Dysphagia (2019) 34:179–191
https://doi.org/10.1007/s00455-018-9956-x

ORIGINAL ARTICLE

Amyloidosis of the Upper Aerodigestive Tract: Management of a Rare Disease and Review of the Literature

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Received: 27 July 2018 / Accepted: 20 October 2018 / Published online: 31 October 2018

Abstract

Amyloidosis in the upper aerodigestive tract is a very rare disease with mainly case reports documented so far. In the pathogenesis, amyloid protein fibers are deposited in organs and tissue. In the upper aerodigestive tract, mostly localized amyloidosis occurs with unspecific symptoms, e.g., dysphagia. We conducted a retrospective multicenter study with two study centers in Germany (tertiary referral hospitals), the University Hospital of Bonn and the University Hospital of Goettingen. For a period of the last 7 years, data were analyzed and patients were recruited consecutively. 14 cases were included to the study. The most common manifestation was in the larynx ($n = 11$); in one case each localized amyloidosis was found in the tongue, trachea and in the pharynx. Since the majority of our cases ($n = 13$; 92.6%) presented with unspecific symptoms, biopsy results confirmed the diagnosis of localized amyloidosis. Resection of the lesion was only performed in patients reporting of symptoms, in asymptomatic patients only a non-invasive biopsy was done. In two patients (14.2%), in addition to the focal lesion a systemic amyloidosis was found. Amyloidosis in the upper aerodigestive tract is a rare disease. Nonetheless, every otorhinolaryngologist should be aware of this disease. When detected it is a straight forward to treat illness. The appearance of a systemic amyloidosis needs to be ruled out; thus, there is a chance to develop a multiple myeloma. Given the slow progressive character of amyloidosis, a long-term follow-up up to 10 years is inevitable.

Keywords Amyloidosis · Upper aerodigestive tract · Dysphagia · Deglutition · Deglutition disorder · Demographics

Abbreviation

AL	Amyloid light chain
CO_2	Carbon dioxide
CT	Computed tomography
ECG	Echocardiography
F	Female
KTP	Potassium titanyl phosphate
M	Male

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MLS Microlaryngoscopy
MRI Magnetic resonance imaging
NI No information
RBC Red blood count
SAA Serum amyloid A protein
SAP Serum amyloid P protein
TTR Transthyretin
UKB University Hospital of Bonn
UMG University Hospital of Goettingen
WBC White blood count

Introduction

Amyloidosis in the upper aerodigestive tract is a fairly rare disease [1–4], mostly presenting with unspecific symptoms, e.g., dysphagia or dysphonia. In general, data about amyloidosis are scarce. The incidence of amyloidosis is estimated between 5 and 13 per million people per year [5]. Concerning pathogenesis, a rearrangement in the immune system with misfolding of extracellular protein is discussed [3, 6–9]. Those non-soluble protein-fibers [10] are deposited in organs and tissue, which is followed by a chronic inflammation with excessive tissue destruction. This leads to an autoimmune disease promoting expansion of amyloidosis [1, 11]. Various biochemical forms are known, depending on the amyloid deposit type. The current classification system relates to a lettering system. The first letter describes the amyloid fibril protein; the subsequent letters are designated to the precursor protein, e.g., AL describes amyloid fibrils derived from immunoglobulin light chains, and transthyretin (TTR) amyloids fibrils derived from transthyretin [1, 12, 13]. The most common ones are as follows: AL protein, serum amyloid A, and TTR. Clinically, amyloidosis can be divided in localized or systemic diseases. Most frequently affected organs in systemic amyloidosis include kidneys, spleen, liver and heart, rarely adrenals, pituitary gland, thyroid, and alimentary tract. The two leading causes of death in systemic amyloidosis are due to extracellular deposition of amyloid in heart and kidneys, which leads to failure of these organs [3]. Only 9–15% of all patients with amyloidosis have a localized disease [14]. Amyloidosis in the upper aerodigestive tract occurs in most cases as localized manifestations, with unspecific symptoms of the upper aerodigestive tract, i.e., dysphagia or hoarseness, and is often diagnosed after retrieving a biopsy. Manifestations involve mostly the tongue or the larynx; 0.2–1.5% of benign lesions in the larynx involve cases with amyloidosis in the head and neck [8, 10, 15–18]. Other more common sites are the oral cavity, or oropharynx. Rather rare, is the localization in the nose or sinuses [17, 19]. Some cases are reported to have been found in the hypopharynx [20], as well as a spread to the tracheobronchial tract [21, 22].

