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Case Report / Olgu Sunumu

Ophthalmoplegia due to Invasive Fungal Sinusitis: A Report of Three Cases

İnvaziv Fungal Sinüzite Bağlı Gelişen Üç Oftalmopleji Olgusu

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Abstract

Invasive fungal sinusitis is an infection of the paranasal sinuses that should be diagnosed early due to its high mortality and morbidity rates. Mucormycosis and aspergillus are the two most important agents of invasive fungal sinusitis. Although usually seen in patients who are immunocompromised, they are rarely seen in immunocompetent patients. In this article, we present three patients with ophthalmoplegia; one patient with hematologic malignancy, and two patients with uncontrolled diabetes. By presenting these three patients with invasive fungal sinusitis, we aimed to emphasize the possible role of fungal sinusitis in the development of ophthalmoplegia in patients with diabetes or immunosuppression due to any reason, and the importance of early treatment.

Keywords: Aspergillus, mycoses, ophthalmoplegia, sinusitis

Öz

İnvaziv fungal sinüzit, paranazal sinüslerin yüksek mortalite ve morbidite nedeniyle erken tanınması gereken bir enfeksiyonudur. Mukormikoz ve aspergillus, invaziv fungal sinüzitin en önemli iki etkenidir. Genellikle immünsüprese kişilerde görülmekle birlikte, nadiren immünsüpresyonu olmayanlarda da görülebilir. Bu yazıda oftalmopleji kliniği ile gelen hematolojik malignitesi olan bir ve kontrolsüz diyabeti olan iki olgu sunulacaktır. İnvaziv fungal sinüzit saptanan bu üç hastanın sunulması ile diyabeti veya herhangi bir nedenle immünsüpresyonu bulunan hastalarda oftalmopleji gelişiminde fungal sinüzitin ön tanılar içinde akla gelmesi ve erken tedavinin öneminin vurgulanması amaçlanmıştır.

Anahtar Kelimeler: Aspergillus, mantar hastalıkları, oftalmopleji, sinüzit

Introduction

Invasive fungal sinusitis is a rapidly progressive, fatal infection that is most commonly observed in patients with diabetes, patients with hematologic malignancies, and in patients with neutropenia due to immunosuppression (1). It was first identified by Plaignaud in 1791, and was classified into invasive and non-invasive forms. Invasive fungal sinusitis was then further divided into sub-groups, such as granulomatous, chronic, and acute fulminant. The fungal elements present in the sinuses can spread to the orbits by causing bone erosion, and to the cavernous sinus and intracranial area through vascular pathways (2). Most invasive fungal sinusitis cases are caused by Mucormycosis and Aspergillus.

Mucormycosis is a saprophytic, filamentous fungal infection caused by Zygomycete fungi from the Mucorace family. Rhizopus, Rhizomucor, Mucor, and Absidia species have been demonstrated as responsible agents. Paranasal sinusitis, headache and facial pain,

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fever, nasal discharge, nasal ulceration, and vision problems are observed in rhinocerebral mucormycosis. The spread of the disease from paranasal sinuses to the intracranial area occurs through the skull base. Aspergillosis is another important factor other than mucormycosis. The most common agents are *A. fumigatus* and *A. flavus.* The maxillary sinus is the most frequently affected sinus.

Fungal sinusitis should be ruled out in cases of headache and ophthalmoplegia that are incompatible with the clinical status of immunocompromised patients. The most common cause of immunosuppression is diabetes mellitus. Cranial magnetic resonance imaging (MRI) to visualize soft tissue involvement, computed tomography (CT) to visualize bone erosion and direct nasopharyngeal examination for the detection of fungal elements should be performed without losing time because of the fulminant course of the disease (3). The definitive diagnosis is made by histologic examination and cultivation of the fungal agent. When suspected clinically, amphotericin B therapy should be initiated without waiting for a definitive diagnosis.

In order to emphasize the importance of early diagnosis and treatment of these patients with a high mortality rate, three patients with hematologic malignancy and uncontrolled diabetes who presented with ophthalmoplegia are reported.

