Original Article

Baseline characteristics predictive of malignancy among patients presenting with lymphadenopathy: A cancer center experience

Huifang Lu, Xerxes Pundole, Shana Palla[1], Khanh Vu

Departments of General Internal Medicine, [1]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

ABSTRACT

Context: Patients who present to tertiary cancer centers solely with radiologic evidence of lymphadenopathy often are diagnosed with malignancy, but it is unclear which baseline characteristics are predictive of a cancer diagnosis. **Materials and Methods:** We conducted a retrospective data review to determine baseline characteristics predictive of a cancer diagnosis and the optimal follow-up time for such patients. **Results:** Sixty-six adult patients with lymphadenopathy were evaluated. Thirty-six patients (55%) were diagnosed with cancer; the most common type was lymphoma. Cancer was diagnosed in 94%, 79%, and 70% of patients with supraclavicular, retroperitoneal, and abdominal lymphadenopathy, respectively. Increasing age and hypertension were associated with a cancer diagnosis in the multivariate analysis. The mean time to diagnosis was 15 days (range, 1-140 days). The average follow-up time was 18 months in patients without a cancer diagnosis. **Conclusions:** Patients presenting solely with lymphadenopathy at a cancer center have a higher likelihood of being diagnosed with cancer if they are at least 50 years old or have hypertension. Supraclavicular lymphadenopathy is highly associated with a malignant diagnosis. We suggest that patients presenting solely with lymphadenopathy should be followed-up for at least 6 months for a definitive diagnosis.

Key words: Hematologic malignancy, lymphadenopathy, lymphoma, sarcoidosis, supraclavicular lymphadenopathy

INTRODUCTION

Reaching a correct diagnosis can be challenging when lymphadenopathy, a condition in which the lymph nodes are enlarged (>1 cm in diameter) or of abnormal consistency or number is a patient's sole presenting symptom. Lymphadenopathy can be associated with infections, autoimmune diseases, or malignancy, making it a nonspecific indicator of a variety of diseases. Cancers associated with lymphadenopathy include Hodgkin disease, non-Hodgkin lymphoma, chronic lymphocytic leukemia, agnogenic myeloid metaplasia, angioimmunoblastic lymphadenopathy, Waldenström macroglobulinemia, multiple myeloma, and Kaposi sarcoma.[1]

Reported prevalence rates of malignancy among all patients presenting with lymphadenopathy are fairly low in most settings. A study conducted by Allhiser *et al*.,[2] in a family practice setting showed that none of the 80 patients who presented with lymphadenopathy was diagnosed with a malignancy, and a Dutch study also conducted in a family practice setting found only that 1.1% of the patients who presented with lymphadenopathy were diagnosed with a malignancy.[3] In primary care, the prevalence of lymphadenopathy has been estimated to be approximately 0.4% in patients aged <40 years to about 4% in patients >40 years.[3,4] In contrast, malignancies are more commonly diagnosed among patients presenting with lymphadenopathy at tertiary care centers than is the case in primary care settings. In referral clinics, the prevalence of malignancy has been estimated to be approximately 17%[5] reaching 40-60% in patients who have a high suspicion of malignancy.[6] In a study conducted at Exeter Health Authority area hospitals (a tertiary care center), the rate

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Address for correspondence: Dr. Huifang Lu, Department of General Internal Medicine, Unit 1465, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas - 77030, USA. E-mail: hlu@mdanderson.org

of malignancy was 19%.[7] A study conducted at a tertiary care center in India by Agrawal *et al.*,[8] found that 55% of patients with chronic lymphocytic leukemia presented with lymphadenopathy before their diagnosis.

The underlying cause of lymphadenopathy varies according to the patient's age and the location of lymphadenopathy.[9] The interval between the initial appearance of lymphadenopathy and the time at which the underlying malignancy or benign disease becomes evident on physical examination or imaging also varies. Therefore, deciding which patients presenting with lymphadenopathy are most in need of long-term follow-up is difficult.

To address this challenge, we reviewed our experience in the evaluation and diagnosis of patients presenting to our tertiary care cancer center with lymphadenopathy. Our primary goal was to identify the baseline characteristics predictive of a cancer diagnosis in patients with lymphadenopathy. Our secondary goal was to determine the most appropriate follow-up period for patients at risk of developing malignancy.

MATERIALS AND METHODS

Institutional review board approval was obtained before any data were collected for this study. The use of patient information in this study complied with the Health Insurance Portability and Accountability Act, and sensitive patient information was protected in our data analysis.

