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Community-acquired infections associated with increased risk of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia

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Summary

Emerging evidence supports the role of immune stimulation in the development of lymphoplasmacytic lymphoma/Waldenström Macroglobulinaemia (LPL/WM). Using the population-based Surveillance, Epidemiology End Results-Medicare database we investigated the exposure to 14 common community-acquired infections and subsequent risk of LPL/WM in 693 LPL/WM cases and 200 000 controls. Respiratory tract infections, bronchitis (odds ratio (OR) 1.56), pharyngitis (OR 1.43), pneumonia (OR 1.42) and sinusitis (OR 1.33) and skin infection, herpes zoster (OR 1.51) were all significantly associated with subsequent increased risk of LPL/WM. For each of these infections, the findings remained significantly elevated following the exclusion of more than six years of Medicare claims data preceding LPL/WM diagnosis. Our findings may support a role for infections in the development of LPL/WM or could reflect an underlying immune disturbance that is present several years prior to diagnosis and thereby part of the natural history of disease progression.

Keywords

Lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia; Infection; respiratory tract infection; herpes zoster; community-acquired infection

Introduction

Lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinaemia (WM) is a rare indolent type of non-Hodgkin lymphoma (NHL), morphologically characterized by the proliferation of lymphoplasmacytic cells in the bone marrow and the demonstration of IgM monoclonal gammopathy (Owen *et al*, 2003). The annual age-adjusted incidence of LPL/WM in the United States is 3.8 per 1 million persons (Wang *et al*, 2012). Risk factors include advancing age, male gender and white race, while familial clustering has also been

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observed (Wang *et al*, 2012). IgM monoclonal gammopathy of undetermined significance (MGUS) carries a 1-1.5% annual risk of progression to LPL/WM (Kyle *et al*, 2002).

Somatic immunoglobulin gene mutations observed in small case studies advocate a role for repeated antigenic stimulation in the development of LPL/WM (Wagner *et al*, 1994; Aoki *et al*, 1995). Inflammation resulting from exposure to infectious antigens may promote malignancy (Mantovani *et al*, 2008). Alternatively, associations may reflect a subclinical immune impairment within patients, increasing the propensity to infections and/or LPL/WM development.

Owing to the rarity of LPL/WM, few studies have investigated the prior infection exposure and subsequent risk of LPL/WM (Koshiol *et al*, 2008; Giordano & Henderson, 2007; Kristinsson *et al*, 2010). In the largest population-based study to date (n=2,470 LPL/WM cases), (total) infections were associated with a 30% increased risk of LPL/WM, with an excess risk observed for pneumonia, sinusitis, influenza, pyelonephritis, herpes zoster and septicaemia (Kristinsson *et al*, 2010). Additionally, positive associations with hepatitis B and C and human immunodeficiency virus (HIV) have been reported (Koshiol *et al*, 2008; Giordano & Henderson, 2007) albeit not consistently in the literature (Leleu *et al*, 2007).

Using the United States, Surveillance, Epidemiology and End Results (SEER) -Medicare database we investigated associations between common community-acquired infections and subsequent risk of LPL/WM.

Materials & Methods

Since 1973, the SEER cancer registry network has been collecting cancer data from state and metropolitan area cancer registries and currently covers 28% of the USA population (Engels *et al*, 2011; <http://seer.cancer.gov/about/overview.html>). Medicare, a federally funded programme, provides health insurance to approximately 97% of US citizens aged 65 years or older (Warren *et al*, 2002; Engels *et al*, 2011). Medicare is provided in two parts – Part A, which all beneficiaries receive, covers inpatient hospital stays and Part B, of which 95% of recipients additionally purchase, covers physician and outpatients services (Warren *et al*, 2002; Gornick *et al*, 1996). Using a deterministic algorithm, individuals in the SEER registries are linked to Medicare claims data by social security number, name, sex and date of birth (Potosky *et al*, 1993). This linkage has successfully matched 94% of SEER cancer cases to Medicare recipients (Engels *et al*, 2011). With the exception of Part A (inpatient hospital claims available from 1986), Medicare claims data is available from 1991 (Warren *et al*, 2002; Engels *et al*, 2011). Medicare beneficiaries may choose to enrol in a health maintenance organization (HMO) scheme, which provides capitated care; claims of this nature are not submitted to Medicare and therefore there is no information on specific medical conditions for these individuals (Engels *et al*, 2011). Use of SEER-Medicare dataset for the current study was approved by the National Cancer Institute. No other ethical review was required.

