

Research Article

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Macroglossia as the first clinical manifestation of systemic amyloidosis associated with multiple myeloma and a literature review

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Clinical practice points

- Macroglossia as initial clinical presentation in systemic amyloidosis is rare.
- We report a case of systemic AL amyloidosis characterized by painless progressive tongue enlargement.
- Systemic AL with macroglossia as a clinical manifestation was associated with MM and clinicians should be aware of it.

Abstract

Objective: To report a case of systemic amyloidosis manifested as macroglossia and summarize review its current literature.

Methods: First, we retrieved patient's disease data from the West China Hospital, Sichuan University, electronic medical record system. For the literature review, we searched Cochrane, Web of Science, PubMed, and EMBASE for relevant articles published from January 1, 1947, to December 31, 2020.

Results: A 43-year-old Chinese Han female patient was presented with tongue painless progressive enlargement. The tongue biopsy showed amyloid by Congo red staining, and the bone marrow aspiration revealed a large clonal plasma cells' number (39%). The systematic examination results revealed extremities thickened skin. The patient was diagnosed with systemic lambda light chain amyloidosis associated with multiple myeloma and received cyclophosphamide combined with bortezomib and dexamethasone. During the 8-month follow-up, symptoms were relieved without recurrence. We found 12 reports describing 19 Amyloid light-chain (AL) amyloidosis patients with multiple myeloma (11 females, 57.89%) in the literature search. The first symptom was macroglossia in all patients. Detailed immunoglobulin light chain analysis was performed in nine patients, with lambda being predominant.

Conclusion: Systemic AL amyloidosis with macroglossia is often associated with multiple myeloma occurrence, and its clinical prognosis is extremely poor. Also, it can be a multiple myeloma paraneoplastic phenomenon and should be watched in clinical practice.

Keywords: Macroglossia; Systemic amyloidosis; Immunoglobulin light chain; Multiple myeloma; Paraneoplastic.

Introduction

Systemic amyloidosis comprehends a group of rare diseases caused by misfolded proteins deposition outside tissue cells, leading to multiple organ dysfunction, failure, and even death [1]. According to the precursor protein type, amyloidosis can be divided into immunoglobulin light chain, amyloid protein A, transthyroxine protein, apolipoprotein A-I, and lysozyme types [2]. Among them, systemic light-chain (AL) amyloidosis is the most common, accounting for 55-65% of all cases in the UK and even 93% in Chinese amyloidosis patients [3,4].

AL amyloidosis is associated with clonal plasma cell proliferative disorders - the amyloid material being formed by misfolding of monoclonal immunoglobulin light chains [3,5]. This amyloidosis tends to occur in middle-aged and elderly patients, the male/female ratio is about 2-3:1, and the median survival time is 36.3 months. Diagnosis is often based on clinical manifestations combined with pathological biopsy [3]. Relevant tissue biopsies should be performed as soon as amyloidosis is highly suspected clinically.

Systemic AL amyloidosis is clinically heterogeneous and often involves organ systems such as kidneys, heart, gastrointestinal tract, liver and spleen, and peripheral nerves, with rare tongue cases as well [1,3]. The classic amyloid deposition manifestation in the oral cavity is macroglossia or buccal mucosa nodular hyperplasia, and, once present, is often instructive for diagnosis [1]. A previous study has shown that the presence of Multiple Myeloma (MM) accounted for 15% of AL amyloidosis patients [6]. However, systemic amyloidosis with MM in which macroglossia is the initial clinical feature is very rare in clinical practice. In this study, we reported a patient with macroglossia as the first manifestation, in whom AL amyloidosis combined with MM was considered for diagnosis. Finally, we also conducted a literature review on this matter.

Materials and methods

The patient's medical records, including history, physical examination, and laboratory tests were collected. A biopsy of the tongue was obtained and stained with Hematoxylin-Eosin and Congo red. We also searched Cochrane, Web of Science, PubMed, and EMBASE for relevant articles published from January 1, 1947, to December 31, 2020. The following terms were used in the literature search: "tongue" and "amyloidosis" and "myeloma multiple", "Plasma Cell Myelomas", "Myelomatoses", "Myelomatosis" "Plasma-Cell Myelomas". The inclusion criteria for this literature review include English case reports and case series published between January 1947, and December 2020, reporting information on systemic amyloidosis with MM with macroglossia as the first clinical manifestation. We excluded articles about limitations and secondary amyloidosis case studies. According to requirements, we obtained written informed consent from the patient included in this study.

Results

Case presentation

A 43-year-old Chinese Han female present to our hospital complaining tongue painless progressive enlargement that had appeared 2 years ago. The patient had been surgically treated with resection in a local hospital in 2018 but recurred in 2019.

Since 2019, the patient presented progressive tongue mass growth with difficulties extending her tongue, occasional lower limb acid swelling discomfort, and had lower limb numbness discomfort at night. She did not report any alterations in appetite, sleeping, or weight.

