Mediastinal Granulomatous Inflammation and Overall Survival in Patients with a History of Malignancy

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Abstract

Rationale: Investigators have postulated that mediastinal granulomatous inflammation is associated with prolonged overall survival in patients with cancer.

Objectives: We sought to determine whether mediastinal granulomatous inflammation affects overall survival in patients with a history of treated cancer.

Methods: Patients with a history of treated cancer who underwent endobronchial ultrasound–transbronchial needle aspiration (EBUS-TBNA) for evaluation of mediastinal or hilar lymphadenopathy were grouped based on whether they had mediastinal granulomatous inflammation or benign mediastinal lymphadenopathy without granulomas. Overall survival from the date of EBUS-TBNA to cancer-related death or to last follow-up in patient groups was compared.

Measurements and Main Results: We reviewed the records of 106 patients (44 with mediastinal granulomatous inflammation and 62 with benign mediastinal lymphadenopathy). The 3-year

survival rate was 90% overall and 93 and 88% in patients with mediastinal granulomatous inflammation and benign mediastinal lymphadenopathy, respectively ($P = 0.40$). After multivariate adjustment, whether patients had mediastinal granulomatous inflammation or benign mediastinal lymphadenopathy did not significantly affect the risk of cancer death (mediastinal granulomatous inflammation to benign mediastinal lymphadenopathy hazard ratio, 1.27; $P = 0.76$).

Conclusions: These results suggest that patients who develop mediastinal granulomatous inflammation after cancer treatment do not have an increased overall survival when compared with patients who develop benign mediastinal lymphadenopathy. EBUS-TBNA is warranted for patients with treated cancer who develop mediastinal and/or hilar lymphadenopathy to avoid erroneous upstaging or misdiagnosis of cancer recurrence that would lead to suboptimal management.

Keywords: mediastinal lymphadenopathy; endobronchial ultrasound–guided fine needle aspiration; granulomatous inflammation

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Granulomatous inflammation is a form of chronic inflammation in which macrophages, epithelioid cells, and multinucleated giant cells in the mononuclear phagocyte system aggregate into well-demarcated focal lesions called

granulomas (1). Mediastinal granulomatous inflammation may develop before, simultaneously with, or months to years after diagnosis or treatment of cancer. Mediastinal granulomatous inflammation associated with cancer is also known as

a sarcoid-type reaction or sarcoid-cancer syndrome (2). The main cause of mediastinal granulomatous inflammation in this patient population is unknown, but it may be associated with the malignancy itself, treatment of the malignancy, or

a foreign body reaction associated with a previous procedure or simply idiopathic (3, 4).

The relationship between mediastinal granulomatous inflammation and overall survival in patients with treated cancer is unknown. Some researchers have postulated that patients with cancer who have mediastinal granulomatous inflammation may have longer overall survival than do patients without mediastinal granulomatous inflammation, whereas other studies have demonstrated the opposite or no link between mediastinal granulomatous inflammation and survival (5–8). In the present study, we sought to determine whether the presence of mediastinal granulomatous inflammation prolongs overall survival in patients with a history of treated cancer. We hypothesized that patients with history of cancer who develop mediastinal granulomatous inflammation will have a prolonged overall survival compared with those who develop benign mediastinal lymphadenopathy.

Methods

Patient Cohort

A retrospective cohort study of patients referred to The University of Texas MD Anderson Cancer Center for evaluation of enlarged mediastinal or hilar lymph nodes using endobronchial ultrasound–transbronchial needle aspiration (EBUS-TBNA) was conducted. Demographic information, clinical characteristics (e.g., comorbid conditions, smoking history), pathologic findings, imaging results (including the lymph nodes sampled and node sizes), and microbiologic and serologic findings were extracted from the patient records stored in the American College of Chest Physicians Quality Improvement Registry Education and Evaluation database and reviewed. This database is part of an ongoing multicenter bronchoscopy registry in which comprehensive patient information is collected prospectively. This study was approved by the MD Anderson Institutional Review Board (protocol number PA12–0466).

The study cohort included patients 18 years of age or older with a history of treated cancer in whom hilar or mediastinal lymphadenopathy developed during routine follow-up chest computed tomography

(CT) or positron emission tomography (PET)-CT. None of the patients in the cohort had a history of granulomatous disease or evidence of mediastinal adenopathy at the time of cancer diagnosis. Patients with evidence of a newly diagnosed malignancy not treated at the time of EBUS-TBNA, patients with no history of cancer, and patients with positive cultures or serologic findings suggestive of an infectious etiology for the lymphadenopathy (mycobacterial, fungal disease, etc.) were excluded.

