



## CASE REPORT

# Expectoration of tonsillar metastasis of pulmonary pleomorphic carcinoma after pseudoprogression: A case report

Tomoki Kuge  | Fukuko Okabe | Yuji Yamamoto | Mikako Ishijima |  
Takeshi Uenami | Masaki Kanazu  | Yuki Akazawa | Yukihiro Yano |  
Toshihiko Yamaguchi | Masahide Mori

Department of Thoracic Oncology, National Hospital Organization Toneyama National Hospital, Osaka, Japan

**Correspondence**

Masahide Mori, Department of Thoracic Oncology, National Hospital Organization Osaka Toneyama Medical Center, 5-1-1 Toneyama, Toyonaka-city, Osaka 560-8552, Japan.  
Email: mori.masahide.fr@mail.hosp.go.jp

**Abstract**

Pulmonary pleomorphic carcinoma is a rare malignant tumor that grows rapidly and has a poor prognosis. Although no effective treatments have so far been established, immune checkpoint inhibitors (ICIs) have shown clinical improvement in some cases of pleomorphic carcinoma. However, pseudoprogression is a major concern for treatment of this carcinoma using ICIs. Here, we report the case of a 61-year-old man who was diagnosed with large cell carcinoma of the lung with brain metastases. Systemic chemotherapy comprising carboplatin and pemetrexed was administered as a first-line therapy; however, disease progression was observed. A tonsillar lesion grew rapidly after the administration of nivolumab as a second-line therapy. Tracheostomy was planned to avoid suffocation, but the patient naturally expectorated the tumor. Pathological examination revealed that it was a palatine tonsillar metastasis of pulmonary pleomorphic carcinoma with infiltration of CD8+/CD4- lymphocytes and necrosis. The primary lesion expanded after nivolumab administration and shrank with no additional nivolumab administration. We therefore concluded that pseudoprogression caused expectoration of the tonsillar metastasis. Hence, ICIs can cause serious adverse events due to pseudoprogression.

**KEYWORDS**

immune checkpoint inhibitor, nivolumab, pseudoprogression, pulmonary pleomorphic carcinoma, tonsillar metastasis

**INTRODUCTION**

Tonsillar metastasis is rare among tonsillar carcinomas, accounting for 0.8% of malignant tonsillar neoplasms.<sup>1</sup> Conversely, pulmonary pleomorphic carcinoma is a rare malignant tumor of the lung and its incidence has been reported to be 0.1%–0.4% among all lung cancers.<sup>2</sup> To the best of our knowledge, only one case of tonsillar metastasis of pulmonary pleomorphic carcinoma has been previously reported.<sup>3</sup>

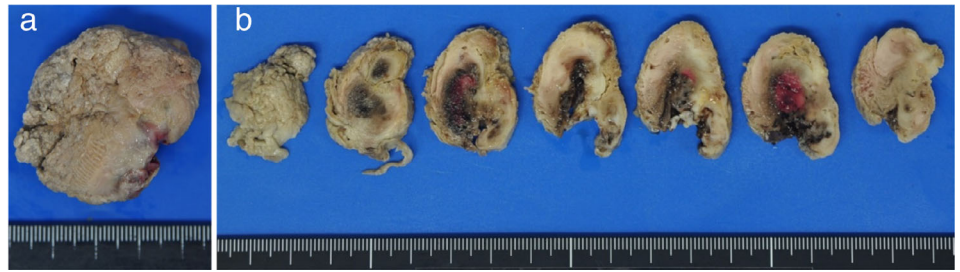
Pulmonary pleomorphic carcinoma has a poor response to systemic chemotherapy and a more progressive clinical course than other types of non-small cell lung cancers (NSCLCs). No effective treatments have so far been established. Immune checkpoint inhibitors (ICIs) have been recently reported to be effective for the treatment of

various cancers, and there are several reports on their effectiveness for the treatment of pulmonary pleomorphic carcinoma.<sup>4</sup> Here, we report an extremely rare case of expectoration of tonsillar metastasis of pulmonary pleomorphic carcinoma following nivolumab treatment.