The patient was neither a smoker nor a drinker and her medical history was unremarkable. Regarding first-degree relatives, the patient's eldest sister had thyroid cancer, and the second had passed away due to a bladder tumor. However, other relatives, including parents, were healthy.

Physical examinations revealed an enlarged tongue with visible swelling around the lip (Figure 1A and B). Multiple masses were palpable submandibular with indistinct borders, hard and without significant tenderness. Multiple enlarged lymph nodes were palpable in the axillae bilaterally, and the extremities' skin was tight.

Her blood routine and liver and kidney function tests were within normal ranges. Blood immunofixation electrophoresis showed that the λ light chain M protein was positive, urine λ light chain was 9.85 g/L, and urine κ light chain was 0.0449 g/L. Bone marrow aspiration showed clonal plasma cells that accounted for 39%, and immunophenotyping showed infiltrating plasmacytoid cells CD38 (+), CD138 (-), CD56 (-), Ig κ (-), and Ig γ (+). Eosinophilic material deposits, within the muscle fibers and interstitium, few hyperplastic fibroblasts and positive Congo red staining were seen on the tongue biopsy (Figure 1C and D). Therefore, amyloidosis was considered.

Finally, the patient was diagnosed with AL amyloidosis associated with MM. Then, she received cyclophosphamide (0.4 g/week), bortezomib (1.3 mg/week), and dexamethasone (15 mg twice a week) combined treatment. During the 8-month follow-up, her tongue was smaller and the clinical symptoms improved.

Literature review of macroglossia as the first symptom of systemic amyloidosis complicating MM.

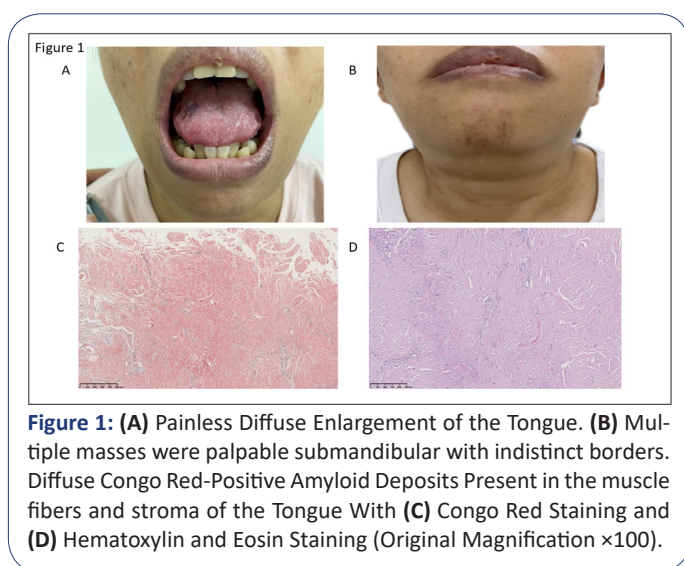
We screened 1782 articles in this literature review, and only 12 were eligible (Table 1). We found 19 relevant cases, including the one that we reported in this study. Among the 19 patients, 8 (42.11%) were male and 11 (57.89%) female. The mean patients' age was 66.13 years for males and 69.7 years for females. Disease duration ranged from 1-60 months. The most frequently reported countries were the United States and the Netherlands (four patients each), followed by Israel (2), India (1), Chile (1), Brazil (1), Ireland (1), Turkey (1), and China (1).

Bone marrow aspiration was performed in all patients. Seventeen had a tongue biopsy, and one had a renal biopsy. One died quickly and did not have a tongue biopsy. All patients with tongue biopsy showed positive Congo red staining. Immunohistochemical analysis was performed in 11 cases, and the light chain type was reported in nine of them (five with λ , three with κ , and one with both λ and κ). In the remaining two cases, only the light chain protein presence was reported, without specific typing analysis. Most patients (18/19) had MM, and, in 11/19 cases, the Bence-Jones protein was found in blood or urine.

In all reported cases, in addition to tongue involvement, other organs were involved including the heart (5), kidney (3),

Table 1: Literature review.

