Brief report

Respiratory tract infections and subsequent risk of chronic lymphocytic leukemia

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Recent evidence suggests that chronic lymphocytic leukemia (CLL) might occur following a response to an infectious agent. We conducted a population-based study including 4249 CLL patients diagnosed in Denmark from 1977 to 1997 and 15 690 frequency-matched controls to quantify risk of CLL following various airway infections. Through data linkage we gathered information on hospital inpatient/outpatient discharges that listed infections present at least 1 year prior to CLL. Using logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs). Personal history of pneumonia was associated with significantly increased CLL risk (OR = 1.4; 1.2-1.8); risk was restricted to 1 to 4.99 years prior to CLL diagnosis (OR = 1.6; 1.2-2.0). Individuals with 3 or more prior pneumonia events had a significant 2.5-fold (1.1-5.6) elevated CLL risk, and risk increased with the number of pneumonia episodes (P_{trend} < .001). None of 9 other respiratory-tract infections was significantly associated with CLL risk. Pneumonia might be a potential CLL trigger or it could represent premalignant immune disruption preceding CLL. (Blood. 2007;109:2198-2201)

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Introduction

Chronic lymphocytic leukemia (CLL) accounts for approximately 30% of all leukemia and is the most common form of leukemia among older adults in Western countries.[1] Currently almost one third of CLL patients do not survive beyond 10 years. CLL originates from B cells (B-CLL) in 95% of patients, with a minority deriving through malignant transformation of T cells (T-CLL).[2] Although male sex, advanced age, white race, and family history of CLL or other hematolymphoproliferative cancers are recognized risk factors,[1,3] the etiology of CLL is largely unknown.

Recent studies have observed restricted V_H gene usage in CLL cells, suggesting that antigens involved in CLL pathogenesis share certain specific features, consistent with the established understanding that clonal V_H mutations seen in B-CLL cells are the product of a classic antigen-driven process.[4-7] Nonetheless, in a recent large population-based study, we found that personal or family history of autoimmune disease was generally not associated with risk of CLL.[8]

We were intrigued by recent reports by Hamblin,[9] Ghiotto et al,[10] and Chiorazzi et al[11] that the development of CLL might be a response to common infectious agents, such as encapsulated bacteria.[10] To test this hypothesis, we conducted a population-based assessment of hospital discharge records for typical respiratory-tract infections among all CLL cases in Denmark over a 20-year period (n = 4249), along with more than 15 000 frequency-matched controls.

Patients, materials, and methods

Patients, controls, and applied classifications

Briefly, in the beginning of the study period, the Kiel diagnostic classification[12] was applied by most hematopathologists in Denmark. This classification system was replaced by the Revised European American Lymphoma (REAL) system in the 1980s and, most recently, the World Health Organization (WHO) classification in the mid-1990s.[13] In Denmark, every physician is obliged by law to report each case of cancer to the registry. Each individual in Denmark receives a unique personal identification number, and every death along with the date of death is recorded in the nationwide Danish Cancer Register.[14] In this study, all incident CLL patients diagnosed from 1977 to 1997 were selected from the Danish Cancer Registry.[14] The Danish Cancer Registry became a nationwide registry in 1943, but we limited the selection of CLL patients (International Classification of Diseases, 7th revision [ICD7] code: 204.0) to those diagnosed after January 1, 1977, because patients with malignant disease who died before that date could not be linked to the Danish Inpatient and Outpatient Registry.[8,15] For each case subject, information on the unique personal identification number (encodes sex and date of birth) and date of diagnosis of CLL was collected. Four control subjects were randomly selected for each case subject from the Danish Central Population Registry.[8,15] Cases and controls were matched by sex, year of birth (within 5 years), and county of residence. Patients and controls were linked with the population-based Danish Inpatient (1977-1997) and Outpatient (1994-1997) Registers to collect information on discharges that listed certain defined airway infections (Table 2). Informed consent was waived, and an exemption from Institutional Review Board (IRB) review was obtained from the National Institutes of Health (NIH) Office of Human Subjects Research because we used existing data without personal identifiers.