To date, no clear guidelines have been developed. With the findings of our study and review of the literature of the last 30 years, we want to provide an algorithm how to handle localized amyloidosis in the head and neck region.

Materials and Methods

We conducted a retrospective multicenter study including two study centers in Germany (tertiary referral hospitals), the University Hospital of Bonn (UKB) and the University Hospital of Goettingen (UMG), of 13 consecutive patients with amyloidosis in the upper aerodigestive tract. The time period investigated was from 01/2000 to 01/2017. We included all patients who were diagnosed with amyloidosis in der upper aerodigestive tract within that time span. Follow-up ranged from 0 to 181 months (mean 23.02 ± 51.17 months).

The data included demographic information, localization of the lesions, development of a systemic amyloidosis, treatment modalities, past medical history, and chief complaint. The hospitals' electronic databases, paper charts, and documentations of the procedures were used for data collection. The study was approved by the local ethics committee of the UKB (377/17), and the UMG (20/1/17).

Histologic examination of the samples was performed by a Congo red staining positive for amyloid with an apple-green birefringence when viewed with polarization microscopy. Subepithelial extracellular deposits of acellular, amorphous, eosinophilic material within the stroma on hematoxylin and eosin stain are pathognomonic for amyloidosis [1].

The data were statistically analyzed with the program R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Mean age was 53.9 ± 18.8 years (Table 1) and 57.1% were male. In all patients, it was the first diagnosis of amyloidosis, and in one patient hereditary systemic amyloidosis was suggested as the primary diagnosis. The most common manifestation was in the larynx (vocal cords $n = 8$, vestibular fold $n = 1$, epiglottis $n = 2$; 78.6%), and in one case each (7.1%) localized amyloidosis was found in the tongue, trachea and in the pharynx (Fig. 1).

All patients presented with unspecific symptoms of the upper aerodigestive tract (Table 1). In one patient (7.1%), a

Table 1 Patient's demographics and treatment; *AL* amyloid light chain, *MLS* microlaryngoscopy, *NI* no information, *TTR* transthyretin amyloid fibers

Patient number	Sex	Age (years)	Localization	Chief complaint	Systemic amyloidosis	Surgery	Comorbidities
1	F	14.5	Vocal cords both sides	Dysphonia	None	MLS with resection and right-sided chordectomy	None
2	M	28.0	Vocal cords	Dysphonia	NI	MLS with resection	None
3	F	41.2	Vocal cords	Dysphonia	None	MLS with biopsy	None
4	M	48.7	Vocal cords	Dysphonia	NI	MLS with resection	None
5	F	51.5	Vocal cords	Dysphonia	None	MLS with resection	None
6	M	58.5	Vocal cords	Dysphonia	Yes, TTR type amyloidosis	None, treatment of comorbidities	Polyneuropathy, cardiac manifestation, gastro-intestinal manifestations
7	M	63.1	Vocal cords	Dysphonia	None	MLS with resection	None
8	M	80.0	Vocal cords	Dysphonia	NI	MLS with biopsy	None
9	M	52.0	Right vestibular fold	Dysphonia	None	MLS with resection	None
10	M	60.7	Epiglottis	Dysphagia	None	MLS with resection	None
11	M	84.5	Epiglottis	Incidental finding in bronchoscopy	None	MLS with biopsy	None
12	F	70.0	Tongue, oral cavity	Macroglossia	Multiple myeloma	Biopsy oral cavity	Cheilitis granulomatosis
13	F	55.0	Trachea	Burning sensation oral, sicca syndrome	None	None	Sjogren, secondary AL
14	F	44.0	Oropharynx, hypopharynx, left vestibular fold, left piriform sinus	Dysphagia, dysphonia	None	MLS with biopsy	none

routine bronchoscopy with biopsy was performed and amyloidosis was found by coincidence.