Years	Disease duration	Sex	Age	Nation region	Bence-Jones protein	Light chain	Other organs and presentations involved	Therapeutic regimen treatments	Outcome
	course month								
1947 [7]	18	M	72	US	+	NA	NA	NA	NA
	60	M	63	US	—	NA	NA	NA	NA
1957 [8]	NA	F	60	NA	+	NA	Joint	NA	Death
	NA	F	68	NA	+	NA	NAe	NA	Death
1985 [9]	2	F	75	NA	+	κ	Heart	CTX, MP	Death
1990 [10]	3	F	55	India	+	κ	Kidney, Joint	Melphalan	Death
1994 [11]	NA	M	65	US	+	κ	NA	NA	NA
2002 [12]	NA	F	82	Netherlands	NA	λ	NA	Chemotherapy	Improve
	NA	F	80	Netherlands	NA	λ	Skin, Heart	Chemotherapy	Death
	NA	F	77	Netherlands	NA	λ	Heart, Intestinum tenue	Chemotherapy	Death
	NA	F	73	Netherlands	NA	λ	Heart, Skin	Chemotherapy	Death
2005 [13]	NA	M	69	Ireland	+	NA	NA	Melphalin and prednisone	Death
2010 [14]	9	M	62	Israel	+	κ	Skin, Nerves, Kidneys	bone marrow transplantation	Death
	36	M	65	Israel	+	κ, λ	Digestive tract	surgical resection	Death
2017 [15]	6	F	54	Turkey	NA	NA	Kidney	Chemotherapy	Death
2018 [16]	12	M	75	Brazil	+	NA	Nerve	NA	Death
2018 [17]	1	F	73	Chile	+	NA	Kidney	Hemodialysis, chemotherapy	Death
2018 [18]	NA	M	58	US	+	λ	Heart	Botizomide, lenamide dexamethasone, AHSCT	Improve
2020(Our's)	24	F	43	China	+	λ	None	Bortezomib, CTX	Improve



gastrointestinal tract (3), skin (2), muscles (1), and joints (1). Ten patients received chemotherapy, 1 received dialysis treatment combined with chemotherapy, 1 received surgery, and 1 received bone marrow transplantation. However, in 3 cases, the treatment regimen and prognosis were not reported. Finally, only 2 patients died during the follow-up.

Discussion

AL amyloidosis is the most common systemic amyloidosis and its clinical presentations are highly heterogeneous and largely depend on the organs affected. Compared with the heart and kidneys, soft tissues (e.g. tongue) are less affected.

The most common amyloid deposition site in the oral cavity is the tongue, and typical manifestations usually include yellow changes, papules, nodules, plaques, and macroglossia [12]. The case described in this study is mainly characterized by painless tongue enlargement, and tongue amyloidosis combined with MM.

A previous study has shown that 21% (4/191) of AL amyloidosis and MM patients developed macroglossia [19]. Nevertheless, there are few studies on tongue manifestations of AL combined with MM. Therefore, we reviewed studies with AL patients combined with MM using macroglossia as the initial clinical manifestation and mainly found case reports. In our review, λ was the main light chain type among AL-MM patients with macroglossia as the first manifestation, and most clinical outcomes were not good. These suggested that complete examinations such as bone marrow puncture and tongue biopsy should be performed as soon as possible in those patients, to not delay MM diagnosis and treatment.

Tongue amyloidosis might be regarded as a plasma cell ma-

lignancy paraneoplastic phenomenon [12]. A previous study found that 7 of 11 patients with oral (tongue and oral mucosa) amyloidosis were diagnosed with MM and that 3 patients had monoclonal gammopathy of undetermined significance [12]. Also, Xu et al. studied 158 patients with MM and found that AL amyloidosis was a poor independent prognostic factor [20]. In this study, 31% (49/158) of patients were diagnosed with AL amyloidosis. The main organs involved were the kidney (36, 73.4%) and the heart (27, 55.1%). At the same time, the survival time of MM with amyloidosis was significantly shorter compared to patients only with MM.

In our study, AL amyloidosis immunoglobulin light chains were dominated by λ light chains. A previous study has reported that in AL amyloidosis, λ immunoglobulin light chain was produced in 80% of cases and κ in the remaining 20% [21]. Also, another study has shown that the λ light chain was predominant in AL amyloidosis patients [22]. In MM, the λ type appears more than the κ type, and one study suggested that λ type MM can be an AL amyloidosis high-risk factor in the disease course [20]. This can be attributed to a greater λ chain "amyloidosis" and an imbalance in the speed of light chain removal and deposition [22,23]. However, liver involvement and severe renal impairment were more frequently found in κ amyloidosis than in λ [24]. Moreover, the incidence of AL amyloidosis in κ type MM was lower but more severe compared to λ MM [25].

Conclusion

Compared with the heart and kidneys, tongue amyloid involvement is rare and does not often attract attention from clinicians. However, in our study, systemic amyloidosis with macroglossia as the first clinical manifestation was mostly complicated by MM (18/19) and had poor outcomes. Mega tongue-like systemic amyloidosis is not frequently considered first as systemic amyloidosis or MM in clinical practice. Diagnosis can only be confirmed when the disease progress to late stages, likely causing irreversible consequences. Therefore, we hope that our research will improve the understanding of patients with macroglossia as the first manifestation, and enhance the use of complete tongue biopsy and bone marrow aspiration, as well as the screening of serum protein electrophoresis or urine Bence-Jones protein, to achieve early diagnosis and intervention.

Disclosure: The authors have stated that they have no conflicts of interest.

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