

Foreign Body Reaction Mimicking Lymph Node Metastasis is Not Rare After Lung Cancer Resection

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Abstract

Background Mediastinal lymphadenopathies with high 18-fluorodeoxyglucose uptake in patients previously operated on for lung cancer are alarming for recurrence and necessitate invasive diagnostic procedures. Peroperative placement of oxidized cellulose to control minor bleeding may lead to a metastasis-like image through a foreign body reaction within the dissected mediastinal lymph node field at postoperative examinations. In this study, we investigated clinicopathological features and the frequency of foreign body reaction mimicking mediastinal lymph node metastasis.

Methods Patients who underwent surgery for lung cancer between January 2016 and August 2021 and who were subsequently evaluated for mediastinal recurrence with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were included. Patients were grouped according to the results of EBUS-TBNA as metastasis, foreign body, and reactive. Clinicopathological features of these patients were compared and characteristics of patients in the foreign body group were scrutinized.

Results EBUS-TBNA was performed on a total of 34 patients during their postoperative follow-up due to suspicion of mediastinal recurrence. EBUS-TBNA pathological workup revealed metastasis in 18 (52.9%), foreign body reaction in 10 (29.4%) and reactive lymph nodes in 6 (17.6%) patients. Mean maximum standardized uptake value (SUVMax) for metastasis group and foreign body group were 9.39 ± 4.69 and 5.48 ± 2.54 , respectively ($p = 0.022$). Time interval between the operation and EBUS-TBNA for the metastasis group was 23.72 ± 10.48 months, while it was 14.90 ± 12.51 months in the foreign body group ($p = 0.015$).

Conclusion Foreign body reaction mimicking mediastinal lymph node metastasis is not uncommon. Iatrogenic cause of mediastinal lymphadenopathy is related to earlier presentation and lower SUVMax compared with metastatic lymphadenopathy.

Keywords

- ▶ lung cancer
- ▶ diagnosis
- ▶ lung cancer treatment
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Introduction

Oxidized cellulose (OC) is an absorbable polyanhydroglucuronic acid polymer that is used to control minor hemorrhage in dissected mediastinal lymph node regions and is left in the surgical field. Surgicel® (Ethicon, North Ryde, New South Wales, Australia) or GELITA-CEL® (Gelita Medical, Eberbach, Germany) are the types that are most frequently used in daily practice. Although the mechanism of hemostasis is not clearly known, when adequate contact is made with blood, it turns into a gelatinous form and accelerates localized coagulation.¹ Furthermore, the low pH it creates helps vasoconstriction and reduces the risk of infection.²

It begins to take effect on small arterial, venous, and capillary hemorrhages approximately 2 to 8 minutes after insertion.³ It is an absorbable material and is expected to be absorbed within 1 to 2 weeks after the operation.⁴ However, the absorption time of OC may vary depending on the amount used and the intensity of contact with blood. In some cases, it might not be completely absorbed and may form a foreign body reaction and granuloma, which may lead to a mediastinal lymph node metastasis-like appearance in radiological examinations. In patients with suspected metastasis in positron emission tomography/computed tomography (PET/CT), the first step of invasive procedure is endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).⁵

Clinicians notice substantial number of cases where pathological workup reveals foreign body reaction in patients who underwent biopsy due to hypermetabolic lymphadenopathies. In the literature, this phenomenon is mostly being published through case reports where OC mimics malignancy by causing a foreign body reaction.⁶⁻⁸ However, there is no study in the literature showing how often this condition is encountered or its differences from genuine mediastinal lymph node metastasis. Therefore, in our study, the frequency of foreign body reactions mimicking mediastinal lymph node metastases caused by OC and comparison of their clinicopathological features with mediastinal lymph node metastases are analyzed.

Materials and Methods

Patient Selection

Patients who underwent anatomical resection (lobectomy, bilobectomy, pneumonectomy) with curative intent for lung cancer in our hospital between January 2016 and August 2021 were retrospectively analyzed. Among those, 34 patients who necessitated EBUS-TBNA during follow-up period were included in the study. EBUS-TBNA is performed in patients with hypermetabolic or enlarged lymph nodes in PET/CT or thorax CT when tissue diagnosis is demanded for the continuation of treatment.