We excluded 20 patients with evidence of granulomas and active infection. Eight of these patients were diagnosed with histoplasma capsulatum, two with actinomycosis, three with *Aspergillus fumigatus*, two with blastomycosis, two with *Mycobacterium tuberculosis*, and three with *Mycobacterium avium intracellulare*.

Our practice is to sample at least one lymph node on each side and one lymph node in the center (i.e., left hilar, right hilar, and subcarinal), with at least three passes on each lymph node. Bronchoalveolar lavage is routinely done if there is a parenchymal infiltrate/abnormality present, and cultures are usually sent only from one representative lymph node.

Definitions

Mediastinal granulomatous inflammation was defined as the presence of a nonnecrotizing granuloma in an EBUS-TBNA specimen obtained from a patient with a history of treated cancer but without evidence of infectious etiology (according to direct staining, cultures, and serology) and no other clinical or radiologic findings suggestive of an infection or inflammatory disorder such as sarcoidosis. Serology studies that routinely are performed in our patients are coccidioides antibody, histoplasma antibody, serum blastomyces antigen, and *Cryptococcus* antibody. Patients with lung parenchyma infiltrates underwent bronchoalveolar lavage studies that included Gram stain and culture, fungus stain and culture, acid-fast bacilli (AFB) stain and culture, *Aspergillus* antigen assay, and respiratory PCR panel. We do not routinely perform genetic testing for tuberculosis (TB), mantoux skin test, or quantiferon TB gold test unless we have suspicion for TB (i.e., if the patient has been exposed to TB or has clinical and radiographic presentation suggestive of TB). Genetic testing for TB is only

performed on patients with clinical suspicion of TB or if there is AFB growth on AFB cultures.

A diagnosis of sarcoidosis was based on clinical-pathologic criteria if granuloma was found, when patient had a compatible clinical history (e.g., erythema nodosum, uveitis), and when other causes of granulomatous disease were excluded.

Benign mediastinal lymphadenopathy was defined as the presence of benign lymphoid tissue in EBUS-TBNA specimens obtained from a patient with a history of treated cancer but without evidence of infectious etiology according to direct staining, cultures, and serology and no clinical or radiologic findings suggestive of another malignancy, infection, or inflammatory disorder.

All patients were required to have new hilar or mediastinal lymphadenopathy, defined radiologically as enlarged lymph nodes of at least 1 cm in short-axis diameter as measured on a chest CT scan or PET-positive mediastinal or hilar lymph nodes. PET-positive lymph nodes were defined as a standardized uptake value >2.5 .

Statistical Methods

Overall survival duration was measured from the date of EBUS-TBNA to the date of death or last follow-up. Time zero was the date of EBUS-TBNA. Time from cancer diagnosis to EBUS-TBNA was included in our model as a continuous variable.

Patients were grouped based on whether they had mediastinal granulomatous inflammation or benign mediastinal lymphadenopathy. We also measured the recurrence-free survival from the date of EBUS-TBNA only because patients may have had treated recurrences before EBUS-TBNA.

Patient and clinical characteristics in the two groups were compared using the chi-square test or Fisher exact test for categorical variables and a two-sample *t* test for continuous variables.

Variables with $P \leq 0.20$ on univariate Cox proportional hazard regression analysis and variables considered to be clinically relevant even with $P > 0.20$ were initially included in the multivariable Cox proportional hazard regression model.

Proportional hazards assumption was confirmed by determining the significance of a time-interaction variable and testing and plotting based on Schoenfeld residuals.

The Kaplan-Meier product limit method was used to estimate unadjusted median overall survival from the time of EBUS-TBNA. Groups were compared using the log-rank statistic test.

P values ≤ 0.05 were considered significant. All tests were two-sided. All statistical analyses were performed using the SAS software program (version 9.4; SAS Institute, Cary, NC).

Results

We reviewed the records of 1,442 patients referred for EBUS-TBNA from September 2009 to April 2012. We excluded 642 patients with newly diagnosed cancer, 17 who had evidence of an active malignancy and granuloma, 27 who did not have a history of cancer but had symptoms and imaging results consistent with a new diagnosis of sarcoidosis, 20 with no history of cancer who had cultures or serologic findings suggestive of an infectious etiology, and 630 who had evidence of cancer recurrence. This left 106 patients for our final analysis (Figure 1).

