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Endobronchial metastases from extrathoracic malignancies

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Abstract

Endobronchial metastases (EBM) from extrapulmonary malignant tumors are rare. The most common extrathoracic malignancies associated with EBM are breast, renal and colorectal carcinomas. In this study, we aimed to evaluate the clinical, radiographic and bronchoscopic aspects of patients with EBM who were diagnosed between 1992 and 2002. Data about patients' clinical conditions, symptoms, radiographic and endoscopic findings, and histopathological examination results were investigated. EBM was defined as bronchoscopically visible lesions histopathologically identical to the primary tumor in patients with extrapulmonary malignancies. We found 15 cases with EBM. Primary tumors included breast (3), colorectal (3), and renal (2) carcinomas; Malignant Melanoma (2); synovial sarcoma (1), ampulla of Vater adenocarcinoma (1), pheochromocytoma (1), hypernephroma (1), and Hodgkin's Disease (1). The most common symptoms were dyspnea (80%), cough (66.6%) and hemoptysis (33.3%). Multiple (40%) or single (13.3%) pulmonary nodules, mediastinal or hilar lymphadenopathy (40%), and effusion (40%) were the most common radiographic findings. The mean interval from initial diagnosis to diagnosis of EBM was 32.8 months (range, 0–96 months) and median survival time was 18 months (range, 4–84). As a conclusion, various extrapulmonary tumors can metastasize to the bronchus. Symptoms and radiographic findings are similar with those in primary lung cancer. Therefore, EBM should be discriminated from primary lung cancer histopathologically. Although mean survival time is usually short, long-term survivors were reported. Consequently, treatment must be planned according to the histology of the primary tumor, evidence of metastasis to other sites and medical status of the patient.

Introduction

Although, the lungs are often involved by extrapulmonary malignancies, endobronchial metastases (EBM) are occasionally reported. The frequency of EBM varies according to definition (from 2 to 28%) [1–3]. King and Castleman [4] firstly reported the incidence of EBM as 18% in patients with extrapulmonary malignancies. Braman and Whitcomb [1] also reported EBM incidence as 2% in a retrospective review of autopsies in patients who died with solid tumors and 4% in patients with pulmonary metastasis. Although various tumors can metastasize to the bronchus, the most common extrathoracic malignancies associated with EBM are breast, renal and colorectal carcinomas.

Because of its capacity to produce airway obstruction that is indistinguishable from bronchogenic carcinoma, diagnosis of EBM has clinical importance. In the majority of cases, the definitive diagnosis is made by presence of the primary malignancy at another site of which histologic appearance is similar with those of endobronchial lesion [5].

In this study, we aimed to investigate the clinical, radiographic and endoscopic aspects of EBM. Also, we searched the mode of metastatic involvement.

Materials and methods

In this retrospective study, we evaluated all fiberoptic bronchoscopy reports between 1992 and 2002 at Dokuz Eylül University Hospital (İzmir, Turkey) and collected EBM cases. Data about patients' clinical conditions, symptoms, radiographic and endoscopic findings and histopathological examination results were investigated retrospectively. Treatment modalities, mean recurrence interval and median survival times were also noted.

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We defined EBM as bronchoscopically visible lesions, histopathologically identical to the primary tumor, associated with or without parenchymal or mediastinal lesions in patients with extrapulmonary malignancies. Nine patients who had extrathoracic malignancies with endobronchial lesions, were excluded due to lack of histological diagnosis.

The mode of the metastatic spread was divided into four groups as follows: Type I, direct metastasis to the bronchus; type II, bronchial invasion by parenchymal lesion; type III, bronchial invasion by mediastinal or hilar lymph node metastasis; and type IV, endobronchial invasion with lymphangitis carcinomatosa.

Results

Fifteen patients were diagnosed as having EBM from extrapulmonary malignant tumors. There were four women and eleven men ranging in age from 31 to 85 years (mean 55 years). Primary tumors included breast (3), colorectal (3), and renal (2) carcinomas; Malignant Melanoma (2), synovial sarcoma (1), ampulla of Vater adenocarcinoma (1), pheochromocytoma (1), hypernephroma (1), and Hodgkin's Disease (HD) (1). Table 1 shows the characteristics of patients.

Presenting symptoms included dyspnea in 12 patients (80%), cough in 10 patients (66.6%) and hemoptysis in five patients (33.3%). Multiple (six patients, 40%) or single (two patients, 13.3%) pulmonary nodules, mediastinal or hilar lymphadenopathies (six patients, 40%), pulmonary masses (five patients, 33.3%), effusion (six patients, 40%), and atelectasis (four patients, 26.6%) were the findings on chest X-ray (CXR) and computerized tomography (CT) of the thorax. At least one of these findings were present in each patient.

