

## Case Report

# Nasopharyngeal carcinoma mimicking Aspergillosis rhinosinusitis: an unusual case report and review of the literature

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**Abstract:** Clinical symptoms and imaging features of fungal infection are confused with those of atypical nasopharyngeal carcinoma (NPC), and therefore development of a more effective diagnostic method is essential. It is a common knowledge that there is a significant association between Epstein-Barr virus (EBV) and nonkeratinizing NPC. However, fungal infection may be considered to be a vital etiologic agent contributing to the NPC and more evidence is needed to be approved this theory. We report on a rare case of a patient with atypical nasopharyngeal carcinoma (NPC) who suffered from chronic fungal infection and was diagnosed initially as Aspergillosis. Following anti-aspergillus infection therapy, the repeated deep biopsy of the maxillary sinus and MRI confirmed the diagnosis of nasopharyngeal carcinoma (NPC).

**Keywords:** Nasopharyngeal carcinoma, atypical symptom, Aspergillosis, fungal infection, diagnosis, pathogenic factor

## Introduction

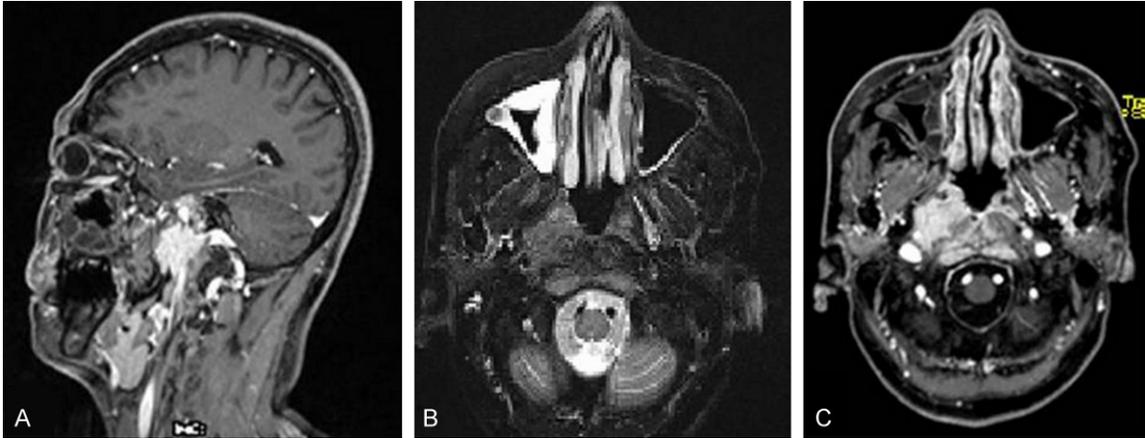
Aspergillosis is an increasingly common fungal infection consistently associated with the inhalation of prevalent airborne mold spores. *Aspergillus fumigatus* is often presented as the most common fungal pathogen of fungal rhinitis and pulmonitis, followed by the meninges, brain, liver, bone, thoracic cavity and others [1-3]. The common symptoms of chronic fungal rhinosinusitis such as mucopurulent nasal discharge, nasal obstruction, sneezing, postnasal drip and epistaxis were likely to be presented in both primary and secondary infections. Sometimes, Aspergillosis presents with some uncommon symptoms of tissue invasion that may erode the natural protective barriers of the sinuses and spread from the ear or nasal sinuses to the CNS, leading to cranial nerves, meningeal and intracerebral infections [4, 5]. What's more, Invasive Aspergillosis may develop ocular, aural and neurologic signs, such as blood-stained nasal discharge, ear effusion symptoms, hearing loss, headache, blurred vision, exophthalmous, diplopia, disorientation and tinnitus [6]. The clinical and radiological find-

ings of Aspergillosis rhinosinusitis may be mimicking those of nasopharyngeal carcinoma, therefore it is difficult to quickly distinguish atypical NPC patients from Aspergillosis. The clinician should be aware of these similarities between NPC and Aspergillosis when investigating patients with multiple nasopharyngeal symptoms. We presented a case of nasopharyngeal carcinoma coexisting with maxillary Aspergillosis that was initially treated as fungal sinusitis, which might be an extremely rare condition presented to otorhinolaryngologists and provide an opportunity to recognize the differential diagnosis between NPC and Aspergillosis. More interesting, although this patient was presented with the repeated treatment, he suffered from recurrent fungal sinusitis that has persisted for seven years. The mass sudden enlargement occurred simultaneously with the serious aspergillus infection. We suspect that chronic fungal infection may be regarded as the underlying cause of NPC.

