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Case Report

Aspergillus Sphenoiditis Associated with an Artificial Bone Graft Used for Transsphenoidal Surgery

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Cerebrospinal fluid (CSF) leakage is a major complication during and after transsphenoidal surgery (TSS) for intra- and suprasellar tumors. To prevent postoperative CSF leakage, various surgical techniques have been used, including sellar floor reconstruction with artificial bone grafts. However, some authors have recently reported infections associated with artificial bone grafts. Most cases are associated with bacterial infection, and fungal infection is extremely rare. We present the case of a 53-year-old woman with sphenoiditis caused by *Aspergillus* infection that developed 8 years after TSS and following local radiation therapy for a non-functioning pituitary adenoma. An artificial bone graft prepared from polymethylmethacrylate was used for sellar floor reconstruction. The patient presented to our department with a complaint of bloody nasal discharge. Magnetic resonance imaging showed that a fungal lump had formed around the bone graft, which had broken into two pieces and dropped out into the sphenoid sinus, without tumor recurrence. Histological examination of an endoscopic biopsy specimen led to a diagnosis of aspergillosis. Subsequent complete removal of both the bone graft and fungal lump resulted in a good postoperative outcome. Although fungal infection is an extremely rare complication after TSS using artificial bone grafts, it should be diagnosed as early as possible, and removal of both the fungal lump and the bone graft should be performed in a timely manner after clinical and radiological confirmation.

Keywords: Aspergillus, sphenoiditis, artificial bone, transsphenoidal surgery, radiation

Introduction

Sellar floor reconstruction using artificial bone grafts is a procedure for prevention of cerebrospinal fluid (CSF) leakage after transsphenoidal surgery (TSS) for intra- and suprasellar tumors. However, infections associated with artificial bone grafts have been reported recently.[1–4] Whereas bacterial infections are infrequently encountered, fungal infection of bone graft is extremely rare, as it has been reported in only one case.[2] We report a case of *Aspergillus*-induced sphenoiditis that developed 8 years after TSS using an artificial bone graft.

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Aspergillus infection comprises 5.5% of isolated sphenoiditis,[5] and sphenoiditis after TSS account for 4.8%.[6] But the frequency of *Aspergillus* sphenoiditis after TSS is unclear. *Aspergillus* infection in the sphenoid sinus may lead to life-threatening sequelae such as intracranial spread and intracarotid artery invasion, unless the pathogen can be detected at an early stage. Previously, *Aspergillus* infection was considered to occur in immunocompromised patients or those with systemic complications such as diabetes mellitus and malignancies. However, it has been increasingly reported that *Aspergillus* infection can occur in healthy hosts.[7] Patients should be screened for fungal infections after bone grafting, and if fungal infection is present, removal of both the fungus and the bone graft should be performed as the first line of treatment.

Case Report

A 53-year-old woman who was not under immunosuppressive state such as having diabetes mellitus or taking steroid underwent TSS two times 8 years previously for a non-functioning pituitary adenoma, which was treated with subtotal resection without any complications such as hypopituitarism or postoperative hemorrhage. Sellar floor reconstruction was successfully performed using an artificial bone graft prepared from polymethylmethacrylate (PMMA). Local radiation therapy (50 Gy) was delivered 3 months after the second surgery, because residual tumor grew in 2 months after first TSS although histopathological examination revealed a low MIB-1 labeling index and it could not be resected completely by two times surgeries. At 6 years after the second surgery, the patient experienced intermittent bloody rhinorrhea without fever and pain for 2 years and then presented at our hospital.

Computed tomography (CT) of the head showed that the bone graft had broken into two pieces and had dropped from the sellar floor into the sphenoid sinus. The graft pieces were completely surrounded by a low-density area (Fig. 1). Magnetic resonance imaging (MRI) of the head revealed the lesion as an isointensity on a T_1-weighted image (WI) and hyperintensity on a T_2-WI; the lesion occupied the entire sphenoid sinus, suggesting sphenoiditis. The area surrounding the bone graft pieces was hyperintense on a T_1-WI and hypointense on a T_2-WI. Gadolinium enhancement was seen around this lesion. However, tumor recurrence was not observed in the sellar region (Fig. 2G–I), which suggested that some type of infection had been induced by the bone graft pieces in the sphenoid sinus.

