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CASE REPORT

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The use of advanced-platelet rich fibrin (A-PRF) in the management of medication-related osteonecrosis of the jaw (MRONJ): A case report

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Abstract

Medication-related osteonecrosis of the jaws (MRONJ) is a serious debilitating disease resulting from long-term treatment with Antiresorptive drugs such as Bisphosphonates or Denosumab, which significantly affects patients' quality of life. A 43-year-old female patient with stage 4 breast cancer and treated with Zoledronic Acid for bone metastases was referred to the Department of Oral Medicine at the Faculty of Dentistry, Damascus University. The main complaint was pain in the right maxilla. Intraoral examination showed an exposure of necrotic bone in the right maxillary region with presence of purulent exudate. The treatment plan was discussed with the patient. Treatment included resection of all necrotic bone and application of Advanced platelet-rich fibrin (A-PRF) clots and membranes. Follow-up and outcome were conducted by clinical measures to assess healing and recurrence (6-month follow-up). Topical treatment with A-PRF demonstrated a reduction in pain and resulted in complete wound healing within 30 days. A-PRF stimulates the release of growth factors and chemotaxis involved in tissue repair mechanisms. This method seemed to be effective in the treatment of MRONJ.

KEYWORDS

A-PRF, bone necrosis, breast cancer, MRONJ

1 | INTRODUCTION

Patients with metastatic breast cancer usually take Antiresorptive drugs such as Bisphosphonate or Denosumab. Medication-related osteonecrosis of the jaws (MRONJ) is one of the side effects of these drugs, which defined as persistent bone exposure within the oral cavity for a minimum period of 8 weeks without a history of radiotherapy in the head and neck region.[1,2] American Association of Oral and Maxillofacial Surgeons (AAOMS) has classified MRONJ into three stages:

Stage 1. Exposed and necrotic bone or fistula that probes to the bone in patients who are asymptomatic and have no evidence of infection/inflammation.

Stage 2. Exposed and necrotic bone or fistula that probes to the bone, with evidence of infection/inflammation (symptomatic).

Stage 3. Exposed and necrotic bone or fistula that probes to the bone, with evidence of infection, and one or more of the following: exposed necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla), pathological fractures, extraoral fistula, oral antral/oral-nasal communication.[1,2]

The pathophysiology of MRONJ is still not completely understood. Multiple hypotheses have been suggested to explain the pathophysiology of this disease. These hypotheses include bone remodeling inhibition, inflammation or infection, angiogenesis inhibition, innate or acquired immune dysfunction, and genetic predisposition.[2,3] The current opinion is that MRONJ is a multifactorial complication that can develop as a result of various pathogenic mechanisms.[2–4]

The developing of MRONJ depends on several factors, including type of medication, duration of medication, dental procedures, and diseases (i.e., dental extraction, dental implant, ill-fitting dentures, periodontal disease), systematic diseases (i.e., cancer, diabetes, hypertension). Other risk factors to consider are age, gender, and smoking.[2,4,5]

Diagnosis of MRONJ in most cases requires the following:

(1) Current or previous treatment with Bisphosphonates or Denosumab.

(2) An area of exposed bone, or bone that can be probed through an intraoral or extraoral fistula that has persisted for more than 8 weeks.

(3) No history of radiation therapy to the jaws or obvious metastatic disease of the jaws.[1,2,4]

The current main treatment approaches for MRONJ are conservative treatment (long term antibiotics and antiseptics) and surgical treatment (ranging from debridement and curettage to wide resection to marginal resection and reconstruction plates). Adjuvant therapies have been applied to treat MRONJ. Which include Hyperbaric Oxygenation Therapy (HBO), Low Level Laser Therapy (LLLT), Ozone Therapy, and local application of Autologous Platelet Concentrates (APCs).[1,2,4]

Advanced Platelet-Rich Fibrin is a second-generation of APCs. It is a modified form of the standard platelet-rich fibrin which differs from it in a preparation method that allows for a better distribution of neutrophils, white blood cells, and platelets within the resulting clot. Also, it is rich in growth factors, cytokines, platelets, and neutrophils, which make an important contribution to the process of bone and soft tissue healing, as well as enhancing blood circulation to the site.[6–8]

2 | CASE PRESENTATION

A non-smoker 43-year-old female patient was referred to the Department of Oral Medicine at the Faculty of Dentistry, Damascus University in September 5/2022. The main complaint was pain in the right maxilla. Intraoral examination revealed an exposure of necrotic bone in the right maxillary region with presence of purulent exudate (Figure 1).

