Oral Mucormycosis and Aspergillosis in the Patient with Acute Leukemia

Oralna mukormikoza i aspergiloloza kod bolesnika s akutnom leukemijom

Abstract

A 54-year-old male patient with acute lymphoblastic leukemia was referred to the Department of Oral Medicine. He had a primary refractory disease and was treated according to HOVON71 and HAM protocol. Sixteen days after the start of the HAM protocol the patient developed palatal dark red/brownish lesion and maxillary vestibular exophytic lesion. Biopsy specimens from oral lesions were taken and microbiologic evaluation confirmed the presence of Aspergillus fumigatus and Rhizopus genus.

The treatment of the patient consisted of the inferior maxillectomy and intravenous posaconazole and amphotericine B for the following 28 days. Since the coinfection with Aspergillus and Rhizopus is extremely rarely seen in the oral cavity, a diagnostic and therapeutic dilemma easily presents itself.

Received: November 23, 2018
Accepted: August 28, 2019

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Key words
Mouth Diseases; Mucormycosis; Aspergillosis; Immunocompromised Host; Leukemia

Introduction

Invasive fungal infections are the major cause of infection-related mortality in hematopoietic stem cells recipients. Although mucormycosis and aspergillosis are the most frequent fungal infections, coinfection in the same host occurs rarely (1). Furthermore, they can be frequently fatal in immunocompromised patients. Treatment options usually combine medical and surgical approaches, often including extended necrosectomies. Nevertheless, the prognosis of generalized fungal infections is very poor (2).

There have been several case reports describing combined aspergillosis and mucormycosis in various parts of the body, usually with a fatal outcome (3). However, one case report depicts a patient with relapsed acute myeloid leukemia...
kemia with a combined *Aspergillus* and *Mucorales* infection (lungs, brain, spleen and bone) who has been a long time survivor (4). The aforementioned coinfection rarely occurs in healthy individuals. The case of a 22-year-old, otherwise healthy US Marine who sustained extensive soft tissue injuries was published (5). Additionally, Pozo-Laderas et al. (6) published a case of a 17-year-old immunocompetent male who developed thiscoinfection 11 days after a motorcycle accident.

The coinfection of mukormycosis and aspergillosis should be considered in immunosuppressed patients in order to establish early management that will lead to the improved prognosis of the patient (1).

**Case report**

A 54-year-old male patient was referred to the Department of Oral Medicine due to the dark red/brownish lesions on the left side of the palate (Figure 1) and vestibular exophytic, later ulcerative, lesion in the area of the teeth 25-27 (Figure 2). The lesion was well demarcated from the surrounding tissue, asymmetric and without hemorrhage.

He was diagnosed in December 2017 with acute lymphoblastic leukemia (Ph negative and pre-B). He had primary refractory disease and was treated according to protocols HOVON 71 (7) and HAM (high dose of cytosine arabinoside and mitoxantrone). During HAM protocol induced aplasia, the patient developed neutropenic colitis and *Aspergillus niger* was identified in his stool samples. At the time of the oral examination, the patient was treated with intravenous levofloxacin, acyclovir, metronidazole, colistine, meropenem and tigecycline.

Oral lesions appeared sixteen days after the start of the HAM protocol. The patient noticed a swelling of his left cheek. The abovementioned oral lesions were identified upon examination. The orthopantomograph (Figure 3) showed a radiopaque lesion within the left maxillary sinus. Teeth 23, 26 and 27 were avital and tooth 24 was vital. Increased loosening of these teeth was noticed. A severe form of periodontal disease was present. The patient had no pain in that area, except sometimes on palpation. No evident pathological peri-

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**Figure 1** Palatal mucormycosis and aspergillosis: the dark red/brownish lesions on the left side of the palate
**Slika 1.** Palatalna mukormikoza i aspergiloza: tamna crveno/smećkasta lezija na lijevoj strani nepca

**Figure 2** Vestibular mucormycosis and aspergillosis: the vestibular ulcerative lesion in the area of the teeth 25-27
**Slika 2.** Vestibularna mukormikoza i aspergiloza: vestibularna ulceracija u regiji zuba 25-27

**Figure 3** Orthopantomograph showed a radiopaque lesion within the left maxillary sinus
**Slika 3.** Ortopantomogram je pokazao radiopaktnu leziju unutar lijevog maksilarnog sinusa
apical pathology within teeth could be noticed. A CT finding showed a non-homogenous bony structure within the maxillary alveolar ridge.

