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**CASE REPORT****Mucormycotic osteomyelitis involving maxilla in SARS-CoV-2 prediabetic patient:  
A case report**

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**Abstract**

SARS-CoV-2, a respiratory corona virus, zoonotic disease and a global pandemic burden demonstrates a myriad of clinical and oral manifestations that have been documented in yester years. The clinical manifestations include sore throat, fever, dyspnea and anosmia (partial or complete loss of smell). The oral manifestations include xerostomia, candidiasis, and hyperpigmentation of melanin, oral ulcerations and ageusia (loss of taste sensation). These findings were further worsened in patients with co-morbidities such as diabetes, cardiovascular diseases, immunosuppression, pro-inflammatory or pro-coagulative states. The possibility of fungal infections with invasive mycosis has also been documented. However, the occurrence of this deadly virus in pre-diabetic case is a rarity that needs to be explored so as to affirm the hypothesis that hyperglycemia was due to viral induced phenomena or thereof. We report here, one such rare case of mucormycotic osteomyelitis of maxilla manifested after few months in SARS-CoV-2 positive patient with no previous history of diabetes but marked increase in blood sugar level, when infected with corona virus, which can be tagged as a case of non-diabetic hyperglycemia/pre-diabetes/impaired glucose regulation (raised blood glucose level but not in the diabetic range).

**Keywords:** Mucormycosis, SARS-CoV-2, Osteomyelitis, Non-diabetic hyperglycemia, Pre-diabetes, Mobile maxillary teeth

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**Introduction**

The Coronavirus (SARS-CoV-2/COVID 19) outbreak in Wuhan, Hubei Province, China has been declared as a pandemic disease by World Health Organization (WHO). It is caused by a single stranded, enveloped RNA virus that is a newly emerging zoonotic agent that causes respiratory illness in humans [1-2]. Recent scientific evidences have highlighted the role of Cross Species Transmission (CST), zoonotic links,

and spillover conjuncture between animals and human transmission, before acquiring direct human-to-human contact [3-4]. Presenting with a myriad of clinical and oral manifestations such as headache, sore throat, cold, fever, fatigue, dyspnea, respiratory failure, xerostomia, anosmia, ageusia, candidiasis, hyperpigmentation of melanin, oral ulcerations, pneumonia and cardiac arrest, this pandemic disease has demanded researchers to

spur new investigations, both basic and clinical, to better understand the pathophysiology and virulence of this deadly virus [5-7]. These findings were further worsened in patients with comorbidities such as diabetes, cardiovascular diseases, etc. The possibility of fungal infections and a high probability of suffering from fungal mycosis have also been documented [8]. However, the occurrence of this pandemic disease in pre-diabetic case is a rarity that needs to be explored so as to affirm the hypothesis that hyperglycemia was due to viral induced phenomena or thereof. We report here, one such rare case of mucormycotic osteomyelitis of maxilla manifested after few months in SARS-CoV-2 positive patient with no previous history of diabetes but marked increase in blood sugar level, when infected with corona virus, which can be tagged as a case of non-diabetic hyperglycemia /pre-diabetes/ impaired glucose regulation (raised blood glucose level but not in the diabetic range).

### Case Report

A 44 year old male patient who works as recovery officer in finance organization visited the Department of Dentistry, Post Graduate Institute, Yashwantrao Chavan Memorial Hospital Pimpri, Pune, Maharashtra, India, in the month of October 2020, with the chief complaint of generalized mobility of maxillary teeth with pus discharge from past one month. Past medical history revealed SARS-CoV-2 positivity in the month of June 2020. The associated symptoms documented were fever, body ache, malaise, anosmia, ageusia and headache. On physical examination, during the same period, an increased SPO<sub>2</sub> level of about 97% on radial artery level was noted. The following

vital signs were reported: blood pressure of about 110/70mm Hg, pulse rate of about 74/min, respiratory rate of about 18/min and temperature was about 98° F.

