Endobronchial metastasis: An epidemiologic and clinicopathologic study of 174 consecutive cases

Alessandro Marchioni a,⁎, Anna Lasagni a, Annalisa Busca b, Alberto Cavazza c, Lorenzo Agostini d, Mario Migaldi e, Paolo Corradini d, Giulio Rossi e

a Department of Oncology and Hematology, Respiratory Diseases Clinic, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy
b Operative Unit of Pulmonology, Hospital “Cattinara”, Trieste, Italy
c Operative Unit of Pathologic Anatomy, Azienda Ospedaliera Arcispedale S. Maria Nuova-IRCCS, Reggio Emilia, Italy
d Operative Unit of Pulmonology, Azienda Ospedaliera Arcispedale S. Maria Nuova-IRCCS, Reggio Emilia, Italy
e Department of Diagnostic Laboratories, Operative Unit of Pathologic Anatomy, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy

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Purpose: Endobronchial metastases from extrapulmonary solid tumors are a rare event and currently available epidemiological and clinico-pathological data mainly derive from anecdotal case reports.

Methods: A series of 174 consecutive cases of endobronchial metastases from extrathoracic solid tumors were collected over a period of 18 years. Immunohistochemistry was performed in 115 cases. Complete imaging features were available in 81 patients, and analysis of the latency period between primitive tumor diagnosis and occurrence of endobronchial metastasis was obtained.

Results: Among all bronchoscopic examinations performed in the same period for malignancy, a mean of 5.6 cases per year consisted of endobronchial metastases (range 2–17 cases), with a statistically significant increase when comparing the periods 1992–2000 (65 cases, 37%) and 2001–2009 (109 cases, 63%) (p = 0.05). Overall, 4% of endobronchial biopsies for suspected malignancy disclosed an endobronchial metastasis from extrapulmonary tumor. Breast (52 cases, 30%), colorectal (42 cases, 24%), renal (14%), gastric (6%) and prostate (4.5%) cancers and melanoma (4.5%) were the most common metastatic neoplasms presenting as endobronchial mass. One-hundred fifty-four cases were identified after the primitive tumor diagnosis (metachronous cases, 89%), 11 cases were simultaneously evidenced in extrapulmonary and endobronchial sites (synchronous cases, 6%), while 9 occult metastatic cases (5%) first presented as endobronchial mass (anachronous cases). Overall, mean latency from extrapulmonary tumor diagnosis and endobronchial metastasis was 136 months (range, 1–300 months). The most frequent symptoms were dyspnea (23%), cough (15%) and haemoptysis (12%), while 26% of patients were totally asymptomatic. At radiology, 53% presented as multiple pulmonary nodules, while other cases presented as hilar and mediastinal mass, single peripheral nodule, atelectasis or pleural effusion.

Conclusions: Endobronchial metastases from extrapulmonary tumors account for about 4% of all bronchoscopic biopsies performed for suspected malignancy and in 5% of the cases the metastasis is the first manifestation of the neoplasm.

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1. Introduction

Metastatic disease to the lungs is a common occurrence in routine oncologic practice and 20–50% of primary extrapulmonary solid malignancies show pulmonary metastases during their biologic course [1,2]. Among all clinico-radiologic presentations, the finding of metastatic tumors manifesting as endobronchial masses is a rare and possibly underestimated event.

Epidemiological studies show a broadly variable incidence of endobronchial metastases ranging from 2 to 50% depending on several factors, including the different clinical settings and/or the length of the period of time considered, the ethnic background which is significantly associated with different incidences of tumor types, as well as the criteria used to identify this unusual occurrence [3–6]. Kiryu et al. [7] proposed a 4 types classification of the development pattern of endobronchial metastases, as follows: type

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⁎ Corresponding author at: Respiratory Diseases Clinic, Azienda Ospedaliero-Universitaria Policlinico, via del Pozzo, 71, 41124 Modena, Italy.
Tel.: +39 059 4225859; fax: +39 059 4222571.
E-mail address: marchioni.alessandro@unimore.it (A. Marchioni).
I: direct metastasis to the bronchus; type II: bronchial invasion by parenchymal lesion; type III: bronchial invasion by mediastinal or hilar lymph node metastasis; type IV: peripheral lesion extending along the proximal bronchus. However, the great majority of endobronchial metastases reported in the literature are of type I due to the difficulty to discriminate these 4 patterns with certainty.

On the clinical ground, it is noteworthy that several patients may be totally asymptomatic and radiological findings are not particularly helpful in hindering differential diagnosis between endobronchial primary and metastatic tumors [6].

