Endobronchial Mucosa-associated Lymphoid Tissue Lymphoma: A Report of Two Cases and a Review of the Literature

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Abstract:
Primary endobronchial mucosa-associated lymphoid tissue lymphoma (EML) is rare. We reviewed 20 cases of EML, including ours and case reports. We found that the location of tumor in 70% of these cases was limited to the trachea and main bronchi, and the form of tumor in 61% of these cases was several nodular protrusions. If a patient exhibits these characteristics, adequate specimen collection on bronchoscopy is important. Because the prognosis for patients with EML is good, tumors on the trachea and main bronchi should be treated, while those on the peripheral airway can be watched carefully.

Key words: endobronchial tumor, primary pulmonary lymphoma, MALT lymphoma

(Intern Med 57: 2233-2236, 2018)
(DOI: 10.2169/internalmedicine.0150-17)

Introduction

Primary tracheal and bronchial tumors are relatively rare, as is primary pulmonary lymphoma (PPL). PPL represents only 0.5-1% of lung neoplasia cases, and most of these are extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (1). The presence of an immune system disorder was identified as a predisposing factor for the development of pulmonary MALT lymphoma (PML), and its distinctive computed tomography (CT) findings are associated with bilateral/multiple lesions and air bronchogram.

Because MALT lymphomas on the trachea and bronchus (endobronchial MALT lymphoma: EML) are rarer still, very few reviews are available. In this study, we reviewed 20 cases of EML, including ours and case reports.

Case Reports

Case 1

A 77-year-old Japanese man with a history of rheumatoid arthritis and hypertension was referred to Miyazaki Prefectural Miyazaki Hospital after a lung cancer screening by low-dose computed tomography (CT). The patient was asymptomatic; however, chest CT revealed endobronchial protrusion and narrowing of the right lower lobar bronchus (LLB). On positron emission tomography (PET)-CT, the lesion and bilateral hilar and mediastinal lymph nodes appeared hypermetabolic (SUVmax 4.6). The patient’s soluble interleukin-2 receptor (sIL-2R) was within the normal range. On flexible bronchoscopy, several nodular protrusions in the right LLB were observed, and the superficial mucosa appeared to be free of infiltration, friability, or discoloration (Fig. 1). An endobronchial forceps biopsy was performed. Biopsy specimens showed diffuse and monotonous infiltration of medium-sized lymphoid cells in the alveolar tissue

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Received: August 30, 2017; Accepted: December 28, 2017; Advance Publication by J-STAGE: March 9, 2018
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and fibrous connective tissue. Immunohistochemically, these lymphoid cells were selectively positive for CD20 and CD79a but negative for CD3, CD45RO, or AE1/AE3. A low MIB-1 index of less than 10% was noted. No definite light chain restriction was detected by kappa/lambda-ISH. We made a diagnosis of EML. Because he was asymptomatic, the patient selected careful watchful waiting.

**Case 2**

A 62-year-old Japanese man with chronic obstructive pulmonary disease (COPD) was involved in a traffic accident. During CT screening for trauma, several nodular protrusions on the carina were observed (Fig. 2A). The patient was referred to our hospital. The findings on a physical examination were normal. PET-CT showed nodular protrusions and bilateral hilar and mediastinal lymph nodes that were hypermetabolic (SUVmax 5.3). The patient's sIL-2R was within the normal range. On flexible bronchoscopy, several nodular protrusions with a surface prone to bleeding on the carina were observed (Fig. 2B), and an endobronchial forceps biopsy was performed. Biopsy specimens showed monotonous infiltration of small to medium-sized lymphoid cells in the mucosa. Immunohistochemically, these lymphoid cells were selectively positive for CD20 and CD79a but negative for CD45RO. A low MIB-1 index of less than 10% was noted. Flow cytometry showed these cells to be positive for CD20, CD20, and κ-chain. The findings of a chromosomal analysis were normal. Based on the morphologic, immunophenotypic, and molecular biological findings, we made a diagnosis of EML. Since a tumor on the carina can cause central airway obstruction, we treated the patient with radiotherapy. A total of 50 Gy was administered, resulting in a complete response of the tumor (Fig. 2C). The patient was administered rituximab as consolidation therapy.

