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Management of Early Case of Maxilla Osteonecrosis in Patient with Bone Metastases on Bisphosphonates Using Platelet-Rich Fibrin as Adjuvant: Case Report

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Abstract | **Case Report**

Although it remains relatively rare, osteonecrosis of the mandible and/or maxilla induced by intravenous infusion of bisphosphonates in patients suffering from bone metastatic cancers is a serious complication that affects the oral and maxillofacial region, its repercussion can be heavy and impacts quite negatively the patient's quality of life, despite its management is uncertain and complicated, a rapid intervention with a conservative approach if it is possible strengthen with the use of platelet-rich fibrin (PRF) as adjuvant seems to be very effective, thus enhancing the bone healing, limiting current manifestations and prevent more serious and extended complications. In this case report, we present a good evolution of an early stage of maxillary osteonecrosis that appeared four weeks after dental extraction by a general practitioner in a 60-year-old female treated with IV Bisphosphonates, IV Herceptin and Arimidex for bone metastatic breast cancer using conservative treatment combined with the use of autologous platelet-rich fibrin.

Keywords: BON, Extraction, Curettage, Maxilla, Osteonecrosis, Platelet-Rich Fibrin, Zometa.

INTRODUCTION

Most often, patients with metastasis bone cancers suffer from a severely altered quality of life, bone metastases cause hypercalcemia, intense bone pain and a high incidence of pathological fractures, overall, these patients are widely treated with bisphosphonates because of their inhibitory effects to the osteoclastic activity, to the proliferation of tumor cells and to angiogenesis, these molecules seem to be very effective for this condition and even for the treatment of some benign pathologies such as Behcet disease and osteoporosis [1], however, several side effects were reported such as acute renal failure after intravenous (IV) administration and gastrointestinal toxicities and esophagitis after oral intake, but also another uncommon complication which is Bisphosphonate-induced osteonecrosis (BON) [2, 3].

Definitely, a total examination of the patient's oral cavity and teeth conditions is highly recommended before starting bisphosphonates therapy, a total care and if possible with a conservative approach is mandatory to avoid as much as possible bisphosphonate-related osteonecrosis of the jaw (ONJ) [4]. Yet its prevalence after antiresorptive drugs oral intake is low (0.1%), it rises to (17%) following IV administration, this serious rare morbid condition presented by an exposed necrotic bone of the jaw should be well and immediately treated [5, 6]. In general, even if its management remains controversial and likely to several opinions, the conservative approach is always favored, this only by giving analgesic, antibiotics and antimicrobial mouthwashes, however, sometimes a curettage, limited debridement or surgeries are required [7-9]. Recently, it is well considered that Platelet-rich fibrin (PRF) is an effective adjuvant in the management of medication-related osteonecrosis of the jaws (MRONJ) to enhance bone healing, and to avoid further complications after teeth extraction or minor oral surgeries in patients receiving antiresorptive drugs [10]. The Platelet-rich fibrin is a fibrin matrix comprised of platelet cytokines, growth factors and cells derived from autonomous blood obtained after its whole centrifugation, this second-generation platelet concentrate showed in several studies a significant improvement of clinical parameters in dental implants, oral surgeries and ONJ management and prevention [11, 12].

CASE PRESENTATION

A 60-year-old female patient consulted the department of Pathology and Oral Surgery of Constantine complaining mainly of an exposed painful

bone appeared following a dental extraction performed by a general practitioner. The medical history reveals that the patient has breast cancer with bone metastases and she received Zometa (4mg) administered by intravenous infusion for 4 years, she was also taking Arimidex 1mg daily and (4mg/kg) IV infusion of Trastuzumab, there is no history of head and neck radiotherapy.

The patient reported that that treatment with Zometa has been discontinued since July, then she underwent several teeth extractions, the last of which was in December, the patient reports that bone exposure and swelling appeared in January. Dental and medical history reports no medical or drug allergy.

An intraoral examination of the area revealed an exposed necrotic bone and unhealed mucosa in the region of second right upper molar (Figure 1).

