Clinica Chimica Acta 494 (2019) 112–115

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Case report

Ptosis and macroglossia in a woman with systemic light-chain amyloidosis

Po-Jen Hsiao[a,b,c,*,1,2], Ya-Chieh Chang[a,b,1], Yuan-Heng Tsao[d,e], Kun-Lin Wu[a,b], Yung-Hsi Kao[c], Jenq-Shyong Chan[a,b], Chih-Hung Wang[d], Yen-Yue Lin[c,f], Chih-Pin Chuu[g,h,2], Yaoh-Shiang Lin[d,i,2]

[a] Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[b] Division of Nephrology, Department of Internal Medicine, Taoyuan Armed Forces General Hospital, Taiwan
[c] Department of Life Sciences, National Central University, Taoyuan City, Taiwan
[d] Division of Otolaryngology-Head and Neck Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[e] Division of Otolaryngology-Head and Neck Surgery, Taoyuan Armed Forces General Hospital, Taiwan
[f] Department of Emergency Medicine, Taoyuan Armed Forces General Hospital, Taoyuan City, Taiwan
[g] Institute of Cellular and System Medicine, National Health Research Institutes, Miaoli County, Taiwan
[h] Graduate Program for Aging, China Medical University, Taichung City, Taiwan
[i] Division of Otolaryngology-Head and Neck Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

ARTICLE INFO

Keywords:
Ptosis
Macroglossia
Light-chain (AL) amyloidosis

ABSTRACT

Background: Amyloidosis is a rare and variable disease, characterized by extracellular deposits of amyloid protein in different tissues and organs. Patients may present with a range of symptoms, depending on the extent of involvement. Rapid, accurate diagnosis is still challenging in clinical practice.
Case report: A 72-y-old woman presented with a 1-y history of droopy upper left eyelid, resulting in decreased visual acuity, and progressive tongue swelling, resulting in dysarthria, dysphagia, and sleep apnea. Physical examination revealed puffy eyes, moderate swelling up to 1 cm of the upper left eyelid, swollen submental region, and protrusion of the tongue, causing an inability to close the mouth. An abnormal serum free light chain ratio implied the presence of monoclonal gammopathies, and Congo red staining revealed amyloid deposits in specimens from both the tongue and left eyelid. Therefore, a diagnosis of systemic light-chain (AL) amyloidosis was confirmed. The patient then received oral melphalan therapy and surgical intervention for macroglossia. Clinical symptoms including dysarthria, dysphagia, and sleep apnea were under control at 6-month follow-up.
Conclusions: We report an uncommon case presenting initially with both ptosis and macroglossia, for which a final diagnosis of systemic AL amyloidosis was made. Detailed history and laboratory investigation must be implemented on suspicion of amyloidosis, because early recognition of amyloid-associated diseases and appropriate treatment can improve clinical outcomes.

1. Introduction

Amyloidosis is a rare, progressive and variable group of diseases characterized by extracellular deposits of amyloid protein in different tissues and organs, which frequently affects the heart, kidneys, liver, spleen, nervous system, and gastrointestinal tract [1–3]. Amyloidosis is classified based on the precursor protein that forms the amyloid fibrils and the distribution of amyloid deposition (localized or systemic). To date, there's still no cure for amyloidosis. But early and appropriate treatment can help limit the production of amyloid protein and minimize the symptoms [1–5].

The gold standard diagnostic procedure for amyloidosis is the demonstration of apple-green birefringence from Congo red stained tissue sections [1]. Immunoglobulin light-chain amyloidosis may be associated with plasma cell dyscrasias. Over 25 proteins have been demonstrated to form insoluble amyloid fibrils, known as precursor proteins; the most common forms of amyloidosis are those caused by immunoglobulin light-chain protein (amyloid light-chain (AL) amyloidosis), mutant transthyretin protein (familial amyloidosis (ATTR)), and serum amyloid A protein (amyloid A (AA) amyloidosis) [1–3]. The age-adjusted incidence of primary and secondary systemic amyloidosis is estimated to be 5.1–12.8 cases per million person-years, with primary

* Corresponding author at: Division of Nephrology, Department of Medicine, Tri-Service General Hospital, Number 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan.
E-mail address: a2005a660820@yahoo.com.tw (P.-J. Hsiao).
[1] These authors contributed equally to this work (co-first author).
[2] These authors also contributed equally to this work (co-corresponding author).

