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Case Report

Palatine tonsillar metastasis of a small pulmonary adenocarcinoma showing an invasive micropapillary carcinoma pattern and Pagetoid spread at the tonsil: a case suggesting retrograde lymphatic metastasis from bulky lymph node metastases of the neck

Shogo Tajima, Kenji Koda

Department of Pathology, Fujieda Municipal General Hospital, Shizuoka, Japan

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Abstract: Metastasis rarely occurs in the palatine tonsils. Among primary pulmonary carcinoma subtypes, small cell carcinoma more frequently metastasizes to this site. Herein, we present an exceedingly rare case of a small pulmonary adenocarcinoma that metastasized to the cervical lymph nodes and the right palatine tonsil in a 62-year-old man. In spite of the small size of the primary site, such extensive metastasis may have occurred because of the invasive micropapillary carcinoma pattern seen in the metastatic sites. The manner of metastasis to the palatine tonsil was considered retrograde lymphatic metastasis originating from carcinoma cells in the cervical lymph nodes. Furthermore, Pagetoid spread was observed at the palatine tonsil. Although there have been only a few cases showing retrograde lymphatic metastasis and Pagetoid spread at the metastatic site, we should be careful when speculating about the primary site based on such metastatic sites, especially when dealing with a biopsy sample exhibiting Pagetoid spread.

Keywords: Palatine tonsils, retrograde lymphatic metastasis, adenocarcinoma, lungs, Pagetoid spread

Introduction

The palatine tonsils are an extremely rare site for metastasis of tumors. In a study, among 1535 malignant tonsillar neoplasms collected for 32 years, only 12 (0.8%) were metastatic [1]; these tumors were gastric carcinoma, colorectal carcinoma, breast carcinoma, renal cell carcinoma, seminoma, and melanoma. Among these 12 cases, 2 cases were unilateral and 10 cases were bilateral. Evidence of metastasis to other tissues was found in 10 of the 12 cases. Another study reporting 76 cases of palatine tonsillar metastasis showed that 10 of the 12 patients with lung carcinoma had small cell lung carcinoma [2]. Lung adenocarcinoma also metastasizes to the palatine tonsils, but it is very rare compared to small cell lung carcinoma [3].

Herein, we present an exceedingly rare case of small pulmonary adenocarcinoma metastasizing to the right palatine tonsil and cervical lymph nodes. The morphology of the carcinoma was unique at the metastatic sites, forming an invasive micropapillary carcinoma (IMPC) pattern.

Clinical summary

A 62-year-old man had a previous history of lobectomy of the right upper lobe of the lung, with a pathological diagnosis of squamous cell carcinoma. Ten years after the operation, a nodule measuring 17 × 15 mm was found at the right lower lobe of the lung with follow-up computed tomography (**Figure 1A**). Mild enlargement of the hilar lymph nodes was observed (**Figure 1B**), but no swelling was observed in the mediastinal lymph nodes. Unexpectedly, several lymph nodes at the right side of the neck were massively swollen (**Figure 1C**, **1D**); the right palatine tonsil was mildly enlarged (**Figure 1D**). Thus, metastasis of the carcinoma from

