THE PROBABLE ROLE OF DESFERRIOXAMINE FOR RHINOCEREBRAL MUCORMYCOSIS IN A DIABETIC PATIENT

Özlem KANDEMİR*, Kemal GÖRÜR, Elif ŞAHİN*, Cengiz ÖZCAN**, Duygu DÜŞMEZ APA*****

*Mersin University School of Medicine, Department of Clinical Microbiology and Infectious Diseases, MERSİN
**Mersin University School of Medicine, Department of Otorhinolaryngology, MERSİN
***Mersin University School of Medicine, Department of Pathology, MERSİN

SUMMARY

Mucormycosis is the term for infections caused by fungi of the order Mucorales. These fungi may produce a severe disease in susceptible individuals, notably immunocompromised patients with diabetes, acidosis and receiving desferrioxamine. Rhinocerebral mucormycosis is a clinical form which is caused by these fungi. If this form of the disease is not treated, it can rapidly progress and cause death. Diabetic ketoacidosis is more important than hyperglycemia alone in rhinocerebral mucormycosis. If the other diseases which cause immunodeficiency are also present, the prognosis of the disease is worse. This case report describes a patient who is diagnosed as rhinocerebral mucormycosis associated with non acidotic diabetes and myelodysplastic syndrome. This case also was administered desferrioxamine to decrease the elevated serum iron level. The disease rapidly progressed and patient died although aggressive therapy (surgical and medical) was performed.

Keywords: *desferrioxamine, diabetes mellitus, rhinocerebral mucormycosis*

ÖZET

Diabetik bir Hastada Rinoserebral Mukormikozis Gelişiminde Desferrioksaminin Olası Rolü

Mukormikozis, Mucorales sınıfındaki mantarların neden olduğu infeksiyonu tanımlar. Bu mantarlar, duyarlı konakta özellikle diabetik, asidotik, immünyetmezlikli ve desferrioksamin tedavisi alanlarda ciddi seyirli hastalığa neden olabilirler. Rinoserebral mukormikozis bu mantarların neden olduğu klinik bir formdur. Hastalığın bu formu tedavi edilmezse hızlı ilerler ve ölüme neden olabilir. Rinoserebral mukormikozis gelişiminde diabetik ketoasidoz tek başına hiperglisemiden daha önemlidir. İmmün yetmezliğe neden olan diğer hastalıklar da varsa hastalığın prognozu kötüdür. Bu olgu sunumunda, nonasidotik diabetik ve miyelodisplastik sendromla ilişkili rinoserebral mukormikozis tanısı olan bir hasta sunulmuştur. Sunulan olguda yüksek serum demir düzeyini azaltmak için desferrioksamin tedavisi uygulanmaktaydı. Agresif tedavi uygulandığı halde olgunun hastalığı hızlı ilerledi ve hasta kaybedildi.

Anahtar sözcükler: *desferoksamin, diabetes mellitus, rinoserebral mukormikozis*

INTRODUCTION

Mucormycosis is the term for infection caused by fungi of the order *Mucorales*. The causative organism is *Rhizopus oryzae* in most cases. Mucormycosis is a rare but serious fungal infection that rapidly attacks and usually kills its untreated victims, who are often in acidosis, immunocompromised or receiving defferioxamine[3]. Many reported cases have been poorly controlled diabetics. Rhinocerebral mucormycosis usually originates in the nasal mucosa from where it spreads to the sinuses, orbit and cranial cavity[8]. The fungi has a remarkable affinity for blood vessel walls, causing thrombosis and infarction of tissues. Because of the rapidity in the progress of the disease, prompt and aggressive therapy is essential[13]. Successful treatment

Corresponding Address: Özlem Kandemir. Mersin Üniversitesi Tıp Fakültesi Hastanesi, Enfeksiyon Hastalıkları Anabilim Dalı, MERSİN
Phone: +90 324 337 43 00/1121
e-posta:kandemirege@hotmail.com
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of rhinocerebral mucormycosis is dependent on three cardinal principles: surgical resection of the infected tissue, reversal of underlying metabolic or immunologic impairments, and administration of amphotericin B.

We present a patient with rhinocerebral mucormycosis who received desferrioxamine and also suffered from uncontrolled type 2 diabetes mellitus. Here, we will discuss the fatality course of the disease although aggressive therapy is performed and possible role of desferrioxamine in the etiopathogenesis.