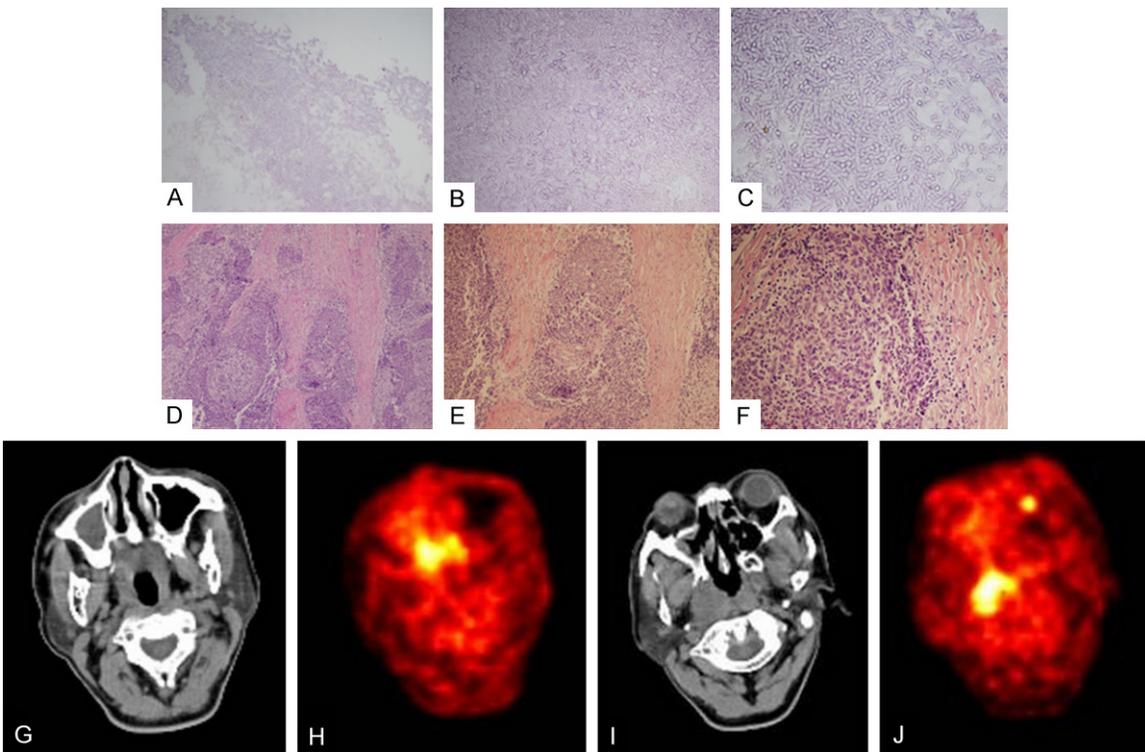
## Case report

A 60-year-old Chinese man presented to the otorhinolaryngologist with a seven-year history

