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Case Report / Приказ болесника

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Management of fulminant mucormycosis of maxillary sinus and orbit with uncontrolled diabetic

Терапија фулминантне мукормикозе максиларног синуса и орбите код пацијента са дијабетесом

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SUMMARY

Introduction Mucormycosis of paranasal sinuses is a rare life-threatening opportunistic fungal disease that requires urgent treatment. The commonly involved are the immunosuppressed and immunocompetent patients. Patients are presented with facial or orbital cellulitis, necrotic palate, paresthesia of facial or trigeminal nerves and loss of vision, signs of meningitis. Radiological examinations are not sensitive in the early stages of infection. Definitive diagnosis is established by biopsy and histological examination of the necrotic tissue.

Case outline In August 2017, a 52-year-old female diabetic was admitted at Clinic for Maxillofacial surgery due to the swelling and pain in the right side of the face, headache, fever, restriction of ocular movements, purulent rhinorrhea lasting for one week. CT examination showed spreading cellulitis of the right side of the face, total right maxillary end ethmoid sinus heterogeneous occupation and osteitis of the maxillary walls. Radical surgical debridement was performed. Histopathology and microbial tests were consistent with the finding of invasive mucormycosis. Liposomal amphotericin B 5mg/kg per day for four weeks was administered and patient's glucose levels were controlled with injectable insulin and local status significantly improved. Patient was reoperated later due to the defect of the right maxilla.

Conclusion Early diagnosis and multidisciplinary approach including microbiology, pathology, radiology, surgery, hematology, infectious disease, intensive care and pharmacology is essential. Treatment of mucormycosis of paranasal sinuses requires prompt and aggressive treatment with antifungal agents, surgical debridement and control of predisposing factors.

Keywords: mucormycosis; paranasal sinuses; fungal infection; diabetes; opportunistic infection

САЖЕТАК

Увод Мукормикоза параназалних синуса ретка је и по живот опасна опортунистичка гљивична инфекција која захтева хитно лечење. Оболели су најчешће имуносупресивни и имунокомпетентни пацијенти. У клиничкој слици среће се целулитис на лица или орбите, некроза непце, парестезија фацијалног или тригеминалног живца, губитак вида и знаци менингитиса. Радиолошки прегледи нису осетљиви у раним фазама инфекције. Дефинитивна дијагноза се поставља биопсијом и хистолошким прегледом некротичног ткива.

Приказ болесника У августу 2017. године 52-годишња дијабетичарка примљена је на Клинику за максилофацијалну хирургију због отицања и бола на десној страни лица, главобоље, повишене температуре, офталмоплегије, гнојне ринореје у трајању од једне недеље. ЦТ прегледом је уочен целулитис десне стране лица, засенченост максиларног и етмоидалних синуса и остеитис максиларних зидова. Учињен је радикални хируршки дебридман и некректомија. Хистопатолошка и микробиолошка микробна показала су инвазивну мукормикозу. Примењен је липосомални амфотерицин Б 5 мг / кг дневно током четири недеље, дијабетес је контролисан инсулином, а локални статус се значајно побољшао. Пацијент је касније поново оперисан због дефекта десне максиле и пода орбите.

Закључак Рана дијагноза и мултидисциплинарни приступ који укључује микробиолога, патолога, радиолога, хирурга, хематолога, инфектолога болести, интензивну негу и фармаколога су од суштинског значаја. Лечење мукормикозе параназалних синуса захтева брзо и агресивно лечење антифунгалним агенсима, хируршки дебридман и контролу предиспонирајућих фактора.

Кључне речи: мукормикоза, параназални синуси, гљивична инфекција, дијабетес, опортунистичка инфекција

INTRODUCTION

Mucormycosis of paranasal sinuses is a rare, fulminant life threatening opportunistic fungal disease that requires urgent treatment because of its progressive and destructive nature

[1, 2, 3]. The commonly involved are the immunosuppressed and immunocompetent patients. Poorly controlled diabetes is the major risk factor for this opportunistic fungal infection, however there is increasing number of reports of patients with mucormycosis undergoing chemotherapy, immunotherapy, and organ transplantation [1, 2, 3]. Due to anatomical factors and compromised immunity, infection from the paranasal sinuses can spread intracranially and is termed as rhinocerebral mucormycosis. Even in the modern medical age, death rates are very high, 40-80% even with antifungal therapy [1, 2, 3]. The infection is caused by the fungi of the order Mucorales which can be found as saprophytic microorganisms in the upper airway tract mucosa, with Rhizopus species most commonly found in the paranasal mucormycosis[1, 2, 3]. In immunocompromised patients due to impaired phagocytic function of granulocites the fungi spores develop into a hyphae form, invade into the blood vessels, causing thrombosis and progressive soft necrosis and bone destruction [1, 2, 3]. Due to early invasion of blood vessels the infection can be disseminated, and rhinocerebral, pulmonary, gastrointestinal and cutaneous are the most often forms [4, 5].