Incisional biopsy of a vestibular lesion was taken. Histopathology showed tissue necrosis together with adipose tissue abundant with fungal hyphae and spores. Microbiological evaluation confirmed the presence of *Aspergillus fumigatus* and *Rhizopus genus*.

Intravenous posaconazole and amphotericin B were given for the following 28 days and inferior maxillectomy was performed. The maxillary defect was to be reconstructed after the completion of hematological treatment. Meanwhile, the patient was given an obturator. Due to poor general condition of the patient, further treatment of leukemia by the transplantation of allogeneic stem cells was not possible. Therefore, the treatment with blinatumomab was initiated. Unfortunately, in June 2018, the patient died due to severe hemorrhagic shock and cardiopulmonary arrest.

Since the coinfection with *Aspergillus* and *Rhizopus* extremely rarely occurs in the oral cavity, it leads easily to the diagnostic and therapeutic dilemma.

Discussion

Acute invasive fungal infections in the paranasal sinuses and surrounding tissues are progressive and carry a high death rate in an immunocompromised patient (8). Gode et al. (8) described 37 patients with acute invasive fungal rhinosinusitis and reported that the palatal involvement was significantly associated with death rate.

There are only a few case reports about a concomitant aspergillosis and zygomycosis infection in the orofacial region (1, 2, 9).

Torres-Damas et al. (1) reported a case of a 78-year-old male patient with type 2 diabetes and ketoacidosis who presented with a swelling of the right side of his face, right facial paralysis, proptosis and a necrotic ulcer on the right palate due to the *Aspergillus fumigatus* and mucormycosis. Chermetz et al. (2) reported the case of a 17-year-old girl with combined aspergillosis and mucormycosis of the right side of her face with frontal maxillary area and upper airway involvement after the treatment of a recurrent glioma.

Maiorano et al. (9) reported a case of aspergillosis and mucormycosis in the patient with stage-IV Castleman disease who presented with a palatal ulceration that progressive-ly involved the palatal mucosa and bone, the paranasal sinuses and the orbit.

Although invasive fungal infections are the major cause of infection-related mortality in hematopoietic stem cell recipients, in this particular patient invasive fungal infection occurred prior to the hematopoietic stem cell transplantation, during the period of post-chemotherapy aplasia.

Differential diagnosis of such cases includes malignancy and because of that, biopsy is mandatory. Due to high frequency of fungal infections in immunocompromised patients, microbiological testing and identification of a causative organism should be performed.

Treatment of these lesions includes surgical resection of the affected tissues as well as intravenous antifungals. Paciji. Nije se mogla uočiti periapeksna patologija zuba. CT nalaz pokazao je inhomogenu koštanu strukturu alveolarnog grebena maksile.

Učinjena je incizijalna biopsija vestibularne lesije. Histopatološki nalaz pokazao je nekrotično vezivno i masno tkivo prorožeto hitama i sporama gljivica. Mikrobiološkom analizom identificirani su u uzorku *Aspergillus fumigatus* i *Rhizopus spp*.

Tijekom sljedećih 28 dana bolesnik je intravenski primao posakonazol i amfotericin B te je obavljena inferiorni mak-silektomija. Maksilarni deformet trebao se rekonstruirati nakon završetka hematološkog liječenja, a u međuvremenu je pacijent opskrbljen opturatortom. Zbog lošeg općeg stanja bole-

snika nije bilo moguće nastaviti s liječenjem leukemijske presa-
divanje alogenih matičnih stanica. Zbog toga je započeto liječenje blinatumomabom. Nažalost, u lipnju 2018. pacijent je umro zbog teškog hemoragičnog šoka i kardiopulmonalnog zastoja.