Cases, defined as individuals with a primary LPL/WM diagnosis between 1992-2005 (International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3] codes 9761/3), were aged 66-99 years with 13 months of prior Part-A, Part-B and non-HMO coverage preceding diagnosis. From a 5% random sample of Medicare beneficiaries without cancer residing within SEER areas (provided as part of the SEER-Medicare database), 200,000 controls were selected to increase the power to detect statistical significance. Controls were matched to all cancer cases in SEER and not just LPL/WM cases (Engels *et al*, 2011). As of 1 July of the selected calendar year, controls were alive, free from malignancy and had 13 months of prior Medicare coverage. Controls were matched to

cases by gender, age and calendar year of diagnosis. Each control had the potential to be selected multiple times within different calendar years or later as a cancer case themselves (Engels *et al*, 2011).

Exposure was defined as having at least one Medicare (inpatient, outpatient or physician) claim for selected community-acquired infections prior to diagnosis/selection. Infections were selected based on their commonality within the general US population (prevalence among controls had to be recorded as 0.5% or greater). Claims occurring <13 months prior to LPL/WM diagnosis/selection were excluded to minimize ascertainment bias or reverse causality resulting from undetected LPL/WM.

Unconditional logistic regression was used to derive odds ratios (OR) and associated 95% confidence intervals (CI) adjusted for age, gender and year of selection. We accommodated for repeated selection of controls and the possibility that controls may have later developed LPL/WM and in doing so became a LPL/WM case themselves in the variance computation analysis (Anderson *et al*, 2008; Quinlan *et al*, 2010). Crude adjustment for multiple comparisons was undertaken using Bonferroni correction, i.e. $p = 0.05/14 = 0.00357$. To determine if a cause and effect relationship was evident, analysis was carried out by assessing associations in time intervals. Analyses were stratified by race; however, findings (with the exception of non-Hispanic whites) were based on small numbers, and so are not presented here. Data is presented including HIV cases ($n=2$) as exclusion produced unaltered results.

Results

A total of 693 LPL/WM and 200,000 population controls were identified. As controls were matched to all cancer cases (and not just LPL/WM cases), minor differences in characteristics were observed; cases were more likely to be female, white, elderly and have longer Medicare coverage than controls (Table I).

An excess risk of LPL/WM was associated with five of the 14 infections investigated (Table II). Following Bonferroni correction, LPL/WM cases were more likely than controls to have had prior claims for respiratory tract infections, including bronchitis (OR 1.56, 95% CI 1.32-1.84), pneumonia (OR 1.42, 95% CI 1.18-1.72), pharyngitis (OR 1.43, 95% CI 1.17-1.76) and sinusitis (OR 1.33, 95% CI 1.12-1.60). Herpes zoster was significantly associated with a 51% excess risk of LPL/WM (OR 1.51, 95% CI 1.12-2.04), however findings were non-significant following crude adjustment for multiple comparisons. For each of the aforementioned infections, findings remained significantly elevated following the exclusion of more than six years of claims data preceding LPL/WM diagnosis.

Discussion

In this large population-based study investigating antecedent infection and subsequent development of LPL/WM, positive associations were observed with common respiratory tract infections and herpes zoster. These findings remained significant following exclusion of more than six years of claims data prior to LPL/WM diagnosis, suggesting the observed associations may not be the result of reverse causality (i.e. undetected LPL/WM). Chronic antigenic stimulation may therefore have an aetiological role in the development of LPL/WM.

To our knowledge, with the exception of pneumonia and sinusitis (Kristinsson *et al*, 2010), this is the first study to report significant associations for respiratory tract infections bronchitis and pharyngitis. We failed to confirm a significant association between influenza

and LPL/WM as previously reported within the Swedish population, despite a greater number of exposed cases (Kristinsson *et al*, 2010). Exposure to a number of pathogenic agents, including encapsulated pyogenic bacteria such as *Haemophilus Influenzae* and *Streptococcus pneumonia*, give rise to respiratory tract infections. Humoral immunity is important in protection against such microbes; however hypogammaglobulinaemia (defined as low levels of immunoglobulins) has been reported in LPL/WM and in other B-cell disorders including MGUS (Karlsson *et al*, 2011; Hunter *et al*, 2010). Hunter *et al* (2010) previously reported that IgA and IgG hypogammaglobulinaemia within newly diagnosed WM patients did not significantly predict risk of recurrent infections, thus suggesting the observed associations may not be explained by hypogammaglobulinaemia alone.

