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MULTIPLE MYELOMA – ORAL RADIOLOGICAL EVIDENCES

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Abstract – *Objective:* *The aim of this article is to summarize the main radiological evidences induced by multiple myeloma at the jaws level.*

Materials and Methods: *The analysis examines the main case reports and reviews on the matter. All relevant publications were searched through the PubMed search engine, using the following keywords: "Multiple Myeloma" and "Radiological evidences", "Maxilla", "Jaw", "TMJ". The purpose of our review is to highlight how oral radiological investigation is extremely useful in detecting any bone alterations associated with cases of multiple myeloma. In addition, we investigate the sites of the jaws where direct bone alteration is more frequently, and we perform a differential diagnosis with other focal alterations of the jaws or those that are the result of certain drug therapies (bisphosphonates). Our research stresses the concept that early diagnosis of multiple myeloma at the jaws level may prevent unnecessary and inadequate treatments.*

Results: *From the evaluation of our research, it is evident that osteolytic lesions are one of the fundamental signs of multiple myeloma, especially in areas undergoing intense hematopoietic activity. Among the radiological techniques used for diagnosis, the most sensitive one appears to be the three-dimensional technique, such as CT or Cone Beam, whereas two-dimensional radiographs (orthopantomography) appear to be exhaustive only when the lesion is very extensive.*

Conclusions: *It is evident that the dentist figure plays not only a supportive role, but also a fundamental part in the diagnostic process, as lesions that may anticipate a systemic manifestation are often encountered at the oral level.*

KEYWORDS: *Multiple myeloma, Oral manifestation of myeloma, Radiological features of myeloma, Multiple myeloma and oral disease, Maxillary bone disease.*

INTRODUCTION

Multiple myeloma (MM) is a neoplasm characterized by the uncontrolled proliferation of malignant plasma cells derived from a single clone in the bone marrow[1]. It represents 13% of all hematological tumors and is the second most commonly known hematological malignancy[2]. It can occur in various body areas, including bones and joints, and it makes for 1% of all malignant tumors. Due to its multi-organ spread, multiple myeloma is of particular interest to many medical specialists, including oral and maxillofacial surgeons and often its diagnosis is accidental[3]. The average age of pa-

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tients at the time of diagnosis is about 65 years old and the disease is more frequently encountered in people in their sixth or seventh decade of life[4,5]. Bone destruction induces osteolytic lesions and bone pain is a typical feature of MM, being one of its four most common symptoms, along with anemia, hypercalcemia and kidney failure. About 60% of patients experience bone pain at the time of diagnosis[6,7]. The clinical features of the disease are due to the proliferation and subsequent replacement of normal bone marrow cells, with a whole monoclonal paraprotein (protein M) and/or its polypeptide subunits, known as Bence Jones proteins[3]. Craniofacial lesions are often asymptomatic and randomly encountered during diagnostic investigations such as computed tomography (CT), magnetic resonance imaging (MRI) of the brain, during check-up of local clinical symptoms or during staging evaluation of other diseases[8]. The main manifestations of MM are evident in the bones, predominantly in the vertebral column, the skull, the pelvis and the ribs. The areas which appear radiolucent upon radiological detection contain proliferations of neoplastic cells at the bone level and a greater number of bone alterations corresponds to a greater tumor aggressiveness[9]. Radiographic findings in the skeleton, which are typical of MM, are usually focal osteolytic lesions with or without areas of diffused osteoporosis[10]. MM presence in the jaws is not a rare condition, but oral lesions rarely occur as the first sign of the disease. When present, the angle and the ramus of the mandible are the most common anatomical sites involved[10,11]. Furthermore, as a consequence of an abnormal accumulation of immunoglobulin light chains, approximately 15% of patients with MM have amyloidosis and this may be the first sign of MM. The oral mucosa, especially the tongue, is commonly affected by amyloidosis, which frequently causes macroglossia[5]. The prognosis of MM has gradually improved, passing from an estimated average survival of 7 months during the pre-chemotherapy era, to an average survival of 24-30 months after the introduction of high-dose chemotherapy with autologous stem cell transplantation (ASCT)[12]. This study aims to summarize in a single article, the main radiological evidences induced by multiple myeloma at the jaws level. The analysis examines the main case reports and reviews in this regard.