On bronchoscopic examination, there were 23 endobronchial lesions. These lesions were located in main carina in two patients (two lesions), main bronchus in four patients (five lesions), trunchus intermedius in two patients (two lesions), lobar bronchus in seven patients (eight lesions) and, segmentary bronchus in five patients (six lesions). Six patients had multiple lesions. There were a polypoid lesion in the right and an endobronchial mass lesion in the left bronchial tree in a patient with renal cell carcinoma. Besides, one of the melanoma patients showed black colored lesions in right and left bronchial tree.

CXR and CT findings and location of lesions are shown in Table 2.

Diagnosis of EBM was achieved by bronchoscopic biopsy in 12 patients, bronchoscopic washing in two patients, and open lung biopsy in one patient. In a patient with pulmonary nodules, biopsy could not be taken because of hemorrhage, and open lung biopsy was performed. In this patient, the primary disease was not known at the time of diagnosis and open lung biopsy showed renal cell carcinoma metastasis. In a patient with renal cell carcinoma, endoscopic biopsy was non-diagnostic whereas bronchial wash was positive. In the patient with pheochromocytoma, endobronchial biopsy could not be taken because of hemorrhage and bronchial wash was positive.

The modes of metastatic involvement were as follows: type I, in three patients (four lesions-17.3%); type II, in 11 patients (13 lesions-56.5%); type III, in three patients (four lesions-17.3%); type IV, in one patient (two lesions-8.7%). In two patients, there were multiple lesions with different types of metastatic involvement. One patient with breast carcinoma had one type III lesion in carina, one type II lesion in the right main bronchus and one type I lesion in the left upper lobe. One patient with

Table 1. Patient characteristics.

Patient, Age, year/sex	Primary site	Time*	Symptoms	Treatment	Survival (mo)
1/31-F	Breast	4	Dyspnea, cough	RT**	4
2/64-M	Colon	96	Dyspnea	CT***	c
3/32-M	Malignant melanoma	12	Dyspnea, cough, hemoptysis	CT + RT	36
4/60-F	Breast	1	Dyspnea, pleural pain	CT + RT	15
5/60-M	Hypernephroma	29	Dyspnea, cough, hemoptysis,	CT + IT[a]	c
6/38-F	Breast	12	Dyspnea,cough, wheeze	CT + RT	18
7/47-M	Hodgkin's Disease	84	Dyspnea, pleural pain	CT	84
8/64-M	Rectum	48	Dyspnea, cough	CT + RT	54
9/51-M	Synovial sarcoma	16	Dyspnea, hemoptysis	CT	48
10/70-M	Ampulla of Vater	7	Cough, hemoptysis	SC[b]	24
11/85-M	Renal	11	Dyspnea, cough	SC	14
12/46-F	Pheochromocytoma	92	Cough	CT	c
13/70-M	Malignant melanoma	8	Dyspnea, hemoptysis, wheeze	CT	c
14/50-M	Rectum	72	Cough	CT	16
15/70-M	Renal	0	Dyspnea, cough	SC	10

*Interval between diagnosis of primary tumor and endobronchial metastasis, **Radiotherapy, ***Chemotherapy.
[a]Immunotherapy.
[b]Supportive care.
[c]Survival is unknown.

Table 2. Chest X-ray and CT findings, and location of lesions.

Radiological findings*	No. (%)	Location of lesions	No. (%)
LAP**	6 (40%)	Main carina	2 (8.7%)
Multiple nodules	6 (40%)	Right bronchial tree	13 (56.5%)
Solitary nodule	2 (13.3%)	–Main bronchus	4
Mass	5 (33%)	–Upper lobe	2
Effusion	6 (40%)	–Middle lobe	2
Atelectasis	4 (26.6%)	–Intermedier bronchus	2
Diffuse infiltration	1 (6.6%)	–Lower lobe	3
		Left bronchial tree	8 (34%)
		–Main bronchus	1
		–Upper lobe	4
		–Lower lobe	3

*More than one abnormality can be seen in a patient, **Lymphadenopathy.

HD had both type III lesions in carina and the left main bronchus and also one type II lesion in the right main bronchus.

The modes of metastatic spread and survival times according to tumor types are shown in Table 3.

