Original Study

Thoracic Complications in Chronic Lymphocytic Leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia. Patients with CLL often present with pulmonary symptoms and diagnoses. We performed a retrospective, single-center chart review evaluating all patients with CLL admitted with a thoracic symptom or diagnosis. Although pneumonia is frequent, there are an increasing number of noninfectious complications, which often require lower respiratory tract sampling.

Background: Chronic lymphocytic leukemia (CLL) is the most common lymphoproliferative disorder worldwide. Although thoracic complications are frequent in CLL, only limited data exist regarding the etiologies of these complications. **Materials and Methods:** A retrospective chart review was performed on all patients admitted to a tertiary care, CLL referral center, with CLL and a respiratory complaint from 2001 through 2013, to categorize pulmonary complaints and diagnoses. **Results:** There were 277 patients with CLL admitted on 409 occasions with respiratory complaints. The median age was 73 years, with a male to female ratio of 2:1. The majority of patients had a high-risk Rai classification and had received prior treatment. Common presenting symptoms included dyspnea, cough, and sputum production. The most common diagnoses were pneumonia (62.8%), with an identified organism in 44.7%, pleural effusions (31.8%), lung cancer (6.9%), and leukemic infiltrates (5.9%). Invasive procedures were performed 138 times: 70 bronchoscopies, 24 surgical lung biopsies, 10 computed tomography-guided lung biopsies, and 34 thoracenteses. In-hospital mortality was 24.9%. In a multivariable analysis, an elevated blood urea nitrogen level and creatinine, thrombocytopenia, and a presenting symptom of dyspnea correlated significantly with in-hospital mortality. **Conclusion:** Thoracic manifestations in CLL are common among hospitalized patients. Although infectious pneumonia remains most common, unusual or opportunistic infections may be increasing, and direct lung damage owing to CLL itself or to newer biologic agents are being diagnosed with lung tissue sampling. Recognition of these complications will allow earlier diagnosis, which may change management including removal of offending biologic agents or augmentation of treatment for CLL when infiltrative leukemic cells are present.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia worldwide. CLL is predominantly a disease of the elderly and is more frequently seen in males and Caucasians.[1] CLL is characterized by progressive accumulation of phenotypically mature CD5-positive malignant B lymphocytes in the peripheral blood, bone marrow, and lymph nodes.[2] The clinical course of CLL is highly variable, and treatment is often deferred in early or stable disease. However, as patients progress to a more advanced stage based on a classification system or develop symptomatic disease, treatment is required.[3] Treatment for CLL has evolved significantly over the last decade with the addition of newer chemotherapeutics and targeted molecular therapies. Owing to advances in therapy, patients with CLL have improved survival and may experience varied treatment regimens and are then subject to these agents' complications.[4]

Thoracic complications in patients with CLL are not uncommon in hospitalized patients, but limited data exist about the incidence and specific etiologies of these complications. Pleural, parenchymal, and airway disease may occur because of CLL itself, adverse events from therapeutic agents, infections from typical or opportunistic organisms, or from preexisting comorbidities. We report a large

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cohort of patients with CLL who presented with thoracic symptoms and signs and describe our diagnostic workup and eventual diagnoses, which illustrate a changing spectrum of diseases.

Materials and Methods

Patient Selection

This study was approved by the Long Island Jewish Hospital Institutional Review Board (IRB #10-188). The medical records of patients with CLL who were hospitalized at Long Island Jewish Medical Center with thoracic symptoms and/or signs between January 2001 and December 2013 were reviewed. These records were identified using International Classification of Diseases codes for respiratory diseases and CLL. Patients who were admitted for elective surgical procedures and developed thoracic complications related to their surgery, or who were admitted for decompensated congestive heart failure were excluded. Information regarding CLL and hospital admission and laboratory values were recorded.