Budući da se koinfekcija gljivicama *Aspergillus* i *Rhizopus* iznimno rijetko vidi u usnoj šupljinii, česte su dijagnostičke i terapijske dvojbe.

Rasprava

Akutne invazivne gljivične infekcije paranazalnih sinusa i okolnih tkiva kod imunokompromitiranih bolesnika progresivne su i imaju visok stupanj smrtnosti (8). Gode i suradnici (8) opisali su 37 bolesnika s akutnim invazivnim gljivičnim rinosinusitisom i istaknuli da je zahvaćenost nepca značajno povezana sa smrtnošću.

Postoji samo nekoliko slučajeva istodobne aspergiloze i zi-
gomikose u orofacialnoj regiji (1, 2, 9). Torres-Damas i suradnici (1) izvijestili su o slučaju 78-godišnjeg pacijenta s dijabetesom tipa 2 i ketoacidozom kojemu je zbog gljivice *Aspergillus fumigatus* i mukormikoze nastala oteškinja i paraliza desne strane lica, poza te nekrotični ulkus desne strane nepca. Chermetz i suradnici (2) opisali su slučaj 17-godišnje djevojke nakon liječenja rekurentnog glioma s kombiniranom aspergilozem i mukormikozom desne strane lica, sa zahvaćenim prednjim maksilarnim područjem i gornjim dišnim putovima.

Maiorano i suradnici (9) pisali su o slučaju aspergiloze i mukormikoze kod pacijenta s IV. stadijum Castlemanove bolesti, što se očitovalo kao ulceracija nepca koja je progresivno zahvatila palatalnu sluznicu i kosti, paranasalne sinuse i orbitu.

Iako su invazivne gljivične infekcije kod primatelja krov-
tvornih matičnih stanica glavni uzrok smrtnosti povezane s infekcijom, kod ovoga se pacijenta invazivna gljivica infekcija dogodila prije transplantacije krvotvornih matičnih stani-

cica, tijekom postkemoterapijske aplazije.

Diferencijalna dijagnoza takvih slučajeva uključuje mali-

gnitet zbog čega je biopsija obvezna. Zbog visoke učestalosti gljivičnih infekcija kod imunokompromitiranih bolesnika, potrebno je obaviti mikrobiološka ispitivanja i identifikaciju uzročnika.

Liječenje tih lezija uključuje kiruršku resekciju zahvaćenih tkiva i protuyljivčne lijeke intravenski. Lijekovi izbora su posakonazol ili amfotericin B. U rezistentnim slučajevima
Posaconazole or Amphotericin BS is the drug of choice. Caspofungine can be added in resistant cases. Nevertheless, the duration of the treatment is long (median 180 days) and the outcome is unpredictable, favorable in only 40-60% of the cases.

This case report highlights the importance of considering the coinfection with *Aspergillus* and *Rhizopus* genera in the orofacial area in patients with leukemia.

**Sažetak**
Bolesnik u dobi od 54 godine s akutnom limfoblastičnom leukemijom upućen je u Zavod za oralnu medicinu. Imao je primarnu refraktornu bolest i liječen je prema protokolima Hovon 71 i Ham. Šestnaest dana nakon početka primjene protokola HAM, bolesniku se pojavila oralna tammocvena/smekastaja lezija nepca i maksilarna vestibularna egozolitica lezija. Iz obiju su uzeti uzorci za biopsiju te su mikrobiološkom obradom potvrđeni *Aspergillus fumigatus* i *Rhizopus* genus. Liječenje bolesnika sastojalo se od inferiore maksilektomije te intravenski posakonazola i amfotericina tijekom sljedećih 28 dana. Budući da se koinfekcija tim dvjema gljivicama iznimno rijetko pojavi u usnoj šupljini, česte su dijagnostičke i terapijske dileme.

**Zaprimljen:** 23. studenog 2018.  
**Prihvaćen:** 28. kolovoza 2019.

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**Ključne riječi**
oralne bolesti; mukormikoza; aspergiloloza; imunokompromitiran domaćin; leukemija

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