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Received: 2 February 2024 | Revised: 18 March 2024 | Accepted: 22 April 2024

DOI: 10.1002/dc.25337

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ORIGINAL ARTICLE

Importance of mediastinal granulomatous/sarcoid-like lymphadenopathy in extrathoracic malignancies

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Abstract

Background: In patients with extrathoracic malignancies (ETM), granulomatous lymph adenopathy called sarcoid-like reactions (SLR) can be seen in the regional or draining lymph nodes. We hypothesized that SLR may be a sign of imminent metastasis and investigated the clinical course and rate of recurrence in patients with ETM and granulomatous mediastinal lymphadenopathy (MLN).

Methods: In this retrospective observational study, we reviewed the medical files of patients with known ETM and who underwent EBUS-TBNA for initial staging or detection of recurrence from 2011 to 2023. Patients with granulomatous MLN were included.

Results: Forty-one patients (29 female) enrolled in the study. Breast and colorectal carcinomas were the most common malignancies. A total of 81 lymph nodes were sampled. The final diagnosis of patients was five sarcoidosis, one tuberculosis, one second primary, one drug reaction, and 33 SLR. Among patients with SLR, in one patient lymph nodes progressed during the follow-up and were accepted as false-negative without confirmatory biopsy. The negative predictive value (NPV) of granulomatous MLN for metastasis was 97.05%.

Conclusion: Granulomatous MLN may be due to tuberculosis, drug reaction, sarcoidosis, or SLR in patients with ETM. SLR has a high NPV in patients with ETM. Follow-up imaging rather than confirmatory biopsy is reasonable in these patients.

KEYWORDS
EBUS-TBNA, extrathoracic malignancy, granulomatous inflammation, lymph nodes

1 | INTRODUCTION

In patients with extrathoracic malignancies (ETM), hilar, and mediastinal lymph node (MLN) enlargement raise the suspicion of metastasis. However, MLN may also be due to benign conditions like infections, or granulomatous inflammation.[1–3]

Granulomatous inflammation may be due to tuberculosis, sarcoidosis, drug reactions, or sarcoid-like reactions (SLR)[4,5] in these patients. SLR is defined as epithelioid cell granulomas in patients with cancer.[6] It can be seen in the primary tumor, regional or draining lymph nodes.[7] Noncaseating epithelioid cell granuloma is present in both sarcoidosis and SLR and differentiation can be made based on clinical findings.

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SLR is very confusing in patients with ETM. Do patients require confirmatory biopsy or is it true negative for metastasis? As occurs in the draining or distant lymph nodes, we hypothesized that SLR may be a sign of imminent metastasis. Thus, we investigated the clinical course and rate of MLN metastasis during long-term follow-up in ETM with granulomatous MLN.

2 | MATERIALS AND METHODS

We retrospectively reviewed the medical files of patients with known ETM who underwent EBUS-TBNA for initial staging or detection of recurrence from 2011 to 2023. Patients with granulomatous MLN were included. Patients were excluded if they had a previous history of granulomatous disease such as tuberculosis, sarcoidosis, or if follow-up data were unavailable.

During follow-up, lymph nodes were classified as enlarged, regressed, or stable according to changes in lymph node diameter. If lymph node diameter increases during follow-up or is proven to be malignant with biopsy it is accepted as false-negative.

All the procedures were performed under conscious sedation with midazolam and/or fentanyl. EBUS-TBNA was performed with a bronchoscope (BF-UC180F; Olympus Medical, Japan) with an electronic convex-array ultrasound processor (EU-ME1; Olympus Medical, Japan) using 21G or 22G needles (NA-201 SX-4021/4022; Olympus Medical, Japan).

Aspirates were smeared onto glass slides, air-dried, and stained with May-Grünwald Giemsa (MGG) and Pap stains. Some amount of aspirate was placed in formaldehyde solution (formalin) to obtain cell blocks (CBs). CBs were embedded in paraffin, and thin sections were obtained and stained with hematoxylin-eosin (Figures 1, 2, and 3). The cytopathological examination of smears and CBs was performed by an experienced cytopathologist. CBs could be obtained from nearly all biopsy samples. The final diagnosis was made using a composite of clinical history, histopathologic findings, and microbiological studies.

The data were analyzed using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.). Continuous variables with normal distribution were presented as mean ± standard deviation and median (minimum and maximum) for non-normal distributed variables. A Kolmogorov–Smirnov test was used to analyze the distribution of variables, and a Levene test was applied to assess the equality of variances. Categorical data were expressed as numbers and percentages. Negative predictive value (NPV) is calculated as true negatives (benign granulomatous)/[true negatives (benign granulomatous) + false-negatives (malign granulomatous)].

