Nutrient-enriched microenvironments: An immunometabolic approach to the management of MRONJ –A case series.

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Abstract

Objective: To test the clinical effectiveness of adjunctive nutrient augmentation of medication-related osteonecrosis of the jaw (MRONJ).

Background: MRONJ represents disordered bone and soft tissue physiology with impaired osseo-immune competence. It often has unacceptable rates of healing particularly in the subgroup of patients suffering osseous malignancies; attempted healing takes place in the context of harsh micro-environmental factors such as hypoxia and nutrient depletions and at times, immune modulating chemotherapy. Immune cell's metabolism is tightly linked to nutrient availability which acts as cues shaping immunological signaling. The resultant immunomodulation is central to adaptive and innate immunity and has profound implications for the healing responses being mediated by myeloid and lymphoid derived cells. We therefore proposed a clinical trial in which we targeted various nutritional sensing pathways via the topical augmentation of MRONJ's nutritional milieu.

Results: 15 consecutive patients were managed over a 7 year period utilizing a comprehensive, nutrient containing hydrogel [CNM] as a wound dressing; this approach was integrated into the overall AAOMS protocol for the management of MRONJ. All patients achieved resolution; the areas of healing remained asymptomatic with intact mucosal coverage for a minimum follow up of 27 months. (Patient 1 in the series improved with a better quality of life before succumbing to her metastatic disease)

Conclusion: The predictable and stable healing responses points to beneficial immuno-modulation of MRONJ's wounds utilising nutritional augmented therapy.

Keywords: MRONJ, Immunometabolism, Chronic wounds, Immunonutrition.

Introduction

As clinicians, we seek more reliable protocols for treating medication-related osteonecrosis of the jaw (MRONJ) [1,2]; it unfortunately is often associated with major repercussions for a patient's quality of life as well as community health care resources [3,4]. Immune cell function, perturbed in anti-resorptive therapy via osteoclastic dysfunction is dependent upon nutrients which act as cues shaping immunological signalling [5]. Unfortunately in chronic wounds such as MRONJ the involved tissues are nutrient scarce and relatively hypoxic. This broadly induces a range of metabolic changes in immune cells as their activity is tightly linked to nutrient availability [6,7]. Stimulating nutrient sensing pathways is a promising therapeutic target as they are integrated into key metabolic regulators such as AKT/mTOR [8-11]. mTOR adapts cellular metabolism and transcriptional responses in nutritionally favorable micro-environments to promote anabolic cellular activity; for myeloid cells this triggers translational machinery to control development and polarization of effector cells, promoting antigen processing, cytokine production and T cell stimulation [12].

We therefore postulated that the direct application of nutrient enriched, bioactive gels might provoke resolution responses in this chronic wound condition. Hydrogels containing a variety of nutritional stimulants with 0.5% Chlorhexdine gluconate was integrated into the overall management of MRONJ [13]. This trial with nutrient augmented treatment (NAT) was commenced in November 2012 with data cut off in November 2019, having been prompted by disappointing prior outcomes. All together the successful outcome of 15 consecutive patients being treated in this manner continues to prove helpful in the management of these chronic wounds.

Materials and Methods

When considering the pathogenesis of MRONJ in the presence of anti-resorptive therapy, the inhibition of osteoclastic

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function is central to the dysphysiology of these wounds. Osteoclasts (OC) are osseo-resorptive multinucleated giant cells with important immunological effector functions. They are pleiotropic and regulated similarly to both migratory and resident osteal macrophages (osteomacs) as well as dendritic cells; OCs have recently been identified with different phenotypes and specifically M1, M2 polarizations in osteonecrosis [14,15]. In favorable nutritional micro-environments, osteoclasts together with other myeloid and lymphoid cells orchestrate immune and inflammatory reparative responses including beneficial T cell metabolic activity [5,6,12,16-19]. Downstream this induces a cascade of specialized pro-resolution lipid mediators (SPMs) and other potent cytokines [20-22].