MATERIALS AND METHODS

All relevant publications were searched through the PubMed search engine, using the following keywords: “Multiple Myeloma” and “Radiological evidences”, “Maxilla”, “Jaw”, “TMJ”. Case reports and reviews that highlighted how multiple myeloma manifested through bone lesions at the jaws level were selected. Radiological techniques and advances in imaging technology have been reviewed and summarized. The significant radiological results of the different imaging techniques in patients with MM are illustrated below.

RESULTS

This review included 22 articles published from 1957 to 2019, 13 of which were case reports and 9 were revisions. The average age of the participants in the studies was around 60 years, with an age range comprised between 40 and 70 years; the majority of patients, out of a total sample of 1495 patients, were aged between 60 and 70 years. In a very recent study out of 145 lesions present in 33 patients with MM, 60% of the lesions concerned the maxilla, while only 40% concerned the mandible[13]. Researchers found that myelomatous lesions of the TMJ are fairly frequent among patients with MM, with an incidence of 32% (28 patients out of a sample of 88 patients), of which 7 patients had pain symptoms and / or joint dysfunctions[13].

Out of 783 patients analyzed in a review, 60% of the suspected patients showed maxillary manifestations and in 14% of cases oral lesions were the first signs of the disease[5].

Another work reported that among 59 cases, all suffering from MM, 17 had evidence in the maxilla (28.1%): 1 exclusively in the upper jaw, 13 only in the lower jaw and in 3 patients both upper and lower jaw were involved. Of these 17 cases, 15 underwent skull radiographs: 14 presented lesions in the skull as well as in the jaws, while one presented no cranial lesions just lesions in the upper jaw. Another 19 patients presented exclusively cranial lesions. In total, there were 36 patients with head-neck injuries. Of the 17 patients with oral lesions, 9 had symptoms and signs on physical examination[14].

In the clinical study of Lambertenghi-Deliliers et al[15] authors documented out of 193 patients with MM and radiologically evident lesions, 10 with lesions at the mandibular level (5.18%), absent in the maxilla. Of these 10, 8 had multiple and diffused lesions and while in one case they were limited to the right side of the mandible, another case presented with a single large lesion in the mandibular angle. Two cases had acute symptoms and 8 were asymptomatic. In 5 patients the lesions were already present at the time of diagnosis, while in the other 5 patients, the lesions were of late onset and occurred after the start of therapy[15].

In 47 cases, followed by Ali et al[16] where MM had caused oral lesions, 28 patients had mandibular lesions (58.5%), 20 at maxillary level (42.5%). Only one case had lesions both at the mandibular and maxillary level[16].

Witt et al[3] reported that out of 77 patients, 10% presented cranial and mandibular lesions, whereas 36 patients presented exclusively cranial lesions.

Data were not homogeneous. The most significant similarities of the articles included the location and appearance of the lesions. All the analyzed articles described osteolytic bone lesions, mostly of the multilocular type with poorly defined and non-sclerotic margins, with a diameter greater than 5 mm. The majority of the articles have described the lesions at the mandibular level as the most common, in particular in the angle, in the body of the mandible in the molar area and in the edentulous areas, in the mandibular branch, in the symphysis and in the mandibular canal.

Where present, maxillary lesions are mainly located in the posterior region, the tuberosity and above all in the maxillary sinuses. The investigations of choice for the evaluation of lesions at the oral level are the CBCT, CT in axial and sagittal vision, OPT and periapical radiographs; however, a PET/CT investigation with contrast medium is also described.