3 | RESULTS

A total of 324 patients with ETM underwent EBUS-TBNA. There were 45 (13.8%), active or history of ETM and granulomatous MLN. Three patients were lost to follow-up, and one patient was excluded due to a history of previous tuberculosis. The remaining 41 patients



FIGURE 1 Preparation of cellblock. Coagulum clot preparation in formaldehyde. [Color figure can be viewed at wileyonlinelibrary.com]

(29 female) aged between 32 and 78 years were enrolled. Breast and colorectal carcinomas were the most common malignancies (Table 1). Fifteen patients (36.5%) had MLN at the time of initial diagnosis and the remaining 26 had it during the follow-up imaging. The median time from the diagnosis to lymph node enlargement was 24 months (6–72 months). Thirty patients had PET scans and the SUVmax range of lymph nodes was between 3 and 83. Most of the patients had hilar and MLN enlargement. A total of 81 lymph nodes were sampled. Among them, subcarinal (82.9%) and right lower mediastinal (4R) (63.4%) were the most sampled lymph node stations (Table 2). The median follow-up time after the first EBUS-TBNA was 48 months (1–120 months).

The final diagnosis of patients is presented in Figure 4. Five patients were accepted as sarcoidosis according to clinical and radiological findings. One patient with leukemia had MLN enlargement at the time of initial diagnosis and *M. tuberculosis* grew in lymph node culture. In one patient with renal cell carcinoma, MLNs enlarged 3 years after the diagnosis. The patient underwent EBUS-TBNA and histopathological examination showed lymphoma at the subcarinal lymph node station and granulomatous inflammation at the lower right paratracheal lymph node. Confirmatory supraclavicular lymph node excisional biopsy was reported as Hodgkin lymphoma and accompanying granulomatous inflammation. One patient had granulomatous inflammation due to nivolumab treatment.

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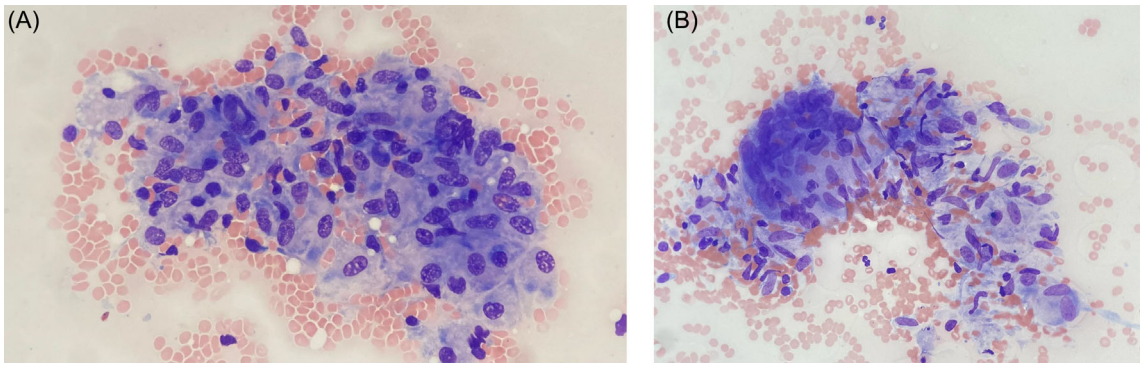


FIGURE 2 Cytological smear from sarcoid-like granuloma: A cluster of epithelioid histiocytes with elongated, boomerang-like nuclei forming syncytial aggregates (A) and a multinucleated histiocytic giant cell accompanying mononucleated epithelioid histiocytes aggregate (B) (MGG stain, X400). [Color figure can be viewed at wileyonlinelibrary.com]

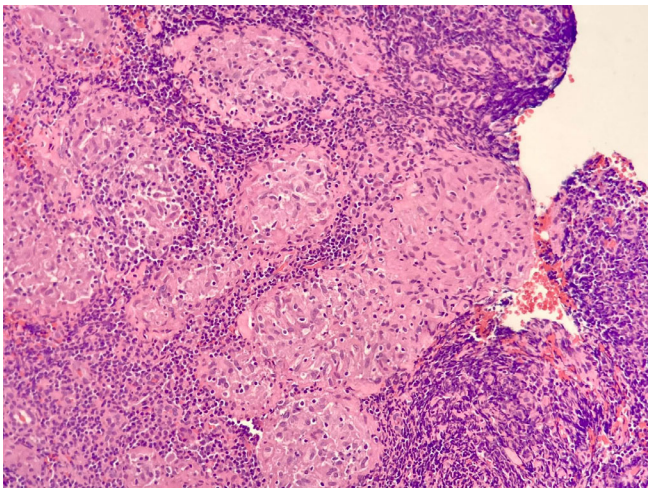


FIGURE 3 The cellblock section depicts multiple non-necrotizing granulomas in the lymphoid background (HE stain, X200). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Type of malignancies.