**Discussion**

Primary tracheal and bronchial tumors are rare. Gelder et al. reviewed 321 primary tracheal tumors and reported that 54.2% were squamous cell carcinoma (SCC), 10.6% were adenoid cystic carcinoma (ACC), and only 4 out of 321 (1.2%) were lymphoma (2). Bronchus-associated lymphoid tissue (BALT) can be found in follicular bronchiolitis and can be associated with various autoimmune disorders, such as Sjögren’s syndrome, but is not found in the normal lung (1). When a primary PML develops from BALT, it is known as BALT lymphoma. While several case reports on EML are available, few reviews of its clinical characteristics have been published. In this study, we reviewed 20 cases of EML, including our own and case reports. The Table shows the main clinical characteristics of the patients at the presentation.

The average age of the reviewed cases was 59 years. Eleven patients (55%) were women. Two patients (10%) had autoimmune disease. These results were similar to those for PML (1, 3). The location of the tumor in 14 patients (70%) was the central airway, and 4 patients (20%) had lobar atelectasis. The smoking rate (50%) was higher among individuals who developed EML than among those with PML or the general population (3). Three patients (15%) had chronic airway disease. Three patients had malignancy. Two patients (10%) had autoimmune disease. These results were

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**Figure 1.** An endobronchial polypoid lesion in the lower lobar bronchus.

**Figure 2.** (A) Chest computed tomography showing nodular lesions on the carina. (B) Several endobronchial nodular protrusions on the carina. (C) Bronchoscopic observation of the trachea after radiotherapy.
Table. List of the Case Reports of the Endobronchial MALT Lymphoma.

| No | Reference | Age | Sex | Co-Morbidity | Location | CT | Endobronchial lesion pattern | Treatment | Follow-up |
|----|-----------|-----|-----|--------------|----------|----|----------------------------|-----------|----------|
| 1  | 5         | 77  | M   | None         | Left MB  |    | Air trapping               | CTx       | 19       |
| 2  | 5         | 48  | F   | None         | Right BI |    | Atelectasis                | ND        | 42       |
| 3  | 6         | 44  | M   | Prostate cancer, MM & HTN | Right LLB |    | Atelectasis                | ND        | 36       |
| 4  | 7         | 46  | M   | None         | Left LLB |    | Diffuse wall thickening    | ND        | 10       |
| 5  | 8         | 83  | F   | Rheumatoid arthritis | Trachea/both MB |    | Atelectasis                | ND        | 25       |
| 6  | 9         | 54  | F   | None         | Trachea/both MB |    | Bronchopneumonia          | ND        | 12       |
| 7  | 10        | 44  | F   | Allergic rhinitis | Trachea/both MB |    | Diffuse wall thickening    | CTx       | 6        |
| 8  | 10        | 48  | F   | None         | Trachea  |    | Solitary intraluminal nodule | RTx       | 30       |
| 9  | 10        | 21  | F   | Allergic rhinitis | Trachea  |    | Solitary intraluminal nodule | Cryo Tx   | 5        |
| 10 | 10        | 57  | F   | None         | Left LLB |    | Air trapping               | Solitary intraluminal nodule | None       | 48       |
| 11 | 10        | 58  | F   | None         | Left ULB |    | Atelectasis                | Solitary intraluminal nodule | RTx       | 36       |
| 12 | 10        | 61  | M   | None         | Trachea  |    | Atelectasis                | Solitary intraluminal nodule | RTx       | 1        |
| 13 | 11        | 49  | F   | None         | Trachea/both MB |    | Several nodular protrusions | Stent/CTx | 12       |
| 14 | 12        | 61  | M   | Small cell lung cancer | Trachea/both MB |    | Nodule                     | Several nodular protrusions | CTx       | ND       |
| 15 | 12        | 82  | M   | Duodenal ulcer | Trachea/both MB |    | Diffuse wall thickening    | CTx       | ND       |
| 16 | 13        | 93  | F   | Breast cancer, HTN & AD | Trachea/both MB |    | Several nodular protrusions | CTx       | 5        |
| 17 | 14        | 50  | M   | Hepatitis C & cryoglobulinemia | Carina, right MB & BI |    | Several nodular protrusions | CTx       | 12       |
| 18 | 14        | 54  | F   | Hepatitis C | Trachea  |    | Several nodular protrusions | Cryo Tx   | 3        |
| 19 | case 1    | 77  | M   | Rheumatoid arthritis & HTN | Right LLB |    | Several nodular protrusions | None       | 19       |
| 20 | case 2    | 62  | M   | COPD         | Carina   |    | Several nodular protrusions | RTx/CTx   | 25       |