The clinical manifestations at the early stages are not specific, but with the disease progression unilateral headache, facial pain, fever, numbness and nasal discharge are common. Patients are presented with facial or orbital cellulitis, necrotic palate, paresthesia of facial or trigeminal nerves and loss of vision, signs of meningitis with intracranial propagation [1, 2, 3]. Radiological examinations are not sensitive in the early stages of infection. Computerized tomography (CT) shows osteitis of maxillary walls and occupation of maxillary sinus. Magnetic resonance (MR) is needed when intracranial propagation is suspected. Definitive diagnosis is established by biopsy and histological examination of the necrotic tissue.

Treatment of mucormycosis of paranasal sinuses must be aggressive and quick, consists of early diagnosis, control of the predisposing disease and aggressive surgical debridement and antifungal therapy.

The aim of this case report is to present a rare case of mucormycosis of maxillary sinus and orbit in patient with newly discovered diabetes, demonstrating the diagnostic dilemmas and treatment algorithm.

CASE REPORT

In August 2017, 52-year-old female patient with newly discovered diabetes mellitus type II was admitted at Clinic for Maxillofacial surgery due to the swelling and pain in the right side of the face, headache, fever, restriction of ocular movements, purulent rhinorrhea lasting for one week (Figure 1). Because of the swelling propagation and suspicion on orbital cellulitis we performed CT examination which showed spreading cellulitis of the right side of the face, total right maxillary end ethmoid sinus heterogeneous occupation and osteitis of the maxillary walls. Because of the rapid progression of infection, ophthalmoplegia and necrosis of skin in infraorbital area, we suspected fungal infection and decided to perform radical surgical debridement consisting of removal of necrotic skin and subcutaneous tissue, partial maxillectomy et ethmoidectomy via intraoral approach and decompression of the orbit. The necrotic skin, mucosa of the maxillary and ethmoid sinuses and orbital preseptal tissue were sent for histopathological examination. Histopathology tests showed fragments of the necrotic tissue with spores and irregularly shaped hyphae with perivascular infiltration, infiltration by neutrophils consistent with the finding of invasive mucormycosis. Culture of biopsy specimens showed colonies were consistent with Mucorales. Antimicrobial susceptibility testing was performed and parenetral liposomal amphotericin B 5mg/kg per day for four weeks was administered. During hospitalization, the patient's glucose levels were controlled with injectable insulin and local status significantly improved. On control CT exams, performed weekly, there were no signs of the infection.

However, after two months patient returned to the clinic due to the cellulitis of the right side of the face and the anthrocutaneous fistula (Figure 2). Blood glucose levels were in normal range and vital signs were normal. The patient was reoperated and radical surgical debridement with removal of necrotic maxillary processus of zygomatic bone, floor of the orbit and medial orbital wall and necrotic skin of the right cheek was performed. The defect was partially reconstructed with local skin flap. Postoperatively parenteral therapy with amphotericin B (5 mg/kg per day) and meropenem. The surgical specimens were sent for pathohistological analysis and bony and soft tissue specimens were positive for fungal spores and hyphes consistent for mucormycosis. Postoperative period was uneventful and patient was released form the hospital in good general health.

In February 2018 six month following first infection, we decided to reconstruct defect of the base of the orbit with titanuim mesh and defect of the skin of the infraorbital region with local skin flap (Figure 3). After this surgery patient was reopearated in the April 2018, November 2018, and October 2019, because of the skin dehiscence and ectropion when the local skin flaps were used to reconstruct skin defect. At a recent follow up two years after mucormycosis was diagnosed, there were no signs of recurrent infection.

