Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignances

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Background and Objectives. Patients with hematologic malignancies are at increased risk of developing tuberculosis because of the T-cell immunodeficiency associated with the disease and/or its treatment. The objective of this study was to evaluate risk factors, clinical findings and the attributable mortality associated with tuberculosis in patients with hhematologic malignancies.

Design and Methods. We performed a retrospective review of the clinical records of 917 patients observed between 1990 and 2000. A risk classification for tuberculosis (low vs. high risk) was developed based on the underlying disease and previous exposure to agents that deplete T-cell mediated immunity. Patients with and without tuberculosis were compared by univariate and multivariate analyses with regard to demographic and clinical characteristics, underlying diseases and their treatment. The attributable mortality was assessed by matching cases and controls using the independent variables identified as risk factors as the matching parameters, and was estimated by subtracting the crude mortality of the controls from the crude mortality of the cases.

Results. We found 24 cases of tuberculosis (2.6%). Risk factors by multivariate analysis were malnutrition (OR 55.66, 95% CI 2.47–1254.82), use of fludarabine (OR 6.08, 95% CI 1.22–30.25), use of corticosteroids (OR 5.32, 95% CI 1.15–24.39) and belonging to the high-risk group (OR 3.73, 95% CI 1.09–12.76). The crude mortality of patients with tuberculosis was 75%, and the attributable mortality was 62.5% (risk ratio 6.0, 95% CI 2.03–17.70).

Interpretation and Conclusions. The mortality attributable to tuberculosis is high in patients with hematologic malignancies. The identification of risk factors may be useful for evaluating strategies to be applied in high-risk patients.

Key words: tuberculosis, cancer, risk factor, mortality.

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Tuberculosis remains a great public health problem worldwide, mainly because of poverty, overcrowding and human immunodeficiency virus (HIV) infection.[1] The association between tuberculosis and cancer has been recognized as significant for many years.[2] The incidence of tuberculosis may be particularly high in patients with hematologic malignancies because of the T-cell immunodeficiency caused by the underlying disease and/or its treatment. In addition, the diagnosis of tuberculosis may be problematic because the symptoms of tuberculosis can overlap those of the hematologic malignancy (particularly lymphoma), and the immunodeficiency may attenuate the clinical symptoms of tuberculosis. The prevalence of tuberculosis in patients with hematologic malignancies has been reported to be between 0.72%[3] and 2.6%.[4] The mortality rate of tuberculosis in these patients may be high,[3] possibly due to diagnosis delay. Therefore, the knowledge of risk factors and symptoms associated with tuberculosis may be useful to allow early interventions. In this study, we analyzed 917 patients with hematologic malignancies to evaluate risk factors, signs and symptoms and the attributable mortality associated with tuberculosis.

Design and Methods

We performed a retrospective review of the clinical records of all patients with hematologic malignancies registered in the Hematology Service of the Hospital Universitário Clementino Fraga Filho, a teaching hospital in Rio de Janeiro, Brazil, from January 1990 to December 2000, to

identify cases of tuberculosis. In addition to the review of clinical records, the cases were searched for by consulting the records of the Microbiology Laboratory and the Pathology Laboratory of the Hospital. Reviews were conducted manually by the authors. The study was approved by the Ethical Committee of the Hospital. A diagnosis of tuberculosis was made in the presence of one of the following criteria: (i) one or more positive cultures for *Mycobacterium tuberculosis*; (ii) biopsy material containing acid-fast bacilli and caseous necrosis; (iii) two sputum smears with acid-fast bacilli; (iv) one sputum smear with acid-fast bacilli plus characteristic radiological signs of tuberculosis in the lungs (alveolar infiltrates or cavities in the upper lobes or in the upper segment of the lower lobe); (v) clinical findings characteristic of tuberculosis (cough for >4 weeks, weight loss >10%, fever, night sweats) plus typical radiological signs (alveolar infiltrates or cavities in the upper lobes or in the upper segment of the lower lobe, miliary pattern) and clinical and radiological improvement with appropriate treatment for tuberculosis. Proven tuberculosis was established by criterion 1 and probable tuberculosis by criteria 2 to 5.

