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Title: A Wolf in Sheep's Clothing: A case report series of oral manifestations of Multiple Myeloma

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TITLE

A Wolf in Sheep's Clothing: A case report series of oral manifestations of Multiple Myeloma

ABSTRACT

Multiple myeloma is the most common haematological malignancy accounting for ten percent of all haematological cancers. Treatment of myeloma has evolved in recent years leading to improved survival. Lesions related to myeloma are frequently observed within the oral cavity and jawbone. In addition, many of the therapeutic agents have side effects with implications for provision of dental treatment. This case series aims to highlight some of these presentations to remind dental practitioners to be vigilant. Observation of suspicious lesions within the oral cavity or jawbone may warrant further investigation.

INTRODUCTION

Multiple myeloma (MM) is the most common haematological malignancy, accounting for 10% of haematological cancers[1] . Globally, there were 159,985 incident cases and 106,105 reported deaths from MM in 2018[2] . The median age at diagnosis is 70 years and the prevalence increases with age[3, 4] .

MM is characterised by proliferation of monoclonal plasma cells in the bone marrow in association with excess monoclonal protein production (M-protein)[5]. Symptomatic disease is defined by hypercalcaemia, renal impairment, anaemia, bony disease (CRAB criteria) with the recent addition of ≥60% plasma cell infiltrate, ratio of the involved and uninvolved light chain ratio of > 100 or >1focal marrow lesions on magnetic resonance imaging (SLiM CRAB)[5].

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Several subtypes have been identified based on genetic and molecular markers, each with unique clinical, pathological and prognostic features[6].

Common manifestations of MM include fatigue, increased infection rates and bone pain, with bone lesions manifesting as osteolytic lesions with or without pathological fractures or bone plasmacytomas[4]. These tumours of monoclonal plasma cells may be solitary, requiring local radiotherapy, or multiple, defining systemic disease, and may arise within the bone or within the soft tissue as extramedullary plasmacytoma[4]. Secondary amyloidosis is an uncommon but important complication of MM due to amyloid deposition in the heart, kidneys, bowel, nerves and tongue.

Oral lesions can be seen in up to 70% of MM cases, with the jawbone being involved in up to 30% of cases. Common manifestations include toothache, loose teeth, paraesthesia and gingival masses[7]. Dental practitioners play an important role in the multidisciplinary care of myeloma patients including the potential diagnosis of MM, the management patients undergoing systemic chemotherapy, and surveillance of the oral cavity for suspicious lesions[7]. Therapy related side-effects such as medication-related osteonecrosis of the jaw (MRONJ) may also present with specific dental and oral signs or symptoms. The challenge with MM patients is that oral manifestations of myeloma can masquerade as dental or oral pain, swelling or infection, which if not correctly diagnosed, may lead to delay in therapy[8].

Our case series describes oral manifestations of MM, each presenting with lesions in the jaw, but at different time points of the patients' diagnosis and treatment.

Written consent was obtained from each living patient described in this case series.

CASE DESCRIPTION WITH RESULTS

CASE 1

A 57-year-old male with long-standing heavily pre-treated IgA kappa MM was referred with swelling and pain of the buccal aspect of teeth 25 and 26. Previous treatment included proteasome inhibitors, alkylating agents, immunomodulators, anti-CD38 monoclonal antibody therapy and two autologous stem cell transplants (AUSCT). The only clinical finding was a 9mm pocket at the mesiolabial aspect of 26. A peri-apical radiograph (**Figure 1**) shows a discrete, oval shaped radiolucent lesion in the region of 25 and 26, with intact lamina dura. Percussion and sensibility testing were unremarkable.

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Cone-beam computed tomography (CBCT) revealed a discrete radiolucent lesion palatal to 25, 26 extending inter-proximally in the coronal third of the root (**Figure 2**). Differential diagnoses for the lesion included MRONJ, MM, periodontal or pulpal pathology. A previously identified IgA kappa paraproteinaemia was not detected.

Positron Emission Tomography (PET) performed concurrently revealed widespread disease progression including a focus of increased uptake within the left maxilla (**Figure 3**). Biopsy of this lesion revealed sheets of atypical plasma cell infiltrates which stained positive on immunohistochemistry for CD138, CD56 and kappa light chain, consistent with extramedullary plasmacytoma.

CASE 2

Case 2 describes a 54-year-old male with IgG lambda MM who was treated with bortezomib, cyclophosphamide and dexamethasone induction, followed by a tandem AUSCT.

He presents two years later with pain and swelling in the labial sulcus superior to teeth 21 and 22, and slow biochemical relapse of his myeloma. On examination, a swelling was present in the labial sulcus, and both 21 and 22 were tender to percussion and unresponsive with sensibility testing. Teeth 11, 21 and 22 were diagnosed as non-vital and endodontic treatment was completed (**Figure 4**). The swelling did not resolve, necessitating surgical excision. Concurrent PET scan revealed PET-avid lesion in this site (**Figure 5**) confirmed on histopathology as extramedullary plasmacytoma. Treatment involved localised radiotherapy followed by systemic therapy including lenalidomide, cyclophosphamide and dexamethasone.