DISCUSSION

At skull level, radiographs show osteolytic lesions, with non-sclerotic cutting edges and, in some cases, cortical erosion. These lesions can develop into larger osteolytic segments. The disseminated form with diffused osteopenia is less frequent in the skull. Likewise, CT reveals multiple lytic foci without sclerotic border. Plasmacytoma, which represents the solitary focal form of this tumor, is rare in the skull. Magnetic resonance imaging is preferred for detecting bone marrow involvement. The lesions are hypo-intense on T1-weighted images, hyper-intense on T2-weighted images and improve after administration of contrast medium. Five different marrow infiltration models have been described in magnetic resonance imaging, with the "salt and pepper" model being the most common. Other possible features are normal bone marrow despite microscopic cell infiltration, focal involvement, homogeneous diffused infiltration and combined diffused and focal infiltration[17]. Mandibular radiographic signs are predominantly located in the premolar/molar region, and the proximity of the lesions to the mandibular foramen or canal on the radiography is only due to the overlap and close association of the canal with the medullary spaces in the lower portion of the mandible and in the branch[11,15,18].

Radiological evidence shows perforated osteolytic lesions, with generalized osteoporosis. Bone lesions due to MM can radiographically manifest themselves in three forms (Figures 1-3):

- Multilocular radiolucency
- Unilocular radiolucency and associations with cystic-like lesions
- Bone reabsorption with undefined edges (ill-defined).

Multiple myeloma is associated with numerous differential diagnoses from a radiographical point of view, some of which include odontogenic and non-odontogenic cysts[18]. During the anamne-

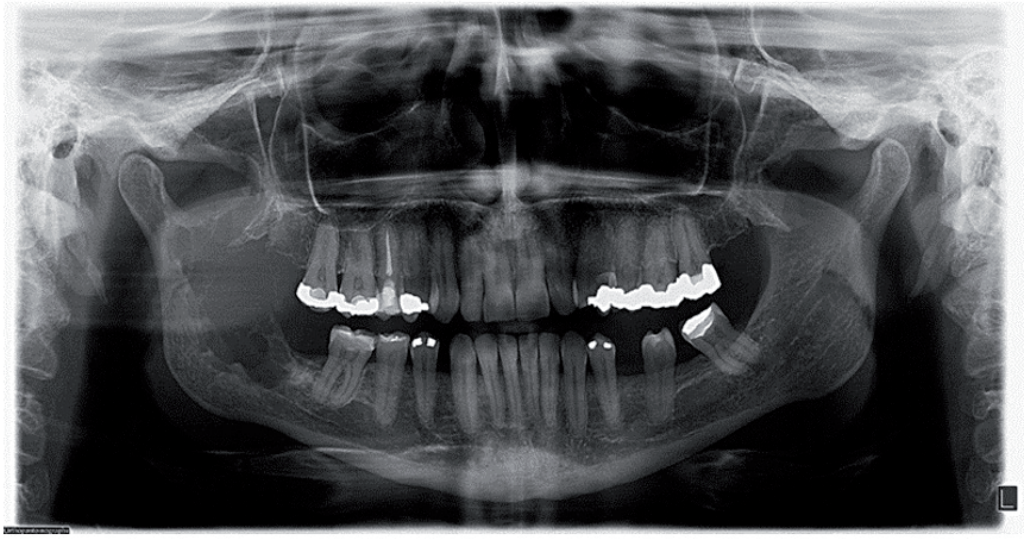

Fig. 1. Panoramic radiograph revealing a multilocular radiolucent destructive lesion in the right mandibular ramus. Courtesy of Perez et al[11].

