Small Cell Lung Cancer Accompanied by Tonsillar Metastasis and Anti-Hu Antibody-Associated Paraneoplastic Neuropathy

A Rare Case Report With Long-Term Survival

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Abstract: Tonsillar metastatic small cell lung cancer (SCLC) is rare, while anti-Hu antibodies are frequently found in SCLC. A 66-year-old man was admitted to our hospital with painful dysesthesia and muscle weakness in the distal extremities for over 1 year, progressive dysphagia for over 1 month, and severe cough and dyspnea for over 1 week. He was diagnosed with SCLC accompanied by tonsillar metastasis and anti-Hu antibody-associated paraneoplastic sensory neuropathy (PSN). The patient tolerated 6 cycles of sequential chemoradiotherapy and gradually recovered. The patient’s disease remained in remission 2 years after the diagnosis with a remarkable reduction of tumor burden and a persisting high titer of anti-Hu antibodies. To our knowledge, this is the first case of tonsillar metastatic SCLC accompanied by anti-Hu antibody-associated PSN, whereby the anticancer immune response was presumed to play a vital role in disease control.

Unilateral tonsillar metastasis of SCLC accompanied by anti-Hu antibody-associated PSN can occur and in certain circumstances, may have a favorable prognosis.

(INTRODUCTION

The tonsil is a rare site in which to find a metastasis, the latter accounting for only 0.8% of all tonsillar tumors, and there is only 1 case of unilateral tonsillar metastasis of small cell lung cancer (SCLC), from left lung to right tonsil, in the scientific literature.1-3 Anti-Hu antibodies are frequently detected in multiple cancers, especially in SCLC, and cause a spectrum of neurological paraneoplastic syndromes, including cerebellar ataxia, limbic encephalitis, Lambert–Eaton syndrome, polyradiculopathy, opsoclonus-myoclonus syndrome, and most commonly, paraneoplastic sensory neuropathy (PSN).4

Here, we present an unusual case of long-term survival in a patient with SCLC accompanied by unilateral tonsillar metastasis and anti-Hu antibody-associated PSN. To our knowledge, this is the first case of a metastatic small cell carcinoma to the tonsil with anti-Hu antibody-associated PSN.

CASE PRESENTATION

In March 2013, a 66-year-old man who was a heavy smoker, presented with painful dysesthesia and muscle weakness in his hands and feet for over 1 year, progressive dysphagia for over 1 month, and severe cough and dyspnea for over 1 week. Physical examination showed a large mass arising from the right tonsil (Figure 1) and several enlarged firm lymph nodes in the right cervical region. Deep tendon reflexes and sensation of the distal extremities were significantly weakened. Lab tests found an increase of neuron-specific enolase (NSE) level (65.2 U/L). Chest computed tomography (CT) demonstrated a mass at the hilum of the left lung, along with severe atelectasis and pleural effusion (Figure 2).

The patient’s general condition deteriorated rapidly, and high fever, apnea, and occasional loss of consciousness developed subsequently. Biopsy of the right tonsil revealed a high-grade small cell carcinoma positive for thyroid transcription factor 1. A high titer of anti-Hu antibodies was also detected and subsequent electromyography confirmed the existence of sensory axonal polyneuropathy of the distal extremities. Consequently, tonsillar metastasis of a SCLC with anti-Hu antibody-associated PSN was suspected.

In April 2013, local radiotherapy of the left lung as well as antibiotics was administered to control the symptoms. Later on, systemic chemotherapy with cisplatin and etoposide was introduced. After 2 cycles of sequential chemoradiotherapy, the patient’s situation gradually improved, and a fiberoptic bronchoscopy was then successfully carried out. The ensuing histological examination supported the diagnosis of SCLC. At the same time, positron emission tomography-computed tomography (PET-CT) was performed, and a nodule in the left lung was detected, in addition to the right tonsillar mass, which exhibited elevated FDG activity. Meanwhile, brain magnetic
resonance imaging found no metastatic deposits in the patient’s central nervous system. Therefore, unilateral tonsillar metastasis of SCLC with anti-Hu antibody-associated PSN was diagnosed.

Afterward, the patient received another 4 cycles of chemotherapy by August 2013 and NSE levels dropped into the normal range (~9.2–10.6 U/L), with a considerable alleviation of his major symptoms. The patient was then discharged and followed up in the clinics every 3 months. Prophylactic cranial irradiation was carried out in January 2014 when the patient was in good condition, and a follow-up CT scan detected recurrent disease neither in the primary site nor in the tonsil. The patient’s disease remained in remission and the progression-free survival exceeded 2 years. The CT scan, performed at the latest follow-up in May 2015, revealed a complete regression of the tonsillar mass and a significant shrinkage of the left pulmonary nodule (Figure 3). Despite a significant reduction of tumor burden and a remarkable improvement in his general condition, the titer of anti-Hu antibodies remained high and the patient still complained of numbness and weakness in his distal extremities.

**DISCUSSION**

SCLC accounts for 13% of all newly diagnosed lung cancer cases worldwide and is one of the leading causes of cancer-related death. A majority of patients with SCLC will be
diagnosed when there is extensive disease, with metastatic lesions spreading to multiple organs. Distant metastases usually involve the liver, bones, brain, abdominal lymph nodes, adrenal gland, skin, kidneys, and the pancreas. Tonsillar metastasis of SCLC is quite rare, with only a few cases reported.