DISCUSSION

Although rare, mucormycosis is a life threatening fungal infection that occurs in immunocompromised patients. Previous papers reported that there is tendency to an increase of incidence of mucormycosis mainly due to the increasing number of immunocompromised patients [2, 6, 7]. Treatment of mucormycosis of paranasal sinuses requires early diagnosis, prompt and aggressive treatment with antifungal agents, surgical debridement and control of predisposing factors. However, despite early diagnosis and the aggressive surgical and medical treatments, the mortality rate is very high and reports from literature show to be 40 to 80% [1, 2, 3]. Thus early diagnosis and multidisciplinary approach including microbiology, pathology, radiology, surgery, hematology, infectious disease, intensive care and pharmacology is essential [2].

Rhinocerebral mucormycosis is typically presented with diabetic patients, while cutaneous and pulmonary forms are common in immunocompetent patients [7, 8]. Rhinocerebral mucormycosis commonly develops in paranasal sinuses, most often in maxillary sinus and subsequently involves orbit, brain and cranial bones. Localized sinus infection when early discovered and aggressively treated have good prognosis, while intracranial propagation, especially in immunocompetent patients, have very poor prognosis [1, 2, 3]. Immunological state, predominantly severe neutropenia, was found to be the most significant negative survival factor, regardless to the extent of fungal infection [1, 2].

Surgical debridement with free margins is still the standard therapy in order to control infection and obtain tissue for histopathological and microbiological diagnosis. Postoperative sequels such as disfigurement, loss of vision, difficulties with oral function, low quality of

life are common with surviving patients [3]. Thus, further researches should be made to redefine the need for radical surgical debridement. First line of antifungal treatment is liposomal amphotericin B in doses 5–10 mg/kg per day, with constant monitoring of serum creatinine concentrations. In cases of acute renal toxicity, isavuconasole and posaconasole were found to be safe alternatives. Several reports demonstrated efficacy of posaconazole and amphotericine B combination, even without the need for surgical treatment [2, 3, 4]. Currently there is no relevant protocol regarding dosage and duration of antifungal treatment. Our patient received antifungal treatment with amphotericine B for four weeks during first hospitalization, but infection relapsed even with good control of diabetes and absence of infection on control CT scan. Thus, we feel that reconstructive surgery for these patients should be delayed for at least 6 months after treating infection.

Treatment of rhinocerebral mucormycosis requires multidisciplinary approach. Facial swelling, orbital cellulitis, headache, ophthalmoplegia and sinusitis in diabetic patients should raise suspicion on rhinocerebral mucormycosis. CT and MRI examinations should be performed. Following radiological examinations, if sinusitis is diagnosed endoscopy or open biopsy should be performed. Surgical debridement in order to control infection and obtain clear margins should be radical in addition to systemic antifungal treatment. Antifungal treatment should be continued until complete local resolution of disease, complete response on radiological images and control of the predisposing factors (Table 1).

Ethical approval: All procedures described in this paper involving were in accordance with the institutional ethical standards and with the 1964 Helsinki declaration. Informed consent was obtained from the patient for being included in the study and use of medical data and clinical pictures.

Conflict of interest: None declared.

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Table 1. Treatment algorithm for rhinocerebral mucormycosis

Suspected mucormycosis	
1. Clinical picture	Facial pain, swelling, sinusitis, ophthalmoplegia, persistent fever, headache Uncontrolled diabetic, neutropenic patient
2. Cranial CT Cranial MRI Chest CT	Bone destruction, sinus involvement Orbit, brain involvement Respiratory symptoms
3. Infected tissue biopsy/endoscopy	Histopathology Microbiology
4. Radical surgical debridement	Obtain clean margins Control the infection Microbiological diagnosis
5. Long term antifungal treatment	Amphotericine B 5–10 mg/kg – first line treatment Posaconasole 200–1000mg/day Isavoconasole 200–1000mg/day
6. Control of predisposing factors	Diabetes Neutropenia
7. Control images	Treatment response assessment
8. Delayed reconstruction	6–12 months folowing local control of infection