CASE 3

A 67-year-old female presented to the Dental Oncology department with a non-healing oral mass which was non-responsive to antibiotics. Three months prior, she underwent a second AUSCT for relapsed IgG kappa myeloma which progressed despite multiple lines of therapy including second-generation proteasome inhibitors and immunomodulatory therapy, but responded with conventional chemotherapy.

On examination, a reddish/purple fungating swelling was evident superior to teeth 22 and 23 in the buccal sulcus (**Figure 6**). Histopathology was consistent with a plasmacytoma prompting a PET scan which revealed widespread disease progression with new moderately intensely avid medullary and extramedullary disease.

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CASE 4

A 53-year-old female diagnosed with light chain myeloma and secondary small bowel amyloidosis in 2007. She was treated with a thalidomide-based induction followed by an AUSCT and maintenance thalidomide. Her disease remained quiescent without therapy but developed new macroglossia and biochemical relapse in August 2018. Biopsy of the tongue confirmed amyloidosis. A response was obtained following salvage treatment, and she was seen in the Dental Oncology department in March 2019 prior to a second AUSCT. There was marked buccal displacement of the mandibular dentition due to macroglossia (**Figure 7**).

CASE 5

Case 5 describes a 50 year-old male diagnosed with IgG lambda MM in 2017 following the fracture of the right ramus from an enlarging right mandibular and maxillary plasmacytoma. OPG imaging revealed a lytic lesion involving the ramus and condyle of the mandible and oroantral fistula associated with 18 (**Figure 8)** also confirmed on PET **(Figure 9**).

CASE 6

Case 6 describes a 57-year-old male with 9-year history of IgG kappa MM over 9 years who presented with swelling of the left mandible, on background of a dental extraction performed 18 months earlier. The patient had received multiple infusions of zoledronic acid for prevention of skeletal events.

Imaging performed revealed a large radiolucent lesion in the left mandible, at the site of extraction (**Figure 10**) consistent with a diagnosis of MRONJ. Treatment involved surgical debridement of the left mandible with primary closure. Following favourable initial healing, it was apparent that an oro-cutaneous fistula had developed, which was managed with long-term antimicrobial therapy. This lesion is now stable with no further surgical intervention indicated.

DISCUSSION

Treatment for MM has evolved dramatically over the last few years leading to improved survival[1]. Dental practitioners play an important role in the supportive care for MM patients' in relation to the malignancy itself, and the therapies used in treatment.

MM can often manifest as lesions in the oral cavity or jaw which may mimic dental or periodontal pathology and may even be the first sign of MM[9]. Myeloma therapies may also

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have implications for the provision of dental treatment, summarised in **Table 1**[10]. An understanding of therapies and open communication with the patients' haematologist are essential to maximise health outcomes. While routine dental treatment should not pose concern, invasive treatments such as periodontal debridement or dentoalveolar surgery, should be carried out with caution and in consultation with the medical specialist.

People with myeloma are at an increased risk of bleeding and infections due to myelosuppression of the bone marrow related to both the disease and therapies[7]. Risk of osteonecrosis following invasive procedures is also of concern with multiple therapies posing a threat[11].

Cases 1, 2 and 3 describe different presentations of plasmacytomas. Plasmacytoma of the jaws and oral cavity represent three distinct manifestations; MM, solitary plasmacytoma of bone, and extramedullary plasmacytoma[12, 13]. Plasmacytomas of the bone appear as a well-defined radiolucency, commonly associated with bone pain, or swelling. In Case 1, the presenting symptom was pain, localised to the periodontium. There was a lack of diagnostic signs indicating a periodontal infection and the radiographic finding was a discrete radiolucency superimposed over the roots of the teeth rather than the typical radiographic findings of periodontal attachment loss[14]. This lesion could have easily been mistaken for a periodontal in origin. In Case 2, the history, clinical signs, and symptoms led to a diagnosis of irreversible pulpitis with subsequent endodontic treatment of teeth 21 and 22. Unresolved bone healing of the peri-apical lesion prompted further investigation and biopsy, resulting in a diagnosis of plasmacytoma.

The clinical presentation of plasmacytoma as a raised red lesion on the alveolar ridge described in Case 3, is consistent with the manifestation of myeloma in the oral cavity[12, 13]. Extramedullary plasmacytomas arise from proliferation of malignant monoclonal plasma cells. Confirmation of the diagnosis is by histopathological examination[15]. Mucosal presentation is rare and unfortunately, is often a sign of late-stage disease[16].

