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POST COVID JAW OSTEOMYELITIS WITH MUCORMYCOSIS - ANINSTITUTIONAL STUDY

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Abstract

Mucoraceae are ubiquitous fungi and are found in, soil, air, contaminated water and hospital environments too. These fungi usually gain entry into host through respiratory tract and sinuses either by direct spread or by angioinvasion. Major sites of infection are sinuses, lungs, skin, brain, and gastrointestinal tract. From sinus it may invade maxilla causing osteomyelitis of jaw. Mucormycosis is an opportunistic infection and the major risk factors include poorly controlled diabetes mellitus (DM), iron overload, prolonged corticosteroid use and immunocompromised status. CORONA virus disease 2019 (Covid-19) is an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The majority of patients have a good prognosis, but some patients become critically ill and even deaths occur. Disease itself decreases cell mediated immunity and increases iron load in covid patients. For treatment of Covid-19 corticosteroids, antiviral drugs and immunomodulatory drugs are being used. Steroid reduces inflammation in covid 19 patients, but it pushes up the blood sugar which causes ketoacidosis, increases iron load, affects cell mediated immunity and favours the mucor mycosis growth. So, there are reported increasing cases of mucormycosis in post COVID-19 patients. Present study includes 25 reported cases of mucormycosis with jaw osteomyelitis in post covid patients with respect to clinical characteristics, past medical history, comorbidities medication received during covid 19, radiographic feature, lab diagnostic methods, histopathological reports, and treatment. So as to gain an insight of this disease as early diagnosis of mucor mycosis and treatment which can significantly reduce the mortality and morbidity of mucormycosis patients

Keywords: COVID, Mucormycosis, Diabetes, Immunity, Histopathology

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INTRODUCTION

Fungal infection may be due to both chemical as well as biological reasons and more common in immunocompromised individuals¹. Most common fungi causing illness are Candida albicans, Aspergillus species, Cryptococcus neoformans, Blastomyces dermatitidis, and Rhizopus species².

Mucormycosis refers to infection caused by fungi belonging to Mucorales order. Mucoraceae are ubiquitous fungi and are found in, soil, air and dust². Phycomycosis or zygomycosis was first described in 1885 by Paltauf, later Baker coined it as Mucormycosis in 1957. Worldwide, the prevalence of mucormycosis varies from 0.005 to 1.7 per million population and in India 0.14 per 1000 which is nearly 80 times higher compared to developed countries, in recent estimate of year 2019–20203³.

COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11, 2020, WHO declared the COVID-19 outbreak as pandemic⁴

There are increasing cases of oral mucormycosis in patients with coronavirus disease 2019 (COVID-19), especially in India. Diabetes mellitus (DM) is a self-supporting risk factor for both severe COVID-19 and mucormycosis⁵. The other risk factors for mucormycosis are use of corticosteroids, neutropenia, malignancies, immunocompromised health state, organ transplant and traumas. Mucor have remarkable affinity for arteries and grow along internal elastic lamina causing thrombosis and infarction. The disease progression is from nose and sinuses, either direct or through blood vessels. Major sites of infection are sinuses, lungs, skin, brain, and gastrointestinal tract⁶.

In post covid patients mucormycosis spores get ideal environment for germination due to high glucose level (DM, new-onset hyperglycemia, and steroid-induced hyperglycemia), high iron levels (increased ferritins), acidic medium (metabolic acidosis, diabetic ketoacidosis), and hypoxia (low oxygen level) and decreased phagocytic activity of white blood cells (WBC), immunosuppression (mediated by steroid and covid 19 virus) during covid. Other risk factors are prolonged hospitalization with or without mechanical ventilators³. This article analyses 25 cases of post covid jaw osteomyelitis with mucormycosis reported to the institute.

Material and Methods:

Post covid mucormycosis patients which were visited to institute from January 2021 - May 2021 were reviewed.

PARAMETERS USED FOR CASE ANALYSIS ARE

Age/ sex, Co morbidity, Covid therapy clinical Presentation, radiographic feature and laboratory diagnosis. Approval from institutional ethical committee was taken.