Of the 106 patients, 44 (42%) had mediastinal granulomatous inflammation, and 62 (58%) had benign mediastinal lymphadenopathy. In the mediastinal granulomatous inflammation group, 43 patients (98%) had bilateral mediastinal

or hilar lymphadenopathy, and in 42 patients (95%), the lymphadenopathy was symmetrical. Twenty-four of 25 patients (96%) who underwent PET had ^{18}F -fluorodeoxyglucose (FDG)-avid lymph nodes. Seven patients underwent endobronchial biopsies: four had evidence of granulomatous inflammation, whereas three had normal endobronchial tissue. Two patients with evidence of mediastinal granulomatous inflammation according to EBUS-TBNA underwent a mediastinoscopy; in both cases, pathologic findings were consistent with mediastinal granulomatous inflammation, with no evidence of malignancy. Five patients with mediastinal granulomatous inflammation (11%) underwent empirical treatment with antifungals. Also, two patients (5%) had received chemotherapy for presumed recurrence of cancer based on imaging studies alone. Both patients received only one cycle of chemotherapy before EBUS-TBNA. None of the patients with mediastinal granulomatous inflammation received steroids.

In the benign mediastinal lymphadenopathy group, 46 patients (74%) had bilateral mediastinal or hilar lymphadenopathy. In 33 patients (53%), the lymphadenopathy was symmetrical. Thirty of 39 patients (77%) who underwent PET had FDG-avid lymph nodes. Five patients underwent endobronchial

biopsies; one had evidence of inflammation, whereas four had normal endobronchial tissue. None of the endobronchial biopsies in this group revealed granulomata. Two patients who had benign lymphocytes according to EBUS-TBNA underwent mediastinoscopy. In both cases, pathologic findings were consistent with benign mediastinal lymphadenopathy, with no evidence of malignancy or granuloma. Two patients underwent empirical treatment with antifungals based on imaging studies alone. None of the patients with benign mediastinal lymphadenopathy received chemotherapy or steroids.

None of the patients was treated with newer immunotherapy antineoplastic agents (e.g., ipilimumab). We had two patients, one in each group, treated with IFN.

All of our patients had new FDG-avid lymph nodes on PET; we did not find statistical differences in the number of patients with FDG-avid lymph nodes between the two groups.

Patient demographics and clinical characteristics in the mediastinal granulomatous inflammation and benign mediastinal lymphadenopathy groups are shown in Table 1. All tests for the detection of fungal pathogens were negative in both groups. None of the patients had symptoms of sarcoidosis or other pulmonary diseases during follow-up.

Figure 1. Flow chart of patient referred for endobronchial ultrasound–transbronchial needle aspiration (EBUS-TBNA).