The modulation of the innate and adaptive immune responses is central to wound healing and a return to tissue homeostasis [23-25]. It necessarily includes the recruiting of mesenchymal stem and vascular progenitor cells from the periosteum, bone marrow and circulation which is likely to explain the proresolution cellular changes seen in resolving MRONJ [26]. Most importantly, therapeutically targeting nutrient sensing pathways would seem not to impede the broad range of M1-M2 hybridizations nor unbalance any of the wound's physiological checks and balances. In testing our hypothesis we formulated a complex mixture of small molecule metabolites with known nutrient sensing triggering capability; these include glucose, glutamine, leucine, arginine and glycine combined with a range a water soluble coenzymes, cofactors and other micronutrients in a hyaluronic acid, glycerol gel. This is combined with 0.5% chlorhexidine gluconate in a pH 7.4 millieu having acid and alkaline buffering properties via balanced amino acid contributions.

The MRONJ wounds were managed according to the AAOMS protocol with areas of inflammation and exposure being adjunctively treated with daily application of NAT. Surgery for non-accessible MRONJ is undertaken after a period of antibiotic stabilization (Generally Doxycycline daily as tolerated]. The hydrogel is also liberally applied per-operatively to the exposed bleeding base of the wound following wide debridement. Surface application of NAT to the healing wound is continued daily until resolution is complete.

Results and Observations

All patients in this series demonstrated resolution with a minimum follow up of 27 months, apart from Case 1 who experienced partial resolution (one of the three areas of exposure spontaneously sequestrated) and a better quality of life before succumbing to her metastatic disease. Eight patients were being treated for malignancy, the remainder osteoporosis. Nine cases (see table 1) with discrete areas of largely accessible, exposed necrotic bone were treated with daily NAT together with adjunctive antibiotics if painful; spontaneous sequestration occurred in 7 patients (2-13

Table 1. *MRONJ Patient Profile - 2012 to 2019.*

No:	Gender-age	Medical Diagnosis and anti-osteoclastic therapy	Initiating Event	Stage	Treatment and Comments
1	F-48	Metastatic breast and colon carcinoma; IV bisphosphonates for greater than 3 years [estimated] - ceased prior to presentation, November 2012	Uncertain, although the patient had been edentulous for many years [? full lower denture trauma]	Stage 2/3	The patient was severely cachectic upon presentation November 2012, with excruciating oral pain - surgery was not considered an option. Utilising CNM cream topically with two, 3 week courses of Doxycycline in addition to her existing analgesic regime gave satisfactory pain control [such that she went camping with her family over Christmas] - see figure 1. Patient passed away mid 2013 with one of the three areas having spontaneously sequestrated - a healing granulation tissue base was noted at 9 months with continued CNM application
2	M-89	Osteoporosis treated with 70mg Alendronate, weekly for 14 years, ceased mid 2013.	Extraction of 37 early 2013 by GDP with subsequent non healing of the socket; presentation some 14 months later	Stage 3	Area progressively worsened with orthodox treatment [see figure 2, mid 2014; note the marked medication related osteosclerosis, **MROS**] together with moderate ongoing pain. CNM cream helped stabilise both pain and tissue quality with surgical sequestrectomy undertaken under LA, 6 months following presentation; healing 3 to 4 months later with continued CNM cream application; treatment time 10 months
3	F-69	Advanced metastatic breast cancer; Denosumab commenced February 2016 and ceased in March [2 doses]	Spontaneous exposure of mandibular lingual alveolus following administration of Everolimus, a mTOR kinase inhibitor	Stage 2	The patient was in severe pain upon presentation, June 2016 with difficulty eating - all standard measures had proved ineffective. CNM cream proved highly effective in this case such that antibiotics were declined. Spontaneous sequestrectomy occurred in December 2016 with full resolution. Denosumab has been subsequently recommenced; treatment time 5 months

