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Causes of Isolated Mediastinal Lymphadenopathy: Analysis of 348 Cervical Mediastinoscopy Patients

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ABSTRACT

Objective: This study was designed to investigate the causes of isolated mediastinal lymphadenopathy, the role of cervical mediastinoscopy (CM) in the diagnosis, and the accuracy of computed tomography (CT) to predict malign and benign pathology in patients with isolated mediastinal lymphadenopathy.

Materials and Methods: The records of 348 patients who underwent CM for isolated mediastinal lymphadenopathy between 2006 and 2018 were analyzed. The group comprised 189 males and 159 females. The cases were evaluated in terms of age, distribution of lymph node stations in which lymphadenopathy was detected and sampled, mortality, morbidity, and histopathological diagnostic parameters.

Results: The median age of the patients was 48 years (min–max: 18–79 years). The median lymph node diameter was 2 cm (min–max: 1–6 cm). Lymphadenopathy was found in a total of 724 lymph node stations. The median lymph node diameter was 3.7 cm in patients with malignant disease and 2 cm in cases of benign disease. The reliability of CT to predict malignancy was 76.8% specificity and 71.1% sensitivity when the lymph node diameter was >2.5 cm (area under the curve: 0.820; 95% confidence interval: 0.774–0.860; p<0.001). Complications occurred in 2 cases, however, no mortality was observed. The histopathological results were sarcoidosis (43.1%), tuberculosis (TB) (20.7%), reactive hyperplasia (14.7%), carcinoma metastasis (8.6%), lymphoma (6%), and other (6.8%).

Conclusion: Although sarcoidosis is the most common cause of isolated mediastinal lymphadenopathy, TB is still prevalent in Türkiye. The sensitivity of CT imaging to identify malignancy increased with a larger lymph node diameter. CM is a safe and effective diagnostic procedure for patients with mediastinal lymphadenopathy.

Keywords: Computed tomography, mediastinal lymphadenopathy, mediastinoscopy, mediastinum, sarcoidosis, tuberculosis

INTRODUCTION

Isolated mediastinal lymphadenopathy is a frequently encountered mediastinal pathology in daily practice. Mediastinal lymphadenopathy is abnormal lymph node enlargement in the chest that may be part of the etiology of many benign or malignant diseases. It may occur due to disparate diseases, such as a metastatic tumor, lymphoma, sarcoidosis, tuberculosis (TB), and other granulomatous or inflammatory causes (1). The treatment required for these diseases varies; therefore, histopathological confirmation of the lymph node is required before initiating treatment.

Cervical mediastinoscopy (CM) is a minimally invasive surgical method used in the diagnosis of mediastinal lymph node disease that offers high diagnostic accuracy and a low mortality and morbidity rate. Although mediastinoscopy is frequently used in the staging of lung cancer, it is also important in the diagnosis of non-lung cancer mediastinal lymph node disease (2, 3).

Computed tomography (CT) is commonly used to evaluate mediastinal lymphadenopathy. There are, however, opinions that it is insufficient to distinguish between malignant and benign lesions (4, 5).

Although there are many studies in the literature on the staging of lung cancer, which frequently causes mediastinal lymphadenopathy, studies of CM used to determine the prevalence and diagnosis of other diseases causing mediastinal lymphadenopathy are limited (6).

The objective of this study was to investigate the causes of isolated mediastinal lymphadenopathy, the role of CM in the diagnosis, and the sensitivity of CT to predict the pathology in patients with mediastinal lymphadenopathy by retrospectively analyzing patients with isolated mediastinal lymphadenopathy who underwent CM.

MATERIALS and METHODS

The İstanbul Education and Research Hospital ethics committee granted approval for this research (no: 2018-KAEK-50/1591) and the study was conducted in accordance with the principles of the Declaration of Helsinki.

The files of 2760 patients who underwent CM between 2006 and 2018 were analyzed retrospectively. The cases were evaluated in terms of age, gender, distribution of lymph node stations in which lymphadenopathy was detected and sampled, intraoperative and postoperative mortality, morbidity, and histopathological diagnostic parameters.