Results:

In a period of five months 25 postcovid mucormycosis patients were found. In this study, we observed commonly affected age group was 40-60 years (44%), site was maxilla (80%), gender was male (68%). Risk factors were diabetes mellitus (48%), hyperglycaemia during covid (28%) and hypertension (8%). Treatment received by patients during covid were steroid (100%), oxygen (76%) and Remdesivir (60%) (Figure 1, 2 and 3)

Discussion:

Mucoraceae are ever present fungi and are found in soil, air, dust and hospital ward rooms. The mucormycosis spores usually gain entry into the host through the respiratory tract. The disease progression from nose and sinuses is either direct or through blood vessels⁴ Person having normal immune system remove these spores by phagocytic leucocytes but in individuals receiving immunosuppressive agents, having uncontrolled DM, malignancies or chronic sinusitis can transform mucor spores in to hyphae which proliferate more easily and invade into vessel walls of the infected region and result in, thrombosis, ischemia and necrosis⁷

Clinically mucormycosis can occur in various forms as cutaneous, pulmonary, rhino cerebral, gastrointestinal, or even disseminated. It commonly occurs in individuals with uncontrolled DM, extensive trauma or receiving high-dose glucocorticoids⁸ India has increased burden of mucormycosis in the world with prevalence of 140 cases per million populations and also it has the second-largest number of adults aged 20–79 years with DM⁹

In covid 19 patients cytokine storm is one of the major causes of acute respiratory distress syndrome (ARDS). It plays an important role in the process of disease aggravation. Corticosteroids are mainly used in critically ill patients suffering from inflammatory cytokine storm¹⁰ In present study all the patients (100%) had received corticosteroid for the cytokine storm and corticosteroids restrain the immune system but can cause glycosuria and hyperglycemia.¹¹ In the present case study all the patients had received steroids for covid 19 (28% patients developed hyperglycaemia during covid (Fig-1)

In covid 19 infection, there is a high expression of angiotensin-converting enzyme 2 receptors in pancreatic islets, along with increased insulin resistance due to cytokine storm resulting in hyperglycaemia and diabetic ketoacidosis¹¹The endothelial expression of glucose-regulated protein 78 (GRP78) is increased in diabetic ketoacidosis. Spores of mucormycosis coat protein CotH of Mucorales fungi bind to GRP78 on endothelial cells, facilitating angioinvasion, which leads to thrombosis and tissue necrosis.¹² This explains the higher risk of mucormycosis in diabetes patients.

Patients with diabetic ketoacidosis have elevated levels of free iron in their serum, and have dysfunctional phagocytes and have impaired chemotaxis which facilitate growth of mucor mycosis.⁵ In our study we observed 24 % of the patients had DM (Fig-1) During the cytokine storm in COVID-19, many inflammatory cytokines are rapidly produced, including IL-6, TNF- α , IL-1 β , IL-12, and IFN- γ , which stimulate hepatocytes, Kupffer cells, and macrophages to secrete ferritin.¹³ Ferritin is favourable for growth of mucormycosis. All the patients suffered from cytokine storm due to covid infection.

Age does not have a major role in the incidence of osteomyelitis, it is commonly seen between 40 -60 years of age. In the study also commonly affected age group was 40-60 years (44%) (fig-2and table 1) Males have more predilection for the fungal osteomyelitis^{14,15} In the study males showed more predilection (68%) than females. (Fig-2).

Osteomyelitis of jaw does not commonly involve the maxilla due to significant collateral blood supply in the midface, but in our study we found maxilla(68%) to be more commonly affected than mandible, this might be due to nasal entry and involvement of maxillary sinus with mucor fungi.(fig 2 and table-1)¹⁴

Hypoxia gives ideal environment for the germination for mucor spores³ In the study 76% of patients had received oxygen therapy during covid infection (Fig-1 and table 1). The clinical presentation of fungal osteomyelitis can be similar to the bacterial osteomyelitis showing exposed bone with pain.¹⁶ In this study, clinical presentation observed as extraoral / intraoral swelling, palatal perforation, multiple draining sinuses, mobile teeth, and exposed necrotic bone (fig-4, fig-5 table -1)