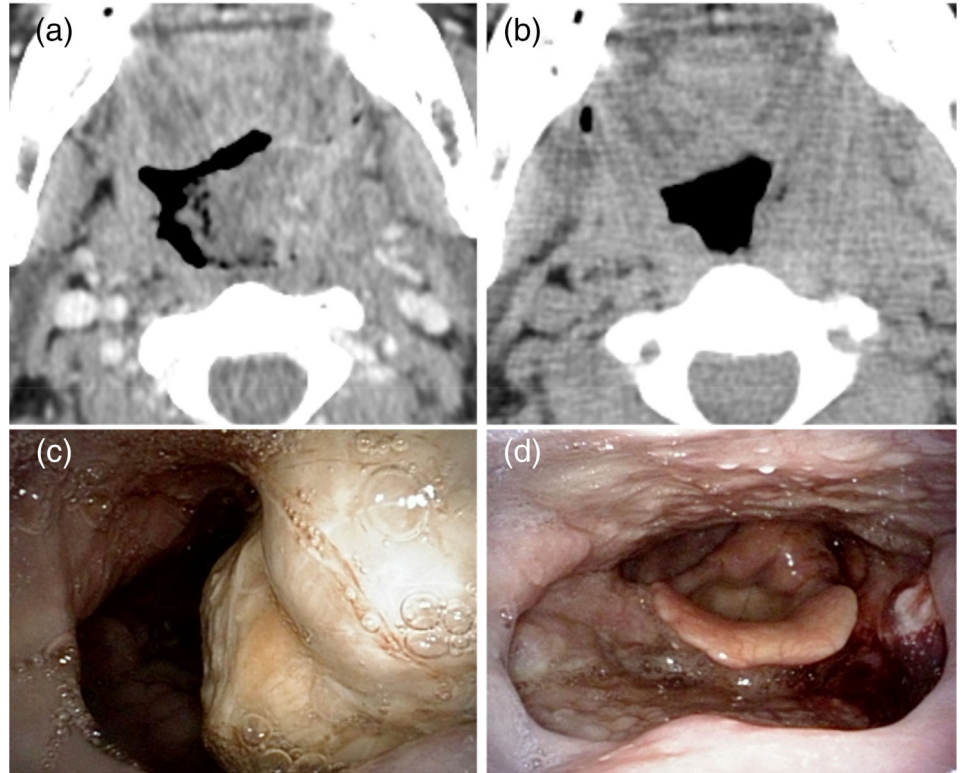
**CASE REPORT**

A 61-year-old man complained of headache, dizziness, and right tinnitus for a week. Magnetic resonance imaging (MRI) showed masses in the dorsal midbrain and right occipital lobe. Moreover, computed tomography revealed a mass in the lower lobe of the right lung. As we were concerned about the deterioration of neurological symptoms in

**FIGURE 1** (a) Macroscopic findings showing the expectorated tonsillar metastasis. (b) Tumor necrosis confirmed in a tissue section



**FIGURE 2** (a) Computed tomography (CT) showing the tonsillar metastasis occupying the pharynx before its expectoration and (b) pharyngeal occupation was improved after expectoration of the metastatic lesion. (c) Laryngoscopy showing tonsillar metastasis occupying the pharynx before its expectoration and (d) pharyngeal occupation was improved after expectoration of the metastatic lesion



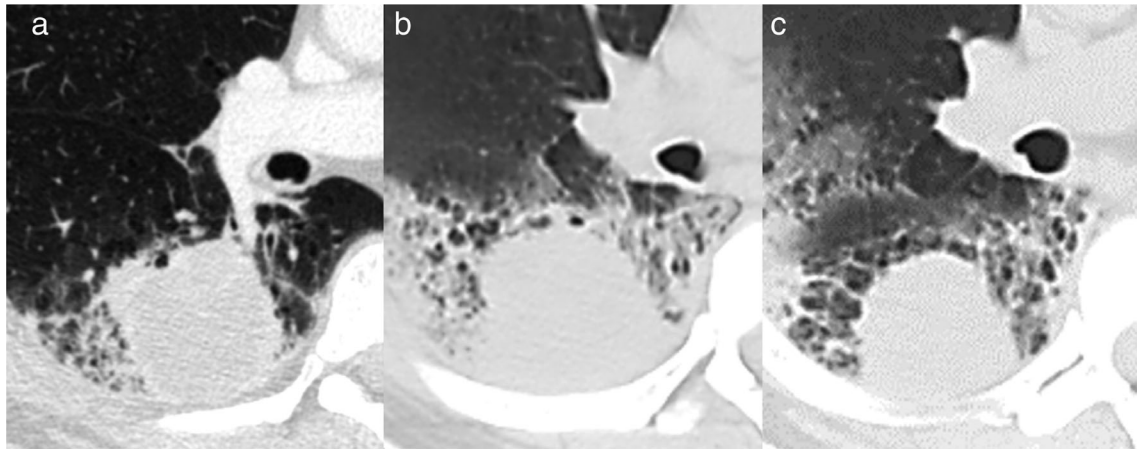
this patient, a brain biopsy was performed and metastasis of large cell carcinoma of the lung, wild-type epidermal growth factor receptor and anaplastic lymphoma kinase negative, was diagnosed. 18F-fluorodeoxyglucose positron emission tomography showed abnormal uptake in the lung tumor, left palatine tonsil, pancreas, and bilateral adrenal glands. Higher brain dysfunction remained because of hydrocephalus after gamma knife radiosurgery for the brain metastases.