Amyloidosis describes the deposition of amyloid, an abnormal protein, in tissues and organs throughout the body[7]. Oral deposition is rare, however may appear as a plaque, nodules or papules, most commonly on the tongue[7]. Amyloid infiltration of the tongue may appear as indurated macroglossia with scalloping of the lateral borders[17]. Anterior open bite has also been reported due to macroglossia and amyloid deposition in the temporomandibular joint[18]. Case 4 describes a patient with macroglossia causing expansion of the mandibular arch with impacts

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on speech, mastication and swallowing. Amyloid deposition may also occur in the salivary glands, manifesting as glandular enlargement or xerostomia[7, 18]. Unusual soft tissue lesions in the oral cavity should be treated with a high index of suspicion in a patient with myeloma, and an urgent referral to the treating haematologist should be initiated.

Case 5 describes a pathological fracture of the mandibular ramus as the presenting feature of myeloma. It is reported that between 5-30% of patients have osteolytic jaw lesions, more common in the posterior mandible than maxilla, and in advanced disease[19, 20]. The typical radiographic appearance is one of 'punched out' radiolucent lesions in the ramus of the mandible. Dental practitioners may see these on routine radiographic imaging such as orthopantomograms. Referral to a specialist and further imaging or other investigations may be warranted.

Case 6 describes a well-documented complication of dental extractions in patients on bone modifying agents, in this case, zoledronic acid. Intravenous bisphosphonates are frequently used to manage cancer-related hypercalcaemia and skeletal-related events associated with lytic lesions in MM[6, 11]. Dental practitioners should be vigilant in recording medical history, and it is not unreasonable to assume that patients with a diagnosis of MM will be on a bone modifying agent or have been in the past. Extreme caution should be taken with invasive dental procedures and referral to a specialist should be considered given that the two main risk factors for MRONJ are the use of high-potency bisphosphonates and dental extraction[21]. Once again, the importance of liaising with the patient's medical oncologist cannot be over emphasised. Dental practitioners need to know how to assess, diagnose and manage ONJ for myeloma patients. More importantly, optimisation of the oral and dental health prior to commencing these therapies is imperative to minimise the future need for invasive procedures[11, 22].

In summary, oral manifestations of multiple myeloma are common and can present as both soft tissue and skeletal lesions, sometimes disguised as something more benign. Awareness of the varying signs, symptoms and presentations of lesions is important for accurate diagnosis and management. Dental practitioners should refer early for appropriate specialist support when suspicious lesions are noted and ensure radiographs are reviewed by a radiologist with expertise in dentofacial radiology. Knowing the side effects of myeloma therapy and the implications for the safe delivery of dental care is necessary for favourable outcomes. Working as part of the multi-disciplinary team in collaboration with the patient's haematologist is integral to achieve optimal patient care.

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Tables

Table 1: Common therapies for myeloma and potential oral/dental side effects

Figures

Figure 1: Peri-apical radiograph of teeth 24-28 showing discrete radiolucency in the mid-third of 25, 26 roots

Figure 2: Cone-beam CT showing discrete radiolucency palatal to teeth 25, 26

Figure 3: PET scan showing extensive bone involvement including the lesion in the left maxilla

Figure 4: PA taken following endodontic treatment of teeth 11, 21, 22 with persisting radiolucency overlying the apices of these teeth

Figure 5: PET image demonstrating lesion in the left maxillary sulcus

Figure 6: Clinical photograph of left anterior labial sulcus with bluish/red lesion

Figure 7: Cone-beam CT of the maxilla (left) and mandible (right) demonstrating expansion of the mandibular arch due to macroglossia

Figure 8: OPG demonstrating large radiolucency of the right ramus with fracture, impacted 18 and oro-antral communication

Figure 9: PET imaging showing uptake in the right ramus (left) and following treatment (right)

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Figure 10: OPG showing large radiolucent lesion in the left mandible

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Table 1 Common therapies for Myeloma and potential oral/dental side effects

(In *MIMS Online*. http://www.mimsonline.com.au)