Among solid tumors occurring as endobronchial metastases, carcinomas from breast, kidney and colon-rectum are the most commonly encountered [4,7–30]. The timeframe between primitive tumor diagnosis and appearance of endobronchial metastases is quite variable although usually long, with an average of 50 months [7–9]. Finally, endobronchial metastases may generally follow identification of the primary site (metachronous cases) or more rarely precede (anachronous) or simultaneously reveal (synchronous) the primary malignancy discovery. Currently, our knowledge on endobronchial metastases from extrapulmonary solid tumors derive from case reports and few studies with a limited series of cases or conducted by using different clinical and radiological data collection methods, then resulting in fragmented and/or controversial data.

The aim of our study is to draw a more homogeneous epidemiological, clinico-radiologic and pathologic scenario of endobronchial metastases through a careful retrospective analysis of 174 consecutive cases along a period of 18 years collected from 2 different Institutions. The results herein presented were then compared with experiences previously appeared in the literature, in the hope to identify helpful features for suspecting metastatic disease when dealing with endobronchial masses.

2. Materials and methods

A series of 174 consecutive cases of endobronchial metastasis from extrapulmonary tumors were collected from the Units of Pathologic Anatomy and Pulmonology of the Azienda Ospedaliero-Universitaria Policlinico Modena and the Azienda Ospedaliera St. Maria Nuova of Reggio Emilia. Diagnoses were made between January 1992 and December 2009 and all cases were first independently diagnosed and then reviewed at a multiheaded microscope by two expert pulmonary pathologists (AC, GR). Endobronchial metastasis was recorded when a bronchoscopically visible, extrapulmonary neoplasm metastasized to the central or segmental bronchus. Lymphoproliferative malignancies were excluded from the study, since lymphomas or plasma cell neoplasms may frequently arise from the mediastinum or involve lymph nodes of this anatomic site then directly invading the bronchial structures. All cases consisted of bronchial biopsies that were formalin-fixed and paraffin-embedded. In all cases, 4-micron sections from the paraffin-block were performed for routine staining with hematoxylin–eosin. However, in 115 cases (66%) the diagnosis required further analysis by means of immunohistochemical stains. When required, immunohistochemistry was performed using an automated immunostainer (Benchmark, Ventana, Tucson, AZ). Both institutions independently performed immunohistochemical analysis, but using the same type of instruments as well as the same antibody clones. The panel of antibodies in each single case was appropriately selected depending on the differential diagnosis. The primary antibodies used in the study were the following: Thyroid Transcription Factor-1/TTF-1 (clone 8G7G3/3, Ventana, prediluted), Thyroglobulin (clone 2H11/6E1, Ventana, prediluted), CDX2 (clone EPR2764Y, Ventana, prediluted), CD10 (clone 013, Ventana, prediluted), estrogen receptors (clone SP1, Ventana; prediluted), progesterone receptors (clone 1E2, Ventana, prediluted), Wilms’Tumor-1/WT-1 (clone 6F–H2, Ventana, prediluted), calretinin (clone SP65, Ventana, prediluted), S100 (polyclona, Ventana, prediluted), melan-A (clone MART-1, Ventana, prediluted), PSA (ER PR8, Ventana, prediluted), smooth-muscle-actin (clone 1A4, Ventana, prediluted), desmin (clone DE-R–11, Ventana, prediluted), pan-cytokeratins (clone AE1/AE3, Ventana, prediluted), CD34 (clone QB-END/10, Ventana, prediluted), CD31 (clone J/C70A, Ventana, prediluted) (6F–H2, Ventana, prediluted), p63 (clone 4A4, Ventana, prediluted), calcitonin (polyclonal, Ventana, prediluted), Epithelial Membrane Antigen/EMA (clone E229, Ventana, prediluted).

Clinical data (sex, age, symptoms, time lapse between primary and metastatic tumors, type of primary extrapulmonary tumor) were available in all cases, while detailed imaging features were obtained in 81 cases.

2.1. Statistical analysis

Contingency tables were used for descriptive and comparative statistical analysis of collected data, and significance was evaluated with Pearson’s chi-squared test and Fisher’s test. All statistical calculations were performed using SPSS 13.0 software (Statistical Package for the Social Sciences, Chicago, IL). Differences were considered statistically significant for probability <0.05.

The study was conducted in accordance with the precepts of the Helsinki Declaration and all recorded data were handled anonymously.