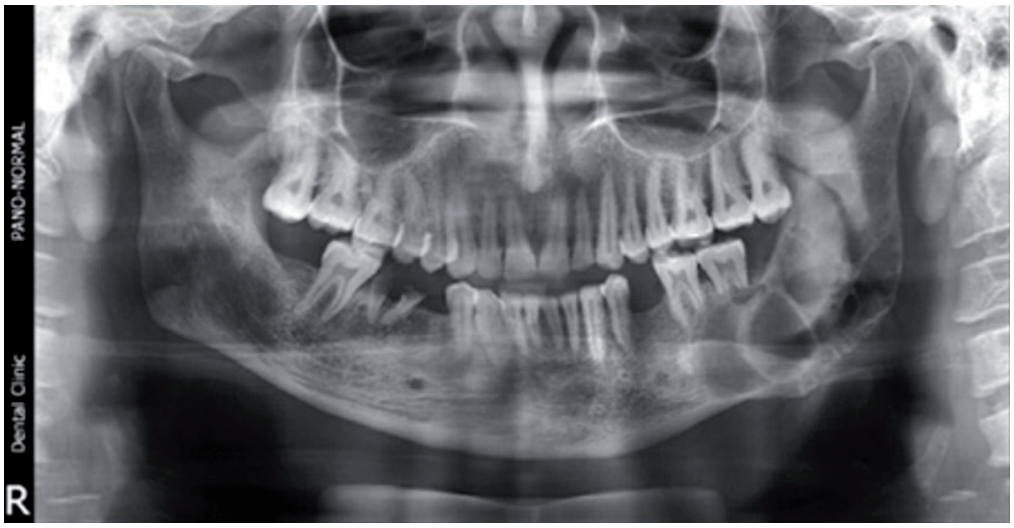

Fig. 2. Panoramic radiograph showing a multilocular radiolucency in mandibular posterior region. Courtesy of Palakshappa et al[10].

sis, patients who report persistent gingival swelling (sometimes accompanied by bleeding) and are over the age of 60 or who present bone lesions at the mandibular level upon radiographic examination, must have a medical check to rule out a diagnosis of MM. It is evident that x-ray is not only a support instrument but also an integral part of the entire diagnostic process, contributing to the assessment of the pathology's severity, as well as being a valid alarm bell for the dentist in the complete evaluation of a given clinical case[18,19].

Radiographically, mandibular osteonecrosis is detected in many patients receiving bisphosphonates as a treatment for multiple myeloma[13,20]. Bisphosphonates and zoledronic acid in particular, represent a good therapeutic treatment against multiple myeloma for their antiresorptive action; however, they disclose a 9.01% possibility of inducing necrosis, according to the case report taken into consideration. It is, therefore, important to combine the specific therapy for MM with an antinecrosis and antiparodontopathy prophylaxis, because patients at MRONJ risk receiving BF for MM are strongly associated with periodontal bone loss and absence of dental elements[21].

Multiple myeloma frequently involves TMJ, although in most cases this involvement is asymptomatic. In the study conducted by Abboud et al[7], the prevalence of lesions at the TMJ level accounted for 32% of the total cases; however, only 25% of these complained about site specific pain[7]. Nonetheless this percentage may actually be higher, as this area is often poorly investigated. Lack of histopathological confirmation increases the risk of a decrease in specificity in diagnosing osteolytic lesions. The reason for this underestimation lies with the use of X-rays, which are not sensitive enough for an accurate diagnosis of these pa-