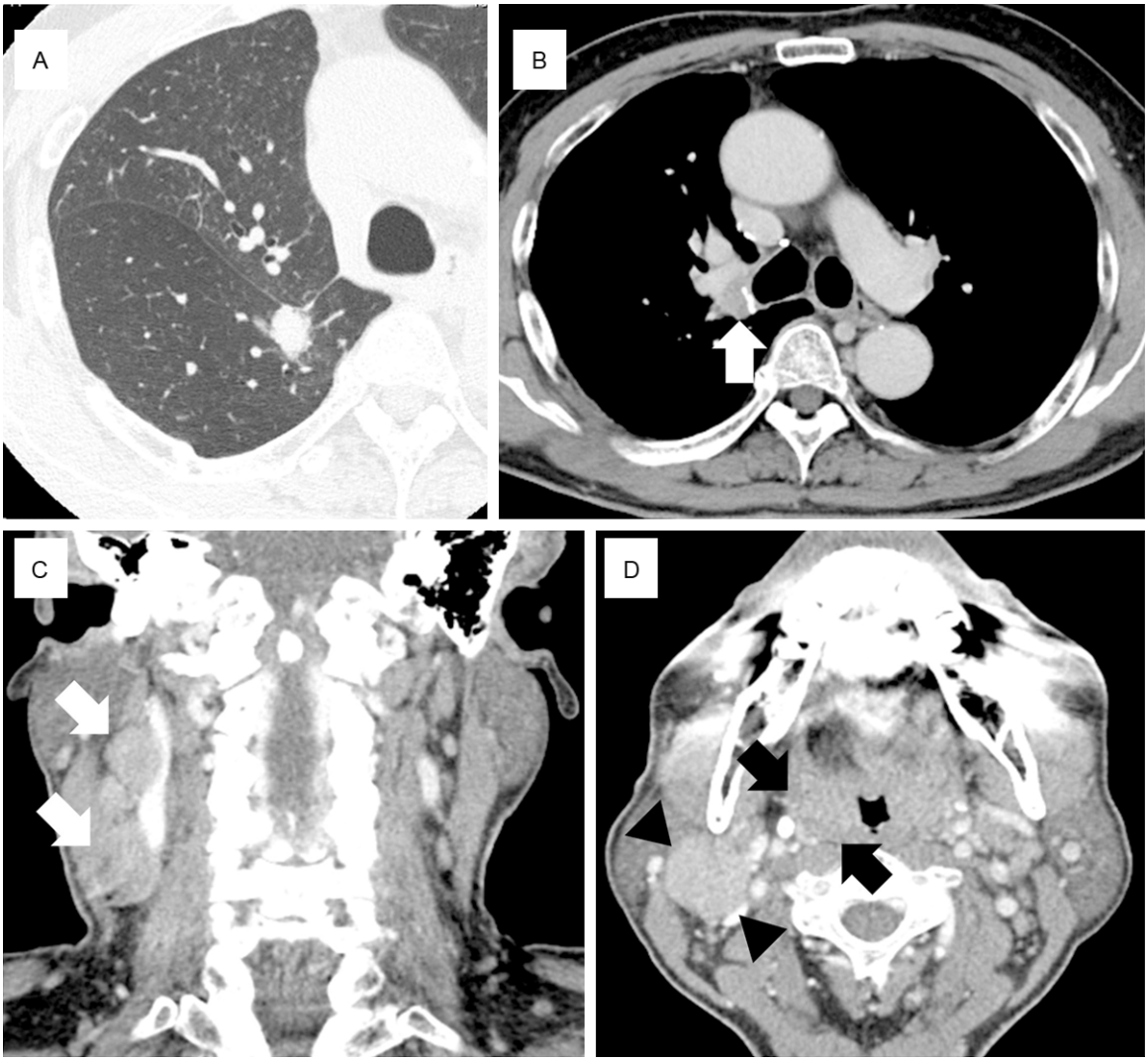

Figure 1. Computed tomography findings. A. A nodule measuring 17 × 15 mm was found in the right lower lobe of the lung. B. Mild enlargement of the hilar lymph nodes was observed (white arrow). C. Several lymph nodes at the right side of the neck were massively swollen (white arrows). D. The right palatine tonsil was mildly enlarged compared with the left side (black arrows). Conspicuous swelling of a lymph node was observed (black arrowheads).

the palatine tonsils to the cervical lymph nodes was first suspected. Subsequently, right-side tonsillectomy and cervical lymphadenectomy were performed. Pathological analysis revealed that the tonsils were not the origin of the carcinoma, but metastasis of the pulmonary adenocarcinoma to these sites had occurred. The primary pulmonary site was not treated with surgery; instead, systemic therapy was planned.

Pathological findings

Gross examination of the surgically resected tonsillar specimen could not be used to identify a focus of the carcinoma. Lymph node swelling was prominent, reaching a maximum diameter of 4 cm.

Microscopically, a carcinoma focus, measuring 1 × 0.8 cm, was observed in the right palatine tonsil. The carcinoma was in direct contact with superficial stratified squamous epithelium, but the epithelium was not neoplastic (**Figure 2A**). Upon closer observation of the carcinoma cells, it was found that the carcinoma nests had an outer smooth membrane distinct from the stroma, which is recognized as an IMPC pattern (**Figure 2A**, inset). A carcinoma component showing another growth pattern was not observed, except for carcinoma cells showing

