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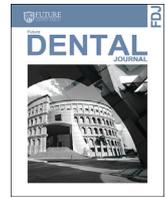
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Management of Post COVID 19 Mucormycosis with Osteomyelitis in The Maxilla, New Combined Consequences of The Pandemic. (Case Report).

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ABSTRACT

Aim: This case report aims to demonstrate among health providers the importance of timely surgical and prosthetic management procedures of patients who suffered from the newly combined clinical entity of post COVID 19 mucormycosis and osteomyelitis of the palate. **Materials and methods:** Elaborate advanced diagnosis of the patients including CBCT, MRI, CT, Pathology examination, 3Ds printing reconstruction of the whole skull and digital design of reconstructive mesh that support the prosthesis were carried out. The patients undergone modified infrastructure maxillectomy and immediate prosthetic obturation of the palatal defect that was replaced later by a delayed obturator. **Results:** Surgical eradication of the necrotic bone and subsequent immediate obturation of the defect minimized morbidity and helped in improving the quality of life of these patients. **Conclusion:** Early diagnosis of this potentially fatal disease and reach-out a treatment plan immediately, is of prime importance in reducing the morbidity and mortality rate and enhance speech and eating in the two patients reported. It also decreases the psychological impact of this radical surgery.

1. INTRODUCTION

Coronavirus disease (COVID-19) that emerged to the surface in 2019, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the leading cause of a global breakthrough pandemic.^{1,2} Beside the Acute Respiratory Distress Syndromes (ARDS) caused by it, COVID-19 patients were found to have multiple symptoms and immune-suppression attributed to an impaired cell mediated immune response with drop in CD4⁺T and CD8⁺T cells.³ This resulted in a wide spectrum of bacterial and fungal infections that may co-exist with possible association with a preexisting morbidity (diabetes mellitus, lung disease) or may develop as a hospital-acquired infection.¹⁻⁷

Acute invasive fungal rhinosinusitis (AIFR) is a time-sensitive condition that must be recognized and treated promptly to avoid life-threatening complications. Madeny et al reported that in a 10-year study that was carried out in Egypt, 45 cases of proven invasive fungal sinusitis were diagnosed which is comparable to the relative incidence present in other countries.⁸ El Kholy et al reported that nearly 5 to 7 invasive fungal sinusitis cases are diagnosed per year.⁹⁻¹⁵

A combination of these factors makes the hospitalized COVID-19 patients a potential high-risk group for fungal infections like aspergillosis and mucormycosis. Aspergillosis is linked with fungus spheres of the sinuses

without tissue invasion, mucormycosis in contrary is an angioinvasive fungal infection, which causes ischemic necrosis of the regions involved. The clinical progressive course is rapid with case fatality rate of 46%.¹⁵ Careful monitoring of immunocompromised patients and COVID-19 patients, with history of hospital admission for oxygen support is necessary, as this category of patients frequently has comorbid conditions like diabetes, renal failure and is usually administered steroids / antibiotics as part of COVID-19 management protocol.^{16, 17}

Maxillary osteomyelitis was considered rare due to the thinner bone and better vascularity as compared to the mandible. Apart from the uncommonness of maxillary osteomyelitis, fungal infection of the maxillary sinuses was also considered infrequent, seen mainly in immune-compromised patients. With the rise in COVID-19 cases, there has been a raise in patients with fungal osteomyelitis coupled with diabetes mellitus, and affect more the maxilla. Diabetes by itself reduces the vascularity of the bone, which, coupled with the fungal organisms compressing the blood vessels, leads to ischemia and necrosis.¹⁸⁻²⁵ Many conditions are well known to lead to perforation of the palate like tumors, disease, and accidents. However, Heroin abuse was also reported to cause palatal perforation.²⁶ The aim of this study is to demonstrate surgical and prosthetic management of two patients who suffered from the newly combined clinical entity of post COVID 19 mucormycosis and osteomyelitis of the palate.

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2. CLINICAL REPORT

This clinical report reported two patients who had post-COVID 19 mucormycosis with osteomyelitis in the maxilla requiring maxillectomy followed by planned rehabilitation. The condition is rare but is of clinical interest. Dentists should be aware of such oral complications after COVID 19.