We classified the patients in two risk groups for tuberculosis based on the predominant type of immunodeficiency, according to the underlying disease and its treatment. Patients with diseases and/or treatments likely to cause significant impairment to T-cell mediated immunity were considered at high risk of developing tuberculosis. This group comprised patients with Hodgkin's disease (HD) and adult T-cell leukemia/lymphoma (ATLL), patients with lymphoproliferative diseases receiving high doses of corticosteroids or fludarabine, and hematopoietic stem cell transplant (HSCT) recipients. On the other hand, patients with conditions less likely to affect T-cell immunity were considered at low risk of developing active tuberculosis and included patients with acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), and lymphoproliferative diseases not receiving high doses of corticosteroids or fludarabine. A high-dose of corticosteroids was defined as a cumulative dose of prednisone (or an equivalent dose of another corticosteroid) of 14 mg/kg (corresponding to a dose of 1 mg/kg daily for 14 days).

In order to evaluate clinical signs and symptoms associated with tuberculosis and to identify risk factors for active tuberculosis we compared patients with (cases) and without tuberculosis (controls) by univariate and multivariate analysis. The following variables were compared: age, gender, underlying disease and its treatment, co-morbidities and clinical presentation. Co-morbidities and clinical manifestations were those present at the time of the diagnosis of tuberculosis for cases, and at any time during the course of the underlying hematologic disease for controls. In order to calculate the attributable mortality associated with tuberculosis, each patient with tuberculosis was matched to the most suitable control by using the independent variables identified in multivariate analysis as the matching parameters. The attributable mortality was determined by subtracting the crude mortality among controls from that among cases. Each patient's outcome (death or survival) was defined at the time of data collection. The risk ratio, which is the ratio of crude mortality rate of relative risk of the cases to that of the controls, was used as a measure of relative risk of death attributable to tuberculosis.

The SPSS 11.0 program was used for the statistical analyses. Dichotomous variables were compared using Fisher's exact test (two-tailed) or the χ^2 test, as appropriate. For continuous variables, the p value was calculated by means of the Wilcoxon rank-sum test. After univariate analysis, variables with a p value <0.1 were analyzed in a multivariate stepwise logistic regression model. Any p value less than 0.05 was assumed as statistically significant.

Table 1. Characteristics of the 917 patients with hematologic malignancies.

Characteristics of the patients	
Age, median (range)	48 (10 – 92)
Gender, male:female	527:390
Underlying disease, n (%)	
Non-Hodgkin's lymphoma	310 (33.8)
Hodgkin's disease	116 (12.6)
Multiple myeloma	112 (12.2)
Acute myeloid leukemia	109 (11.9)
Acute lymphoid leukemia	78 (8.5)
Chronic lymphoid leukemia	72 (7.8)
Myelodysplasia	66 (7.2)
Chronic myeloid leukemia	46 (5)
Hairy cell leukemia	8 (1)

Results

We identified 917 patients with hematologic malignancies. As shown in Table 1, the median age was 48 years, and non-Hodgkin's lymphoma (NHL) was the most frequent underlying disease (310 patients, 33.8%), followed by HD (116 patients, 12.6%) and MM (112 patients, 12.2%). Tuberculosis was diagnosed in 24 patients (2.6%). The diagnosis was based on positive culture in 14 patients (proven tuberculosis), two of whom also had histopathologic

Table 2. Characteristics of the 24 patients with tuberculosis.