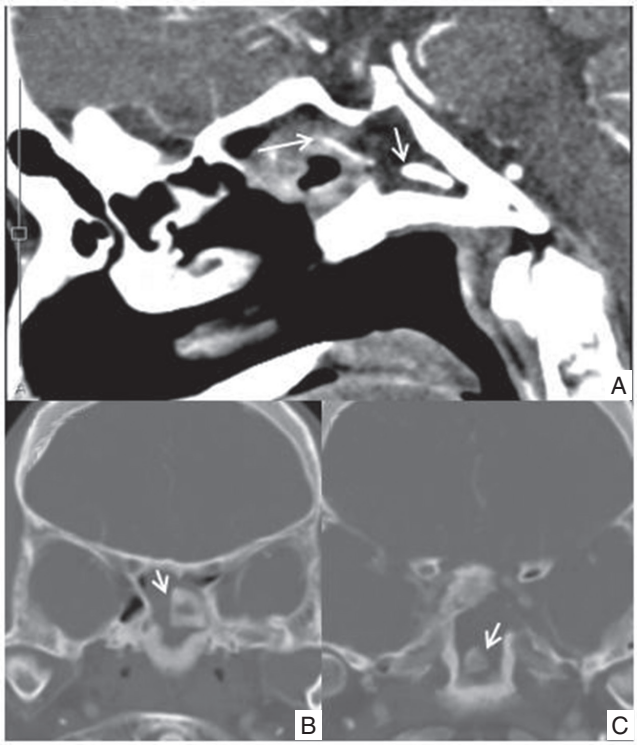

Fig. 1 Computed tomography scans on admission (A: sagittal section, B, C: coronal section, bone images) showed that the bone graft was divided into two pieces (arrows) and dropped out into the sphenoid sinus; there was no evidence of skull base destruction with sphenoiditis.

An otolaryngologist at our hospital diagnosed *Aspergillus* infection in the sphenoid sinus after examining an endoscopic biopsy specimen of the mass. The specimens showed massive *Aspergillus* hyphae on Grocott staining (Fig. 3A, B). Retrospective evaluation of postoperative MRIs revealed that the bone graft had dropped out into the sphenoid sinus 3 years after TSS and that it was exposed to air anteriorly and embedded in proliferated mucosa posteriorly with gadolinium enhancement (Fig. 2A–C). Two years later, a mass lesion on the air-exposed anterior side of the bone graft revealed as an isointensity on a T_1-WI and hypointensity on a T_2-WI. Gadolinium bright enhancement was present around the bone grafts (Fig. 2D–F). But the patient complained of no symptom, such as bloody rhinorrhea, therefore the lesion was left untreated not to recognize as *Aspergillus* infection. The patient was admitted to our department for removal of the bone graft and the entire fungal lump through endoscopic transnasal surgery. In the sphenoidal phase of surgery, the two graft pieces were found to be surrounded by clay-like material that appeared to be infected granulation tissue (Fig. 3C). The sellar floor and its surrounding bony structures were intact. The bone grafts and the fungal lump were completely removed.

Postoperatively, an anti-fungal agent, amphotericin B, was administered for 4 days. After discharge without any neurological complications, intranasal irrigation with saline was continued once a week as an outpatient treatment at the otolaryngology department for 1 year. Clinical manifestation of