We performed a retrospective chart review of patients aged 18 years or older at the time of admission who presented solely with radiologic evidence of lymphadenopathy without a pathologic diagnosis or any evidence of a solid organ mass. Patients included presented to either the Mary Ann Weiser Suspicion of Cancer Clinic or the rheumatology clinic at The University of Texas MD Anderson Cancer Center between January 1, 2003, and June 30, 2007. We reviewed follow-up data for these patients through December 31, 2011. Patients with an apparent mass at other sites, such as the breast or prostate, were not referred to these clinics and therefore were excluded from this study.

Data extraction

Data collected from the patients' charts were age, sex, medical history (i.e., comorbid conditions), B symptoms (i.e., fever, pain, weight loss, and night sweats), follow-up time from the initial visit, results of baseline laboratory tests, imaging studies, and time to diagnosis. Baseline laboratory data included white blood cell and platelet counts as well as levels of neutrophils, monocytes, lymphocytes, hemoglobin, lactate dehydrogenase, albumin, glucose, creatinine, angiotensin-converting enzyme (ACE), β_2-microglobulin, and rheumatoid factor; however, these tests were not performed on every patient. Physical examination and results of imaging studies (computed tomography and/or magnetic resonance imaging), were used to determine the location of the lymphadenopathy. Patients with lymphadenopathy in two or more anatomic locations were considered to have generalized lymphadenopathy. Data on diagnosis over time were gathered. Patients were divided into two groups for analysis: those diagnosed with cancer and those diagnosed with benign disease. Patient's charts were reviewed from the initial day of presentation until December 2011, to determine the mean follow-up time.

Statistical analysis

Descriptive statistics such as means, medians, and ranges were used to summarize continuous baseline patient characteristics. Frequency tables were generated for categorical variables. The Wilcoxon rank-sum test was used to determine the relationship between continuous patient characteristics (i.e., laboratory values) and clinical diagnosis of cancer or benign disease. The Chi-square or Fisher's exact test was used to evaluate the relationship between categorical baseline characteristics (i.e., lymphadenopathy location) and diagnosis.

Univariate and multivariate logistic regression models were constructed to identify predictors of a cancer diagnosis. Factors initially included in the models were baseline patient characteristics such as age, dichotomized age (arbitrarily chosen cut-point: <50 vs. ≥50 years), history of smoking, history of alcohol use, history of prior cancer, hypertension, and rheumatologic disease. Backward stepwise elimination was adopted for each multivariate logistic regression model. Only factors that were considered significant ($P \leq 0.05$) remained in the final models. A stratified two-way table was employed to display the relationship between significant baseline characteristics left in the final model and cancer diagnosis. All analyses were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Of the 66 patients included in the study, 34 were men and 32 were women. More than half (58%) of the patients were diagnosed with cancer [Table 1]. The most common type of cancer was lymphoma, which was seen in 52% of patients. Sarcoidosis (17%) and reactive hyperplasia (23%) were the most common benign causes of lymphadenopathy [Table 1].

Thirty-three patients (50%) were diagnosed with cancer after the initial biopsy. Five patients (8%) were diagnosed with malignancy after a second biopsy; one of these patients required a follow-up time of 90 days for the final cancer diagnosis.

The abdomen was the most common site of lymphadenopathy presentation, as abdominal lymphadenopathy was seen in 37 patients (56%). Lymphadenopathy presenting in the supraclavicular, retroperitoneal, and abdominal regions was more likely to be seen in patients diagnosed with cancer than in those diagnosed with benign disease; whereas isolated cervical, thoracic, and inguinal lymphadenopathy was not associated with cancer status [Table 2]. Localized lymphadenopathy was seen in 14 patients, 9 of whom (64%) were diagnosed with benign disease. In contrast, only 19 (37%) of the 52 patients with generalized lymphadenopathy were diagnosed with benign disease [Table 2].

In the univariate logistic regression analysis, increasing age (as a continuous variable) and being 50 years of age or older (a dichotomized variable) were associated with a cancer diagnosis [Table 3]. Hypertension was also significantly related to a cancer diagnosis. No other baseline characteristics were found to be significantly associated with a cancer diagnosis. Fewer than five patients had diabetes, coronary artery disease, cerebrovascular disease, or chronic obstructive pulmonary disease; so these characteristics were not included in the univariate logistic regression model.

After the backward stepwise elimination strategy was applied to the results of the multivariate logistic regression, increasing age (as a continuous variable), and hypertension remained as significant predictors of a cancer diagnosis in one model, whereas being 50 years of age or older (a dichotomized variable) and hypertension remained significant in another model [Table 4]. These final models indicate the consistent statistical significance of hypertension and age as independent factors predicting a cancer diagnosis, regardless of whether age is treated as a continuous or dichotomized variable.