The first upper right premolar was extracted 2 months ago. Patient was diagnosed with a stage 4 breast cancer with bone metastases. She was treated with a right radical mastectomy with axillary scraping. The patient received Intravenous Zoledronic acid (4 mg/month) for 2.5 years for the management of metastatic breast cancer. The number of doses were 30. Patient had no history of any systemic disease and family history revealed no systemic or inherited disease. No history of radiotherapy in the head and neck region therefore osteoradionecrosis was excluded.

The case was reviewed and approved by the Local Research Ethics Committee at Damascus University (No: 092020629). A written informed consent was obtained for publication of this case report and accompanying images.

Full blood tests were performed before surgery: general count and formula [Rbcs (10^9/L): 7.12, Hemoglobin (g/dL): 13.2, WBC (10^6/L): 9.3], prothrombin time (PT): 12.2, partial thromboplastin time (PTT): 26, liver enzymes [ALT (IU/L): 52.5, AST (IU/L): 31.1, ALP (IU/L): 62.3],

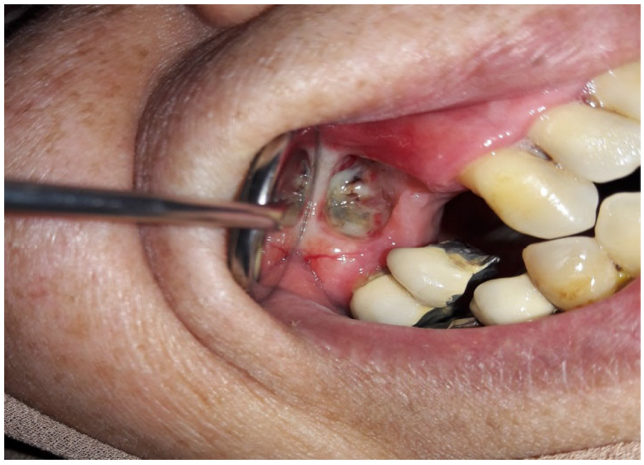

FIGURE 1 Intraoral examination, exposed necrotic bone with purulent exudate.

urea (mg/dL): 32.3 and creatine (mg/dL): 1.1 (all were within normal limits). As well as cardiac, anesthesia, thoractic and oncologic consultations.

3 | A-PRF PREPARATION

60 mL of autologous venous blood was collected intosix glass red cap tubes of 10 mL each. After collection, the blood was immediately centrifuged with a force of 208 g for 14 min at 1500 rpm[6].

Then A-PRF clots were removed from the collection tubes and separated from red blood cells (Figure 2A,B,C,D). Due to the unavailability of Xpression™ box (a special box for preparing membranes), A-PRF clots were placed between two glass plates to compress them into A-PRF membranes.

(Figure 2E) shows A-PRF membranes after gentle compression; the red area of the membrane represents the face side, where most leukocytes, platelets, and stem cells are concentrated (Figure 2E).

A-PRF clots were cut into small pieces by surgical scissor to fill the bone defect (Figure 2F).

4 | SURGICAL PROCEDURES

The surgery was done under general anesthesia in September 23/2022.The skin around the mouth was disinfected with polyvidone iodine solution, and the surgical area was isolated using sterile surgical scrubs. A trapezoid-shaped, full-thickness mucoperiosteal buccal flap was elevated and mobilized to facilitate tension-free closure (Figure 3A).