Table 1. Demographic and clinical characteristics of the study patients

Characteristic	All Patients (n = 106) (%)	Mediastinal Granulomatous Inflammation (n = 44) (%)	Benign Mediastinal Lymphadenopathy (n = 62) (%)	P Value
Age, yr				
Median (range)	55 (20–80)	50 (24–80)	58 (20–79)	
Mean (SD)	54 (13)	51 (11)	56 (13)	0.02*
Time from cancer diagnosis to EBUS, mo				
Median (range)	25 (2–251)	26 (2–198)	22 (2–251)	
Mean (SD)	48 (56)	44 (48)	52 (60)	0.72 [†]
Sex				
Female	54 (51)	22 (50)	32 (51.6)	
Male	52 (49)	22 (50)	30 (48.4)	0.87
Race				
White	87 (82.1)	38 (86.4)	49 (79)	
Black	9 (8.5)	4 (9.1)	5 (8.1)	
Hispanic	5 (4.7)	1 (2.3)	4 (6.5)	
Asian	4 (3.8)	1 (2.3)	3 (4.8)	
Other	1 (0.8)	0 (0.0)	1 (1.6)	0.78 [‡]
Smoking				
Never	55 (51.9)	24 (54.5)	31 (50)	
Prior or current	51 (48.1)	20 (45.5)	31 (50)	0.64
Cancer diagnosis				
Lymphoma	17 (16)	10 (22.7)	7 (11.3)	
Head and neck	11 (10.4)	6 (13.6)	5 (8.1)	
Breast	15 (14.2)	5 (11.4)	10 (16.1)	
Melanoma	11 (10.4)	6 (13.6)	5 (8.1)	
Lung	11 (10.4)	3 (6.8)	8 (12.9)	
Esophageal	10 (9.4)	0 (0)	10 (16.1)	
Colon	5 (4.7)	0 (0)	5 (8.1)	
Testicular	4 (3.8)	3 (6.8)	1 (1.6)	
Renal	4 (3.8)	2 (4.5)	2 (3.2)	
Other	18 (17)	9 (20.5)	9 (14.5)	0.02 [‡]
Tumor type				
Liquid tumor	17 (16)	10 (22.7)	7 (11.3)	
Solid tumor	89 (84)	34 (77.3)	55 (88.7)	0.11
Cancer stage at diagnosis				
Localized	23 (21.7)	7 (15.9)	16 (25.8)	
Locally advanced	53 (50)	22 (50)	31 (50)	
Metastatic	30 (28.3)	15 (34.1)	15 (24.2)	0.36
History of asthma				
No	99 (93.4)	42 (95.5)	57 (91.9)	
Yes	7 (6.6)	2 (4.5)	5 (8.1)	0.70 [‡]
History of COPD				
No	100 (94.3)	42 (95.5)	58 (93.5)	
Yes	6 (5.7)	2 (4.5)	4 (6.5)	1.00 [‡]
History of sarcoidosis				
No	106 (100)	44 (100)	62 (100)	
Yes	0	0	0	NA
Initial cancer therapy				
Surgery	64 (60.4)	28 (63.6)	36 (58.1)	
Chemoradiation	20 (18.9)	7 (15.9)	13 (21)	
Chemotherapy	18 (17)	9 (20.5)	9 (14.5)	
Radiation therapy	4 (3.8)	0 (0)	4 (6.5)	0.32 [‡]
Cough				
No	95 (89.6)	36 (81.8)	59 (95.2)	
Yes	11 (10.4)	8 (18.2)	3 (4.8)	0.05 [‡]
Dyspnea				
No	98 (92.5)	42 (95.5)	56 (90.3)	
Yes	8 (7.5)	2 (4.5)	6 (9.7)	0.46 [‡]
Skin complaints				
No	105 (99.1)	43 (97.7)	62 (100)	
Yes	1 (0.9)	1 (2.3)	0 (0)	0.42 [‡]
Rheumatologic complaints				
No	106 (100)	44 (100)	62 (100)	
Yes	0	0	0	NA

(Continued)

Table 1. (Continued)

Characteristic	All Patients (n = 106) (%)	Mediastinal Granulomatous Inflammation (n = 44) (%)	Benign Mediastinal Lymphadenopathy (n = 62) (%)	P Value
Nephrolithiasis				
No	106 (100)	44 (100)	62 (100)	
Yes	0	0	0	NA
Fever of unknown origin				
No	106 (100)	44 (100)	62 (100)	
Yes	0	0	0	NA
Hypercalcemia				
No	106 (100)	44 (100)	62 (100)	
Yes	0	0	0	NA
Number of lymph node biopsies				
1	24 (22.6)	3 (6.8)	21 (33.9)	
2	32 (30.2)	11 (25)	21 (33.9)	
3	39 (36.8)	27 (61.4)	12 (19.4)	
4	7 (6.6)	2 (4.5)	5 (8.1)	
5	4 (3.8)	1 (2.3)	3 (4.8)	0.0001 [‡]
Size of lymph node 1 on CT scan, cm				
n	106	44	61	
Median (range)	1.1 (0.5–2.9)	1.2 (0.5–2.5)	1.1 (0.6–2.9)	
Mean (SD)	1.2 (0.5)	1.3 (0.5)	1.2 (0.5)	0.35*
Size of lymph node 2 on CT scan, cm				
n	81	41	40	
Median (range)	1.0 (0.4–2.3)	1.1 (0.4–2.3)	1.0 (0.6–2.0)	
Mean (SD)	1.1 (0.4)	1.2 (0.5)	1.0 (0.3)	0.03*
Lymph node with FDG avidity				
No	10 (9.4)	1 (2.3)	9 (14.5)	
Yes	54 (50.9)	24 (54.5)	30 (48.4)	
NA	42 (39.6)	19 (43.2)	23 (37.1)	0.11 [‡]
Finding on follow-up imaging				
Lymph nodes enlarging	3 (3.3)	2 (5.3)	1 (1.9)	
Lymph nodes shrinking	23 (25.3)	13 (34.2)	10 (18.9)	
Unchanged	65 (71.4)	23 (60.5)	42 (79.2)	0.13 [‡]
Symptoms suggesting sarcoidosis				
No	106 (100)	44 (100)	62 (100)	
Yes	0	0	0	NA
Recurrent malignancy				
No	91 (85.8)	37 (84.1)	54 (87.1)	
Yes	15 (14.2)	7 (15.9)	8 (12.9)	0.66

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; EBUS = endobronchial ultrasound; FDG = ¹⁸F-fluorodeoxyglucose; NA = not available.