CASE REPORT

A 71 yearold man was presented to emergency department with complaints of headache, fever and blindness in the left eye. His medical history revealed that severe headache in frontal region, behind the eyes had begun about five days ago. Following this uncomforting sense, blindness occurred on fourth day in the left and on sixth day in the right eyes respectively. There was a history of uncontrolled type 2 diabetes mellitus; hypertension and myelodysplastic syndrome. The patient was administered desferrioxamine for the relief of possible complication of blood transfusion during the past 15 years. The patient was consulted by neurologist and cavernous sinus thrombosis was thought out and he was referred to radiology department for cerebral computerized tomographical (CT) evaluation. During neuroradiologic evaluation, the patient was also consulted by an otorhinolaryngolog. After the nasal endoscopical examination, the patient was transferred to the otorhinolaryngology department.

Physical examination revealed that general health status of the patient was serious and complete vision loss was observed in both eyes. There was no pupillary reaction and oculoplegia was detected in both eyes. There was no other neurological deficit. The patient had pyrexia with a temperature of 39°.2 C. Hematological investigations revealed leukocytosis. WBC: 17,700/mm^3, Hb: 10.6 g/dL, CRP: 245 mg/L, ESR 111 mm/hour. The random blood sugar was high at 229 mg/dL, BUN: 63 mg/dL, creatinin: 1.5 mg/dL. The maxillofacial coronal CT revealed a soft tissue mass filled the left anterior ethmoid, maxillary, sphenoid sinuses (Figure 1 A and B). Rigid endoscopy of the nose showed

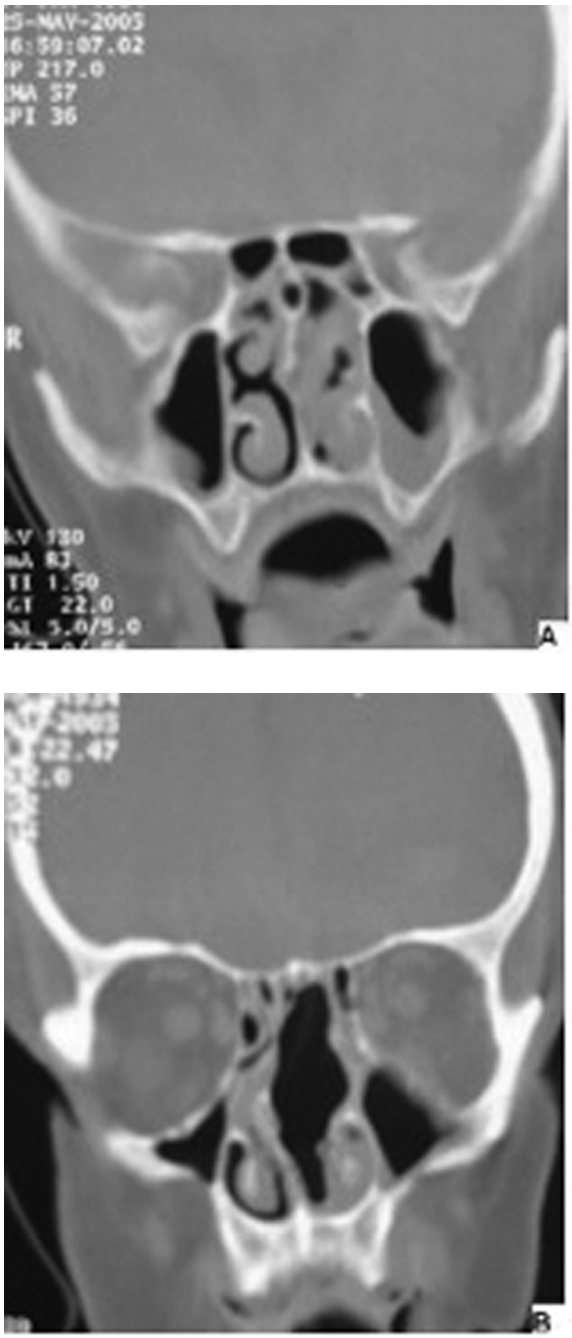

Figure 1: *Soft tissue mass filled the left anterior ethmoid, maxillary and sphenoid sinuses (A) and postoperative changes (B) is shown in maxillofacial coronal CT.*

a black color tissue in the left middle, superior turbinates, left side of nasal septum and cribriform area. But there was no discharge in the nasal cavity. Examination with a mucoperiosteal elevator of the aforementioned sides revelaed that the tissues were rigid, fragile and avascularized. Extensive debridment of the necrotic tissues was performed under the guidance of nasal endoscope with a presumable diagnosis of rhinocerebral mucormycosis. The resected tissues were sent for pathological and microbiological examinations. On the microbiological examination, Gram and KOH stains were performed; it was also inoculated in blood agar, MacConkey agar, and Sabouraud agar. Culture results were found negative but it was reported as "mucormycosis" by pathologic examination (Figure 2, 3), and liposomal amphotericine B was started (3 mg/kg/day) as suggested by infectious diseases specialist. In order to regulate diabetes mellitus, the patient was consulted by an endocrinologist. The general condition of the patient detoriated, and consciousness was lost on the fifth day of amphotericine B treatment and the patient died at the same day.