An increased risk of LPL/WM following herpes zoster infection has been consistently reported in the literature (Koshiol *et al*, 2008; Kristinsson *et al*, 2010) and associated with other haematological malignancies including other NHL subtypes (Tavani *et al*, 2000). Herpes zoster involves reactivation of the latent varicella zoster virus (VZV). Cell-mediated immunity is very important in controlling VZV and preventing reinfection, with the risk greatest among immunocompromised individuals (Engels *et al*, 1999). Low levels of antibodies to VZV have been reported in 25% of elderly WM patients (Karlsson *et al*, 2011), suggesting diminished cellular immunity in a subset of patients.

The observed associations may be a manifestation of an underlying immune disturbance, and thereby part of the natural history of disease progression to LPL/WM. IgM MGUS precedes LPL/WM in many cases (Steingrimsdottir *et al*, 2007; Morra *et al*, 2004). Infectious antigens may promote progression from IgM MGUS to LPL/WM (Kristinsson *et al*, 2012). Individuals with IgM MGUS have been shown to be at an increased risk of both bacterial and viral infections (Kristinsson *et al*, 2012). In a recent study, prior infection did not alter the risk of progression to WM (Kristinsson *et al*, 2012). Findings were, however, based on a small number of patients who progressed (n=20 WM and related malignancies), highlighting the need for large population-based studies within this area.

Recurrent infections, particularly those affecting the respiratory tract, are common in LPL/WM patients (Karlsson *et al*, 2011). However, a number of infections remained significantly elevated following exclusion of more than 6 years of claims data prior to LPL/WM diagnosis, arguing against the possibility of undetected underlying LPL/WM as an explanation for the associations observed.

Alternatively, inflammation resulting from exposure to infectious antigens may promote and support tumour development by suppressing cell-mediated immunity, decreasing apoptosis, and promoting angiogenesis (Mantovani *et al*, 2008). With the exception of herpes zoster, each of the infections for which positive associations were observed cannot be restricted to one pathogen, thereby implying that inflammation, rather than stimulation by a specific antigen may be associated with the development of LPL/WM. Future studies utilizing laboratory and clinical variables and which involve isolation of the causative pathogen are required to elucidate the potential mechanisms by which these infectious agents may promote the development of LPL/WM.

Our study benefits from large sample size, high quality and accurate ascertainment of cases and random selection of population-based controls. Although limited to individuals 66 years, LPL/WM largely affects older adults, with a median age at diagnosis of 73 years in a recent SEER study (Wang *et al*, 2012). By utilizing the Medicare claims data we eliminated the possibility of recall bias. However, infections that did not involve interaction with the healthcare provider may have been missed. Given the multiple infections investigated, some associations may have resulted from chance; however a number of infections remained

significant after crude adjustment for multiple comparisons. Using claims data may have resulted in misclassification of exposure but this is likely to be non-differential in the lagged analyses and thus this bias is conservative and likely to shift the ORs towards the null. The role of reverse causality cannot be eliminated entirely as medical record validation was not available; nor can we rule out the potential for misdiagnosis or underreporting of LPL/WM among controls. We were unable to ascertain the causative pathogen that gave rise to the infection claim, and as such cannot rule out the role of non-infective processes, such as allergy or inflammation. We were also unable to adjust for other potential confounders, such as lifetime exposure, patient immune status, monoclonal protein concentration, lifestyle factors and other comorbidities that may promote infections and/or cancer development.

In conclusion, herpes zoster and a number of respiratory tract infections were significantly associated with an increased risk of LPL/WM. Our findings imply an underlying immune disturbance is present several years prior to the diagnosis of LPL/WM. Alternatively, infections or inflammation resulting from exposure to infectious antigens may promote the development of LPL/WM. Further population-based studies are warranted within this area.

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Table I

Characteristics of LPL/WM cases and controls

	LPL/WM cases (n=693)	Controls (n=200,000)
<i>Gender</i>		
Male	328 (47.3%)	106172 (53.1%)
Female	365 (52.3%)	93828 (46.9%)
<i>Age, years</i>		
66-69	99 (14.3%)	33780 (16.9%)
70-74	149 (21.5%)	52008 (26%)
75-79	200 (28.9%)	50440 (25.2%)
80-84	140 (20.2%)	36097 (18%)
85+	105 (15.2%)	27675 (13.8%)
<i>Selection year</i>		
1992-1994	91 (13.1%)	31364 (15.7%)
1995-1998	127 (18.3%)	39843 (19.9%)
1999-2005	475 (68.5%)	128793 (64.4%)
<i>Race/ethnicity</i>		
Non-Hispanic White	625 (90.2%)	166827 (83.4%)
Non-Hispanic Black	30 (4.3%)	13949 (7%)
Other	38 (5.5%)	19223 (9.6%)
<i>Duration of Medicare coverage, months</i>		
13-60	183 (26.4%)	57440 (28.7%)
61-120	306 (44.2%)	97485 (48.7%)
121-180	158 (22.8%)	35805 (17.9%)
181-240	46 (6.6%)	9270 (4.6%)