Complete blood count profile was investigated on daily basis. On day 1, White Blood Cell (WBC) count level was 29600/mm<sup>3</sup>, Red Blood Cell (RBC) count was 5.09 millions/mm<sup>3</sup>, platelet count was 296000/mm<sup>3</sup>, hemoglobin of about 14.8 gm/dL and fibrinogen level was 476.3 gm/L. Biochemical investigations of interleukin level showed 16.90 pg/ml. Consecutively on day 2 and day 3, there was marked increase in platelet count of about 315000/ mm<sup>3</sup> and 309000/ mm<sup>3</sup> respectively. A marked increase in blood sugar level i.e. estimated Average Glucose (eAG) level was about 128.7 mg/dL, glycosylated Hemoglobin (HbA1c) level was about 6.1% and fasting glucose level was about 106 mg/dL was noticed. On anamnesis, the patient said he had no past history of diabetes and was not on any medications.

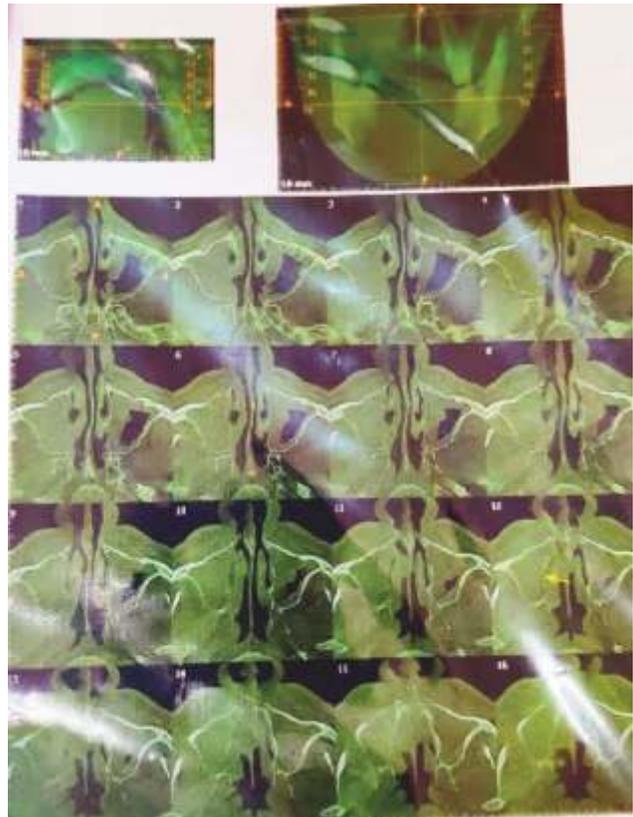
Radiographic investigation with High-resolution Computed Tomography (HRCT) of chest revealed ground glass opacities with multiple patchy areas and well delineated sharp margins on both the lobes of lungs. Chest X Rays (CXR) showed normal results. The patient was hospitalized for 3 days for the same, after which he was kept under home quarantine.

Post three months of SARS-CoV-2 positive symptoms, the patient developed mobility with multiple teeth in the maxillary anterior area. On intra oral examination, grade 3 mobility with 11,12,13,14,15,16,17,21,22 teeth and multiple gingival swellings with pus discharge and draining sinuses were noticed (Figure 1). Cone Beam

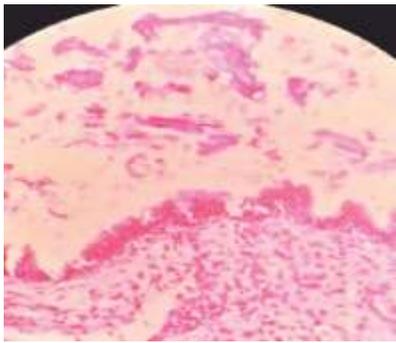
Computed Tomography (CBCT) report revealed an ill-defined radiolucent lesion, indicating an osteolytic expansile type, extending from distal to 17 to mesial of 14 region antero-posteriorly and from the crest of alveolar bone to floor of maxillary sinus was seen (Figure 2). Slight obliteration of the sinus with dome shaped haziness was noticed. Slice no 19-21 of axial sections of CBCT revealed perforation of the floor of maxillary sinus with involvement of medial and lateral wall up to the mid-palatine region. Perforation of buccal, palatal and nasal floor was spotted. Associated loss of alveolar bone present in the vicinity of the lesion comprehended for the mobility of teeth. Radiographic differential diagnosis of a secondary infective lesion or cyst/tumor was made. Further investigations with swab culture revealed presence of fungal pathogen. With patients consent, soft tissue biopsy under general anesthesia was done and sent for histopathological examination that revealed ciliated, pseudostratified columnar epithelium of maxillary sinus with necrosed bony trabeculae interspersed in the connective tissue area. At places, formation of new bony trabeculae surrounded by chronic inflammatory infiltrate was seen. There were presence of few non septae fungal hyphae elements demonstrating acute angled, broad hyphae when viewed on  $40 \times$  magnification (Figures 3 and 4). The final impression made was maxillary osteomyelitis with mucormycosis in SARS-CoV-2 pre-diabetic patient. Treatment was initiated with debridement of the area with antibiotic and antifungal coverage.