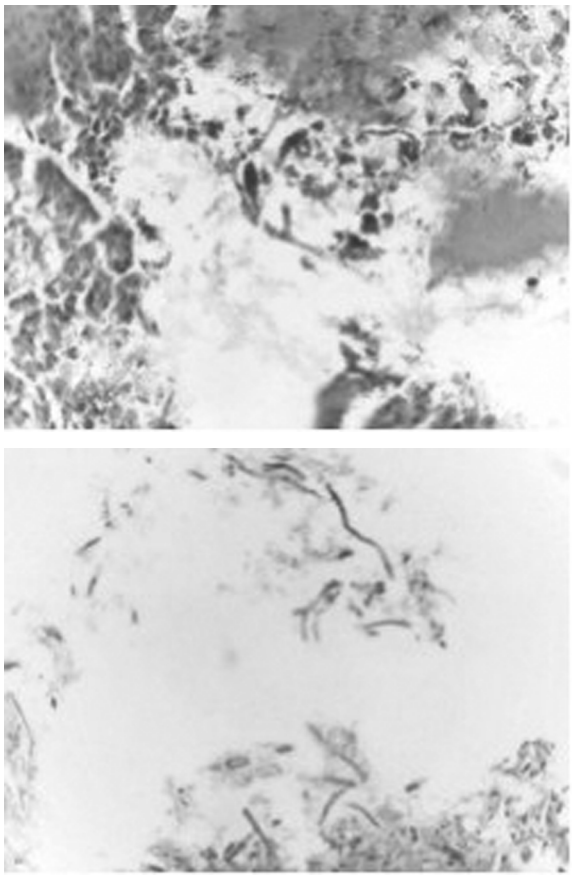

Figure 2 and 3: *The histopathological appearances of Mucoraceae.*

DISCUSSION

Mucormycosis is an invasive fungal infection which is seen occasionally. Although the disease is rare in healthy subjects, it is common in immunocompromised patients, in diabetics, and in cases treated with desferrioxamine[6]. Up to 40 % - 50 % of patients who present with mucormycosis have diabetes mellitus type 2[10]. Because of decreased neutrophile function in diabetics, mucormycosis more commonly occurs in these patients. The other reason is reduced iron binding capacity of transferrin in diabetics causing easy use of iron by the fungus leading their rapid growth. In addition fungus grows rapidly in acidothic environment. When fungus grows, they cause ischemia by vascular invasion and increased acidosis cause fungal growth with vicious circle[4]. Among the diabetic patients, the role of metabolic acidosis is more critical than hyperglycemia[3]. Although our patient has uncontrolled type 2 diabetes mellitus, the absence of acidosis may be revealed with the other factors which may play a role in infection.

Desferrioxamine chelating treatment for iron or aluminum overload is a well recognized risk factor for disseminated or rhinocerebral mucormycosis[5]. Van Cutsem and Boelaert[14] hypothesized that the rapid progression of experimentally induced zygomycosis in healthy guinea pigs after administration of desferrioxamine. Fe3+ citrate or both was mediated through the in vivo formation of the iron chelate of desferrioxamine, feroxamid for which fungi may have a receptor. Therefore, desferrioxamine could function as a siderophore providing iron to promote growth and sporulation of Rhizopus strains. This hypothesis has been supported by in vitro studies[14]. The blood transfusion was performed often in our case because of myelodysplastic syndrome and for this reason

serum iron level was increased. Desferrioxamine was given in this case in order to reduce the serum iron level.

There are at least 6 clinical syndromes of mucormycosis: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, disseminated and miscellaneous[13]. The term rhinocerebral mucormycosis should only be used if the orbit, paranasal sinuses, and brain are involved[12]. Patients with rhinocerebral mucormycosis will present with facial pain, headache, diplopia, lacrimation, nasal stuffiness or discharge and fever[3,13]. If the infection extends to the nasal turbinates, the orbit can be involved. Infection may lead to proptosis, periorbital edema, chemosis, ophthalmoplegia, and loss of vision if the orbital apex becomes involved. Our patient presented with such clinical signs and symptoms. A definitive diagnosis in a patient with suspected mucormycosis requires biopsy of infected tissue. Because cultures may be negative, recognition of the characteristic hyphal morphology (broad, ribbonlike, irregular branching nonseptate hyphae) is important. CT and MRI scanning are important adjuncts to staging of infection and monitoring the course of therapy. Sinus opacification, bone erosions and obliteration of deep fascial planes may be found in rhinocerebral mucormycosis[11]. Our case was diagnosed definitely by histopathologically. Although CT did not support the clinical findings, mucormycosis was considered by nasal endoscopic examination. Examination showed that the infection extended to upper turbinate, the upper region of septum and the cribriform plate. Therefore, this condition was considered that the infection might reach the ophthalmic area and intracranial region rather than paranasal sinuses.