Isolated mediastinal lymphadenopathy was defined as the presence of ≥1 enlarged mediastinal or hilar lymph node on a thorax CT (>1 cm in short axis view) without pulmonary nodules or evidence of intrathoracic and extrathoracic malignancy. The preoperative thorax CT scans of patients who underwent a diagnostic mediastinoscopy for mediastinal lymphadenopathy were evaluated by experienced radiologists, and patients with a lymph node diameter of >1 cm were included in the study. Mediastinoscopy was performed in all cases within 1 month after the CT scan.

Patients previously diagnosed with primary lung cancer, pulmonary parenchymal mass, or primary lung cancer diagnosed by mediastinoscopy, and patients whose radiological examinations could not be reviewed were excluded from the study. Only patients who underwent a diagnostic CM without an earlier finding of malignancy were included.

All of the CM procedures were performed under general anesthesia. The aorticopulmonary lymph node station was sampled using the extended CM technique (7). Multiple samples were retrieved from the pathological mediastinal lymph node station and all of the removed lymph nodes were histopathologically examined by pathologists who specialized in thoracic pathologies. The International Association for the Study of Lung Cancer (IASLC) lymph node map was used to number and classify the samples (8).

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the demographic characteristics and collected data. Quantitative variables were reported using mean, maximum, and minimum values, while number (%) values were used for qualitative variables. Normal distributions were reported as the mean±SD, and Student's t-test was used for comparisons between groups. The Pearson chi-squared test was to assess qualitative variables. Non-parametric continuous variables were recorded as the median and interval distribution and compared using the Mann-Whitney U test. A p value of <0.05 was considered statistically significant. A receiver operating characteristic (ROC) curve was created and the area under the curve (AUC) was evaluated to determine the reliability of CT to predict lymph node metastasis. The values with sensitivity and specificity closest to the value of the AUC were accepted as cut-off values. MedCalc Statistical Software (MedCalc Software bv, Ostend, Belgium) was used to draw the ROC curves.

Table 1. Lymph node stations where lymphadenopathy was detected using computed tomography

Stations	n	%
2R	127	17.5
2L	18	2.5
4L	56	7.7
4R	293	40.5
5	10	1.4
6	6	0.8
7	214	29.6
Lymph node	724	100

R2: Right upper paratracheal; 4R: Right lower paratracheal; 4L: Left upper paratracheal; 2L: Left lower paratracheal; 7: Subcarinal; 5: Aortopulmonary lymph node

RESULTS

A total of 348 patients were included in the study. Of the study group, 54.3% (n=189) were female and 45.7% (n=159) were male. The median age was 48 years (min–max: 18–79 years; interquartile range [IQR]: 22 years). In all, 91.1% were aged <65 years and 8.9% were aged >65 years. The most common reason for admission was a cough (35.4%, n=123). Other reasons for presentation were dyspnea (16%, n=57), chest pain (15%, n=52), fatigue (7%, n=24), fever (6%, n=22), weight loss (4.6%, n=16), muscle/joint pain (4%, n=15), hemoptysis (2%, n=8), hoarseness (1.4%, n=5), aphagia (0.9%, n=3), and visual impairment (0.6%, n=2). Some patients reported >1 complaint. In addition, 92 (26.4%). patients were asymptomatic.

CT imaging revealed lymphadenomegaly in a median of 2 stations (min–max:1–6 stations). The median lymph node diameter on the CT scans was 2 cm (min–max: 1–6 cm; IQR: 1.5 cm).

At least 1 interventional procedure was performed in 284 patients (81.6%). Endobronchial ultrasound (EBUS) bronchoscopy was performed in 84 patients (24.1%) and transbronchial needle aspiration (TBNA) was performed in 200 patients (57.5%). No interventional procedure was performed before the CM in 64 (18.3%) patients.

Mediastinal lymphadenopathy was detected in a total of 724 nodal stations in radiological examinations. The most common sites of lymphadenopathy detected on a thorax CT were lymph node station 4R (right lower paratracheal, 84.2%) and station 7 (subcarinal, 61.5%). The localizations of lymphadenopathy observed with CT are presented in Table 1.

