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Dental implants in the patient with multiple myeloma: Literature review and case report

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Multiple myeloma is a blood dyscrasia involving plasma cells in the bone marrow. Much new information and many management strategies exist for these disorders. For dental care, there are a number of issues for the clinician to consider. This review discusses current management of this disease and a case report. *(doi: 10.3290/j.qi.a33929)*

Key words: blood dyscrasia, bone disease, dental implants, multiple myeloma

Multiple myeloma (MM) is a blood dyscrasia involving plasma cells. It is most commonly found in 50- to 70-year-old men although it can occur in any age group. Its annual incidence in the US is 3 to 4 per 100,000.[1] MM is associated genetically with abnormalities in t(4;14)(p16;q32) or t(14;16)(q32;q23).[2] While its incidence in the population is low, the dentist should be knowledgeable about MM as there can be a significant impact on the oral cavity and disease management.

The findings and symptoms of MM are generally associated with the production of abnormal immunoglobulins and the invasion of organs and vital structures with neoplastic cells (end organ disease). End organ disease in MM has been defined by the "CRAB" criteria of hypercalcemia (serum levels > 11.5 g/dL), renal insufficiency (creatinine levels > 1.95 mg/dL), anemia (hemoglobin levels < 10 g/dL), and skeletal lesions.[3,4] Both the hypercalcemia and the lytic lesions in bone are associated with increased osteoclast activity and depressed osteoblastic differentiation and new bone formation. As lytic lesions require 30% to 50% loss of mineral to be visible, MRI and PET have provided earlier, improved diagnostic information regarding progress of the disease.[5]

Normally the B cells in the marrow respond to antigenic challenges, differentiate into plasma cells, and leave the marrow to respond to antigens in other areas of the body. In the case of MM, B cells differentiate into a single clone of malignant plasma cells that remains in the bone and invades the marrow, displacing normal cells.[3] Secondary complications such as infections, renal insufficiency, and interferences with clotting mechanisms can result.[3] The malignant plasma cells stimulate macrophage inflammatory protein (MIP-1α), thereby increasing expression levels of receptor activator of nuclear factor kappa B (RANKL), which in turn upregulates osteoclast activity and mediates bone destruction.[6] The nuclear factor kappa B facilitates production of inflammatory cytokines interleukin 6 (IL-6), IL-11, and

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tumor necrosis factor α (TNF-α).[1] At the same time resorption is increased, and there is suppression of osteoblast differentiation and reduction in alkaline phosphatase and osteocalcin activity associated with bone formation.[1] Localized plasmacytomas may form in areas of bone resorption.[3,7] The net result is an increased likelihood of skeletal fractures (greater than 30%).

The clonal plasma cells produce abnormal immunoglobulins, particularly IgG (52%) and IgA (21%).[3] These are termed M-proteins. In some subjects (approximately 16%) light-chain immunoglobulins are secreted in the urine, then termed Bence Jones proteins.[3,7] The concentration of M-proteins in the blood can result in a condition known as hyperviscosity syndrome which interferes with normal blood clotting mechanisms and may predispose to anemia, neutropenia, and thrombocytopenia from displacement of normal hematopoietic tissues.[3,8] Thromboembolic events are also a risk factor. Other constitutional complications include fatigue, fever, bone pain, and paresthesia.[3,7]

Several classifications of MM have been identified. The severity of the disease and management protocols are based upon the diagnostic criteria previously described under CRAB as well as symptomatology from end organ involvement. It is common for asymptomatic individuals not to receive treatment.[3] Two systems are utilized for staging and prognostic information for newly diagnosed patients: the traditional system which uses hemoglobin and calcium levels, amount of M-protein, and presence of lytic bone lesions as depicted by radiographs; and the newer International Staging System (2005) which uses serum albumin and beta-2 microglobulin levels based from a multivariate statistical analysis.[9] As there are limitations for each of these staging systems, it is now recommended for practitioners to use them concurrently.[3] More recently, the immunophenotype profiles of the bone marrow plasma cells along with either the quality and quantity of IgM or platelet count have been utilized for further prognostic value.[10]