Postoperative Follow-Up

Patients with early-stage disease who do not require adjuvant treatment were followed up with thorax CT every 6 months for the first 2 years and once a year for the next 3 years. For patients necessitating adjuvant treatment, thorax CT was performed every 3 months for the first 2 years and then every

6 months for 5 years. As a result of these examinations, patients with findings indicative of mediastinal lymph node metastasis were scanned with PET/CT. No specific radiological appearance on CT that could definitively differentiate foreign body reaction from lymph node metastasis was spotted.

Positron Emission Tomography/Computed Tomography

Whole body iPET-CT (Integrated positron emission tomography/computed tomography) Gemini Dual system (Philips, Cleveland, Ohio, United States) was executed followed by 6 hours of abstaining from oral intake. It was verified that glucose levels of the patients were between 60 and 150 mg/dL right before PET/CT scan. Whole body scanning was carried out 60 to 90 minutes after administration of 18-fluorodeoxyglucose (FDG) at 0.14 mCi per kg, followed by a spiral CT scan to be incorporated with PET images. Maximum standardized uptake values (SUVMax) were determined as the proportion of the regional radioactivity concentration divided by the administered portion of radioactivity normalized to body weight. Patients with mediastinal lymph nodes with increased FDG uptake suggestive of mediastinal lymph node metastasis in PET/CT were referred to EBUS-TBNA.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Patients were taken in an assigned endoscopy room as an outpatient procedure following fasting for 6 hours. After being situated in a supine position, patients are administered local anesthesia and intravenous phentanyl, midazolam, and/or propofol midazolam in order to obtain conscious sedation. EBUS-TBNA through orotracheal passage is performed with a 7.5 MHz, EB-530US convex probe bronchoscope and a model FUJIFILM-3500HD processor (FUJIFILM Corporation, Tokyo, Japan) to assess mediastinal and hilar lymph nodes. International Association for the Study of Lung Cancer Lymph Node Map is used for accurate identification of lymph nodes. A 22-gauge NA-201SX-4022-C needle (Olympus Optical Tokyo, Japan) was used for the procedure. Biopsy samples from mediastinal and hilar lymph nodes were fixated with 95% alcohol and for each lymph node station a cell block was made ready for cytological workup.

Patient Classification

Patients are grouped as metastasis, foreign body, and reactive according to postoperative EBUS-TBNA results. The pre-EBUS-TBNA SUVMax and the detection time, which is the time from operation to EBUS-TBNA were compared between each group. The clinicopathological features of the patients in the foreign body group were examined in detail.

Ethical Considerations

This study is approved by the ethics committee of Kartal Dr. Lutfi Kirdar City Hospital with number 2023/514/246/1.

Statistical Analysis

Chi-square and Fisher's exact test (when expected value <5) were used to compare categorical data. Categorical data are

expressed as counts. For two independent groups, Student's *t*-test was preferred for parametric values and Mann-Whitney U test was preferred for nonparametric values for comparison of continuous variables. For three or more independent groups, analysis of variance was preferred for parametric values and Kruskal-Wallis test was preferred for nonparametric values of continuous variables. Continuous variables are expressed as mean \pm standard deviation. *p*-values below 0.05 were considered to be statistically significant. Statistical analyses were performed with SPSS (Statistical Program for Social Sciences 25.0; IBM Corporation, Armonk, New York, United States).

Results

A total of 459 patients who had been operated upon for lung cancer were inspected. Among those, 227 (49.5%) patients were scanned with PET/CT during follow-up period due to suspected recurrence. FDG avid sites were observed on 151 (32.8%) patients. Ninety-nine (21.5%) patients had increased FDG uptake in mediastinal lymph nodes. Among those, patients with PET avid lesions in the lung parenchyma and distant organs were biopsied with fine needle aspiration when necessary.

A total of 34 patients who underwent EBUS-TBNA for suspected isolated mediastinal lymph node metastasis after

surgery for lung cancer were included in the study. Of these, a total of 18 (52.9%) patients had mediastinal lymph node metastasis and 6 (17.6%) had reactive lymph nodes. In 10 (29.4%) patients, EBUS-TBNA was reported as foreign body reaction.

Twenty-four (70.6%) patients were male and 10 (29.4%) were female. The mean age of the patients was 59.3 years. The mean ages of the groups for metastatic, reactive, and foreign bodies are, respectively, 60.4, 59.5, and 57.1 years ($p = 0.65$).