Case	Gender	Underlying Disease	Risk group*	Site of tuberculosis	Radiographic Pattern	Diagnosis	Therapy	Outcome
1	M	HD	High	Pulmonary	Unknown	AFB, culture	None	Death
2	M	CLL	High	Pleuro-pulmonary	Pleural effusion	Clinical	REH	Death
3	F	MM	Low	Pulmonary	Unknown	Culture	None	Death
4	M	CLL	High	Lymphnode	Normal	Culture, histopathology	RHZ	Death
5	F	NHL	High	Pulmonary	Reticulonodular	Culture	RHZ	Death
6	F	NHL	Low	Pulmonary	Interstitial diffuse	Culture	RHZ	Death
7	M	NHL	High	Pulmonary	Alveolar; fibrosis in upper lobe	Culture	RHZ	Death
8	M	CLL	High	Pulmonary	Micronodular, diffuse	Culture, histopathology	RHZ	Death
9	M	NHL	High	Pulmonary	Interstitial, diffuse	Clinical	RHZ	Death
10	M	ATLL	High	Pulmonary	Alveolar	Culture	RHZ	Death
11	M	CLL	High	Pulmonary	Interstitial in upper lobe	Clinical	RHZ	Unknown
12	F	NHL	High	Pulmonary	Alveolar	Clinical	SEEO	Alive
13	F	NHL	High	Lymphnode	Normal	AFB, culture	RHZ	Death
14	M	NHL	High	Pulmonary	Reticular	Clinical	RHZ	Death
15	M	NHL	High	Pulmonary	Reticulonodular	Clinical	RHZ	Alive
16	F	MDS	High	Pulmonary	Interstitial	Culture	RHZ	Death
17	F	ALL	High	Pulmonary	Alveolar	AFB	SEO	Death
18	M	NHL	High	Pulmonary	Alveolar + cavitation	AFB	RHZ	Death
19	M	CLL	High	Pulmonary	Alveolar	Culture	RHZ	Death
20	F	MM	High	Pulmonary	Alveolar	AFB	RHZ	Alive
21	F	MDS	High	Pulmonary	Interstitial	AFB	RHZ	Death
22	M	LMC	High	Pulmonary	Fibrosis in upper lobe	AFB, culture	RHZ-S	Alive
23	M	HD	Low	Pulmonary	Alveolar	Culture	RHZ	Alive
24	M	NHL	Low	Pulmonary	Interstitial + alveolar	AFB, culture	SEEO	Death

**See definition in Design and Methods; M: male; F: female; HD: Hodgkin's disease; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; ATLL: adult T-cell leukemia/lymphoma; MM: multiple myeloma; MDS: myelodysplastic syndrome; AFB: acid-fast bacilli; REH: rifampin, ethambutol, isoniazid; RHZ: rifampin, isoniazid, pyrazinamide; SEEO: streptomycin, ethambutol, ethionamide, ofloxacin; SEO: streptomycin, ethambutol, ofloxacin; RHZ-S: rifampin, isoniazid, pyrazinamide, streptomycin.*

evidence of caseous necrosis, and four had positive acid-fast staining on direct examination of sputum. In four patients the diagnosis was based on the finding of positive acid-fast staining by direct examination of the sputum, and in the remaining six patients the diagnosis was based on clinical and radiological findings compatible with pulmonary tuberculosis associated with clinical improvement in response to treatment for tuberculosis (probable tuberculosis). Twenty-two patients had pulmonary tuberculosis, and the remaining two cases presented tuberculosis lymphadenopathy (Table 2).

The most frequent underlying disease among patients with tuberculosis was NHL with 11 cases, followed by chronic lymphocytic leukemia (CLL) with five cases. There were two cases each of HD, MDS and MM and one case each of CML and AML. The prevalence of tuberculosis was highest in CLL (6.9%), followed by NHL (3.5%), MDS (3%), CML (2.2%), MM (1.8%), HD (1.7%) and AML (0.9%). Only one patient had undergone an autologous HSCT (among 155 transplants performed during the study period).

Fever and cough were the most frequent clinical symptoms of tuberculosis, occurring in all patients with pulmonary tuberculosis. These manifestations were significantly more frequent in patients with tuberculosis than in those without tuberculosis (95.8% vs. 75.7%, p=0.02 and 95.8% vs. 40.9%, p<0.001, respectively). Shortness of breath was present in 66.7% of patients with tuberculosis and in 29.3% of patients without tuberculosis (p<0.001), and a weight loss of >10% was observed in 50% of patients with tuberculosis compared to 29.7% of patients without tuberculosis (p=0.04). Other clinical manifestations statistically significantly associated with tuberculosis were productive cough (75% vs. 24.3%, p<0.001), chest pain (41.7% vs. 14.9%, p=0.002) and hemoptysis (16.7% vs. 4.7%, p=0.03). By multivariate analysis, only cough (OR 14.72, 95% CI 1.73 – 125.48, p=0.01) and shortness of breath (OR 2.51, 95% CI 1.04 – 6.09, p=0.04) remained significantly associated with a diagnosis of tuberculosis.