	N (%)
Breast cancer	9 (22)
Colorectal carcinoma	9 (22)
Ovary and endometrium	5 (12.2)
Sarcoma	3 (7.3)
Renal cell carcinoma	2 (4.9)
Germ cell	2 (4.9)
Leukemia lymphoma	2 (4.9)
Malignant melanoma	2 (4.9)
Laryngeal squamous cell carcinoma	2 (4.9)
Papillary thyroid carcinoma	1 (2.4)
Skin squamous	1 (2.4)
Prostate cancer	1 (2.4)
Pancreatic cancer	1 (2.4)
Bladder cancer	1 (2.4)

TABLE 2 The site and sampled lymph node stations.

Site of lymph nodes	***N* (%)**
Only hilar	1 (2.4)
Hilar + mediastinal	32 (78.1)
Only mediastinal	8 (19.5)
Sampled stations	***N* (%)**
7 (subcarinal)	34 (82.9)
4R	26 (63.4)
10 L	13 (31.7)
10R	5 (12.2)
4 L	3 (7.3)

The remaining 33 (80.6%) patients had sarcoid-like granulomatous reactions. Among these patients, three underwent mediastinoscopy and four underwent a second EBUS-TBNA for confirmation. The final diagnosis was the same with the first EBUS-TBNA and metastasis was ruled out in these patients. In only one patient lymph nodes progressed during the follow-up and were accepted as false-negative without confirmatory biopsy. The NPV of granulomatous MLN for metastasis was 97.05% in these patients.

4 | DISCUSSION

In this study, we investigated the long-term results of patients with ETM and mediastinal granulomatous/sarcoid-like lymphadenopathy.

The frequency of granulomatous MLN in patients with ETM differs between 5.2% and 36.9%.[1,8–12] It was 13.8% in our study. In addition to SLR; sarcoidosis, tuberculosis, drug reactions, and second primary cancer are possible differential diagnoses of granulomatous MLN in patients with ETM.[8,10,13–15] In line with these studies, there were five sarcoidoss, one tuberculous mediastinal lymphadenitis, one second primary, and one drug reaction in our study.

EBUS-TBNA is a reliable method for MLN sampling.[1–3] Slides may be sufficient for the diagnosis of malignancy. However, CBs increase

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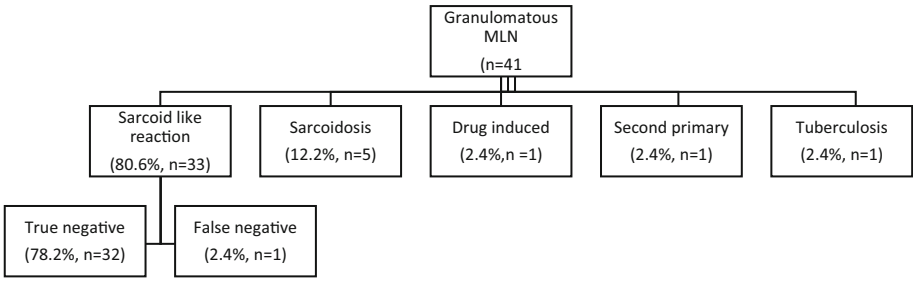


FIGURE 4 Final diagnosis of patients.

the diagnostic yield of EBUS-TBNA in the diagnosis of granulomas on cytology.[16,17] This is possible due to the disruption of the granuloma's structure when the aspirates are smeared between glass slides. Thus, efforts should be made to obtain CBs in every patient.

SLR is a long-known phenomenon.[18] The mechanism can be a local response in the draining lymph nodes or may be an immune response to cancer cell antigens like vimentin which results in distant lymphadenopathy.[12,13] Some researchers postulated that granulomas may have a protective role against tumor spread.[9]

Regardless of the mechanism, SLR has a high NPV for metastasis. Bellinger et al.,[12] found 100% NPV. In the study by Butt et al.,[13] there were 2 recurrences among the 26 ETM. Also, Huh et al.,[14] did not observe any disease recurrence in patients with ETM. Also, Murthi et al.,[9] found a correlation between granulomatous lymphadenopathy and reduced risk of metastasis and increased survival. They postulated that granulomas may have a protective role against tumor spread. Grosu et al.[15] did not find any survival or recurrence advantage of granulomatous MLN compared to benign lymphadenopathy. However, they found that in only 5.3% of patients lymph nodes enlarged during follow-up. Also, in our study, only one patient had false-negative EBUS-TBNA and NPV for MLN metastasis was 97.05%.

