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ORIGINAL ARTICLE

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Role of oral examination in newly diagnosed multiple myeloma patients: A safe and simple way to detect light chain amyloidosis

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Abstract

Objective: Up to 30% of multiple myeloma (MM) patients have subclinical amyloid deposits. These patients are under-recognized and are more susceptible to drug toxicity, bleeding and death. Early diagnosis and adjustment of treatment are crucial. Biopsies of oral mucosa might be a potentially useful diagnostic tool. The objective of this study was to assess the prevalence and characteristics at presentation of oral amyloidosis in a large cohort of MM patients.

Methods: The prevalence and characteristics of oral amyloidosis in a large cohort of MM patients who were referred for oral evaluation before and during bisphosphonate therapy were assessed, retrospectively.

Results: Among 212 patients analysed, 13 (6%) were diagnosed with concomitant light chain (AL) amyloidosis. In 54% (n = 7), lesions in the oral cavity compatible with amyloid deposition were detected by examination.

Conclusions: The salient feature of this study is the high prevalence of oral manifestations among MM patients with amyloidosis. These results highlight the value of routine oral cavity examination and biopsy as a safe and simple method for detecting light chain amyloidosis.

KEYWORDS

amyloidosis, multiple myeloma, oral manifestation

1 | INTRODUCTION

Multiple myeloma (MM) is characterized by the proliferation of malignant plasma cells derived from a single clone in the bone marrow. It accounts for 13% of all haematologic cancers and is the second most common haematologic malignancy (Ludwig et al., 2010; Raab, Podar, Breitkreutz, Richardson, & Anderson, 2009; Rajkumar, 2009). The median age of patients at diagnosis is approximately 65 years (Kyle et al., 2003). Common clinical features of MM are bone pain and pathologic fractures secondary to lytic lesions, renal failure, fatigue secondary to anaemia and recurrent infections (Lin, 2009).

The prognosis of MM has gradually improved from an estimated median overall survival of 7 months in the prechemotherapy era, to a median overall survival of 24–30 months following the introduction of high-dose chemotherapy with autologous stem cell transplantation (ASCT) (van de Donk & Lokhorst, 2013). The introduction of novel agents, including immunomodulatory drugs (thalidomide, lenalidomide and pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib), has dramatically expanded the therapeutic

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armamentarium for myeloma. Currently, median survival exceeds 60 months with these novel agents (Brenner, Gondos, & Pulte, 2008; Kumar et al., 2008; Ludwig, Hajek, & Tóthová, 2009; Palumbo & Anderson, 2011).

According to current guidelines, ASCT is recommended for any myeloma patient younger than 65 years of age, following induction therapy with immunomodulatory agents/proteasome inhibitors. Accordingly, eligible patients receive induction treatment for a period of 4–6 months and are subsequently treated with high-dose melphalan followed by ASCT (Kumar et al., 2017).

Some myeloma patients have concomitant amyloidosis, a term used to describe extracellular deposition of abnormal monoclonal immunoglobulin (Ig) light chains (LC). This complication results from changes in the secondary or tertiary structures of the monoclonal protein. This conformational change is responsible for abnormal folding of the LC, rich in β leaves, which assemble into monomers that stack together to form amyloid fibrils (Desport et al., 2012).

Despite impressive therapeutic advances in the field of MM, under-recognition of subclinical amyloidosis may result in suboptimal care and poor transplantation outcomes. For example, MM patients demonstrating cardiac amyloidosis or involvement of more than two organs represent a group with higher mortality risk during ASCT. These patients might need smaller doses of melphalan conditioning to avoid severe complications after ASCT (Comenzo & Gertz, 2002). Moreover, patients with cardiac involvement should be monitored for life-threatening bradycardia if they are treated with thalidomide (Palladini et al., 2001, 2005). Therefore, early diagnosis of AL amyloidosis in the setting of MM is crucial, especially when making therapeutic decisions regarding the choice of induction therapy or the intensity of the conditioning regimen.

The nonspecific and often vague nature of symptoms associated with AL amyloidosis frequently leads to delays in diagnosis such that organ dysfunction is advanced by the time treatment is initiated. Moreover, it is well known that lambda chain (LC) is two to four times more amyloidogenic than kappa LC (Husby, 1983). Accordingly, screening for amyloidosis should be considered in asymptomatic MM patients having a lambda monoclonal component, or in patients with unexplained proteinuria, cardiomyopathy, neuropathy or hepatomegaly, and patients with MM and atypical manifestations.