https://doi.org/10.1016/j.cca.2019.03.1624
Received 23 February 2019; Received in revised form 19 March 2019; Accepted 20 March 2019
Available online 21 March 2019
0009-8981/

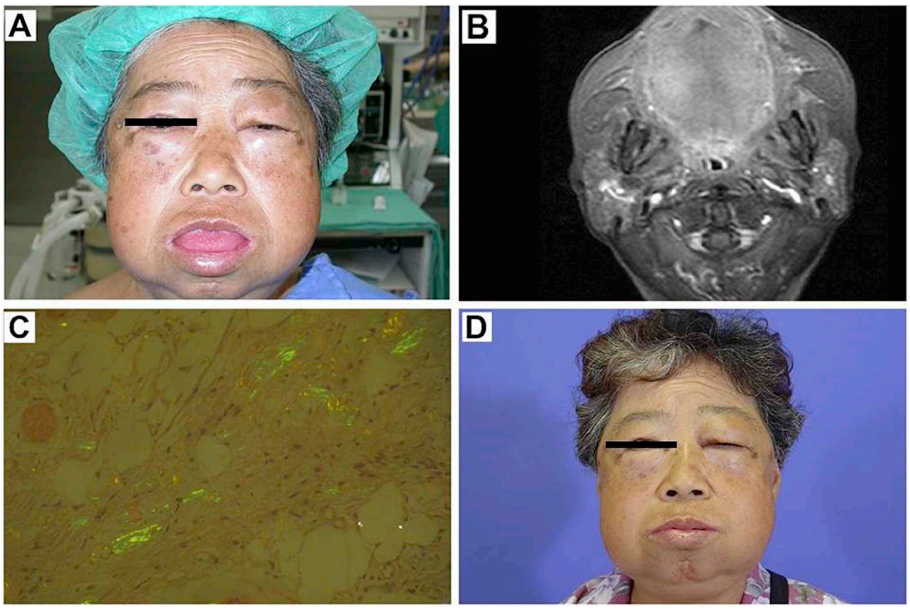

Fig. 1. A. Physical examination showed puffy eyes and moderate swelling up to 1 cm of the upper left eyelid, swollen submental region and tongue protrusion, causing inability to close the mouth. B. Post-contrast T1-weighted axial MRI view showed an increased tongue volume resulting in narrowing of the oropharyngeal inlet. *C. Congo* red staining of the tongue biopsy tissue revealed strong positive amyloid depositions (Congo red stain 400×). D. At 6-month follow-up, the patient was able to close their mouth well. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cases accounting for approximately 56% [2]. Amyloidosis subtypes are difficult to diagnose and therefore diagnosis and treatment are delayed in some cases.