DRUG NAME	CLASS	MECHANISM OF ACTION	ORAL/DENTAL RELEVANT SIDE EFFECTS
Thalidomide **Lenolidamide**	Immunomodulator	Unknown. The potential modes of action of thalidomide includes direct inhibition of myeloma cell growth and survival, anti-angiogenesis, suppression of the production of tumour necrosis factor-α (TNF-α), inhibition of selected cell surface adhesion molecules that assist leukocyte migration, shifts in the ratio of CD4+ lymphocytes (helper T-cells) to CD8+ lymphocytes (cytotoxic T-cells) and effects on interleukins (IL) and interferon-γ.	Impaired wound healing, skin rash, mucosal ulceration, increased risk of ONJ, neutropenia, thrombocytopenia, neuropathy, cardiac and respiratory dysfunction, potentiates other sedatives, antidepressants
Bortezomib **Carfolizomib**	Proteasome Inhibitor	Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells that degrades ubiquitinated proteins. This disruption of normal homeostatic mechanisms can lead to cell death. Bortezomib may increase osteoblast differentiation and activity and inhibits osteoclast function.	Blood dyscrasias (thrombocytopenia, anaemia, neutropenia), neuropathy, pain, congestive cardiac failure, gastro-intestinal upset, reactivation of Herpes Zoster Virus and Hepatitis B, hepatic disease, pulmonary disease, pancreatitis, encephalopathy, drug interactions (azoles, antifungals), hypotension, impaired wound healing, potential for ONJ
Prednisolone **Dexamethasone**	corticosteroid	Glucocorticoids prevent the development of the inflammatory response, redness, swelling, tenderness and inhibit capillary dilation and phagocytosis and appear to prevent the hypersensitivity responses which occur after antigen-antibody reactions.	Impaired wound healing, increased infection risk, mask signs or symptoms of infection, osteoporosis, adrenal insufficiency, drug interactions (amphotericin B, macrolides, azoles, antifungals, NSAID's)
Cyclophosphamide	Cytotoxic/alkylating agent	Alkylating antineoplastic agent/cytostatic alkylating agent. Cyclophosphamide itself is not an alkylating agent but is converted by a series of reactions in the liver to its active form which interferes with the growth of susceptible neoplasms and to a certain extent, with	Immunosuppressive, impaired renal function, blood dyscrasias, mucositis, impaired wound healing, liver and kidney toxicity, mutagenesis

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		normal tissue regeneration.	
Melphalan	Cytotoxic/alkylating agent	Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chloroethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross linking two DNA strands and thereby preventing cell replication. Active against both resting and rapidly dividing tumour cells.	Bone marrow suppression (Blood dyscrasias), mucositis, liver disorders
Daratumumab	Monoclonal antibody (CD38 inhibitor)	Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of cells in a variety of haematological malignancies, including multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.	Blood dyscrasias, peripheral neuropathy
Zolendronate Pamidronate	bisphosphonate	The action of bisphosphonates on bone is based on their high affinity for mineralised bone. Intravenously administered Zolendronic acid is rapidly distributed to bone. The main molecular target of zolendronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase,	fever, myalgia, flu-like symptoms, arthralgia, headache, ONJ
Denosumab	Monoclonal antibody RANK-ligand inhibitor	RANKL exists as a transmembrane or soluble protein which is essential for the formation, function and survival of osteoclasts. Denosumab binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone	Hypocalcaemia, skin infections, pancreatitis, ONJ

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		surface. Prevention of RANKL/RANK interaction inhibits osteoclast formation, function and survival.	

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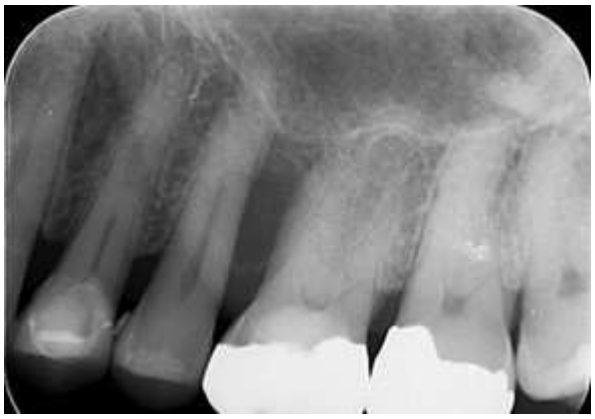

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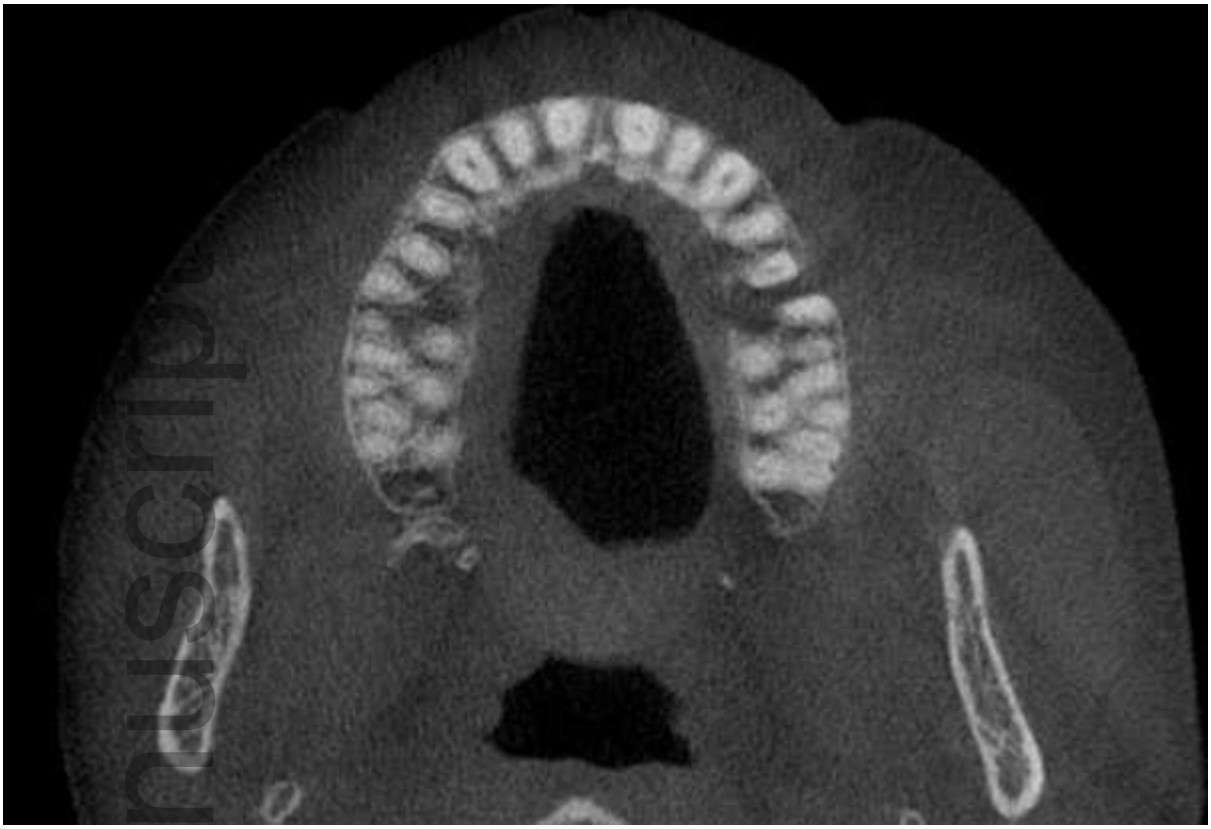

