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Case report

Clinicopathological feature of a resected large mixed squamous cell and glandular papilloma: A case report

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ABSTRACT

Introduction and importance: Solitary endotracheal papilloma is a rare benign lung tumor. It is classified into the following three histological subtypes: squamous cell papilloma (SP), glandular papilloma (GP), and mixed squamous cell and glandular papilloma (MSGP). MSGP is the rarest among them. Herein, we describe a case of a large MSGP.

Case presentation: A 59-year-old woman underwent computed tomography for the examination of cough, and an 8.2-cm-sized lung mass was noted in the left lingual segment. Bronchoscopy revealed that the left B^5 lumen was completely occluded by a tumor. Transbronchial lung biopsy suggested GP; thereafter, a left upper lobectomy was performed. Macroscopic findings showed that the dilated B^5 lumen was filled with cauliflower-like tumors. Histopathological findings showed that the majority of the tumors had pseudostratified columnar epithelium, while some had stratified squamous epithelium. The patient was diagnosed with MSGP. Although koilocytosis-like changes, such as perinuclear halo and nuclear deformation, were observed in some portions of the squamous epithelium, immunohistochemical staining was negative for human papillomavirus (HPV).

Clinical discussion: HPV infection is reportedly associated with SP but not with GP and MSGP. Therefore, MSGP is considered to be caused by squamous metaplasia of a part of GP; this hypothesis is consistent with the present case. However, only one case of MSGP with HPV infection was recently reported, and the etiology and histological features of MSGP remain unclear.

Conclusion: There are few reported cases of MSGP, and further case reports are needed to clarify its pathogenesis.

1. Introduction

Solitary endobronchial papilloma (SEP) is a rare benign neoplasm of the lower respiratory tract that accounts for <0.5% of all lung neoplasms [1]. SEPs are classified into the following three categories: squamous cell papilloma (SP), glandular papilloma (GP), and mixed squamous cell and glandular papilloma (MSGP), with frequencies of 65.6%, 18.8%, and 15.6%, respectively [2]. Thus, MSGP is the rarest subtype of SEP, and its etiology and clinicopathological characteristics remain unclear. In most cases, MSGP is reported to be ≤3 cm in size; a large MSGP is very rare [3]. To the best of our knowledge, the largest MSGP reportedly measured 11 cm in size to date, and this case is unique as it occurred in the periphery of the lung and was associated with interstitial pneumonia [4]. Herein, we report the clinical course and histopathological findings of a case of an 8.2-cm-sized MSGP; notably, this is the largest case of MSGP that developed in the central airway.

This case report was reported in line with the SCARE Criteria [5].

Abbreviations: SP, squamous cell papilloma; GP, glandular papilloma; MSGP, mixed squamous cell and glandular papilloma; HPV, human papillomavirus; SEP, solitary endobronchial papilloma; CT, computed tomography; CEA, carcinoembryonic antigen; SLX, sialyl-Lewis X; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; SUVmax, maximum standard uptake value; TBLB, transbronchial lung biopsy; PCR, polymerase chain reaction..

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2. Presentation of case

The patient was a 59-year-old woman with hypertension. Computed tomography (CT) was performed to examine cough, and a left lung mass was revealed. The patient was referred to our hospital for treatment. The patient was allergic to montelukast sodium; additionally, she had no smoking history but had a family history of hypertension, renal cell carcinoma, and bronchial asthma. The patient was taking amlodipine besylate, ambroxol hydrochloride, and famotidine. The laboratory tests revealed the following levels of tumor markers: carcinoembryonic antigen (CEA) 11.0 ng/mL (≤5.0 ng/mL) and Sialyl-Lewis X (SLX) 52.2 U/mL (≤38.0 U/mL). Chest radiography showed decreased permeability of the left lower lung field (Fig. 1a). An enhanced CT scan showed an 8.2- × 4.9-cm-sized lung mass that was irregularly enhanced in the left lingual segment (Fig. 1b, c). An ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan revealed the maximum standard uptake value (SUVmax: 20.2) in the lung mass (Fig. 1d). Bronchoscopy revealed that the left B^5 lumen was completely occluded by the protruded tumor (Fig. 1e), and transbronchial lung biopsy (TBLB) was performed. Although the lesion was suspected to be a GP by TBLB, histopathological findings of the material showed that 5%–10% of p53 strongly positive cells were present; hence, a malignant tumor could not be ruled out. Accordingly, we considered surgical resection assuming lung cancer, and informed consent was obtained from the patient.

