Review article

Can dentists detect multiple myeloma through oral manifestations?

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ARTICLE INFO

Article history:
Received 29 March 2017
Accepted 24 August 2017
Available online 24 November 2017

Keywords:
Multiple Myeloma
Oral Manifestations
Mouth
Jaws

ABSTRACT

Objective: To review published data on oral manifestations of multiple myeloma.

Methods: An electronic database search was performed of articles published from 1971 to November 2016 in order to identify studies that reported oral manifestations of patients with multiple myeloma. Case reports and case series with oral manifestations of multiple myeloma in English were included in the study. An additional search was performed of the references of the selected articles.

Results: Thirty-seven articles that reported 81 patients with oral manifestations of multiple myeloma were selected: 30 case reports (82%) and seven case series (18%). The most common clinical features in the dental cavity were swelling (65.4%), bone pain (33.3%), paresthesia (27.1%) and amyloidosis lesions (11.1%). Osteolytic lesions detected on imaging exams were reported in the majority of the patients (90.1%) as plasmacytomas or ‘punched-out’ lesions.

Conclusions: Swelling and osteolytic lesions represent the most common clinical and radiographic signs of the jaws relating to multiple myeloma, respectively.

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Introduction

Multiple myeloma (MM) is a common bone malignancy of unknown etiology that affects mainly older age groups. Nearly 80% of diagnosed MM is preceded by an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS). The classical form of MM is characterized by signs such as hypercalcemia, Renal insufficiency, Anemia, and Bone lesions (CRAB). The main clinical signs and symptoms of MM are bone pain (accompanied or not by pathologic fractures), fatigue, infections and secondary...
Commonly, bone lesions may be represented by diffuse or localized osteolytic lesions, named plasmacytomas, or by a ‘punched-out’ pattern. The maxillary and mandibular bones may be affected by these lesions, and nearly 35% of patients diagnosed with symptomatic MM present lesions in the jaws.

It is important that clinical manifestations of MM are recognized at early stages. Some features of MM may manifest in the oral structures and dentists should be able to detect lesions that may represent oral manifestations of MM during the routine oral clinical and imaging exams that are periodically performed for dental treatment.

The oral signs and symptoms of patients presenting MM are characterized by pain, bleeding, dysphagia, paresthesia and osteolytic lesions. However, literature on the oral manifestations of MM is poor and mainly restricted to case reports. The aim of this study was to perform a search of the literature on the oral manifestations of MM, highlighting the most common clinical and imaging findings of the oral cavity and related conditions.

Method

An electronic database search of the literature was performed in order to identify studies published from January 1971 to November 2016 that reported oral manifestations in patients with MM. The Pubmed/Medline database was used employing the mesh terms “oral manifestations” (and associated entry terms “manifestation, oral” and “manifestations, oral”) AND “multiple myeloma”. Study criteria were applied and duplicated articles were eliminated. Clinical and epidemiological studies reporting oral manifestations of MM in English were eligible for the study. Reviews, letters to the editors, papers written in languages other than English, and those not available in the full version were excluded. An additional manual search was made of the references of the primary selection using the same criteria.

Results

Sixty-six different abstracts were found in the electronic database search. Twenty articles were selected after the elimination of articles published in languages other than English (n=8), articles published before 1971 (n=5), articles that did not address the topic (n=20), articles that were not found (n=2), and literature reviews (n=11). Three hundred and 63 articles were found in the manual search of the references of the selected articles. After applying study criteria to these references, 346 articles were excluded. Thus, 37 studies were selected for this review: 30 case reports (82%), and seven case series (18%). No epidemiological or intervention studies were found in the search. Figure 1 shows the flowchart for the study selection process.