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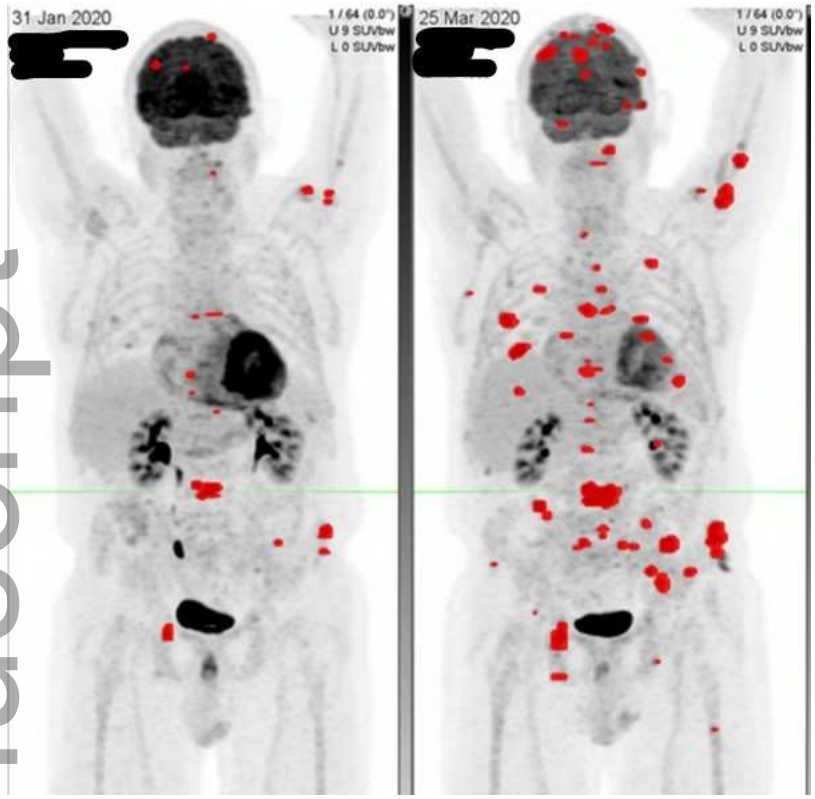

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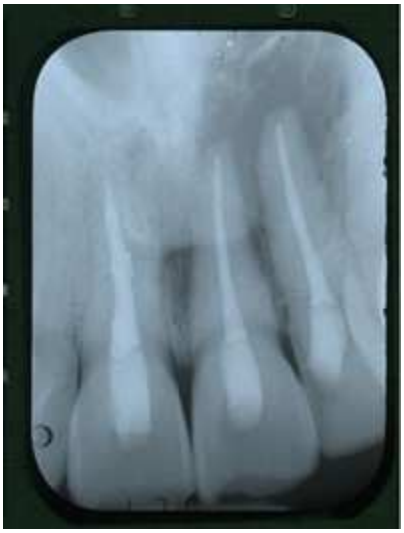

