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Features of endobronchial metastases from extrathoracic malignancy and positron emission tomography-computerized tomography findings

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Abstract

OBJECTIVE: We aimed to investigate radiological and bronchoscopic aspects of endobronchial metastases (EBMs) from extrapulmonary cancers and the correlation of EBM with findings of integrated positron emission tomography-computed tomography (PET-CT) findings.

MATERIALS AND METHODS: Patients who underwent bronchoscopic evaluation between January 2013 and December were analyzed retrospectively. Patients with endobronchial lesions in the airways and histopathologically diagnosed with extrapulmonary cancer metastasis were included in the study.

RESULTS: A total of 16 patients with EBM who underwent bronchoscopic biopsies were evaluated. The patients consisted of 10 (62.5%) females and 6 (37.5%) males and the mean age was 61.8 ± 9.1. The common primary cancer related to EBM was breast 9 (%56.4). The mean interval from diagnosis of primary cancer to EBM was 55.1 ± 48.5 (1–180) months. A total of 13 (81.2%) cases were assessed with the PET-CT report. The mean SUV_{max} value of the lung lesions was calculated as 9.8 ± 4.3. According to PET-CT, 92.4% of the cases had extrapulmonary metastasis. The mean survival duration from diagnosis of EBM was 8.5 ± 6.7 (1–21) months in 9 deceased patients.

CONCLUSION: The most frequent extrapulmonary primary tumors with endobronchial metastasis were breast and the mean survival time was usually short. It was reported that most cases were multimetastatic. It was concluded that PET-CT can play a role in identifying the EBM and other organ metastasis and was important tool in planning the treatment.

Keywords:

Bronchoscopy extrathoracic cancer, endobronchial lesions, metastases

Introduction

Its intensive blood supply makes the lungs a common site of cancer metastasis. Nevertheless, endobronchial metastasis (EBM) is a rare event. EBM is defined as a lesion located in a bronchoscopically visible segment of the bronchus (either subsegmental or in the more proximal part of the bronchus), which is histopathologically proven to match the primary cancer in a patient with a history of extrathoracic cancer.[1] The earliest change in the histopathology of EBM is increased passage of malignant tumor cells from lymphatic canals and mucosal lymphatics. This is followed by a tendency of lymphatics to converge beneath the bronchial epithelium. Advanced stage is characterized by bronchial epithelial

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ulcerations and protrusion of the tumor into the lumen.[2] The incidence of EBM is reported between 1.1% and 50% in different clinical studies and autopsy series.[3,4] To establish the pathological diagnosis of EBM and to differentiate it from primary bronchogenic cancer may not always be easy. The management and prognosis of EBM depends on the type of primary cancer, its biological behavior, patient's performance status, and the existence of metastatic lesions in other systems and organs. Thus, early diagnosis and treatment of EBM is critical.[5,6] EBM is usually identified after the primary tumor is diagnosed. Although this may vary according to the histopathology of the primary tumor, the survival rate of patients diagnosed with EBM is usually poor. Studies usually report a survival rate between 1 and 2 years.[7-9]

There are numerous studies, mostly case reports, on the clinical, radiographic, and pathological characteristics of EBMs of extrathoracic cancers.[10-12] Studies to date underscore the important role of fiber-optic bronchoscopy (FOB) and computerized tomography (CT).[13] There are, however, only a few publications on positron emission tomography CT (PET-CT) findings of EBMs in the literature. Our study aims to investigate the clinical, radiographic, and bronchoscopic characteristics along with PET-CT findings of EBMs.

Materials and Methods

FOB records made at the bronchoscopy unit of the pulmonology department of our hospital between January 2013 and December 2016 were reviewed retrospectively. The clinical records of patients with a history of extrathoracic malignancy, who had FOB to investigate a second primary focus or metastatic lesion after a pulmonary mass was identified on thoracic CT or integrated PET (PET-CT) were reviewed separately. Patients who had an endobronchial lesion that directly protruded into the airway or that manifested in the form of a mucosal/submucosal tumor infiltration in the airway and whose biopsy specimen was histopathologically diagnosed as extrathoracic cancer metastasis were included in this study [Figure 1]. Patients with no endobronchial lesions were excluded from the study.

Information from HIS, including the type of primary cancer, time of diagnosis of the primary cancer, time until EBM diagnosis was established, oncological treatments provided before and after the diagnosis of EBM, clinical, radiographic, and demographic findings, as well as time to death for expired patients obtained from the national death reporting system, and maximum standard uptake level (SUV_{max}) for patients with PET-CT scans, and other systems and organs with metastatic involvement on PET-CT were documented. No Ethics Committee approval was required as the study design was retrospective.