Table 3 shows the univariate analysis of risk factors for tuberculosis. A total of 641 patients (70%) were classified as at high risk for tuberculosis and 276 were at low risk. The incidence of tuberculosis among high and low risk patients was 3.3% and 1.1%, respectively (OR 3.1, 95% CI 0.9–10.4, p=0.057). Neutropenia was present in 1.8% of patients with tuberculosis and 59.4% of patients without tuberculosis (OR 0.49, 95% CI 0.51–1.28, p=0.49). Factors associated with tuberculosis by univariate analysis were CLL (OR 3.24, 95% CI 1.03–9.59, p=0.03), malnutrition (OR 38.78, 95% CI 2.35–639, p=0.05), use of corticosteroids (OR 5.18, 95% CI 1.92–14.0, p=0.001) and fludarabine (OR

Table 3. Univariate analysis of risk factors for tuberculosis.

Variable	Tuberculosis		P value	OR (95% CI)
	Yes n=24	No n=893		
Gender, male:female	15:9	512:381	0.61	1.24 (0.54-2.86)
Age (y), median (range)	56 (12-86)	50 (10-92)	0.46	NA
Underlying disease				
Acute myeloid leukemia, n (%)	0	109 (12)	0.10	NA
Acute lymphoid leukemia, n (%)	1 (4)	77 (9)	0.71	0.46 (0.06-3.46)
Chronic myeloid leukemia, n (%)	1 (4)	45 (5)	1.00	0.82 (0.11-6.20)
Chronic lymphocytic leukemia, n (%)	5 (21)	67 (8)	0.03	3.24 (1.17-8.96)
Myelodysplasia, n (%)	2 (8)	64 (7)	0.69	1.18 (0.27-5.12)
Hodgkin's disease, n (%)	2 (8)	114 (13)	0.76	0.62 (0.14-2.68)
Non-Hodgkin's lymphoma, n (%)	11 (46)	299 (33)	0.21	1.68 (0.74-3.80)
Multiple myeloma, n (%)	2 (8)	110 (12)	0.76	0.65 (0.10-2.90)
Hairy cell leukemia, n (%)	0	8 (0.9)	1.00	NA
Autologous HSCT, n (%)	1 (4)	71 (8)	1.00	0.50 (0.02-3.58)
Allogeneic HSCT, n (%)	0	6 (0.7)	1.00	NA
Use of corticosteroids, n (%)	19 (79)	378 (42)	<0.001	5.18 (1.81-15.97)
Use of fludarabine, n (%)	2 (8)	10 (1)	0.03	8.03 (1.66-38.80)
Neutropenia, n (%)	9 (38)	389 (44)	0.55	0.78 (0.34-1.80)
Malnutrition, n (%)	1 (4)	1 (0.1)	0.05	38.8 (2.35-639)
Diabetes mellitus, n (%)	1 (4)	52 (6)	1.00	0.70 (0.09-5.31)
HIV infection, n (%)	2 (8)	44 (5)	0.34	1.75 (0.40-7.70)
Alcoholism, n (%)	0	6 (0.7)	1.00	NA
Chronic renal failure, n (%)	0	9 (1)	1.00	NA
High risk (risk stratification),* n (%)	21 (88)	620 (69)	0.05	3.08 (0.91-10.40)

OR: odds ratio; 95% CI: 95% confidence interval;
**see definition in Design and Methods. NA: not applicable.*

8.03 95% CI 1.66– 38.8, p=0.04). These variables plus risk classification for tuberculosis were entered in a logistic regression analysis. Risk factors for tuberculosis after multivariate analysis were malnutrition (OR 55.66, 95% CI 2.47–1254.82, p=0.01), use of corticosteroids (OR 5.32, 95% CI 1.15–24.39, p=0.03), use of fludarabine (OR 6.08, 95% CI 1.22–30.25, p=0.03) and risk classification (OR 3.73, 95% CI 1.09–12.76, p=0.04).