Discriminating between granulomatous inflammation and malignancy based on CT and/or PET-CT findings is difficult. Both are FDG avid[8] and SUV values are similar.[11] However, unilateral or asymmetrical enlargement, presence of coalescence, blurred margins, or necrosis suggest metastasis, lymphoma, or tuberculosis.[19,20] In some studies, diameters were increased in malignant group.[3,8,21,22] However, a decision based on diameter may cause to missing of malignancy. As shown before, there may be normal-sized metastasis lymph nodes or benign lymph nodes with increased diameters and FDG uptake.[22–24] In our study, 78.1% of patients had bilateral hilar and mediastinal lymphadenopathy (MLN). The presence of bilateral hilar and MLN may be a sign of granulomatous inflammation rather than metastasis.[15,25]

Epithelioid histiocytes of sarcoid granulomas may be confused with spindle cells of metastatic malignant melanomas[25] and in those cases, immuhisto/cytochemical study is essential for the differential diagnosis. In our study, we have not faced with this kind of problem. Yet, in some cases, particularly sclerotic or hyalinized granulomas including very few epithelioid histiocytes, the correct diagnosis of granuloma was challenging. The use of combined cytology and CB histology was very helpful for the problem cases.

Immune checkpoint inhibitor-related sarcoid-like granulomatous lymphadenopathy is a new phenomenon. And an important problem for both cytopathologists and clinicians. CT findings are indistinguishable from sarcoidosis. But as previously explained morphological features such as the presence of numerous large cellular granulomas without hyalinized fibrosis and multinucleated giant cells may help to distinguish immune checkpoint inhibitor-related sarcoid-like granulomatous inflammation from true sarcoidosis.[25]

5 | CONCLUSION

Granulomatous MLN in patients with ETM may be due to sarcoidosis, tuberculosis, second primary, or SLR. Thus, efforts should be made to obtain CBs. SLR, it is true negative in most of the cases and follow-up imaging rather than confirmatory biopsy is reasonable.

AUTHOR CONTRIBUTIONS

S. E, A. G. K, and F. A contributed to the design, data collection, and analysis of the study. All authors contributed to the construction of the body of the manuscript, critical reviewing for its intellectual content.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Demirdöğen E, Ursavaş A, Aydın Güçlü Ö, Acet Öztürk NA, Özkaya G, Karadağ M. Diagnostic performance of EBUS-TBNA and its interrelation with PET-CT in patients with extra-thoracic malignancies. *Tuberk Toraks*. 2020;68(3):285-292. doi:10.5578/tt.70045
2. Erer OF, Anar C, Erol S, et al. The utility of EBUS-TBNA in mediastinal or hilar lymph node evaluation in extrapulmonary malignancy. *Turk J Med Sci*. 2016;46(1):112-119. doi:10.3906/sag-1407-113
3. Martin-Deleon R, Solarat B, Moisés J, et al. EBUS-TBNA in Extrathoracic malignancies: diagnostic and prognostic implications. *Lung*. 2022; 200(6):747-753. doi:10.1007/s00408-022-00584-5
4. Hiraki T, Hatanaka M, Arimura A, et al. Granulomatous/sarcoid-like reactions in the setting of programmed cell death-1 inhibition: a