Based on these criteria, three different stages of MM disease have been recognized: MGUS (monoclonal gammopathy of unknown significance), SMM (smoldering multiple myeloma), and MM. The first two are not considered an active disease process. Nevertheless, MM is now considered a constellation of progressive disorders. There is increasing evidence that early intervention may delay or prevent further progress of the disease.[4] Today, while there is more utilization of M-protein characterization and immunophenotype profiles for disease classifications, the traditional criteria of M-protein levels and bone marrow plasma cell concentrations as well as end organ involvement are still being utilized to determine prognosis of treatment protocols.[4] In SMM, serum M-proteins are ≥ 3 g/dL and/or bone marrow clonal plasma cells are ≥ 10%.[4] No evidence of significant end organ involvement is present.[11] However, MRI and PET both demonstrate abnormalities in bone structure even in the absence of lytic lesions.[4,12] It is therefore prudent for whole body MRI to be planned in patients with SMM, as it may help assess the risk of progression and lead to a better definition of symptomatic disease.[13] The conversion rate to MM is from 10% to 14% annually.[14] MGUS patients demonstrate a minor conversion rate of 1% annually and have serum M-protein and bone marrow plasma cell values less than those seen in SMM.[15]

Another complication of MM is light chain amyloidosis (AL). There is infiltration of organs with amyloid, a protein precipitate that, treated with the Congo red stain, appears green under birefringent light. Amyloidosis is also considered a monoclonal gammopathy, but AL and MM are considered separate entities. However, AL is found in association with MM in 13% to 36% of MM cases.[16] Amyloid can be deposited subcutaneously along the eyelids, lips, oral cavity, neck, inguinal, and anogenital areas. Systemically, it can be found in the gastrointestinal tract and the skeleton as well as the liver, spleen, kidneys, and the heart. The presence of amyloid deposits in cases of MM reduces the prognosis for the patient.

DENTAL TREATMENT

Dental treatment of the MM patient must be approached with caution. The patient's status, current

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diagnosis, and prognosis must all be considered. Individuals with overt disease must be carefully evaluated for the progress of their disease and the degree of end organ damage. If dental disease and oral pathology are present, these must be carefully managed. Gingival, periodontal, and endodontic disease, particularly if the periapical bone is invaded, should be conservatively treated. The presence of clonal infiltration of the mandible or maxilla should be radiographically evaluated. The reduced white cell count and thrombocytopenia as well as the possibility of hyperviscosity syndrome may result in difficulty for hemostasis and possible fulminating infection in the jaw and associated soft tissue.[9]

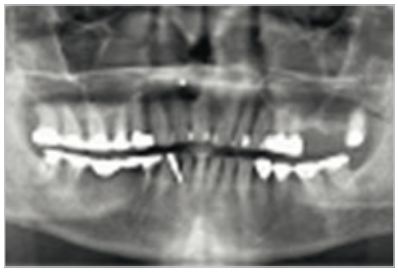
The lytic lesions, most common in the mandible, are expansile, can displace teeth, and frequently are painful. If the patient is a candidate for hematopoietic stem cell transplantation (HSCT), all oral and perioral infection must be eliminated prior to treatment. If the patient is to be managed with chemotherapy, osteonecrosis of the mandible must be considered as bisphosphonates, prescribed to slow the osteolytic lesions, are part of the chemotherapy. Prednisone and other corticosteroids that suppress the ability to fight infection are also employed in treatment of MM. Preventive measures to preclude the development of dental caries and periodontal disease must be regularly monitored and reinforced. Teeth that have been destroyed by caries or have endodontic disease must be evaluated if options other than surgical removal are available. In the situation where the diagnosis is SMM, the fact that end organ disease is minimal or not evident should not allow the dental clinician to have a sense of security. The conversion rate to overt disease is approximately 10% per year for the first 5 years. In addition, there is a growing opinion, particularly by the Mayo group, that aggressive treatment may delay or in some cases prevent conversion of SMM to the overt disease.[4] As such, it behooves the astute dental clinician to carefully monitor the patient for any dental disease and apply preventive treatment. As noted before, parameters to stage the SMM and perhaps identify patients at a greater risk for conversion to overt MM are being developed. In addition, there appear to be subclinical changes that occur in the bone that may be significant if surgical options are selected for treatment.[5,12] The presence of amyloid in oral tissues, particularly the tongue, can result in a macroglossia that can interfere with the function of dental prostheses.