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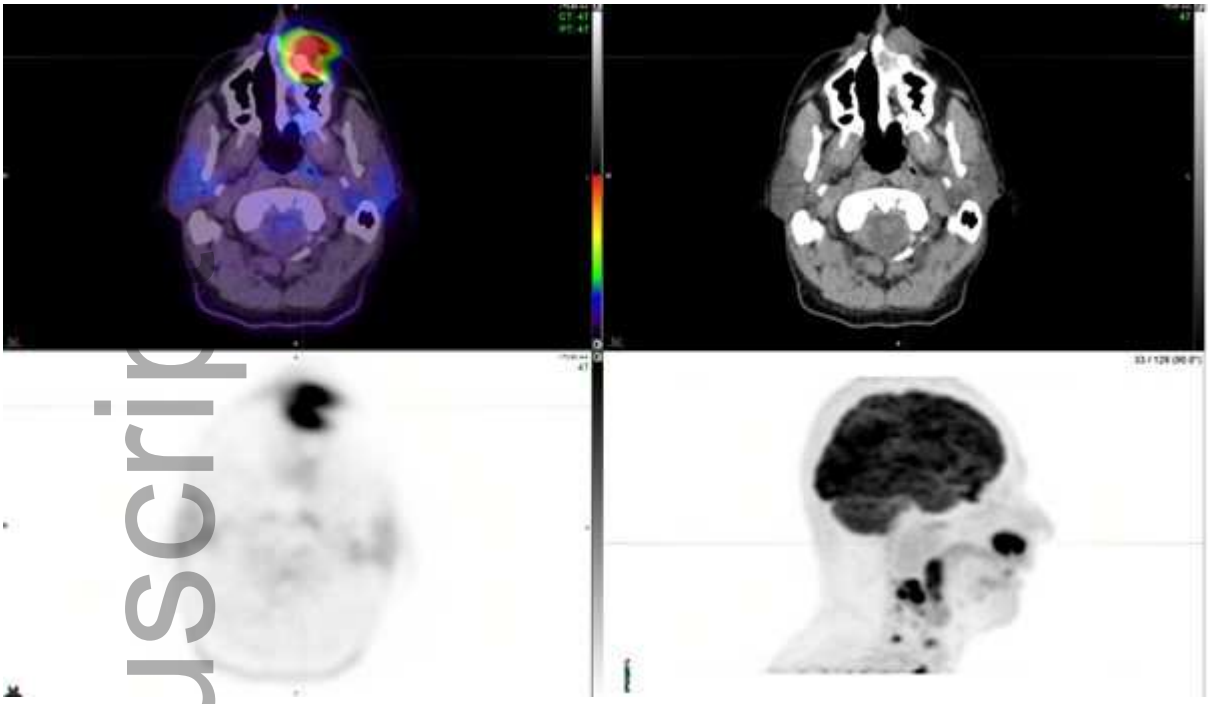

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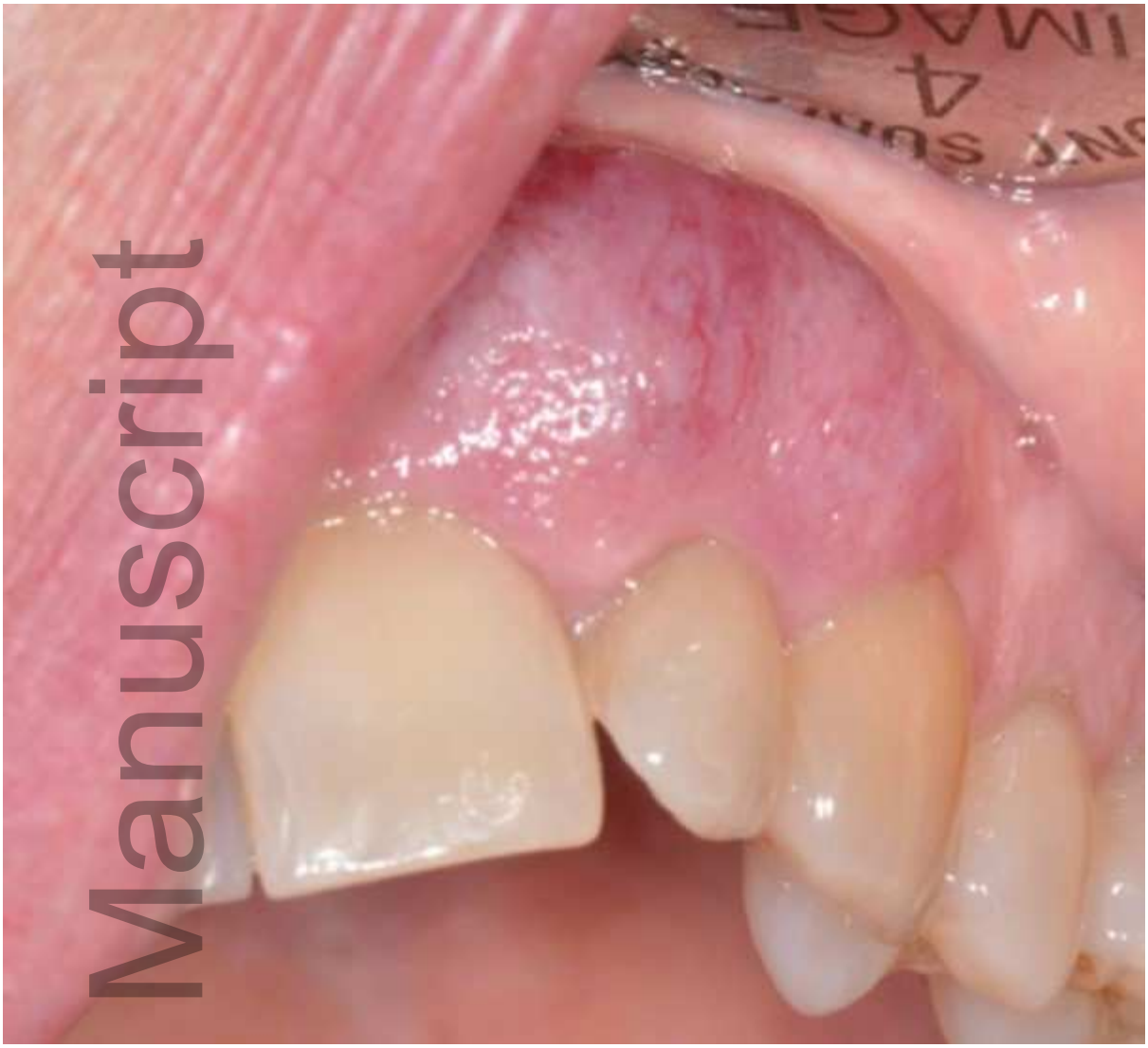