The mean interval from initial diagnosis to diagnosis of EBM and median survival times were 32.8 and 18 months, respectively. Four patients did not have the orderly data about follow-up, therefore we reported survival times of 11 patients. EBM was detected at the same time with diagnosis of the primary tumor in a patient with renal cell carcinoma. The longest interval from the initial diagnosis to diagnosis of EBM was 96 months in a patient with colon adenocarcinoma. Although the range was wide, a patient with breast carcinoma had the shortest survival time (four months), whereas the patient with HD had the longest (84 months).

At the time of EBM diagnosis, 9 of 15 patients (60%) had metastatic diseases in other sites. These metastatic sites were liver (1), adrenal glands (2), bone (5), brain (3), peritoneum (1) and spleen (1). Four patients had multiple metastasis.

Table 3. Survival times according to primary tumor.

Primary site	Patient, no. (no. of lesions)	Survival (mo)
Breast	3 (5)	13
Colorectal	3 (4)	35[a]
Renal	2 (3)	12
Malignant Melanoma	2 (3)	36[b]
Sarcoma	1 (1)	48
Pheochromocytoma	1 (1)	*
Hypernephroma	1 (2)	*
Hodgkin's Disease	1 (3)	84
Ampulla of Vater	1 (1)	24

*There were no data about survival times.
[a]Survival times of two patients.
[b]Survival time of one patient.

The treatments and management of all patients were planned multidisciplinary. Treatment modalities were chemotherapy in eight, radiotherapy in one, chemotherapy combined with radiotherapy in three and supportive care in three patients. Only one patient with ampullary adenocarcinoma was candidate for surgical therapy but he refused all therapies. One patient with renal cell carcinoma had refused operation for primary tumor. After 11 months, endobronchial and adrenal gland metastases were detected and supportive care was given. For the other patient with renal cell carcinoma, immunotherapy was planned. But he was suffering from congestive heart failure and, thus only supportive care could have been given. Median survival time of 8 patients who were treated was 27 months, whereas the mean survival time of three patients with supportive care was 16 months.

Discussion

Although pulmonary metastases from extrapulmonary malignancies are common, endobronchial invasion has been reported rarely. Since bronchoscopic examination is not performed routinely to all patients presenting with pulmonary metastasis, it is possible that EBM is underdiagnosed. In addition, there are discrepancies in definition of EBM. Its frequency depends on how it is defined. If definition includes invasion of the tracheobronchial tree by parenchymal masses or lymph nodes, frequency will be higher. In our study, we defined EBM as bronchoscopically visible lesions histopathologically identical to the extrapulmonary primary tumor, in association with or without parenchymal or mediastinal lesions.

Breast carcinoma, renal carcinoma and adenocarcinoma of the colon are the most common neoplasms responsible for EBM [1, 6–11]. Our experience is consistent with these findings. However, in our series, there are two unusual cases of EBM including ampulla of Vater adenocarcinoma and pheochromocytoma. We searched the English language literature and found no

case of ampullary adenocarcinoma associated with EBM. According to our knowledge, this is the first case of EBM from ampullary adenocarcinoma. Endobronchial invasion of pheochromocytoma is a rare condition. The first case of pheochromocytoma with EBM was reported by Sandur et al. [12]. To our knowledge, the patient with pheochromocytoma in our series is the second one in the English language literature.

Pulmonary parenchymal disease occures in 38% of HD [13]. However, endobronchial invasion is rare in this disease [13, 14]. In our series, there was a patient with HD responsible for EBM. Brinchault et al. [14] reported two cases of bronchial erosions due to mediastinal lymphadenopathy associated with HD. Argyros et al. [15] also reported nine patients in lymphoma group diagnosed as having EBM.

The most common symptoms are coughing and hemoptysis followed by dyspnea and wheezing in patients with EBM [6–10, 16]. Although dyspnea was the most frequent symptom followed by cough and hemoptysis in our series, it is ubiquitous and not specific for EBM [16]. However, if there is one of these symptoms in a patient with extrapulmonary malignancy, especially breast, colon or renal tumors, bronchoscopic examination is recommended [8]. EBM could also be found in asymptomatic patients. Kiryu et al. [7], Heitmiller et al. [8], and Poe et al. [16], reported that 62.5, 52, and 62.5%, of their patients were asymptomatic, respectively.

There are a variety of radiographic findings in EBM. The most commonly reported findings on CXR include atelectasis, hilar enlargement, and multiple or single nodules [9, 16, 17]. Consistent with Kiryu's report [7] (25%), atelectasis was rare (26.6%) in our series. Surprisingly, we detected effusion frequently (40%) as a coexisting finding, although other authors reported rarely [9, 15, 18].