In the determination of the attributable mortality, using the four variables identified as risk factors matching the cases with 24 controls was successful in 100% of the cases for all variables. Eighteen of the 24 patients with tuberculosis died, this being a crude mortality rate of 75%, while the crude mortality rate of the controls was 12.5% (p<0.0001). The attributable mortality rate was 62.5% (OR 21.00, 95% CI 3.84-134.72). The risk ratio was 6.00 (95% CI 2.03-17.70).

Discussion

Our study yielded several relevant findings. First, the prevalence of tuberculosis in patients with hematologic malignancies was 2.6%, and was highest in patients with CLL. Second, tuberculosis was associated with non-specific symptoms such as cough and shortness of breath (OR 14.72 and 2.51, respectively). Third, the risk stratification proposed was able to discriminate patients at higher risk for tuberculosis, with an odds ratio of 3.7. Fourth, neutropenia was not associated with tuberculosis (as expected), whereas situations associated with severe impairment of T-cell immunity, such as malnutrition, use of fludarabine and corticosteroids, were risk factors for tuberculosis. Finally, the mortality attributable to tuberculosis was high (62.5%).

The reported prevalence of tuberculosis in patients with hematologic malignancies has ranged from less than 1% to greater than 10% in different studies.[3-10] This broad range may be due to different patients' characteristics, diagnostic criteria, as well as the prevalence of tuberculosis disease and infection in the regions where the studies were performed. In a review of 201 cases of tuberculosis complicating malignant diseases between 1950 and 1971 at a cancer center in the USA, the prevalence of tuberculosis was 0.96% in HD and 0.88% in NHL, and in contrast to patients with solid tumors, tuberculosis occurred more frequently after the use of chemotherapy.[3] In areas with a greater incidence of tuberculosis in the general population, the prevalence has been even higher. In an autopsy study in India, the prevalence was found to be 2.7%, and in a retrospective review of the clinical records of 2,321 patients with hematologic malignancies from Russia, the prevalence was

the same as that found in our study (2.6%).[4] In the present study, tuberculosis was more frequent in patients with CLL (6.9%), and contrary to older reports,[3] HD was not significantly associated with tuberculosis. CLL is classically associated with B-cell mediated immunodeficiency, with hypogammaglobulinemia and impaired opsonization.[11] In addition, although T-cell mediated immunity is also altered,[12] its clinical relevance seems to be much lower than B-cell immunodeficiency.[13] This is illustrated by the low incidence of tuberculosis (1 case in 60 patients) in CLL reported in older series.[14] By contrast, with the introduction of fludarabine and other agents that impair T-cell immunity, such as alemtuzumab (Campath), infections associated with T-cell immunodeficiency have emerged.[15-17] Fludarabine inhibits the cytokine-induced activation of STAT1, a molecule that plays a major role in cell-mediated immunity.[18] The introduction of fludarabine into the treatment of CLL caused a change in the spectrum of infections, with a higher incidence of infections associated with T-cell immunodeficiency, including tuberculosis.[19,20] In our study, patients with CLL were more likely to have tuberculosis, most probably because of the use of fludarabine, since CLL was significantly associated with tuberculosis only in the univariate analysis, whereas the use of fludarabine remained significant in the multivariate analysis.

The majority of our patients (58%) had a proven diagnosis of tuberculosis. Although we acknowledge that patients with possible tuberculosis could have other diagnoses, from a practical perspective, the management of such patients is the same as that of patients with proven tuberculosis.

Pulmonary involvement was present in more than 90 percent of our cases, and no case of miliary disease was diagnosed. Indeed, disseminated tuberculosis seems to be rather unusual in such patients, as shown by another series of tuberculosis in patients with cancer, in which pulmonary tuberculosis accounted for 63 percent of cases, and only one case of disseminated disease was identified.[21]

The most frequent symptoms of tuberculosis are persistent cough, fever, night sweats, weight loss, shortness of breath, hemoptysis and chest pain.[22] Since these findings are also frequent in patients with hematologic malignancies, the diagnosis of tuberculosis in these patients may be difficult. Furthermore, in addition to the overlap in clinical symptoms, the two diseases may occur simultaneously. In a study of 73 patients with confirmed or suspected malignancy who had samples of pulmonary secretions or tissue, six patients (8%) had a diagnosis of tuberculosis concomitant with the diagnosis of cancer.[7] In our study, most of the characteristic symptoms of tuberculosis occurred more frequently in patients with tuberculosis, but multivariate analysis identified only cough and shortness of breath as the statistically significant symptoms associated with tuberculosis. Therefore, no specific clues to the diagnosis of tuberculosis seem to arise from the analysis of symptoms.

