Radiographic Evaluation of the Maxilla and Mandible of Patients Diagnosed with Multiple Myeloma: Retrospective Study

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Avaliação Radiográfica da Maxila e da Mandíbula de Pacientes Diagnosticados com Mieloma Múltiplo: Estudo Retrospectivo

Evaluación Radiográfica del Maxilar y de la Mandíbula de Pacientes Diagnosticados de Mieloma Múltiple: Estudio Retrospectivo

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ABSTRACT

Introduction: Multiple myeloma is defined as a plasma cells malignant neoplasm with abnormal proliferation of clonal plasma cells in the bone marrow of unknown etiology. **Objective:** To characterize patients with multiple myeloma treated at INCA's Department of Stomato-Dentistry and Prosthodontics, utilizing sociodemographic, clinical, laboratory and radiographic data. **Method:** Retrospective cross-sectional study of patients diagnosed with multiple myeloma from 2000 to 2018 who underwent panoramic radiography at the diagnosis of the disease. The sociodemographic and clinical-radiographic data of the study population were collected from the patients' medical records stored in a database, analyzed descriptively and submitted to the X^2 non-parametric test (chi-square). **Results:** In the final sample, 163 cases were obtained, mostly men (56.4%), white (55.8%), aged ≤55 years (54%), with incomplete elementary education (30.7%), non-smokers (54.6%), and non-alcoholics (54.6%). There were lytic lesions in 46 patients (28.2%) concentrated in the mandible (82.6%; p=0.000). Higher frequency of partially defined margins (50.0%), non-sclerotic (78.2%) and unilocular aspect (43.5%) were found. Of the 46 patients who presented with a maxillomandibular lytic lesion, 27 were older than 55 years (p=0.042). **Conclusion:** There was higher occurrence of bone lesions in the mandible when compared to the maxilla.

Key words: multiple myeloma/diagnosis; mandible; maxilla; radiography, panoramic; diagnostic imaging.

RESUMO

Introdução: O mieloma múltiplo é caracterizado como uma neoplasia maligna plasmocitária com a proliferação anormal de plasmócitos clonais na medula óssea de etiologia desconhecida. **Objetivo:** Caracterizar os pacientes com mieloma múltiplo atendidos no Setor de Estômato-Odontologia e Prótese do INCA, por meio de dados sociodemográficos, clínicos, laboratoriais e radiográficos. **Método:** Estudo transversal retrospectivo de pacientes com diagnóstico de mieloma múltiplo, no período de 2000 a 2018, que realizaram radiografia panorâmica no período do diagnóstico da doença. Os dados sociodemográficos e clínico-radiográficos da população em estudo foram coletados nos prontuários dos pacientes, armazenados em banco de dados, analisados de forma descritiva e submetidos ao teste não paramétrico X^2 (qui-quadrado). **Resultados:** Na amostra final, foram totalizados 163 casos. A maioria era de homens (56,4%), brancos (55,8%), com idade ≤55 anos (54%), ensino fundamental incompleto (30,7%), não fumantes (54,6%) e não bebedores (54,6%). Havia lesões líticas em 46 pacientes (28,2%) com predileção pela mandíbula (82,6%; p=0,000). Houve maior frequência de margens parcialmente definidas (50,0%), não escleróticas (78,2%) e de aspecto unilocular (43,5%). Dos 46 pacientes que apresentaram lesão lítica maxilomandibular, 27 pacientes tinham >55 anos (p=0,042). **Conclusão:** Há maior ocorrência de lesões ósseas na mandíbula quando comparada à maxila.

Palavras-chave: mieloma múltiplo/diagnóstico; mandíbula; maxila; radiografia panorâmica; diagnóstico por imagem.

