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Endobronchial Metastases from Extrapulmonary Solid Tumors

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Malignancy detected during endobronchial biopsies is usually regarded as proof of lung cancer. It may, however, represent endobronchial metastases from extrapulmonary primary tumors. The literature was reviewed to describe how frequent extrapulmonary tumors have been reported to metastasize to the endobronchial epithelium. English language literature was searched from 1962 through 2002. Primary lung cancer and lymphomas were excluded. Endobronchial metastases were reported in 204 patients, originating from 20 different extrapulmonary primary tumors, usually cancers of the breast, kidney, colorectal, uterine cervix, sarcoma and skin. The mean time from diagnosis of primary tumor was 50 months (range 0–300 months) and mean survival time from diagnosis of endobronchial metastasis was 15.2 months (range 0–150 months). It is important to make a distinction between endobronchial metastases from primary lung cancer, as treatment possibilities may be different. The possibility of endobronchial metastasis should be considered if the patient has a history of malignancy in other organs.

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The lungs are among the most common sites of metastases from non-pulmonary malignancies. Metastases are usually scattered in the lung parenchyma or pleura, and often infiltrate adjacent structures, among them the respiratory bronchi. Endobronchial metastases, on the other hand, defined as primary involvement of the bronchial epithelium, are rare. Various tumors have been associated with endobronchial metastasis, most commonly renal and breast carcinomas.

The purpose of this literature review is to present all published cases of endobronchial metastases from primary tumors apart from lung cancer and primary pulmonary lymphoma. We describe which tumors have been reported to metastasize to this location, the clinical presentation and, if possible, give an estimate of the frequency of endobronchial metastasis.

MATERIAL AND METHODS

The literature for English language reports, letters and articles were searched on the Medline database from 1966 through 2002. The reference lists in each article were also used to complete the search. Only articles describing endobronchial metastasis from extrapulmonory tumours were reviewed, while cases of lung cancer were excluded.

Information about the patients on age, gender, primary diagnosis and histology, time interval since the primary diagnosis and the endobronchial metastasis, disease status and a description of the chest x-rays were extracted from the articles and letters. Information was registered on how the endobronchial metastasis was verified, e.g. by bronchoscopy with biopsy, by surgery or autopsy. If the authors had stated that the histology of the endobronchial metastasis was compared with the original histology of the primary tumor, this was also noted.

Patients were excluded if our definition of endobronchial metastasis was not met. In this review endobronchial metastasis is defined as a bronchoscopically diagnosed metastatic involvement to the respiratory bronchi from a histologically verified extrapulmonary primary tumor. Patients without histological verification of both the primary tumor and the endobronchial metastasis were excluded.

RESULTS

A total of 204 cases fulfilling the criteria of being clinically diagnosed by bronchoscopy with biopsies were reported. In addition, the issue has been dealt with in three autopsy studies (1–3) and in two studies of surgically removed lung metastasis (4, 5). It was not possible from the latter series to separate the results of metastasis limited to the endobron-

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chial epithelium from that of direct invasion into the bronchus from parenchymal lung metastasis.

Autopsy series

King & Castelman were the first to emphasize the frequency of bronchial involvement in pulmonary metastasis in 1942 (1), though not in a clinical series but in an autopsy study. The report included 109 patients with extrapulmonary malignancies and metastases to the lungs, among whom 20 cases (18%) had definitive infiltration of the bronchial wall or mucosa. King & Castelman pointed out that the autopsies were done in a routine fashion and suspected that the incidence of bronchial involvement would have been much higher if more attention had been given to the bronchial tree (1).

In another autopsy series of 380 cases with extrapulmonary carcinomas, Rosenblatt et al. (2) observed involvement of the bronchus in 97 patients (26% of cases). In this autopsy series 189 patients had pulmonary metastases, and 50% of them had bronchial involvement. Also Braman & Whitcomb (3) reported an autopsy series of 244 patients with solid tumors, excluding primary lung neoplasm. Among these patients, 130 had pulmonary metastases (53%), but only five cases (2%) had endobronchial metastases (3).