## NPC occurring with Aspergillosis



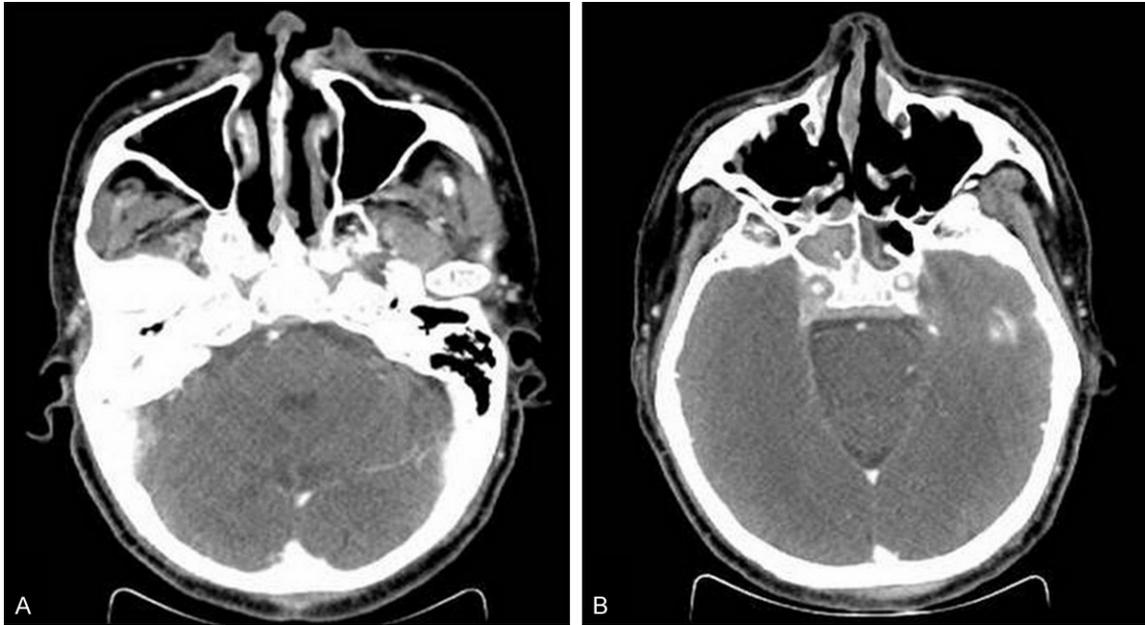
**Figure 1.** Contrast-enhanced MRI scan found an apparent contrast-enhancing soft tissue lesion in the right nasopharyngeal mucosa which filled with maxillary.



**Figure 2.** A, B. Before treatment of voriconazole, histopathologic examinations with eosin staining of the right maxillary sinus mucosa revealed abundant of aspergillus with a negative result of malignant cells; C. Under higher magnification of the aspergillus component, aggregation of fungal hyphae and branches were observed in the affected region ( $\times 400$ ); D-F. Deep nasopharyngeal biopsies confirmed the diagnosis of nonkeratinizing NPC after anti-fungal therapy; G-J. PET/CT images shows that abnormal FDG hypermetabolic foci filled with the right maxillary sinuses and invaded the orbital apex, petrous apex and the right sinus cavernosus.

of sneezing, rhinorrhoea and rust-colored stuff, was diagnosed as nasopharyngeal candidiasis and allergic fungal sinusitis. He also suffered an insulin-dependent, poorly controlled diabetes that had impaired peripheral nervous. Se-

veral therapies were introduced to control his fungal infection, without adequate control of the mucous lesion. Five months ago, the patient showed the symptom of blood-stained nasal discharge as it got worse. On clinician examina-



**Figure 3.** CT scan revealed the lesions was obviously shrunk following anti-fungal treatment and chemotherapy.

tion, the patient was in bad condition and presented with frontal headache, dizziness, blurred vision, diplopia and abducens nerve palsy. Nasopharyngoscopy showed bilateral smooth and slight swelling mucosa of the nasopharynx. Immunofluorescence serological tests for immunoglobulin (IgA) antibody against Epstein-Barr virus were negative. CT scan of the skull revealed a mild thickened of the right nasopharyngeal mucosa. Evidence from the Biopsies and cultures of biopsy specimens manifested aspergillus sinusitis. In addition to living in the epidemic area of nasopharyngeal carcinoma (NPC), no risk factors such as Epstein-Barr virus infection, consumption of salt-preserved fish, tobacco smoking, and familiar susceptibility of NPC were verified. However, the clinical and radiological features raised suspicion of NPC. The patient has been treated by fluconazole for fourteen days without the improvement of symptom. Then, he was presented to a contrast-enhanced MRI scan examination 2 months ago. Contrast-enhanced MRI scan found an apparent contrast-enhancing soft tissue lesion in the right nasopharyngeal mucosa which filled with maxillary, ethmoid and sphenoid sinus. The soft tissue lesion damaged the bone of the right ethmoid sinus (**Figure 1**). The repeated biopsies and cultures of biopsy specimens revealed an abundance of aspergillus and around calcium-depositing with a negative