Patient # 1:

A 65-year uncontrolled diabetic male patient has suffered from COVID 19 virus in January 2021 and was referred for prosthetic consultation on July 2021. Reviewing the history and the course of treatment, it was found that patient has the COVID 19 virus and was admitted to a hospital for 4 weeks. He was in the intensive care and on oxygen support. During his hospital stay, he has treated with antibacterial and steroid medicines. After discharge from the hospital, he felt an opening in his right part of the maxilla. He was readmitted to the hospital and all investigations were carried out again. The diagnosis was post COVID 19 mucormycosis that required surgical debridement, extraction of all his maxillary teeth and anti-fungal drugs administration.

On a thorough intraoral examination, the patient has undergone an extensive debridement surgery by an ENT surgeon. All his teeth were extracted and left with palatal perforation in his right maxilla 4 cm long and 1 cm width. As radiographic examination is very important at this stage to detect the extension of the destruction of the invasive mucormycosis in the maxilla and the surrounding organs. A Cone Beam 3 Ds radiographs were made to evaluate the extension of destruction in three dimensions. The DICOM file of the patient's whole skull was 3Ds printed to resin in order to facilitate visualization of the defect and help communication with the patient. The amount of destruction was huge, invaded almost completely right palatine bone and approached the infraorbital bone Fig. (1). Insufficient bone for implant placement was detected in both the right and left maxilla and in the pre-maxilla. All this destruction occurred in only one-month period post hospitalization. An alternative treatment plane that includes fabrication of subperiosteally reconstructive mesh that is fixed with fixation screws to the remaining bone. This mesh has implants protruding in the oral cavity to support the prosthesis. This was achieved with the aid of special digital software (Fig. (2)). Working with three-dimensional (3D) intra-oral scanning it was possible to combine the data of the intra-oral situation, like the position of the ridge and remaining bone, with CBCT and magnetic resonance imaging (MRI) data of the surrounding tissues in an augmented model. This 3D virtual model provides more insight into the implications and complexity of surgical and prosthetic rehabilitation. Segmentation of the DICOM file was done by the aid of (Mimics, Materialize software) to transform the DICOM file to STL file. The reconstruction mesh was designed by (Meshmixer software)

However, after seven months from the beginning of the COVID 19, and during finalization of the rehabilitation treatment plan, the patient got a cerebral stroke that affected his left arm and leg and impaired his ability to walk without support. After consultation with medical and dental teams and assessment of the investigations and the general health of the patient, the decision was to abort this treatment plan and avoid any further surgical intervention and go only for removable obturator prosthesis to close the defect. The patient was reluctant to accept this line of treatment as he had hoped to have implant-supported fixed prosthesis instead, which was completely contra indicated at this stage.

Patient #2:

A 55-year male patient was referred for prosthetic consultation. The history of the patient and investigation findings were consistent with a diagnosis of COVID-19 at the beginning of January 2021. During his hospital stay, he has treated with antibacterial and steroid medicines. By the end of February 2021, the patient developed an opening in the palate. An ENT surgeon subsequently did debridement of the right sinus and extracted his right maxillary teeth. The debris was sent for a pathology examination on

March 2021. Microscopic examination of the specimen revealed ulcerated markedly inflamed respiratory mucosal fragments mixed with fungal hyphae and spores predominantly *Macour* species. Dense diffuse mixed inflammatory cellular infiltrate was seen that included acute and chronic inflammatory cells predominated by plasma cells associated with few multinucleated inflammatory giant cells, fibrotic bands were also seen. The fibro-inflammatory reaction presented the included necrotic bony trabeculae. The diagnosis was right ethmoid lesions FESS: Invasive deep fungal sinusitis (mucormycosis) with osteomyelitis. The CT and MRI reports confirmed the pathology results and indicated that current findings are suggestive of osteomyelitis of the bony boundaries of right sided PNS together with intracranial enhancing lesions. The CT report considered this lesion is a sequel of invasive fungal sinusitis.



Figure (1) — STL files that were converted from the DICOM files of the patient's skull and were 3Ds printed into resin to demonstrate the huge destruction in right and left sides of the maxilla.