2. Case report

A 72-y-old Taiwanese woman presented with complaints of a 1-y history of droopy left upper eyelid resulting in decreased visual acuity in left eye (OS), and progressive tongue swelling, resulting in dysarthria, dysphagia, and sleep apnea. The patient had previously undergone a modified radical mastectomy for right breast carcinoma approximately 3 years earlier, and there was no evidence of recurrence. Family history of the patient was unremarkable. On clinical examination, blood pressure was 135/72 mmHg, pulse rate was 85 beats/min, and respiratory rate was 22 breaths/min. Puffy eyes and moderate swelling to an increase of 1 cm were observed on the left upper eyelid. Furthermore, swollen submental region and protrusion of the tongue were present, causing an inability to close mouth. Tongue examination revealed a mild nodular appearance of the surface, with obvious indentations along the bilateral margins, pink color, firmness, and hypertrophy (Fig. 1A). Visual acuity test was 20/25 for the right eye (OD) and 20/50 for OS. Polysomnography confirmed a diagnosis of obstructive sleep apnea (OSA). Subsequently, a complete systemic evaluation was carried out. The workup included a complete blood count and measurement of prothrombin time, activated partial prothrombin time, serum biochemistries, serum autoantibodies associated with autoimmune diseases, serum protein electrophoresis, serum immunoelectrophoresis, urine analysis, skeletal survey, abdominal ultrasound, electrocardiography and echocardiography. A serial serum biochemical data was shown in (Table 1). Her skeletal survey did not show any lytic lesion and 24 h urine protein was 180 mg with a negative test for Bence Jones protein. Electrocardiography revealed normal sinus rhythm, however left ventricular hypertrophy was noted. Echocardiography reported minimal pericardial effusion and decreased left ventricular compliance, with an ejection fraction of around 80%. The kappa chain concentration in the serum was 323.4 mg/l (normal range, 3.3–19.4 mg/l), lambda chain concentration was 15.4 mg/l (normal range, 5.7–26.6 mg/l). Thus the serum kappa/lambda free light chains ratio (323.4/15.4) was measured at 21 (normal range, 0.26–1.25), suggesting the presence of free monoclonal kappa light chains gammopathy. Serum protein electrophoresis revealed as followings: total proteins: 6.7 g/dl (normal range: 6–8.3 g/dl); albumin: 46.4% (normal range: 53.3–60.2%); α_1-globulin: 3.9% (normal range: 1.6–4.8%); α_2-globulin: 33.7% (normal range: 10–12%); β-globulin: 9.6% (normal range: 10–15.6%); γ-globulin: 6.4% (normal range: 11.6–18%). Immunoelectrophoresis of serum showed kappa chain 2.710 g/dl (normal range: 0.629–1.350 g/dl) and lambda chain 0.128 g/dl (normal range: 0.313–0.723 g/dl), which was compatible with serum free light chains ratio result. Magnetic resonance imaging (MRI) revealed oropharyngeal narrowing caused by increased tongue volume (Fig. 1B). The patient subsequently underwent tongue reduction surgery to relieve symptoms of OSA.

Table 1
Blood biochemistry data.

Parameters		Normal value
Hemoglobin (g/dl)	11.8	12–16
BUN (mg/dl)	18	6–20
Creatinine (mg/dl)	0.8	0.5–0.9
Sodium (mmol/l)	135	136–145
Potassium (mmol/l)	3.9	3.5–5.1
GPT (U/l)	32	0–41
Total calcium (mg/dl)	8.5	8.5–10.3
Albumin (g/dl)	3.6	3.5–5.2
Troponin I (ng/ml)	0.2	< 0.3
BNP (pg/ml)	258	< 100
IgA (mg/dl)	352	70–400
IgG (mg/dl)	895	700–1600
IgM (mg/dl)	186	40–230
Prothrombin time	11.4	8–12
INR	1.0	–

Abbreviation: BUN: blood urea nitrogen, BNP: brain-type natriuretic peptide, GPT: glutamate pyruvate transaminase, IgA: Immunoglobulin A, IgG: Immunoglobulin A, IgM: Immunoglobulin M, INR: International normalized ratio.

Microscopic examination of tongue specimens using hematoxylin and eosin staining revealed distribution of amorphous eosinophilic material among muscular fragments. Following Congo red staining, the samples displayed characteristic red-green birefringence and dichroism under polarized light microscopy, consistent with amyloidosis (Fig. 1C). The patient also underwent skin biopsy of the upper left eyelid; Congo red staining also revealed amyloid deposition in this tissue. In general, the most important criterion in diagnosing multiple myeloma is the presence of plasma cells > 10% in bone marrow examination. Therefore bone marrow aspiration was performed in this patient and biopsy

Table 2
Ptosis in patients with systemic AL amyloidosis: a review and comparison of the literature.

Reports	Age/Sex	Eye	Underlying diseases	Location	Other involved organs	Clinical manifestation
Oishi A [16]	62/M	OS	NA	Eyelid	Heart	Ptosis, proptosis, orbital mass, optic nerve head ischemia
Topalkara A [17]	72/F	OD	Sjögren syndrome, Rheumatoid arthritis, Discoid lupus erythematosus, Hypertension	Conjuntiva	Stomach	Ptosis, salmon-colored conjunctival mass
Abdallah AO [18]	47/F	OD	NA	Eyelid	Bone marrow, gastrointestinal tract	Ptosis, eyelid swelling, diarrhea
Current case	72/F	OS	Breast carcinoma status post modified radical mastectomy	Eyelid	Tongue	Ptosis, eyelid swelling, dysarthria, dysphagia, sleep apnea

NA, not available.

revealed normal cellularity for the patient's age. The plasma cells comprised approximately 5% of nucleated marrow cells. Finally, the patient was diagnosed with kappa type systemic AL amyloidosis. Because the patient was older than 70 years of age, she received treatment with oral melphalan. At six-month follow-up, the patient's clinical manifestation was obviously improved, including visual acuity, respiration, ingestion of liquid food, and cosmetic appearance. The patient was also able to close her mouth well (Fig. 1D).