Left upper lobectomy and mediastinal lymph node dissection (ND2a-2) were performed using video-assisted thoracoscopic surgery. The operative time was 265 min, and the volume of blood loss was 10 mL. Postoperatively, pleurodesis was performed with OK-432 (picibanil) and minocycline for a prolonged air leak, and the chest tube was removed on postoperative day 9. The patient was discharged on postoperative day 15.

Macroscopic findings showed that the dilated B^5 lumen was filled with cauliflower-like tumors and mucoid impaction (Fig. 2a, b). Obstructive pneumonia was suspected around the tumor. Histopathological analysis revealed that the majority of the tumor cells were glandular or pseudostratified columnar epithelium with mucin production (Fig. 3a, b). Stratified squamous epithelium was observed in a small portion of the tumor, and some of the squamous epithelial cells showed koilocytosis-like changes such as perinuclear halo and nuclear deformation (Fig. 3c). Although human papillomavirus (HPV) infection was suspected, immunohistochemical staining was negative for p16, HPV6, 11, and 18 in both glandular columnar and squamous epithelial components. Immunohistochemical staining showed that p53- and ki-67-positive rates were not high (approximately 10% and 5%, respectively), and the aforementioned markers were located in the basal and parabasal portions of the epithelial layer of the tumor tissue. None of the superficial tumor cells were positive for p53 and ki-67 staining (Fig. 4a, b). The intensity of p53-immunostaining was not strong enough to suggest malignancy (Fig. 4a). Based on the abovementioned findings, the patient was diagnosed with MSGP. Moreover, cytokeratin 7 and p40 (basal cells only) were positive, and cytokeratin 20, thyroid transcription factor-1, napsin A, mucin 5AC, mucin 6, and mucin 2 were negative in the glandular (columnar) epithelial components. Inflammatory cell infiltration, mainly macrophages, was observed in the lung parenchyma surrounding the tumor and was diagnosed as obstructive pneumonia (Fig. 3d). Additionally, immunohistochemical staining for CEA showed 30% CEA-positive cells in both glandular (columnar) and squamous epithelial components of MSGP, while positive cells were not observed in the site of occurrence of obstructive pneumonia (Fig. 5). There were no malignant findings in the dissected lymph nodes.

At a 1-year follow-up, CT examination showed no recurrence of MSGP, and the levels of the tumor markers CEA and SLX were normalized postoperatively.

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

3. Discussion

MSGP is defined as a mix of squamous and glandular (columnar) epithelium papilloma, with a glandular component comprising at least one-third of the tumor [6]. MSGPs are reported to occur more frequently in men who smoke, at an average age of 58.3 years [7]. Subjective symptoms of MSGPs include cough (40.6%), hemoptysis (25.0%), dyspnea (21.8%), and fever (15.7%) [2]. SEPs are reported to occur more often in the left lingual segment (37.5%), followed by the right bronchus intermedius (28.0%) [2]. In the present case, age, subjective symptoms,