4	F-62	Osteoporosis treated with 2 years; 6 monthly Denosumab injections	Spontaneous exposure of lingual mandibular alveolus, 2 weeks following Denosumab administration, February 2017	Stage 2	Patient was in considerable pain requiring administration of CNM cream upon presentation together with periodic antibiotic courses; most of the sequestrum was lost in January 2018 with a small spicule lost in March 2018; treatment time 13 months
5	M-51	Early onset osteoporosis treated for 20 years with oral bisphosphonate then switched to Denosumab 6 monthly for 2 years	Spontaneous exposure of mandibular lingual alveolus - presented July 2018	Stage 2	Painful on presentation; good pain control with CNM cream together with episodic antibiotics. Area sequestrated in February 2019 with full resolution. Commenced low dose aspirin in an effort to aid healing. Moderate **MROS** noted radiographically; treatment time 10 months
6	M-69	Multiple myeloma treated with IV Zolendronic acid for more than 2 years; failed to inform GDP who extracted 36	'Dry socket' with non-resolution and exposure of alveolar bone, 4 months duration [see figure 3]	Stage 2	Moderately painful upon presentation; maintained CNM cream applications and Doxycycline 100mg daily - OH not always optimal with periods of neutropaenia. Dexamethasone, Lanalidomide and low dose aspirin; treatment time 9 months
7	M-71	Metastatic prostate cancer -treated with monthly Denosumab injections, commencing 2015 with the last November 2017 combined with two anti-androgenic medications	Referred June 2017 for a symptomatic horizontally impacted 38; 6months following this surgery, Garres osteomyelitis type symptoms with buccal expansion were present	Stage 0	Open exploration was undertaken in March 2018 which demonstrated reactive new bone with inflammation and fibroblastic proliferation and no evidence of osteoclastic activity -subsequently has remained stable; treatment time 9 months
8	F-62	Multiple myeloma [active] with persistent nuetropaenia and marginally low lymphocytes. Monthly IV Zometa commenced 2010 and ceased in March 2013	37 surgically removed in August 2017 with a relatively slow healing response - exposed painful lingual alveolar ridge, March 2018	Stage 2	Treated with CNM cream and periodic Amoxycillin - good pain control. Patient continued with Lanalidomide and Dexamethasone with symptoms of hypoadrenalism and unstable diabetic control; monthly Denosumab. White cell count presently 1.7x10/9 /L;. treatment time 5 months.
9	M-84	Multiple myeloma in remission; Palmidronate IV for 20 years, ceased in September 2018	Presented May 2018 -15 vertically fractured with an endo-perio lesion ; non painful - exposed bone distally for more than 6 months [see figure 6]	Stage 3	Operation January 2019 - large amount of non-vital bone [2x2 cm plus] with a sizable antral communication- microscopy showed necrotic bone, granulation tissue and filamentous organisms. Healing proceeded well with a small sequestrum removed in March 2019 - moderate to dense MROS noted; treatment time 10 months
10	M -67	Multiple myeloma [active] being treated with chemotherapeutics; 3 monthly Zolendronic acid for 3.5 years with last dose March 2018	Surgical removal of 25 in March 2018 with confirmed PA inflammation; a partial denture was fitted subsequently by the GDP which resulted in ulceration and exposure of bone distal to 24	Stage 1	Managed by not wearing PU denture, relieving the pressure necrosis plus daily CNM cream [no Zolendronic acid was administered in June]; area resolved in 10 weeks without a sequestrum forming
11	M-72	Metastatic prostate cancer being treated with anti-androgenic medications, seven rounds of specific chemotherapy, prednisolone and 6 weekly Denosumab commenced March 2018 and ceased in October	Extraction of 37 in December 2018 following jaw pain in this region; slow healing with the area demonstrating continuing low level inflammation [no fistula evident] with subsequent breakdown of lingual/ mylohyoid ridge	Stage 2	Area was managed with antiseptic mouthwashes, CNM cream tds and periodic antibiotics with generally good pain control. Surgical debridement was undertaken after 6 months with the removal of a non-functional 38, attached necrotic bone down to the mylohyoid ridge as well as a chronically inflamed granuloma in the 37 area; fully healed 4 weeks PO - 7 months overall treatment time
12	F-65	Severe osteoporosis having been treated previously with Risedronate for 3 years then switched to Denosumab for 2 years, the last dose given one month before presentation. Patient is also treated for SLE with immune therapy and the secondary effects of renal impairment	Area of exposed bone 37 region moderately painful, having been present for some months; predisposing factor likely to be an ill-fitting PL, opposed by a lone standing 27	Stage 1	Treated with mouthwashes and CNM cream, together with Doxycycline although subsequently not well tolerated, switched to low dose Penicillin PRN for additional pain control. Spontaneous sequestration at 6 months. Incidentally the patient's Endocrinologist substituted Teriparatide, pulsed dosage PTH analogue with pleasing effect and is now being considered for alterative anti-resorptive medication - Note: no mention of anti-resorptive medication on medical history -approx. 6 months treatment time.