The time interval between operation and EBUS-TBNA, which resembles detection time for metastasis group, reactive group, and foreign body group was 23.72 ± 10.48 , 8.33 ± 4.23 , and 14.90 ± 12.51 months, respectively. The difference between these three groups is found to be statistically significant ($p = 0.002$). When the reactive group is ignored and the metastasis group and the foreign body group are compared, it is seen that the difference between those is statistically significant as well ($p = 0.015$).

SUVMax of metastasis, reactive, and foreign body groups are compared. The values obtained are 9.39 ± 4.69 , 5.48 ± 2.54 , and 2.30 ± 2.89 , respectively. The difference between them was statistically significant ($p = 0.001$). Post hoc analysis reveals a statistically significant difference between the foreign body group and the metastasis group ($p = 0.042$); however, there is no statistically significant

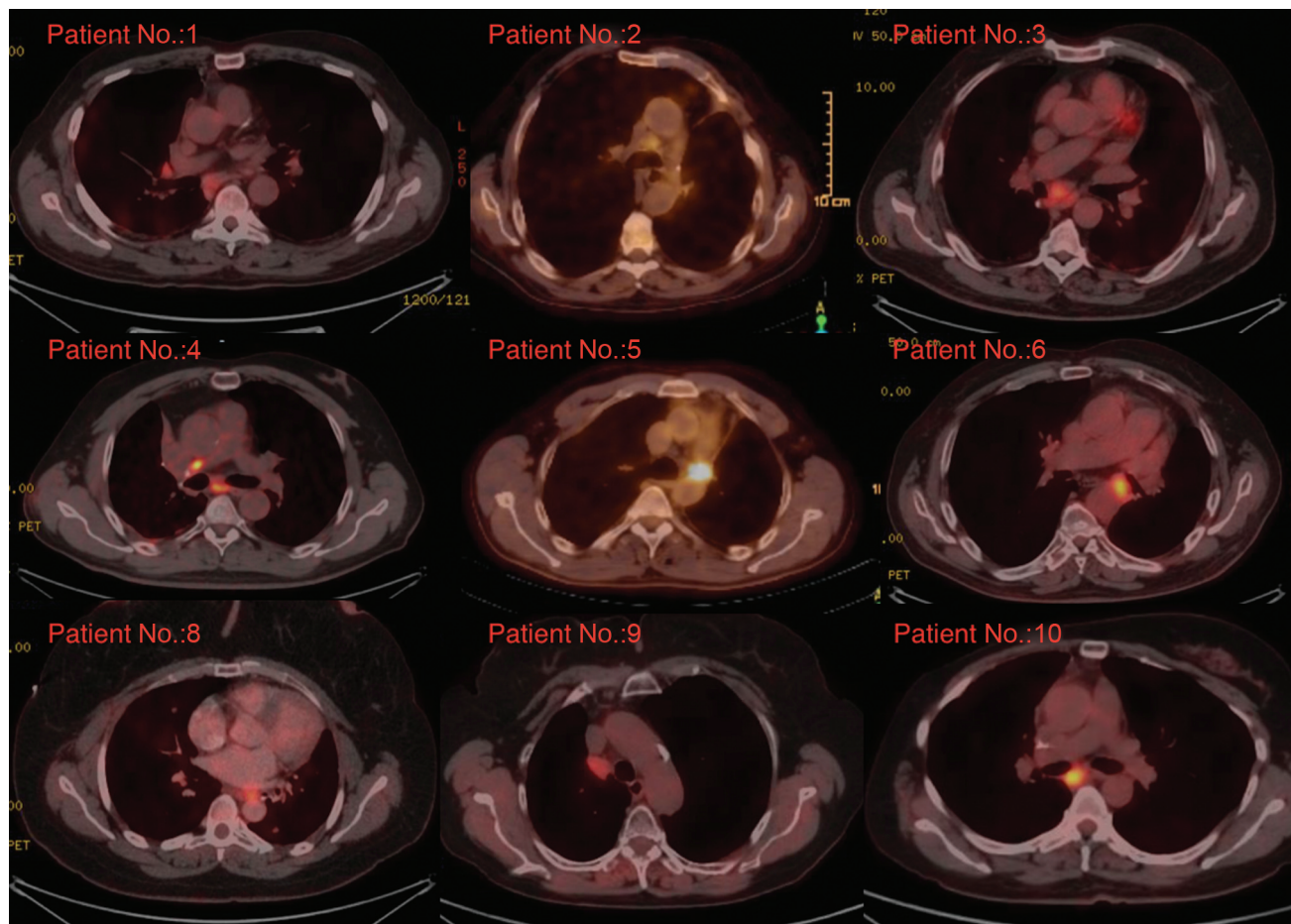


Fig. 1 PET/CT images of patients in foreign body group. PET/CT, positron emission tomography/computed tomography.