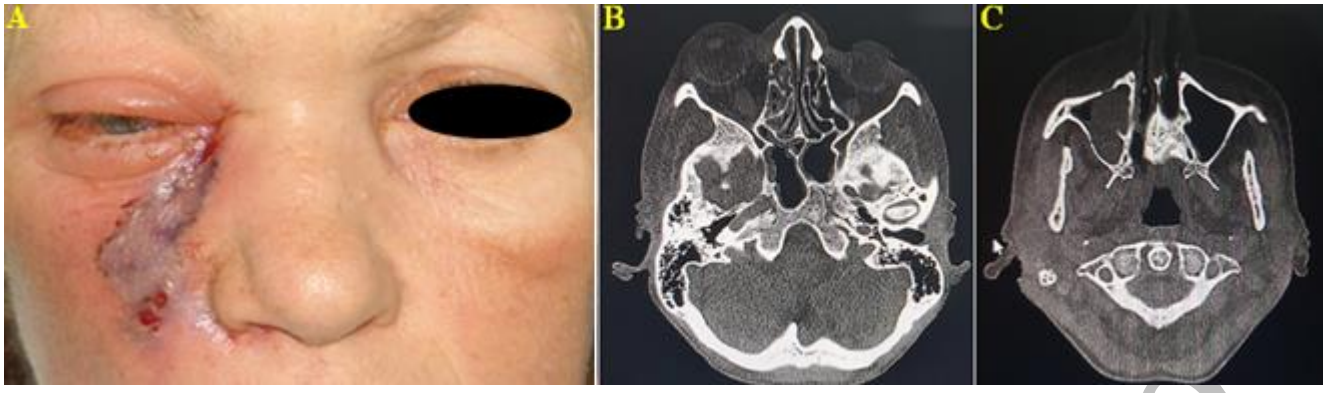

Figure 1. A) Patient presenting with cellulitis of the right side of the face and necrotic skin of paranasal area; B) computed tomography showing right ethmoid cells with heterogeneous density and osteitis; C) computed tomography showing right maxillary sinus with heterogeneous density and osteitis

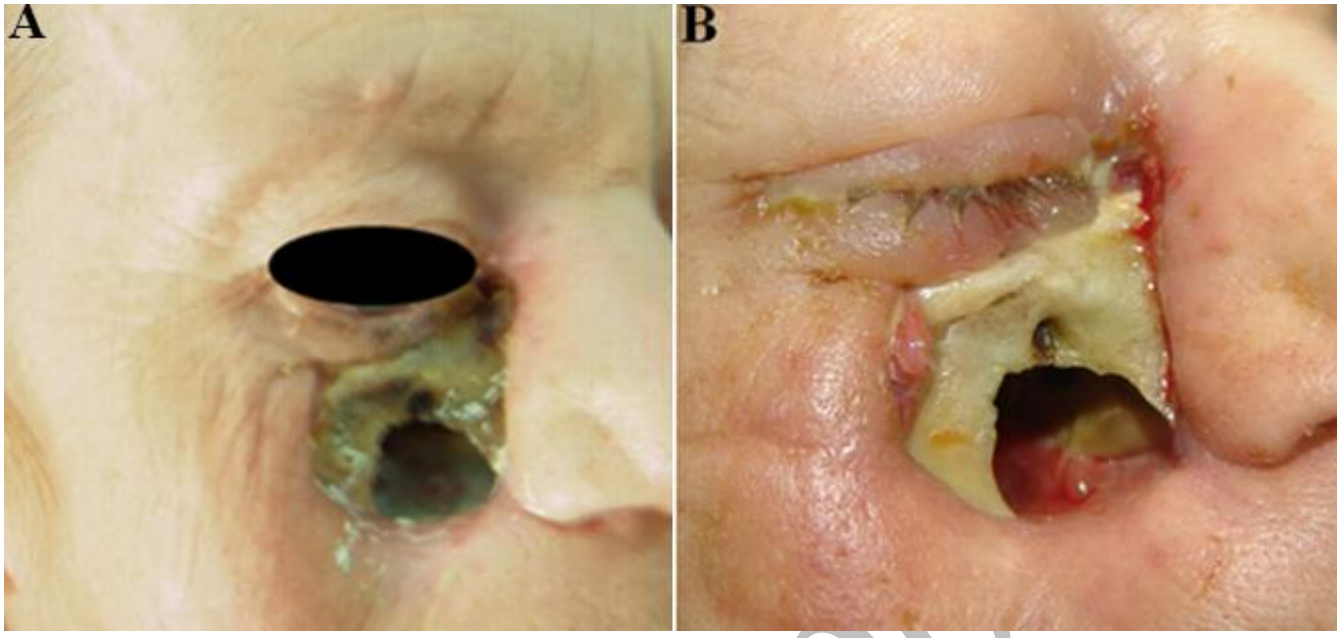

Figure 2. Relapse of the infection two months after first treatment; A) defect of the skin and right maxilla; B) necrotic bone of anterior maxilla, floor of the orbit and zygomatic bone