3. Discussion

We report a rare case that highlights coexisting ptosis and macrogloosia in systemic AL amyloidosis. We propose the incidence of ophthalmic region and tongue involvements caused by systemic amyloidosis may be more prevalent than previous thought because of its asymptomatic nature at the beginning of amyloid-associated diseases.

Systemic amyloidosis develops when circulating proteins obtain misfolded, β-pleated sheet configurations and are deposited in extracellular compartments of numerous tissues in the form of insoluble amyloid fibrils. This process can lead to cell death and organ dysfunction and in some cases can be life-threatening [1–5]. Depending on the extent of involvement, amyloidosis can be classified as local, in which amyloid deposits are confined to a particular organ or tissue, or systemic, in which amyloid is present in more than two different sites [1–3]. Amyloidosis is mainly a systemic disorder. The most common form of systemic amyloidosis in western countries is AL amyloidosis, with an approximate incidence of nine cases per million person-years [6,7]. AL amyloidosis possesses a slight male predominance, and middle-aged adult patients are most often affected. The average age of patients diagnosed with amyloidosis is 65 years old, and approximately 10% of patients are below 50 years of age. Less frequently, amyloidosis manifests as a local disorder, related to focal infiltration of plasma cell clones secreting amyloid-forming light chain, which do not progress to multi-system involvement. Aside from the central nervous system, all organs can be affected by systemic AL amyloidosis, with kidney involvement being the most frequent. Kidney involvement presents as heavy proteinuria and decreased glomerular filtration rate in around 40% of cases. The heart is the second most commonly involved organ in AL amyloidosis patients, followed by the liver [7]. Only around 9% of these patients have dominant soft tissue involvement [8]. Different classes of immunoglobulin light chain are capable of causing AL amyloidosis, with monoclonal lambda light chain being the most frequently involved [4]. In addition, 20% of AL amyloidosis patients also have multiple myeloma. Conversely, only around 15% of multiple myeloma patients develop AL amyloidosis [9].

Amyloidosis rarely affects the head and neck, and most cases which do are of the AL subtype. Although any site of the head and neck can be involved, the most common sites are the larynx and tongue, which are typically secondary to systemic disease. Tongue involvement manifests as a firm to rubbery macroglossia, the most frequent oral manifestation of amyloidosis. Macroglossia may be observed as the only presenting symptom of disease, present in 10–20% of systemic AL amyloidosis patients. It sometimes presents as yellowish nodules or a bulging white lesion [10]. Clinical presentation of the enlargement of the submandibular gland may also be observed in patients with macroglossia caused by AL amyloidosis. Differential diagnosis, including malignant tumors of the tongue, vascular abnormalities, hypothyroidism and vitamin B12/folic acid deficiency, should be excluded in advance of an AL amyloidosis diagnosis [11]. Conversely, amyloidosis with ophthalmologic involvement usually presents as localized lesions. Primary eyelid amyloidosis is an uncommon clinical entity which often leads to misdiagnosis. Differential diagnosis includes basal cell or squamous cell carcinoma, lachrymal gland carcinoma or lymphoma [12–14]. Mora-Horna ER et al. reported that in 83 patients with periocular and orbital amyloidosis in 2016, 23 (27%) presented with ptosis [15]. Reviewing the literatures, four cases (including our case) with ptosis were

diagnosed with systemic AL amyloidosis, and only our patient was reported to be accompanied by macroglossia (Table 2) [16–18]. Clinical features of ocular amyloidosis vary depending on the localization. Most patients present with a conjunctival mass which may result in reduced visual acuity. The second most common symptom is subconjunctival hemorrhage, also known as hyposphagma, driven by the fact that amyloid infiltration into vessel walls induces rigidity and disruption of conjunctival vessels [19]. Eneh AA et al. reported that most cases of hyposphagma were initiated by the downward mechanical effect of amyloid deposits on the eyelid, instead of levator muscle infiltration by amyloid [20]. To the best of our knowledge, our patient is the first case diagnosed with systemic AL amyloidosis, presenting with ptosis and macroglossia concurrently.