RESUMEN

Introducción: El mýeloma multiple se caracteriza por ser una neoplasia maligna de células plasmáticas con proliferación anormal de células plasmáticas clonales en la médula ósea de etiología desconocida. **Objetivo:** Caracterizar a los pacientes con mýeloma multiple atendidos en el Departamento de Estomato-Odontología y Prostodoncia del INCA, utilizando datos sociodemográficos, clínicos, de laboratorio y radiográficos. **Método:** Estudio transversal retrospectivo de pacientes diagnosticados de mýeloma multiple de 2000 a 2018 a los que se les realizó una radiografía panorámica durante el período de diagnóstico de la enfermedad. Los datos sociodemográficos y clinicorradiográficos de la población de estudio fueron recolectados de la historia clínica de los pacientes, almacenados en una base de datos, analizados descriptivamente y sometidos a la prueba no paramétrica X2 (chi-cuadrado). **Resultados:** En la muestra final, había un total de 163 casos, en su mayoría hombres (56,4%), blancos (55,8%), edad ≤55 años (54%), con educación primaria incompleta (30,7%), no fumadores (54,6%) y no bebedores (54,6) %). Hubo lesiones líticas en 46 pacientes (28,2%) con predilección por la mandíbula (82,6%; p=0,000). Hubo una mayor frecuencia de márgenes parcialmente definidos (50,0%), no escleróticos (78,2%) y de apariencia unilocular (43,5%). De los 46 pacientes que tenían lesión lítica maxilomandibular, 27 pacientes tenían >55 años (p=0,042). **Conclusión:** Existe una mayor ocurrencia de lesiones óseas en la mandíbula en comparación con el maxilar.

Palabras clave: mieloma múltiple/diagnóstico; mandíbula; maxilar; radiografía panorámica; diagnóstico por imagen.

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INTRODUCTION

The most recent world estimate indicated that 160 thousand new cases and 106 deaths would occur in 2028 by multiple myeloma (MM)[1]. It accounts for 1% of all neoplastic diseases and 13% of all the hematologic cancers, being the third most common worldwide[1]. The mean age of the patients at the diagnosis is approximately 60.5 years[2]. Chemotherapy, radiotherapy, autologous stem-cell transplant, corticosteroids and bisphosphonates are prescribed to improve the patients' quality-of-life and survivorship[2,3].

MM is a plasma cell malignant neoplasm with abnormal proliferation of clonal plasmacytes in the bone marrow of unknown etiology. Abnormal plasmacytes are responsible for the production of non-functional antibodies associated with organic dysfunctions, signs and symptoms[3,4]. Signs are attributable by CRAB features: C = calcium elevation; R = renal insufficiency; A = anemia; B = bone lesions[4].

Bone injuries are caused by monoclonal proteins inducing osteoclasts differentiation from pre-osteoclasts and inhibit the activity of osteoblasts[5]. Osteolytic lesions result from poor osseous resorption and formation typically manifesting in the spine, femoral, humeral shafts, ribs, pelvis and skull[6]. Approximately 35% of the patients diagnosed with symptomatic MM present maxillary lesions, 30% in the mandible, commonly found in the mandible body, angle and rami[7-13].

According to the International Myeloma Working Group (IMWG)[14], for each patient recently diagnosed, a complete bidimensional imaging of the areas of interest is recommended. Nearly 80% of all the new cases diagnosed are detectable in whole body imaging tests[14]. Detection of osteolytic lesions is a criteria to define symptomatic MM requiring treatment, regardless of the presence of other clinical symptoms[14-16].

Bone manifestations detected in panoramic radiography can be classified in regular findings when there is mild or undetectable bone resorption, multiple radiolucency (punctured) resulting from focal proliferation of plasmatic cells and generalized osseous thinning with diffuse osteoporotic changes[9,11]. This imaging test can be useful for patients diagnosed with MM because of full availability and low cost[17].

The paucity of scientific publications about the prevalence of bone lesions in the jaw and mandible in patients diagnosed with MM shows the necessity of more studies for better dental planning. The objective of this study was to characterize the patients with MM consulted at the "*Setor de Estômato-Odontologia e Prótese*" of the National Cancer Institute (INCA) with sociodemographic, clinical, laboratory and radiographic data.