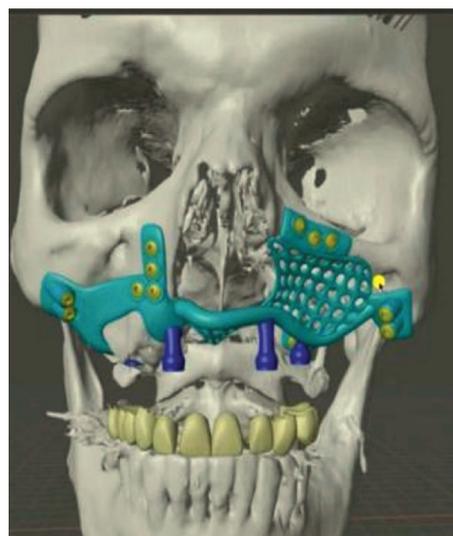


Figure (2) — Digitally designed reconstructive mesh with its fixation screws and its protruding implants.

At that stage, the patient was referred to the prosthodontist who requested a CBCT image. CBCT scan was taken with Field of view 10 × 10 and reconstructions were made in axial, coronal, and sagittal planes. CBCT report on October 2021 revealed that the findings were indicative of invasive

destruction of the right maxillary alveolus extending from tooth 23 to tooth 28, secondary to a lesion originating from the maxillary sinus. Integrating the findings of the CBCT scan and the pathology reports, a final diagnosis of mucormycosis with osteomyelitis of the right maxilla secondary to fungal infection was reached. His glycated hemoglobin (HbA1c) was 7% in the beginning; therefore, blood sugar levels were controlled with subcutaneous insulin during the hospital stay. He recovered satisfactorily and was released from the hospital on antifungal medicine (itraconazole - Sporanox). Fig. (3-6)

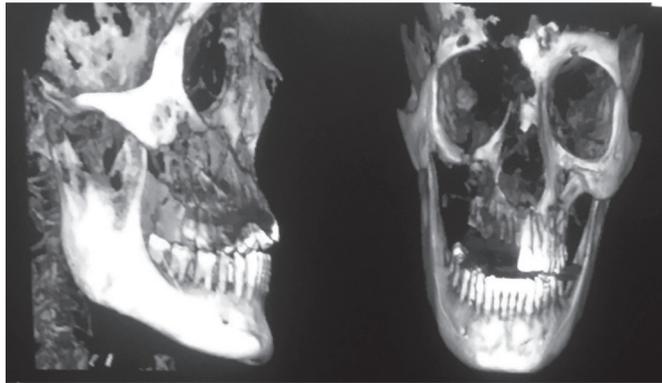


Figure (3) — CBCT images showing the extent of destruction in the right maxilla



Figure (4) — Pre-operative intraoral view of the palate showing the sequestrum and the opening of the right maxilla

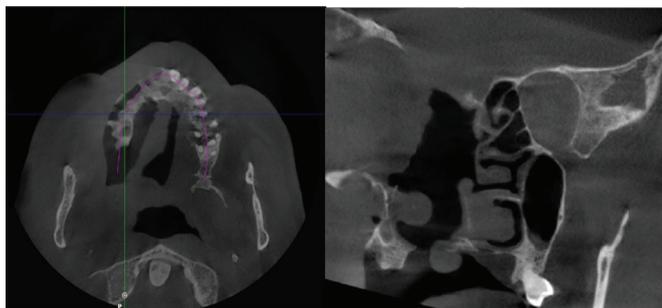


Figure (5) — Cone beam computed tomography scan in (a) Axial section-mixed density lesion showing the sequestrum and the opening of the right maxilla (b) Coronal section-unilateral breach of maxillary sinus and floor of the nose with blocked sinus ostium

On intra oral examination, the alveolar process of the upper jaw on the right side, the gingiva is absent, alveolar bone is bared, bone color is yellowish-cyanotic, during this period all right maxillary teeth are missing, the gum mucosa is not red, no swelling, mucosa does not show signs of acute inflammation. Pathological displacement of the bone of the hard palate

(sequestration separation) was observed, on palpation, a bone area of about 5.5 X 2.5 cm has a slight mobility.

A treatment plan that included surgical removal of sequestration and remnants of the right maxilla, and obturation the defect with immediate obturator prosthesis was initiated.