Thoracic surgery series

Higginson (4) reported on a smaller series of 35 cases having lung resections because of pulmonary metastatic malignancy. Nine patients (26%) had histologically proven involvement of the bronchus.

Seiler et al. (5) also reviewed 62 cases of patients who had a pulmonary resection for metastatic malignant lesions. Information was available concerning the presence or absence of involvement of a major bronchus in 27 of these cases, and bronchial involvement was present in 17 cases. The investigators presumed that in those cases where bronchial involvement was not stated, this feature was not present, leading to their conclusion that the incidence of bronchial involvement in secondary pulmonary malignancies was 27%, which is thus a minimum figure in this material (5).

Histopathology of endobronchial metastasis

Rosenblatt et al. (2) described the histological changes observed in the bronchus at the site of metastatic involment. They reported the earliest changes to be permeation of the mucosal lymphatics by malignant cells and distension of the lymph channels. This is subsequently followed by coalescence of the swollen lymphatics to form solid tumor masses under the bronchial epithelium. In the more advanced stages the tumor tissue ulcerates through the epithelial layer

Table 1

Extrapulmonary primary tumors in 204 patients with endobronchial metastasis diagnosed by bronchoscopy with biopsies

Primary extrapulmonary tumor (reference no.)	n	Lead time (months) median (range)	No other signs of tumor/ metast. n	Survival (months) median (range)
Breast (6, 7, 10–24, 62)	72	67 (0–300)	19	15 (1–58)
Kidney (10, 11, 13, 16, 25–39, 62)	34	35 (0–114)	15	20 (0–150)
Colorectal (10, 11, 13, 15, 16, 23, 37, 40, 41, 62)	30	43 (0–112)	3	15 (6–26)
Sarcoma (13, 42–47)	11	51 (0–168)	4	6 (2–37)
Cervix (13, 15, 48, 49)	9	24 (4–60)	3	18 (2–48)
Skin (10, 15, 37, 50, 51)	9	77 (24–204)	3	10 (4–12)
Head and neck (11, 15, 23, 62)	7	48 (22–196)	3	14 (NR)
Urinary bladder (10, 11, 37, 62)	5	69 (12–144)	1	12 (1–36)
Corpus uteri (10, 15, 23, 62)	5	NR	1	2 (NR)
Testicles (10, 11, 16, 52)	4	60 (36–84)	NR	NR
Prostate (53–55, 62)	4	24 (0–48)	1	NR
Salivary glands (23, 56)	3	31 (NR)	3	NR
Stomach (10, 37, 57)	3	NR	NR	2 (NR)
Ovaries (11, 58)	2	38 (3–78)	0	11 (NR)
Liver (10)	1	9	NR	NR
Penis (15)	1	39	NR	14
Olfactory nerve (10)	1	10	NR	NR
Plasmacytoma (59)	1	39	NR	14
Thyroid papillary carcinoma (60)	1	12	NR	NR
Malignant chondroid syringoma (61)	1	48	NR	NR
TOTAL	204	50 (0–300)	56 (27%)	15 (0–150)

Abbreviations: NR = not reported.
Lead-time: Time from diagnosed extrapulmonary primary tumor to histologically verified endobronchial metastasis.