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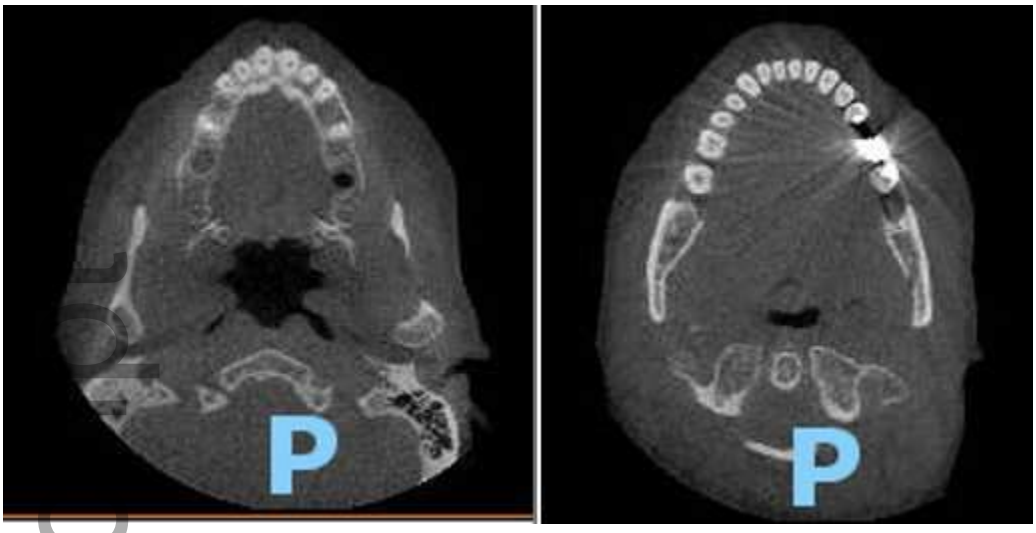

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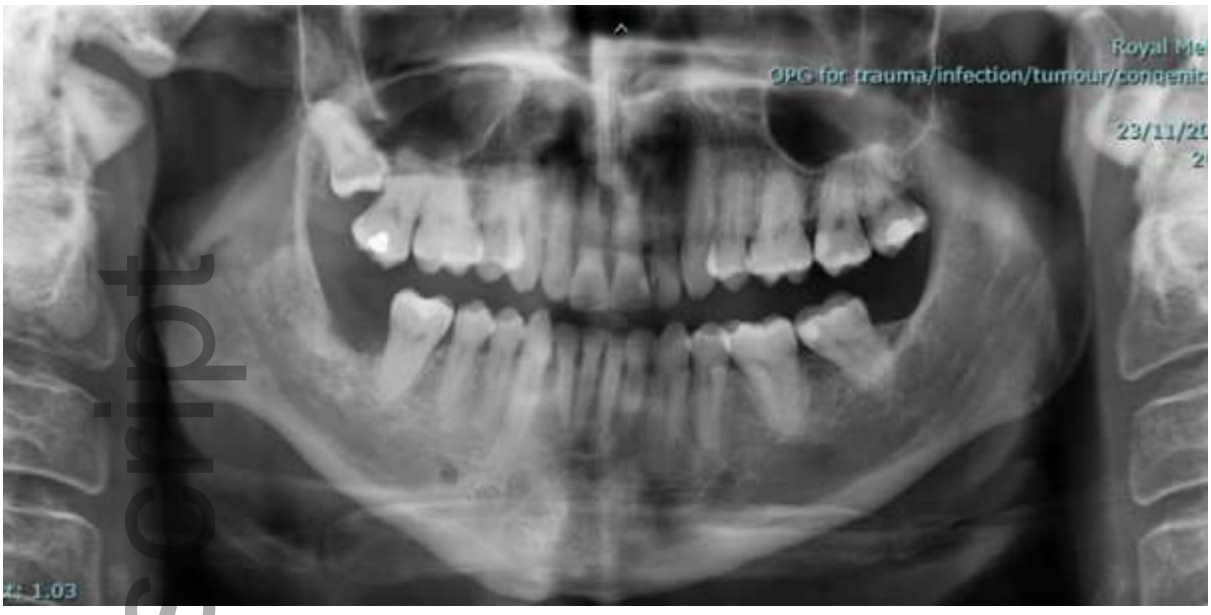