Statistics

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) as measures of relative risk using unconditional logistic regression, adjusting for sex, age at diagnosis, and year of diagnosis. Airway infection data were restricted to those infections that occurred more than 1 year before CLL diagnosis for patients and matched controls. We also examined the association between CLL risk and number of infection events (1, 2, and 3 or

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more) and time from discharge that listed a defined airway infection until CLL diagnosis (1-4.99, and 5 or more years latency). In addition, we performed separate analyses to examine the association between CLL risk and airway infections occurring less than 1 year before CLL diagnosis for patients and matched controls.

Results and discussion

A total of 4249 CLL patients and 15 690 matched population-based controls were included. Median age (interquartile range) at diagnosis for patients was 71 years (63-79 years); the fraction of subjects younger than 65 years was 31%. The majority of persons were males (Table 1).

Pneumonia and CLL risk

In analyses restricted to infections that occurred more than 1 year before CLL diagnosis for patients and their corresponding controls, we found significantly increased risk of CLL associated with personal history of pneumonia (OR = 1.4, 95% CI 1.2-1.8; Table 2). Elevated risk was restricted to 1 to 4.99 years prior to CLL diagnosis (OR = 1.6, 95% CI 1.2-2.0; Table 2). Risk rose substantially among subjects with 3 or more pneumonia events (OR = 2.5, 95% CI 1.1-5.6). In addition, we observed a highly significant dose-response trend between number of pneumonia episodes and CLL risk ($P_{trend} < .001$).

Because the incidence of CLL is almost 2 times higher in males than in females[1] and the incidence of both CLL and pneumonia increases with age,[1,16] we also conducted analyses stratified by sex and age. Risk of CLL associated with pneumonia did not differ significantly by sex ($P = .57$) or by age (< 65 years versus ≥ 65 years, $P = .55$; Table 2).

In a separate analysis restricted to the period less than 1 year before CLL diagnosis, we observed the most prominent elevation of CLL risk associated with pneumonia (OR 5.9, 95% CI 4.5-7.7; 147 CLL patients versus 92 controls). Part of this elevation might reflect diagnostic evaluation for CLL following hospitalization for pneumonia. Although there was a suggestion of increased CLL risk associated with a range of other respiratory infections (Table 2), the precision of the risk estimates for most infection events was limited due to small numbers.

Table 1. Characteristics of chronic lymphocytic leukemia patients and controls

Variable	Patients	Controls
Total no.	4 249	15 690
Age, median (interquartile range), y	71 (63-79)	71 (63-78)
Age group, n (%)		
Younger than 65 y	1 286 (30)	4 875 (31)
65 y or older	2 963 (70)	10 815 (69)
Sex, n (%)		
Male	2 552 (60)	9 448 (60)
Female	1 697 (40)	6 242 (40)
Calendar year, median (interquartile range)	1988 (1983-1993)	1988 (1983-1993)
Personal history of any defined airway infection, n (%)*		
1 infection	152 (3.6)	444 (2.8)
2 infections	40 (0.9)	126 (0.8)
3 or more infections	34 (0.8)	116 (0.7)

*Pneumonia, bronchitis, lower-airway unspecified, laryngitis, nasopharyngitis/pharyngitis, upper-airway unspecified, sinusitis, otitis media/mastoiditis, influenza, and tuberculosis.