Table 2

Symptoms reported in 166 patients with endobronchial metastases from extrapulmonary primary tumors diagnosed by bronchoscopy with biopsy

Symptom	No. of patients (%)
Cough	80 (48%)
Shortness of breath	61 (37%)
Hemoptysis	61 (37%)
Thoracal pain	12 (7%)
Other symptoms	
Tiredness	3 (2%)
Weight loss	8 (5%)
Fever	10 (6%)
No symptoms	34 (20%)

Table 3

Chest x-ray findings in 106 patients with endobronchial metastases from extrapulmonary primary tumors diagnosed by bronchoscopy with biopsy

x-ray findings	No. of pts. (%)
Normal	4 (4%)
Visible tumor	28 (26%)
Atelectasis	62 (58%)
Pleural fluid	8 (8%)
Multiple nodules	18 (17%)
Mediastinal lymphadenopathy	4 (4%)

to form a polypoid mass within the bronchial lumen. Eventually, the entire mucosal lining is replaced by malignant tissue resulting in a stenosis of the bronchial lumen (2). Other investigators (6–8) report on similar findings. Various other means by which tumor may reach the bronchial wall are through bronchial arteries and by aspiration of tumor cells (7–9).

Literature review on 204 cases diagnosed clinically by bronchoscopy with biopsies

All patients included in the study had histologically verified endobronchial metastasis diagnosed by bronchoscopy with biopsy. The histology of the metastasis was compared to that of the primary tumors, but immunohistopathologic examinations were only reported on in four studies (22, 24, 54, 56) including a total of 5 patients (2.4%) with breast cancer, prostate cancer or salivary gland cancer as primary tumors. The median age of the 152 patients for whom information was available was 56 years (range 25–84). Gender was reported on in 135 cases and in this patient group more women (73 patients, 54%) than men (62 patients, 46%) were reported with endobronchial metastases, partly due to the prevalence of reported endobronchial breast cancer metastases.

The primary tumors in patients with endobronchial metastases are listed in Table 1 (10–62). The most frequent primary diagnoses were cancer of the breast (72 cases), kidney (34 cases), colon and rectum (30 cases). Sarcoma, uterine cervix, and skin tumors are also among the most frequent primary diagnoses (11, 9 and 9 cases, respectively). More rarely reported primary tumors include cancers in thyroid gland, urinary bladder, testicle, prostate gland, uterine corpus, penis, head and neck, salivary glands, ovary, stomach, liver, olfactory nerve, plasmacytoma and malignant chondroid syringoma (Table 1). The time from diagnosis of the primary tumor to the diagnosis of endobronchial metastasis (Table 1) was a mean of 50 months (range 0–300 months).

The clinical presentation of the patients was reported in 166 patients (Table 2). Two-third of the patients had two or more pulmonary symptoms. Two symptoms out of the triad of cough, shortness of breath and hemoptysis was seen in 30% of all patients. Twenty percent of the patients were asymptomatic.

Descriptions of the chest radiography findings were givenfor 106 patients (Table 3). Only four images were normal. Atelectasis was the most frequent finding, occurring in 58% of all cases reported.

Location of the endobronchial metastasis was reported on in 147 patients (Table 4). Metastases were equally distributed between the right and left lungs (41% and 41%

Table 4

Location of endobronchial metastases diagnosed by bronchoscopy with biopsy in 136 patients with extrapulmonary primary tumors

Location	No. of patients			
		Left	Right	No specification
Trachea	8 (5%)			
Multiple sites	12 (8%)			
Main bronchus		13 (9%)	8 (5%)	6 (4%)
Upper lobe bronchus		23 (16%)	18 (12%)	
Middle lobe bronchus			17 (12%)	
Lingula		1 (1%)		
Lower lobe bronchus		23 (16%)	18 (12%)	
Total no. of cases	20 (14%)	60 (41%)	61 (41%)	6 (4%)

Table 5

Treatment of bronchoscopically verified endobronchial metastasis from extrapulmonary primary tumors in 179 patients. Some patients received combined treatments

	No. of pts. (%)
No treatment	30 (17)
Any kind of treatment	149 (83)
Surgery	41 (23)
Ext. radiotherapy	40 (22)
Chemotherapy	47 (26)
Brachytherapy	13 (7)
Hormonal therapy	6 (3)
Stent	1 (0.5)
Nd-YAG laser	1 (0.5)

of cases, respectively), while in 5% of cases were located in the trachea and 8% at multiple sites.