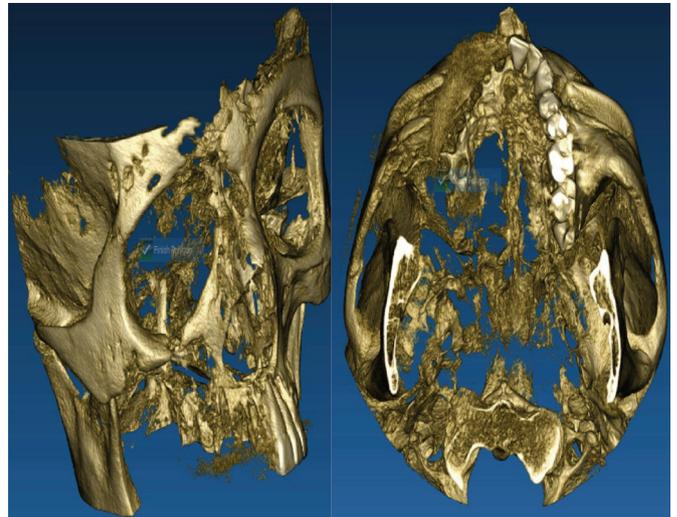


Figure (6) — DICOM images after converted to STL showing the destruction in the right maxilla: (a): side view (b); from the base of the skull

The planned surgery with the amount of excision expected was studied with the surgical team. The team expected that the resection would result in a defect matching to Aramany's Class I. Maxillary and mandibular irreversible hydrocolloid impressions (Zelgan, Dentsply) were made with stock trays. The casts were poured in type III gypsum and the expected line of resection was marked on the cast, which was altered to conform to the proposed surgical resection. Immediate surgical obturator prosthesis was fabricated of heat cure acrylic resin. It was retained using multiple wrought wire clasps Fig. (7). Insertion of the immediate surgical obturator was carried out immediately in the operating room after the surgical resection was completed. The borders of the obturator were adjusted to ensure a passive fit and not to cause any irritation to the reconstructed flap.



Figure (7) —Pre-planning of the surgery and immediate obturator extension on the cast

Surgical procedures:

The patient was admitted to a hospital, prepared for a modified infraorbital maxillectomy that include removal the hard palate (roof of the mouth), lower part of the maxilla, and teeth in the right maxilla. It does not necessitate the removal of the orbital floor (bone below eye). An incision lateral to the nose then curving around ala to reach the lateral philtrum column was done. Cutting through the whole thickness of the lip then sub periosteal dissection was carried out protecting the mucosa overlying the maxilla to use it as a lining of the reflected flap. Osteotomies were done anteriorly at the alveolar margin between two central incisors then the anterior wall of the maxilla at the zygomatic-maxillary junction by osteotome and mallet. The resected segment was pushed down to expose the infratemporal fossa where structures were clamped and cut to free the resected maxilla. Hemostasis was completed then a pack was applied to fill the cavity. This is followed by applying the temporary immediate prosthesis and the wound was closed in layers using 3/0 vicryl sutures by an experienced plastic surgeon. Fig. (8-10).

Prosthetic procedures:

Two weeks after the surgery, a delayed hollowed obturator replaced the immediate obturator. After removal of the surgical packing, and the sutures. Minimal scar was noticed. Major medial undercut was blocked-out with Vaseline gauze before making the impression. A stock tray was modified by adding putty rubber base on the fitting surface of the right side to fill partly the defect space (to be away from incompletely healed tissue). Irreversible hydrocolloid was loaded in the modified stock tray and used to make the final impression. The tray with the hydrocolloid was positioned and the impression was made. The prosthesis was fabricated from acrylic resin, hollowed, adjusted and delivered to the patient. During the denture insertion appointment, the patient's occlusion, phonetics, and esthetics were checked, and the patient was asked to drink water to check for nasal regurgitation of fluids.

This new design of hollow obturator has certain advantages like light in weight, enhancement in retention with restoring form and function for the patient over the conventional obturator design. The patient experienced immediate improvement in speech and reproduction of palatal contour that allowed easier swallowing of food. It also, preserved the contour of the cheek.



Figure (8) — Immediate obturator in place after closure of the flap in the operating room.



Figure (9) — The fitting surface of the delayed obturator



Figure (10) —The delayed obturator in place after two weeks from the surgery. The flap sutures were almost concealed.