Table 2. Association between prior history of airway infection and risk of chronic lymphocytic leukemia

Infection category/site	Patients	Controls	OR (95% CI)
Lower airways			
Pneumonia	127	330	*1.4 (1.2-1.8)*
Latency interval, y*			
1-4.99	93	221	*1.6 (1.2-2.0)*
5 or more	44	124	1.3 (0.9-1.8)
No. of infections			
1	100	267	*1.4 (1.1-1.8)*
2	17	48	1.3 (0.8-2.9)
3 or more	10	15	*2.5 (1.1-5.6)*
Age at CLL diagnosis, y			
Younger than 65	6	21	1.1 (0.4-2.7)
65 or older	121	309	*1.5 (1.2-1.8)*
Sex			
Male	77	210	*1.3 (1.0-1.8)*
Female	50	120	*1.5 (1.1-2.2)*
Bronchitis	76	278	1.0 (0.8-1.3)
Lower-airway infection, unspecified	20	54	1.4 (0.8-2.3)
Upper-airways, sinus, and middle ear			
Laryngitis	9	20	1.7 (0.8-3.7)
Nasopharyngitis/pharyngitis	3	10	1.1 (0.3-4.0)
Upper-airway infection, unspecified	6	27	0.8 (0.3-2.0)
Sinusitis	6	11	2.0 (0.8-2.0)
Otitis media/mastoiditis	10	25	1.5 (0.7-3.1)
Other			
Influenza	10	28	1.3 (0.6-2.7)
Tuberculosis	11	30	1.3 (0.7-2.7)

ORs were adjusted for age, calendar time of CLL diagnosis, and sex. The table includes only events that occurred more than 1 year prior to CLL diagnosis. Applied ICD 8th and 10th revisions codes are as follows: pneumonia: ICD 8: 480, 481-482, 483.08, 483.09, 484-486; ICD 10: J12-J16, J18; bronchitis: ICD 8: 491; ICD 10: J41, J42; lower-airway unspecified: ICD 8: 466; ICD 10: J208, J209, J218, J219, J22; laryngitis: ICD 8: 506; ICD 10: J37; nasopharyngitis/pharyngitis: ICD 8: 460, 502; ICD 10: J00, J31; upper-airway unspecified: ICD 8: 461-465; ICD 10: J01, J208, J209, J308, J309, J04-J06; sinusitis: ICD 8: 503; ICD 10: J32; otitis media/mastoiditis: ICD 8: 381.19, 381.29, 383.19; ICD 10: H652, H653, H701; influenza: ICD 8: 470-474; ICD 10: J10, J11; tuberculosis: ICD 8: 011-019; ICD 10: A15-A19, B90.

Since outpatient data were only available beginning in 1994, we examined the association separately for infections diagnosed from 1977 to 1993 and 1994 to 1997; risk estimates were virtually the same. Because subjects could contribute pneumonia episodes to more than 1 latency interval, the latency totals do not sum to the total number of people with pneumonia. Risk estimates stratified by latency were virtually unchanged when the 1- to 4.99- and 5-or-more–year intervals were analyzed simultaneously in a multivariate model.

OR indicates odds ratio; CI, confidence interval; and italic entries have *P* values less than .05.

*Time from discharge listing a defined airway infection until CLL diagnosis.

Common airway pathogens triggering CLL development?

Recent literature has described restricted V_H gene usage in CLL cells, suggesting that there might be a common antigen involved in CLL pathogenesis and that clonal V_H mutations seen in B-CLL cells are the product of a classic antigen-driven process.[4-7] The presence of somatic hypermutation in immunoglobulin genes indicates that precursor cells for CLL derive from cells that have participated in the germinal-center reaction and further supports this hypothesis.[6] Our findings of a significant 60% elevated risk of CLL in the 1- to 4.99-year latency interval fit well within this framework and suggest that respiratory-tract infectious agents causing pneumonia might be triggers for CLL development. Consistent with this, we observed a significant ($P_{trend} < .001$) dose-response relationship between pneumonia and CLL (ie, individuals who experienced 3 or more episodes of pneumonia had a substantially higher risk of CLL compared with those who had only 1 prior pneumonia event).