Computed tomography (CT) and magnetic resonance imaging (MRI) findings may include bone destruction of sinus walls, cavernous sinus filling defect, mucosal thickening or opacification of the involved paranasal

Case no	Age/ sex	Clinical features	Site	Radigraphy	Co morbidity		Cov	rid the	rapy	Fes	Anti Fungal	KOH Mount	Tissue biopsy	Culture
10	JCA	icatur es			DM	HTN	Ster oid	Ox ygen	Re md esi vir		therapy	wount		
1	71/F	Difficultyin swallow ng I/O- Mobilitywith 12- 17 and Palatal perforation		CT- thickening of maxillary and ethamoidal sinuses.	Hdc	No	Yes	No	Tt No	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
2	45/M	E/O- swelling on lower left mandibular region,I/O - draining sinuses with 35- 38 region	dible	Loss of normal trabecular pattern inleft angle region of mandible	No	No	Yes	Yes	Yes	No	No	-ve	osteomylitis with muc omrycotic fungi	Candida parapsilosis positive
3	45/M	E/O - diffuse swelling on left maxilla I/O - Pus discharge from 21- 22 and Exposed palatalbone	Maxilla	CT- thickening of maxillary sinus wall.	Hdc	No	Yes	No	Yes	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
4	45/M	E/O- diffuse swelling on left mandible I/O - swellingand pus discharge with 35- 37 region.	Man dible	OPG- radiolucencie with 35- 38 and 45- 48.	No	No	Yes	Yes	Yes	No	No	+ve	Osteomyelitis	No growth
5	40/M	I/O/E - Mobilityand multiple draining sinuses with 16 - 26	Maxilla	CT - thickeningof bilateral maxillary sinus wall.	Hdc	No	Yes	Yes	Yes	Yes	Yes	+ve	osteomylitis with muc omry coticfungi	Mucor positive

6	30/M	E/O - Diffuse swellingon right maxilla I/O - Mobilityand multiple draining sinuses with 11- 14		CT - thickeningof both maxillary sinuses. Deviated nasal septum to right side.	No	No	yes	No	No	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
7	65/F	I/0- Mobility with 14 - 27 Exposedmid palatine bone		CT - thickeningof both maxillary sinus wall.	Yes	No	yes	Yes	No	No	No	+ve	osteomylitis with muc omry coticfungi	Mucor positive
8	40/F	E/O – Swellingon right side of face with 11- 17	Maxila	CT - thickeningof right maxillary sinus wall.	HDC	No	Yes	Yes	No	No	No	-ve	osteomylitis with muc omry coticfungi	Mucor positive
9	40/F	E/O – Swellingon right side of face with 11- 17	Maxila	CT - thickeningof right maxillary sinus wall.	HDC	No	Yes	Yes	No	No	No	-ve	osteomylitis with muc omry coticfungi	Mucor positive
10	57/M	H/O - Exfoliation of 33- 43 I/O – Missing33- 43 and exposed bone	Mand ble	CBCT- multiple radiolucencies with 33- 43.	No	No	yes	No	No	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
11	69/F	I/O - mobility with 11- 17	Maxila	thickeningof both maxillary sinus wall.	No	Yes	yes	Yes	Yes	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
12	33/M	E/O - Diffuse swelling on right side of mandible	Man dible	CBCT - multiple radiolucencies seen on right side of mandible.	Yes	No	yes	Yes	Yes	No	No	-ve	osteomylitis with muc omrycotic fungi	Mucor positive