We established a risk classification based on an assumption of the predominant immunodeficiency, according to the underlying disease and its treatment. Patients classified in the high-risk group had a three-fold greater risk of developing tuberculosis as shown by multivariate analysis. The other risk factors identified were the use of fludarabine, corticosteroids and malnutrition (limited due to the small number of patients with this characteristic), all factors associated with significant impairment in T-cell immunity.

There was no association between tuberculosis and HSCT in our study. This may be due to the fact that the large majority of HSCT in the present study were autologous (there were only 6 allogeneic HSCT). In a large study of more than 8,000 HSCT, the risk of tuberculosis after autologous HSCT was not different from that in the general population, whereas allogeneic HSCT recipients were at a greater risk (2.95 times, compared to the general population).[23] As more allogeneic transplants have been performed in our institution since 2000, we suppose that there will be a larger number of cases of tuberculosis in the future.

In the present study, the mortality associated with tuberculosis was very high, despite the fact that most patients (22 of 24) received appropriate therapy. This is in contrast with the 23 percent observed in a series of 30 cases in patients with cancer.[21] However, it is possible that our patients were more immunosuppressed: all patients in our study had a hematologic malignancy, compared to 63 percent in the other study, and only four patients (13%) in the other study had received corticosteroids (all died), compared to 79 percent in our study. The high mortality rate observed may be a consequence of a combination of severe immunosuppression and possible delay in the diagnosis.

The most important limitation of this study is its retrospective nature, with the possibility that some data might have missed in the process of reviewing the clinical records. In addition, considering the difficulty in making the diagnosis of tuberculosis, we cannot rule out the possibility that some controls had tuberculosis, especially those who died with an undiagnosed infection. In addition, some potentially important data (such as a history of tuberculosis prior to the diagnosis of the hematologic disease) could not be analyzed because this information was not available for a large proportion of patients. However, despite these limitations, our study may have some implications. Tuberculosis is a relevant health prob-

lem not only in regions with a high incidence in the general population because migration is becoming a common practice worldwide and also because a large number of individuals in developed and underdeveloped countries have latent tuberculosis (acquired in the past). In fact, the incidence of tuberculosis has increased worldwide, including in developed countries, especially in large cities.[24] The physician faces a dilemma when taking care of a patient with a hematologic malignancy and tuberculosis. The clinical manifestations are non-specific, and the mortality is high. Whereas in non-immunosuppressed individuals the tuberculin skin test usually defines whether the patient should receive prophylaxis, immunocompromised patients usually have negative skin tests. The risk stratification presented in our study may be of help in providing a rapid means of screening. Patients in this category who present with symptoms of cough and shortness of breath should be extensively screened for the diagnosis of tuberculosis. In addition, high-risk asymptomatic patients, especially those receiving corticosteroids or fludarabine, could be candidates for prophylaxis. Isoniazid is usually considered for prophylaxis in the general population, but its hepatic toxicity may be a limitation to its use among patients with hematologic diseases, especially HSCT recipients.

Therefore, clinical trials are needed to evaluate its efficacy and side effects in this setting. One strategy would be to select patients at high risk of developing tuberculosis and to randomize them to receive or not prophylaxis. Future research should also focus on the evaluation of the impact of newer therapies that impair T-cell defenses on the risk of tuberculosis, and the role of more rapid diagnostic tools, such as nucleic acid amplification and automated culture systems, in the management of tuberculosis in hematologic patients.

In conclusion, our study shows that the prevalence of tuberculosis in patients with hematologic malignancies is high, the diagnosis is difficult, the symptoms are non-specific, and the attributable mortality is high.

MN, FCQM: designed the study; FAS, JOM: collected and validated the clinical data; MN, FAS, JOM: analyzed the clinical data; MN, FAS: drafted the paper; MN, FCQM: approved the final version to be published. MN is primarily responsible for the paper. FAS and MN created the tables. All authors also declare they have no potential conflict of interest.

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