It is not always possible to biopsy the affected organ in cases with overt signs and symptoms of amyloidosis. In this scenario, it is advised to screen for amyloidosis by blinded sampling, such as fat pad biopsy. Some physicians use a similar strategy in asymptomatic patients with a lambda monoclonal component.

Although 12%–15% of MM patients develop overt clinical amyloidosis during the course of their disease, up to 30% have subclinical amyloid deposits in subcutaneous fat pad aspirates, bone marrow biopsies and biopsies of other vital organs such as the heart, liver and kidneys (Desikan et al., 1997; Gertz, Lacy, & Dispenzieri, 1999; Rajkumar, Gertz, & Kyle, 1998). These patients are prone to bleed due to vascular wall amyloid deposition, amyloid affinity for clotting factors and interference of fibrin formation (Gamba et al., 2000; Sucker, Hetzel, Grabensee, Stockschlaeder, & Scharf, 2006). Thus, simple and safe methods for amyloid screening are desirable. Biopsies of oral mucosa might represent a potentially useful diagnostic tool.

To the best of our knowledge, studies of oral amyloidosis as a manifestation of MM are rare. The few studies we found were mostly case reports or involved small patient samples, in which mucosal colour changes, yellow or orange papules, nodules, plaques and macroglossia were described (Aono, Yamagata, & Yoshida, 2009; Silva et al., 2015). Less common oral manifestations of amyloidosis, such as haemorrhagic bullae, ulcerations, bruising, haematoma/ecchymosis and tongue necrosis were described. These were associated with pain, burning sensation and dysphagia. (Elad et al., 2010; Lin, Wang, Collins, & Stone, 2011; Viggor et al., 2009.

In a small, retrospective study, AL amyloidosis was detected in 18 of 34 MM or monoclonal gammopathy of unknown significance (MGUS) patients based on biopsies of labial salivary glands (LSG), bone marrow and skin due to clinical suspicion of the condition. The sensitivity for detecting amyloid deposition was highest in biopsies of LSG at 89%, followed by 77% for bone marrow, and 72% for skin (Suzuki et al., 2016). A prospective study found evidence of amyloid deposition in LSG of 2 of 11 MM patients, but not in abdominal fat pad or tongue samples (Stoopler et al., 2011).

This study assessed the prevalence and characteristics at presentation of oral amyloidosis in a large cohort of MM patients who were referred for oral evaluation before and during bisphosphonate therapy.

2 | MATERIALS AND METHODS

2.1 | Population

The study population included all patients with a diagnosis of MM who were examined at the Oral and Maxillofacial Department of the Chaim Sheba Medical Center, Tel Hashomer, Israel, from 2003 to 2016. All patients were diagnosed and treated at the Hemato-Oncology Department of the same institution. Patients were referred for oral and dental evaluation before bisphosphonate therapy. The diagnosis of MM was based on the 2014 International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma (Rajkumar et al., 2014). Patients without a definitive diagnosis of MM or with insufficient clinical data were excluded from the study.

2.2 | Study design

This was a retrospective, cross-sectional, medical record review. We benefited from our institutional protocol requiring each patient to be evaluated by an oral medicine specialist before starting bisphosphonate treatment.

Demographic and medical data were recorded. MM data included date of diagnosis, disease stage and cytogenetic results from FISH analysis, chemotherapeutic and other medical treatments, and autologous bone marrow transplantation.

TABLE 1 Demographic characteristics[a]

Characteristic	Study population (*N* = 212)	Amyloidosis (*N* = 13)	No amyloidosis (*N* = 199)
Gender (% male)	52%	62%	51%
Age at diagnosis, years (mean and range)	60.2 (39–88)	57 (47–73)	60.4 (39–88)
Ethnicity			
Ashkenazi Jews	54%	50%	54%
North African Jews	44.5%	50%	44.5%
Muslim Arabs	1.5%	0	1.5%
Christian Arabs	0	0	0
Druze	0	0	0

Note. [a]*P*-value for all intergroup differences > 0.05.

Clinical evaluation of the oral cavity for amyloidosis was part of routine patient care. All patients were evaluated by the same oral medicine specialist (NY) under standard clinical conditions using standard dental office lighting, dental mirror and gauze. Oral mucosal findings including colour, texture, shape and consistency of the tongue were recorded. Incisional biopsies (depth of about 3–5 mm) were taken from any suspected lesion (e.g., induration of the tongue and other oral soft tissues, and indentations on the lateral border of the tongue), according to the specialist's discretion.

The diagnosis of amyloidosis was established by histologic examination with Congo red staining.