The majority ($n = 11$; 78.6%) of the patients suffered from localized amyloidosis in the larynx (Fig. 1b). All of those patients presented with dysphonia, and, except for one, received a microlaryngoscopy (MLS) in order to retrieve a biopsy. In patients with a small amyloidosis lesion, a biopsy was taken and the patients received logopedic training. In patients with larger manifestations, a partial or complete resection was performed. One patient developed a systemic amyloidosis (TTR type), in seven patients a systemic amyloidosis was ruled out and in three patients the status of systemic disease remained unknown. In seven patients (50%), the lesion was resected, one declined the resection and in three a biopsy only was performed.

A 70-year-old female (7.1%), presented with dysphagia, macroglossia, painful swelling in the base of the mouth, weight loss and unspecific volume gain in the shoulder region. Examination found oral ulcerations, swelling of the lower lip and a distinctive macroglossia (Fig. 1d). After biopsy in the vestibulum oris, results confirmed an AL-type amyloidosis. The patient received complete work up to rule out a systemic disease. Within 6 months of follow-up, a multiple myeloma was found and treated with chemotherapy (Melphalan). After 2 months of progressive macroglossia, a hemiglossectomy and due to long time ventilation, a tracheostomy was performed. At the time of last follow-up (after 10 years), a reduced but stable general health status was reported.

In one patient (7.1%), amyloidosis in the trachea was found. The 55-year-old female presented with sicca symptoms and burning sensation in the mouth. After performing an MLS, a yellowish lesion was found in trachea. Biopsy results confirmed an AL-amyloidosis secondary to Sjogren's syndrome. A systemic amyloidosis was ruled out.

Our study included one case of amyloidosis manifestation in the posterior pharyngeal wall reaching the pyriform sinus on the left side (Fig. 1a, c). The patient presented with dysphagia and required a resection of the lesion due to extreme dysphagia and dysphonia. Within a couple of