*Two-sample *t* test.

[‡]Wilcoxon rank-sum test.

[‡]Fisher exact test.

Cancer Diagnosis to EBUS-TBNA

The median time from cancer diagnosis to EBUS-TBNA was 25 months (range, 2–251 mo). The presence of mediastinal granulomatous inflammation or benign mediastinal lymphadenopathy was not associated with time from cancer diagnosis to EBUS-TBNA ($P = 0.72$).

Overall Survival from EBUS-TBNA

The median follow-up period in all patients was 33 months (range, 0.1–59 mo). At the time of this study, 11 patients (10%) had died of cancer. The 3-year survival rate was 90% overall and 93% and 88% in patients with mediastinal granulomatous inflammation and benign mediastinal lymphadenopathy, respectively ($P = 0.40$).

On univariate analysis (see Table E1 in the online supplement), older age and chemo-radiation were associated with worse overall survival compared with younger age and surgery alone as initial cancer therapy. On multivariate analysis (Table E2), the presence of mediastinal granulomatous inflammation or benign mediastinal lymphadenopathy did not affect the hazard risk for death (mediastinal granulomatous inflammation versus benign mediastinal lymphadenopathy: hazard ratio [HR], 1.27; $P = 0.76$), and only older age increased the HR of death.

The Kaplan-Meier overall survival curve from time of EBUS-TBNA is shown in Figure 2 ($P = 0.40$, Log-rank test).

Overall Recurrence Rates from EBUS-TBNA

Median time to recurrence after EBUS-TBNA was 10 months (range, 0.9–41 mo) for 18 patients who had recurrence or who had died of cancer. At the time of this study, 18 patients (17%) had experienced cancer recurrence or had died of cancer. Similarly to overall survival, on univariate analysis age and chemo-radiation were found to be significantly associated with recurrence-free survival (Table E3), and, on multivariate analysis, the presence of mediastinal granulomatous inflammation or benign mediastinal lymphadenopathy did not affect the hazard risk for death (Table E4). The 3-year recurrence-free survival rate after EBUS-TBNA was

	Months					
Patients at risk	0	10	20	30	40	50
MGI	44	40	35	23	11	4
BML	62	57	54	44	20	6

Figure 2. Kaplan-Meier overall survival curve for the study patients from endobronchial ultrasound–transbronchial needle aspiration. BML = benign mediastinal lymphadenopathy; EBUS = endobronchial ultrasound; MGI = mediastinal granulomatous inflammation.

82% overall and 83 and 82% in patients with mediastinal granulomatous inflammation and benign mediastinal lymphadenopathy, respectively ($P = 0.90$) (Figure 3).

Discussion

Our results show that patients with malignancies that develop mediastinal granulomatous inflammation after cancer treatment do not have an overall survival advantage over a similar group of patients with benign mediastinal lymphadenopathy. Also, we did not find a difference in recurrence-free survival between the two groups. As expected, only older age increased the HR of death. However, in our cohort metastatic disease at presentation did not have a worse overall survival. This is explained by the fact that stage IV lymphomas were labeled as metastatic disease (10 in mediastinal granulomatous inflammation and 7 in the benign mediastinal lymphadenopathy group). Selection bias plays a role as well because in our study we selected only patients without active disease at the time of EBUS-TBNA.

In contrast with previous reports indicating that mediastinal and hilar lymphadenopathy disproportionately occur in patients with testicular germ cell tumors or lymphomas (9–11), we found evidence of mediastinal and hilar lymphadenopathy in patients with various types of cancer.

Granulomas generally form as a means of defending hosts from constant irritants of either exogenous or endogenous origin. The most common cause of mediastinal granulomatous inflammation in patients without cancer is a mycobacterial or fungal infection (4). As per Centers for Disease Control data, the incidence proportion for TB in Texas for the year 2013 was 4.7 per 100,000 population. We do not have an exact number reported for endemic fungal infections, but, based on a study looking at older individuals and endemic fungal infections by state during the period from 1999 to 2008, the incidence rate of endemic fungal infections in Texas ranged from 1.18 to 1.25 per 100,000 person-years (12). In our cohort, out of 1,442 patients reviewed, we found and excluded 20 patients with active infection. Two patients were diagnosed with TB, and 10 patients were

diagnosed with an endemic fungal infection.

