

Squamous cell carcinoma occurring with aspergillosis in the maxillary sinus: a case report and histological study

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The coexistence of aspergillosis and squamous cell carcinoma (SCC) in the maxillary sinus was very rare. To our knowledge, this is the second report of coexistent SCC and aspergillosis in the maxillary sinus. A 58-year-old man underwent surgery for unilateral maxillary sinus infection with oroantral fistula. In the surgical specimen, SCC and aspergillosis were co-detected with routine and immunohistochemical stainings. Moreover, human papillomavirus 18 (HPV-18) was detected by polymerase chain reaction in the sinus specimen. The patient was re-operated with subtotal maxillectomy and has been followed up for two years without any evidence of recurrence or metastasis. Although it is not understood how aspergillosis could induce carcinoma formation, the chronic inflammation caused by prolonged fungal infection might be carcinogenic. Moreover, HPV-16 and -18 were another causative pathogens of SCC in the head and neck region. We recommend careful examination, including preoperative cytology, in patients with maxillary sinus fungal infections because of the potential for cancer development.

Key words: Aspergillosis, Squamous cell carcinoma, Maxillary sinus

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I. Introduction

Aspergillosis of the paranasal sinuses is uncommon, but its incidence has markedly increased in recent years¹. This phenomenon might be related to the long-term use of steroids, antibiotics, or immunosuppressive agents and the existence of uncontrolled diabetes. Aspergillosis of the paranasal sinuses has been classified into four types: allergic, noninvasive, invasive, and fulminant. Immunocompromised patients are at particular risk for fulminant invasive aspergillosis. The most frequent site of human aspergillus infection is the lung, followed by the liver, spleen, bone, meninges, and paranasal sinuses². In several reports, the coexistence of fungal infection and malignancy has been noted in the brain and thoracic cavity³⁻⁶. Moreover, Tanaka *et al.*⁷ reported the coexistence of aspergillosis and squamous cell carcinoma (SCC) in the maxillary sinus. That case was diagnosed using preoperative cytologic study of routine sinus washings.

Recently, several investigators have shown that human papillomavirus (HPV) appears to play an etiologic role in oral and paranasal sinus carcinoma⁸⁻¹⁰. In a large cohort study, 25% of head and neck SCCs were found to be positive for HPV infection¹⁰. HPV-16 was the most common subtype, whereas HPV-18 was observed in only 2% of HPV-positive head and neck cancers.

We present a case of SCC concomitant with aspergillosis and HPV-18 infection in the unilateral maxillary sinus. Initially, the patient was misdiagnosed as having only bacterial or fungal sinusitis according to clinical and radiologic appearance and was treated with simple enucleation of the sinus mucosa. However, SCC and HPV-18 were detected in the surgical specimen, so the patient was re-treated with subtotal maxillectomy. We recommend careful preoperative examination for detection of other possible pathogens in maxillary sinus fungal infections.

II. Case presentation

A 58-year-old man presented with complaints of pain and purulent discharge from the site of an upper left first molar extraction. The extraction had been performed approximately 20 days previously at a private dental clinic. A pus-exuding oroantral fistula subsequently developed. It did not heal,

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despite long-term antibiotic therapy. The patient also reported intermittent throbbing pain in the left cheek and nasal obstruction over the previous year, but he had no history of symptoms indicating immunocompromised status prior to this presentation.

On visual inspection, the patient had completely edentulous ridges in both jaws and an oroantral fistula at the extraction site. Routine radiography demonstrated generalized opacification of the left maxillary sinus, and computed tomography (CT) showed calcified masses in a soft tissue density lesion in the left maxillary sinus.(Fig. 1. A) The patient was tentatively diagnosed with an oroantral fistula and chronic maxillary sinusitis due to bacterial or fungal infection. Surgical access to the left maxillary sinus was achieved by opening the sinus anterior wall. Abundant, grey, caseous material and the affected mucosa were enucleated from the sinus.(Fig. 1. B)