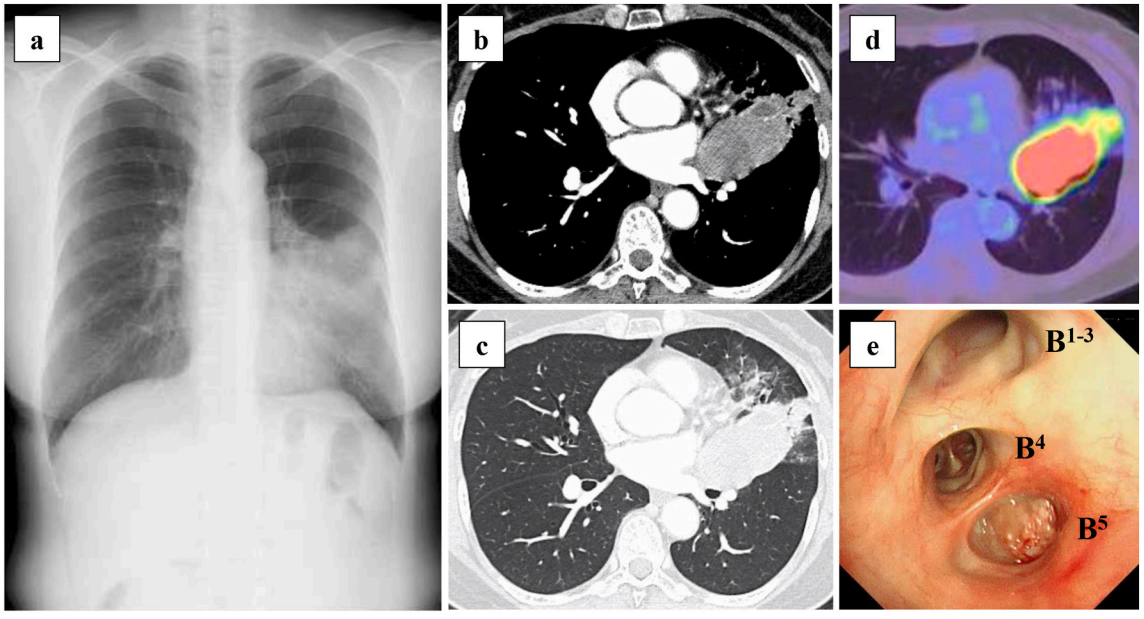

Fig. 1. Preoperative imaging findings.
(a) Chest radiograph showing decreased permeability of the left lower lung field. (b, c) Enhanced computed tomography (CT) image showing an 8.2- × 4.9-cm-sized lung mass, irregularly enhanced in the left lingual segment. (d) ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan showing maximum standard uptake value (SUVmax: 20.2) in the lung mass. (e) Bronchoscopy shows that the left B^5 lumen is completely occluded by the protruded tumor.

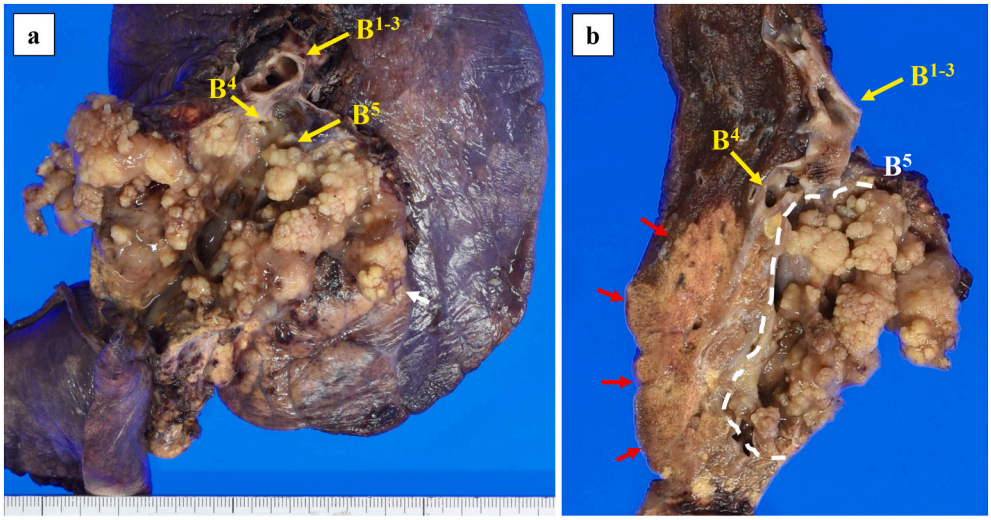

Fig. 2. Macroscopic findings of mixed squamous cell and glandular papilloma.
(a, b) The dilated B^5 lumen is filled with cauliflower-like tumors and mucoid impaction (white dotted line; bronchial wall of B^5). Obstructive pneumonia is suspected around the tumor (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