Table 1 Clinicopathological features of patients in foreign body group

Patient no.	Age (years)	Tissue diagnosis	Stage	Type of resection	Incision type	Neoadjuvant treatment	Adjuvant treatment	SUVMax	Time interval between surgery and EBUS (months)	Sampled LN	Pathology report
1	63	AD	T2aN0	RUL	T	No	No	2.7	12	10R	Filamentous fragments, some of which are birefringent of polarized light, multinuclear giant cells, histiocytes
2	66	AD	T1bN0	LUL	T	No	No	5.2	5	4L	Fibrocollagenous fragments
3	63	SCC	T1aN0	RLL	V	No	No	4.7	45	7	Amorphous fragments causing non-necrotizing granuloma
4	52	AD	T1cN0	RUL	T	CT	No	9.4	5	4R, 7	Multinuclear giant cells, foreign body material, necrotic debris
5	50	LCC	T1bN0	LUL	T	No	No	8.6	12	10L	Filamentous fragments, some of which are birefringent of polarized light, multinuclear giant cells, histiocytes
6	64	SCC	T3N1	LLL	T	No	No	6.9	8	11L	Foreign body type multinuclear giant cells, filamentous fragments, some of which are birefringent of polarized light
7	55	SCC	T1aN0	LBL	T	CT	CT	1.65	15	4R	Some polygonal-filamentous, some irregular nodular structures or granular amorphous material fragments, sparse histiocytic and multinuclear giant cells
8	42	ACC	T2aN0	LLL	T	No	No	4.6	12	11L	Multinuclear giant cells, foreign body material
9	73	AD	T2bN0	RUL	T	CT	RT	3.6	7	4R	Fragments of amorphous material, multinuclear giant cells
10	43	AD	T1bN0	RUL	T	No	No	7.4	28	7	Filamentous fragments, some of which are birefringent of polarized light, multinuclear giant cells, histiocytes

Abbreviations: ACC, adenoid cystic carcinoma; AD, adenocarcinoma; CT, chemotherapy; EBUS, endobronchial ultrasound; LBL, lower bilobectomy; LCC, large cell carcinoma; LLL, left lower lobectomy; LN, lymph node; LUL, left upper lobectomy; RLL, right lower lobectomy; RUL, right upper lobectomy; RT, radiation therapy; T, thoracotomy; V, video-assisted thoracic surgery.

Table 2 Characteristics of foreign body reaction on endobronchial ultrasound-guided transbronchial needle aspiration

Patient No.	Shape	Echogenicity
1	Round; distinct border	Isoechoic
2	Distinct border	Isoechoic
3	Oval; distinct border	Isoechoic
4	Oval; distinct border	Isoechoic
5	Oval; indistinct border	Isoechoic
6	Oval; distinct border	Isoechoic
7	Round; distinct border	Heterogeneous hyperechoic
8	Oval; distinct border	Isoechoic
9	Oval; distinct border	Isoechoic
10	Oval; distinct border	Heterogeneous hypoechoic

Table 3 Comparison of all cohorts with patients who underwent EBUS-TBNA in terms of time interval from operation to PET/CT, highest SUVMax on PET/CT and SUVMax of mediastinal lymph nodes

	Time from operation to PET/CT (months)	Highest SUVMax	SUVMax on mediastinal lymph nodes
All cohorts	16.93 ± 12.49	10.93 ± 6.29	7.54 ± 4.76
Patients with postoperative EBUS-TBNA	18.42 ± 11.79	7.92 ± 4.19	7.91 ± 4.19
<i>p</i> -Value	0.52	0.014	0.7

Abbreviations: EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; PET/CT, positron emission tomography/computed tomography; SUVMax, maximum standardized uptake value.

difference between the foreign body group and the reactive group ($p = 0.27$). When the reactive group was ignored and the metastasis group and the foreign body group were compared, it was seen that the difference between them was statistically significant ($p = 0.022$). PET/CT images of the foreign body reaction group obtained before EBUS-TBNA are shown in ►Fig. 1.