METHOD

Retrospective, cross-sectional study with patients diagnosed with MM treated between 2000 and 2018 approved by the Institutional Review Board (IRB), report number 016533/2019, CAAE: 08615319.6.0000.5274.

The inclusion criteria were patients ≥18 years old diagnosed with MM who underwent panoramic radiography at the diagnosis. Patients with diagnosis of plasma dyscrasia other than MM (monoclonal gammopathy of undetermined significance, solitary plasmacytoma and plasma cells leukemia) were excluded like cases of latent myeloma, bone metastasis and those with second primary tumor in the maxilla or mandible.

The sociodemographic data were extracted from the patients' charts as sex, age, ethnicity, education, tobacco and alcohol use, Durie-Salmon staging system (DSS) and International Staging System (ISS) and death. Clinical and radiologic data were extracted as well from the charts, including hemoglobin, calcium, creatinine, alkaline phosphatase, IgG, IgA, IgM, lactic dehydrogenases (LDH), albumin, beta-2-microglobulin (B2M) and Bence Jones protein, protocol of chemotherapy, bisphosphonates, radiotherapy, hematopoietic stem-cells transplantation and presence of lytic lesions identified by bone inventory. Panoramic radiography were stored at an imaging database and analyzed later. Orthophos Plus DS Ceph (Sirona Dental Systems − Bensheim, Germany) with 60-90 Kv and 9-12 mA was utilized for x-rays and Eagle 3D Pan/Tele (Dabi Atlante − Ribeirão Preto, São Paulo, Brazil) with 60-85 kV and 4-8 mA.

For an estimated prevalence of 30% of mandibular lesions with absolute accuracy of 5% and level of significance of 5%, at least 323 patients would have to be included. However, this number was unable to be reached in the eligible population for the study period.

The panoramic radiographs were evaluated in a low-light environment by two evaluators in a 17-inches computer images visualizer according to the protocol already described in the literature[20].

It was determined that the mandible would be evaluated prior to the maxilla, first at the right condyle followed by the rami, angle and regions of the same body side. Next, the symphysis, body, angle, rami and left condyle. The evaluation was divided in three anatomic regions: right posterior maxilla, left posterior and anterior maxilla.

Once the osteolytic lesion was identified, the following criteria were applied in the evaluation: **(1)** anatomic location of the mandible or maxilla – it was determined that the condyle would extend since its upper cortical covering the neck up to the mandibular incisure. The

mandible rami covers the mandible incisure up to the upper limit of the mandible curve angle. The mandible angle starts in the curve of the base up to the retromolar region limit. The bilateral pattern of the anatomic region is that the body of the mandible starts in the retromolar region up to the corresponding region to the distal face of the canine of the side evaluated. The symphysis of the mandible extended from the equivalent region of the distal face of the right canine up to the distal face of the left canine. The anterior region of the maxilla extended from the corresponding distal face of the right canine up to the equivalent region of the left canine. And the right and left posterior region of the maxilla extended from these regions across the midline up to the tuberosity, respectively; **(2)** size – diameter ≥5 mm or <5 mm; **(3)** Margins – defined with precise limits, partially defined with partial limits, undefined without defined limit, sclerotic with partial radiopaque halo around the lesion and non-sclerotic with absence of radiopaque halo in the periphery of the lesion; **(4)** inner aspect – unilocular or multilocular; **(5)** relationship with adjacent structures: mandible − mandibular canal, mental foramen, rupture of cortical bone; maxilla − tuberosities, maxillary sinuses, teeth, rupture of the cortical bone; **(6)** characterization or not of the "punctured pattern".

Other typical dental findings were evaluated as the presence of residual roots, extensive caries and lack of teeth to characterize the dental profile of the population investigated.

Sociodemographic and clinical-radiograph data were collected and later registered and stored in a Windows Microsoft Excel® 2007 spreadsheet; next, the descriptive analysis was carried out.

