

Unexplained Lymphadenopathy in Family Practice

An Evaluation of the Probability of Malignant Causes and the Effectiveness of Physicians' Workup

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This study reported here was undertaken to determine the probability of malignancy in patients presenting with unexplained lymphadenopathy in primary care practice and to estimate the effectiveness of current referral patterns by family physicians in relation to malignant disease. Clinical characteristics that may be discriminatory for malignant causes were also investigated.

A retrospective analysis was performed of 82 patients who underwent biopsy for unexplained lymphadenopathy from 1982 to 1984; data regarding the incidence of unexplained lymphadenopathy and the referral rate for this problem were obtained from registration projects. A total of 29 malignant lymphadenopathies were identified for a prior probability of 1.1 percent and a posterior (after referral) probability of 11 percent. The ability of the family physician to refer malignant cases within four weeks after initial consultation (sensitivity of referral) was 80 to 90 percent; 91 to 98 percent of benign cases were not referred (specificity of referral). An increased likelihood of malignancy was associated with age over 40 years (4 percent) and supraclavicular lymphadenopathy (50 percent).

The incidence of malignancy in patients presenting with unexplained lymphadenopathy to the family physicians is very low (1 to 2 percent). Nevertheless, despite the paucity of validated discriminatory factors, the family physicians perform a reasonably effective selection process toward referral and biopsy.

Lymphadenopathy is a common presenting symptom in family practice. In the Netherlands the incidence of lymphadenopathy from undetermined cause is around 0.6 percent per year.¹ In these cases, physicians and patients often are concerned that the enlarged lymph node is due to cancer. According to some medical textbooks^{2,3} a biopsy is often indicated to confirm or refute a malignant cause. In several studies⁴⁻⁷ malignancy was reported in 40 to 80 percent of lymph node biopsies. On the other hand, two studies^{8,9} in family practice indicate that lymphadenopathy in the majority of cases is related to self-limiting or easily treatable conditions not requiring extensive diagnostic workup.

To save unnecessary alarm and expense, family physicians should select for referral and biopsy only those

patients with a high risk of malignancy. The success of this selection process is dependent on the prior probability of malignancy and the application of validated discriminating factors. Since very few data in this respect are available, a retrospective study was performed to determine the probability of malignancy in patients presenting with unexplained lymphadenopathy in primary care practice and to estimate the effectiveness of current referral patterns in relation to malignant disease. In addition, clinical characteristics that may indicate high-risk groups were investigated.

METHODS

Using the registration system of the Department of Clinical Pathology in the hospital of Maastricht, all patients (n = 400) with histologic or cytologic examination of lymph node tissue in 1982, 1983, and 1984 were identified. Subsequently, patients were excluded who were not referred for unexplained lymphadenopathy (n = 281) or not living

Submitted, revised, July 1, 1988.

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TABLE 1. AGE AND SEX DISTRIBUTION OF THE POPULATION OF MAASTRICHT

Age (years)	Percent	Percent Female
0-9	10	49
10-19	16	50
20-29	16	52
30-39	15	48
40-49	13	49
50-59	12	52
60-69	9	54
70-79	6	61
80-89	3	70
All	—	51.6

Source: population register, Maastricht, The Netherlands 1983

in the Maastricht area (n = 37). From all remaining patients (n = 82), the following characteristics were collected: age; sex; time from first symptoms to first consultation, to referral, and to biopsy or aspiration; the presence of weight loss and pain; localizations of enlarged nodes; the erythrocyte sedimentation rate; and the white blood cell count. When these data could not be found in the hospital record, the family physician was contacted to provide additional information. All patients were followed for a period of at least 18 months after biopsy to establish a final diagnosis of the absence of malignancy.

The area of Maastricht has only one outpatient aspiration or biopsy facility, which is the Academic Hospital Maastricht. According to national hospital registration, the referral rate in this particular area to this hospital is more than 90 percent. Data on age and sex of the population of 142,000 in 1983 are given in Table 1. In this area 57 family physicians are responsible for primary care.