The main clinical and radiographic features found in the 37 selected studies are shown on Table 1. In more than half of the studies (20 studies), these characteristics were
<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Sample size/number of patients with oral manifestations</th>
<th>Symptom</th>
<th>Clinical sign</th>
<th>Imaging aspects of lesions</th>
<th>Type of image</th>
<th>First detected sign of MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barret al.³</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Swelling</td>
<td>Multiple diffuse lytic</td>
<td>Non specified</td>
<td>No</td>
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<tr>
<td>Yoshimura et al.⁹</td>
<td>Case report</td>
<td>2/2</td>
<td>Pain</td>
<td>Swelling</td>
<td>Multiple diffuse lytic</td>
<td>Skull and periapical radiograph</td>
<td>Yes</td>
</tr>
<tr>
<td>Kraut et al.¹⁰</td>
<td>Case report</td>
<td>1/1</td>
<td>Difficulty chewing</td>
<td>Amyloidosis in upper lip</td>
<td>Multiple diffuse lytic</td>
<td>Skull radiograph</td>
<td>No</td>
</tr>
<tr>
<td>Flick et al.⁴⁰</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Amyloidosis in the tongue</td>
<td>Punch-out</td>
<td>CT</td>
<td>Yes</td>
</tr>
<tr>
<td>Salisbury et al.⁴⁴</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Amyloidosis in the tongue</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>Epstein et al.¹¹</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Trismus</td>
<td>Punch-out lytic with root resorption</td>
<td>Pantomographic radiograph</td>
<td>No</td>
</tr>
<tr>
<td>Babajews et al.⁴¹</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Amyloidosis in the tongue</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Raubenheimer et al.⁴⁶</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Dysphagia</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacobs et al.⁴⁵</td>
<td>Case report</td>
<td>1/1</td>
<td>Dyslalia</td>
<td>Amyloidosis in the tongue</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>Lambertenghi et al.¹²</td>
<td>Case series</td>
<td>193/10</td>
<td>Pain</td>
<td>Paresthesia</td>
<td>Multiple lytic (9 cases)</td>
<td>Skull radiograph</td>
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<tr>
<td>Tamir et al.¹³</td>
<td>Case report</td>
<td>3/3</td>
<td>None</td>
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<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Reinish et al.³⁷</td>
<td>Case report</td>
<td>1/1</td>
<td>Dysphagia</td>
<td>Amyloidosis</td>
<td>Multiple lytic (4 cases)</td>
<td>Skull and panoramic radiographs</td>
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</tr>
<tr>
<td>Furutani et al.¹⁴</td>
<td>Case series</td>
<td>38/5</td>
<td>Pain</td>
<td>Pathological fracture</td>
<td>Multiple lytic (4 cases)</td>
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<tr>
<td>Lee et al.⁵</td>
<td>Case report</td>
<td>2/2</td>
<td>Pain</td>
<td>Bleeding gum</td>
<td>Single (1 case)</td>
<td>Panoramic radiograph</td>
<td>No</td>
</tr>
<tr>
<td>Witt et al.⁷</td>
<td>Case series</td>
<td>77/12</td>
<td>Paresthesia in the mandible</td>
<td>Bleeding gum</td>
<td>Single lytic (1 case)</td>
<td>Skull, panoramic and periapical radiographs</td>
<td>No</td>
</tr>
<tr>
<td>Gray et al.³¹</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Swelling in the left maxilla</td>
<td>Multiple lytic (11 cases)</td>
<td>Panoramic radiographs</td>
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</tr>
<tr>
<td>Ho et al.¹⁵</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling in the mandible</td>
<td>Single lytic</td>
<td>Skull and panoramic radiographs</td>
<td>No</td>
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<tr>
<td>Mozaffari et al.¹⁶</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling</td>
<td>Multiple lytic (11 cases)</td>
<td>Panoramic radiographs</td>
<td>Yes</td>
</tr>
<tr>
<td>Anacak et al.¹⁷</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling in the mandible</td>
<td>Single lytic</td>
<td>Panoramic radiograph</td>
<td>No</td>
</tr>
<tr>
<td>Author</td>
<td>Study type</td>
<td>Sample size/number of patients with oral manifestations</td>
<td>Symptom</td>
<td>Clinical sign</td>
<td>Imaging aspects of lesions</td>
<td>Type of image</td>