Distributions of simple and percent frequencies, arithmetic means, medians, standard-deviation, minimum and maximum values, non-parametric X^2 (chi-square) test of the variables, Student *t* test to compare arithmetic means and ages were calculated for the statistical analyzes.

Cohen's Kappa test was utilized to evaluate the interrater reliability; the classification was: fair for 0.20-0.40, moderate or intermediate for 0.40-0.60; substantial or strong for 0.60-0.80 and almost perfect for 0.80-1.00[21].

The Statistical Package for the Social Sciences (SPSS) version 20.0 was utilized with level of significance of 5% and ($p<0.05$)[22].

RESULTS

190 patients with diagnosis of MM consulted at the institution's Dental-Stomatology and Prosthetics clinic and who underwent panoramic radiology from 2000 to 2018 were found in the databases. Of these, 17 charts were not found and ten patients presented plasma cell dyscrasia of MM, totaling 163 in the final sample.

Sociodemographic and clinic data collected for 163 patients revealed predominance of males (56.4%), White (55.8%), aged ≤55 years (54%), with incomplete elementary school (30.7%), non-smokers (54.6%), non-alcoholic (54.6%), with predominance of type IIIa DSS (58.9%) and type 3 ISS (36.3%) according to Table 1.

There was predominance of low concentration of hemoglobin (57.0%), IgA (38.7%) and IgM (52.8%) in the lab tests and high concentration of IgG (44.2%) and B2M (62.6%). In most of the cases, the Bence Jones protein was negative (27.6%). Calcium, creatinine, alkaline phosphatase, LDH and albumin were normal in most of the cases.

Patients who underwent first line chemotherapy (98.8%) with dexamethasone and thalidomide (40.4%) predominated, most of them did not undergo second (58.3%), third (89.9%) and fourth (97%) lines. There was predominance of patients who utilized bisphosphonates (81.6%) and submitted to hematopoietic stem-cells transplantation (76%) but most of them did not undergo radiotherapy (58.3%).

In 76% of the cases, bone lesions predominated, the most frequent were lytic (70.5%) and the most affected location was skull (60.1%) as shown in Table 2 and Figure 1.

Cohen's Kappa test to evaluate the interrater reliability showed substantial strong and very strong agreement in the range of 0.70-1.00 for the variables, ensuring that the radiograph analysis was reliable.

The presence of bone lesions in the maxillomandibular complex was detected in 28.2% of the cases. They were predominant in the mandible angle (82.6%), with different pattern than punched out (52.2%), size >5 mm (71.7%), partially defined margin (50%), non-sclerotic (78.2%) and unilocular aspect (43.5%). Patients who did not present extensive carious lesions predominated (65.6%) with loss of one to eight teeth (34.4%) as shown in Table 3 and Figure 2.

The following variables were associated: sex and lytic lesion; lytic lesion and race; lytic lesion and DSS staging; lytic lesion and staging ISS; lytic lesion and IgG; lytic lesion and IgA; lytic lesion and B2M. No significant association among the variables investigated were found, and the frequencies are presented similarly.

Among patients with lytic lesions, 21 (38.9%) presented normal IgM, 24 (27.9%), low IgM and one (5.0%), the information were missing. There was significant association (p=0.023) between normal IgM and lytic lesion (p=0.023).

Table 1. Clinical and demographic profile of the study population (n=163)