There is no significant difference between Video-assisted thoracoscopic surgery (VATS) and thoracotomy by means of foreign body reaction development during follow-up ($p = 0.184$).

Clinicopathological features of patients in foreign body group are displayed in ►Table 1.

EBUS-TBNA findings of 10 patients with foreign body reaction are depicted in ►Table 2.

Indication for further investigation in 10 patients diagnosed with foreign body reaction by EBUS-TBNA was lymphadenopathy in the first CT after surgery in eight (80%) patients and delayed progression of lymphadenopathy through follow-up in two (20%) patients.

Comparison of all cohort with patients who underwent EBUS-TBNA in terms of time interval from operation to PET/CT, highest SUVMax of PET/CT and SUVMax of mediastinal lymph nodes are displayed in ►Table 3.

►Table 4 presents a comparison among all 459 patients undergoing resection, the group with PET/CT avid lymph

nodes and the PET/CT avid lymph nodes with foreign body reaction in terms of time interval from operation to PET/CT and highest SUVMax of PET/CT.

Histologic images of foreign body reaction are displayed in ►Fig. 2.

Table 4 Comparison between all cohorts, the group with PET/CT avid lymph nodes and the PET/CT avid lymph nodes with foreign body reaction in terms of time interval from operation to PET/CT and highest SUVMax on PET/CT

	Time from operation to PET/CT (months)	Highest SUVMax
Whole group	16.99 ± 1.13	10.16 ± 0.89
PET/CT avid lymph nodes	17.7 ± 1.29	10.99 ± 0.61
PET avid lymph nodes with foreign body reaction	14.0 ± 3.95	5.48 ± 2.54
<i>p</i> -Value	0.362	0.03

Abbreviation: PET/CT, positron emission tomography/computed tomography; SUVMax, maximum standardized uptake value.