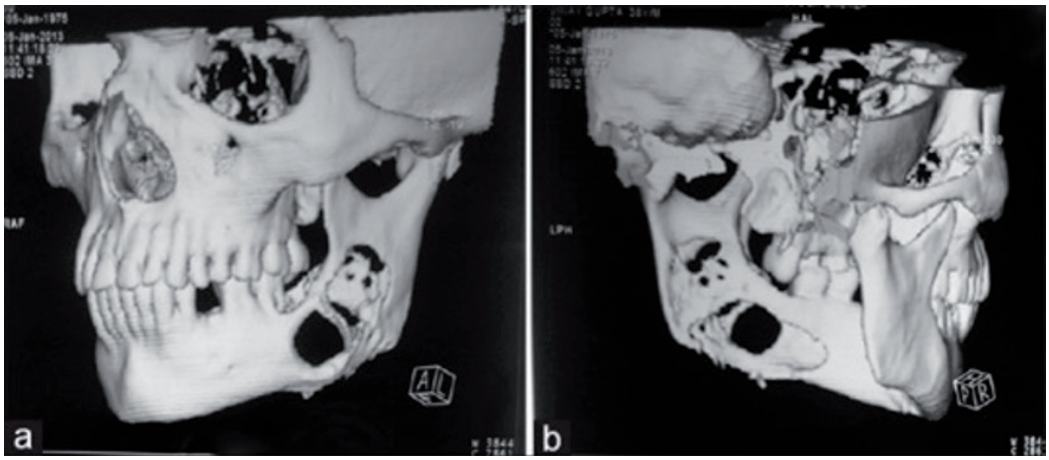

Fig. 3. *A*, Three-dimensional computed tomography image showing a large osteolytic lesion with erosion of buccal cortex. *B*, Three-dimensional computed tomography image showing a large osteolytic lesion with erosion of lingual cortex. Courtesy of Palakshappa et al[10].

thologies, especially when compared to the more profound CT. The presence of any degenerative changes excludes the diagnosis of myelomatous lesions (flattening of joint surfaces, subchondral bone sclerosis, osteophytes and resorption of joint surfaces)[6]. Multiple myeloma may enter into differential diagnosis with other pathologies that are hypo-dense, although these are rare in the specific condylar site, such as benign bone tumors and fibro-bone lesions, which therefore do not increase the number of false positives[7]. Bone destruction causing osteolytic lesions and bone pain is a feature of MM and must be carefully considered and evaluated by the clinician together with the other signs previously mentioned. 60% of patients reported bone pain at the time of diagnosis[4,6,7]. Many patients with temporomandibular pain had MM; bone lesions detected after CT might be wrongly mistaken for intra-articular degeneration due to the lack of specific signs and symptoms of MM.

Regarding the myelomatous involvement of the TMJ, it was concluded that the clinical results are not specific, and that adequate diagnostic imaging is essential for the identification and diagnosis of lesions[22-25].

The evolution of myeloma induces an imbalance between the activity of osteoblasts and osteoclasts, with the suppression of bone formation by osteoblasts and the decoupled activation of osteoclasts[26-28]. In early stages of MM, bone formation was found to increase when compared to resorption. As the disease progresses, bone formation decreases and resorption increases, leading to accelerated bone loss[29]. Extended bone resorption caused by MM predisposes the patient to pathological bone fractures[5] and sometimes the disease can develop to such a severity invading soft tissues after having infiltrated the cortex and periosteum, assuming the appearance of a palpable mass[14,30].