A stratified two-way table showed that only 29% of young patients with no hypertension received a cancer diagnosis, whereas 85% of older patients with hypertension received such a diagnosis.

Mean and median baseline laboratory test results for patients diagnosed with cancer compared with those diagnosed with benign disease are summarized in Table 5. No significant differences between patients diagnosed with cancer and those diagnosed with benign disease were found in mean or median values for any of the laboratory test results. B symptoms such as fever, fatigue, and weight loss also showed no correlation with diagnosis (data not shown).

The mean follow-up time was approximately 3 years. The mean time to reach a conclusive diagnosis was 15 days (range, 1-140 days). The 29 diagnosed with benign diseases were periodically followed-up to determine that they did not develop a malignancy. One of the patients diagnosed with reactive hyperplasia developed lymphoma 3 months after initial presentation. None of the other patients developed a malignancy during follow-up, with

Table 1: Diagnosis for patients presenting with lymphadenopathy (*n*=66)

Final diagnosis	*n* (%)
Hodgkin lymphoma	5 (8)
NHL (follicular, large B cell, mantle cell)	29 (44)
SLL/CLL	4 (6)
Sarcoidosis	11 (17)
Histoplasmosis	1 (1)
Mycoplasma avium	1 (1)
Reactive hyperplasia	15 (23)

NHL: Non-Hodgkin lymphoma, SLL/CLL: Small lymphocytic lymphoma/chronic lymphocytic leukemia

Table 2: Relationship between site of lymph node involvement at presentation and diagnosis with cancer or benign disease in patients presenting with lymphadenopathy (*n*=66)

Site of lymph node involvement	Total [*n*]	Cancer diagnosis [*n* (%)]	Non-cancer diagnosis [*n* (%)]	*P* value*
Cervical	29	17 (59)	12 (41)	0.879
Supraclavicular	16	15 (94)	1 (6)	(0.009)
Thoracic	33	18 (55)	15 (45)	0.618
Abdominal	37	26 (70)	11 (30)	0.018
Inguinal	34	20 (59)	14 (41)	0.832
Retroperitoneal	28	22 (79)	6 (21)	0.003
Generalized†	52	33 (63)	19 (37)	0.062

**P* values were calculated using the Chi-square test; the *P* value in parentheses was calculated using the Fisher's exact test, †Generalized refers to lymphadenopathy at two or more sites

Table 3: Univariate logistic regression analysis of baseline patient characteristics potentially predictive of a cancer diagnosis

Characteristic	Cancer/Total [*n* (%)]	Odds ratio	95% CI	*P* value
Age*	-	1.05	1.01–1.09	0.007
Age ≥50 years	29/42 (69)	3.72	1.30–10.67	0.015
History of smoking	16/28 (57)	0.97	0.36–2.60	0.951
History of alcohol	16/32 (50)	0.55	0.20–1.46	0.229
History of prior cancer	5/9 (56)	0.91	0.22–3.75	0.895
Hypertension	14/16 (88)	7.58	1.56–36.89	0.012
Rheumatologic disease	8/12 (67)	1.60	0.43–5.69	0.484

*Age used as a continuous variable. CI: Confidence interval

the average follow-up time being 18 months in this set of patients.

DISCUSSION

We found that the baseline characteristics predictive of a cancer diagnosis in lymphadenopathy patients at a cancer center were age ≥ 50 years and hypertension. The cut point for dichotomizing age was arbitrarily chosen to be 50 years and hypertension was deemed to be a significant predictor of a cancer diagnosis. When age was modeled as a continuous variable, hypertension remained a significant predictor of a cancer diagnosis. This suggests that changing the cut point for age would not affect the significance of hypertension as an independent variable in predicting cancer in this patient population. On average, patients were followed for a period of 3 years. We recommend a follow-up period of at least 3-6 months, because one of our patients progressed to a cancer diagnosis after 3 months of follow-up.