3. Results

The baseline characteristics of the entire case series are summarized in Table 1.

The case histories collected included 174 cases of endobronchial metastasis, with a slight prevalence of male patients (54%), an average age of 67 years and a range between 27 and 89 years. Diagnosis of endobronchial metastasis was obtained after a diagnosis of extrapulmonary tumor (metachronous cases) in 154 cases (89%), while in 11 cases (6%) the tumor was detected on an endobronchial level simultaneously to that on the extrapulmonary site (synchronous cases). In the remaining 9 cases (5%), the endobronchial metastasis was the first manifestation of an occult extrapulmonary tumor (anachronous cases). Distribution of the primary tumors and time of endobronchial metastasis occurrence is summarized in Table 2.

It should be noticed that around 50% of anachronous cases were secondary to renal carcinoma. On average, in the overall 18-year period, 5.6 cases of endobronchial metastasis were observed per year (range: 2–17 cases), with statistically significant differences for the periods between 1992–2000 (65 cases, 37%) and 2001–2009 (109 cases, 63%) (p = 0.05).

To allow a better understanding on the extent of the issue and on how this could influence the clinician’s activity, we referred to the bronchoscopy service of the Azienda Ospedaliero-Universitaria Policlinico in Modena to review all the reports of the bronchoscopic investigations performed between 2006 and 2009. In these 4 years, 4208 procedures were performed, 781 (18.5%) on patients for whom endoscopic findings were suggestive of tumors in the tracheobronchial tree. Of note, 31 out of 781 (4%) bronchoscopic examinations revealed endobronchial metastases from nonthoracic malignancies.

Bronchoscopy was performed for the following reasons: radiological features (nodules, masses and hilar-mediastinal and/or peripheral lymphadenomegaly), atelectasis, and symptoms such as dyspnea, haemoptysis and persistent cough. Biopsies were
Table 1
Clinico-pathologic characteristics of patients with endobronchial metastasis.

| Variable                  | Frequency (%) |
|---------------------------|---------------|
| **Sex and age**           |               |
| Male (mean age: 69 years) | 94 (54)       |
| Female (mean age: 66 years) | 80 (46)     |
| **Symptoms**              |               |
| Asymptomatic              | 42 (24)       |
| Cough                     | 38 (22)       |
| Dyspnea                   | 30 (17)       |
| Haemoptysis               | 20 (12)       |
| Dysphonia                 | 2 (1)         |
| Not available             | 24 (14)       |
| **Primary tumors**        |               |
| Breast                    | 52 (30)       |
| Colon-rectum              | 42 (24)       |
| Kidney                    | 24 (14)       |
| Stomach                   | 11 (6)        |
| Prostate                  | 8 (4.5)       |
| Melanoma                  | 8 (4.5)       |
| Thyroid                   | 5 (3)         |
| Endometrium               | 3 (2)         |
| Liver                     | 3 (2)         |
| Small bowel               | 2 (1)         |
| Ovary                     | 2 (1)         |
| Leiomysosarcoma           | 3 (2)         |
| Bladder                   | 2 (1)         |
| Renal pelvis              | 1 (0.5)       |
| Meothelioma               | 1 (0.5)       |
| Solitary fibrous tumor    | 1 (0.5)       |
| Vagina                    | 1 (0.5)       |
| Cervix                    | 1 (0.5)       |
| Esophagus                 | 1 (0.5)       |
| Liposarcoma spermatic cord| 1 (0.5)       |
| Nasopharynx               | 1 (0.5)       |
| Meningioma                | 1 (0.5)       |
| **Type of metastasis**    |               |
| Metachronous              | 154 (89)      |
| Synchronous               | 11 (6)        |
| Anachronous               | 9 (5)         |

* 3 papillary type, 1 each anaplastic and medullary type.
* 2 cutaneous type and 1 uterine type.

Table 2
Distribution of metastasis primary and time of endobronchial metastasis occurrence.