A total of 505 lymph node (67%) stations were sampled (Table 2). The median number of lymph node stations sampled was 1 (min–max:1–4 stations). The most frequently sampled lymph node stations during the CM were station 4R (right lower paratracheal, 81.9%) and station 7 (subcarinal, 30.7%) (Table 2).

All of the cases were diagnosed with CM. A wound site infection was observed in 2 (0.57%) patients and treated with dressing and antibiotherapy; no mortality was observed.

Table 2. Sampled lymph node stations

Stations	n	%
2R	75	21.6
2L	7	2
4L	26	7.5
4R	285	81.9
5	1	0.3
6	4	1.1
7	107	30.7
Lymph node	505	100

R2: Right upper paratracheal; 4R: Right lower paratracheal; 4L: Left upper paratracheal; 2L: Left lower paratracheal; 7: Subcarinal; 5: Aortopulmonary lymph node

Table 3. Histological diagnosis

Diagnosis	n	%
Sarcoidosis	150	43.1
Tuberculosis	72	20.7
Reactive hyperplasia/anthracosis	51	14.7
Carcinoma metastasis	30	8.6
Lymphoma	21	6.0
Granulomatous diseases	20	5.7
Other	4	1.1
Total	348	100

Histopathologically, sarcoidosis (43.1%, n=150) was the most common result, followed by TB (20.7%, n=72). Other findings were reactive hyperplasia/anthracosis (14.7%, n=51), carcinoma metastasis (8.6%, n=30), lymphoma (6.0%, n=21), granulomatous disease (5.7%, n=20), and other disease (1.1%, n=4) (Table 3).

The median lymph node diameter observed on the thorax CT of the patients with a diagnosis of lymph node metastasis was larger than that of those without a diagnosis of lymph node metastasis (3.3 cm vs. 2.1 cm, respectively), and this difference was statistically significant (p<0.001). Similarly, the median lymph node diameter recorded on the thorax CT of patients diagnosed with lymphoma was larger than that of those without a diagnosis of lymphoma (3.5 cm vs. 2.0 cm, respectively), which was also statistically significant (p=0.001).

The median lymph node diameter of patients diagnosed with lymph node metastasis or lymphoma (malignancy) was larger than that of those without a diagnosis of malignancy (i.e., TB, sarcoidosis, reactive hyperplasia, other) (3.5 cm vs. 1.0 cm, respectively), and the difference was statistically significant (p<0.001).

The thorax CT comparison performed after excluding patients diagnosed with malignancy (carcinoma metastasis and lymphoma) revealed that patients diagnosed with TB/sarcoidosis had a larger median lymph node diameter than other patients with a benign finding (2.1 cm vs. 2.0 cm, respectively), with a difference that approached statistical significance (p=0.06).

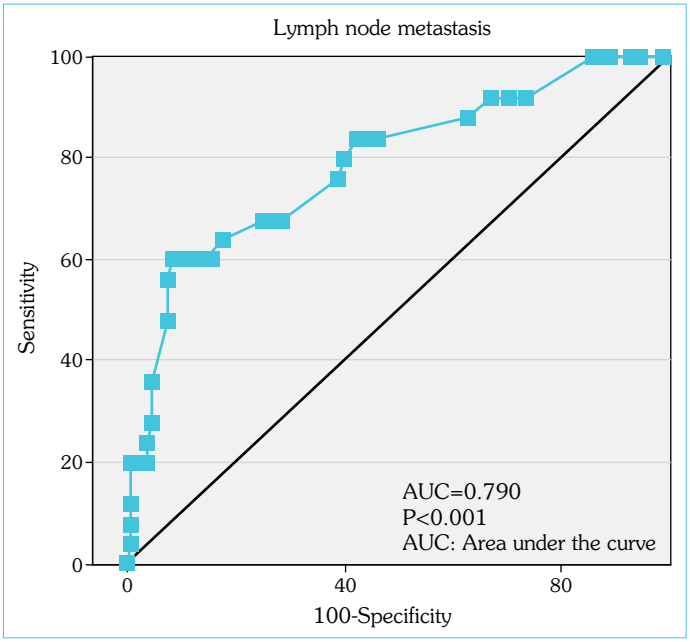

Figure 1. Receiver operating characteristic curve for thoracic computed tomography image ability to predict lymph node metastasis