Successful treatment of rhinocerebral mucormycosis is dependent on surgical resection of the infected tissue, treatment of underlying metabolic or immunologic disorders and administration of amphotericin B. Only amphotericin B therapy is rarely curative in the treatment of rhinocerebral mucormycosis[9]. A lipid formulation of amphotericin B at 35 mg/kg per day or desoxycholat amphotericin B 1 mg/kg per day intravenously is used until there is clinical and radiological evidence of resolution. Besides to the medical treatment, surgical resection should be performed and infected tissue should be removed completely. In our patient, infected tissues included in the ethmoid, maxillary and sphenoid sinuses were removed. Although the pathologic findings pointed out to the involvement of the brain tissue, any surgical intervention was not performed to this region. Hyperbaric oxygen therapy has been recommended to be a useful adjunct to treatment[7]. However, no prospective controlled studies have been performed, and a recent experimental study questions its utility[1]. Hyperbaric oxygen therapy should be administered as an investigational modality. When diabetic patients are regulated and acidosis is prevented, the environment of growing of mucor is inhibited and the cure is increased. However the treatment is more difficult in immunocompromised patients[2]. The disease progression is rapid and invasive in patients with predisposing factors who are untreated. Although aggressive treatment is performed, the mortality rate is % 60[3]. In this case the disease progressed in days and did not respond to the medical and surgical treatment and resulted in exitus.

In summary, although the treatment may be aggressive, the prognosis of rhinocerebral mucormycosis is not well and the progression is rapid in immunocompromised diabetic patients receiving desferrioxamine.

REFERENCES

1. Barratt DM, Van Meter K, Asmar P et al: Hyperbaric oxygen as an adjunct in zygomycosis: randomized controlled trial in a murine model, Antimicrob Agents Chemother 2001;45(12):3601-2.
2. Cagatay A, Oncu S, Calangu S, Yıldırmak T, Ozsut H, Eraksoy H: Rhinocerebral mucormycosis treated with 32 gram liposomal amphotericin B and in complete surgery: a case report, BMC Infect Dis 2001;1:22-4.
3. Cortez KJ, Walsh TJ: Space-occupying lesions, In "Sceheld WM, Whitley RJ, Marra CM (eds): Infectious of the Central Nervous System, p.713-34":

Lippincott Williams & Wilkins, Philadelphia (2004).
4. Coskun H, Heper Y, Hizalan I et al: Rhinocerebral mucormycosis: report of three cases, Turkish Arch Otolaryngol 2004(1);42:41-50.
5. Daly AL, Velazquez LA, Bradley SF, Kauffman CA: Mucormycosis: association with deferoxamine therapy, Am J Med 1989;87(4):468-71.
6. Del Valle Zapico A, Rubio Suarez A, Mellado Encinas P, Morales Angulo C, Cabrera Pozuelo E: Mucormycosis of the sphenoid sinus in an otherwise healty patient. Case report and literature review, J Laryngol Otol 1996;110(5):471-3.
7. Ferguson BJ, Mitchell TG, Moon R, Camporesi EM, Farmer J: Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis, Rev Infect Dis 1988;10(3):551-9.
8. Gillespie MB, O'Malley BW: An algorithmic approach to the diagnosis and manegement of invasive fungal rhinosinusitis in the immunocompromised patient, Otolaryngol Clin North Am 2000;33(2):23-34.
9. Gollard R, Rabb C, Larsen R, Chandrasoma P: Isolated cerebral mucormycosis: case report and therapeutic considerations, Nurosurgery 1994;34(1):174-7.
10. Kim J, Fortson JK, Cook HE: A fatal outcome from rhinocerebral mucormycosis after dental extractions: A case report, J Oral Maxillofac Surg 2001;59(6):693-7.
11. Mandava P, Chaljub G, Patterson K, Hollingsworth JW: MR imaging of cavernous sinus invasion by mucormycosis: a case study, Clin Neurol Neurosurgery 2001;103(2):101-4.
12. Parfrey NA: Improved diagnosis and prognosis of mucormycosis: a clinicopathologic study of 33 cases, Medicine (Baltimore) 1986;65(2):113-23.
13. Sugar AM: Mucormycosis, Clin Infect Dis 1992;14(Suppl 1):S126-9.
14. Van Cutsem J, Boelaert JR: Effects of deferoxamine, ferroxamine and iron on experimental mucormycosis (zygomycosis), Kidney Int 1989;36(6):1061-8.