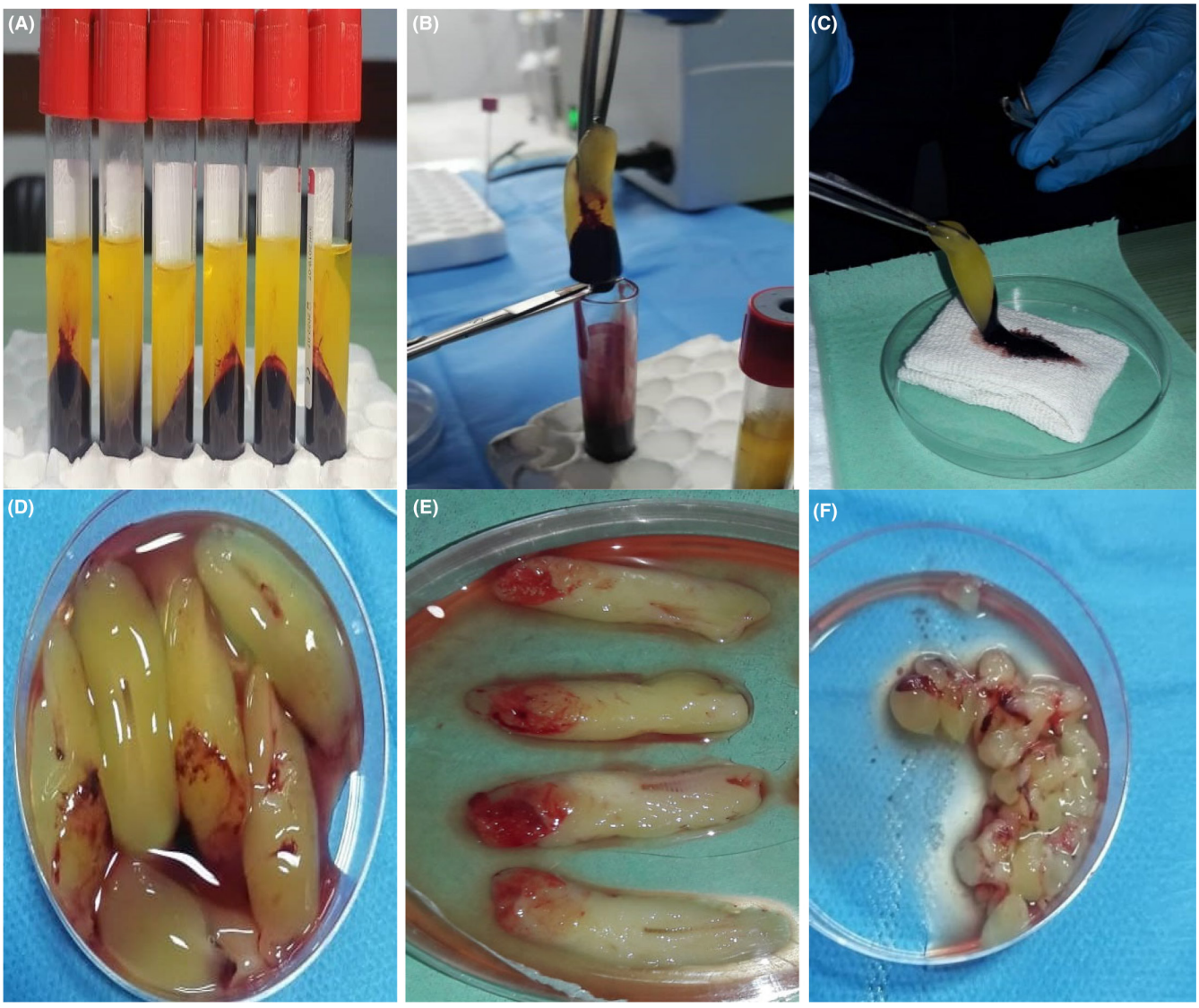

FIGURE 2 A-PRF Preparation Procedures. (A). A-PRF in tubes. (B, C) Remove clot from tube and separate clot from red blood cells. (D) A-PRF clots. (E) A-PRF membranes. (F) A-PRF clots after cutting them into small pieces.