Hematoxylin and eosin staining of the surgical specimen revealed two distinct pathogens. Moderately differentiated SCC and aspergillosis were co-detected with separated boundaries.(Fig. 2. A) However, an aspergillus-like component was

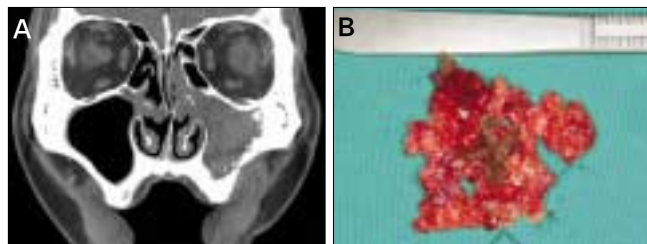


Fig. 1. Preoperative computed tomography (CT) and post-operative sinus mucosa. A. Preoperative CT showing calcified masses in the soft tissue density lesion of the left maxillary sinus. (arrows) B. Abundant, grey, caseous material and affected mucosa were removed from the left maxillary sinus.

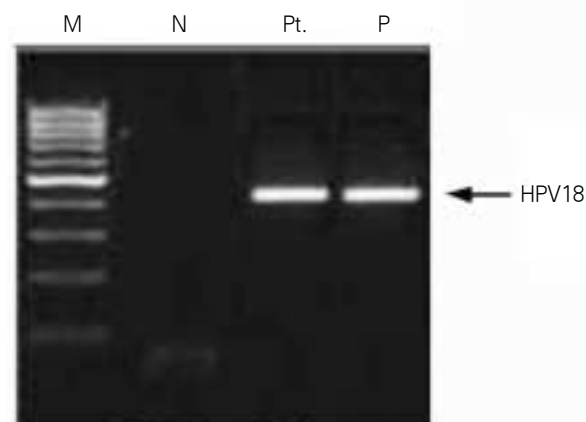


Fig. 3. Polymerase chain reaction revealed human papillomavirus-18 DNA in the maxillary sinus lesion. (M: 100bp marker, N: negative control, Pt: patient's sample, P: positive control)

also detected in the carcinoma component.(Fig. 2. C) Epithelial koilocytosis was noted at multiple locations in the peripheral portion of the carcinoma component.(Fig. 2. E) Polymerase chain reaction (PCR) analysis for the detection of HPV infection revealed HPV-18 DNA in the surgical specimen.(Fig. 3) For the immunohistochemical study of aspergillus antibody, a 1:1,600 dilution of primary rabbit polyclonal antihuman aspergillus (ab20419, Abcam, Cambridge, UK) was used to visualize aspergillus infection. Immunostaining was conducted using an automated immunostainer. (Lab Vision Autostainer, Lab Vision, Thermo Fisher Scientific Inc., Fremont, CA, USA) Under lower magnification of microscope, the SCC and aspergillosis appeared to be separate components.(Fig. 2. B)