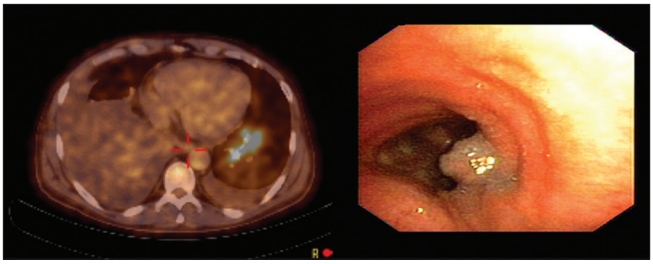

Figure 1: Bronchoscopic and positron emission tomography-computerized tomography image of an endobronchial lesion located in the left lower lobe

Fiber-optic bronchoscopy procedure

FOB at our bronchoscopy unit is performed on patients with potential tumor lesions either inside or near the airways on thoracic CT or PET-CT scans. Before the procedure, complete blood count and coagulation workup are completed in all patients to rule out coagulopathies (international normalized ratio >1.3) and the procedure is not performed if patient's platelet count is <20.000/mm^3. Patient's consent for the FOB procedure is obtained and documented before the procedure is performed. The FOB procedure is performed under conscious sedation using intravenous midazolam and local anesthesia using 2% lidocaine, with the patient in supine position through the oral or nasal route. A video bronchoscope (Olympus Co; Tokyo, Japan) was used for the FOB procedure.

Positron emission tomography/computerized tomography scan

Patients were NPO for at least 8 h before the procedure, which was performed on patients with blood glucose levels in normal range. The PET/CT scan was performed in a Philips Gemini TF Ultra Hi-Rez integrated PET-CT imaging system. The CT slice thickness was 5 mm and PET emission images between the vertex and thigh region were obtained. The scan was performed 60 min after the 370–550 MBq (5–15 mCi) F-18 FDG injection. Oral contrast FDG was administered simultaneously.

Statistical analysis

Statistical analysis was done using SPSS 17.0 (IBM Inc., Relased 2008. SPSS Statistic for Windows Chicago, USA) computer software. In the descriptive statistics, continuous variables and categorical variables were expressed as mean ± standard deviation and in percentages, respectively.

Results

During the study period, FOB was performed on 2546 patients for a variety of indications. Eighty-one of

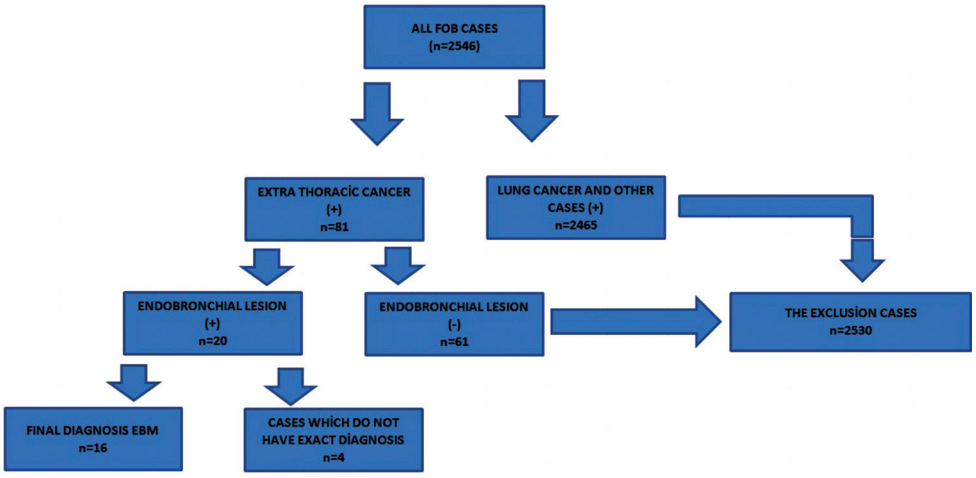

Figure 2: A flow diagram regarding the subjects included in and excluded from the study

those had a history of extrathoracic malignancy and the FOB procedure was performed because a pulmonary mass/nodule was identified on their radiographic images (PET-CT/thoracic CT). Endobronchial lesions were identified in 20 of the 81 patients. Four of these 20 cases (four patients with laryngeal carcinomas) were excluded from the study as bronchogenic carcinoma could not be excluded from the histopathological diagnosis. The histopathological diagnosis of the remaining 16 patients (19.7%) was reported as metastasis of an extrathoracic organ malignancy [Figure 2]. These 16 patients were included in the study. The primary tumors of the patients with EBM include nine breast cancer (56.4%), two colon cancer (12.6%), and one of renal cell carcinoma, prostate cancer, lymphoma, malignant melanoma, and salivary gland carcinoma each (6.2%).