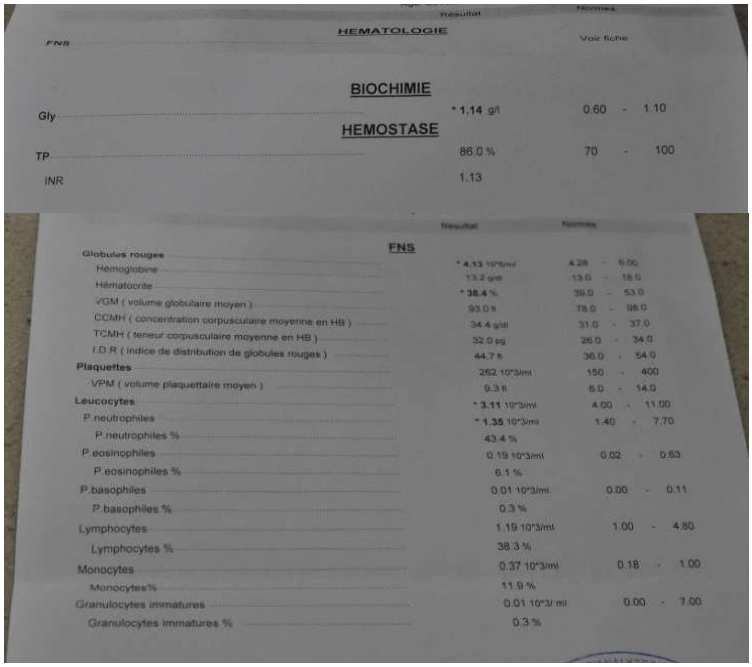
Fig-1: Clinical appearance of necrotic exposed bone at the maxillary second molar

Considering the several heavy anticancer drugs that the patient is receiving, a complete blood count (CBC) was requested for a better assessment of the patient's health status. The Panoramic radiograph demonstrated evidence of radiopaque image suggestive of bone necrosis involving the region and unhealed alveolar sites (Figure 2).

Fig-2: Panoramic radiograph showing persistent sockets and osteolytic area in segment 1

Even though the diagnosis of Bisphosphonate-induced osteonecrosis is established, clinical and radiographic images have confirmed an early stage of this complication which has directed the treatment to a conservative approach. Since its effectiveness in the prevention and the management of bone osteonecrosis was reported, an autologous platelet-rich fibrin has been used as an adjuvant. The patient was informed of this procedure and her agreement was obtained.

Prior to the intervention, the patient was asked to keep a good oral hygiene, the CBC showed no abnormalities or contraindication (Figure 3), however an Antibiotic prophylaxis two days prior to the act was required (Amoxicillin 1mg twice daily) to ensure a suitable intervention area without increased risk of infection.


HEMATOLOGIE

FNS

BIOCHIMIE

Gly * 1,14 g/l 0.60 - 1.10

HEMOSTASE

TP 86.0 % 70 - 100

INR 1.13

FNS

Globules rouges	* 4.13 10^6/ml	4.28 - 5.00
Hemoglobine	13.2 g/dl	13.0 - 18.0
Hématocrite	* 38.4 %	39.0 - 53.0
VGM (volume globulaire moyen)	93.0 fl	78.0 - 98.0
CCMH (concentration corpusculaire moyenne en Hb)	34.4 g/dl	31.0 - 37.0
TCMH (teneur corpusculaire moyenne en Hb)	32.0 pg	26.0 - 34.0
I.D.R (indice de distribution de globules rouges)	44.7 fl	36.0 - 54.0
Plaquettes	252.10^3/ml	150 - 400
VPM (volume plaquettaire moyen)	9.3 fl	8.0 - 14.0
Leucocytes	* 3.11 10^3/ml	4.00 - 11.00
P.neutrophiles	* 1.35 10^3/ml	1.40 - 7.70
P.neutrophiles %	43.4 %	
P.eosinophiles	0.19 10^3/ml	0.02 - 0.63
P.eosinophiles %	6.1 %	
P.basophiles	0.01 10^3/ml	0.00 - 0.11
P.basophiles %	0.3 %	
Lymphocytes	1.19 10^3/ml	1.00 - 4.80
Lymphocytes %	38.3 %	
Monocytes	0.37 10^3/ml	0.18 - 1.00
Monocytes%	11.9 %	
Granulocytes immatures	0.01 10^3/ ml	0.00 - 7.00
Granulocytes immatures %	0.3 %	

Fig-3: Results of the patient's blood count show no contraindications or morbidities

The day of the intervention, after the patient examination, the intervention is started by the preparation of autologous platelet-rich fibrin, first the blood collection when around 10 ml of whole venous blood is obtained from the patient, then immediately centrifugation using a tabletop centrifuge 1500 revolutions per minute for 13 minutes, then comes the separation of the blood clot and finally the pressure of the clot to obtain membranes and plugs ready for use (Figure 4).