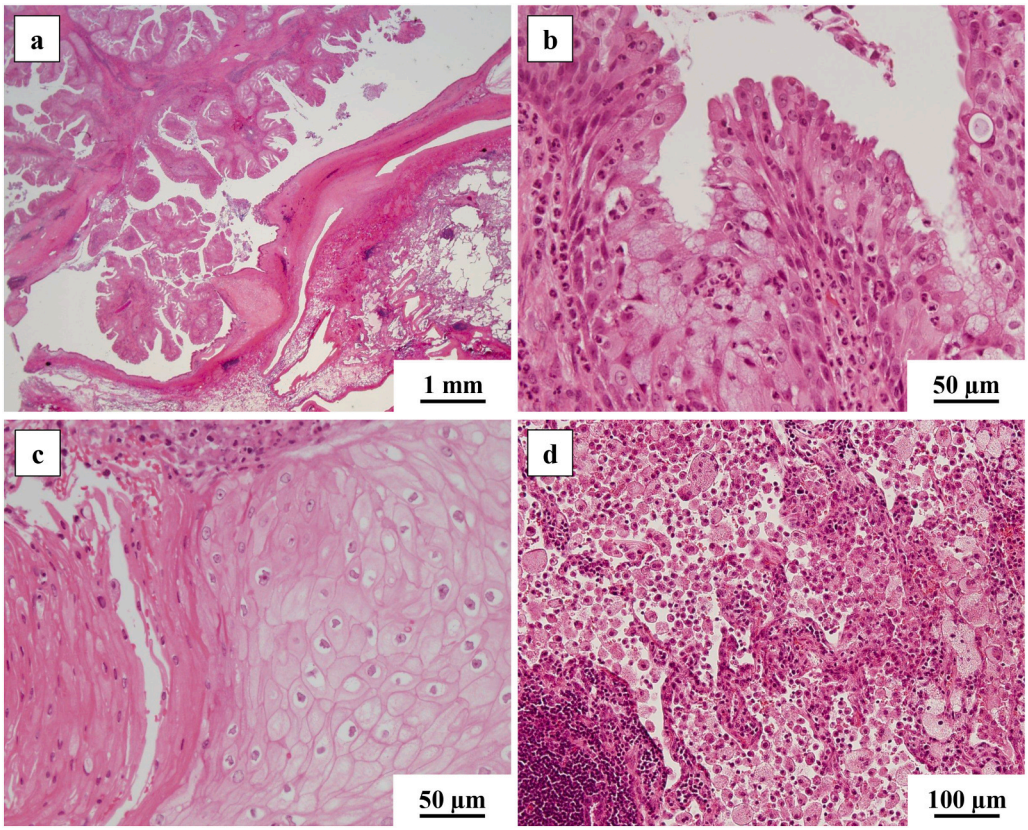

Fig. 3. Histopathological findings of mixed squamous cell and glandular papilloma.
(a, b) The majority of the tumor cells have glandular or pseudostratified columnar epithelium with mucin production. (c) Stratified squamous epithelium is observed in a small portion of the tumor, and some of the squamous epithelial cells show koilocytosis-like changes such as perinuclear halo and nuclear deformation. (d) Inflammatory cell infiltration, mainly macrophage infiltration, is observed in the lung parenchyma surrounding the tumor; obstructive pneumonia is diagnosed.

and site of occurrence were consistent.