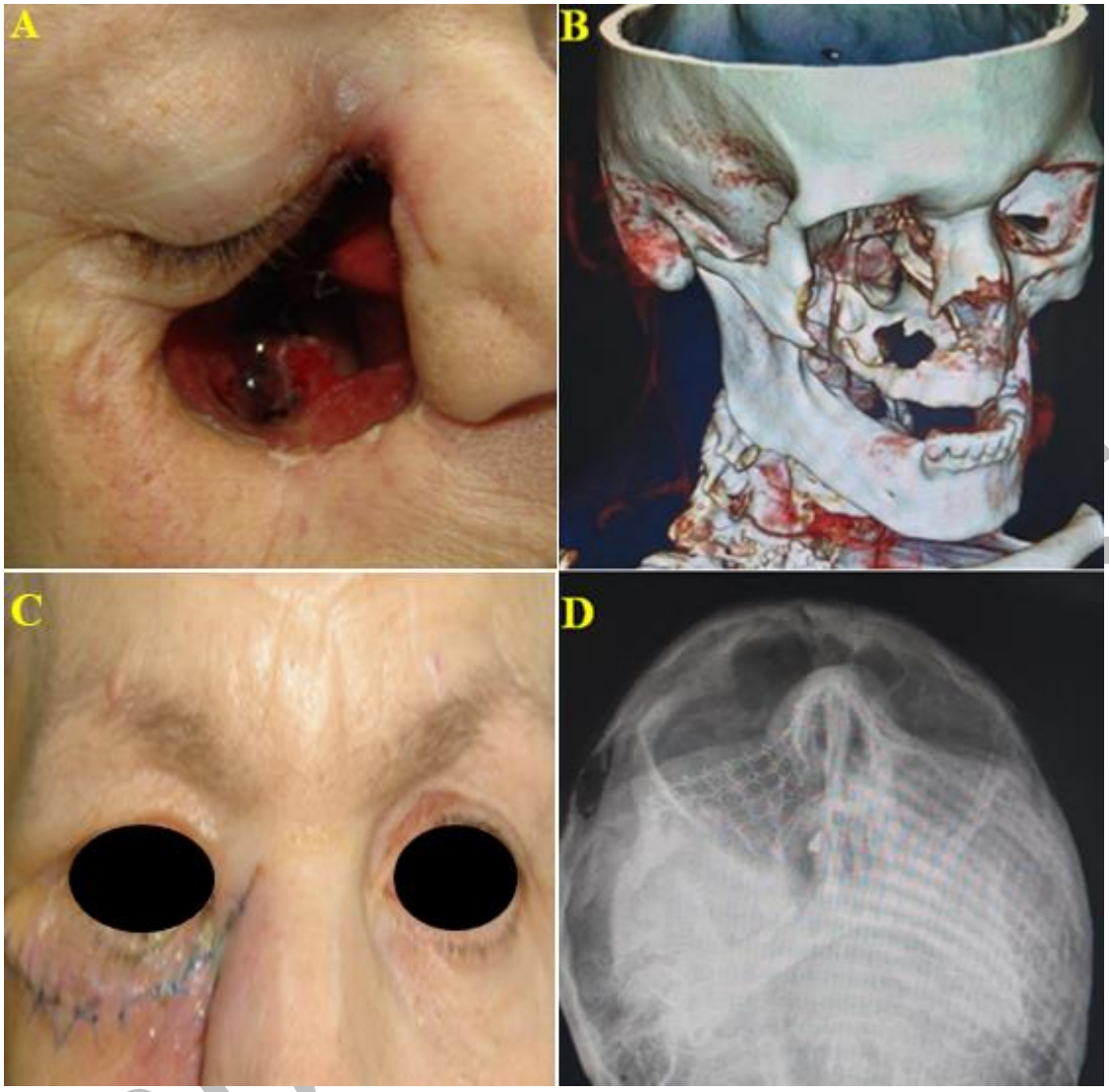

Figure 3. Reconstruction of the defect of the right maxilla six months after first treatment; A) clinical appearance of the defect; B) 3D reconstruction of the defect of the right maxilla; C) postoperative appearance of the patient after reconstruction of the floor of the orbit and skin; D) control radiographic picture