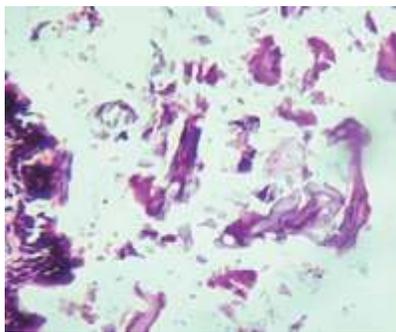
**Figure 1: Depicts mobility with maxillary teeth and pus discharge with draining sinuses**



**Figure 2: Cone beam computed tomography images revealed an ill-defined radiolucent lesion extending from distal of 17 to mesial of 14 region antero-posteriorly and from the crest of alveolar bone to floor of maxillary sinus was seen.**



**Figure 3: H & E stained section demonstrate ciliated, pseudostratified columnar epithelium of maxillary sinus with fungal hyphae.**



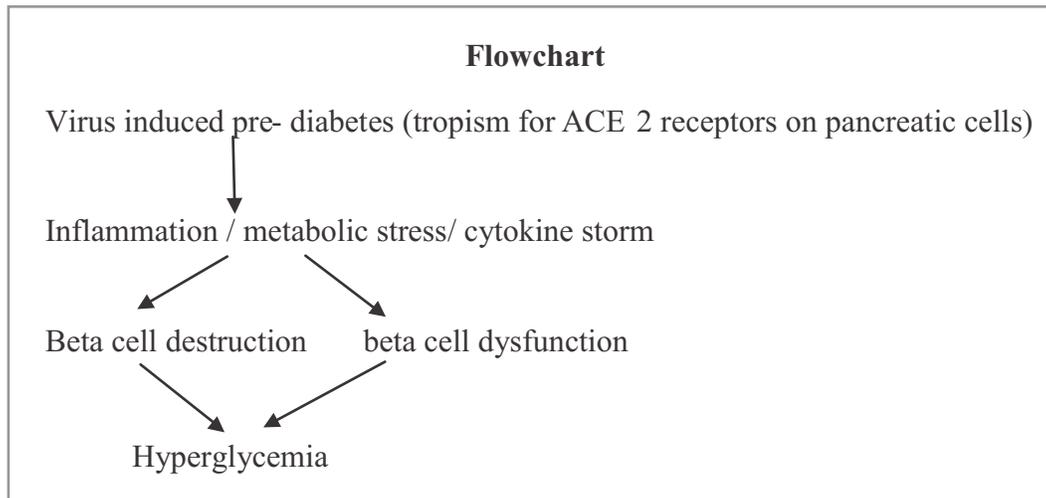
**Figure 4: Depicts presence of non septae fungal hyphae elements demonstrating acute angled, broad hyphae when viewed on 40 × magnification.**

### Discussion

SARS-CoV-2, is a zoonotic, pandemic disease that hit all across the globe, spreading like a wildfire, across 212 countries with more than a million deaths worldwide [8] caused by spherical-shaped, enveloped, single-stranded RNA virus with helical symmetry and belonging to the family of “Nidovirales” (group of viruses that utilize a nested set of mRNAs for their replication). Nidovirales are further classified into four genera- alpha, beta, gamma and delta coronaviruses.

Among these, only 2 genera, i.e., alpha and beta corona virus infect humans [1]. SARS-CoV-2 is an example of beta coronavirus. To detail the structure, the RNA genomes of this deadly virus is considered to be the largest (27–32 kb) and is made up of four proteins i.e SEMN-S for spike protein, E for envelope protein, M for membrane protein and N for nucleocapsid protein [9].