The study was approved by the Sheba Medical Center International Review Board for Human and Animal Trials-Helsinki Committee on 5 November 2015, number 2486-SMC.

2.3 | Data analysis

Fisher's exact test and chi-square test were used to analyse intergroup differences, with $p < 0.05$ as the threshold for statistical significance. Statistical analysis was performed using SPSS software.

3 | RESULTS

A total of 212 patients met the inclusion criteria. The study population was balanced with respect to gender (52% males). The mean age at diagnosis was 60 years.

Thirteen patients (6%) were diagnosed with amyloidosis as well. In this subpopulation, 62% were male with a mean age slightly younger than that of the entire study population. No statistically significant differences in demographic characteristics were found (Table 1).

Oral findings consistent with amyloidosis were present in seven of these 13 patients (54%). These cases had histologic confirmation of amyloid deposits (*five from biopsy of oral lesions, one from the abdominal fat pad and one from synovial knee articulation*).

Oral manifestations mainly involved the tongue ($n = 5$) with either macroglossia, teeth indentations on the lateral borders (Figure 1a,b), or rubbery or firm consistency of the tongue. One patient presented with petechial and ecchymoses in the oral cavity and skin of the head and neck, and one had an amyloidoma in the oropharynx. None of the patients had salivary gland symptoms such as xerostomia that may indicate salivary gland involvement (Table 2).

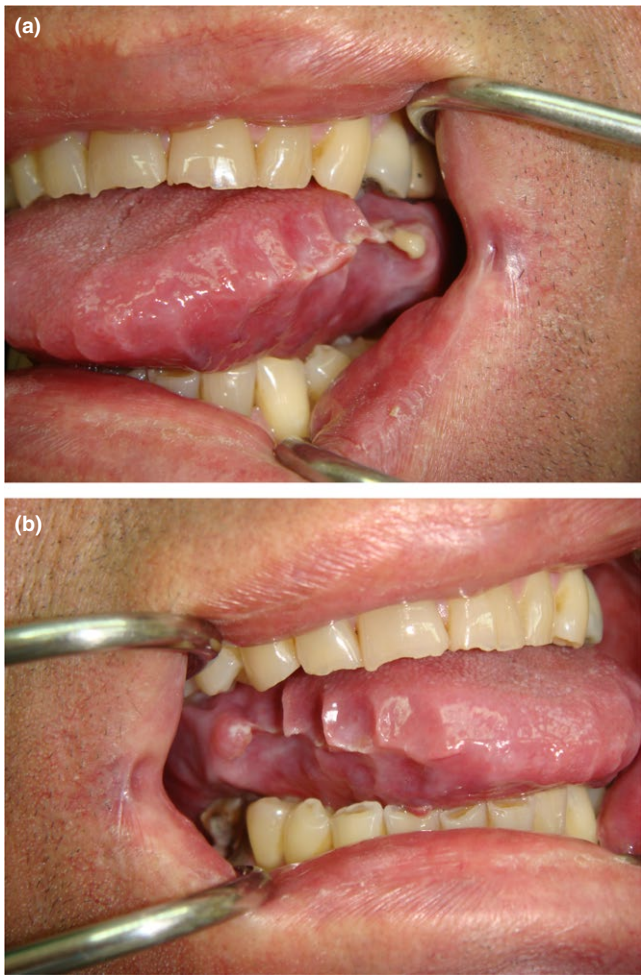

FIGURE 1 Enlarged and indurated tongue in a patient with MM and amyloidosis. Note the pronounced indentations of the lateral borders of the tongue (a—left, b—right)

TABLE 2 Patients diagnosed with oral amyloidosis

Patient number	Sex	Age at MM diagnosis	Years between MM and amyloidosis diagnoses	Bone marrow transplantation	Site of amyloidosis diagnosis	Oral presentation	Oral Symptoms
1	F	64	0	No	Skin, abdominal fat pad	Petechiae in oral cavity mucosa and in head and neck skin	Oral cavity bleeding
2	M	50	0	Yes	Tongue	Indurated, enlarged tongue	Minor speech difficulties
3	F	67	0	Yes	Soft palate	Amyloidoma in the oropharynx	No further complaint after lesion removal
4	F	73	0	No	Tongue	Indurated tongue, thickening of buccal mucosa	Difficulties opening mouth and chewing
5	M	57	14	Yes	Tongue and buccal mucosa	Enlarged tongue, partially indurated	Swallowing and speech difficulties
6	M	50	8	Yes	Tongue	Enlarged tongue and lips	Speech difficulties, sleep disturbances
7	M	55	0	Yes	Synovial knee articulation	Enlarged tongue	Minor speech difficulties

The six patients with no oral manifestations were followed by a haematologist, nephrologist or cardiologist. Amyloidosis was detected in fat pad (n = 1), kidney (n = 1), bone marrow (n = 1) and endocardium (n = 3). One patient with cardiac involvement showed intestinal compromise as well.