In this investigation the possibility of malignant disease was considered to be the main justification for referral. As a consequence, early referral (defined as referral within four weeks after the first contact between patient and family physician) with a biopsy positive for malignancy was considered to be a true-positive test result of the diagnostic workup. A referral later than four weeks was considered as physicians' delay (false-negative). Early referral in the absence of malignant disease was assumed to be a false-positive result. These assumptions are illustrated in a 2 × 2 table (Table 2). With these criteria the sensitivity of the referral process can be considered as the percentage of patients with malignant lymphadenopathy who were referred within four weeks, whereas the specificity is calculated as the percentage of patients with benign causes who were referred after four weeks or not at all. The result of cytologic or histologic examination was used as the "gold standard" for malignant and benign lymphadenopathy, with corrections by results obtained during the 18 months of follow-up (necessary in three cases).

TABLE 2. UNEXPLAINED LYMPHADENOPATHY: CRITERIA FOR THE ANALYSIS OF THE EFFECTIVENESS OF PHYSICIANS' WORKUP

Referral	Malignant Causes	
	Present	Absent
Within 4 weeks	True positive	False positive
After 4 weeks or not at all	False negative	True negative

Data from two Dutch registration projects were used for some of the calculations. In these studies, of which one was carried out in Maastricht, the incidence of unexplained lymphadenopathy in family practice (codes ICHPPC-2;63,209,266) was found to be 0.6 percent¹ (C. A. de Geus, personal communication, 1984). Using this figure, it can be estimated that, in a population of 142,000, 2,556 patients with this condition will be seen over a three-year period.

RESULTS

Eighty-two patients were identified who were referred for unexplained lymphadenopathy and who underwent lymph node aspiration or biopsy. This number represents about 3 percent of all patients presenting with this symptom in family practice. Of these 82 patients, 29 had a malignant cause for a prior probability of 1.1 percent (29/2256) and a posterior probability after referral of 11.0 percent (29/256). Diagnoses included 14 malignant lymphomas, 15 metastases, 37 reactive lymph nodes without specific diagnosis, and 16 benign causes.

The sensitivity of referral by the family physicians with regard to malignant causes of lymphadenopathy is given in Table 3. Of 29 patients with malignant causes, 26 were referred within four weeks for a sensitivity of 90 percent. A physician delay exceeding four weeks was present in three cases, all with a diagnosis of malignant lymphoma. As can be seen in the same table, a total of 36 patients were referred within four weeks but turned out to have benign lymphadenopathy, for a specificity of 98 percent.

The significance of several patient characteristics in relation to malignancy is given in Table 4. As can be seen, only age over 40 years and the presence of an enlarged supraclavicular node were clearly related to an increased likelihood of malignancy; borderline significance was obtained for an increased sedimentation rate and weight loss. Because of the relatively low number of cases, a multivariate analysis was not deemed appropriate. By applying various combinations of variables, however, only 17 percent of patients with malignancy were found to be both younger than 40 years and without supraclavicular nodes;

TABLE 3. SENSITIVITY AND SPECIFICITY OF EARLY REFERRAL FOR UNEXPLAINED LYMPHADENOPATHY

Referral	Malignant Causes	
	Present	Absent
Within 4 weeks	26	36
After 4 weeks or not at all	3	2,491
Sensitivity for malignant lymphadenopathy: 90%		
Specificity for malignant lymphadenopathy: 98%		

85 percent of patients with benign causes fell into this category.

DISCUSSION

Early referral can be considered to be the strategy of choice for patients with malignant lymphadenopathy. Although this study was not prospective, this strategy appears to have been followed in 90 percent of patients. The true sensitivity of the referral may be lower since the calculation does not take into account the patients presenting with malignant lymphadenopathy but not biopsied. On the other hand, 80 percent of patients with unexplained lymphadenopathy due to malignant lymphoma, in which cases the diagnostic workup almost always includes a histological or cytological lymph node examination, were referred within four weeks; this group of patients more often presents at younger age and without discriminating symptoms. It may be concluded, therefore, that the sensitivity of early referral for the presence of malignant lymphadenopathy is between 80 percent and 90 percent.