This report describes an individual who had a long-term diagnosis of SMM and was successfully treated with surgical placement of dental implants and preventive management.

CASE HISTORY

A 70-year-old man came to the clinic with a request for dental treatment. His chief complaint was a bad taste in his mouth adjacent to a four-unit bridge in the mandibular right quadrant. His past medical history was complex. He had been diagnosed 15 years previously with MGUS, a precursor to MM. Eight years later his disease had progressed to SMM. In a recent physical examination he had demonstrated paraprotein infiltrate in the pelvis, osteoporosis in a DXA (dual-energy x-ray absorptiometry) examination, and testicular amyloidosis secondary to the SMM. His blood serum studies showed a slight anemia, normal white cell and platelet counts, and his clotting screen was within normal limits. His kidney function was normal and MRI did not demonstrate amyloid in the GI system, heart, or lungs. Significant serum kappa paraprotein and light chains were present but not at a sufficient degree to result in hyperviscosity syndrome. A liver biopsy did not show amyloid deposition. As he had been stable with little disease advancement or end organ involvement, his physician did not feel it appropriate to institute treatment for the SMM. In addition to his diagnosis for SMM, he was being treated for depression, hypogonadism, and benign prostatic hyperplasia (BPH). He recently had his depression medication regime changed because it resulted in sinus tachycardia, and he was much improved. His blood pressure was 118/72 with a normal pulse rate.

Dentally his soft tissue examination was within normal limits. His mucus was dry as a result of the drugs used to treat his depression. No significant pocket



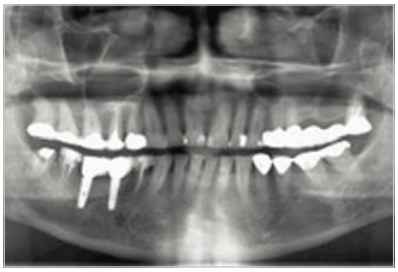
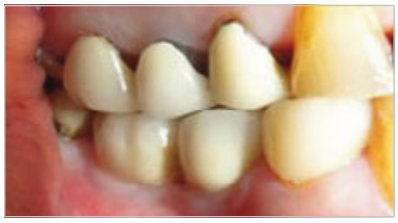


Fig 1 (left) Pretreatment radiograph demonstrating FDP on mandibular right first premolar to second molar (teeth 44 to 47).

Fig 2 (right) Posttreatment radiograph with crowns on mandibular right first premolar and second molar (44 and 47), and implant-supported crowns on second premolar and first molar (45 and 46).



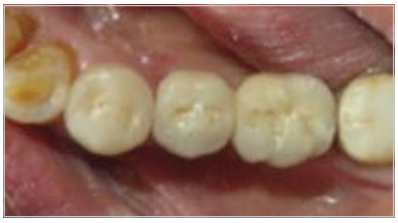


Fig 3 (left) Facial view of final restorations (44 to 47).

Fig 4 (right) Occlusal view of final restorations (44 to 47).

depths greater than 4 mm were detected; however, there were isolated sites with materia alba and plaque present. The dentition was complete to the second molar with the exception of the maxillary left second premolar and first molar (teeth 25 and 26 according to FDI notation). Multiple single restorations of teeth were present as well as a fixed dental prosthesis (FDP) from the mandibular right first premolar to second molar (teeth 44 to 47) with marginal recurrent decay of 44 and 47 abutments. No pulpal exposures were seen when the FDP was removed. Rather than a replacement FDP, the patient wanted individual crowns on 44 and 47 with individual implant placements in sites 45 and 46. After consultation with the patient's internist, the treatment was approved.

A panoramic radiographic evaluation demonstrated good quality bone in the area (Fig 1). The height of the edentulous ridge in the area was 14 mm with adequate width for 4-mm-wide implants. The occlusal plane was uniform. The treatment plan was to place implants in the second premolar and first molar sites using Osstem 4.0 mm × 11.5 mm ET implants (Osstem Implant) and restore teeth 44 and 47 with metal-ceramic crowns. Endodontic treatment was not required. There was no evidence of other caries but the patient was put on a preventive regime using a fluoride gel.