13	M 81	Metastatic prostate cancer -treated with Zoledronic acid up to 2016 then monthly Denosumab injections; ceased mid 2018	Extraction of 14, mid 2018 with the area remaining mildly symptomatic, without a discernable fistula	Stage -0	Wide excision of the 14 site with localised ostectomy in August 2019; histopathology revealed necrotic bone with no evidence of osteoclastic activity [How ships lacunae] together with intensely inflamed granulation tissue. Necrotic bone was extensively eroded by the inflammatory reaction; above treatment resulted in prompt resolution, 4 weeks PO.
14	F 86	Osteoporosis: treated with Zolendronic acid following a hip replacement in 2014 followed by Denosumab in 2016 ceased in January 2019	Extraction of a grossly periodontally infected 13, June 2019; area did not heal with continuing discharge although not painful	Stege-1	Wide excision in August 2019 with localised ostectomy; demonstrated necrotic bone and granulation tissue with actinomyces species [negative staining for fungus] with acute inflammation; fully healed, treatment time 3 months
15	F 69	Osteoporosis: treated with 6 monthly Denosumab for 3 years, last dose, April 2019; variable use of Prednisone for severe eczema	Spontaneous exposure of the 37 lingual alveolar ridge in May, 2019	Stage-1	Application of CNM cream with relief of previously variable pain; spontaneous sequestration with full epithelialisation upon subsequent review - treatment time two months

months, average 6.8) leaving a healthy granulation base. The other two proceeded to open surgery having more extensive, inaccessible submucosal necrosis. NAT was continued until complete coverage was evident. All areas have remained stable even in cases with continuation chemotherapy. Antiresorptive therapy had usually been ceased by the Oncologist prior to referral for those patients being managed for osseous malignancy. None of the patients in this series had suffered crush vertebral or other fractures prior to or during the antiresoptive therapy abstinence. Reinstatement of this therapy following healing was encouraged for all particularly for those actively treated chemo-therapeutically.

Discussion

The above case series points to outcomes which compare favorably with the many reports of variable but often disappointing rates of MRONJ resolution, a condition described by On S-W et al [27] in 2021 as still being 'refractory'. Ristow et al [28] reported that early staged lesions managed non surgically generally did not resolve but tended towards progression, a view supported by El-Rabbany et al [3]. In a 2019 Japanese case and literature review [29], resolution of the disease was achieved in 137 out of 275 MRONJ patients (49.8%). One-year cumulative curative rates were 39.8% in stage 1 patients, 26.3% in stage 2, and 19.0% in stage 3. Schiodt M et al, 2017 [30] reported an international multicenter study of patients with MRONJ in the presence of advanced cancer, just over a third of patients remaining at the conclusion of the study were considered to have the osteonecrosis resolved.

We note with interest that two cases treated beyond the data cut off with continuing chemotherapy for progressive metastatic disease developed second, contralateral areas of MRONJ of the mandible, one spontaneous the other via trauma from an ill-fitting denture. This apparent resistance to further breakdown of the original area of osteonecrosis may point to a degree of adaptive immunity being induced with cellular repopulation via the mesenchymal cell, macrophage immunometabolic axis (**Figures 1-6**).

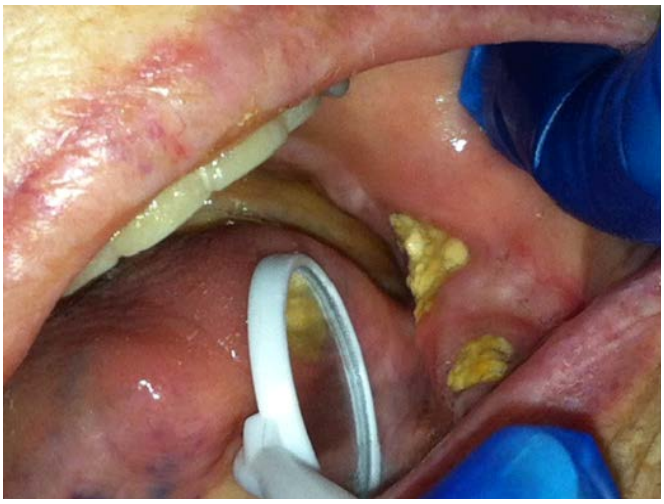

Figure 1. *Patient One: with severe Stage 2/3 MRONJ - widespread hard and soft tissue involvement with three areas of exposed bone which were exceedingly painful.*