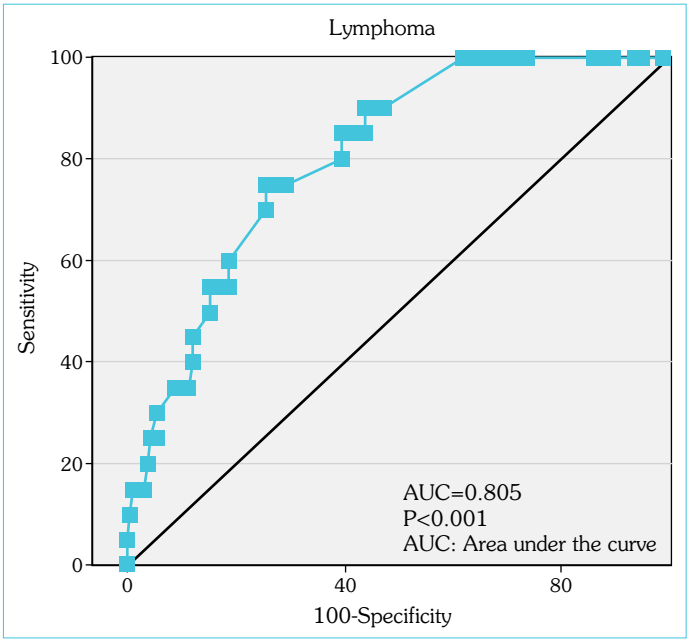

Figure 2. Receiver operating characteristic curve for thoracic computed tomography image ability to predict lymphoma

When the thorax CT scans of patients diagnosed with reactive hyperplasia were compared with those of other patients (TB, sarcoidosis, malignancy, lymphoma, etc.), it was observed that the patients with reactive hyperplasia had a smaller median lymph node diameter (1.7 cm vs. 2.6 cm, respectively), which was highly significant. (p=0.001).

Examination of the reliability of lymph node diameter calculated on a thorax CT image to predict lymph node metastasis using ROC

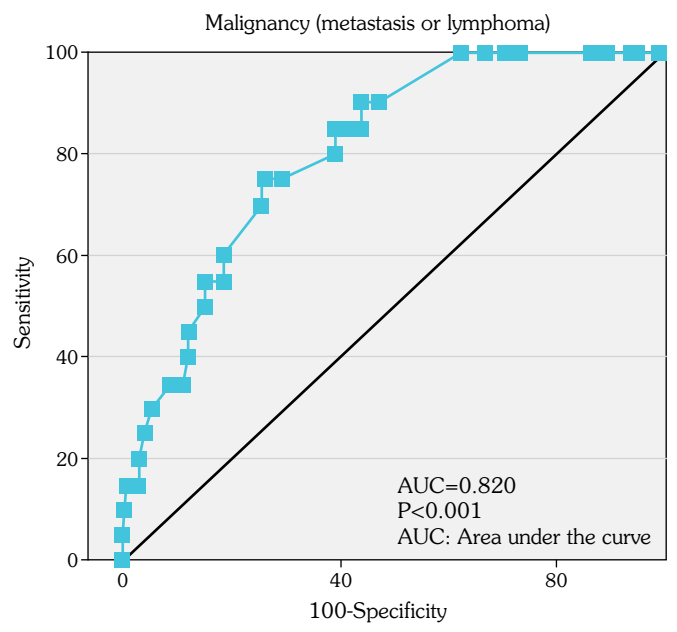

Figure 3. Receiver operating characteristic curve for lymph node diameter on thoracic computed tomography image to predict malignancy

curves revealed a specificity of 91.6% and a sensitivity of 60% if the lymph node diameter was >3.7 cm (AUC: 0.790; 95% CI: 0.741–0.833; p<0.001) (Fig. 1). The specificity was as 73.2% and the sensitivity was 75% if the lymph node diameter was >2.7 cm (AUC: 0.805; 95% CI: 0.758–0.846; p<0.001) (Fig. 2). If the lymph node diameter was >2.5 cm, the specificity was 76.8% and the sensitivity was 71.1% (AUC: 0.820; 95% CI: 0.774–0.860; p<0.001) (Fig. 3).