The surgical procedure was uneventful. A midcrestal incision from the distal of the canine to the mesial of the second molar was made, the tissue reflected, and the osteotomies created with a standardized drill sequence. The implants were placed with acceptable primary stability. To minimize postoperative bleeding, the implant placement was done as a two-stage procedure. Cover screws were placed and the flap sutured with primary closure using 4-0 black silk sutures. A postoperative radiograph was obtained. Three months later, the implants were uncovered with small midcrestal incisions and checked for stability. Healing abutments were placed. After 2 weeks, a closed tray impression was taken of the implants and first premolar and second molar abutment teeth. Metal-ceramic crowns for all four units were made, fitted, and cemented. The occlusion was carefully evaluated using the Tek-scan system for occlusal analysis and equilibrated until all units occluded uniformly. This patient has been followed for 2½ years, and the implants and their restorations are successful (Figs 2 to 4).

DISCUSSION

This report describes dental management of a patient with a series of complex medical problems. He had been diagnosed with SMM which, while in itself is not an active disease process, nevertheless is associated with pathology that may influence dental treatment. There was a family history of Type 2 diabetes, and

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although he was overweight, he did not have a diagnosis of Type 2 diabetes. His anemia was not severe enough to influence the surgical management of the patient at this time. The xerostomia that contributed to the recurrent decay in the FDP abutment teeth may have been associated with his medication for depression.[17] Of further concern is the possibility that his SMM could convert to the active disease. Cigarette smoking was a further risk factor for osseointegration although the patient had ceased smoking the year before.[18]

The conversion to active disease cannot be predicted, and the osteoporotic lesions associated with the disease and the use of bisphosphonates, especially zoledronic acid intravenously, for treatment of active MM could compromise the healing of the implants. Administration of bisphosphonates, a current treatment for MM, has a 50% incidence of oral osteonecrosis of the mandible.[19] It should be noted that data are limited in regards to duration of treatment with intravenous bisphosphonates for MM; there exists no evidence from randomized clinical trials. However, dosing of bisphosphonates is suggested monthly for a 2-year period, and those with responsive or stable disease can stop bisphosphonate therapy.[20]

While it is common to observe osteoporotic lesions in this disease and possible amyloid or paraprotein infiltration of long bones, this patient did not have any lesions in the area of the implants. The flap design was conservative to minimize the risk of uncontrolled bleeding. The osteotomies were carefully prepared to ensure maximum initial stability of the implants. Postoperatively, the patient had little pain and minimal bleeding. In this case, careful management avoided the most common risk factors in patients with MM. In spite of the patient's medical history, healing was uneventful with clinical osseointegration evident at 3 months postinsertion.

It is certainly the responsibility of the treating clinician who is treating the patient for dental disease to be knowledgeable about systemic disease that either may impact dental treatment or exacerbate dental and oral disease. MM as a disease is relatively uncommon. Nevertheless, dental management of a monoclonal gammopathy (ie, MM and its precursors MGUS and SMM) requires the dentist to be aware of the clinical manifestations of these disorders and their impact upon dental disease and its management. While bony lesions, pain, infection, tooth migration, and blood clotting have classically been described, there are other factors that should be seriously considered. These include elimination of dental disease prior to hematopoietic stem cell transplant and management of oral side effects of drugs such as dexamethasone, thalidomide, bisphosphonates, and proteasome inhibitors such as bortezomib. There is also increasing evidence that early treatment of MM (ie, while still diagnosed as SMM) improves the patient survival, and thus elimination of all oral disease should be part of the patient's treatment plan.[4] Finally, the effects of some subclinical changes should be viewed with caution relative to initiation of dental treatment. As an example, in a retrospective study with 126 patients in whom there were no overt signs of amyloidosis, bone biopsies identified amyloid deposits in 51 patients.[21] The effects of these deposits in the progression of periodontal disease and peri-implantitis are not known. Thus, dental treatment of these patients should be approached with a cautious but informed eye in consultations with the medical team.

This implant treatment has been followed for more than 2½ years, and currently the patient is doing well without any evidence of bone loss around the implants. This report suggests that in carefully selected individuals with MM for whom implant therapy is prescribed, the results of treatment can be successful, provided the nature of the disease and its clinical course are understood by the clinician. There are many risks associated with treating such individuals. It goes without saying that treatment on such patients should not be performed by the dental practitioner without the consultation of the patients' primary care physicians and/or oncologists.

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