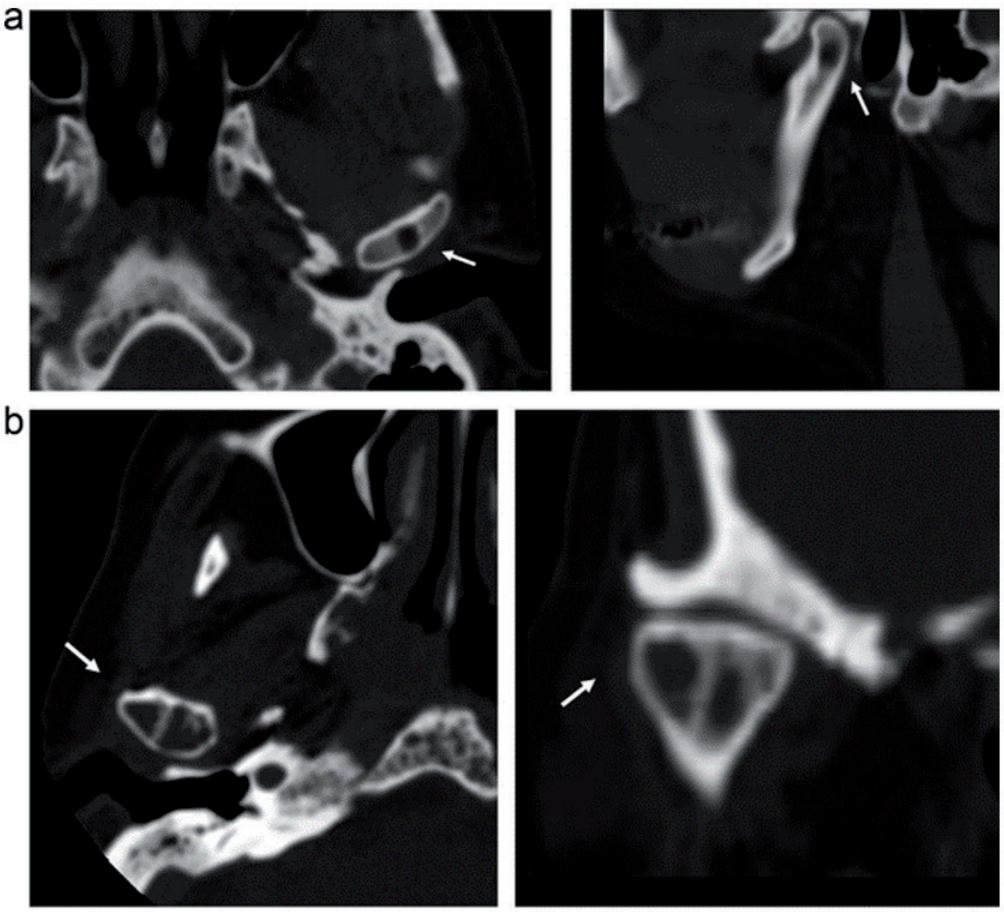

Fig. 4. Examples of focal osteolytic lesions (solitary myelomas) involving the condylar head. *A*, Axial and sagittal CT scans demonstrating a focal osteolytic lesion (white arrow) of the left condylar head. Note the intact articular cortex and the normal contour of the articular surfaces. The osteolytic lesion lies at a considerable distance from the cortical surface, as opposed to subchondral cysts which lie subjacent to the cortex. *B*, Axial and coronal CT scans demonstrating focal osteolytic lesions (white arrow) occupying most of the right condylar head. Although there is significant narrowing of the joint cavity, the articular cortex of the condyle and fossa are intact with no erosions or osteophytes. Courtesy of Abboud et al[7].

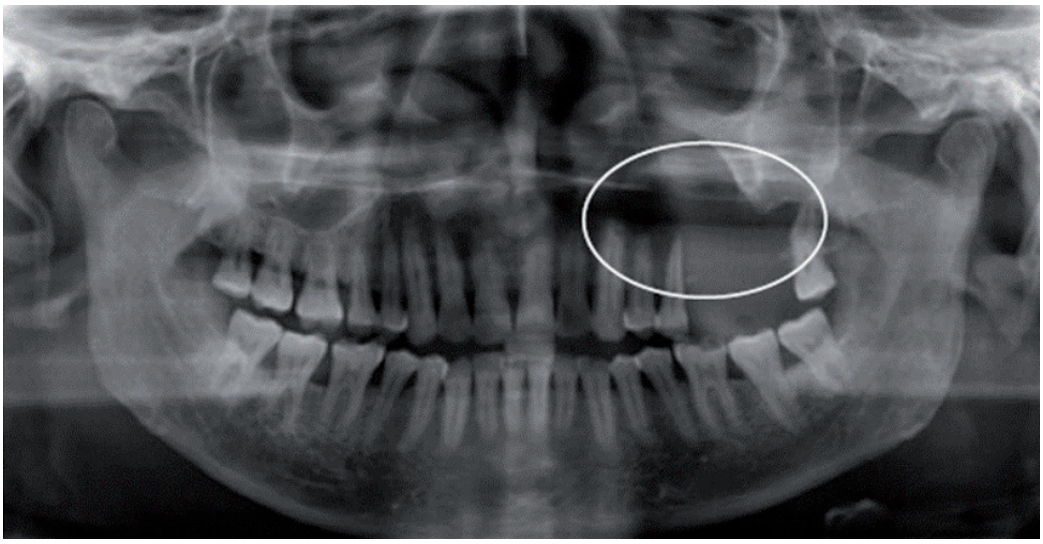

Fig. 5. A panoramic radiograph shows an osteolytic lesion in the left posterior maxilla, with resorption of the hard palate and the floor of the maxillary sinus. Courtesy of Ramaiah et al[31].