DISCUSSION

Mediastinal lymphadenopathy, frequently encountered in daily practice, may be associated with many benign and malignant diseases. The underlying cause can be influenced by variables such as demographic factors, geographic location, and socioeconomic status.

In a study conducted in the UK with a population of 100 patients diagnosed with isolated mediastinal lymphadenopathy, reactive lymphadenopathy was most common in the British patients, while lymphadenopathy secondary to granulomatous disease was more common in patients of Asian and African origin (76%). All of the patients diagnosed with TB in the study were of Asian/African ethnicity (9).

Among 300 patients in India, the most common etiologies were the granulomatous diseases of TB and sarcoidosis (53%), while malignancy (17%) was the third most frequent diagnosis. Anthracosis was a rare etiology encountered as a cause of lymph node enlargement in the same study (5%) (10). Granulomatous diseases were also found to be common causes of isolated intrathoracic lymphadenopathy in non-neoplastic patients in Brazil (11). In another study conducted in South Asia, TB was the predominant disease, followed by sarcoidosis (12).

Two relevant studies have been conducted in different periods in Türkiye. Onat et al. (13) found that among 229 patients with non-lung cancer mediastinal lymph node diseases, sarcoidosis (43%) was the most common cause, and TB was reported in 28%. Another study of 84 patients with mediastinal lymphadenopathy who underwent a diagnostic CM noted that TB was the most common cause (34%) and sarcoidosis was reported to be the second (6).

In our study, sarcoidosis (43%) was the most common cause of mediastinal lymphadenopathy, followed by TB (21%). Other causes were reactive hyperplasia, carcinoma metastasis, and lymphoma. It is noteworthy that TB is still one of the most common causes of mediastinal lymphadenopathy in our country. Although a specific pathology may not be defined in tissue samples of the reactive lymphadenopathy seen among the rarer causes, similar results have been reported in the literature (9, 13) In our group, patients with reactive hyperplasia demonstrated the smallest lymph node diameter. These patients were followed up clinically and radiologically for 2 years. No newly-emerging mediastinal lymphadenopathy was detected, and no new clinical diagnosis was made.

Cough and dyspnea are among the most common reasons for presentation to a clinic among patients with mediastinal lymphadenopathy (9, 14). Evison et al. (9) reported that a cough (65%) was the most common complaint, while 13% of the patients were asymptomatic. The most common reason to seek medical attention seen in the current study was a cough (35%), which is consistent with the literature, however, in contrast to the literature, we found that 26% of the patients were asymptomatic.

Determining the cause of mediastinal lymphadenopathy is of considerable significance. Treatment options for malignant conditions, such as primary thoracic malignancies and extra-thoracic carcinoma metastasis, will vary substantially from the treatment for benign conditions, such as TB, sarcoidosis, and granulomatous disease. Clinical, radiological, and pathological findings should be evaluated together in mediastinal lymphadenopathy cases to ensure appropriate care.

CM offers high diagnostic value for the histopathological verification of mediastinal lymphadenopathy (15). The method provides for easy sampling of bilateral paratracheal lymph node stations and subcarinal lymph node stations. Extended mediastinoscopy may be preferred for sampling both aorticopulmonary and paraaortic lymph node stations that cannot be sampled with classic CM. Another option is to sample these stations using video-thoracoscopic surgery.

Complication rates reported in the literature after CM range between 0.83% and 5.2% (16, 17). In studies with large series, the sensitivity of CM has been reported to be between 93% and 100% (13, 18, 19). In our study, all of the patients were diagnosed using CM. Complications developed in only 2 (0.57%) patients and no mortality was observed. This confirms that CM is a reliable diagnostic method. Before CM, the cause could not be determined in some 82% of the patients with mediastinal lymphadenopathy, despite an interventional procedure (EBUS/TBNA). TB, sarcoidosis, and lymphoma have a low rate of diagnosis based on EBUS and TBNA, and these are not uncommon among our population (20). Nonetheless, EBUS/TBNA should be the first choice for a mediastinal lymphadenopathy biopsy since they are minimally invasive methods that do not required general anesthesia.