| Primary tumors | Metachronous | Synchronous | Anachronous |
|----------------|--------------|-------------|-------------|
| Breast         | 48 (89%)     | 2 (6%)      | 2 (5%)      |
| Colon-rectum   | 40 (2%)      | 2 (6%)      | 1 (11%)     |
| Kidney         | 19 (4%)      | 1 (6%)      | 1 (11%)     |
| Stomach        | 6 (4%)       | 4 (6%)      | 1 (11%)     |
| Prostate       | 7 (6%)       | 1 (6%)      | 1 (11%)     |
| Melanoma       | 8 (6%)       | 1 (6%)      | 1 (11%)     |
| Thyroid        | 5 (2%)       | 3 (6%)      | 2 (11%)     |
| Endometrium    | 3 (2%)       | 1 (6%)      | 1 (11%)     |
| Liver          | 3 (2%)       | 1 (6%)      | 1 (11%)     |
| Small bowel    | 2 (2%)       | 2 (6%)      | 2 (11%)     |
| Ovary          | 2 (2%)       | 2 (6%)      | 2 (11%)     |
| Leiomyosarcoma | 3 (3%)       | 2 (6%)      | 1 (11%)     |
| Bladder        | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Renal pelvis   | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Meothelioma    | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Solitary fibrous tumor | 1 (2%) | 1 (6%) | 1 (11%) |
| Vagina         | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Cervix         | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Esophagus      | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Liposarcoma spermatic cord | 1 (2%) | 1 (6%) | 1 (11%) |
| Nasopharynx    | 1 (2%)       | 1 (6%)      | 1 (11%)     |
| Meningioma     | 1 (2%)       | 1 (6%)      | 1 (11%)     |

* 3 papillary type, 1 each anaplastic and medullary type.
* 2 cutaneous type and 1 uterine type.

Table 3
Clinico-pathologic characteristics of patients with endobronchial metastasis performed on macroscopically visible endobronchial lesions without complementary methods.

On the full cohort of 174 patients, extrapulmonary tumors most often resulting in endobronchial metastasis included breast carcinoma (52 cases, 30%), colorectal carcinoma (42 cases, 24%), renal carcinoma (24 cases, 14%), stomach carcinoma (11 cases, 6%), prostate carcinoma (9 cases, 5%), and melanoma (8 cases, 4.5%).

Although endobronchial metastases from epithelial-derived tumors (carcinomas) significantly overridden mesenchymal neoplasms (5 cases) and melanomas (8 cases), it is important to notice that virtually all types of solid tumor can metastasize into the bronchial tree. Supporting this, three types of tumor included in the current series (liposarcoma of the spermatic cord, solitary fibrous tumor and cutaneous leiomyosarcoma) have not so far reported in the literature (Figs. 1 and 2).

Although not statistically significant, endobronchial metastases more frequently affected the right (102 cases, 59%) than the left bronchus (72 cases, 41%) (p = 0.07).

The overall median latency period between the detection of extrapulmonary tumor and the occurrence of endobronchial metastasis was 136 months (range, 1–300 months). Among the most frequent extrapulmonary malignancies leading to endobronchial metastasis, a significant difference was observed between breast carcinoma (median, 86 months; range, 1–300 months) or renal carcinoma (median, 82 months; range, 18–270 months) and colorectal carcinoma (median, 53 months; range, 9–168 months) (p < 0.001) (Fig. 3).

### 3.1. Clinico-radiologic features

The patterns of clinical and radiological presentation, ordered by frequency, for the 81 analyzed patients were summarized in Table 3 (supplement material) and Table 4 (supplement material), respectively. Of the collected case histories, 21 patients (26%) were asymptomatic, while the most common symptoms reported were dyspnea, cough and haemoptysis, in 19 (23%), 15 (19%) and 10 (12%) cases respectively. In one single case the only symptom was dysphonia secondary to left laryngeal nerve compression. For 16 patients, the presenting symptoms were not reported in clinical charts.

See Tables 3 and 4 as supplementary files. Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jlungcan.2014.03.005.

Only standard chest x-rays were available for 7 patients, while chest x-rays and CT scans were available for the remaining patients. “Nodules” were defined as lesions with a maximum diameter equal to or less than 30 mm; “masses” were defined as lesions with a diameter over 30 mm; “lymphadenomegaly” was defined as hilar-mediastinal lymph nodes with a maximum diameter over 10 mm. Multiple nodules were present in 43 cases (53%), hilar-mediastinal lymphadenomegaly in 38 cases (47%), a peripheral mass in 24 cases (30%), atelectasis in 23 cases (28%), pleural effusion in 19 cases (23%) and a hilar-mediastinal mass in 13 cases (16%).