Case Reports

Case 1

A woman aged 50 years with diabetes was admitted to our clinic due to worsening right retroorbital headache for one month and diplopia during the last five days. Her neurologic examination revealed limited outward, inward, and upward gaze in the right eye (Figure 1A). Blood test results were as follows: C-reactive protein (CRP): 1.47 mg/dL, leucocytes: 10.18 /µL, sedimentation: ½ 7 mm/hr, hemoglobin: 12.3 g/dL, thrombocytes: 207.000 /mm^3, glucose (fasting): 164 mg/dL and glycosylated hemoglobin (HbA1c): 11.7%. These results showed that the patient had uncontrolled diabetes.

Fat-suppressed T2-weighted sequence cranial MRI and orbital MRI revealed hyperintensity extending from the periphery of the right optic nerve sheath to the orbital medial segment, superior oblique muscle, orbital apex, and superior orbital fissure in the intraconal orbital compartment. Contrast enhancement was present in the same region on post-contrast T1-weighted images (Figure 1B).

A paranasal sinus CT examination revealed a focal soft tissue density filling the right middle meatus and the air space of the right maxillary sinus ostium (Figure 1B). Absidia corymbifera was cultivated from the samples obtained during a direct nasopharyngeal examination by ear, nose, and throat (ENT) specialists.

Intravenous (IV) amphotericin B at a dose of 350 mg and oral posaconazole 40 mg at a dose of 2x2 were initiated. Ethmoidectomy and sphenoidectomy surgeries were performed by ENT specialists. Amphotericin B treatment was completed and discontinued in 21 days. During the post-operative follow-up period, there was no significant change in the patient's clinical status and he was referred for outpatient clinic follow-up.

Case 2

A woman aged 72 years with diabetes was admitted to our clinic due to pain in the left eye for 6 months and diplopia for 1 month. It was learned that she was admitted to another hospital and was treated with 10 mg oral prednisolone, and her symptoms were partially relieved. She was hospitalized for the investigation of the etiology of the ophthalmoplegia and for its treatment, and the neurologic examination revealed limited outward gaze, myosis, and ptosis in the left eye. Laboratory examinations were as follows: CRP: 0.55 mg/dL, leukocytes: 5.41/µL, glucose (fasting): 115 mg/dL, and HbA1c: 8%.

Fat-suppressed T2-weighted sequence cranial MRI revealed increased signal intensity in the left retroorbital area extending into the optical foramina and cavernous sinus, and a heterogeneous contrast enhancement pattern on post-contrast T1-weighted images (Figure 2A).

Lumbar puncture performed for etiologic diagnosis revealed a cerebrospinal fluid (CSF) protein of 27 mg/dL and CSF glucose of 90 mg/dL. Concurrent blood glucose was 219 mg/dL, electrolytes were within normal limits, and bacteriologic and mycologic tests of direct examination were normal.

No pathologic findings were detected in the otorhinolaryngologic evaluation in order to exclude possible fungal sinusitis because of the concomitant diabetes of the patient. The patient was diagnosed as having Tolosa-Hunt syndrome and was