Abbreviations: LPL/WM: Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinaemia

Table II

Associations between community-acquired infections and subsequent risk of LPL/WM

Infection	LPL/WM cases n (%)	Controls n (%)	Odds Ratios (95% CI)⁺	p-value
Cellulitis	144 (20.8)	34426 (17.2)	1.18 (0.97 - 1.43)	0.09
Herpes Zoster	47 (6.8)	8557 (4.3)	1.51 (1.12 - 2.04)	0.007
<i>Within time interval[†]</i>				
13-30 months			1.22 (0.67 - 2.23)	
31-48 months			1.13 (0.56 - 2.28)	
49-72 months			1.93 (1.15 - 3.23)	0.21
More than 72 months			1.79 (1.03 - 3.12)	
<i>p trend</i>				
Bronchitis	225 (32.5)	45215 (22.6)	1.56 (1.32 - 1.84) [‡]	<0.001
<i>Within time interval[†]</i>				
13-30 months			1.37 (1.03 - 1.83)	
31-48 months			1.77 (1.31 - 2.38)	
49-72 months			1.67 (1.28 - 2.19)	0.75
More than 72 months			1.48 (1.12 - 1.96)	
<i>p trend</i>				
Cold	25 (3.6)	7322 (3.7)	0.92 (0.61 - 1.37)	0.68
Influenza	60 (8.7)	14726 (7.4)	1.11 (0.85 - 1.45)	0.45
Laryngitis	30 (4.3)	6584 (3.3)	1.22 (0.84 - 1.77)	0.29
Pharyngitis	112 (16.2)	22472 (11.2)	1.43 (1.17 - 1.76) [‡]	<0.001
<i>Within time interval[†]</i>				
13-30 months			0.90 (0.55 - 1.45)	
31-48 months			1.98 (1.37 - 2.86)	
49-72 months			1.55 (1.08 - 2.24)	0.29
More than 72 months			1.43 (1.00 - 2.03)	
<i>p trend</i>				
Pneumonia	145 (20.9)	30201 (15.1)	1.42 (1.18 - 1.72) [‡]	<0.001
<i>Within time interval[†]</i>				
13-30 months			1.43 (1.05 - 1.95)	
31-48 months			1.40 (0.97 - 2.03)	
49-72 months			1.31 (0.92 - 1.87)	0.83
More than 72 months			1.55 (1.11 - 2.17)	
<i>p trend</i>				
Sinusitis	166 (24)	36249 (18.1)	1.33 (1.12 - 1.60) [‡]	0.001
<i>Within time interval[†]</i>				
13-30 months			1.49 (1.10 - 2.03)	
31-48 months			1.34 (0.94 - 1.92)	

Infection	LPL/WM cases n (%)	Controls n (%)	Odds Ratios (95% CI)[*]	p-value
<i>49-72 months</i>			1.02 (0.72 - 1.45)	0.77
<i>More than 72 months</i>			1.47 (1.10 - 1.97)	
<i>p trend</i>				
Gingivitis	<11 (<1)	917 (0.5)	1.78 (0.80 - 4.00)	0.16
Gastroenteritis	19 (2.7)	5312 (2.7)	0.95 (0.60 - 1.50)	0.82
Cystitis	227 (32.8)	56813 (28.4)	1.11 (0.93 - 1.31)	0.24
Prostatitis[§]	62 (18.9)	16203 (15.3)	1.20 (0.90 - 1.58)	0.21
Pyelonephritis	13 (1.9)	3529 (1.8)	0.98 (0.56 - 1.70)	0.94

Legend Observations in which the number of exposed patients is between one and 10, are listed as '<11' to preserve subjects' anonymity, in accordance with the SEERMedicare data use agreement.

Abbreviations: LPL/WM: Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinaemia

^{*} Odds ratios were adjusted for age (66-69, 70-74, 75-79, 80-84, and 85-99 years old), gender and year of selection

[†] Preceding LPL/WM diagnosis or control selection

[‡] Association is significant at P 0.00357 (Bonferroni correction for 14 comparisons).

[§] Restricted to Males. Percentages reflect this restriction