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potential mimic of disease recurrence. *J Cutan Pathol*. 2020;47(2):154-160. doi:10.1111/cup.13569
5. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;201(8):e26-e51. doi:10.1164/rccm.202002-0251ST
6. Asano S. Granulomatous lymphadenitis. *J Clin Exp Hematol*. 2012;52(1):1-16. doi:10.3960/jslrt.52.1
7. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/world Association of Sarcoidosis and Other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999;16(2):149-173.
8. Navani N, Nankivell M, Woolhouse I, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: a multicenter study. *J Thorac Oncol*. 2011;6(9):1505-1509. doi:10.1097/JTO.0b013e318223c3fe
9. Murthi M, Yoshioka K, Cho JH, et al. Presence of concurrent sarcoid-like granulomas indicates better survival in cancer patients: a retrospective cohort study. *ERJ Open Res*. 2020;6(4):00061-02020. doi:10.1183/23120541.00061-2020
10. Kennedy MP, Jimenez CA, Mhatre AD, Morice RC, Eapen GA. Clinical implications of granulomatous inflammation detected by endobronchial ultrasound transbronchial needle aspiration in patients with suspected cancer recurrence in the mediastinum. *J Cardiothorac Surg*. 2008;3:8. doi:10.1186/1749-8090-3-8
11. Mehta RM, Biraris P, Patil S, Singla A, Kallur K, Gasparini S. Utility of EBUS-TBNA in PET-positive mediastinal lymph nodes in subjects with extra-thoracic malignancy. *PLoS One*. 2019;14(3):e0213437. doi:10.1371/journal.pone.0213437
12. Bellinger CR, Sharma D, Ruiz J, Parks G, Dotson T, Haponik EF. Negative predictive value of granulomas on EBUS-TBNA in suspected Extrathoracic malignancy. *Lung*. 2016;194(3):387-391. doi:10.1007/s00408-016-9878-z
13. Butt S, Alzebdeh R, Kable TD, et al. Non-caseating granulomas in patients after the diagnosis of cancer: clinical characteristics and outcome. *Sarcoidosis Vasc Diffuse Lung Dis*. 2011;28(1):44-49.
14. Huh JY, Moon DS, Song JW. Sarcoid-like reaction in patients with malignant tumors: long-term clinical course and outcomes. *Front Med (Lausanne)*. 2022;9:884386. doi:10.3389/fmed.2022.884386
15. Grosu HB, Ost DE, Morice RC, et al. Mediastinal granulomatous inflammation and overall survival in patients with a history of malignancy. *Ann Am Thorac Soc*. 2015;12(10):1534-1541. doi:10.1513/AnnalsATS.201506-318OC
16. Erer OF, Erol S, Anar C, et al. Contribution of cell block obtained by endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of malignant diseases and sarcoidosis. *Endosc Ultrasound*. 2017;6(4):265-268. doi:10.4103/2303-9027.180763
17. Schwartz LE, Griffin AC, Baloch Z. Cell block interpretation is helpful in the diagnosis of granulomas on cytology. *Diagn Cytopathol*. 2012;40(10):939-940.
18. Ten Seldam REJ. Sarcoid-like lesions in lymph nodes draining carcinoma. *M J Australia*. 1956;1:916-922.
19. Lee GM, Pope K, Meek L, Chung JH, Hobbs SB, Walker CM. Sarcoidosis: a diagnosis of exclusion. *AJR Am J Roentgenol*. 2020;214(1):50-58. doi:10.2214/AJR.19.21436
20. Valeyre D, Brauner M, Bernaudin JF, et al. Differential diagnosis of pulmonary sarcoidosis: a review. *Front Med (Lausanne)*. 2023;10:1150751. doi:10.3389/fmed.2023.1150751
21. Burkhard-Meier A, Jurinovic V, Berclaz LM, et al. Differentiation of benign and metastatic lymph nodes in soft tissue sarcoma. *Clin Exp Metastasis*. 2024;41:131-141. doi:10.1007/s10585-024-10273-7
22. Ganeshalingam S, Koh DM. Nodal staging. *Cancer Imaging*. 2009;9(1):104-111. doi:10.1102/1470-7330.2009.0017
23. Wang H, Li QK, Auster M, Gong G. PET and CT features differentiating infectious/inflammatory from malignant mediastinal lymphadenopathy: a correlated study with endobronchial ultrasound-guided transbronchial needle aspiration. *Radiol Infect Dis*. 2018;5(1):7-13. doi:10.1016/j.jrid.2018.01.002
24. Kumar A, Dutta R, Kannan U, Kumar R, Khilnani GC, Gupta SD. Evaluation of mediastinal lymph nodes using F-FDG PET-CT scan and its histopathologic correlation. *Ann Thorac Med*. 2011;6(1):11-16. doi:10.4103/1817-1737.74270
25. Rodriguez EF, Lipson E, Suresh K, Cappelli LC, Monaco SE, Maleki Z. Immune checkpoint blocker-related sarcoid-like granulomatous inflammation: a rare adverse event detected in lymph node aspiration cytology of patients treated for advanced malignant melanoma. *Hum Pathol*. 2019;91:69-76. doi:10.1016/j.humpath.2019.07.001

How to cite this article: Erol S, Kaya AG, Arslan F, et al. Importance of mediastinal granulomatous/sarcoid-like lymphadenopathy in extrathoracic malignancies. *Diagnostic Cytopathology*. 2024;1-5. doi:10.1002/dc.25337

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