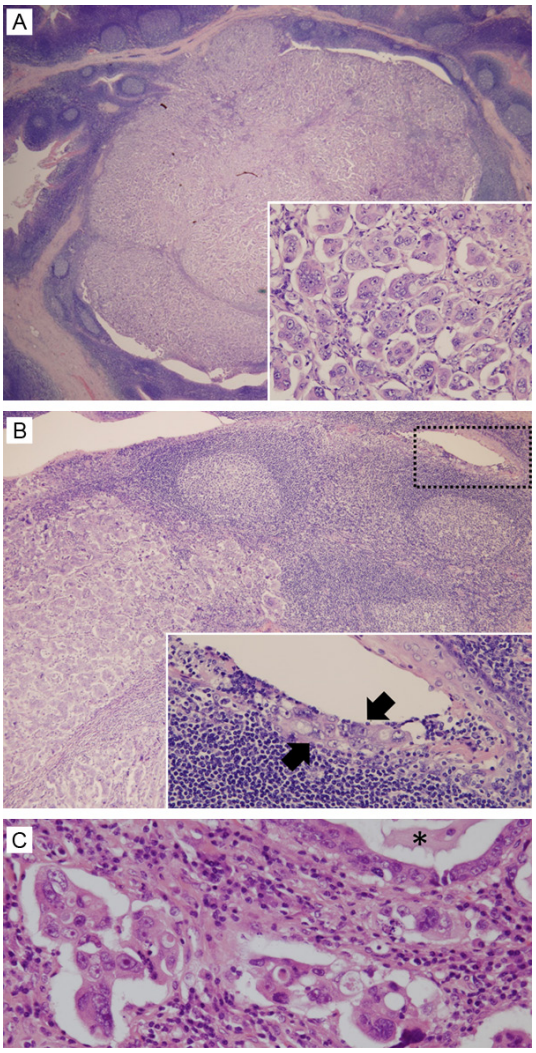

Figure 2. Microscopic findings. A. A carcinoma focus was observed in the palatine tonsil. The carcinoma was situated in direct contact with superficial stratified squamous epithelium, but the epithelium was not neoplastic. Inset: carcinoma nests showed an outer smooth membrane separating from the stroma, which is recognized as an invasive micropapillary carcinoma (IMPC) pattern. B. Carcinoma cells showing Pagetoid spread were identified in the superficial stratified squamous epithelium (dotted box). Inset: High-power view of the dotted box showing Pagetoid spread of the tumor cells (black arrows). C. Cervical lymph nodes were largely infiltrated by carcinoma cells showing an IMPC pattern; carcinoma cells forming glands (asterisk) were scarcely observed.

Pagetoid spread in the superficial stratified squamous epithelium (**Figure 2B**). The cervical lymph nodes were largely infiltrated by carcinoma cells showing an IMPC pattern; carcinoma cells forming glands were scarcely observed (**Figure 2C**).

On immunohistochemical analysis, the carcinoma cells in the palatine tonsils and cervical lymph nodes were positive for TTF-1 (8G7G3/1, 1:100; Dako, Glostrup, Denmark) (**Figure 3A**) and napsin A (IP64, 1:100; Novocastra, Newcastle, UK) (**Figure 3B**) but negative for CK5/6 (D5/16 B4, 1:100; Dako) and p40 (polyclonal, 1:1500, Calbiochem/EMD Biosciences, Billerica, MA). The IMPC pattern was highlighted by exaggerated staining of EMA (E29, 1:100; Dako) and MUC1 (Ma695, 1:100; Novocastra) (**Figure 3C**) at the rim of the nests.

A polymerase chain reaction for mutational analysis of *EGFR* [exons 18, 19 (deletions), 20, and 21] and fluorescence in situ hybridization for *ALK* rearrangement were performed at a commercial laboratory. No mutation was found in *EGFR*; *ALK* rearrangement was not observed.

Discussion

With respect to the route of metastasis to the palatine tonsils, it may be assumed that the carcinoma cells underwent hematogenous or lymphatic spread. The hematogenous route is presumed to be the most common route for metastases to the palatine tonsils [4]. Meanwhile, the palatine tonsils do not have afferent lymphatic vessels, so tonsillar involvement from the lymphatic vessels is usually not expected. However, metastasis to the palatine tonsils could be considered to occur as a result of retrograde movement of tumor cells through the lymphatic vessels of the neck [5]. This manner of movement occurs in cases of inversion of lymphatic flow owing to massive involvement of the cervical lymph nodes [6]. In our case, involvement of the cervical lymph nodes was conspicuous; thus, it is probable that metastasis to the palatine tonsils occurred in a retrograde manner. Interestingly, the possibility of direct implantation of carcinoma cells to the tonsil from instruments, which were used during bronchoscopy, has been suggested in patients with lung carcinoma [5].

Focusing on the concept of the retrograde lymphatic spread of carcinoma cells, it appears that this manner of spread is a non-negligible mechanism of carcinoma metastasis to various organs, such as the lungs, esophagus, heart, spleen, ovaries, vulva, prostate, penis, and testes [7-9]. To achieve an antegrade lymphatic output, periodic stresses to the tissues need to