Variable	Category	n (%)
Sex	Male	92 (56.4%)
	Female	71 (43.6%)
Race	Caucasian	91 (55.8%)
	Brown	55 (33.8%)
	Black	17 (10.4%)
Age	≤55 years	88 (54.0%)
	>55 years	75 (46.0%)
Education	Illiterate	4 (2.4%)
	Literate	4 (2.4%)
	Incomplete Elementary	50 (30.7%)
	Complete Elementary	20 (12.3%)
	Incomplete High School	3 (1.8%)
	Complete High School	43 (26.4%)
	Incomplete University	7 (4.3%)
	Complete University	30 (18.4%)
	Not informed	2 (1.2%)
Tobacco use	Yes	57 (35.0%)
	No	89 (54.6%)
	Not informed	17 (10.4%)
Alcohol use	Yes	56 (34.4%)
	No	89 (54.6%)
	Not informed	18 (11.0%)
DSS Staging	Ia	3 (4.9%)
	Ib	0 (0%)
	IIa	15 (9.2%)
	IIb	0 (0%)
	IIIa	96 (58.9%)
	IIIb	25 (15.3%)
	Not informed	19 (11.6%)
ISS Staging	1	50 (30.7%)
	2	36 (22.0%)
	3	59 (36.3%)
	Not informed	18 (11.0%)
Death	Yes	56 (34.3%)
	No	100 (6.3%)
	Not informed	7 (4.3%)

Captions: DSS = Durie-Salmon Staging System; ISS = International Staging System.

Table 2. Bone inventory of the study population (n=163)

Variable	Category	n (%)
Bone lesion	Yes	124 (76.0%)
	No	30 (18.4%)
	Not informed	9 (5.5%)
Bone lesion (classification)	Lytic	115 (70.5%)
	Fracture	40 (24.5%)
Bone lesion (local)	Skull	98 (60.1%)
	Pelvis	51 (31.3%)
	Spine	56 (34.3%)
	Thorax	44 (27.0%)
	Upper limbs	20 (12.3%)
	Lower limbs	35 (21.5%)

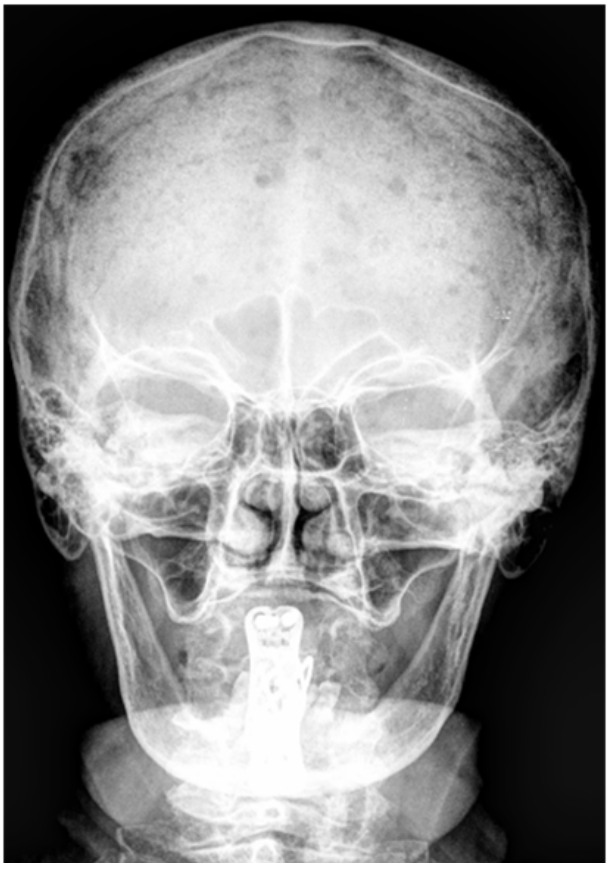

Figure 1. Frontal digital radiography of the skull showing lytic lesions in the skullcap

Of the 46 patients with lytic maxillomandibular lesion, 38 (82.6%) were in the mandible (p=0.000) and 27 were aged >55 years (p=0.042).