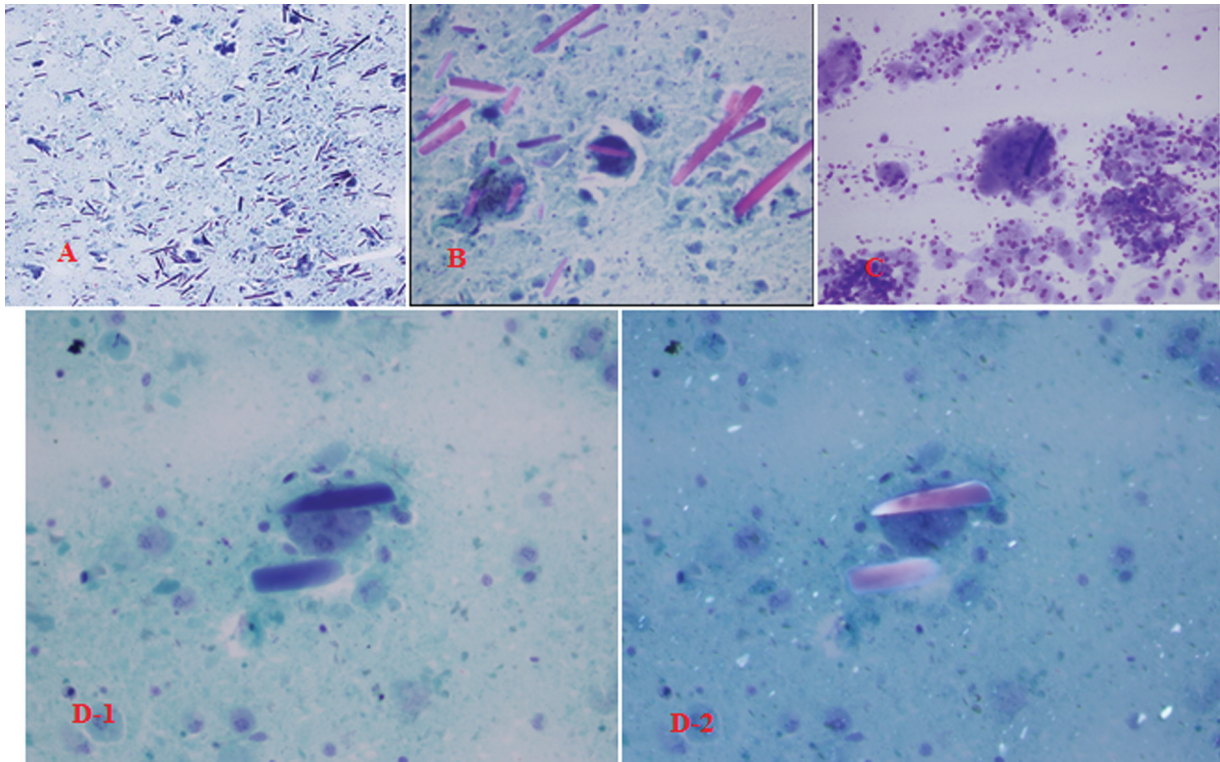


Fig. 2 Histologic images of foreign body reaction in mediastinal lymph nodes. (A) Foreign material fragments in the background containing histiocytes and multinuclear giant cells (EBUS-guided transbronchial fine needle biopsy, Papanicolaou $\times 40$). (B) Fragments of foreign material birefringent of polarized light, some of which have been phagocytosed by multinuclear giant cells (EBUS-TBNA, polarized light $\times 200$). (C) Multinuclear giant cell phagocytized by foreign material on histiocyte-rich background (EBUS-guided transbronchial FNA, Magnesium Green $\times 200$). (D) Foreign material phagocytosed by multinuclear giant cell (EBUS-guided TBNA: (1) Papanicolaou $\times 400$ and (2) polarized light $\times 400$). EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration.

Discussion

OC is an absorbable hemostatic material that has been shown to be effective in the hemostasis of minor hemorrhages and is used in many disciplines, such as abdominal surgery, neurosurgery, and thoracic surgery. In thoracic surgery practice, it is used more frequently to control oozing like hemorrhages at mediastinal lymph node dissection regions and it is generally left in place. Although it is absorbable, it has been shown that excessive use of OC may lead to various complications in the early postoperative period and may require repeat surgery.^{9,10} Foreign body reaction due to OC may also mimic infection.¹¹ However, in the long term, OC causing foreign body reaction that mimics malignant mediastinal lymphadenopathy (LAP) is a more common complication. This occurs when peroperatively placed OC creates a foreign body reaction during follow-up that imitates a mediastinal LAP with increased SUVMax. Although it is stated that SURGICEL® is completely absorbed within 2 months,¹² there are studies showing that another type of OC, GELITA-GEL®, may create granuloma even 67 months after the operation.¹³ It should also be noted that false positive mediastinal lymph nodes can also be encountered in granulomatous conditions such as tuberculosis or sarcoidosis as well as reactive changes or foreign body reactions due to materials other than OC such as talc and silk sutures.

Close follow-up during the postoperative period is crucial for patients with lung cancer to ensure timely detection of

any potential recurrence or metastases. In patients with suspected recurrence or distant metastasis, PET/CT is one of the most robust tools that can guide whether further intervention is required.¹⁴ In a study examining patients diagnosed with a postoperative foreign body reaction, it is stated that the median SUVMax for foreign body reaction is 3.5.² Another similar study states that the mean SUVMax is 6.4 and the median detection time of the foreign body reaction is 139 days (range: 52–208 d).¹⁵

Current literature is devoid of studies comparing detection time and SUVMax of mediastinal foreign body reaction and metastatic lymphadenopathies. Furthermore, to our knowledge, there are no studies specifying the incidence of these patients among those who need invasive diagnostic procedures. In our study, it was observed that a significant portion of the patients who underwent EBUS with the suspicion of mediastinal lymph node metastasis had a foreign body reaction. Foreign body reaction is associated with a significantly lower SUVMax and shorter detection time than proven mediastinal lymph node metastasis.

Limitations

There are several limitations in our study. First limitation is the retrospective nature of the study. However, patients' records are kept meticulously in our center. Second, the number of patients is limited. However, it is successful in

revealing the dissimilarities between foreign body reaction and mediastinal lymph node metastases in terms of SUVMax and detection time.

Conclusion

Metastasis-like mediastinal lymphadenopathies in the postoperative period in patients operated upon for lung cancer may also develop due to foreign body reaction. SUVMax of such lymphadenopathies tend to be lower than metastatic lymphadenopathies, and foreign body reaction manifests itself sooner than metastatic lymph nodes. It should be kept in mind that foreign body reaction is not an uncommon cause of mediastinal lymphadenopathy and may mimic mediastinal lymph node metastasis in the postoperative follow-up period.

Conflict of Interest

None declared.

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