Out of the sixteen patients, ten (62.5%) were female and 6 (37.5%) were male. The mean age was 61.8 ± 9.1 years (range 50–80). The most common type of cancer with EBM in lungs was breast carcinoma with 9 (56.4%) cases.

The average span of time between the primary cancer diagnosis and EBM diagnosis was 55.1 ± 48.5 (1–180) months. The longest time span was established in breast carcinoma (81.2 ± 48.6 months).

A review of the oncological/surgical management history of the patients before and after EBM was diagnosed indicates that 12 (75%) of them had a surgical treatment for the primary malignancy before EBM diagnosis, while 4 (25%) had no surgery. 12 (75%) of the cases had chemotherapy (CT) and 2 (75%) had radiation therapy (RT) for the primary tumor before EBM was diagnosed. Ten patients (62.5%) received CT and RT for the primary tumor after the EBM diagnosis while one patient (6.2%) only had RT. No patient received thoracic RT after EBM diagnosis.

Table 1: Clinical, radiographic, demographic, and bronchoscopic findings of subjects

Clinical findings and demographics	*n* (%)
Age (year/SD)	61.8±9.1
Sex	
Male	5 (31.3)
Female	11 (68.7)
Smoking history	
Smoker	4 (25)
Nonsmoker	12 (75)
Average smoking history (package-years/SD)	40.7±9.4
Symptoms	
No symptom	5 (31.3)
Symptoms present	11 (68.7)
Chest X-ray	
Central mass	11 (68.7)
Atelectasis	3 (18.7)
Pleural fluid	3 (18.7)
Nodule	2 (12.5)
Thoracic CT	
Central mass	16 (100)
Parenchymal metastatic nodule	8 (50)
Mediastinal-hilar LAP	8 (50)
Pleural fluid	6 (37.5)
Atelectasis	5 (31.3)
Bronchoscopic localization	
Right upper lobe	1 (6.3)
Right middle lobe	3 (18.7)
Right lower lobe	6 (37.5)
Left upper lobe	2 (12.5)
Left lower lobe	4 (25)

CT: Computerized tomography, LAP: Lymphadenopathy, SD: Standard deviation

A review of the clinical and radiographic findings and demographics of patients indicates that 5 (31.3%) patients were diagnosed with EBM during routine oncological follow-up in the absence of any symptoms. Otherwise, the most common symptom reported by four patients (25%) was shortness of breath [Table 1]. A review of radiographic and bronchoscopic findings indicates that some patients

had multiple radiographic findings. A centrally located mass proved to be the most common chest X-ray finding in 11 patients (68.7%) and the most common CT-scan finding in 16 patients (100%). The average lesion size was 4.6 ± 1.5 (2–8) cm based on calculations on CT images. The most common bronchoscopic localization of the endobronchial lesion was the right lower lobe in 6 (37.5%) patients. Bronchoscopic appearance of the lesions included submucosal infiltration in 10 patients (62.5%), endobronchial tumoral lesion in 5 patients (31.2%), and external compression in 3 patients (18.7%) [Tabel 1].

PET-CT reports were available for 13 patients (81.2%) and absent in 3 patients (18.7%). The mean SUV_{max} of pulmonary lesion was 9.8 ± 4.3 [Table 2]. A review of organ and system metastases based on PET-CT scan of the patients after they are diagnosed with EBM showed that 12 patients (92.4%) had pulmonary (EBM, mediastinal LAP, and pulmonary parenchymal metastasis) and extrathoracic system or organ metastasis in addition to the primary tumor. Only one patient (7.3%) had primary mass involvement and lung metastasis. The most common extrathoracic involvement was bone metastasis in eight patients (43.7%) [Table 3]. Nine of the patients included in the study (56.2%) died after a mean of 8.5 ± 6.7 (1–21) months after the EBM diagnosis and eight patients (43.7%) were still alive. The survival rate for breast cancer patients with EBM was 12.5 ± 5.4 months.

Discussion

This study looked into the characteristics of patients with extrathoracic malignancies and pulmonary EBM. In our series, breast cancer was the most common type of cancer with endobronchial metastasis with 9 patients (56.4%). The mean survival of patients after the diagnosis of EBM was 8.5 months and the mean time from the diagnosis of primary extrathoracic tumor to the diagnosis of the metastatic lesion was 55 months. Five patients were free of symptoms, and the lung pathology was identified during a routine radiographic control. This study is significant as it highlights the facts that EBMs may not be associated with any respiratory symptoms, the mean survival after EBM diagnosis is as short as 8.5 months, patients diagnosed with EBM have multiple metastatic sites, and that there is a high likelihood that breast cancer spreads to the lungs and causes EBMs.