DISCUSSION

MM is a disease that results in the synthesis of plasma cells which produce antibodies extensively affecting the

Table 3. Radiographic characteristics of bone lesions in the maxilla and mandible (n=46)

Variable	Category	Number of lesions (%)
Location	Mandible	38 (82.6%)
	Maxilla	6 (13.0%)
	Mandible and maxilla	2 (4.4%)
Location at the mandible and maxilla	Rami	33 (71.7%)
	Angle	38 (82.6%)
	Body	10 (21.7%)
	Symphysis	4 (8.7%)
	Mandible condyle	1 (2.2%)
	Posterior maxilla	8 (17.4%)
	Anterior maxilla	0
Bone lesion in punched out aspect	Yes	22 (47.8%)
	No	24 (52.2%)
Size	>5 mm	33 (71.7%)
	<5 mm	13 (28.3%)
Margin	Partially defined	23 (50.0%)
	Defined	21 (45.7%)
	Undefined	2 (4.3%)
Margin	Sclerotic	1 (2.2%)
	Partially sclerotic	9 (19.6%)
	Non-sclerotic	36 (78.2%)
Aspect	Unilocular	20 (43.5%)
	Multilocular	16 (34.8%)
	Unilocular and multilocular	10 (21.7%)
Relation with structure	Yes	20 (43.5%)
	No	26 (56.5%)
Relation with structure	Mandibular canal	17 (51.6%)
	Mental foramen	3 (9.0%)
	Mandibular cortical	5 (15.2%)
	Tuberosity	6 (18.2%)
	Tooth	2 (6.0%)

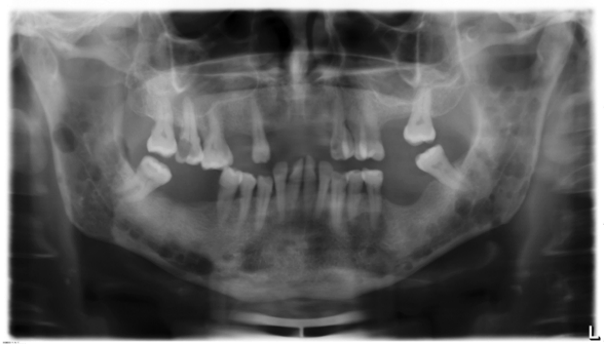

Figure 2. Panoramic digital radiography showing lytic lesions in the right and left mandible rami with punched-out aspect

bone marrow. White, ≤55 years old males, incomplete elementary school, non-smokers and non-alcoholic predominated in the study sample, concurring with the literature[3], corroborating the assumption that there is no direct association with tobacco and alcohol. Unsurprisingly, it was found significant association between age and the presence of lytic lesions in the maxillomandibular complex, suggestive that older patients are more prone to develop these lesions. To the best of the existing knowledge, there are no other studies showing this type of correlation.

The patients investigated in this study were at advanced stage of MM also reported in former studies[23], which can be attributed to the difficulty of diagnosing this neoplasm because of very common signs and symptoms in older patients and the asymptomatic stage of the disease that needs to be considered[16].

The signs and symptoms the patients with MM presented can be characterized as anemia, fatigue, hemostasis disorders and immunodeficiency[4]. Anemia can be detected by hemoglobin lab tests. 57% of the study patients had low levels of hemoglobin leading to anemia as a sign in the plasma cells neoplasm, corroborating data formerly described[4].

B2M lab tests are considered as prognostic features associated with lower global survival and events-free survivorship[24]. This study identified high frequency of high rates of B2M, suggesting poor prognosis and reiterating advanced staging in the population investigated.

Treatments like chemotherapy, radiotherapy, autologous bone marrow transplant, corticosteroids and bisphosphonates are prescribed to improve patients' quality-of-life and survival[14,16]. 98.8% of the study patients submitted to first line chemotherapy and combination of dexamethasone and thalidomide was the main regimen of choice for 40.4% of the cases. In addition to the well-defined initial chemotherapy regimen in the literature[25], regimens with new medications were not included in the study sample because of the year the treatment was made and availability of the drugs at Brazil's National Health System.

Furthermore, the use of bisphosphonates as modality of treatment of bone complications is well acknowledged in the literature[14,16]. This drug was utilized by 81.6% of the study sample, indicating advanced stages of the disease. Hematopoietic stem-cell transplantation is another therapeutic option[14,16,25] that 76% of the study patients utilized.