MM: malignant melanoma, HTN: hypertension, AD: Alzheimer’s disease, COPD: chronic obstructive pulmonary disease, CT: computed tomography, ND: no data, BI: bronchus intermedius, LLB: lower lobar bronchus, MB: main bronchus, ULB: upper lobar bronchus, RLL: right lower lobe, LLL: left lower lobe, CTx: chemotherapy, RTx: radiotherapy, Cryo Tx: cryotherapy
nodular protrusions, 22% had solitary intraluminal nodules and 17% had diffuse wall thickening. Hiraishi et al. reported two cases with EML, and found that the characteristic features of EML were multiple, widely stalked, fleshy polyps covered with smooth bronchial mucosa (12). These characteristics are shared by both of our cases but are in contrast to the major pathological type of endobronchial tumors, SCC and ACC, which usually present as a solitary polyp. We believe that the lesion pattern of several nodular protrusions is an important finding suggestive of EML.

Controversy persists regarding the utility of PET-CT findings in evaluating MALT lymphoma. Although the PET-CT findings were positive in both of our cases, Yoon et al. reported that PET-CT findings were negative in three of seven patients with EML (10). Recently, Albano et al. reported that pulmonary lymphoma is FDG-avid in most cases, and FDG avidity is correlated with the tumor size (15).

The diagnosis of MALT lymphoma is based on the identification of morphologic, immunophenotypic, genotypic, and molecular features, including flow cytometry of the tumor (WHO recommendation). However, evaluating such features is difficult at times due to the small size of the specimens collected by bronchoscopy. In the case of Dincer et al., a second bronchoscopy was performed to obtain more specimens (7). Because a molecular biological analysis uses fresh or frozen tissue samples, the freeze-preservation of biopsy tissue is important if EML is suspected. In our second case, since the morphological and immunohistochemical features were not sufficient to establish a diagnosis of lymphoma, flow cytometry and chromosomal analyses were performed using a frozen tissue sample.

The prognosis for patients with MALT lymphomas is good, with overall 5-year survival rates surpassing 80% and median survival rates of over 10 years (3). No fatal cases were reported in the follow-up period in our study, which ranged between 1-48 months. The prognosis for patients with EML is likely also good. The main therapeutic options for PML include surgery, chemotherapy and radiotherapy. Most of the cases we evaluated underwent chemotherapy and/or radiotherapy, and two patients had undergone chemotherapy. There were no cases of recurrence. Two patients selected careful watchful waiting. Ding et al. reported a case with tracheal obstruction treated successfully with tracheal stenting (11). It seems reasonable to treat tumors on the trachea and main bronchus and carefully watch those on the peripheral airway. It is necessary to follow up patients opting for non-treatment for an extended period.

In conclusion, a tumor location limited to the trachea and main bronchus, and a tumor form of several nodular protrusions were characteristic features of EML. In patients exhibiting these characteristics, adequate specimen collection on bronchoscopy is important. Because the prognosis for patients with EML is good, tumors on the trachea and main bronchus should be treated, while those on the peripheral airway can be watched carefully.

The authors state that they have no Conflict of Interest (COI).

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