Even when the condition is suspected clinically, tissue biopsy of the organ involved should be performed to confirm the diagnosis. At present, Congo red stain test remains the gold standard diagnostic procedure for amyloidosis. Under polarized light, Congo red-stained material generates an apple-green birefringence, indicative of amyloid deposition. Determining the specific type of amyloid protein involved is another important issue. The free light chain assay, when used alongside serum and urine protein electrophoresis and immunofixation, markedly improves the detection of monoclonal proteins in AL [21], with an abnormal kappa/lambda ratio implying the presence of monoclonal gammopathy [21–23]. Other diagnostic tools including subcutaneous fatty tissue aspiration and biopsy of subcutaneous fatty tissue are also highly sensitive, with sensitivity of 73% and specificity of 90%. Such techniques also pose the advantage of a low risk of bleeding and therefore can be used as screening tests in patients with no clinical symptoms or evidence of organ dysfunction [24]. In addition to biopsy, a systemic evaluation should be performed when amyloidosis is suspected, including the following baseline examinations: complete blood count, serum electrolyte measurements, renal, liver and heart function tests, β2-microglobulin assay, prothrombin time, and activated partial prothrombin time, urine analysis, 24-h urinary protein, Bence Jones protein analysis, electrocardiography and skeletal survey.

Treatment of systemic AL amyloidosis relies largely on chemotherapy, with dosage depending on the age of the patient and the extent of disease. Any treatment strategy which has shown efficacy in the treatment of multiple myeloma or lymphoproliferative disorders is suitable for the treatment of systemic AL amyloidosis. Common therapeutic approaches include high dose mephalan followed by autologous blood stem cell transplantation (HDM/SCT), bortezomib-based triplet regimen, high dose dexamethasone-based regimens and the conventional treatment, the oral melphalan-based regimen [7,9,25]. Surgical intervention may also be required in some cases to relieve symptoms, such as airway obstruction, or OSA caused by severe macroglossia in patients with systemic amyloidosis [26]. Overall survival rates are still inconsistent, therefore the choice of first-line treatment for systemic AL amyloidosis is still debated. Current treatments are derived from regimens against multiple myeloma, however systemic AL amyloidosis patients are more fragile. Organ dysfunction caused by amyloid deposition can represent a contraindication for the use of specific therapeutics, and risk-adapted and response-tailored approaches are imperative [7,9,27].

In conclusion, simultaneous ptosis and macroglossia may present as manifestations of AL amyloidosis. In each case, systemic disease should be thoroughly investigated. Careful history taking, physical examination, and appropriate laboratory investigation can enable clinicians to reach a rapid and accurate diagnosis. Early recognition of amyloid-associated disease and appropriate treatment are crucial.

Acknowledgments

We thank the patient's consenting to publish the clinical information.