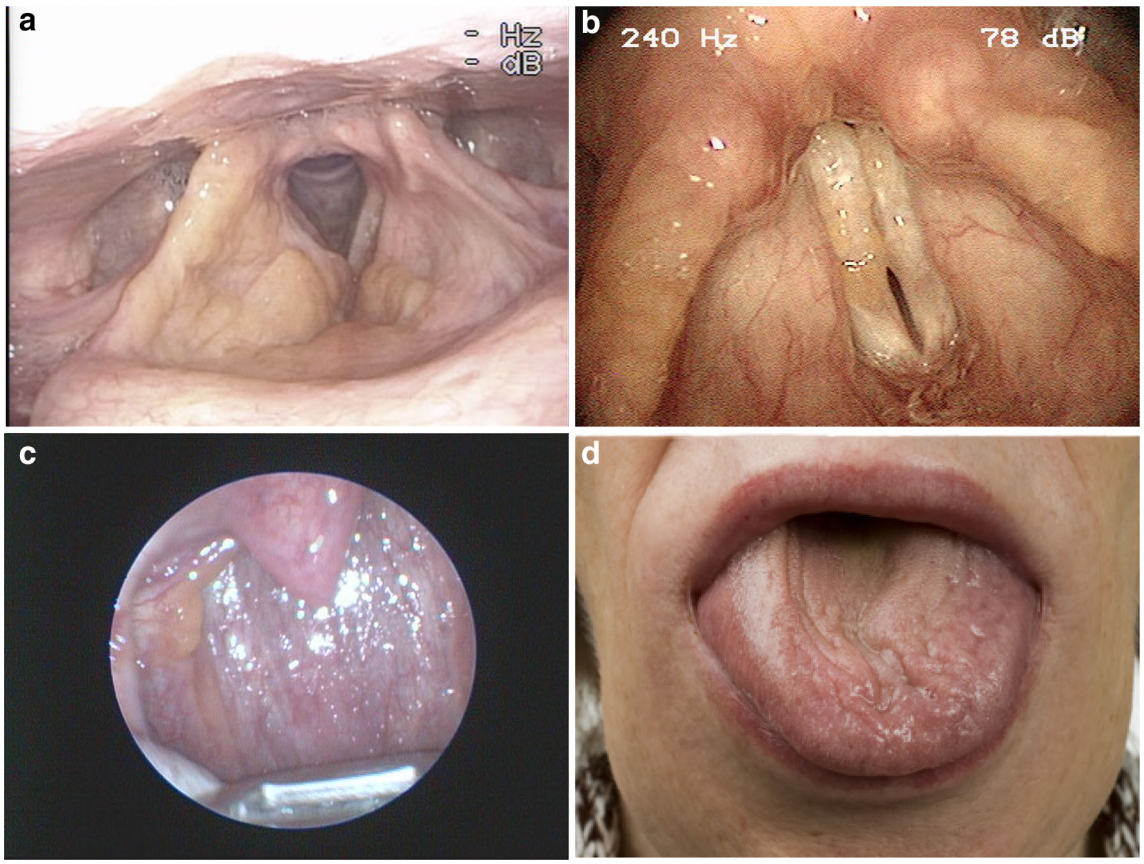

Fig. 1 Typical macroscopic amyloid lesions in the supraglottis (**a**), vocal folds (**b**), oropharynx (**c**), and macroglossia (**d**)

months, the symptoms reoccurred and a recurrence was found. An MLS with resection of the lesions was performed and the patient was asymptomatic ever since. No systemic disease was found.

In two patients (14.2%), the diagnosis for amyloidosis was made macroscopically. Since the majority of our cases ($n = 13$; 92.9%) presented with unspecific symptoms of the upper aerodigestive tract, biopsy results (Fig. 2) confirmed the diagnosis of localized amyloidosis. Resection of the lesion was only performed in patients reporting of symptoms, in asymptomatic patients a biopsy only was done. All patients received a medical check-up in order to rule out a systemic disease. In two patients (14.2%), a systemic amyloidosis was found. Almost two-thirds of the patients had a follow-up of less than 3 months ($n = 9$, 64.3%).

Discussion

Amyloidosis in the upper aerodigestive tract is a very rare disease, mostly underestimated, and not detected until incidental pathologic findings. As mentioned above, no clear guidelines have been developed so far. Therefore, the findings of our study and review of the literature of the last 30 years serve as an algorithm how to cope with localized amyloidosis in the upper aerodigestive tract and head and neck region (Fig. 3).

Presentation

Throughout literature and our study, presentation of patients with amyloidosis in the upper aerodigestive tract mostly includes unspecific symptoms and provides a challenge uncovering the diagnosis. Thus, symptoms depend on the anatomic region and the size. Manifestations in the larynx or the tongue are the most common ones [5, 23, 24]. In the following, we present the different localization of amyloidosis which are reported in our cohort and so far within the last 30 years.

Larynx

Our cohort included 11 cases (60.0%) of amyloidosis in the larynx (Fig. 1b). Except for one patient, the other ten patients presented with dysphonia. Concerning the larynx, symptoms depend on the dissemination and anatomical localization. The most common symptoms are dyspnea and