CT is the imaging method most frequently used to define mediastinal lymphadenopathy. An important reason for conducting this study was to evaluate the radiological and pathological findings together in order to determine whether thoracic CT imaging serve as a diagnostic guide for patients with isolated mediastinal lymphadenopathy.

Studies examining the location of lymphadenopathy in diseases with mediastinal lymphadenopathy are very limited. One study noted that the mediastinal lymph node stations where lymphadenopathy was most frequently detected on a thorax CT were the right lower paratracheal (32%) and subcarinal (25%) stations (6), while in another study it was reported that the paratracheal station (36%) was most common (21). Studies suggest that diagnostic CM sampling is frequently performed from the right paratracheal lymph nodes. Çaylak et al. (6) and Onat et al.(13) have reported that biopsies were conducted most frequently on the 4R (50% and 41% respectively), and the results of the study performed by Porte et al. (19) noted both right paratracheal (76%) and subcarinal (12%) stations as the most common localizations.

In our study of 348 patients, mediastinal lymphadenopathy was detected in a total of 724 lymph node stations in radiological examinations, and 505 lymph node stations were sampled. The most frequently sampled were station 4R (right lower paratracheal) and station 7 (subcarinal). Thorax CT scans most frequently revealed lymphadenopathy in the right lower paratracheal (84%) and subcarinal (61%) stations. The right paratracheal and subcarinal lymph nodes appear to be highly involved in lymphadenopathy-related diseases.

Determining the cause of lymphadenopathy and distinguishing between benign and malign development is initially based on the size of the lymph nodes as observed on CT (22). The literature reports indicate that the probability of malignancy increases with greater lymph node diameter (23). A meta-analysis published by de Langen et al. (24) noted that the prevalence of malignancy was 29% (95% CI: 0.23–0.36) in the group with a lymph node diameter of 10–15 mm on CT, while the prevalence of malignancy increased to 66% (95% CI: 0.42–0.83) in the group with a lymph node diameter of >20 mm.

We also observed a significant correlation between lymph node diameter and the presence of malignancy. Examination of the thorax CT scans of the patients revealed that the lymph node diameter of the patients diagnosed with a malignancy was significantly larger than that of those diagnosed with benign disease ($p<0.001$). When the reliability of the lymph node diameter on thorax CT to predict the possibility of malignancy was evaluated, the specificity was 77% and the sensitivity was 71% for a lymph node diameter of >2.5 cm (AUC: 0.820; 95% CI: 0.774–0.860; $p<0.001$). Consistent with the literature, the sensitivity of CT to identify malignancy increased as the lymph node diameter increased.

CT sensitivity was reduced in cases of a lymph node diameter of <2 cm. The prevalence of other conditions that may cause lymphadenomegaly, such as TB, sarcoidosis, and anthracosis, in our country was probably a factor.

Limitations of the study include its retrospective design and the resulting heterogenous cohort, which makes reliable statistical conclusions more difficult.

CONCLUSION

CT is a useful tool to help differentiate between benign and malignant mediastinal lymphadenopathy. The sensitivity of CT increases with the size of the lymph node diameter. CM is a safe and effective diagnostic method that can be performed with low mortality and morbidity rates in patients with undiagnosed mediastinal lymphadenopathy. Although sarcoidosis was the most common cause of isolated mediastinal lymphadenopathy in this study, TB remains a significant concern in our country.

Ethics Committee Approval: The İstanbul Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 21.12.2018, number: 2018-KAEK-50/1591).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – YA; Design – VE; Supervision – NÇ; Resource – AP, YA; Materials – CBS, NÇ; Data Collection and/or Processing – EYE; Analysis and/or Interpretation – NÇ; Literature Search – ÖS; Writing – YA; Critical Reviews – MM.

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