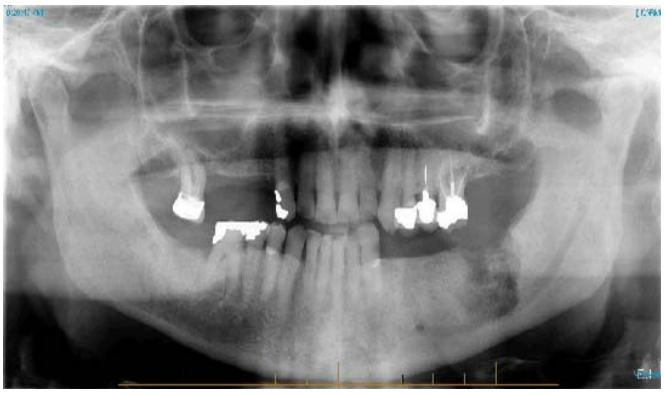

Figure 2. *Patient Two: MRONJ following the extraction of 37 some 14 months earlier. Note the marked degree of osteosclerosis (MROS) following some 14 years of continuous oral bisphosphonate therapy.*

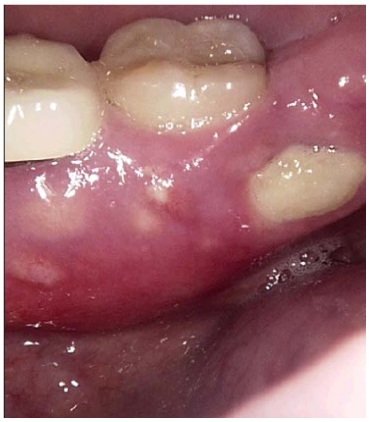

Figure 3. *Patient Five: upon presentation – note the widespread pus formation with exposed lingual alveolus posteriorly.*

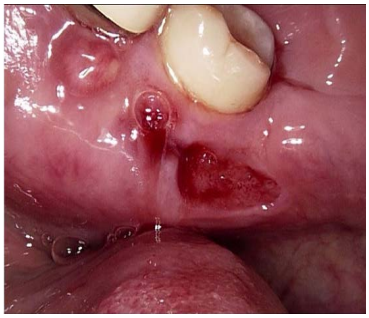

Figure 4. *Patient 5: immediately following assisted sequestectomy; one area of pus collection remained anteriorly at 6 months of treatment.*

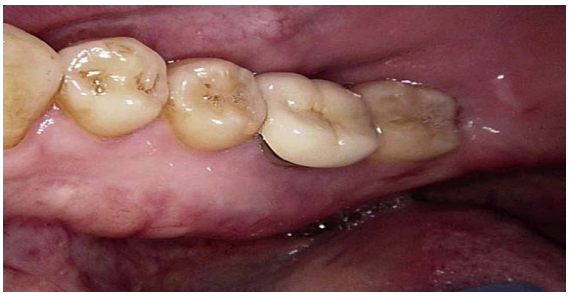

Figure 5. *Patient Five: fully healed 3 months after sequestrectomy – no periodontal defect is detectable and has remained stable (>48 months).*

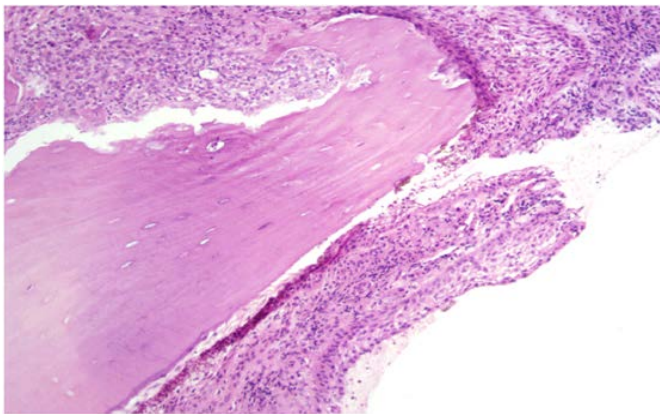

Figure 6. *Patient 13: low grade symptoms persisted following the extraction of 14 some 12 months earlier with no detectable fistula-Stage 0, MRONJ. Histopathology revealed necrotic bone and inflamed granulation tissue.*

Conclusion

Although this case series is relatively small, it does support the adjunctive use of NAT in the management of these chronic wounds. The predictability of the observed pro-resolution wound responses via both non-surgical (spontaneous sequestrectomy) and open surgical interventions is most welcome. The resulting stability of wound healing points to effective physiological and immunologic processes beneficially influencing outcomes. Overall, the NAT approach integrated into the management of MRONJ suggests the immuno-metabolism of these wounds can be positively supported towards resolution.

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