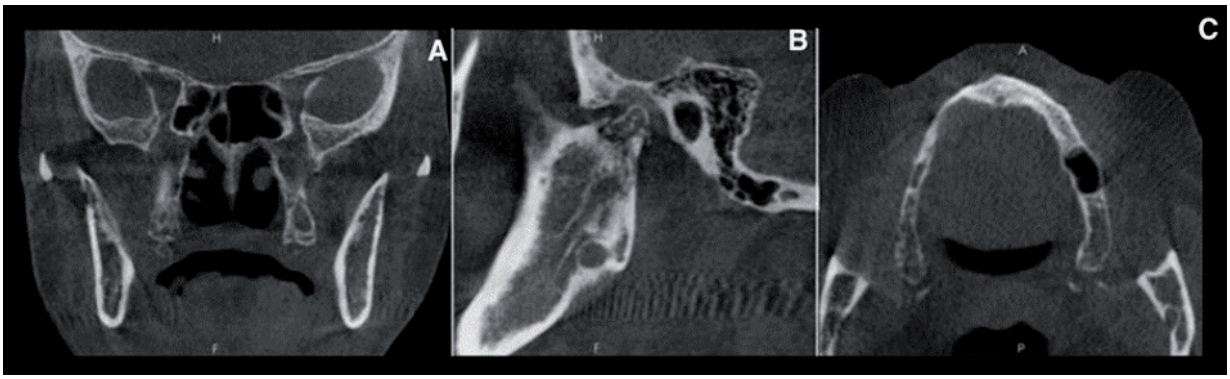

Fig. 6. Tomographic reconstructions highlighting osteolytic lesions in a patient with multiple myeloma. *A*, Coronal; *B*, sagittal; *C*, axial. Courtesy of Maiolino et al[13].

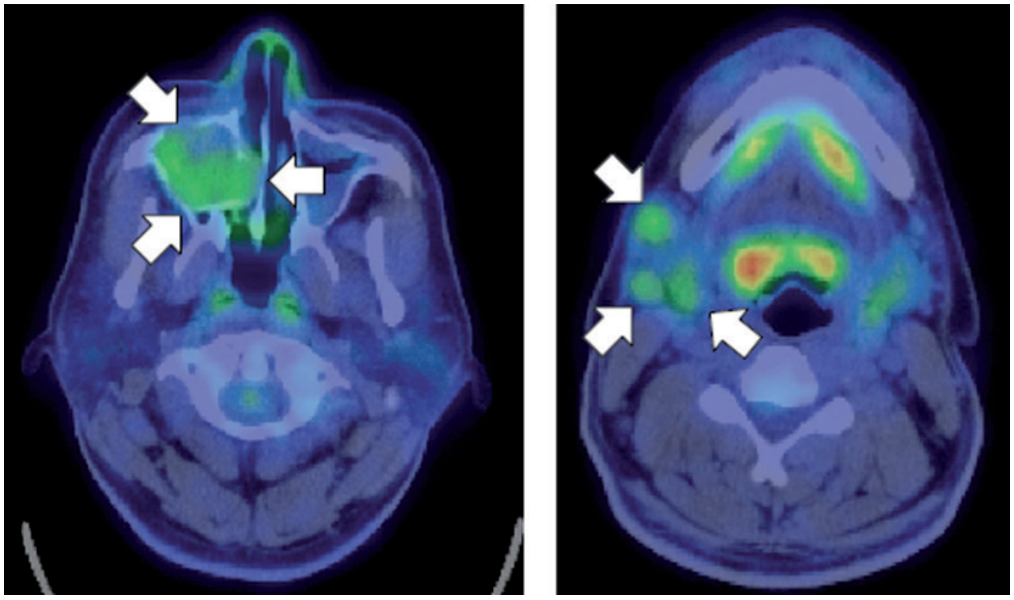

Fig. 7. Strong SUVs are found in the right maxillary sinus (*A*, arrows), right submandibular region (*B*, arrows), and left pubic bone (*C*, arrows) on an 18F-FDG PET/CT scan. Courtesy of Kasamatsu et al[44].