The location of lymphadenopathy may be useful in predicting whether a patient has cancer or a benign disease. For example, in our study, 94% of patients with supraclavicular lymphadenopathy were diagnosed with cancer. Similar results were observed in a pediatric study by Kumral *et al.*,[10] in which 26 of the 32 patients with supraclavicular lymphadenopathy (81%) were diagnosed with cancer.[10] Our study also found that a cancer diagnosis was more common among patients with generalized lymphadenopathy than among patients with localized lymphadenopathy, although the difference was not statistically significant. This lack of significance may be attributable to our study's small sample size. Kumral *et al.*,[10] found that 57% of patients with generalized lymphadenopathy had a diagnosis of benign disease compared with 37% of such patients in our study; this difference may be attributable to differences between the study populations. Information on baseline lymph node size may be useful in such a study population, but since lymph node size was not determined in all patients using standardized methods, due to the retrospective nature of our study; we were unable to determine its correlation in the analysis. A prospective study to determine if lymph node size at baseline is a predictor of a cancer diagnosis is warranted.

In our study, a cancer diagnosis was significantly more common among patients who were at least 50 years old than in those younger than 50 years. A study by Lee *et al.*,[6] showed a similar association between being 50 years of age or older and a cancer diagnosis among patients presenting with lymphadenopathy. Although hypertension was also associated with a cancer diagnosis in our study, the clinical significance of this relationship remains to be determined. We found no significant associations between cancer diagnoses and any other patient characteristics or symptoms, but this may be attributable to our small sample size.

All the patients in our study diagnosed with a cancer were suffering from hematologic malignancy, the most common type of which is lymphoma. This may be attributed to the fact that the study excluded patients that had a solid organ mass. Our findings may, thus, be skewed by a selection bias. Caution is, therefore, necessary when generalizing the results of this study to other patient populations.

Because the same baseline laboratory tests were not conducted in all patients in the period studied, the statistical power of our analysis of each test varied. For example, although we found that mean and median ACE levels tended to be higher in patients with a diagnosis of benign disease than in patients with a cancer diagnosis, ACE levels were tested in only 24 of the 66 patients. In addition, none of the patients with a cancer diagnosis had an elevated level of ACE when checked. This relationship needs to be explored in a larger prospective study.

Table 4: Final multivariate model for predicting a cancer diagnosis, derived by backward stepwise elimination

Characteristic	Odds ratio	95% CI	*P* value
Model 1 (age as a continuous variable)			
Age	1.04	1.00–1.08	0.034
Hypertension	5.47	1.08–27.68	0.040
Model 2 (age as a dichotomized variable)			
Age≥50 years	3.10	1.03–9.38	0.045
Hypertension	6.38	1.27–32.05	0.024

CI: Confidence interval

Table 5: Baseline angiotensin-converting enzyme, β2-microglobulin, and lactate dehydrogenase levels for patients presenting with lymphadenopathy diagnosed with cancer or benign disease (*n*=66)

Laboratory test	Mean±SD, median (range), Total *n* tested		*P* value*
	Cancer diagnosis	Noncancer diagnosis	
ACE	45.7±14.5 U/L (nkat/L), 41 (24–63) U/L, 9	72±52.4 U/L (nkat/L), 63 (30–251) U/L, 15	0.060
β2-MG	3.1±1.6 mg/L, 2.8 (1.3–8.9) mg/L, 36	2.6±1.4 mg/L, 2.1 (1.3–6.6) mg/L, 22	0.158
LDH	557.4±196.2 U/L (μkat/L), 505 (324–1,238) U/L, 38	498.2±185.6 U/L (μkat/L), 444 (334–1,212) U/L, 28	0.112

**P* values were calculated using the Wilcoxon rank-sum test. ACE: angiotensin-converting enzyme, β2-MG: β2-microglobulin, LDH: lactate dehydrogenase, SD: standard deviation

In our study, we found that a higher rate of patients presenting with lymphadenopathy were diagnosed with a malignancy (58%) than previous studies did.[6,7] The higher rate of cancer diagnosis in our study maybe attributable to differences between the study populations seen at general hospitals and those seen at cancer centers.

It should also be reiterated that inferences from this study are technically limited to patients presenting at a tertiary cancer center solely with lymphadenopathy and no other solid organ mass; however, there is no reason to believe that patients that present to other settings with similar presentations would not have similar risk factors.

In conclusion, our results indicate that patients presenting solely with lymphadenopathy at a cancer center are more likely to be diagnosed with cancer if they are at least 50 years old or have hypertension. Abdominal, retroperitoneal, or supraclavicular lymphadenopathy may also be useful in identifying patients at risk of malignancy. For patients with these characteristics but without pathologic evidence of malignancy or any other solid organ mass, we recommend a follow-up period of at least 3-6 months to monitor for the development of malignancy. A larger prospective study is needed to determine whether other factors, such as localized compared with generalized lymphadenopathy, baseline lymph node size, or ACE levels and other laboratory serum test results, can provide additional predictive information in patients that present solely with lymphadenopathy.

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