### 4. Discussion

Lungs are the commonest site of metastatic deposits from extra-pulmonary malignancies, but metastases presenting as endobronchial growth are quite unusual and epidemiologic and/or clinic-pathologic data on large homogeneous series are lacking. The present study collected the largest series to date of consecutive endobronchial metastases from extrapulmonary tumors disclosed in routine practice without selection biases (174 cases), underlying the clinically relevant occurrence of this phenomenon.
Among all bronchoscopic procedures performed in the suspicion of lung tumor, the overall incidence was about 4% per year, a figure higher than 1% reported by Kreisman et al. in 1983 [31]. However, this result is difficult to compare with epidemiological references of other studies, due to the variability of classification criteria in considering endobronchial metastasis, the length and type of the period of time considered as well as the different ethnic background of the study including malignancies with different incidence. It could be reasonable to assume that the increasing number of diagnostic procedures, including bronchoscopy examinations, performed in the current work-up of oncologic patients has lead to higher possibility to disclose endobronchial metastases.
In literature, endobronchial metastases generally were reported as single case descriptions or very limited case series [4,8,32,33]. Although the development of pulmonary metastases is in fact a common occurrence, their endobronchial location is considered to be a rare event. Frequency estimates are still based on rather outdated studies and primarily on autopsy series [3,6], but it can vary considerably depending on the study and the definition of endobronchial metastasis, ranging from 2 to 50% [3,4,12-16,32,33]. Therefore, the epidemiology of this type of metastasis is still quite unclear.

In our bronchoscopy service, endobronchial metastasis was diagnosed in 4% of the biotic procedures performed as a result of suspected malignancy. Considering that bronchoscopy is not routinely performed on all patients with tumors, it may be implied that both incidence and frequency of endobronchial metastases are probably underestimated.

The latency period between primary extrapulmonary tumor and endobronchial metastasis may be very long [36].

For patients presenting with tumors that most commonly cause endobronchial metastasis, the systematic use of chest CT scans and bronchoscopy could be useful. In particular, breast, colon and renal lesions are reported in the literature as being most often associated with endobronchial metastasis [17-24,32,33]. This finding was confirmed in our study that reported how tumors arising in these sites account for over 60% on the total (see Table 1). For gastric cancer, prostate carcinoma and melanoma, accounting for 16% of endobronchial metastases in our case series, careful monitoring of the tracheobronchial tract could also facilitate the detection of secondary lesions in a greater number of cases.

Another interesting aspect concerns the capacity of virtually all solid tumors of various cell differentiation to produce endobronchial metastases. So far, this fact was only documented by sporadic single case descriptions [25-30]. Regarding the clinical/radiological presentation, collected data strongly confirm the literature findings [3-6,10,11,32,33], and reassert evidence of a presentation that is difficult to differentiate from that of a primary pulmonary tumor. Among 81 patients for which complete clinico-radiologic data were available, 21 (26%) were entirely asymptomatic. Previous studies, depending on the case histories included, reported a highly variable percentage of asymptomatic patients, ranging from 0 to 52% of cases [8-10,14,32,33]. When present, dyspnea, cough and haemoptysis were the most common symptoms. Radiological findings evidenced multiple pulmonary nodules and hilar- mediastinal lymphadenomegaly as the most frequent conditions, detected in about half of the examined cases. A peripheral mass and atelectasis were reported in about 1/3 of cases, while pleural effusion and hilar-mediastinal masses were less common.

In some cases, radiological differential analysis vs primitive tumor was extremely difficult, as showed in Fig. 4 where radiological appearance strikingly suggested a primary lung cancer presenting as an excavated pulmonary mass, but the patient had an unknown renal cell carcinoma. In most cases, a diagnosis of endobronchial metastasis follows the diagnosis of the primary lesion, with a largely variable time interval between them. Our data evidenced an average interval of 134 months, with a very
Distal tumor typing of the described lesions was of insignificant value (Fig. 5). All the carcinomas, including some malignant neoplasms, demonstrated areas of hemorrhage, necrosis, and extracellular matrix deposition. The tumor cells showed varying degrees of pleomorphism and mitotic activity, with occasional foci of giant cell formation. Immunohistochemical staining with antibodies against desmin and vimentin was positive in most cases, and the Ki-67 proliferation index ranged from 10% to 50%. The histologic features were consistent with a diagnosis of leiomyosarcoma, which is a rare and aggressive tumor of smooth muscle origin.

In conclusion, the current study represents the largest series of consecutive extrapulmonary tumors presenting with endobronchial metastases. The diagnostic approach, which included imaging studies, bronchoscopic evaluation, and histologic examination, was crucial in establishing the correct diagnosis. The role of cytopathology and molecular testing cannot be overstated, as they provided critical information for the management of these patients. The findings of this study highlight the importance of a multidisciplinary approach in the diagnosis and management of endobronchial metastases.

Conflict of interest statement
No conflicts of interest for all authors.

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