Systemic chemotherapy comprising carboplatin and pemetrexed was initiated as first-line therapy for the lung cancer. However, there was evidence of disease progression in spite of administration of two cycles of chemotherapy. The patient received nivolumab as a second-line therapy but complained of fever and sore throat the same evening. We suspected tonsillitis based on his symptoms and antibiotics were administered. Whilst his subjective symptoms improved, the laboratory data did not. He was referred to the otolaryngology department at another hospital. A pathological diagnosis of metastasis of lung pleomorphic carcinoma was obtained from the biopsy of a left tonsillar lesion.

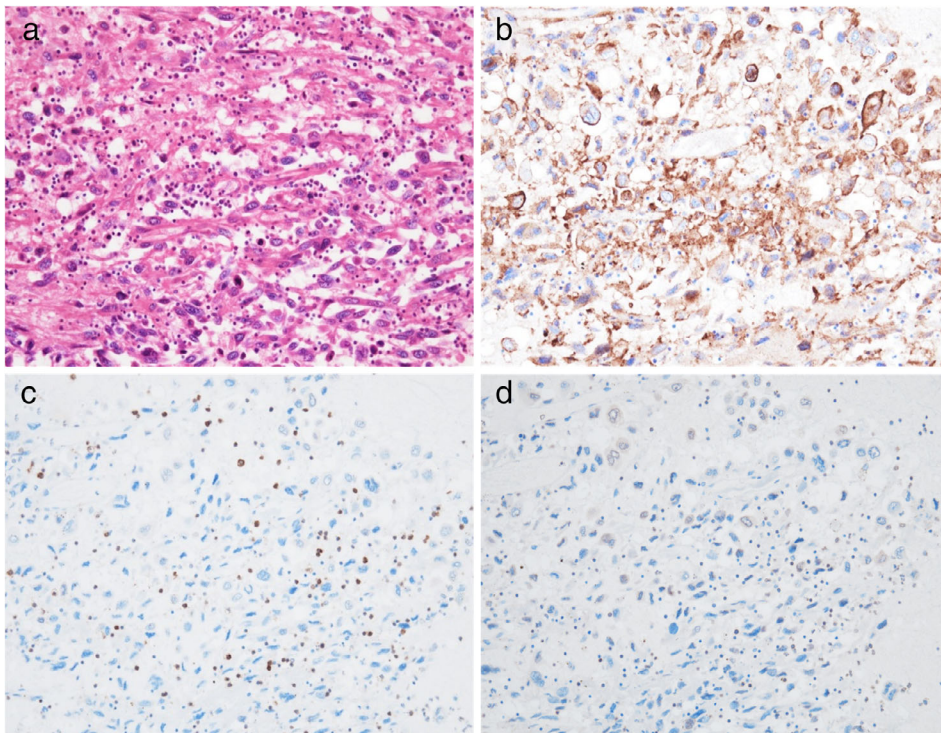
The lesion grew sufficiently rapidly to cause dyspnea. We planned palliative radiotherapy and tracheostomy to avoid suffocation. However, the patient expectorated the tonsillar metastatic lesion before admission to receive radiotherapy (Figures 1 and 2). He received radiotherapy of 33 Gy/11 Fr to the residual tonsillar lesion.

The primary lesion grew until the expectoration of the tonsillar metastasis and shrank at the completion of radiotherapy (Figure 3). We administered only one cycle of nivolumab because of the onset of nivolumab-induced organizing pneumonia; however, shrinkage of the lesion lasted for three months. The regrowth of the carcinoma and improvement of the organizing pneumonia resulted in the initiation of carboplatin/nab-paclitaxel as a third-line therapy. Subsequently, the patient received whole-brain radiotherapy to control brain metastases because of his neurological symptoms. Although chemotherapy was continued, he developed pneumonia and died as a result of this complication.