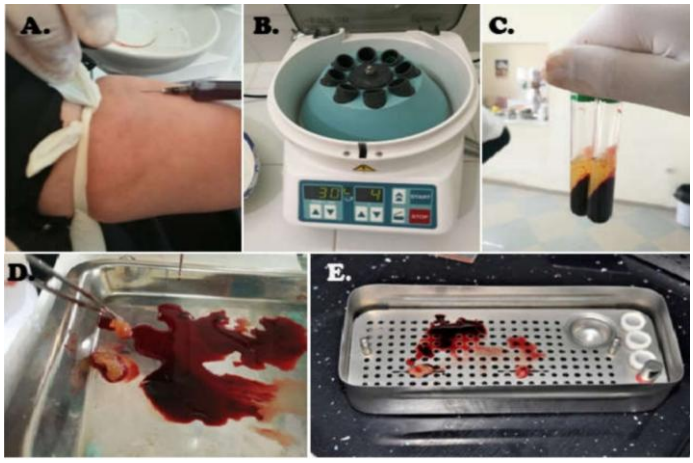


Fig-4: (a) Venipuncture; (b) Blood centrifugation; (c) Results after centrifugation; (d) The PRF clot removed from the tube; (e) Clots pressing into PRF plugs

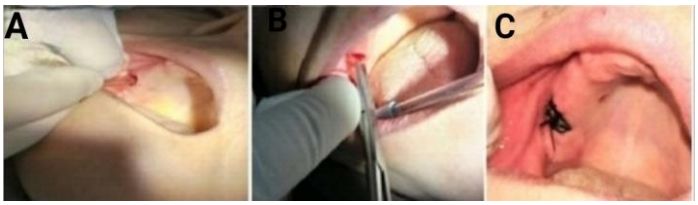


Fig-5: (a) Wound curettage; (b) Placement of the PRF membrane; (c) The realization of hermetic sutures

After the antisepsis of the area, a curettage of the necrotic bone under local anaesthesia was performed, the socket was washed with saline solution and the autologous PRF membrane was placed opposite the bone defect of the osteonecrosis area, hermetic sutures was performed and medical prescription was carried out consisting of Analgesics (Paracetamol), Antibiotics (Amoxicillin) 3 g daily until healing and antibacterial mouthwashes, the patient was insisted on strict oral hygiene measures (Figure 5).

Results after one week and 21 days showed good evolution, results after 6 weeks report total healing of the wound with good scarring, no further infections or complications were reported (Figure 6).

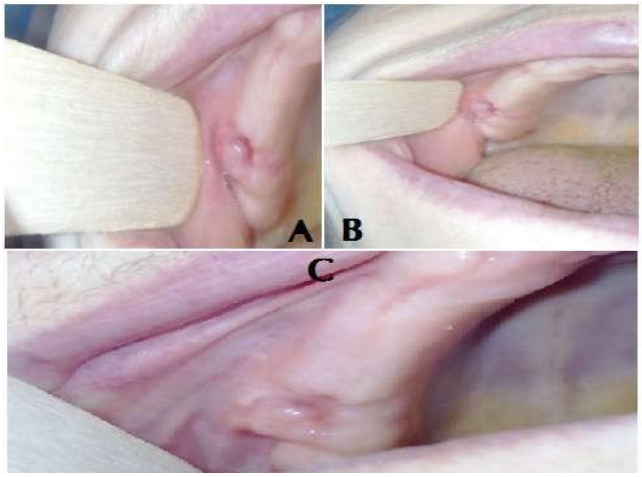


Fig-6: (a) Wound check after 8 days, sutures are removed, good healing is remarkable; (b) 21 days after the wound care showing almost total healing; (c) 6 weeks after, the healing is complete with no complication

The radiographic control after 6 weeks shows healing and stabilization of the osteolytic process of osteonecrosis (Figure 7).

Fig-7: Radiographic control after 6 weeks showing good healing of the area

DISCUSSION

Bisphosphonates have been usually used for the treatment of bone metastases cancers, Overall, the must used drugs to reduce skeletal events are Oral Clodronate, IV Pamidronate and Zoledronic acid, even if it bring good results with potent inhibition of osteoclast-mediated bone resorption, this therapy can in rare cases cause jaws bone necrosis, this complication is directly linked to the administered molecule, its dosage, the duration and triggering factors, in this case, the dental extraction by the general practitioner triggered the maxillary osteonecrosis [1,10,13].