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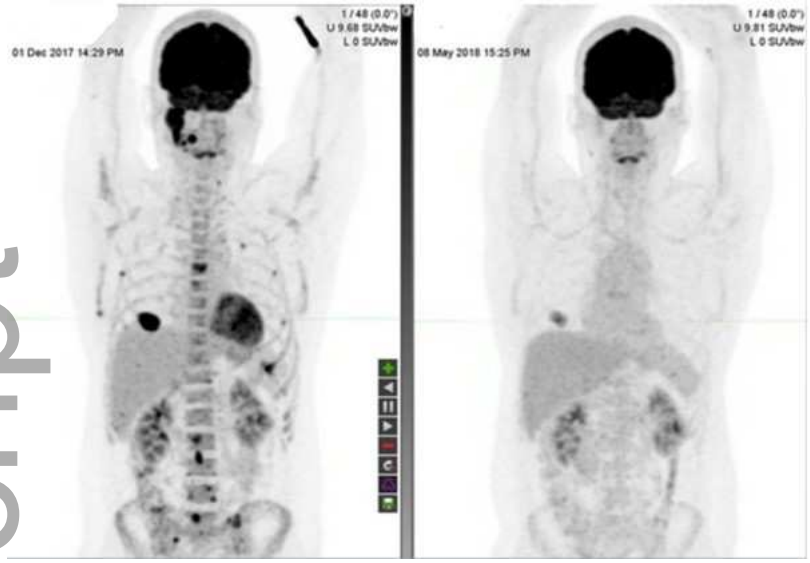

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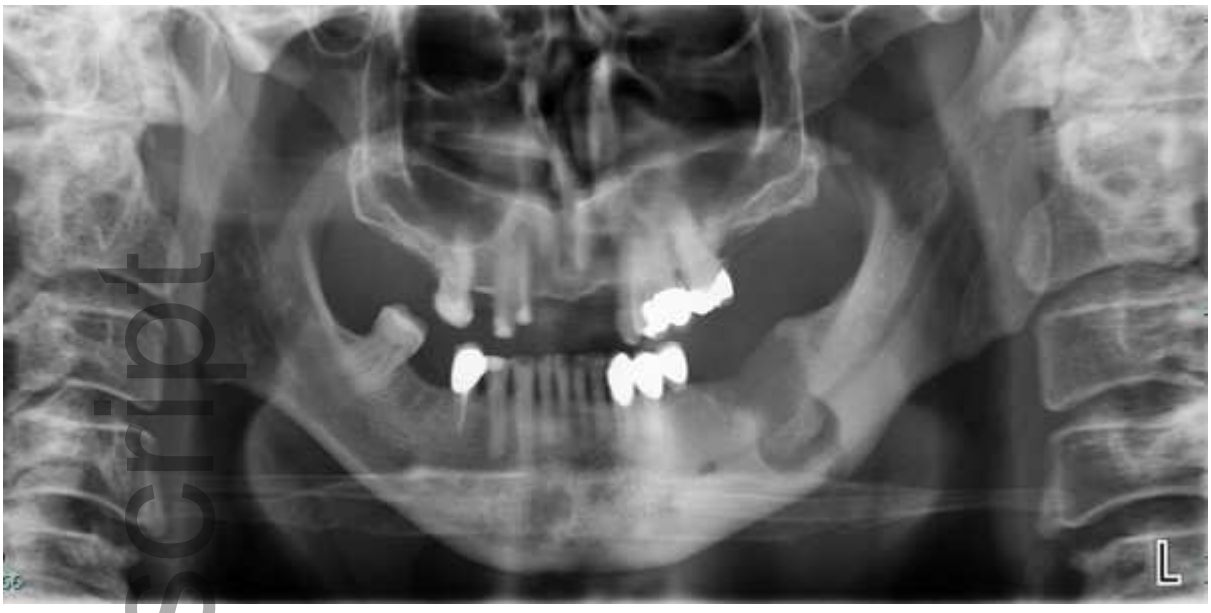

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