HPV infection has been reported to be associated with the etiology of SP, but not with that of GP or MSGP [1,3]. Therefore, MSGP is considered to be caused by squamous metaplasia of a part of GP [8]. In this case, the majority of the tumor had glandular or pseudostratified columnar epithelia, and a small portion had stratified squamous epithelium with a perinuclear halo and nuclear deformation. Immunohistochemical staining suggested that squamous metaplasia was not caused by HPV infection; rather, it was caused by a pseudo-koilocytosis change associated with squamous metaplasia. Most cases of MSGP, including the present case, reportedly tested negative for HPV infection on immunohistochemical staining or in situ hybridization [1,3,8]. However, one case of MSGP with HPV (HPV 16, 35, and 51) infection diagnosed by polymerase chain reaction (PCR) was recently reported [9]. Since PCR is a more sensitive test, HPV infection was considered to have probably been detected. At present, we believe that HPV is not a major cause of MSGP; however, future research, including more cases of MSGP tested for HPV by PCR, could provide new insights into the relationship between HPV infection and MSGP.

SEPs are sometimes associated with malignant transformation, with

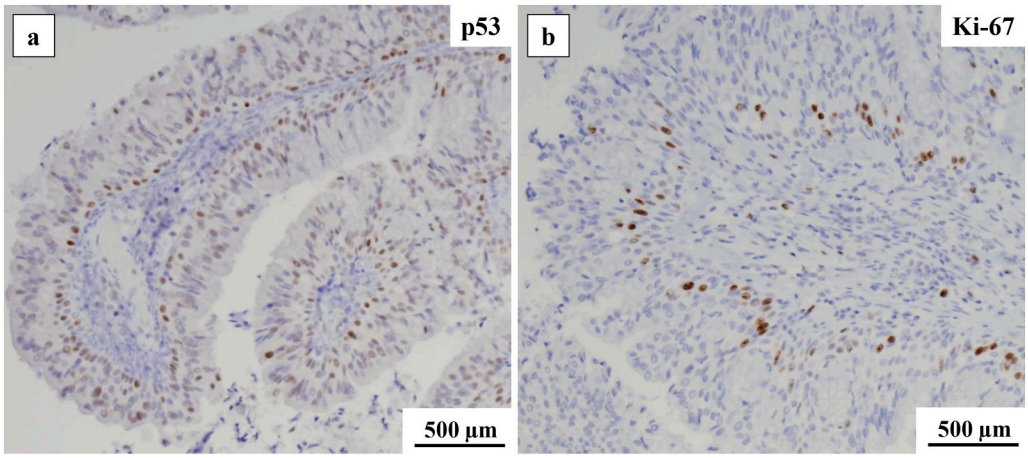

Fig. 4. Immunohistochemical staining findings of mixed squamous cell and glandular papilloma.
p53- and ki-67-positive rates are not high (approximately 10% and 5%, respectively), and the aforementioned markers are located in the basal and parabasal portions of the epithelial layer of the tumor tissue. None of the superficial tumor cells is for positive p53 and ki-67 staining. The intensity of p53 immunostaining is not strong enough to suggest malignancy.