result of malignant cells (**Figure 2**). Surgical access to the right sinuses was achieved by opening the sinus. Meanwhile, the repeated deep nasopharyngeal biopsies of the right maxillary sinus were presented to exclude malignant disease. What's more, the patient has been dealt with voriconazole to control fungal disease for one month. PET/CT images showed that abnormal FDG hypermetabolic foci filled with the right maxillary sinuses and invaded the orbital apex, petrous apex and the right sinus cavernosus (**Figure 2**). The last diagnosis of nonkeratinizing NPC depends on imaging findings, endoscopic studies and pathologic evaluation of immunohistochemistry (**Figure 2**). The patient underwent three courses of chemotherapy with paclitaxel, cisplatin and fluorouracil and was relieved of symptoms. A CT scan revealed that the lesion was obviously shrunk (**Figure 3**). The cultures of secretion revealed no evidence of aspergillus infection.

#### Discussion

Although NPC associated with Epstein-Barr virus infection has a low incidence in most parts of the world, it appears as a serious public health problem in Southeast Asia and to a lesser extent in North Africa [7]. Compared with the incidence rates of NPC at 85,000 new cases all over the world, its incidence approaches 50 per 100,000 persons per year in south-

ern China [8, 9]. It is the commonest head and neck cancer in highly populated areas of Southeast Asia. Patients of NPC usually present typical symptom including nasal obstruction, painless neck lumps and blood stained-nasal discharge. However, there are few cases which presented with atypical signs such as headaches, aural or ophthalmic symptoms and multiple cranial nerves dysfunction. In south-eastern China, when our patients are presented with similar symptoms, it is necessary to quickly exclude malignant disease before other diagnoses were considered. Diagnosis of NPC is always confirmed by histopathological staining of tissue biopsy, because mass is usually obvious on endoscopy of the nasopharynx. We also encounter a problem when NPC mimicking Aspergillosis only presented with the symptoms of fungal rhinitis. Aspergillosis within the center of an antral mass may co-exist with a carcinoma. Given the devastating consequences of nasopharyngeal carcinoma, early diagnosis and rapid treatment remains a major goal. In comparison, immunosuppressive patients are at higher risk of fungal infection. The levels of serological inflammatory markers, such as fungal cell wall beta-1,3-glucan, ESR, CRP, may markedly elevate and the biopsy of painless neck lumps may help establish a diagnosis. Cytological study of nasal-lavage washings and smear, fungal culture and multiple deep nasopharyngeal biopsies possess great value in the investigation of the aetiological agent. Additionally, effective imaging techniques play an increasingly important role in facilitating the improvement of early diagnosis. CT and MRI scans are conducive to establish an earlier diagnosis and exclude the possibility of other conditions from the differential diagnosis. CT examination is seen as an essential imaging tool for sinonasal lesions, which is a sensitive diagnostic modality revealed in the hazy inflammation reaction, mass filling sinus, orbital invasion, bone erosion or intracranial extension. The radiological findings show that the common characteristics of fungal sinusitis are haziness, bone destruction, calcification in CT scans. 80% of the primary and 69% of the secondary cases of fungal sinusitis revealed calcific densities in soft tissue masses [9]. It is useful to establish the diagnosis of the early invasive disease, and in addition to make the differentiation between NPC and fungal disease. CT offers the advantages in delineation of the bony anatomy erosion or destruc-

tion, although bony destruction is common characteristic of both aspergilus and NPC. Compared to CT, MRI is superior in offering high soft tissue contrast. When CT suggests fungus masses and bony erosion of sinus, MRI should be performed to establish a diagnosis and provide subtle signs of coexisting fungal infection and malignancy. With the recent development of MRI, it is regarded as a more sensitive and accurate method to demonstrate fungus ball and mucosal thickening of cavity, which can distinguish the thickened mucosa of inflammation from malignant disease. MRI scans show a low signal intensities on T1-weighted images of fungal rhinitis, but a markedly decreased signal with surrounding hyperintensities signal on T2-weighted images [10, 11]. In comparison, neoplastic disease is presented with an equally low signal intensities on T1-weighted image but an increased signal on T2-weighted image. MRI must be performed to determine the extent of intracranial or orbital invasion, which is more characteristic than CT [12].