<td>First detected sign of MM</td>
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<tr>
<td>Lae et al. \textsuperscript{18}</td>
<td>Case series</td>
<td>12/12</td>
<td>None</td>
<td>Swelling</td>
<td>Multiple lytic</td>
<td>Panoramic radiograph</td>
<td>No</td>
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<tr>
<td>Vucicevic-Boras et al. \textsuperscript{13}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
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<tr>
<td>Baykul et al. \textsuperscript{19}</td>
<td>Case report</td>
<td>1/1</td>
<td>Paresthesia in the mandible</td>
<td>None</td>
<td>Multiple diffuse lytic punch-out</td>
<td>Panoramic and periapical radiograph CT CT</td>
<td>Yes</td>
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<tr>
<td>Owotadeet et al. \textsuperscript{20}</td>
<td>Case series</td>
<td>30/3</td>
<td>None</td>
<td>Bleeding gum</td>
<td>Multiple lytic</td>
<td>CT</td>
<td>No</td>
</tr>
<tr>
<td>Pinto et al. \textsuperscript{21}</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Swelling</td>
<td>Single lytic</td>
<td>Periapical radiograph</td>
<td>Yes</td>
</tr>
<tr>
<td>Segundo et al. \textsuperscript{22}</td>
<td>Case report</td>
<td>1/1</td>
<td>Paresthesia in the lower lip</td>
<td>Swelling</td>
<td>Multiple lytic</td>
<td>Panoramic radiograph</td>
<td>Yes</td>
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<tr>
<td>Talamo et al. \textsuperscript{5}</td>
<td>Case series</td>
<td>170/1</td>
<td>None</td>
<td>Amyloidosis in the tongue</td>
<td>–</td>
<td>–</td>
<td>No</td>
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<tr>
<td>Shah et al. \textsuperscript{22}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling in the maxilla tooth mobility</td>
<td>Single lytic</td>
<td>Panoramic radiograph</td>
<td>Yes</td>
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<tr>
<td>Ghosh et al. \textsuperscript{24}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling</td>
<td>Lytic</td>
<td>Skull and panoramic radiographs</td>
<td>Yes</td>
</tr>
<tr>
<td>Vinayachandran and Sankarapandian \textsuperscript{25}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling</td>
<td>Single lytic</td>
<td>Panoramic radiograph CT</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardoso et al. \textsuperscript{26}</td>
<td>Case series</td>
<td>5/5</td>
<td>Pain Disphagia Paresthesia Lip anesthesia</td>
<td>Swelling</td>
<td>Multiple lytic (1 case) Single (4 cases)</td>
<td>Panoramic, CBCT, periapical radiographs and MRI</td>
<td>No</td>
</tr>
<tr>
<td>Troeltzsch et al. \textsuperscript{27}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Tooth mobility in the mandible Ulcerated lesion Swelling Trismus</td>
<td>Single lytic Root resorption Single lytic</td>
<td>Non specified CT MRI</td>
<td>No</td>
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<tr>
<td>Zhao et al. \textsuperscript{6}</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Swelling in the maxilla tooth mobility</td>
<td>Punch-out</td>
<td>Panoramic radiograph CT</td>
<td>Yes</td>
</tr>
<tr>
<td>Ramaiah et al. \textsuperscript{1}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Gingival swelling and tooth mobility</td>
<td>None</td>
<td>Skull radiograph</td>
<td>Yes</td>
</tr>
<tr>
<td>Jain et al. \textsuperscript{5}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling in the maxilla Tooth mobility</td>
<td>Single lytic with resorption of the floor of the maxillary Sinus Multiple lesions punch-out</td>
<td>Panoramic radiograph CT MRI</td>
<td>Yes</td>
</tr>
<tr>
<td>Kasamatsu et al. \textsuperscript{13}</td>
<td>Case report</td>
<td>1/1</td>
<td>None</td>
<td>Swelling in the mandible Amyloidosis</td>
<td>Single lytic in the right mandibular ramus</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sreeja et al. \textsuperscript{32}</td>
<td>Case report</td>
<td>1/1</td>
<td>Pain</td>
<td>Swelling in the mandible</td>
<td></td>
<td>Panoramic radiograph</td>
<td>Yes</td>
</tr>
<tr>
<td>Fregnani et al. \textsuperscript{34}</td>
<td>Case report</td>
<td>1/1</td>
<td>Trismus Paresthesia</td>
<td>Swelling in the mandible</td>
<td></td>
<td>Panoramic radiograph</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Patients may present more than one oral manifestation.