Previous studies reported an EBM incidence of 2%–28% in patients with extrathoracic cancers.[10,14-17] Types of cancer most commonly associated with EBM include breast carcinoma, colorectal carcinoma, and renal carcinoma.[14] Akoglu *et al*.,[15] in their study that reviewed 15 EBM cases over 10 years, demonstrated that breast (3 patients) and colorectal cancer (3 patients) are most commonly associated with EBMs. In this study, the incidence of EBM in patients who had FOB was 19.7%, which is comparable to other reports in the literature. This is the rate we identified only in patients who had a FOB procedure. Patients who are diagnosed with EBM using different diagnostic methods (transthoracic biopsy) should not be ignored. Similar to other reports, breast cancer was found to be the type of cancer most commonly associated with EBM in this study. This finding, which is in line with literature reports, may suggest that breast cancer has a high potential to cause EBM, but it should be kept in mind that breast cancer is the most common type of cancer in women and thus many associated EBM cases are bound to occur.

Güven *et al*.[18] reported the rate of symptomatic patients as 16% in his study on patients with lung metastasis. The authors suggest that the low percentage of symptomatic patients may be due to the fact that metastatic lesions are identified incidentally or during routine oncological follow-up imaging scans. Other related studies report the rate of asymptomatic patients between 65.4% and 87%.[19-21] In our series, the rate of asymptomatic patients was lower than other studies (31.3%). We believe that this is because the lesions were centrally located, mimicking the primary tumor. The most common symptom reported by the patients was shortness of breath followed by cough, bloody sputum, and chest pain. Similar symptoms including shortness of breath, cough, bloody sputum, localized rhonci, and chest pain are reported from other studies.[3,6,22,23] These are nonspecific pulmonary symptoms which are common to multiple pulmonary conditions, but EBM should be borne in mind in patients with a history of extrathoracic cancer and any of these symptoms.

Table 2: Mean maximum standard uptake level on positron emission tomography-computerized tomography based on the type of primary cancer

Type of primary cancer	Number of subjects	SUV_{max} (mean)	SD	Minimum-maximum
Breast carcinoma	7	10.9	4.5	6.4-17.4
Colon carcinoma	2	7	1.2	6.2-7.9
Renal cell carcinoma	1	7.9	-	7.9
Prostate carcinoma	1	5.3	-	5.3
Lymphoma	1	18.2	-	18.2
Malignant melanoma	1	9.6	-	9.6

PET-CT: Positron emission tomography-computerized tomography, SUV_{max}: Maximum standardized uptake value, SD: Standard deviation

Table 3: Positron emission tomography-computerized tomography findings

PET-CT	*n*-ss (%)
PET-CT available	13 (81.2)
PET-CT not available	3 (18.7)
SUV_{max} (mean/SD)	9.8±4.3
Lung metastasis and other system or organ metastasis.	13 (100)
Lung metastasis only	1 (7.3)
Central mass	13 (100)
Mediastinal LAP involvement	9 (56.2)
Bone involvement	8 (50)
Multiple parenchymal metastatic nodules	7 (43.8)
Cervical LAP involvement	4 (25)
Abdominal LAP involvement	2 (12.5)
Metastatic involvement of brain	2 (12.5)
Other (liver, adrenal)	4 (25)

LAP: Lymphadenopathy, PET-CT: Positron emission tomography-computerized tomography. SUV_{max}: Maximum standardized uptake value, SD: Standard deviation

One of the largest series on this topic was reported by Sørensen[22] 204 patients diagnosed with EBM over a time period of 40 years were included in this meta-analysis. Similarly, this study also concluded that breast cancer is most commonly associated with EBMs. Based on their review of chest X-rays from 106 patients, the investigators report atelectasis (58%), mass (26%), and multiple nodules (17%) as the most common findings on the chest X-ray. In our series, central mass ranked first with 68.7% followed by atelectasis with 18.7%. Tumors with EBM are expected to frequently display atelectasis and mass radiographically. Based on the review of CT scans of our patients, we identified mass lesion in our patients along with multiple parenchymal metastatic nodules in 50% and hilar-mediastinal LAPs of pathological size (>1 cm) in 50%. Atelectasis was the rarest CT scan finding with 31.3%. In their very large series with 174 cases, Marchioni *et al*.[24] identified multiple nodules in 53%, hilar-mediastinal LAPs in 47%, peripheral mass in 30%, and atelectasis in 28% of the patients. Interestingly, the authors reported central mass as the rarest CT finding with 16%.