More interesting, this patient presented with long established and uncontrolled fungal sinusitis and it has been supposed that this situation might expose the sinus mucus to carcinogens originated from the chronic infection. It is a common knowledge that there is a significant association between Epstein-Barr virus (EBV) and nonkeratinizing NPC, as shown by the raised levels of the EBV genome in the transformed epithelial cells. Nonetheless, chronic fungal infection is seldom regarded as the underlying cause of NPC, which shows the unresolved gaps in understanding this fascinating disease. Chronic fungal rhinosinusitis is a symptomatic inflammation of nasal or paranasal cavity, which is defined as disease processes persisting for 12 weeks or longer. It is well-established that the continuous chronic inflammatory stimulation can elevate the risk of cancer, which also may contribute to the genesis of NPC. As more cases of fungal infection co-existing various malignancy were reported, there is a possibility that fungal infection is the chronic stimulation which is a critical factor during oncogenesis [13-15]. Yuan et al suggested that Compared to control group, patients who suffered the chronic inflammation of ear and nose were more susceptible to NPC [12]. Firstly, chronic airway inflammation may reduce mucociliary clearance and stimulate epithelial cell transfor-

mation [16]. Then, carcinogenic compounds may be produced by fungi such as nitrosamines [17]. It is well-known that nitrosamine compounds triggered esophageal cancer in rats [18], which also could contribute to the genesis of the Oral [18, 19], bronchial, and nasopharynx cancer [20]. These carcinogens will bind with critical sites on DNA, such as hydrogen bonding sites or phosphate residues, which may lead to miscoding or irregularities with DNA replication [21]. The fungus with more exposure to nitrosation compounds is more likely to suffer advanced precancerous changes. What's more, the inflammatory process plays an essential role in eradicating pathogens, while increasing the incidence of cancer [22]. NPC may share the common inflammatory-mediated carcinogenic process that cytokines, eosinophilic proteases, radicals or chemically reactive oxidants recruit and activate additional immune cells, so as to impair the epithelial barrier [22, 23]. This evidence provided support for the hypothesis that chronic fungal infection created an environment conducive to cell bio-transformation and facilitates the initial steps in carcinogenesis [24].

Among patients with head and neck cancer, about two-thirds of patients presented with regionally advanced cancer are usually treated with surgery, radiotherapy and concomitant chemotherapy [25]. Patients receiving multimodality treatment often suffer from malnutrition, neutropenia and acute or chronic mucositis and present with debilitation and immunosuppression [26]. Mucositis is one of the most troublesome therapy-induced reactions. A complex pathobiological process ensures patients with fungal infection may discontinue the irradiation and cannot effectively locally control these cancers [27, 28]. Another even more importantly, the interaction between fungal and non-fungal predisposing factors is therefore considered to result in recurrence or progress of NPC.

In conclusion, we presented an extremely rare case of nonkeratinizing nasopharyngeal carcinoma co-existing with chronic fungal infection of maxillary sinus. This finding is especially important because an effective method was provided in differential diagnosis of atypical NPC and *Aspergillus* rhinitis. It also supports that fungal infection may be thought to be a vital etiologic agent contributing to the naso-

pharyngeal carcinoma. It is necessary to seek effective management to decrease both the tissue burden and the risk of subsequent development of NPC. However, none of these pathogenic theories are confirmed. It is certainly worth calling for large-scale laboratory experiments, molecular epidemiologic examination and controlled prospective clinical studies to illuminate the causative factor of this disease.

### Disclosure of conflict of interest

None.

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## NPC occurring with Aspergillosis

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