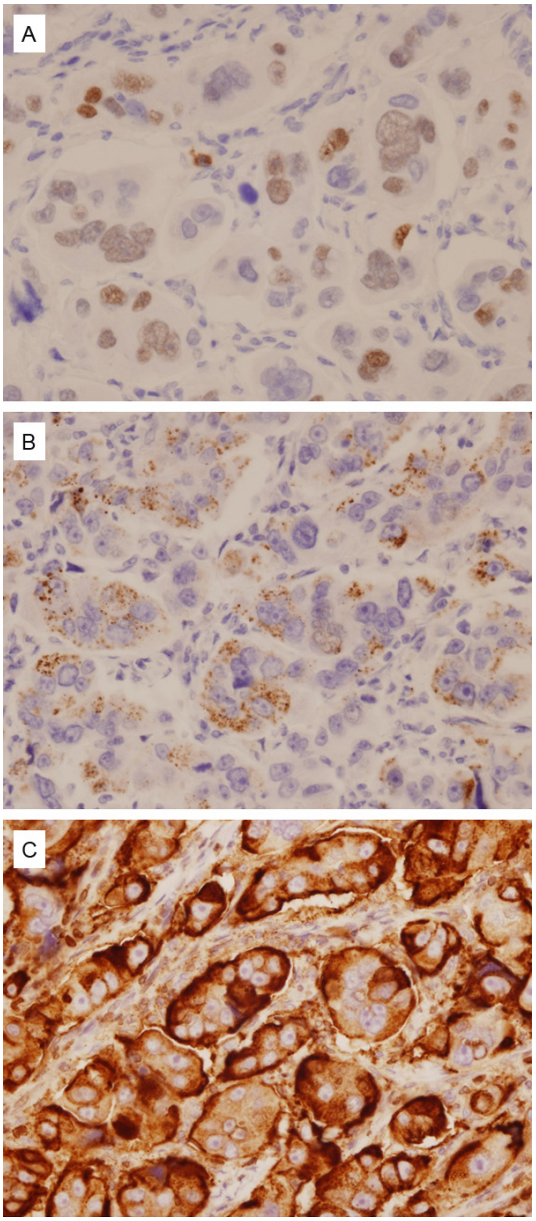

Figure 3. Immunohistochemical findings. A. Positivity for TTF-1. B. Positivity for napsin A. C. Positivity for MUC1 especially at the rim of the carcinoma nests.

be applied, as small lymphatic vessels do not have smooth muscle in their wall. They include arterial pulsations; arteriolar vasomotion; skeletal muscle contractions and the movement of the alimentary tract; and external pressure, such as that occurring during walking, running, and respiration [10]. An increase in downstream intralymphatic pressure, which hampers antegrade lymphatic flow, could occur after carcinoma invasion to a lymphatic vessel, even when downstream lymph node metastases are not identified; retrograde lymphatic spread was histologically confirmed in a case of esophageal carcinoma without metastasis to the downstream lymph nodes [11]. It should be noted that retrograde flow of lymph is usually protected by the presence of bileaflet valves. With respect to dysfunction of the valves, adhesion of carcinoma cells to lymphatic endothelial cells, presumably via adhesion-related molecules, such as intercellular adhesion molecule-1, leads to contractile obstruction of the lymphatic wall and regurgitation of the lymphatic valve [11-13]. Considering these facts, retrograde lymphatic spread might be an under-recognized manner of carcinoma spread, which might often occur, in spite of antegrade lymphatic spread usually becoming a much more conspicuous finding.

The IMPC pattern observed in this case is interesting. Carcinomas with this pattern are likely to invade lymphovascular spaces [14]. In our case, metastatic sites were composed of an IMPC pattern, which could explain the widespread lymphatic metastasis. In breast carcinoma, which relatively frequently shows an IMPC pattern, it has been demonstrated that a high frequency of genetic alterations involving chromosome 8 are present in the IMPC [15, 16]. In addition, an expression profiling study has found out a unique molecular profile for IMPC [17]. The size of the primary lung carcinoma in our case was relatively small for it to metastasize to the cervical lymph nodes. Thus, unique genetic and/or expression profiles were anticipated for this carcinoma; however, such molecular analyses were beyond the scope of this study.

Retrograde lymphatic metastasis accompanied by Pagetoid spread in the palatine tonsil was another unique finding in this case. In cases of urothelial carcinoma, retrograde lymphatic metastasis with concordant occurrence of Pagetoid spread has been noted in the penis or even in the vulva [18, 19]. Although this manner of extension is rare, it should be noted that Pagetoid spread is not seen only in sites of direct epithelial continuity with the primary site. This fact is especially important when diagnosing samples showing Pagetoid spread.

In conclusion, even small pulmonary adenocarcinomas could metastasize to the cervical lymph nodes and further to the palatine tonsil

through retrograde lymphatic metastasis. In spite of the small size of the primary lesion, such extensive metastasis could probably occur because of the IMPC pattern seen in the metastatic sites. Retrograde lymphatic metastasis is often under-recognized, but even cases showing Pagetoid spread in metastatic sites have been reported. Thus, we should be careful when speculating about the primary site based on such metastatic sites.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shogo Tajima, Department of Pathology, Fujieda Municipal General Hospital, Shizuoka, Japan. Tel: +81-54-285-6171; Fax: +81-54-285-5179, E-mail: stajima-tky@umin.ac.jp

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