3. DISCUSSION

Fungal osteomyelitis is a rare entity in the maxillofacial region. However, the COVID-19 pandemic has caused a rise in the number of cases with post-covid fungal osteomyelitis of jaws. Mucormycosis that is associated with osteomyelitis is a possibly fatal infection that is found mostly in immune-compromised patients and considered the most harmful subtype of fungal sinusitis with subsequent serious morbidity and mortality. The most often affected individuals with invasive fungal infections include those with malignancy, uncontrolled diabetes, AIDS, immunosuppressive, and chemotherapeutic drugs and recently, COVID.^{4,5} Literature review regarding association of AIFR with COVID-19 revealed only sparse case reports.^{6,7}

Reports indicated that patients who were hospitalized in intensive care units for COVID-19 has risk for invasive fungal infections particularly in individuals having chronic respiratory diseases, corticosteroid therapy. In recent studies observed that, in COVID-19 infected patient who treated with widespread use of broad-spectrum antibiotic or steroid and recovered developed secondary bacterial or fungal infection in 8% of patients.²⁵ Auluck reported a case of Maxillary necrosis by mucormycosis,²⁷ and indicated that tissue necrosis; a character of mucormycosis is often a late sign. Mehta et al reported two cases having clinical features, which pointed towards fungal maxillary osteomyelitis.⁷ Mucormycosis cases have been reported in India

as well as in many other countries like Brazil, Chile, Honduras, Mexico, Paraguay, the United States, Uruguay, Italy, and the United Kingdom.²⁸ In a recent report by WHO indicated that globally, the highest number of cases has been reported in India, where it is estimated that there are more than 4,000 people with COVID-19 associated Mucormycosis (CAM). In a retrospective multicenter study conducted in India between September to December 2020, it was found that among 287 patients with mucormycosis, 187 (65.2%) had CAM; with a prevalence of 0.27% among hospitalized patients with COVID-19. When comparing the period under study with the same period in 2019, a 2.1-fold increase in mucormycosis was observed. Regarding the characteristics of the 187 patients with CAM, 80.2% were male, 32.6% had COVID-19 as the only underlying disease, 78.7% were treated with gluco-corticosteroids for COVID-19, 60.4% had diabetes mellitus, 62.6% had rhino-orbital mucormycosis, and 23.5% had rhino-orbital-cerebral mucormycosis²⁸.

Mucormycosis in the bone marrow may promote fungal growth by ruining the endothelial lining of vessels, resulting in vascular inadequacy and leading to bony necrosis and fungal osteomyelitis. This complication is more harmful than the more common bacteria-associated osteomyelitis.²⁸ The fatality rate of mucormycosis is 46% globally.¹⁵

The Steroids are also used to reduce inflammation in the lungs in Covid-19 cases and reported that it minimizes the end organ damage. However, they also reduce immunity and raise up blood sugar levels in both diabetics and non-diabetic COVID 19 patients. This reduction in immunity can lead to mucormycosis.²⁹ A recent report suggested also, that melatonin deficiency is a key factor that increases the susceptibility of the patients to mucormycosis.³⁰

In this clinical report, two post- COVID 19 mucormycosis patients were referred for prosthetic obturation. Both patients have mucormycosis that evoked after infection with COVID 19 and subsequent hospitalization and being in intensive care units. Both patients share almost the same history and manifestations. Their history includes uncontrolled diabetes during their first stay at the hospital and treatment with antibiotics and steroids. Also, includes presence of tissue invasion by fungal elements over very short clinical course of less than 4 weeks. One of them developed osteomyelitis with mucormycosis that invaded his right maxilla and turned the bone in this area into necrotic sequestered bony remnants. Despite his severely debilitated conditions, compromised general health, suffered from stroke, which is a major complication of mucormycosis,²⁸ and low volume of bone in both sides that negate the use of implants, the first patient refused to have removable non-invasive obturator. He was lost to follow-up and did not complete the proposed treatment plan.