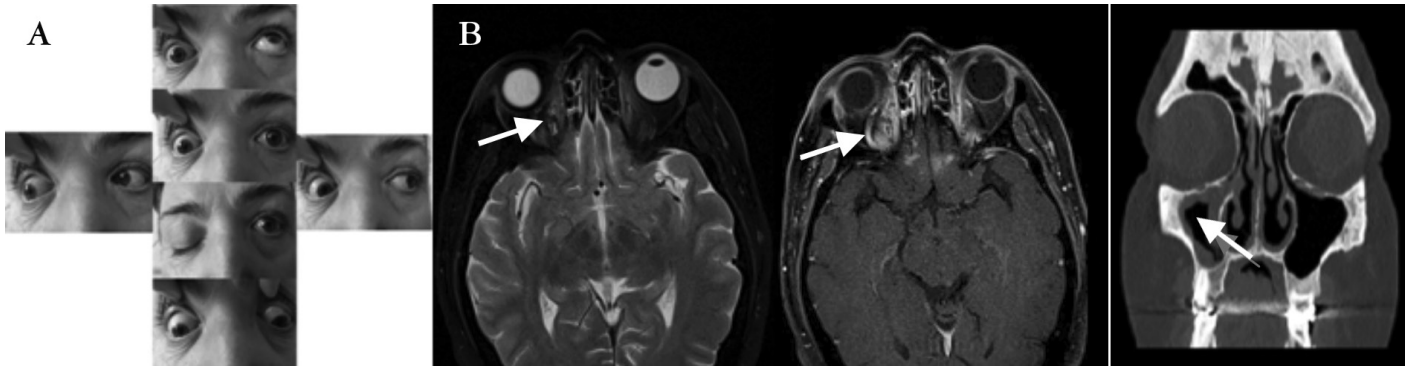

Figure 1. A) Limited outward, inward, and upward gaze, and complete ptosis in the right eye. B) Right retro-orbital hyperintensity showing infective tissue on T2-weighted cranial magnetic resonance images and contrast enhancement in the same region on post-contrast T1-weighted images. Soft tissue density in the right maxillary sinus was observed in the paranasal sinus computed tomography. Pathological features are indicated by arrow.

administered pulse steroid therapy for 5 days because no secondary cause was detected in the imaging and CSF examination of the patient. Regression was observed in the severe pain around the eyes. However, the diagnosis was reconsidered on the recurrence of pain around the eye. Paranasal sinus CT (Figure 2A) revealed a defect on the left lateral wall of the sphenoid sinus and soft tissue density extending from the orbital apex to the sinus through this defect. In comparison with the previous MRI, the soft tissue extending towards the anterior wall of the cavernous sinus in the left orbital apex was thought to be associated with a small abscess within the sphenoid sinus on follow-up cranial MRI (Figure 2B).

Worsening was observed in the clinical status of the patient during the follow-up period. In a neurologic examination, the gaze in the left eye in all directions was completely limited and full