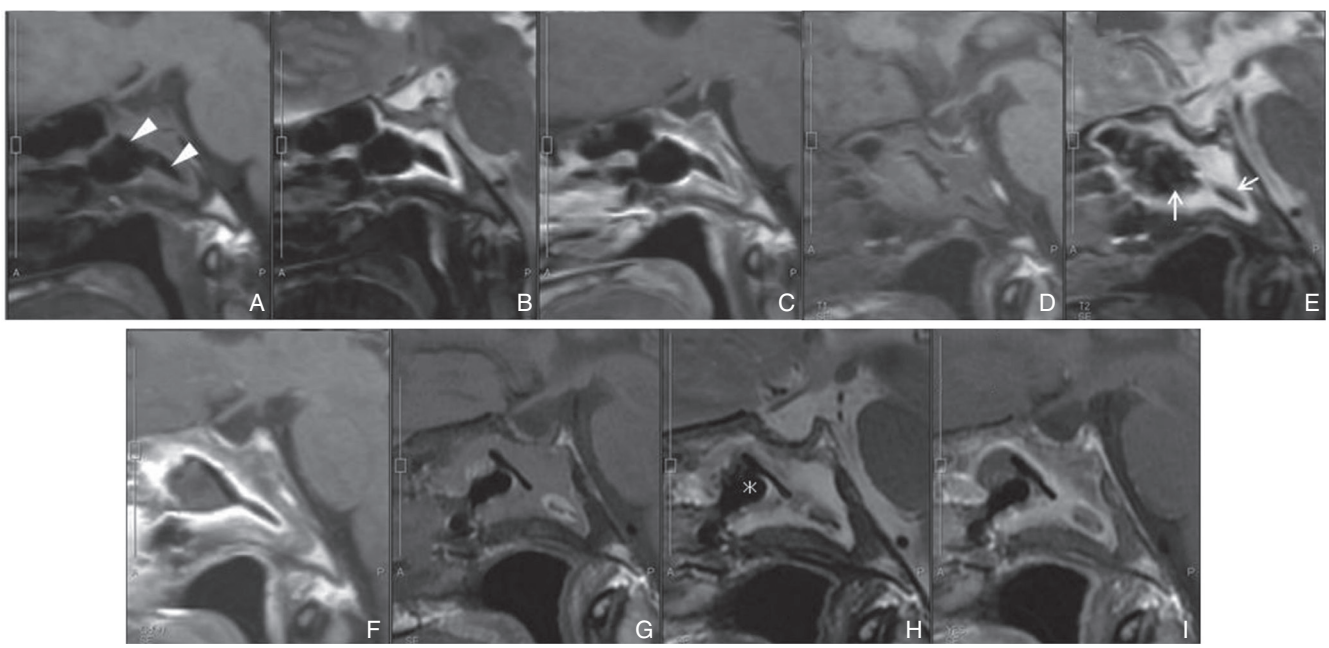

Fig. 2 MRI 3 years after second TSS [A: T_1-weighted image (WI), B: T_2-WI, and C: gadolinium enhancement image] revealed the dropped-out bone grafts (arrowheads) were exposed to air. MRI 5 years after TSS (D: T_1-WI, E: T_2-WI and F: gadolinium enhancement image) showed a hypointense area (arrows) appeared at the area exposed to air and gadolinium bright enhancement was present around the bone grafts, suggesting that an airborne fungal infection had developed. MRI 8 years after the TSS (G: T_1-WI, H: T_2-WI, and I: gadolinium enhancement image) indicated presence of sphenoiditis. The area surrounding the bone grafts were observed as hyperintensity on the T_1-WI and hypointense on the T_2-WI with gadolinium enhancement around the mass, suggesting fungal lump. A biopsy was performed (asterisk) to detect *Aspergillus*. MRI: magnetic resonance imaging, TSS: transsphenoidal surgery.

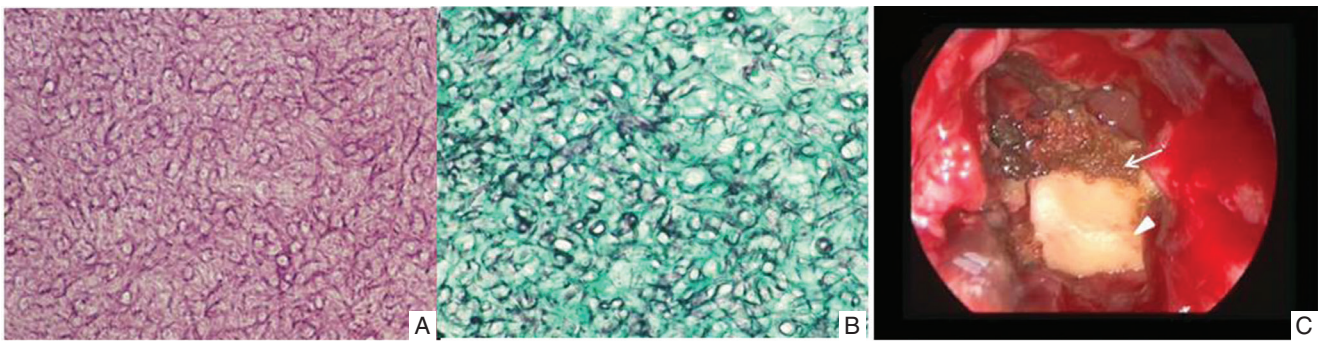

Fig. 3 Photomicrographs of the biopsy specimen (A: hematoxylin-eosin stain, B: Grocott's methenamine silver stain) show septated hyphae and dichotomous branching typical of *Aspergillus* species. (C) Intraoperative photograph shows that the dropped-out bone graft (arrowhead) was surrounded by infected granulation tissue (arrow).

nasal rhinorrhea and recurrent sphenoiditis on MRI has not been detected for 2 years.