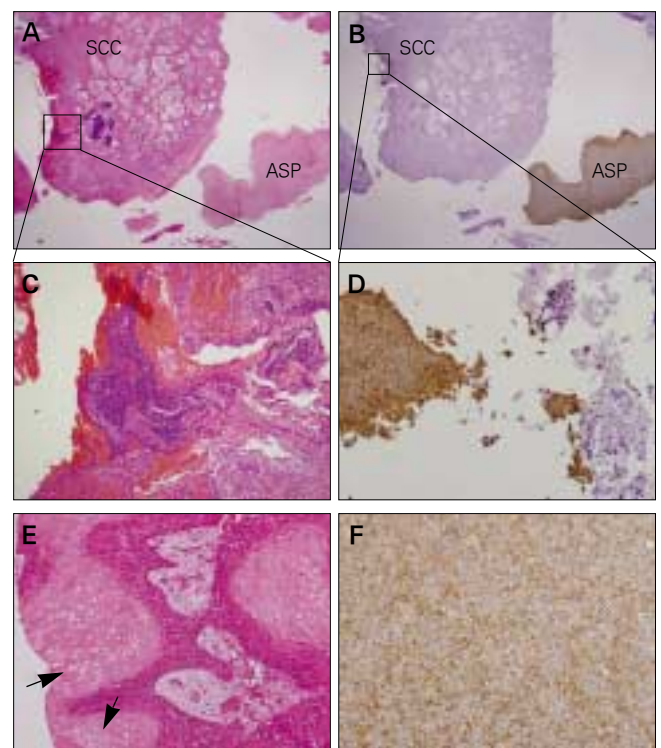


Fig. 2. Histopathologic examinations of the affected maxillary sinus mucosa. A. Microphotograph after hematoxylin and eosin staining. The coexistence of moderately differentiated squamous cell carcinoma (SCC) and aspergillosis (ASP) was confirmed in the surgical specimen. (x12 magnification) B. Microphotograph after immunohistochemical staining with aspergillus antibody. Strong positive expression was detected in the partial portion of the SCC (square portion), as well as in the aspergillosis component. (x12) C, D. Under higher magnification of the SCC component, some aspergillus looked like a mixed form within the carcinoma tissues. (C: x100, D: x200) E. Epithelial koilocytosis was observed on the epithelial surface of the SCC.(arrows) (x200) F. Under high magnification of the immunostained aspergillosis component, aggregation of septated fungal hyphae with acute-angle branches was observed in the aspergillosis-affect region. (x400)

However, some aspergillus was detected in the SCC component, giving the appearance of a mixed form.(Fig. 2. D) In the aspergillosis component, we noted strong immunostaining for aspergillus antibody, with aggregation of fungal hyphae.(Fig. 2. F)

The patient was re-diagnosed with coexistent aspergillosis and SCC in the maxillary sinus mucosa. Two weeks after the first operation, he underwent left subtotal maxillectomy and split-thickness skin grafting. He has been followed up for two years without any evidence of recurrence or metastasis.

III. Discussion

Aspergillus is the most common fungal sinus pathogen. Grossly, muddy or necrotic fungus balls are observed in most surgical specimens¹¹. Generally, two methods of paranasal sinus contamination by fungus have been suggested: via the aerogenic pathway, whereby spores are inhaled directly into the antrum and multiply in anaerobic conditions^{12,13}; or via the iatrogenic pathway, whereby spores are introduced into the antrum during dental procedures, such as root canal perforation, canal overfilling, or dental extraction¹¹⁻¹⁴. However, the relation between fungal infection and tumor formation is not understood. Several studies have shown that aspergillus infection can cause aspergilloma formation at various sites²⁻⁷, and some studies have described bronchogenic carcinoma caused by pulmonary aspergilloma⁶, whilst others have described only the coexistence of aspergilloma and carcinoma in the same cavity^{5,7}. Although it is not understood how aspergillosis could induce carcinoma formation, the chronic inflammation caused by prolonged fungal infection might be carcinogenic. Moreover, it is well known that chronic inflammatory cells can facilitate the initial steps in carcinogenesis¹⁵. With respect to the present case, it is uncertain as to whether the aspergillus originated from the respiratory tract or the extracted socket. However, it is believed that the aspergillus infection preceded extraction, because hyperdense lesion formation and bony destruction require considerable time after initial fungal infection¹¹.

A number of researchers have implicated HPV-16 and -18 in the pathogenesis of SCC arising from the nasal cavities and paranasal sinuses^{8,9}. In the present case, histopathologic features of koilocytosis were found throughout the epithelial surface adjacent to the neoplasm, which agrees with a previously published description of the histological features of koilocytosis, hyperkeratosis, and parakeratosis considered pathognomonic for papillomavirus infection^{16,17}. In the present case, HPV-18 DNA was detected using PCR, however, this type of HPV is rarely detected in HPV-positive oral or genital cancers. The authors believe that, in the present case, chronic inflam-

mation due to chronic fungal infection and HPV infection were causally associated with the development of SCC in the maxillary sinus.

We have presented a rare case of maxillary sinus aspergillosis with coexisting malignancy and HPV infection. We recommend careful examination, including preoperative cytology, in patients with maxillary sinus fungal infections because of the potential for cancer development.

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