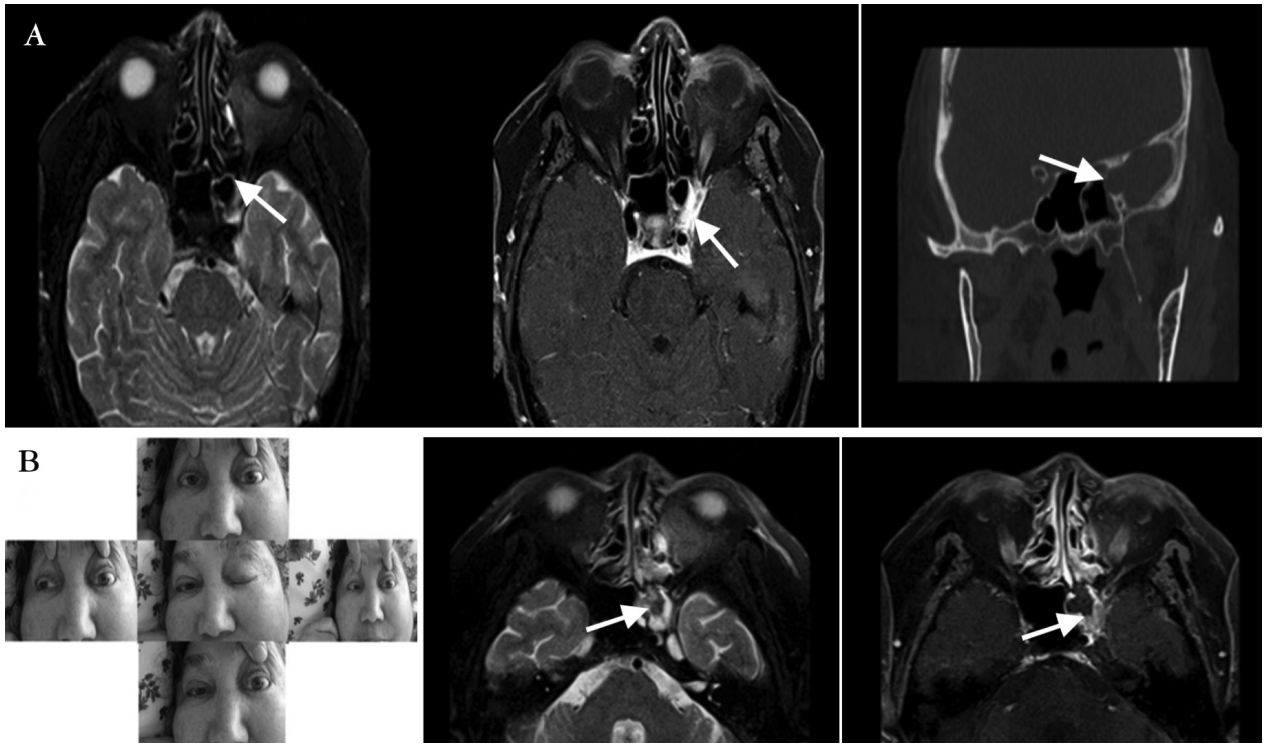

Figure 2. A) Hyperintensity extending from the periphery of the left optic nerve sheath to the orbital medial segment, superior oblique muscle, orbital apex, and superior orbital fissure in the intraconal orbital compartment on fat-suppressed T2-weighted magnetic resonance images and heterogeneous contrast enhancement on post-contrast T1-weighted images. Defect on the left lateral wall of the sphenoid sinus and a soft tissue density extending from the orbital apex to the sinus through this defect. B) The gaze in the left eye in all directions was completely limited and full ptosis was present. Cranial magnetic resonance imaging showed progression and abscess formation. Contrast enhancement was noted on post-contrast T1-weighted images. Pathological features are indicated by arrow.

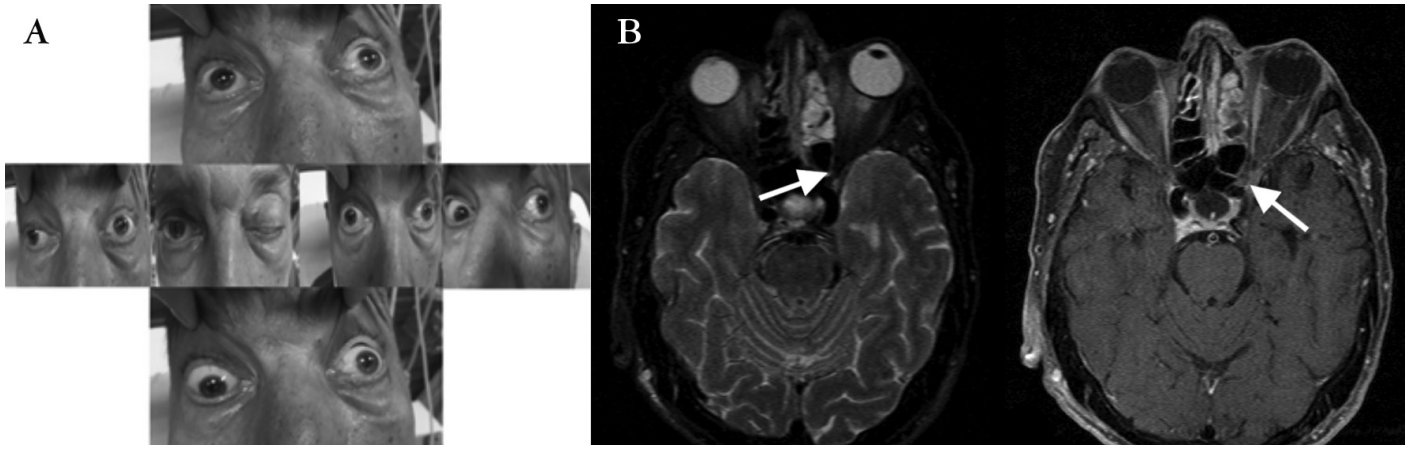

Figure 3. A) Gaze was restricted in all directions and there was complete ptosis in the left eye. B) Soft tissue intensities and contrast enhancement around the left optic nerve are noticeable on fat-suppressed T2-weighted images. Pathological features are indicated by arrow.

ptosis was present (Figure 2B). Abscess drainage was performed by ENT specialists. Mycelia were seen in the specimen taken from the abscess material. Aspergillus was detected by incubation of the material. IV amphotericin B therapy at a dose of 50 mL was initiated.