However, in the second patient, an extensive surgery to remove the necrotic sequestrum and immediate obturator prosthesis to close the defect were carried out promptly. The outcome of this treatment plan resulted in complete eradication of the necrotic bone and tissue and stopped progression of the disease to the neighboring organs. The timing of the intervention and surgical procedures is very crucial; it is well documented now that the prompt identification and management of these lesions would significantly reduce morbidity and mortality.²⁹⁻³⁵

This patient received an immediate obturator the day of the surgery and then a delayed obturator replaced it (by partly filing the defect cavity) after two weeks. The immediate obturator provided a surgical matrix on which the surgical packing was placed. It also, enabled the patient to speak and eat more effectively postoperatively without nasal regurgitation. The surgical sutures were concealed around the ala of the nose and showed satisfactory cosmetic results. This obturator lessens also, the psychologic impact of this extensive surgery and made it easier to bear. The obturator prosthesis restored the patient's self-image of his appearance by reproducing the contour of the lost oral structures that support the cheeks and allowed the patient to function socially and normally. In some cases, prosthetic retentive considerations are critical to achieve successful prosthetic rehabilitation. The obturator was made hollow to be light in weight and help in enhancing the retention of the

prosthesis. The size of the defect and number of critical remaining teeth that may serve as anchorage for conventional clasp supported removable partial denture framework add challenges to the maxillofacial prosthodontists. Thus, a prosthodontist plays a vital role in the rehabilitation of total/subtotal maxillectomy patients by separating the oral and the nasal cavities, restoring the normal speech and mastication, along with improved aesthetics. In the presented case, the emphasis was more on the intaglio surface and occlusion with reduced cusp angles for better retention and stability of the prosthesis functionally. Though an acrylic prosthesis was fabricated, metal could have been a better option; however, owing to the cost factor and the increase in the number of visits, acrylic was preferred. An implant-supported prosthesis was a viable treatment option for better retention, but conventional obturators were preferred to avoid further surgical intervention. Several studies have reported the successful rehabilitation of maxillectomy patients with conventional obturators. The major role of a prosthodontist in treating maxillectomy patients does not end by rehabilitation of the lost oral function and aesthetics but also by rehabilitating and restoring the patient's mental health³⁸.

4. CLINICAL IMPLICATIONS

Proper strict recommendations are essential to limit the intake of drugs related to reduced immunity in the COVID-19 patients, survivors and COVID-19 people with additional illness like diabetes, inflammatory disorders and those undergoing chemotherapies or other treatments to recognize the mycoses in its initial stages to increase their livelihood.³⁶

According to The US Centre for Diseases Control and Prevention (CDC), an overall all-cause mortality rate of 54% was reported for Mucormycosis. The mortality rate depends upon the underlying condition of the patient, fungus type, and affected site in the body (for example, the mortality rate reported was 46% for patients with sinus infections, 76% for pulmonary infections, and 96% for disseminated mucormycosis) (CDC, 2021). The difficulty and delay in diagnosing Mucormycosis affects the outcome of the disease and may lead to poor prognosis because of its high invasiveness and its intrinsic low susceptibility to antifungal agents. Therefore, early diagnosis and treatment are necessary.³⁷ According to recent WHO report, prevention of COVID-associated mucormycosis needs to focus on addressing the underlying risk factors such as better glycemic control in those with diabetes, appropriate use of systemic corticosteroids and prevention of unnecessary use of antibiotic, antifungal and other immunomodulators.^{28,38} Dentists also, have an important role and should be aware of the increased incidence of mucormycosis in Post COVID patients, especially in poorly controlled diabetes and other immunocompromised individuals. The role of dentist and prosthodontist in identifying the disease and its management is essential. Symptoms such as atypical facial or sinus pain, blackish discharge, unexpected toothache, bare bone and perforation of the palate should make the dental practitioners alert and ready to manage.

5. CONCLUSION

There are a rising numbers of COVID-19 recovered patients who are presenting with an increasing number of fungal osteomyelitis of the jaws. A multidisciplinary team approach is crucial for the early diagnosis and management of Mucormycosis, such a devastated disease. The proper diagnosis with all the available advanced investigations, pathology and 3 Ds radiographs and models are the keys for proper management of this aggressive disease. The timing of the intervention has a significant impact on reducing morbidity and mortality. Combining surgical eradication and prosthetic obturation could help stopping progress of the mucormycosis and osteomyelitis. The obturator prosthesis delivered to this patient reduced the morbidity that may occur because of this extensive surgery and helped enhancement of the patient's quality of life.

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