At the upper jaw level, the radiological evidences are more restrained; a study conducted by Epstein et al[5] shows radiolucent lesions of the premaxilla, which are normally rare in comparison to lesions present in the posterior mandible. The reason for this minor maxillary involvement is due to the higher content of hematopoietic tissue of the mandible; however, according to a study by Ramaiah et al[31], the lower incidence of maxillary lesions comes as a result of its greater content of haematopoietic tissue, in contrast to other articles which affirm the opposite[5,15].

Injuries to maxilla appear ill-defined due to the trabeculae of the thinner and more fragile aspect of the upper jaw[32]. Another reason for the lower frequency of lesions at the maxillary level can be accounted for the use of X-rays, which are not very sensitive for the diagnosis of these pathologies, compared to CT[13]. The presence of these lesions has been highlighted in patients who have had involvement of the skull in addition to other bone areas and therefore their presence could represent a clinically advanced stage of the disease[15].

The bone lesions deriving from multiple myeloma in the mandible and maxilla are radiologically different from each other. In addition to being less frequent, maxillary lesions have poorly defined contours and share a common appearance of bone resorption with multilocular areas[13].

Radiography has a fundamental role, since the detection of osteolytic lesions of MM determines an indication of the treatment in the absence of other clinical manifestations[33-35]. As far as extensive bone lesions are concerned, it is believed today that CBCT, among the three-dimensional imaging techniques, can replace two-dimensional radiographs thanks to its high precision and lack of overlap between adjacent structures[36-38].

However, according to some authors, this diagnostic method should not replace routine exams, due to the superiority of MRI and also because staging does not change compared to exams conducted with two-dimensional radiographs. Resonance and CT scanning have proven to be more valuable than conventional radiography for evaluating bone destruction and for soft tissue involvement in each individual lesion[39]. The big limitation of two-dimensional investigations, however, is that of not intercepting lesions that do not compromise at least 30% of the trabecular bone[40].

As for the radiographic aspects of MM lesions in panoramic radiographs, small and round osteolytic lesions, without sclerotic margins, are more frequently reported than the osteoporotic aspect typical of the extension of the pathology[41]. With regard to the internal aspects, hypodense lesions have been detected and bone destruction containing multilocular areas rather than unilocular aspects has been commonly observed. Lesions with undefined edges and cortical bone destruction are associated with aggressive lesions[42,3,5,43].

As part of radiographic research, the support instruments are manifold and a valid support is given by the PET/CT nuclear medicine examinations which, in the study by Kasamatsu et al[44], are used to highlight metabolically active areas and signs of possible neoplastic lesions. More specifically, thanks to the radiopharmaceutical 18F-FDG (18F-fluorodeoxyglucose) and its selective accumulation, active areas have been accentuated at the submandibular and right maxillary sinus level, despite the fact that any intercepted lesion must always be confirmed by a histological examination.

CONCLUSIONS

Osteolytic lesions are one of the fundamental signs of multiple myeloma, particularly in areas with intense hematopoietic activity. Three-dimensional techniques are more comprehensive in detecting lesions, while two-dimensional techniques are only useful in cases of extensive lesions. It is evident that the dentist figure plays not only a supportive role, but also a fundamental part in the diagnostic process, as lesions that may anticipate a systemic manifestation are often encountered at the oral level. It is, therefore, undoubtedly clear how early diagnosis of multiple myeloma at the jaws level prevents both unnecessary and inadequate treatments.

Further research on the presence of lesions related to the hematopoietic activity of the bone is needed to broaden the current knowledge and a diagnostic protocol at the dental practice level should be established to encourage early diagnosis of the pathology.

Conflict of Interest Statement:
Authors declare no conflict of interest.

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