MM: multiple myeloma; CT: Computed tomography; CBCT: cone beam computed tomography; MRI: Magnetic resonance imaging; NS: not specified.
Oral manifestations which may be explained by shows the type
of image used in each study and the reported findings. The
figures 29–49 of the papers included in this review, but other imaging exams
such as computed tomography, intraoral radiographs, conventional craniofacial radiographs and magnetic resonance imaging were also reported. The panoramic radiograph is a
common method for screening bone alterations of the jaws,
but computed tomography has some advantages over radiographic examinations because of its tri-dimensional aspect
and more accurate differentiation of tissue types, without
superimposed overlying anatomy and no secondary and dif-
fuse radiation degradation.

Most of the reported bone lesions were associated to clinical swelling,1,8,9,12,13,15–26,31–34 which may be explained by
tumor expansion with neoplastic plasma cell activity in the
bone.15 It may be assumed that swelling is a late stage of jaw
lesions, after the tumor has expanded. Since more cone beam
computed tomography images are being performed for den-
tal treatment nowadays, it is possible that early lesions of MM
will be detected.

Hemorrhagic episodes are observed in 15–30% of MM
patients.35 In the present review, bleeding gums were reported
in nearly 10% of the reported cases. Thrombocytopenia can
cause major bleeding, but there may also be local causes for
bleeding such as periodontal disease.

MM is a hematologic malignancy characterized by the pro-
lifeation of clonal plasma cells in the bone marrow and
secretion of a monoclonal protein (M-pts) in the serum and/or
urine.4 Commonly, tumoral cells secrete intact monoclonal
immunoglobulin (heavy and light chains) with the most com-
mon isotypes involved in MM being immunoglobulin (IgG, IgA
and light chains kappa or lambda).7 Besides myeloma, other
monoclonal gammapathies and intermediary pre-malignant
states, such as MGUS, smoldering myeloma (SMM), light
chain amyloidosis and Waldenstrom macroglobulinemia,represents distinct entities with diagnostic criteria defined by
the International Myeloma Working Group (IMWG).2 The most
prevalent of the gammapathies is MGUS, affecting about 3%
of the over 50-year-old population. In spite of this, long-
term follow up studies have shown that only one-third of
the patients will progress to MM, amyloidosis, Waldenstrom
macroglobulinemia or other lymphoproliferative disorders in
30 years.36

Primary amyloidosis is a distinct entity characterized by a fibrillar ultrastructure deposit in target tissues (e.g. heart, kidney, nerves, liver, mucosa and gut) which may represent
a single entity or, in nearly 10% of the cases, it may be part
of a syndrome, overlapping MM.1 Oral manifestations
have been reported to affect one third of the patients with
amyloidosis.9 In the cases reported by the studies of this
review, amyloidosis was present in 11.1% of the MM cases.
When an amyloid deposit is in the tongue it may result in
macroglossia.37 The enlarged tongue caused by amyloid
Neurological complications may also occur due to swelling on the borders of the tongue and open bite marks. If the tongue becomes too big to fit inside the mouth, it may become dehydrated, and present ulcerations with secondary infection. In cases of severe macroglossia, airway obstruction may occur. Neurological complications may also occur due to amyloid infiltration of the nerves.

Most of the oral conditions found in patients with MM are not specific, so the differential diagnosis with other oral conditions and with manifestations of systemic diseases is important. Other oral conditions that have been reported in these patients are less frequently described and may not be directly associated to MM. Once the diagnoses of oral lesions are clarified, patients are referred to the proper specialist for further investigation and management of the condition.

In many studies, oral conditions were the first detected sign of MM. In other studies, oral manifestations of MM were detected during the patient's follow up and dentists were able to participate in the diagnosis of the oral condition. These patients need to be followed by a multidisciplinary team, who may improve their quality of life. Besides contributing to the diagnosis, dentists in the team need to take care of the dental health to prevent further complications, especially in patients who are candidates for antiresorptive therapy.

Some limitations were found during the review process. After applying study criteria, there were only case reports and case series in this review. Thus the incidence and prevalence of the oral manifestation could not be estimated. The absence of longitudinal and epidemiological studies on oral features of MM hampers the development of a meta-analysis. Future cross-sectional and longitudinal studies should be carried out to observe the prevalence and incidence of oral manifestations of MM, as well as the relationship of these findings with the prognosis of the condition.

The second limitation of this study is related to the imaging exams. Imaging was poorly described in many studies, and no description was available in some. Another difficulty was to compare the different types of imaging exams used, as recent studies used computed tomography scans, while in the past only radiographic examinations were used.

MM develops mainly in individuals aged 50–80 years. Thus, it is important that dentists are aware of clinical and imaging changes suggestive of MM lesions in patients of this age group. Dentists should be encouraged to detect oral manifestations of MM in routine examinations early. In this way, they will be contributing to increased survival and better prognosis.

**Conclusions**

Swelling was the most common oral manifestation of MM and osteolytic lesions of the jaws were the most common radiographic sign. Dentists should be aware of the clinical and imaging signs of MM in the jaws, so that early diagnosis of oral lesions can be reached and patients referred for treatment.

**Acknowledgements**

This research was supported by Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) JCNE E-26/103.046/2012, grants to Dr. Sandra R. Torres.

**References**