4 | DISCUSSION

Advances in MM treatment in the last two decades have been unprecedented. Although the introduction of novel drugs has significantly prolonged progression-free survival (PFS) and overall survival, the disease remains incurable. Concomitant AL amyloidosis worsens the prognosis and impacts therapy; thus, early diagnosis is crucial (Roy & Roy, 2006). The salient feature of this study is the high prevalence (54%) of oral manifestations among MM patients with amyloidosis.

The lethal consequences of AL amyloidosis are due to toxic protein deposition and not to malignant behaviour of the plasma cell clone. Early and accurate diagnosis is the key to effective disease management. Furthermore, treatment of the plasma cell dyscrasia should be modified according to the presence or absence of amyloidosis, which affects the intensity of the conditioning regimen. In addition, the presence of amyloidosis requires more intensive cardiac monitoring, including echocardiography and troponin and BNP plasma levels.

About 15% of myeloma patients develop overt clinical amyloidosis during the course of their disease. MM patients are not routinely screened for amyloidosis. Rather, the search for amyloidosis is initiated when a suspicion arises based on clinical observation. Tissue biopsies are required to establish the diagnosis of amyloidosis, and biopsy sites that have been suggested to provide a good predictive value include subcutaneous abdominal fat (Duston, Skinner, Shirahama, & Cohen, 1987), the kidneys (Osawa et al., 2004) and the rectum (Hachulla & Grateau, 2002).

Abdominal fat represents an accessible source for a less invasive biopsy. It is specially recommended either for those asymptomatic cases of monoclonal gammopathy lambda LC-related, or for suspected compromise of organs that are difficult to reach (i.e. heart, kidney).

Given our results, combined with the ease of surgical access and the minimal risk of bleeding, as compared to that from internal organs, biopsy of oral mucosa may represent a potentially another useful tool for detection of amyloidosis in MM patients. As mentioned, controversy still exists in the literature regarding the yield of the biopsy from specific oral sites, such as LSG (Stoopler et al., 2011; Suzuki et al., 2016). Delgado and Mosqueda (1989) reported 100% sensitivity in 19 patients, whereas Caporali et al. (2008) showed only 20%. This may be explained by differences in the study design (routine biopsies versus biopsy from suspected oral lesions) and populations (MM or MM with light chain amyloidosis).

The aim of the current study was to assess the prevalence and characteristics at presentation of oral amyloidosis in a large cohort

of MM patients. Suspected systemic amyloidosis was not a prerequisite for referral for oral evaluation, as patients were referred for clearance before bisphosphonate therapy.

According to our results, half of the patients with amyloidosis exhibited oral mucosa manifestations, and the tongue was almost invariably involved. Moreover, oral findings clinically suspected as amyloidosis were confirmed by pathologic analysis in all cases.

Interestingly, petechial haemorrhage was observed in one patient. This patient did not have thrombocytopenia. Severe, symptomatic thrombocytopenia is unusual as a presenting feature in MM or amyloidosis. The cause of petechiae in amyloidosis patients is usually monoclonal autoantibodies to factor X. In rare cases of thrombocytopenia, it is impossible to distinguish between amyloidosis and myeloma-induced thrombocytopenia. A biopsy can help rule out amyloidosis as an aetiology.

Considering the prevalence of oral amyloidosis found in our series, we suggest routine oral examination by a specialist and biopsy of any detected abnormality (including macroglossia) in all newly diagnosed MM or lambda light chain-based gammopathy patient.

5 | CONCLUSION

The results presented here highlight the value of routine oral cavity examination and biopsy of any suspected lesion as a safe and simple tool for diagnosing systemic AL amyloidosis.

CONFLICTS OF INTEREST

None to declare.

AUTHORS' CONTRIBUTION

Merav Leiba, Adrian Duek and Noam Yarom were responsible for the study design; acquisition, analysis and interpretation of data, and drafting and revising the manuscript. Suha Jarjoura and Waseem Abboud were responsible for the study design, acquisition of data and revising the manuscript. Arnon Nagler and Ran Yahalom participated in designing the study and revising the manuscript.

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