Common noninfectious etiologies for mediastinal granulomatous inflammation are sarcoidosis and foreign body reactions (13). Chemotherapy is used extensively for both solid and hematologic malignancies, and granuloma formation is most commonly reported with use of the chemotherapeutic agents methotrexate and IFN (14). Newer antineoplastic agents, such as ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte–associated protein 4, are known to induce sarcoid-like reactions (15). In many cases, a granulomatous reaction to a chemotherapeutic agent is indistinguishable from sarcoidosis (16). In our study, we did not find a correlation between surgery, chemotherapy, or radiation therapy and development of mediastinal granulomatous inflammation, and we believe that the etiology of mediastinal granulomatous inflammation in patients with a history of cancer is highly variable; however, none of our patients was treated with newer immunotherapy antineoplastic agents.

	Months					
Patients at risk	0	10	20	30	40	50
MGI	44	38	32	20	11	4
BML	62	54	50	40	16	6

Figure 3. Kaplan-Meier recurrence-free survival curve for the study patients from endobronchial ultrasound–transbronchial needle aspiration. BML = benign mediastinal lymphadenopathy; EBUS = endobronchial ultrasound; MGI = mediastinal granulomatous inflammation.

Researchers have proposed many hypotheses concerning the etiology of granuloma formation, such as immunologic dysfunction related to cancer and “antigenic shedding” from the tumor. However, numerous reports indicate that patients with resected cancer who do not have metastasis may exhibit a radiographic and pathologic pattern of bilateral hilar lymphadenopathy and mediastinal granulomatous inflammation that is indistinguishable from that of sarcoidosis (3). As observed in our study, these reactions may occur years after resection of the cancer and may resolve spontaneously without specific therapy. None of the patients in our cohort underwent treatment with steroids. Also, radiation therapy and chemotherapy are not required for the development of mediastinal granulomatous inflammation (3, 10, 17, 18). Similar to prior reports, of 64 patients with no evidence of metastatic disease who underwent surgery alone, 28 (44%) had mediastinal granulomatous inflammation, and 36 (56%) had benign mediastinal lymphadenopathy (3, 10).

Our study is the largest reported cohort study to date to address the presence of

mediastinal granulomatous inflammation in patients with a history of cancer and to compare their outcomes with those in a similar cohort of patients with cancer who have benign mediastinal lymphadenopathy. All of the patients in our cohort had prolonged follow-up periods after EBUS-TBNA, indicating that most of them reasonably can be assumed to have experienced lymphadenopathy as a result of inflammation rather than cancer recurrence. This suggests that, in most patients with a history of cancer who have lymphadenopathy without any evidence of cancer recurrence, prolonged follow-up would be reasonable, and additional invasive testing would not be needed unless patients have changes suggestive of recurrence on follow-up imaging studies.

Our study has some limitations, the first of which is the retrospective nature of the data collection. We acknowledge that mediastinal granulomatous inflammation represents a nonspecific histologic pattern that may be associated with other disorders, even when extensive workups are performed, as in our patients. None of the patients in our cohort had symptoms

suggestive of sarcoidosis at follow-up, and all of them had negative stains, cultures, and serology.

In conclusion, EBUS-TBNA is warranted for patients with treated cancer having mediastinal and/or hilar lymphadenopathy. If recurrent disease is demonstrated, appropriate treatment can be implemented. If, on the other hand, EBUS-TBNA demonstrates benign mediastinal lymphadenopathy or mediastinal granulomatous inflammation with negative stains, cultures, and serology, we recommend serial radiographic follow-up rather than additional invasive testing unless the patient has a particularly high clinical suspicion of cancer recurrence. Although a consensus regarding the optimal follow-up time is lacking, our current practice is to have the first repeat CT or PET-CT 3 months after the initial image showing abnormal mediastinal lymph nodes and, if the lymphadenopathy has resolved, to continue observation as required by the patient’s primary cancer protocol. If the lymphadenopathy is persistent but unchanged at 3 months, we recommend follow-up with serial imaging every 6 to 12 months for approximately 2 years. If the

lymph nodes increase in size during follow-up, we perform another biopsy, either surgical or EBUS-TBNA.

Our findings reinforce the importance of appropriate diagnostic

tissue sampling in patients with a history of cancer and evidence of mediastinal and/or hilar lymphadenopathy to avoid erroneous upstaging or misdiagnosis of cancer recurrence

that would lead to suboptimal management. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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