The specificity of the primary diagnostic workup was defined as the percentage of patients with benign lymphadenopathy who were not referred to the hospital within four weeks. Here the retrospective nature of the study introduced uncertainty about the number of patients with benign lymphadenopathy who were referred but not biopsied. Although 36 patients with benign lymphadenopathy who were referred within four weeks were identified, this figure may in fact be higher because of the presence of early referrals with no biopsy. With a 10 percent referral rate (unpublished observation in Maastricht and Utrecht), around 257 instead of 82 patients may be expected to have been referred. If it is assumed that this difference of 175 consisted exclusively of early referrals and benign causes, the specificity would still be 91 percent. The true specificity is therefore concluded to be between 98 percent and 91 percent.

With the sensitivity and specificity around or exceeding 80 and 90 percent, respectively, the diagnostic workup by

TABLE 4. PATIENT CHARACTERISTICS AND DIAGNOSTIC OUTCOME IN UNEXPLAINED LYMPHADENOPATHY

	Malignant Lymphadenopathy		P Value
	Yes	No	
Age (years)			
≥40	20	7	<.01
<40	9	46	
Sex			
Female	12	31	NS
Male	17	22	
Weight loss			
>10 percent	7	3	<0.1
≤10 percent	20	37	
Nodal pain			
Yes	8	11	NS
No	20	32	
Duration of symptoms			
≤4 weeks	15	28	NS
>4 weeks	14	24	
Number of enlarged nodes			
1	17	28	NS
>1	12	24	
Localization of nodes			
Supraclavicular	13	2	<.01
Other neck	9	25	NS
Axillary	4	16	NS
Inguinal	7	13	NS
Erythrocyte sedimentation rate			
>30 mm/h	7	3	=.1
≤30 mm/h	22	38	
White cell count			
>10 × 10 ⁹ /L	4	4	NS
≤10 × 10 ⁹ /L	25	34	
<i>χ² test with Yates' correction</i>			
NS—not significant			

the family physician, although not easily divided into separate findings of history and physical examination, can be described as a reasonably effective process. In a way this success is amazing, given the very few available data regarding the predictive value of patient characteristics toward malignancy.

Variables and models discriminating among causes of peripheral lymphadenopathy have almost exclusively been studied in referred or selected populations similar to the population studied here. Some other studies^{2-4,10-14} indicate that malignancy is more likely with older age, supraclavicular localization, presence of general symptoms, and abnormal chest x-ray findings. In selected populations these variables could be useful, but they cannot be applied in primary care without caution. Patient characteristics with high specificity in selected populations may have a much lower specificity in unselected populations presenting to the family physicians; indiscriminately applying

these characteristics may therefore lead to a tremendous increase in unnecessary referrals.

Regarding the unselected population in primary care medicine, about 20 percent of patients with unexplained lymphadenopathy are older than 40 years.¹ Further, supraclavicular localizations have been found to be present in around 1 percent of primary care patients.⁸ By linking these data with the findings of this study, the prior probability of malignancy can be expected to be around 4 percent for patients aged over 40 years and 0.4 percent for patients aged below 40 years. Also, patients with supraclavicular lymphadenopathy would have a 50 percent probability of malignancy. For patients aged over 40 years and having supraclavicular lymphadenopathy, the probability of malignancy might be 90 percent; for those younger than 40 years, it might be 25 percent.

In conclusion, the probability of malignancy in patients presenting to the family physician with peripheral lymphadenopathy is low (1 to 2 percent); nevertheless, without the aid of validated discriminating tests, the family physician performs a reasonably effective selection process. In view of a positive predictive value of early referral of 11 percent and a negative predictive value of nonreferral of >99 percent, improvement should mainly be directed toward reduction of the number of false-positive referrals, ie, referrals with benign causes. For this improvement, the identification of relevant variables with a high specificity in primary care populations is necessary, since models based on discriminating variables as described in this and other highly selected populations are most likely to be of only limited value.

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