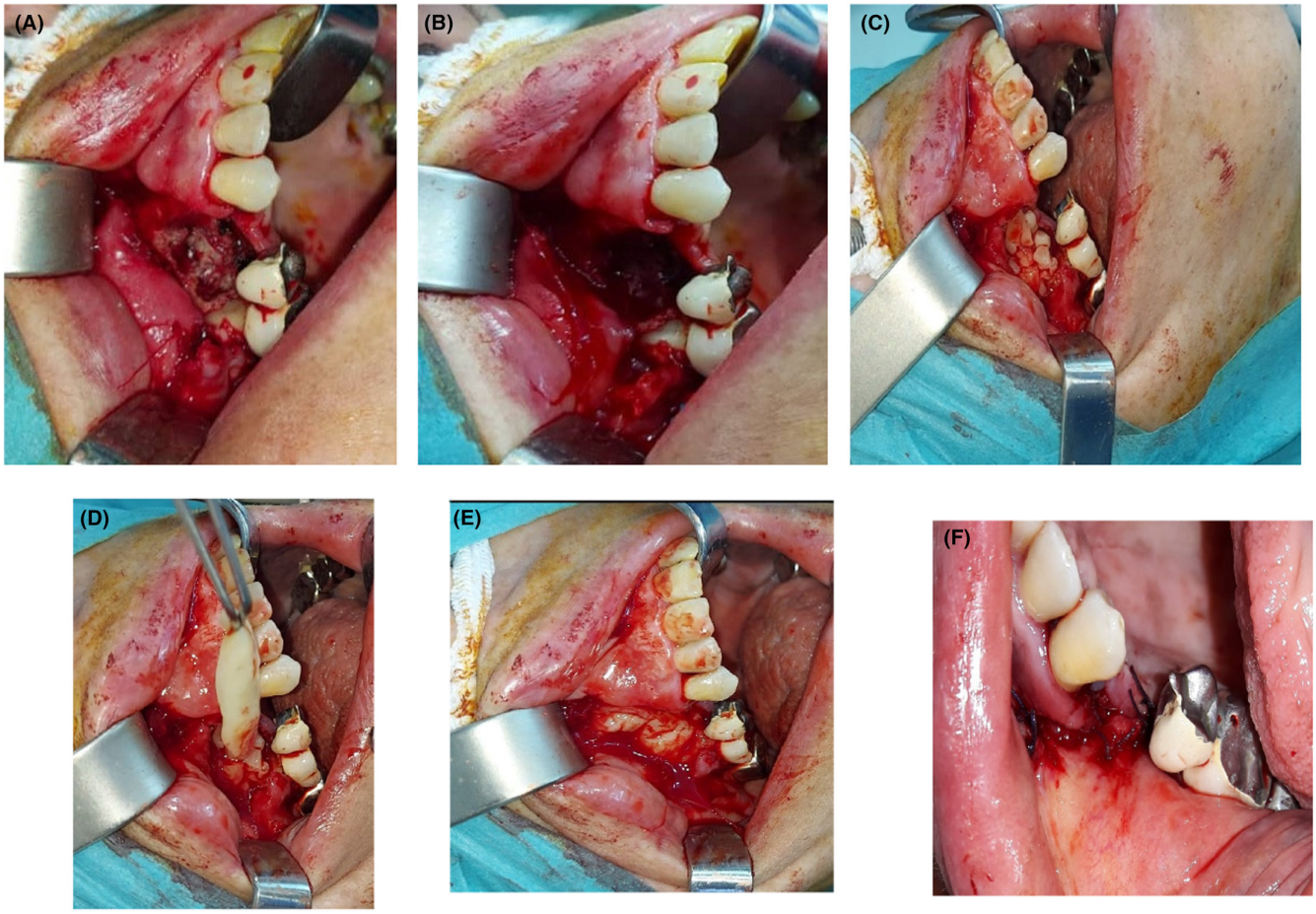

FIGURE 3 Surgical Prucedures. (A) Necrotic bone. (B) Surgery included the resection of all infected and necrotic bone until reaching healthy bone. (C) A-PRF clots filled into the bone defect. (D) Before applying A-PRF membranes. (E) A-PRF membranes covering the clots. (F) Interrupted suturing using 0/3 nylon sutures.