References

[1] L.M. Dember, Amyloidosis-associated kidney disease, Am. Soc. Nephrol. 17 (2006) 3458–3471.
[2] R.A. Kyle, Bayrd E.D. Amyloidosis, Review of 236 cases, Medicine (Baltimore) 54 (1975) 271–299.
[3] M. Grogan, A. Dispenzieri, M.A. Gertz, Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response, Heart 103 (2017) 1065–1072.
[4] M. Nuvolone, G. Merlini, Systemic amyloidosis: novel therapies and role of biomarkers, Nephrol. Dial. Transplant. 32 (2017) 770–780.
[5] P.J. Hsiao, W.F. Chiang, T.K. Chao, S.H. Lin, Life-threatening hematuria in a hemodialysis patient with systemic light-chain amyloidosis, Clin. Chim. Acta 451 (2015) 180–182.
[6] N.S. Nielsen, E.T. Poulsen, G.K. Klintworth, J.J. Enghild, Insight into the protein composition of immunoglobulin light chain deposits of eyelid, orbital and conjunctival amyloidosis, J. Proteome Bioinform. (Suppl. 8) (2014) 002.
[7] E. Desport, F. Bridoux, C. Sirac, et al., Al amyloidosis, Orphanet J. Rare Dis. 7 (2012) 54.
[8] T. Prokaeva, B. Spencer, M. Kaut, et al., Soft tissue, joint, and bone manifestations of AL amyloidosis : clinical presentation, molecular features, and survival, Arthritis Rheum. 56 (2007) 3858–3868.
[9] M.A. Gertz, Immunoglobulin light chain amyloidosis: 2014 update on diagnosis, prognosis, and treatment, Am. J. Hematol. 89 (2014) 1132–1140.
[10] I. Thibault, I. Vallières, Macroglossia due to systemic amyloidosis: is there a role for radiotherapy, Case Rep. Oncol. 4 (2011) 392–399.
[11] A. Shahbaz, K. Aziz, M. Umair, Z.R. Malik, S.I. Awan, I. Sachmechi, Amyloidosis presenting with macroglossia, Cureus 10 (2018) e3185.
[12] O. Aryasit, P. Preechawai, K. Kayasut, Clinical presentation, treatment, and prognosis of periocular and orbital amyloidosis in a university-based referral center, Clin. Ophthalmol. 7 (2013) 801–805.
[13] A. Caggiati, A. Campanella, S. Tenna, A. Cogliandro, C. Potenza, P. Persichetti, Primary amyloidosis of the eyelid: a case report, In Vivo 24 (2010) 575–578.
[14] D. Suesskind, F. Ziemssen, J.M. Rohrbach, Conjunctival amyloidosis-clinical and histopathologic features, Graefes Arch. Clin. Exp. Ophthalmol. 253 (2015) 1377–1383.
[15] E.R. Mora-Horna, R. Rojas-Padilla, V.G. López, M.J. Guzmán, A. Ceriotto, G. Salcedo, Ocular adnexal and orbital amyloidosis: a case series and literature review, Int. Ophthalmol. 36 (2016) 281–298.
[16] L.J. Correa, J.P. Maccio, E. Esposito, et al., Systemic amyloidosis with bilateral conjunctival involvement: a case report, BMC Ophthalmol. 15 (2015) 77.
[17] A. Oishi, K. Miyamoto, N. Yoshimura, Orbital amyloidosis-induced compressive optic neuropathy accompanied by characteristic eyelid pigmentation, Ophthalmic Plast. Reconstr. Surg. 22 (2006) 485–487.
[18] A. Topalkara, Y. Ben-Arie-Weintrob, J.A. Ferry, C.S. Foster, Conjunctival marginal zone B-cell lymphoma (MALT lymphoma) with amyloid and relapse in the stomach, Ocul. Immunol. Inflamm. 15 (2007) 347–350.
[19] A.O. Abdallah, C. Westfall, H. Brown, J. Muzaffar, S. Atrash, B. Nair, Unilateral conjunctival AL kappa amyloidosis with trace evidence of systemic amyloidosis, Am. J. Case Rep. 13 (2012) 102–105.
[20] A.A. Eneh, J. Farmer, V. Kratky, Primary localized orbital amyloid: case report and literature review; 2004-2015, Can. J. Ophthalmol. 51 (2016) e131–e136.
[21] E. Jenner, Serum free light chains in clinical laboratory diagnostics, Clin. Chim. Acta 427 (2014) 15–20.
[22] A.P. Piehler, N. Gulbrandsen, P. Kierulf, P. Urdal, Quantitation of serum free light chains in combination with protein electrophoresis and clinical information for diagnosing multiple myeloma in a general hospital population, Clin. Chem. 54 (2008) 1823–1830.
[23] S. Kumar, A. Dispenzieri, J.A. Katzmann, et al., Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features, Blood 116 (2010) 5126–5129.
[24] B. Bogov, M. Lubomirova, B. Kiperova, Biopsy of subcutaneus fatty tissue for diagnosis of systemic amyloidosis, Hippokratia. 12 (4) (2008) 236–239.
[25] V. Sanchorawala, Light-chain (AL) amyloidosis: diagnosis and treatment, Clin. J. Am. Soc. Nephrol. 1 (2006) 1331–1341.
[26] F. Angiero, R. Seramondi, S. Magistro, et al., Amyloid deposition in the tongue: clinical and histopathological profile, Anticancer Res. 30 (2010) 3009–3014.
[27] E. Kastritis, M.A. Dimopoulos, Recent advances in the management of AL amyloidosis, Br. J. Haematol. 172 (2016) 170–186.