Diagnostic Criteria

Diagnostic criteria included: (1) Pneumonia was diagnosed if a pulmonary infiltrate was present on radiography with symptoms and/or signs of cough, shortness of breath, or abnormal lung sounds with or without fever. Organisms were attributed to pneumonia if they were identified in blood, sputum, or from biopsy specimens. A diagnosis of pneumonia was excluded if an alternative diagnosis was discovered in the absence of an identifiable organism. (2) Bronchopulmonary leukemic infiltrates (BPLI) were defined by radiographic opacities in addition to parenchymal infiltration by leukemic cells on lung biopsy. (3) Malignant pleural effusions were defined by the presence of malignant cells on cytologic examination of the pleural fluid. They were further subdivided as leukemic effusion if confirmatory flow cytometry suggested leukemia. (4) Pulmonary leukostasis was defined as dyspnea with a leukocyte count $\geq 250 \times 10^9$/L with or without radiographic evidence of infiltrates and without signs of an infectious etiology and was subsequently treated with leukopheresis. (5) A diagnosis of organizing pneumonia was made on pathologic examination showing the presence of buds of granulation tissue ranging from fibrin exudates to collagen-containing fibroblasts in the absences of an infectious cause.[5] (6) Richter syndrome was defined as evidence of transformation of CLL to a more aggressive B-cell lymphoma via biopsy of the bone marrow, lymph nodes, or lung.

Statistical Analysis

Data are reported as medians and ranges. Continuous and categorical variables were summarized using descriptive statistics. Univariable comparisons between groups for continuous variables were performed using either the *t* test or the Mann-Whitney test, as appropriate. The χ^2 test or Fisher exact test was used as appropriate to examine associations between categorical variables.

We performed a multivariable logistic regression analysis to examine associations between in-hospital death and demographics, presenting symptoms, and laboratory markers, using records from patients' first admission. Some variables were dichotomized to facilitate comparison and clinical interpretation. All candidate variables that were individually associated with the outcome were entered into the regression model in order to assess their aggregate effect on in-hospital death. We then applied a backward selection algorithm in order to remove factors that did not contribute significantly to the model, thus arriving at a more parsimonious one. The Hosmer-Lemeshow goodness-of-fit statistic and area under the receiver operating characteristic curve were used to assess model fit. Odds ratios (ORs) (unadjusted and adjusted) are presented along with the corresponding 95% confidence intervals (CIs). All analyses were generated using SAS 9.3 (SAS Institute Inc, Cary, NC).

Results

There were 2602 hospital admissions of patients with CLL from 2001 through 2013: 277 eligible patients were identified, accounting for 409 (15.7%) admissions that were attributed to a thoracic diagnosis. The majority of patients, 197 of 277, were admitted only once, 54 patients were admitted twice, 12 had 3 admissions, and 14 patients were admitted more than 3 times. Patient characteristics are described in Table 1. Of the 409 admissions, 157 (57%) were high-risk, Rai Stage III to IV indicating advanced disease, 64 (23%) patients were intermediate risk (Stage I-II), and 177 (64%) of 277 patients had received prior treatment for CLL.

The majority of patients presented with multiple respiratory complaints, as described in Table 2. The most common presenting symptoms were as follows: dyspnea (71%), cough (68%), sputum production (34%), and chest pain (21%). Additionally 205 (50%) patients had fever on presentation. Admission median leukocyte count was 19.1 $\times 10^9$/L (range, 0.2-415.6 $\times 10^9$/L), median absolute neutrophil count was 4.72 $\times 10^9$/L (range, 0.0-59.3 $\times 10^9$/L), and the median platelet count was 145 $\times 10^9$/L (range, 1-894 $\times 10^9$/L). A lactate dehydrogenase was obtained in 185 patients, and the median value was 300 units/L (range, 95-11,083 units/L). The median blood urea nitrogen (BUN) was 24 mg/dL (range, 5-150

Table 1 Characteristics of Patients With CLL Hospitalized With Thoracic Complaints

Characteristics (n = 277 Patients)	No. Patients (%)
Age, y	
Median	73
Range	40-96
Race	
White	215 (78)
Black	39 (14)
Asian	11 (4)
Not reported	12 (4)
Gender	
Male	179 (65)
Female	98 (35)
Ever-smoker	148 (57)
Rai risk group	
Low-risk (Stage 0)	56 (20)
Intermediate (Stage 1-II)	64 (23)
High-risk (Stage III-IV)	157 (57)
Prior treatment for CLL[a]	177 (64)

Abbreviation: CLL = chronic lymphocytic leukemia.
[a]Prior treatment includes any combination of chemotherapeutic and/or biologic agents used for the treatment of CLL.