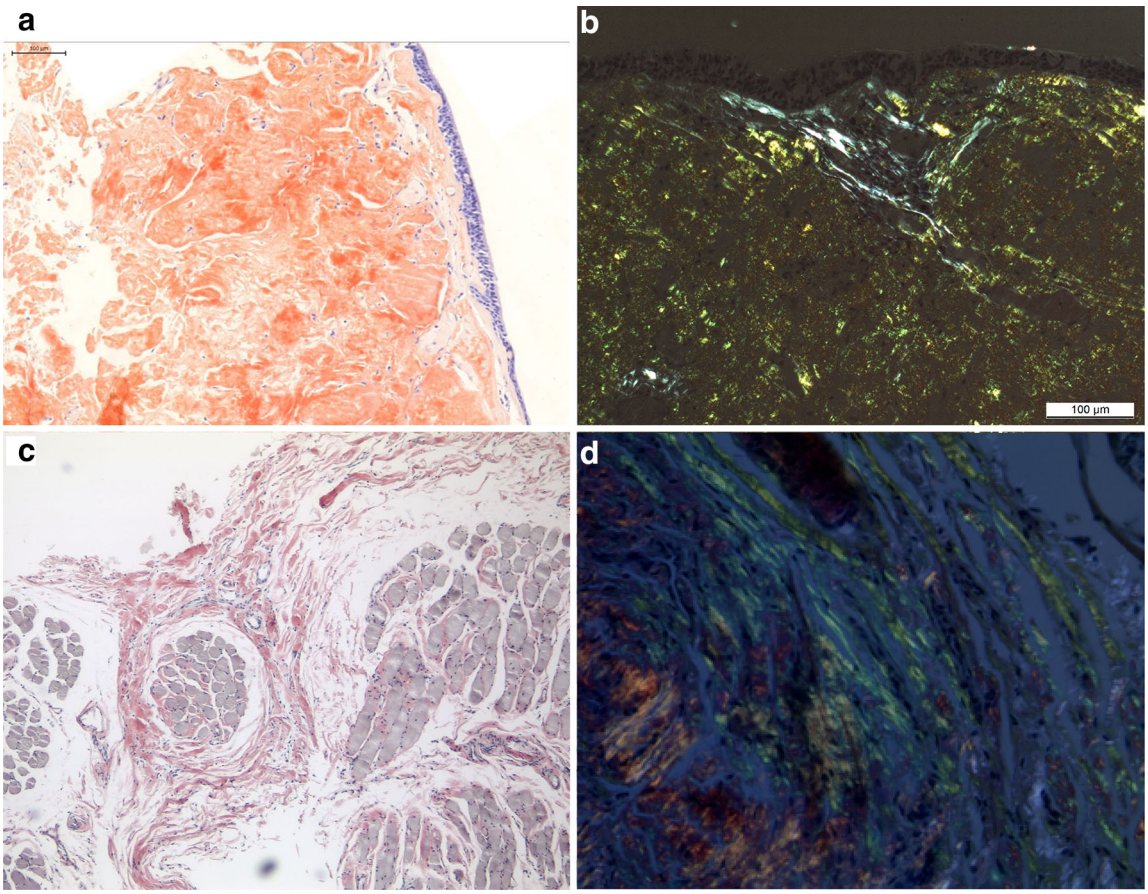

Fig. 2 Characteristic Congo red staining of the larynx (**a**) and the tongue (**b**) with apple-green birefringence (**c** larynx; **d** tongue) when viewed with polarization microscopy

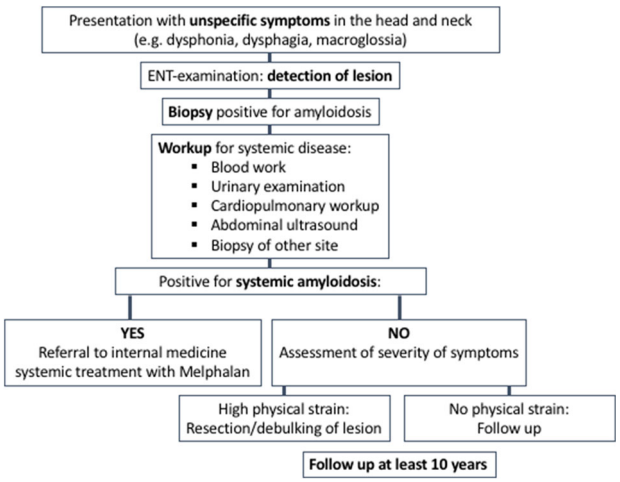

Fig. 3 Algorithm how to proceed in localized amyloidosis in the head and neck region

hoarseness with coughing, hemoptysis, and dysphagia are more seldom [25, 26]. It is estimated that the larynx is involved in 9–15% of all amyloidosis cases [27]; benign laryngeal lesions account for 0.2–1.2% [8]. Within literature, mostly case reports of amyloidosis in the larynx are found. Larger cohorts are reported as well [25, 26, 28, 29] (Table 2). Regarding systemic involvement, a recent analysis of Rudy et al. [13] found systemic amyloidosis in 18% of their cohort, which underlines the importance of performing a workup in order to rule out a systemic disease. In our cohort, in one patient a systemic amyloidosis was found simultaneously and in another a multiple myeloma consecutively. Laryngeal amyloidosis is found rather early, due to the anatomic localization and resulting symptoms. The relevance of the disease and following treatment, which in most of the cases results in resection or debulking of the lesion, lies in the physical strain of the patient and ambition of the treating physician to obtain relief of the symptoms. Treatment modalities need to be carefully balanced against the resulting potential morbidities of each therapy. As a result of the aggressiveness of the treatment, quality of life and voice are affected [25]. Therefore, follow-up care of those patients includes the involvement of a phoniatric specialist.