13	55/M	gingival swellingwith 12- 17. And mid Palatine region.		CT - thickeningof right maxillary sinus wall.	Yes	No	Yes	Yes	Yes	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
14	51/M	I/O – swellingwith 12- 14 mobility with 11 - 18	maxilla	CT - thickeningof right maxillary sinus wall.	No	No	Yes	Yes	Yes	No	No	-ve	osteomylitis with muc omrycotic fungi	Aspergils and mucor positive
15	42/M	E/O - swellingon left side ma5xilla I/O - denuded mid palatine bone with pus discharge	maxilla	CT - thickeningof both maxillary sinus wall.	Yes	No	Yes	No	No	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
16	49/M	I/O – multiple draining sinuses with 18- 28	Maxilla	OPG - multiple radiolucencies seen with 18- 28	Yes	Yes	Yes	Yes	Yes	No	Yes	+ve	osteomyelitis	Aspergils positive
17	51/M	I/O - swellingwith 22- 24, mobility with 12 - 17 and 23 - 28	Maxilla	CT - thickeningof both maxillary sinus wall	Hdc	No	Yes	Yes	Yes	No	No	-ve	osteomylitis with muc omry coticfungi	Mucor positive
18	32/F		Maxilla	MRI oedema onhard palateand soft tissue of right maxillary region.	No	No	Yes	Yes	No	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
19	32/F	I/O- multiple draining sinuses in12- 16 region	Maxilla	MRI oedema onhard palateand soft tissue of right maxillary region.	No	No	Yes	Yes	No	No	No	+ve	osteomylitis with muc omrycotic fungi	Mucor positive

20	48/F	I/O/ - multiple draining sinuses 17- 27region and palatinel perforation	Maxi lla	CBCT- obliterationof left maxillary sinus with osteolytic changes.	No	No	yes	Yes	yes	Yes	Yes	-ve	osteomylitis with muc omrycotic fungi	Mucor positive
21	39/M	I/O - Mobility with22- 26	Maxi lla	CT - thickeningof both maxillary sinus wall.	No	No	yes	Yes	yes	yes	Yes	+ve	osteomylitis with muc omrycotic fungi	Mucor positive
22	51/M	I/O – swellingwith 12- 14 mobility with 11 - 18	Maxi lla	CT - thickeningof right maxillary sinus wall.	No	No	yes	yes	yes	No	No	-ve	osteomylitis with muc omrycotic fungi	Aspergils and mucor positive
23	71/F	E/O- diffuse swellingon right maxilla I/O – multiple draining sinuses with 12- 17	Maxi Ila	CT - mucosal thickening involving both maxillary sinus wall.	HD C	No	yes	No	No	Yes	yes	+ve	osteomylitis with muc oryc otic fungi	Mucor positive
24	38/M	I/O– mobilitywith 16- 26	Maxi lla	CT - thickeningof both maxillary sinus wall.	No	No	yes	Yes	yes	Yes	yes	-ve	osteomylitis	No growth
25	36/M	I/O/- Pus discharge with 24- 25.	Maxi lla	CT - thickeningof left maxillary sinus wall.	HD C	No	yes	No	no	Yes	yes	-ve	osteomylitis with muc ormycotic fungi	Mucor positive
		ARI- magnetio	c reson		G - G	orthopan	tomograi	m DM	– diabe	etes ma	llites, HTN	- hyper	CT- cone beam comp tension, HDC- Hypo de.	

sinuses, in this study similar feature were seen.^{6,16} On orthopantomogram (OPG) of mandible multiple radiolucency with diffuse borders were seen (fig-6and table 1). The lab diagnosis is based on mucor fungi found as broad aseptate ribbon-like hyphae on KOH wet mount. In our study 64% samples were KOH positive and 36% were KOH negative (fig3) which could be due to contamination of samples or antifungal treatment received.

Mucor fungi was confirmed by Lactophenol cotton blue (LPCB) stain after 72 h of culture on Sabouraud dextrose agar (SDA) which revealed broad aseptate ribbon like hyphae branching at right angles with sporangia¹⁷(fig-7-e, f and table 1)

On culture 76% samples of patients showed mucor, 8% Candida 4% Aspergillus, and 4% were with both mucor and aspergillus. No growth was seen in 8% of cases due to antifungal treatment. (Fig3 and table 1) The tissue biopsy in mucormycosis stained with H &E and PAS stain revealed broad obtuse aseptate fungal hyphae.7In the study 84% cases showed osteomyelitis with fungi and 16% only osteomyelitis without fungi. This might be due antifungal treatment received by patients. (Fig-7 a, b, c fig 3 and table 1)

According to Bernier S. et al, surgical therapy consists of sequestrectomy of the affected bone, removal of necrotic tissues and involved teeth along with antifungal treatment¹⁸ In our study we followed same guidelines. After surgical debridement of lesion antifungal treatment (Amphoteracin B and posaconazol) was given. Prognosis of mucormycosis is usually fair to poor depending on comorbidities present¹⁹ In the present case series, two patients having DM succumbed to death due to rhinocerebral involvement from maxillary sinus to brain.