Among all 204 patients in the review, 56 patients (27%) had endobronchial metastases as the only malignant disease manifestation, without other signs of disease dissemination from the previously treated extrapulmonary primary tumor (Table 1). Comparing the time interval from initial diagnosis of the primary tumor to the time of diagnosis of endobronchial metastasis, there was no difference in recurrence time between these 56 patients and the 140 patients who had additional metastatic spread (49 months for 56 patients with only endobronchial metastases vs. 50 months for patients with additional extrathoracal disease manifestations). Eight patients had endobronchial metastases diagnosed simultaneously with the extrapulmonary primary tumor.

Information regarding treatment was available for 179 patients and the results are presented in Table 5. Twenty-one patients (12%) did not receive any specific antineoplastic therapy.

The mean survival time after the diagnosis of endobronchial metastasis from extrapulmonary primary tumors was 15 months (range 0–150 months). The longest mean survival time was reported in cancer of the kidney (20 months) and cancer in the uterine cervix (18 months).

DISCUSSION

The symptoms associated with endobronchial metastases from primary extrapulmonary tumors (Table 2) and the findings on chest x-rays (Table 3) are obviously similar to the findings in primary lung cancer. The subsequent bronchoscopy with a positive histologic finding will usually lead to the conclusion that it is a primary lung cancer, which is by far the most likely diagnosis. This also holds true even where there is a history of another, previously treated, extrathoracic malignancy, because lung cancer is such a common malignant disease that, solely by chance, it could occur in some patients surviving long enough after treatment for another tumor, especially, of course, in smokers. However, in some rare cases, the positive biopsies from the bronchus indicate the presence of another, extrapulmonary malignancy, which may have considerable implications for the choice of treatment for the particular patient.

It is truly a rare event when the positive endobronchial biopsy indicates metastasis from an extrapulmonary primary tumor, as in this review we were able to detect only 204 published cases since the first report published in 1931 (33). One of the implications is that one must be aware of the phenomenon in cases having a positive endobronchial biopsy combined with a history of previous extrapulmonary primary tumor. A total of 148 such patients have been reported, in whom there were additional metastatic sites. Probably these cases are the most likely to be to be given the correct diagnosis, even though in the clinic an unknown number are probably erroneously categorized as having a new primary lung cancer. The cases in which an endobronchial metastasis is the only sign of recurrent disease are more difficult to diagnose, such as those reported in a total of 56 patients (Table 1). Bearing the autopsy studies in mind, which showed endobronchial metastasis in 2% to 26% of cases, it is likely that both the clinical diagnosis is missed in a number of cases and there is some underreporting in the literature of this phenomenon.

Revision of the endobronchial histologic specimen together with the histologic specimens from the extrathoracic primary tumor is of paramount importance in order to reach the correct diagnosis, and should be performed in all cases where there is a history of previous malignant disease. The use of immunohistochemistry may make it easier to differentiate between an endobronchial metastasis and a new primary tumor of the central airways. Furthermore, newer molecular biological tools for evaluating genomic differences, e.g. loss of heterozygosity, may be useful. However, in this review of patient reports, only 4 papers out of 54 reported on the use of such immunohistochemistry. Eleven of the references were earlier than 1970, which is too early for this technique to have been used, since it was gradually taken into use in the 1970s. This left 43 papers that were published between 1970 and 2002, with the majority (30 papers) dating from 1980 or earlier. Probably immunohistochemistry was used in a much larger number of these studies but this was considered implicit, and it is simply stated that the endobronchial biopsy was compared with the extrathoracic primary tumor and considered identical. This is, however, only an assumption, and it highlights the problem concerning the reliability of case reports that are often presented in a somewhat heterogeneous way. On the other hand, when dealing with relatively rare phenomena, e.g. endobronchial metastases, we are often bound to use such case reports because large prospective patient series are impossible to establish.

