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【 CASE REPORT 】

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 bronchus, 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 bronchus should be treated, while those on the peripheral airway can be watched carefully.

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

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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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and fibrous connective tissue. Immunohistochemically, these lymphoid cells were selectively positive for CD20 and CD 79a 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 CD19, 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.

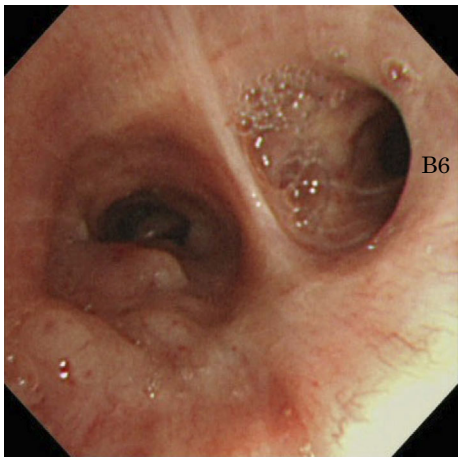

Figure 1. An endobronchial polypoid lesion in the lower lobar bronchus.

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

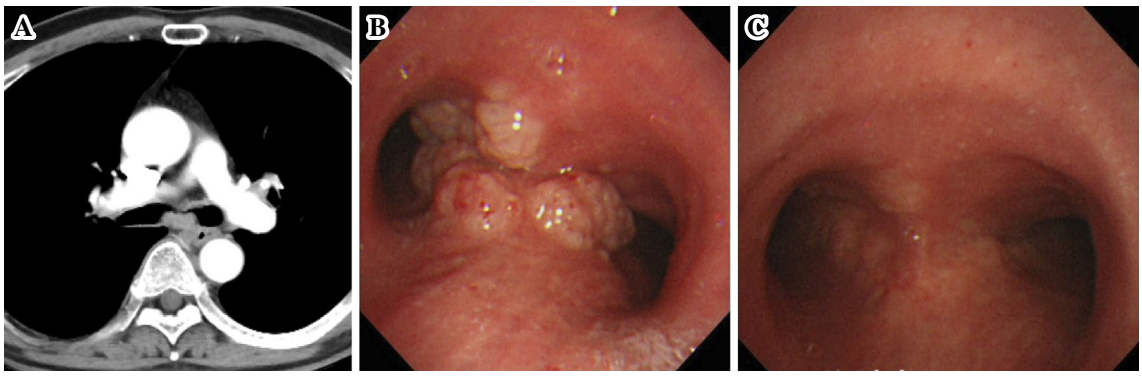

Figure 2. (A) Chest computed tomography showing nodular lesions on the carina. (B) Several endobronchial nodular protrusions on the carina. (C) Bronchoscopic observation of the trachea after radiotherapy.

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	32	F	None	Left MB	Air trapping	Several nodular protrusions	CTx	36
2	6	61	M	-	Right BI	Atelectasis	ND	RTx	48
3	7	82	M	Prostate cancer, MM & HTN	Right LLB	-	Diffuse wall thickening	ND	ND
4	8	46	M	-	Left LLB	Atelectasis	ND	CTx	10
5	9	83	F	-	Trachea/both MB	Atelectasis	Several nodular protrusions	CTx	ND
6	10	54	F	Rheumatoid arthritis	Trachea/right MB	Bronchopneumonia	Diffuse wall thickening	CTx	10
7	10	44	F	Allergic rhinitis	Trachea/both MB	-	Several nodular protrusions	CTx	25
8	10	48	F	-	Trachea	-	Solitary intraluminal nodule	RTx	42
9	10	21	F	Allergic rhinitis	Trachea	-	Solitary intraluminal nodule	Cryo Tx	5
10	10	57	F	-	Left LLB	Air trapping	Solitary intraluminal nodule	None	48
11	10	58	F	-	Left ULB	Atelectasis	Solitary intraluminal nodule	RTx	36
12	10	61	M	-	Trachea	-	Several nodular protrusions	RTx	1
13	11	49	F	-	Trachea/left MB	-	Several nodular protrusions	Stent/CTx	12
14	12	61	M	Small cell lung cancer	Trachea/left MB	Nodule	Several nodular protrusions	CTx	ND
15	12	82	M	Duodenal ulcer	Trachea	-	Diffuse wall thickening	CTx	ND
16	13	93	F	Breast cancer, HTN & AD	Trachea/left MB	-	Several nodular protrusions	CS	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

similar to those seen in cases of immune system disorder in PML. Two patients were positive for hepatitis C virus (HCV). Although a relationship between HCV infection and splenic marginal zone lymphoma has been established (4), no reports describe the relationship between PML and viral infection.

Yoon et al. reviewed seven patients with EML and reported the endobronchial lesion patterns (10). They classified the lesions into three patterns: solitary intraluminal nodules, several nodular protrusions and diffuse wall thickening. We adopted this classification for our study. Eleven (61%) out of 18 patients whose data were available had several

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 cryotherapy. 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 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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