Overall, spine, pelvis, ribs and skull are the most prevalent regions as concluded in studies reporting MM-related osteolytic lesions[6,12,26] and the mandible was affected in 30% of the cases. The present study found

frequency of 60.1% of skull lesions and 28.2% of bone lesions in the maxilla and mandible, corroborating data previously described, reflecting advanced stages of the disease, requiring antineoplastic therapy even if clinical symptoms are not present[14,15,26]. Regardless of significant association between the presence of lytic lesion and IgM, these data are not clinically relevant because it is known that cases of IgM are rare and more aggressive[27], possibly an outcome bias of the study.

Full evaluation is required to detect bone lesions. Conventional radiography has low cost and is easily available, but the disadvantage is its poor accuracy to detect these lesions; in addition, they are only detectable radiographically if more than 30% of the trabecular bone is destroyed[20].

According to IMWG[3], other imaging methods can be utilized to identify bone lesions as magnetic resonance, whole body low-dose computed tomography (WBLDCT) and positron emission tomography (PET-CT)[3] with fluorodeoxyglucose (FDG) but are contingent on availability and access.

It was found significant association between bone lesion and location due to the maxillomandibular complexity, indicating more frequency of mandibular bone lesions when compared to the maxilla. Corroborating the studies of Witt et al.[7], Vieira-Leite-Segundo et al.[10], Mozaffari et al.[11], Lee et al.[12], Yoshimura et al.[13] and Faria et al.[23], the most affected regions were the mandibular angle, followed by the rami and body reinforcing data previously described[10-13]. In addition, bone lesions detected in more than one anatomic site were counted according to the number of anatomic regions.

The radiograph findings of MM lesions taken from panoramic radiographs revealed that little rounded osteolytic lesions were more frequent without sclerotic margin, very characteristic of the aspect punched out[7,12,28]. But in the sample analyzed, there was no predominance of the radiologic pattern described, possibly attributed to the number of cases evaluated.

Most of the lesions had bigger diameter (≥5 mm), concurring with the studies by Epstein et al[9], Mozaffari et al.[11] and Lee et al.[12]. Unilocular aspect lesions were predominant regarding radiotransparent inner aspects compared to multilocular aspect.

Epstein et al.[9] described MM lesions as radiolucent, rounded, with defined limits and absence of cortical or bone neoformation. The results of this study concur with the description these authors have proposed[9] since lesions with fully sclerotic margins were not encountered. Other authors, in contrast, reported that sclerotic lesions of several aspects are detected[7,28].

Bone lesions should be well evaluated because quite often they are sub-notified or ill-diagnosed as periapical lesions. Palakshappa et al.[29] described a case report where the patient was initially diagnosed with odontogenic-caused facial cellulitis evolving to dental extraction which, two months later was still unhealed, provoking an incisional biopsy with histopathology of MM.

Retrospective studies inherent difficulties as loss of clinical data and imaging in the physical and electronic charts of the patients is the limitation found, which has hampered the analysis and interpretation of the data.

CONCLUSION

This study corroborates the literature through the description of the clinical and demographic profile of the patients. MM was diagnosed at advanced stages and anemia was one of the most frequent. B2M lab test is a potential prognostic factor present in ISS staging. Chemotherapy, radiotherapy, bone marrow autologous transplant, corticosteroids and bisphosphonates are prescribed to improve the quality-of-life and survivorship of the patients.

Bisphosphonates were utilized in nearly 80% of the recently diagnosed patients, indicating the presence of bone lesion in this group, which are considered relevant to initiate the antineoplastic treatment contributing to the staging and prognosis of MM and affecting approximately 30% of the maxilla with more incidence at the mandible when both areas are compared. Radiologic imaging provide the required support to detect osteolytic lesions due to easy access. Thus, panoramic radiography of the maxilla and mandible is required at the diagnosis of MM for better staging of the disease and dental management of the patients.

CONTRIBUTIONS

All the authors contributed substantially to the study design, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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