It is clear that endobronchial metastasis is a rare event, but the more exact incidences in various tumor types are difficult to establish. In an autopsy series by Braman & Whitcomb (3), endobronchial metastases were reported in 5 out of 244 patients (2%). However, two out of the five patients had parenchymal metastasis of the lung with direct growth into the bronchus, thus not qualifying as an endobronchial metastasis. In another autopsy study, by King & Castelman (1), including a total of 109 patients with lung metastases, the authors describe bronchial invasion in 20 patients, but 7 of these patients had tumor extension from surrounding structures. Endobronchial metastasis was thus seen in 13 patients, among whom 7 patients had only microscopic disease, while 6 (5.5%) had visible metastases to the bronchi, which potentially could be diagnosed clinically. Though rare, probably a number of cases are underdiagnosed, thus hampering more exact estimation of incidence figures. Newer diagnostic techniques such as fluorescence bronchoscopy may facilitate detection of microscopic endobronchial disease. This may lead to a higher detection rate and also to detection at an earlier stage with less tumor burden, subsequently leading to better treatment results.

It is not obvious why endobronchial metastases are most frequently reported in patients with cancer of the breast, kidney, colon or rectum. These carcinomas, like many others, share the ability to metastasize via the lymphatic system, although they also have the ability to spread hematogenously. In their analysis of the histological changes in the bronchial involvement of malignancy, Rosenblatt et al. noticed that the first changes appeared in the bronchial lymphatics (4). However, these three types of carcinomas also have in common high incidence, and a relatively good prognosis for subgroups of patients, leading to long survival time as compared with other malignant diseases. This means that chance alone can explain why endobronchial metastases are the most often reported in these tumor types. The prevalence of renal cell carcinomas may be underestimated here since this review only includes histologically confirmed endobronchial metastasis. These metastases may cause bleeding complications and physicians may therefore be somewhat reluctant to carry out biopsies of endobronchial lesions that might be renal cell carcinoma metastases.

The endobronchial metastases are on average diagnosed about four years after the diagnosis of the primary neoplastic disease, which is a relatively long lead-time, given the average time to progression in these solid tumors. There is no obvious explanation for this finding.

The distressing airway symptoms caused by endobronchial metastasis may be relieved by use of newer intrabronchial therapies, e.g brachytherapy (delivery of radiation from an endobronchial source), photodynamic therapy (involving intravenous administration of a photosensitizer with subsequent endobronchial illumination of the lesion with the appropriate wavelength of light), laser evaporation, e.g. using the Nd-YAG laser, and stenting. Stent and laser use has rarely been reported in the treatment of endobronchial metastasis, most likely because of underreporting and because some of the reports were published before these techniques were in general routine use.

Fractionated intraluminal HDR ^{192}Ir brachytherapy used as palliative treatment in 11 patients with endobronchial metastases from non-bronchogenic primaries was reported by Stranzl et al. in 2002 (62). A total of 11 patients were treated between 1991 and 1998 and received HDR ^{192}Ir brachytherapy at a total dose of 15–20 Gy delivered in 3–4 fractions of 5–6 Gy once a week. No palliative chemotherapy was added. The median follow-up after palliative brachytherapy was 15 months and objectively complete endoscopic response was observed in 3 patients (27%) while partial opening of the initially obstructed airway was achieved in another 5 patients (46%). Relief from symptoms occurred in the majority of patients (8 patients, 73%). Thus, HDR intraluminant brachytherapy is a valuable tool in the palliation of symptoms in patients suffering from endobronchial metastases and should be considered in these cases.

In conclusion, endobronchial metastases from extrapulmonary primary tumors are a rare disease manifestation. Since the first report in 1931, only 204 cases have been reported. The therapeutic implications may be very different from those of primary lung cancer. Hence, it is necessary to be aware of the phenomenon, and it is advocated that histologic revision of the endobronchial tumor material together with the previous histologic specimens should be carried out in patients with a history of extrapulmonary malignant disease, and also in cases with a time interval of several years between the two incidents.

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