This patient has already undergone mastectomy and was put on IV Zoledronic acid 4mg infusion for 4 years, after stopping the treatment, she was taking Arimidex 1mg daily and IV Trastuzumab, however, despite the fact that the combination of Herceptin to the hormonal therapy Arimidex significantly increases progression-free survival (PFS) compared to Herceptin alone [14], it remains a complex and heavy therapy for the patient since anastrozole reduces the circulating estrogen and thus causes a decreased bone mineral density (BMD) and an increase risk of fracture [15] the near history of antiresorptive drugs combined to Arimidex and Herceptin use in the patient's menopause period that results on drop estrogen levels and increased bone loss would be alarming at the highly increased risk of osteonecrosis and bone pathologies, however definitely, the performed multiple teeth extraction without special precautions were the main triggering factor in the in the very early appearance of the maxilla osteonecrosis only one month after the last tooth extraction [10, 16, 17].

In fact, the oncologist's advice pushed the patient to consult quickly in case of suspicious oral lesions and thus the condition detection on early stage which in this case strongly improved the prognosis. Overall, in front of an early stage of this complication, a conservative treatment approach is preferred, the pain is controlled with analgesics, prevention of secondary infections is ensured by prescribing antibiotics and motivating the patient to a strict oral hygiene while inducing the use of mouthwashes, the patient should be also educated to be careful not to cause damages to the mucous membranes [17]. Nevertheless, in this case, a curettage was scheduled to remove the necrotic bone in purpose to ensure better healing and improve prognosis, due to its wide effectiveness, an autologous platelet-rich fibrin was combined, this biomaterial derived from the human blood, part of a platelet concentrate obtained through a centrifuge separating it has shown a high efficiency in improving the prognosis of several dental procedures such as dental implants, oral surgeries but also in the management and prevention of jaws osteonecrosis with the haemostatic, adhesive and healing properties of fibrin plasma and therefore the improve of the cicatricial process and the acceleration of bone and mucosa healing [18].

In view the patient's current and previous treatment, the CBC was mandatory, results reported that renal parameters, blood calcium levels and blood cells were normal and hence the intervention was deemed possible, before the intervention, an antibiotic coverage was performed because of the increased risk of infection especially with the immunosuppression status of the patient [19], the necrotic bone has been eliminated by curettage which allowed the removal of necrotic tissue with minimal trauma, the PRF membrane was grafted opposite the bone defect of the osteonecrosis area thus acting as biodegradable scaffold, the hermetic sutures ensured the absence of exposure of the bone with the oral cavity and the external irritations which can cause the procedure's fail, a mandatory antibiotics and analgesics was performed in purpose to control pain and avoid infections, antiseptic mouthwashes were also prescribed for twice daily use in order to protect against viral and bacterial infections and refresh the oral cavity [10, 17, 19].

After the intervention, the stop of the bone necrosis evolution and the establishment of a rapid cicatricial process followed by the complete healing of the area proved the effectiveness of the conservative treatment combined with autologous platelet-rich fibrin, this effect is obtained by the significant increase in recruitment and proliferation of several cells, including endothelial cells, gingival fibroblasts, chondrocytes and osteoblasts, thus strongly promoting tissue repair and angiogenesis at the lesion site [10, 12].

Management of necrotic defects of jawbones is often challenging. This is due to the compromised host healing process and existing tissue destruction that cannot be reversed into regeneration. However, in early stages, a good combination of a conservative approach with autologous PRF as an adjuvant in a patient who maintains strict oral hygiene seems to be promising in

the management of this rare morbidity condition [10, 12].

Regarding late diagnosis, it seems to have poor prognostic and the treatment remains complicated, controversial, with several sequelae and without guaranteed effectiveness, treatments can include removal of sequestra, jaw bone resection and bone graft, in this case, generally, the patient's quality of life is strongly altered, hence the importance of early detection and management [20, 21].

CONCLUSION

This case highlights the largely beneficial contribution of autologous platelet-rich fibrin in the management of maxillary osteonecrosis, the achievement of an effective management is extremely important to avoid further complex morbidities and thus the maintain of a good quality of life for the patient. It should be noted that even if bisphosphonate-related osteonecrosis of the jaw remains a rare uncommon condition, the best preventive management of this complication remains performing perfect dental and oral care before the beginning of the antiresorptive treatment, carrying out thorough oral assessment and favouring always conservative approaches when possible, it is also mandatory to educate the patient to maintain good oral hygiene and regular visits to ensure early stage detection and therefore better management.

ABBREVIATION

BON: Bisphosphonate-induced osteonecrosis
CBC: Complete blood count
HER2: Human epidermal growth factor receptor
IV: Intravenous
MRONJ: Medication-related osteonecrosis of the jaws
ONJ: Osteonecrosis of the jaw
PFS: Progression-free survival
PRF: Platelet-rich fibrin

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