Because of the possibility of revealing other pulmonary metastases or hilar-mediastinal lymphadenopathies, CT of the thorax should be performed [15, 19, 20]. However, CT is not always able to demonstrate luminal lesions. In our series, four patients showed mediastinal-hilar lymphadenopathy, two showed atelectasis and one showed a mass on CT examination in addition to CXR findings.

On bronchoscopic examination, six patients showed multiple lesions. The primary tumors were carcinoma of the breast, rectum and kidney; hypernephroma, HD and Malignant Melanoma. Of the 21 lesions except two which were carinal, 13 (61.9%) were recognized in the right side and 8 (38%) in the left side. Kiryu et al. [7] also reported that, 20 of 25 lesions were in the right side. The reason of this predilection is not clear.

Kiryu et al. [7] studied the mode of metastasis in EBM patients on the basis of four developmental conditions. These are as follows: type I, direct metastasis to the bronchus; type II, endobronchial invasion of parenchimal mass; type III, endobronchial invasion of mediastinal or hilar lymphadenopathy; type IV, extention of peripheral tumor along the proximal bronchus. In our study, we defined the mode of metastasis as follows; type I, direct metastasis to the bronchus; type II, bronchial invasion by parenchymal lesion; type III, bronchial invasion by mediastinal or hilar lymph node metastasis; and type IV, endobronchial invasion with lymphangitis carcinomatosa. We think that, when Kiryu's definition is used, it can be difficult to differentiate type II and type IV. Therefore we accepted all EBM associated with parenchymal lesion as type II. In our series, type II was the most common mode of metastasis (56.5%), whereas type IV was the most common in Kiryu's series. However, in each type of metastasis, parenchymal lesion is associated with the bronchial invasion.

Interval between the primary tumor diagnosis and metastasis is usually long [6, 7, 9]. Sorensen [6] reported that the interval from initial diagnosis to diagnosis of EBM was 50 months (range, 0 to 300 months). In our series, the mean interval was 32.8 months (range, 0 to 96 months). According to the biological behavior of primary tumor, this interval is quite variable.

EBM is frequently a manifestation of a far advanced disease stage. Kiryu et al. [7], Salud et al. [10] and Heitmiller et al. [8] reported that, at the time of EBM diagnosis, 56%, 53% and 87% of patients had extrabronchial metastatic diseases, respectively. These findings are consistent with ours (60%).

Although it depends on the biological behavior of the primary tumor, the mean survival time is usually short [7–9]. Sorensen [6] reported that, the mean survival time was 15.2 months in 204 cases of EBM in their 40-year review. Longer survival times were reported by Heitmiller et al. [8] in patients with renal and breast cancer. Baumgartner and Mark [11] reported, long-term survival as 32 months. In our series, median survival time was 18 months (range 4–84). We agree with Baumgartner and Mark's suggestion about consideration of aggressive treatment in EBM patients, as survival after treatment is not necessarily short. However, it is doubtful whether long survival times are the result of aggressive treatment or it reflects the natural history of a slow progressing tumor [9].

Treatment of EBM must be planned according to the histology of the primary tumor, location of the lesion in the bronchial tree, number of lesions, evidence of other metastatic sites and medical status of the patient. In our series, chemotherapy (11 patients) and radiotherapy (four patients) were the primary therapies. In patients with chemotherapy or radiotherapy, survival time was longer than those with supportive care. But this finding couldn't be attributed directly to the specific treatment. It can also be due to the disseminated disease in patients with supportive care.

Intraluminal radiotherapy is one of the treatment choices for the palliation of symptoms [21–23]. However, its effect on survival time has not yet been fully elucidated. Nd-Yag laser debulking is another choice of treatment in patients with endobronchial obstruction

[16]. Carlin et al. [18] reported that, the Nd-Yag laser debulking, in combination with external radiotherapy and endobronchial radiation therapy, can improve survival in selected patients. Our study is limited by the fact that there were no patients treated with local therapies such as intraluminal brachytherapy or Nd-Yag laser debulking. Unfortunately, these therapies were not available in our hospital and could not be used for the treatment of these patients.

In conclusion, many different types of extrapulmonary tumors can metastasize to the bronchus. EBM is usually a consequence of bronchial invasion by parenchymal or mediastinal metastatic lesions and most patients have CXR abnormalities. Since the interval between primary disease and metastasis is usually long and symptoms and radiographic findings are similar with those in primary lung cancer, EBM should be discriminated from primary lung cancer histopathologically. Although mean survival time is usually short, long-term survivals were reported. Therefore, treatment must be planned according to tumor type, evidence of other metastatic sites and the medical status of the patient.

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