In his study, Sørensen[22] reported that the mean time to diagnosis of EBM after the primary tumor is 50 (0–300) months, and the mean survival following EBM diagnosis is 15.2 (0–150) months. Similarly, Marchioni *et al*.[24] reported the mean time to diagnosis of EBM after the primary tumor is 136 (1–300) months. In our study, the time to diagnosis of EBM after the primary tumor was 55.1 (1–180) months. This is in line with Sørensen's study, but discrepant from the results reported by Marchioni *et al*. Other studies reported this time period between 32.8 and 65.3 months.[1,5,15,22,25]

The mean survival after the EBM diagnosis in our series, which mostly included breast cancer patients, was 8.5 (1–21) months. Katsimbri *et al*.[3] reported a mean survival of 9 months in their series that mostly consisted of patients with renal cell carcinoma (37.5%), while Kiryu *et al*.[1] reported a mean survival of 15.5 months from their study that mostly included patients with colorectal carcinoma (37.5%) and Akoglu *et al*.[15] reported a survival of 18 months for patients most of which had breast carcinoma (20%). The wide range in mean survival can be explained by the differences in the type of primary cancer, its biological behavior, patient's performance status, metastasis to other systems and organs, systemic treatment targeting primary cancer, and local therapies targeting the EBM.[5,26]

A search of the literature in English language produced no results related to studies that looked into the relationship between the EBMs of extrathoracic cancers and PET-CT findings. In their study on the value of PET-CT to distinguish between malignant and benign endobronchial lesions, Cho *et al*.[27] determined a mean SUV_{max} of 2.5 ± 0.84 versus 11.8 ± 5.95 for benign and malignant lesions, respectively, and the difference was shown to be statistically significant ($P < 0.001$). The authors suggested a potential role for the PET-CT to characterize endobronchial lesions. This study included 84 subjects, of which 63 were malignant and 18 were benign, and only 2 of the malignant lesions were found to be EBM of extrathoracic cancer while the remaining 61 were cases of endobronchial involvement of lung cancer. In this series, one of the EBMs was breast carcinoma with a SUV_{max} of 3.5, whereas the other was a case of hepatocellular carcinoma with a SUV_{max} of 2.5. Jeong *et al*.[28] *et al*. identified EBMs in 5 of 12 salivary gland cancers and reported a mean SUV_{max} of 4.42 (1.5–6.5). There was one salivary gland cancer in our series. This was, however, one of the three cases with no CT scan available. Meka *et al*.[29] reported a SUV_{max} of 26 in a patient with endobronchial non-Hodgkin's lymphoma. The SUV_{max} of one patient diagnosed with non-Hodgkin's lymphoma in our series was 18.2. Dong *et al*.[30] identified endobronchial involvement on the PET-CT scans of two patients with breast cancer and hepatocellular carcinoma each and established the EBM diagnosis using FOB. SUV_{max} was reported 7.9 and 5.7 for the patient diagnosed with breast carcinoma and hepatocellular carcinoma, respectively. The authors point out that EBM should be considered in case of endobronchial FDG uptake, especially in patients with a history of a malignant tumor. The mean SUV_{max} of the seven breast cancer cases in our series was 10.9 ± 4.5 (6.4–17.4). There was no patient with hepatocellular carcinoma in our series.

Our study reflects the experience of one center only and is a retrospective analysis of a small number of patients. As this is a retrospective study, data loss is inevitable. Subgroups of extrathoracic tumors with EBMs, in

particular, are limited in number. It is, therefore, not possible to draw definite conclusions or generalize its results.

In spite of its limited sample size, we were able to draw two important conclusions with regard to the role/benefits of PET-CT in patients with extrathoracic cancer who developed EBM based on the results of this study. The first and most important conclusion is that almost all of the patients with EBMs (92.3% percent of cases) had metastasis to at least one extrathoracic system or organ on the PET-CT. Only one case has FDG uptake associated with primary cancer and pulmonary EBM while the remaining 12 cases had multiple system or organ metastases at the time of EBM diagnosis. This finding not only explains why survival after EBM diagnosis is as short as 8.5 months in our study but also suggests that these patients may benefit from systemic treatment rather than local therapies. This underscores the importance of this study.

CONCLUSION

Based on our results, we concluded that breast carcinoma is the type of malignancy most commonly associated with EBM, the mean survival of patients after EBM diagnosis is short, and that PET-CT not only provides information about the extent of the disease but also plays a role in planning the treatment. We believe that a larger multicenter, prospective study may shed a better light on the issue at hand.

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Conflicts of interest
There are no conflicts of interest.

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