A specimen of the expectorated tonsillar metastasis showed infiltration of many CD8+ lymphocytes and few



**FIGURE 3** (a) Computed tomography (CT) showing the primary lesion of the pulmonary pleomorphic carcinoma in the lower lobe of the right lung before nivolumab administration. (b) The lesion progressed after expectoration of the tonsillar metastasis. and (c) shrunk after radiotherapy administered to the residual tonsillar metastatic lesion



**FIGURE 4** Histological findings of the tonsillar metastatic lesion. (a) Hematoxylin and eosin (H&E) staining showed lymphocytes infiltrated in the tonsillar metastasis. Immunohistochemical staining (IHC) for PD-L1 antibody (Ab). (b) Tumor proportion score of programmed cell death ligand-1 was 80%–90%. (c) IHC for CD8 Ab and (d) CD4 Ab: tumor tissue infiltration by CD8+ T cells and CD4+ T cells was high and low, respectively

CD4+ lymphocytes. The tumor proportion score of the programmed cell death ligand-1 was 80%–90% (Figure 4).

## DISCUSSION

Tonsillar metastasis is rare among tonsillar carcinomas. In a study of malignant palatine tonsillar tumors, only 12 out of 1535 cases (0.78%) were metastases from an extra-tonsillar primary lesion.<sup>1</sup> Although the pathways of metastasis to the tonsils remain unclear, there are two reasons which have

been suggested to explain its rarity. First, the palatine tonsils do not have afferent lymphatic vessels. Second, the palatine tonsils can exclude cancer cells because they are involved in the reticuloendothelial system.<sup>1</sup> The major histological type of tonsillar metastases from lung cancer is small cell carcinoma. Monforte et al. reported that 12 out of 89 cases of tonsillar metastases originated from lung cancer, and 11 out of the 12 cases had small cell carcinoma as the histological type.<sup>5</sup> Brownson et al. reported that 12 out of 76 cases of tonsillar metastases originated from lung cancer, all of which were small cell carcinomas.<sup>6</sup>

Pulmonary pleomorphic carcinoma is a rare malignant tumor of the lung with an incidence ranging from 0.1% to 0.4% of all lung cancers.<sup>2</sup> Therefore, tonsillar metastasis of pulmonary pleomorphic carcinoma is extremely rare and has only been reported in the Japanese literature.<sup>3</sup> Furthermore, pulmonary pleomorphic carcinoma has a poor response to chemotherapy and a more progressive clinical course than other types of NSCLCs. No standard treatments or effective management strategies have been established. However, there have been previous reports on the effectiveness of ICIs for treating pulmonary pleomorphic carcinoma.<sup>4,7</sup>

To the best of our knowledge, there are no studies on expectoration of a tonsillar metastasis, as in the case described here. We speculate that the expectoration of tonsillar metastasis is related to pseudoprogression. Pseudoprogression is a phenomenon involving initial increase in tumor size and subsequent decrease in lesion size following the administration of ICIs, which is confirmed by biopsy as inflammatory cell infiltrates or necrosis.<sup>8</sup> In our case, the primary lesion grew temporarily after administration of one cycle of nivolumab and continued to shrink thereafter. Moreover, the tonsillar metastasis was infiltrated by CD8+ lymphocytes and exhibited necrosis. Taken together, these observations indicate pseudoprogression. Although the mechanism of pseudoprogression has not been completely elucidated, the necrosis resulting from the pseudoprogression might have caused the expectoration of the tonsillar metastasis. This rare behavior of histologically confirmed pseudoprogression may assist in understanding the pathology of pseudoprogression, considering histologically confirmed pseudoprogression of lung cancer has been reported in only seven cases to date.<sup>8–14</sup>

In general, one of the problems of pseudoprogression is its misinterpretation as disease progression, thereby leading to erroneous treatment decisions.<sup>15</sup> However, pseudoprogression itself can induce serious organ dysfunction because the increase in tumor size causes physical pressure against organs, causing conditions such as pericardial tamponade, renal dysfunction, and severe tracheal stenosis.<sup>16–18</sup> We planned to perform a tracheostomy to avoid suffocation from the metastatic lesion exhibiting pseudoprogression in this case. The risk of immunotherapy depends on the sites of metastasis.

In conclusion, to the best of our knowledge, this is the first case of expectoration of tonsillar metastatic pulmonary pleomorphic carcinoma reported in the literature. It is particularly interesting that histologically confirmed pseudoprogression following administration of ICIs induced a serious clinical condition and expectoration of the tumor. Clinicians should therefore pay attention to the site of the metastatic lesions before considering administration of ICIs.