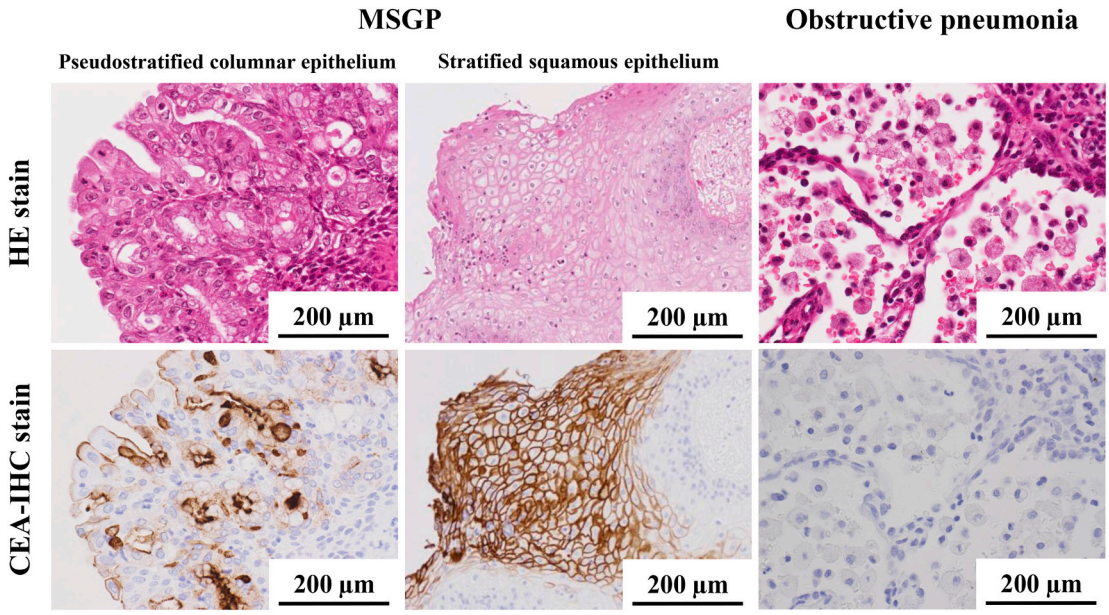

Fig. 5. Immunohistochemical staining findings for carcinoembryonic antigen (CEA).
CEA-positive cells account for 30% of both glandular (columnar) and squamous epithelial components of MSGP, while CEA-positive cells are not observed in the site of occurrence of obstructive pneumonia.
HE stain, hematoxylin and eosin staining; IHC stain, immunohistochemical staining; MSGP, mixed squamous cell and glandular papilloma.

a reported frequency of 10% in SP, rare in GP, and 25% in MSGP [2]. In this case, although a GP was suggested by TBLB, malignancy could not be ruled out before the surgery owing to FDG-PET/CT imaging findings, elevated tumor marker levels, and histopathological findings of biopsy materials. Generally, malignancy is only revealed by postoperative histopathological examination of resected tumors in patients with SEP [2,3]. In the present case, the tumor was large, and left upper lobectomy was performed, instead of lingual segmentectomy, for complete resection with a sufficient surgical margin. Although no malignancy was observed on postoperative histopathological examination, the choice of surgical procedure was considered appropriate. Although there have been no cases of recurrence after complete resection of MSGP in previous reports [2,3], we plan to carefully follow-up with the patient.

It has been reported that 71.4% of patients with MSGPs have elevated tumor marker levels [3]. Additionally, the levels of the tumor markers CEA and SLX may be elevated in benign lung diseases, such as obstructive pneumonia, interstitial pneumonia, and chronic bronchitis [10,11]. In this case, the levels of the tumor markers were elevated before surgery and normalized after surgery. Immunohistochemical staining for CEA was positive in both glandular (columnar) and squamous epithelial components of MSGP and negative in any cells within the site of occurrence of obstructive pneumonia; thus, we speculated that the elevated levels of tumor markers are caused by the tumor itself rather than obstructive pneumonia.

A limitation of this study is that there are still few reported cases of MSGP. Therefore, further studies regarding MSGP are required to clarify the etiology and histopathological findings.

4. Conclusion

We report a rare case of a large MSGP. In this case, MSGP was presumed to have been caused by the squamous metaplasia of GP, as previously hypothesized. The number of reported cases of MSGP remains small, and accumulation of case reports is needed to elucidate its pathogenesis, including etiology and relationship with HPV infection.

Provenance and peer review

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Ethical approval

Ethical approval was not required for our paper because case reports are exempt from ethical approval at our institute.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Nobutaka Kawamoto performed the operation, acquired the data, and drafted the manuscript.

Riki Okita conducted the study.

Masataro Hayashi assisted in the operation.

Hisayuki Osoreda performed bronchoscopy.

Hidetoshi Inokawa attended to the patient postoperatively.

Tomoyuki Murakami diagnosed the patient based on the pathological findings.

All authors have read and approved the final manuscript.

Research registration

Not applicable.

Guarantor

Nobutaka Kawamoto.

Declaration of competing interest

All authors have no conflicts of interest.

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