Case 3

A man aged 70 years with chronic lymphocytic leukemia was admitted to the emergency department due to headache, left-sided ptosis, and decreased visual acuity for about 1 week. In a neurological examination, there was complete ptosis in the left eye and gaze was restricted to all directions (Figure 3A). Fat-suppressed T2-weighted sequence cranial MRI revealed soft-tissue intensities around the left optic nerve, and contrast enhancement was detected on post-contrast T1-weighted images (Figure 3B). Cranial CT examination revealed findings of left ethmoid and maxillary sinusitis. Findings suggesting fungal infection were detected in a direct nasopharyngeal examination that was performed by ENT specialists with a preliminary diagnosis of ophthalmoplegia due to fungal sinusitis. Rhizopus was detected by incubation of the debridement material and amphotericin B treatment was initiated. Despite treatment, the post-operative clinical status and radiologic appearance of the patient deteriorated, and the patient died about one month after the diagnosis.

Discussion

Invasive fungal sinusitis is a rapidly progressive and fatal infection that is common in patients with diabetes, hematologic malignancies, and neutropenia due to immunosuppression. It can spread to the orbit by causing bone erosion, and to cavernous sinus and intracranial area through vascular pathways. There was spread to the orbital apex also in all our cases.

The survival rate in patients with invasive fungal sinusitis is close to 50% (4). This rate is also dependent on the presence of predisposing factors such as immunosuppression and malignancy. The predisposing factor was uncontrolled diabetes mellitus in two of our patients, and chronic lymphocytic leukemia in our last patient.

Mucormycosis constitutes most cases of invasive fungal sinusitis. Mucormycosis is a common name given to diseases formed by Mucor, Rhizopus, and Absidia species, with similar properties to the Mucorace family, which are characterized by organ involvement. The most common clinical form is rhinocerebral involvement (5). The most common predisposing factor is diabetes. The more frequent occurrence of mucormycosis in patients with diabetes is due to the reduction of iron binding capacity of transferrin in these patients and the more rapid proliferation of fungi by using the iron more easily. Aspergillus is also an important agent in invasive fungal sinusitis. With the majority of these caused by *A. fumigatus*, there has been an increase in infections with other Aspergillus species such as *A. terreus* and *A. flavus* in recent years (6). In our study, the causative agent was Absidia in the first case, *Aspergillus fumigatus* in the second case, and Rhizopus infection in the third case.

Imaging has critical importance for diagnosis. Although cranial and orbital MRI provides superiority over CT in the visualization of soft tissue, paranasal sinus CT examination should be performed in cases with suspected invasive fungal sinusitis for the demonstration of bone erosion on the sinus walls. Although orbital and cranial MRI were consistent with Tolosa-Hunt syndrome in our second case, the presence of a defect in the sphenoid sinus wall on paranasal sinus CT was the main support for the diagnosis.

Invasive fungal sinusitis requires early and aggressive treatment. Treatment includes correction of the underlying predisposing factors, aggressive debridement, and systemic antifungal drug administration. Amphotericin B is the first-line treatment effective against mold. Liposomal forms of amphotericin B are preferred due to their fewer adverse effects. In terms of effective treatment, all necrotic tissues should be debrided and the operation area should be irrigated with antifungal solutions after debridement (7,8). Irrigation with antifungal solutions was also performed in all our cases, and ethmoidectomy and sphenoidectomy were performed in addition to debridement in the first case. Amphotericin B was administered systemically in all three cases. We observed improvement in visual findings and diplopia in our cases with early diagnosis and appropriate treatment. For this reason, diagnosis and appropriate treatment of these cases are important for the prevention of sequelae.

Ethics

Informed Consent: Consent forms were completed by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y.Ç., N.C., Concept: A.Y.Ç., F.G., N.Ç., A.G., A.GÜ., H.P., R.M., S.G., Design: A.Y.Ç., F.G., N.Ç., Data Collection or Processing: A.Y.Ç., F.G., N.Ç., A.GÜ, A.G., Analysis or Interpretation: A.Y.Ç., F.G., N.Ç., A.G., A.GÜ., H.P., R.M., S.G., Literature Search: A.Y.Ç., F.G., N.Ç., Writing: A.Y.Ç., F.G., N.Ç., A.G., A.GÜ.

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