Conclusion:

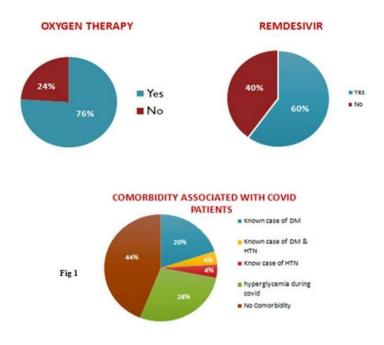
Mucormycosis is fast spreading infection with poor prognosis, so early diagnosis is very important. Imaging plays a key role in the early identification of mucormycosis and delineating the extent of infection. For the treatment of post covid mucormycosis aggressive surgical debridement with antifungal therapy is needed. In post covid patient's risk factors for mucormycosis are high blood glucose level, high iron level, acidic medium, hypoxia and decreased phagocytic activity due to immunosuppression mediated by steroid received during covid treatment. So, all efforts should be made to maintain optimal glucose level and judicious use of steroids in patients with covid 19.

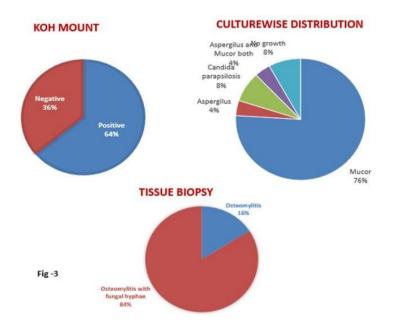
Financial support and sponsorship:

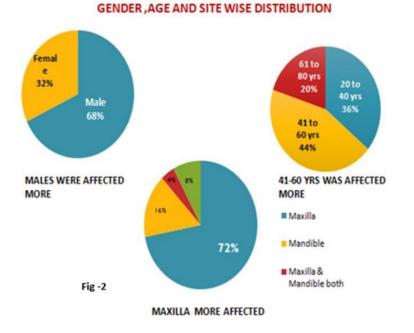
Nil

Conflicts of interest:

There are no conflicts of interest







CLINICAL FEATURES SHOWING MANDIBULAR INVOVEMENT



EXTRAORAL MANDIBULAR SWELLING



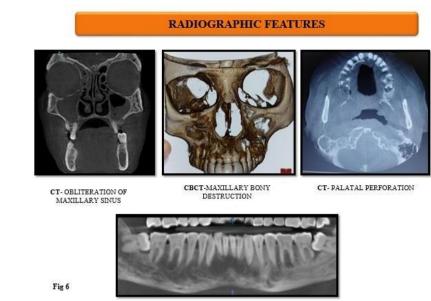
Fig-5 NECROTIC BONE



NO INTRAORAL FINDINGS



GINGIVAL SWELLING



OPG-MULTIPLE RADIOLUCENCIES IN MANDIBLE

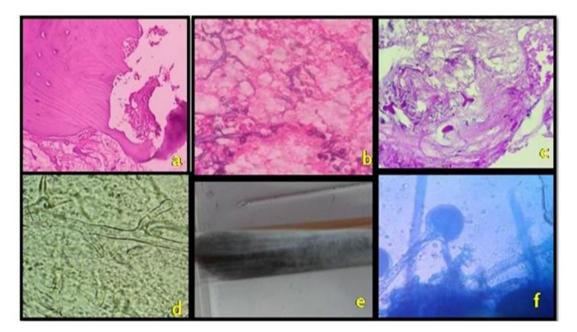


Fig-7: a and b- Bony trabeeulae with empty lacunae of osteocytes, e-Broad aseptate obtuse angle fungal hyphae,d-Broad wide angle a aseptate hyphaes were seen on KOH I mount, e- Grayist black coloured growth on Sabouraud agar medium was seen, f- Broad aseptate ribbon like hyphae with sporangium seen on lactophenol cotton blue (LPCB) stain after 72 hrs of culture on Sabouraud dextrose agar(SDA)