The average age of incidence of SARS-CoV-2 infectivity ranges from 47-56 years, wherein males dominated comprising about more than 50% of cases and approximately 98% of them manifested the symptoms. The average incubation period documented was 5.2 days for the infectivity to manifest into variable clinical outcomes [2]. The common clinical and oral manifestations observed were headache, sore throat, cold, fever, fatigue, dyspnea, chemosensory alterations, respiratory failure, pneumonia and cardiac arrest. The increased risk among co-morbidities such as diabetes, cardiovascular diseases and the probability of fungal pathogen has also been documented in yester months especially in diabetes [8]. In the present case report, the rare finding of occurrence of mucorales in pre-diabetic SARS-CoV-2 positive patient with tooth mobility post infection, created a curiosity to rule out if the virus induced the rise in blood sugar level and increased susceptibility to fungal pathogen during its infectivity period. However, the tropism of the virus to ACE 2 receptors and its expression on pancreatic cells (although unknown) [10], this can be correlated for the hyperglycemia state induced during the infectivity period and further research studies on the same line should be conducted to affirm the hypothesis.

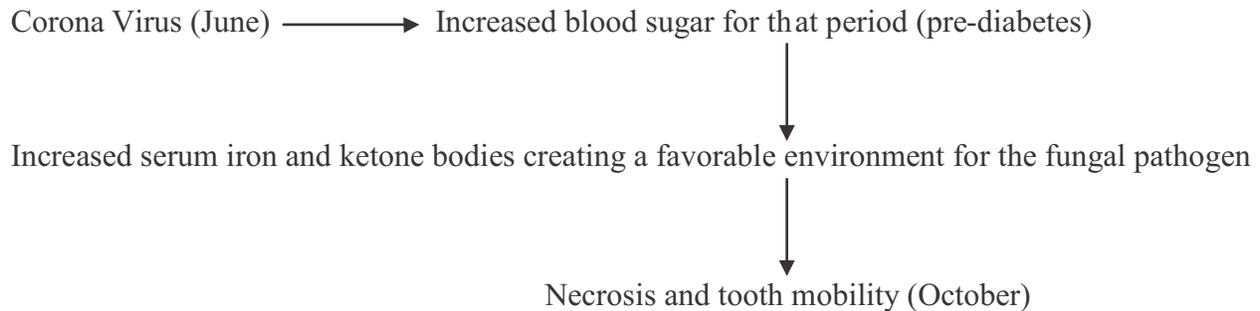


Mucormycosis, a life-threatening invasive infection, occurs commonly in immunocompromised patients especially diabetes. Belonging to the class Zygomycetes and the order Mucorales, an annual incidence of its occurrence has been reported as 0.07% and 0.29%. Increased hyperglycemia leads to glycosylation of proteins such as transferrin and ferritin, thereby decreasing their iron affinity and increased accumulation of ketone bodies, thus favoring the growth of the pathogen, ultimately leading to diabetic ketoacidosis. Additionally, the decreased neutrophils function in turn slows down the immune response for the pathogen [11]. Hyperglycemia and acidosis are known to impair the ability of phagocytes to move toward and kill the organism by both oxidative and non-oxidative mechanisms [12]. Since it is an invasive pathogen, it has a tendency to invade the facial bone and as maxilla has rich vascularity, the mucorales can further lead to necrosis and osteomyelitis as in the present case.

The perspectives of increased susceptibility of this virus in diabetes was further explained by

Muniyappa *et al.* who correlated the presence of increased ACE2 expression in alveolar AT2 cells, myocardium, kidney, and pancreas and its binding to cell surface ACE2 receptors leading to its subsequent entry into cells via endosomal pathway. Furthermore, the proximal serine proteases such as Transmembrane Serine Protease 2 (TMPRSS 2) are involved in S protein priming and cleavage of the spike and the proteases such as furin subsequently release the spike fusion for viral replication leads to the formation of mature virions and its spread. Because of the rise in blood sugar level, the early recruitment and function of neutrophils and macrophages are impaired, thereby causing a delay of adaptive immunity and dysregulation of the cytokine response that may lead to the initiation of cytokine storm [2]. This can also be correlated in the present case report.

To conclude, the hypothetical phenomenon in the present case i.e. correlation of pre-diabetes, corona virus and fungal involvement can be summarized as shown in the flowchart below:

**Flow chart 1: Depicting the correlation of corona virus, pre-diabetes & mucormycosis****References**

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