sahara region who are HIV-negative and present with symptoms highly suggestive of TB (clinical and radiological) should be promptly and initially treated with a four-drug (first-line) regimen following an acid-fast smear of the sputum. Further investigation might be delayed and reserved for non-responders or for those whose sputum culture is negative. Physicians should have a higher index of suspicion for EPTB in this population.

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Capsule

Enforced viral replication activates adaptive immunity and is essential for the control of a cytopathic virus

The innate immune system limits viral replication via type I interferon and also induces the presentation of viral antigens to cells of the adaptive immune response. Using infection of mice with vesicular stomatitis virus, Honke et al. analyzed how the innate immune system inhibits viral propagation but still allows the presentation of antigen to cells of the adaptive immune response. The researchers found that expression of the gene encoding the inhibitory protein Usp18 in metallophilic macrophages led to lower type I interferon responsiveness, thereby allowing locally restricted replication of virus. This was essential for the induction of adaptive antiviral immune responses and, therefore, for preventing the fatal outcome of infection. The authors conclude that enforced viral replication in marginal zone macrophages was an immunological mechanism that ensured the production of sufficient antigen for effective activation of the adaptive immune response.

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Capsule

Treg cells are important regulators of immune homeostasis

Many people with autoimmune diseases experience disease flares in which disease symptoms worsen. These flares often subside for a while, only to return again. Rosenblum and collaborators sought to understand the immunological basis for this phenomenon using a mouse model of inducible T cell-driven autoimmunity in the skin that resolves spontaneously. Disease induction was accompanied by an initial expansion of effector T cells in the skin that was followed by an expansion of regulatory T cells (Tregs). Although Treg cells were present in the skin before disease induction, they proliferated in response to autoantigen expression and were more potent immune suppressors. Moreover, disease resolution was critically dependent on Treg cells. Treg cells persisted in the skin in high numbers after disease resolution and were better able to control autoimmune symptoms when autoantigens were reexpressed in the skin. These results demonstrate that Treg cells are important regulators of immune homeostasis and may be critical for containing disease flares often seen in autoimmune diseases.

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"To be capable of embarrassment is the beginning of moral consciousness. Honor grows from qualms"

John Leonard (1939-2008), American literary, television, film and cultural critic