All infected and necrotic bone was resected until reaching healthy bone using surgical handpiece and surgical burs (and abundant irrigation with 0.9% saline solution to avoid heating the remaining bone) (Figure 3B).

Adequate resection of bone margins was determined by the clinical appearance of bleeding bone. Any sharp edge was removed. After bone resection the bone defect was filled with A-PRF clots (Figure 3C), and then covered with A-PRF membranes (Figure 3D,E). Then the flap was reducted and interrupted suturing was done with nylon sutures (0/3 size) (Figure 3F).

The patient had post-surgery instructions and a medical prescription which included antibiotic drugs (Amoxicillin 500 mg and Metronidazole 500 mg every 8 h), nonsteroidal anti-inflammatory drug (diclofinac potassium 50 mg every 8 h) for 1 week.

The sutures were removed within 15 days and the patient received regular clinical follow-up until 6 months after surgery (Figures 4 and 5).

5 | RESULTS

Topical treatment with A-PRF demonstrated relief in pain, infection and inflammation within 10 days, and resulted in complete healing within 30 days. The patient was followed up for 6-months and there was no recurrence.

6 | DISCUSSION

APCs are products that result from the centrifugation of a blood sample.

They concentrate platelets, fibrin and leukocytes (depending on the used protocol) converting them into a clinical and useful form.[10]

The first generation include platelet-rich plasma (PRP) and plasma rich in growth factors (PRGF). While, the second generation include leukocyte-platelet-rich fibrin (L-PRF) and advanced platelet-rich fibrin (A-PRF).[10]

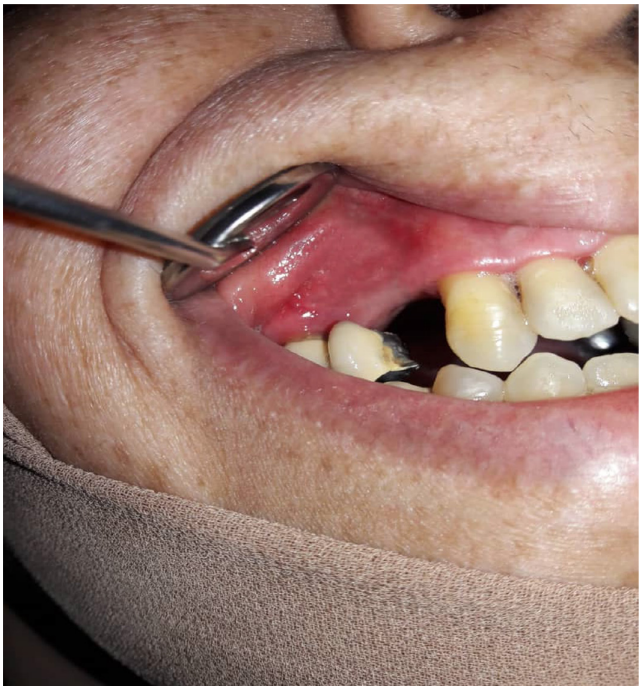

FIGURE 4 1- month follow-up complete healing. 23/10/2022.