Discussion

Currently, several types of artificial bone graft materials, such as PMMA, ceramic and titanium, are available for cranioplasty. These bone grafts are useful for achieving a good cosmetic outcome and protection against infection and trauma. Infections caused by bone grafts are infrequently reported.[1–4] Matsuno et al. found that the rates of postimplantation infection in bone grafts are 12.7% for PMMA, 2.6% for custom-made titanium mesh, and 5.9% for custom-made ceramics.[3] Regarding etiological agents, Tokoro et al. found that most cases of bone graft infections were caused by bacteria.[4] Morrow reported a case of cranioplasty infection caused by *Sporobolomyces*.[2] However, fungal infection of bone grafts is extremely rare. Fungi can colonize implanted foreign bodies such as central venous catheters, pacemaker leads, and prosthetic joints, resulting in systemic complications.[8–11] Feely and Steinberg described two cases of *Aspergillus* infection caused by a transsphenoidal ^{90}Y pituitary implant mounted on stainless steel screws to destroy the pituitary by interstitial irradiation.[12] To the best of our knowledge, this is the first report of *Aspergillus* infection in an artificial bone graft.

Aspergillus commonly infects immunocompromised hosts through aerial transmission. The risk factors for fungal infection include hematologic malignancy, diabetes mellitus, steroid therapy, and acquired immunodeficiency syndrome.[13] Although the precise mechanism remains unknown, *Aspergillus* infection is increasing among healthy hosts.[7] Fungal rhinosinusitis is divided into invasive and non-invasive forms. Invasive fungal infection can lead to fatal sequelae, and the mortality rate is reported to be 50–80%.[14] Patients are likely to present nasal discharge, pain, and swelling of the face, but these symptoms are not specific. MRI features of Aspergillosis are characteristic. T_1-WI shows as an iso- to hypointensity and T_2-WI as extremely hypointensity because of the presence of ferromagnetic elements such as iron, zinc, magnesium, and manganese in fungus. Gadolinium-enhanced image shows bright homogeneous enhancement suggesting solid nature of *Aspergillus* mass or ring enhancement suggesting cystic nature of pus.[15] Biopsy is essential for the final diagnosis.[16] Aggressive surgical removal is considered to be the first line of treatment.[17]

In the present case, an immunocompetent woman developed *Aspergillus* sphenoiditis. We address the two following features in this case. First, the patient underwent radiation therapy after two TSS. Second, the artificial bone graft dropped into the sphenoid sinus. Under normal conditions, bone grafts applied to bone defects at the sellar floor are held in place by the mucous membrane in the sphenoid sinus, which regenerates immediately after the TSS procedure. Langendijk et al. described that acute inflammation and subsequent chronic mucosal atrophy are among the side effects of radiation therapy.[18] The medical records of the present patient indicated that the target area for the radiation was the posterosuperior part of the sphenoid sinus. If radiation-induced mucosal atrophy occurred at the sellar floor, the support of the bone graft would be unstable, possibly resulting in the graft dropping into the sphenoid sinus. Some reports have also suggested side effects of radiation therapy such as a decreased local immune response. Bensadoun et al. reviewed cases of oropharyngeal candidiasis in head and neck cancer patients after radiation therapy and found that the fungal infection was associated with local mucosal injury secondary to cancer therapy and hyposalivation caused by radiation.[19] Ogawa et al. reviewed six cases including a case of laryngeal aspergillosis following radiation therapy and speculated that local irradiation could play an important role in the onset of fungal infection as a local aggravating factor.[20] Rivera et al. and Crompton et al. addressed the immunological defensive mechanism of CD4 T-lymphocytes which are indispensable to eliminate *Aspergillus* but undergo apoptosis upon irradiation.[21,22] Therefore, in the present case, radiation therapy may have induced a local immunocompromised state that allowed transient spread of *Aspergillus* in the sphenoid sinus.

Our case may have involved three possible mechanisms of *Aspergillus* infection spreading of the fungal infection into the sphenoid sinus from the respiratory tract, hematological

metastasis from the infected respiratory tract, and direct iatrogenic implantation of the pathogen during TSS. Because our patient did not present with any respiratory fungal disease for 8 years after the first TSS, hematological metastasis and direct implantation of aspergillosis during or after TSS can be excluded as the infection mechanism. Transient sphenoiditis caused by fungal infection may occur even in healthy hosts. MRI following TSS showed that the bone graft had dropped into the sphenoid sinus and had been exposed to air prior to fungal infection. Therefore, the mechanism of sphenoiditis development most likely involved fungal transfer from the respiratory tract to the dropped-out bone graft in the sphenoid sinus.

We have presented a case of *Aspergillus* sphenoiditis associated with an artificial bone graft used for sellar floor reconstruction. Radiation therapy and bone grafting can be risk factors for fungal infection even in immunocompetent hosts. It is therefore necessary to diagnose and treat *Aspergillus* infection as early as possible once it occurs. Long-term attention should be paid to the patient's clinical condition after TSS using an artificial bone graft.

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Conflicts of Interest Disclosure

All authors declared no conflicts of interest.

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