References

1. Lenka S, Swain SK, Bhuyan R, Sahu MC. Fungal infection in the oral cavity: A Review. Int J Cur Res Rev Vol. 2020 Sep 22;12(18):149.

2. Tran D, Schmit B. An Aggressive Case of Mucormycosis. Cureus. 2020 Aug;12(8).

3. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021 May 21.

4. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, Lu Y. COVID-19 treatment: close to a cure?–a rapid review of pharmacotherapies for the novel coronavirus. International journal of antimicrobial agents. 2020 Jul 4:106080.

5. Negi P, Kumari P, Negi S. Review on the oral manifestations of Covid-19 disease and Mucormycosis. Journal of Advanced Medical and Dental Sciences Research. 2021 Jun 1;9(6):64-7.

6. Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V. Sino-orbital mucormycosis in a COVID-19 patient: A case report. International Journal of Surgery Case Reports. 2021 May 1;82:105957.

7. Veisi A, Bagheri A, Eshaghi M, Rikhtehgar MH, Rezaei Kanavi M, Farjad R. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: a case report. European Journal of Ophthalmology. 2021 Apr 10:11206721211009450.

8. Alekseyev K, Didenko L, Chaudhry B. RhinocerebralMucormycosis and COVID-19 Pneumonia. Journal of Medical Cases. 2021 Mar;12(3):85.

9. John TM, Jacob CN, Kontoyiannis DP. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. Journal of Fungi. 2021 Apr;7(4):298

10. Ye Q, Wang B, Mao J. The pathogenesis and treatment of theCytokineStorm'in COVID-19. Journal of infection. 2020 Jun 1;80(6):607-13.

11. Langarizadeh MA, Tavakoli MR, Abiri A, Ghasempour A, Rezaei M, Ameri A. A review on function and side effects of systemic corticosteroids used in high-grade COVID-19 to prevent cytokine storms. EXCLI journal. 2021;20:339.

12. Nichols L, Rios DA. How could hypoglycemia-inducing glycogen storage disease lead to hyperglycemia-induced mucormycosis?. Autopsy and Case Reports. 2020;10(1).

13. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, Li Y. Ferritin in the coronavirus disease 2019 (COVID - 19): A systematic review and meta - analysis. Journal of clinical laboratory analysis. 2020 Oct;34(10):e23618.

14. Shalini M. An Unusual Case of Maxillary Osteomyelitis in a Young Female.

15. Anehosur V, Agrawal SM, Joshi VK, Anand J, Krishnamuthy K, Kumar N. Incidence and treatment protocol for maxillofacial fungal osteomyelitis: a 12-year study. Journal of Oral and Maxillofacial Surgery. 2019 Nov 1;77(11):2285-91.

16. Urs AB, Singh H, Mohanty S, Sharma P. Fungal osteomyelitis of maxillofacial bones: Rare presentation. Journal of oral and maxillofacial pathology: JOMFP. 2016 Sep;20(3):546.

17. Awal SS, Biswas SS, Awal SK. Rhino-orbital mucormycosis in COVID-19 patients—a new threat?. Egyptian Journal of Radiology and Nuclear Medicine. 2021 Dec;52(1):1-6.

18. Mehra H, Gupta S, Gupta H, Sinha V, Singh J. Chronic suppurative osteomyelitis of mandible: a case report. Craniomaxillofacial trauma & reconstruction. 2013 Sep;6(3):197-200.

19. Sahota R, Gambhir R, Anand S, Dixit A. Rhinocerebral mucormycosis: report of a rare case. Ethiopian journal of health sciences. 2017 Feb 6;27(1):85-90.



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