In various cancers, tumor cells can ectopically express one of the Hu antigens, which are normally expressed throughout the nervous system, and trigger a vigorous immune response, leading to a spectrum of neuropathological lesions. Furthermore, anti-Hu antibodies have been shown to indicate an underlying neoplasm in 88% of cases, most of which are SCLC and in more than 80% of the cases, unexplainable neurological manifestations accompanied by high circulating titers of anti-Hu antibodies precede the cancer diagnosis.

The prognosis of patients with extensive stage SCLC is dismal and the median progression-free survival is about 6 months. Similarly, the average life expectancy of patients with tonsillar metastases was reported to be less than 9 months, unrelated with the histology of the primary tumor. However, our patient was still alive, with no signs of disease progression 2 years after the diagnosis. It is interesting to note that patients with SCLC and positive anti-Hu antibodies generally have a better prognosis, especially for those who did not manifest an anti-Hu antibody-associated syndrome but harbored low titers of anti-Hu antibodies, as they tend to respond better to therapy and live longer than cancer patients not producing anti-Hu antibodies. In addition, extraordinary long-term survival of patients with SCLC accompanied by anti-Hu antibody-associated PSN has been reported.

Accumulating evidences suggests that an anti-Hu antibody-triggered antitumor immune response may play an important role in tumor rejection and disease control and immunotherapies based on this hypothesis are under development. The symptoms of PSN still bothered our patient and it has been reported that anti-Hu antibody-associated paraneoplastic neuropathy can continue to progress even after tumor remission. The currently proposed immunosuppressive therapies such as plasma exchange, intravenous immunoglobulin G, and cyclophosphamide are generally unsatisfactory, and sometimes in SCLC patients with anti-Hu antibody-associated paraneoplastic neuropathy, the prognosis may depend on the outcome of the neurological disorders rather than on tumor progression. However, it is widely perceived that potent immunosuppressive modulation may favor tumor growth and disease flare. Consequently, novel treatment approaches are highly needed and an intensive investigation of the biology of Hu antigen-specific cytotoxic T-lymphocytes should be carried out.

Our study has limitations and we could not rule out a differential diagnosis. Although extremely rare, primary small cell carcinoma of the tonsil has been reported and it can metastasize to the lung. Without cutting-edge technologies such as transcriptome and proteomic analyses, it is quite difficult to discern the origin of the primary tumor site, in case of synchronous tumor masses. However, the treatment modalities for these 2 diagnoses are almost the same and the patient is doing well under current management.

CONCLUSIONS

Unilateral tonsillar metastasis of SCLC is rare, but it does occur. To the best of our knowledge, this is the first case of tonsillar metastatic SCLC accompanied by anti-Hu antibody-associated PSN. An antitumor immune response may have played an important role in the disease control.

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FIGURE 3. Contrast-enhanced computed tomography scan at follow-up performed in May 2015. Two years after the diagnosis, the pulmonary atelectasis and pleural effusion were completely resolved. The remaining mass close to the left pulmonary artery showed mild enhancement.
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REFERENCES

1. Hisa Y, Yasuda N, Murakami M. Small cell carcinoma of the lung metastatic to the palatine tonsil. Otolaryngol Head Neck Surg. 1997;116:563–564.

2. Unsal M, Kutlar G, Sulu Y, Yurtlu S, et al. Tonsillar metastasis of small cell lung carcinoma. Clin Respir J. 2015doi: 10.1111/crj.12275. [Epub ahead of print].

3. Kim EJ, Kim SR, Jin Gang S, et al. Tonsillar metastasis of small cell lung cancer in a patient with idiopathic pulmonary fibrosis: a case report. Medicine (Baltimore). 2015;94:e565.

4. Koike H, Tanaka F, Sobue G. Paraneoplastic neuropathy: wide-ranging clinicopathological manifestations. Curr Opin Neurol. 2011;24:504–510.

5. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011;378:1741–1755.

6. Seddon DJ. Tonsillar metastasis at presentation of small cell carcinoma of the lung. J R Soc Med. 1989;82:688.

7. Arroyo HH, Takehara J, Ogawa AI, et al. Small cell lung carcinoma metastasis to palatine tonsils. Braz J Otorhinolaryngol. 2013;79:645.

8. Chen XH, Bao YY, Zhou SH, et al. Palatine tonsillar metastasis of small-cell neuroendocrine carcinoma from the lung detected by FDG-PET/CT after tonsillectomy: a case report. Iran J Radiol. 2013;10:148–151.

9. Pignolet BS, Gebauer CM, Liblau RS. Immunopathogenesis of paraneoplastic neurological syndromes associated with anti-Hu antibodies: a beneficial antitumor immune response going awry. Oncoimmunology. 2013;2:e27384.

10. Graus F, Keime-Guibert F, Rehe R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001;124:1138–1148.

11. Darnell RB, DeAngelis LM. Regression of small-cell lung carcinoma in patients with paraneoplastic neuronal antibodies. Lancet. 1993;341:21–22.

12. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;385:36–42.

13. Graus F, Dalmou J, Rehé R, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. J Clin Oncol. 1997;15:2866–2872.

14. Poepel A, Jarius S, Heukamp LC, et al. Neurological course of long-term surviving patients with SCLC and anti-Hu syndrome. J Neurol Sci. 2007;263:145–148.

15. Ehrlich D, Wang B, Lu W, et al. Intratumoral anti-HuD immunotoxin therapy for small cell lung cancer and neuroblastoma. J Hematol Oncol. 2014;7:91.

16. Sehdev A, Zhao Y, Singh AK, et al. Primary small cell carcinoma of the tonsil: a case report and review of the literature. Case Rep Oncol. 2012;5:537–541.