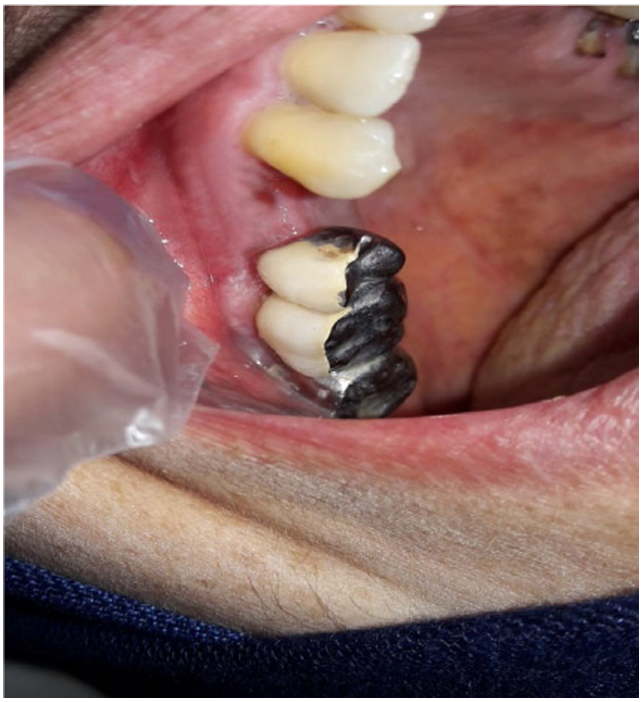

FIGURE 5 Six months follow-up, there was no recurrence. 23/3/2023.

These forms have been used in dentistry for regenerative procedures and seem mainly to promote soft-tissue wound healing by delivering more than natural concentrations of autologous growth factors and cytokines, which are key in the process of tissue regeneration.[7]

The regeneration process includes: cell proliferation and differentiation, extracellular matrix formation, angiogenesis and osteogenesis. It was found that all of these processes stimulate healing of soft and bone tissues.[8]

A-PRF is a modified form of PRF, where Ghanaati et al; 2014 found that decreasing the rate of time of centrifugation gave improved cells in addition to an increase in the release of growth factors for a longer period, which may affect the regeneration and healing of soft and bone tissues.[5] Also, the reduction of Relative Centrifugal Force (RCF) enhanced the number of the included inflammatory cells and platelets and led to a more even cellular distribution.[5]

Masuki et al; 2016 found that levels of growth factors and platelet content were higher in A-PRF compared to other types.[11]

When comparing A-PRF and PRF, the number of neutrophilic granulocytes were significantly higher in A-PRF compared to that in PRF.[6]

Kobayashi et al; 2016 concluded that A-PRF stimulated significantly higher growth factors release over time when compared to PRF. Furthermore, A-PRF released significantly higher total protein accumulated over 10-day period when compared to PRF.[12]

APCs have been used by many authors for treatment of MRONJ. According to the systematic review of Fortunato et al; 2020, the most used forms were PRP, PRGF, and PRF. The treatment outcome showed complete response in 87% of lesions.[9]

Giudice et al; 2020 used A-PRF and the liquid form (I-PRF) in the treatment of a stage 3 MRONJ. This study showed complete healing 25 days after treatment.[13]

In our case report, dental extraction was the trigger of developing of MRONJ which occurred 2 months after the extraction. The patient was taking Zoledronic acid for treating bone metastases. The number of doses were 30. The drug was not interrupted before surgery. A-PRF membranes and clots were used for the treatment of a Stage 2 MRONJ. Initially this topical treatment allowed to reduce infection, inflammation and pain within 10 days. The use of A-PRF may play a role in improving vascularization and thus a complete healing when treating MRONJ.

7 | CONCLUSIONS

The application of A-PRF lead to a complete healing when treating MRONJ.

AUTHOR CONTRIBUTIONS

Maan Ahmad Rafik Asfour: Investigation; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing. **Abeer**

Ahmad Aljoujou: Conceptualization; methodology; project administration; resources; supervision; validation; writing – original draft; writing – review and editing. **Maher Sadik Saifo:** Methodology; project administration; resources; writing – original draft; writing – review and editing. **haya Al Jabban:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval was obtained from ethical review committee of Damascus University.

CONSENT

A written consent was obtained from the patient to publish clinical details and photographs.

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