## ACKNOWLEDGMENTS

The authors would like to thank Enago (www.enago.jp) for the English language review.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Full APC

## ORCID

Tomoki Kuge  <https://orcid.org/0000-0002-9787-1659>

Masaki Kanazu  <https://orcid.org/0000-0003-4405-1929>

## REFERENCES

1. Crawford BE, Callihan MD, Corio RL, Hyams VJ, Karnei RF. Oral pathology. *Otolaryngol Clin North Am.* 1979;12:29–43.
2. Chang YL, Lee YC, Shih JY, Wu CT. Pulmonary pleomorphic (spindle) cell carcinoma: Peculiar clinicopathologic manifestations different from ordinary non-small cell carcinoma. *Lung Cancer.* 2001;34:91–7.
3. Fujimoto H, Furuhashi N, Adachi K, Ibata H, Kobayashi T, Taguchi O. A case of pleomorphic carcinoma with tonsillar metastasis successfully treated with S-1 following chemoradiation therapy. *Haigan (Jpn J Lung Cancer).* 2013;53:771–7. (in Japanese).
4. Matsumoto Y, Miura T, Horiuchi H, Usui K. The successful treatment of pulmonary pleomorphic carcinoma with pembrolizumab: A case report. *Case Rep Oncol.* 2017;10:752–7.
5. Monforte R, Ferrer A, Montserrat JM, Picado C, Palacín A. Bronchial adenocarcinoma presenting as a lingual tonsillar metastasis. *Chest.* 1987;92:1122–3.
6. Brownson RJ, Jaques WE, LaMonte SE, Zollinger WK. Hypernephroma metastatic to the palatine tonsils. *Ann Otol Rhinol Laryngol.* 1979;88:235–40.
7. Kanazu M, Edahiro R, Kurebe H, Nishida K, Ishijima M, Uenami T, et al. Hyperprogressive disease in patients with non-small cell lung cancer treated with nivolumab: A case series. *Thorac Cancer.* 2018;9:1782–7.
8. Ito K, Hataji O, Katsuta K, Kobayashi T, Gabazza EC, Yatabe Y, et al. “Pseudoprogression” of pulmonary pleomorphic carcinoma during nivolumab therapy. *J Thorac Oncol.* 2016;11:e117–9.
9. Tanizaki J, Hayashi H, Kimura M, Tanaka K, Takeda M, Shimizu S, et al. Report of two cases of pseudoprogression in patients with non-small cell lung cancer treated with nivolumab-including histological analysis of one case after tumor regression. *Lung Cancer.* 2016;102:44–8.
10. Doherty MK, Jao K, Shepherd FA, Hazrati LN, Leighl NB. Central nervous system pseudoprogression in a patient treated with PD-1 checkpoint inhibitor. *J Thorac Oncol.* 2015;10:e100–1.
11. Kim HK, Baek SW, Jeong Y, Yang Y, Kwon J, Han HS, et al. Pseudoprogression presenting as intestinal perforation in non-small cell lung cancer treated with anti-PD-1: A case report. *Mol Clin Oncol.* 2019;11:132–4.
12. Izumida T, Kawagishi Y, Tsuji H. Pseudoprogression in lung adenocarcinoma during treatment with nivolumab. *BMJ Case Rep.* 2017;2017:bcr2017219919.
13. Bearz A, Perin T, Cancian L, Berto E, Sartor I, Tirelli U. Immune checkpoint inhibitors and response analysis: A tough challenge. A case report. *BMC Res Notes.* 2016;9:349.
14. Wang X, Zhao Y, Chen Z. A case of pseudoprogression during atezolizumab therapy in lung adenocarcinoma. *Zhongguo Fei Ai Za Zhi.* 2019;22:389–94.
15. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. *J Clin Oncol.* 2015;33:3541–3.
16. Masahiro Y, Wakako D, Naomi S, Funaishi K, Okada T, Kawamoto K, et al. Pericardial effusion with tamponade in lung cancer patients during treatment with nivolumab: A report of two cases. *Front Oncol.* 2019;9:4.

17. Alvin SW, Yee-Liang T, Jeevesh K, Leong CN, Kee P, Lee CT, et al. Pushing the limits of immune-related response: A case of “extreme pseudoprogression”. *Cancer Immunol Immunother*. 2018;67:1105–11.
18. Himeji D, Tanaka GI, Fukuyama C, Yamanaka A, Shiiba R, Moriguchi S, et al. Severe tracheal stenosis after first administration of pembrolizumab rescued by Dumon Y-stent in a lung cancer patient. *Respir Med Case Rep*. 2019;28:100923.

**How to cite this article:** Kuge T, Okabe F, Yamamoto Y, et al. Expectoration of tonsillar metastasis of pulmonary pleomorphic carcinoma after pseudoprogression: A case report. *Thorac Cancer*. 2021;12:1935–1939. <https://doi.org/10.1111/1759-7714.13948>