Because there is selective V_H usage in CLL, it is plausible that 1 or a few related microbes could be implicated. *Streptococcus pneumoniae* and *Haemophilus influenzae* are major causal agents for pneumonia and both are encapsulated bacteria, for which antibody response is crucial. Potentially, one might conjecture that CLL is a result of such microbe stimulation of lymphocytes in a germinal center, influenced by other extrinsic factors and/or in combination with biologic host susceptibility. Unfortunately, in our study we did not have information on V_H mutation status or other clinical measures for individual patients. Therefore we were unable to test if individuals with a history of pneumonia are more likely to develop mutated or unmutated CLL disease.

Premalignant immune disruption preceding CLL?

As an alternative explanation for the observed association between pneumonia and CLL risk, the occurrence of pneumonia could be a premalignant manifestation due to immune disruption preceding CLL. Multiple myeloma (MM) is associated with the premalignant condition monoclonal gammopathy of undetermined significance (MGUS)[17-19]; however, it is unknown whether MGUS precedes all MM cases or if MM can arise de novo.[20,21] CLL has a parallel precursor state, monoclonal lymphocytosis of undetermined significance (MLUS; also called monoclonal B-cell lymphocytosis; MBL), which has been suggested as the cellular counterpart of MGUS.[22-24] Very similar to the relationship between MGUS and MM, it remains unclear whether MLUS precedes all CLL cases or if a subset of cases has an alternate route that develops rapidly and bypasses any precursor state. It is possible that late-stage precursor disease (MLUS and MGUS) might lead to decreased IgG, IgA, and IgM levels enhancing vulnerability to pneumonia. We have also recently reported an increased risk of MM among subjects with a previous personal history of pneumonia.[25]

Influence of undetected early stage CLL

It is also possible that the observed association between pneumonia and subsequent CLL risk might arise due to the influence of undetected early stage CLL. However, given the increased risk of CLL among individuals with a pneumonia event in the rather extended period (5 years) preceding CLL, we do not feel that this is the plausible explanation. Since a complete blood count would be a standard diagnostic study in subjects being evaluated and followed with pneumonia, early stage CLL would likely be detected at or shortly after onset of pneumonia. However, in certain cases, it cannot be entirely ruled out that an early stage CLL diagnosis was missed. For example, in an older patient, a manual differential showing lymphocytes in excess might have been overlooked if a leukocytosis was present. Unfortunately, the information available in our database does not allow retrieval of individual detailed clinical data that would allow us to evaluate the role of MLUS or undetected early stage CLL directly. Thus, our findings need to be tested in future epidemiologic studies that include medical-record validation of detailed clinical, diagnostic, prognostic, and treatment data.

We used a register-based case-control design that minimized recall bias and allowed us to evaluate risk by age and sex in a very large population–based sample. An important limitation was the unavailability of outpatient data for most years (1977-1993), which led to underascertainment of certain infections. Also, although it would have been interesting to study CLL risk subsequent to other infection sites, our data collection included only airway infections. Another limitation is the reliance on hospital data, which likely caused overascertainment of more severe infections and infections complicated by other medical illness. Furthermore, although history of infections was assessed among matched controls using the same hospital discharge registries, theoretically, bias might have been introduced if subjects who were predisposed to develop CLL also had more severe infections, leading to more frequent hospitalization. The lack of information on factors related to pneumonia, such as smoking, might be considered a limitation, but because there are no extrinsic environmental established risk factors for CLL, it is unlikely that this lack introduced bias.

Our findings suggest that lower–respiratory-tract infectious agents causing pneumonia might be potential triggers for CLL development. An alternative explanation is that pneumonia could be a consequence of immune disruption in late-stage precursor (MLUS) disease preceding CLL.

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Authorship

Contribution: O.L. and E.A.E. designed the study. L.M., G.G., and L.R.G. obtained data. J.S.R., O.L., and E.A.E. analyzed data. O.L. initiated this work and wrote the report. All authors (O.L., J.S.R., N.E.C., L.M., G.G., L.R.G., and E.A.E.) were involved in the interpretation of the results, read, gave comments, and approved the final version of the manuscript. J.S.R., O.L., and E.A.E. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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