Table 2 Amyloidosis in the larynx; *AL* amyloid light chain, *CO_2* Carbon dioxide, *NI* no information

Patient number	Author	Year	No. of patients	Type	Age	Sex	Presentation	Treatment	Systemic
1–22	Lewis et al. [26]	1992	22	AL	56	M (50%)	Dysphonia	Resection	No
23–33	Thompson et al. [8]	2000	11	NI	37.8	M (72.7%)	Dysphonia	Resection, 1 laryngectomy	54.5% (recurrent/multifocal/ systemic)
34–49	Pribitkin et al. [14]	2003	16	NI	49.8	M (56.3%)	Dysphonia, dyspnea, dysphagia	Resection (blunt or CO_2)	No (87.5%)
50	Motta et al. [30]	2003	4	NI	14	F	Dysphonia	CO_2	No
51				NI	21	F	Dysphonia	CO_2	No
52				NI	34	F	Dysphonia	CO_2	No
53				NI	47	F	Dysphonia	CO_2	No
54–59	Bartels et al. [29]	2004	6	AL	NI	NI	Dysphonia	Resection	No (83.3%)
60	Alaani et al. [6]	2004	4	AL	36	F	Dysphonia	Resection	No
61				AL	58	M	Dysphonia	Resection	No
62				AL	33	M	Dysphonia	Resection	No
63				AL	50	M	Dysphonia	Speech and language training	No
64	Penner et al. [28]	2006	3	AL	18	F	Dysphonia	Resection	No
65				AL	47	M	Dysphonia	Resection	No
66				AL	53	M	Dysphonia	Resection	No
67–82	Wierzbicka et al. [31]	2012	16	AL	NI	NI	Dysphonia	Resection	No
83	Deviprasad et al. [43]	2013	5	NI	74	F	Dysphonia, dyspnea	KTP	No
84				NI	37	F	Dysphonia	KTP	No
85				NI	68	M	Dysphonia	KTP	No
86				NI	52	F	Dysphonia	KTP	No
87				NI	50	F	Dysphonia, dry cough	KTP	No
88	Philipps et al. [25]	2017	5	NI	9	M	Dysphonia, dyspnea	CO_2	No
89				NI	31	F	Dysphonia, dyspnea	CO_2	No
90				NI	42	F	Dysphonia, dyspnea	CO_2	No
91				NI	57	F	Incidental finding on upper GI endoscopy	CO_2	No
92				NI	75	F	Dysphonia, dyspnea	CO_2	No
93–114	Rudy et al. [13]	2017	22	AL (64%)	52.8		Dysphonia, dyspnea	Resection (86%)	18%

Oral Cavity

Manifestations in the tongue typically result in macroglossia, tongue protrusion beyond the alveolar ridge, impairment of speech, and dysphagia [11, 23, 28]. It is known that about 25% of amyloidosis patients suffering from a systemic amyloidosis suffer from macroglossia as well [32]. Localized amyloidosis in the oral cavity occurs predominantly in the tongue [5, 23, 24]. In our analysis, one patient with amyloidosis of the tongue was reported who presented with macroglossia and dysphagia (Fig. 1d). In the course of disease, this patient developed a multiple myeloma which was treated with Melphalan. The findings

in our case are in line with data in the literature. So far, ten studies have reported from cases with amyloidosis in the oral cavity [23, 28, 33] (Table 3). The majority of the cases presented with macroglossia, lesions on the buccal mucosa or lip, which were treated with resection or partial glossectomy when disturbing the patient. Systemic amyloidosis was found in the majority and was treated with chemotherapy.

Nasopharynx

Our study cohort did not include any patients with amyloidosis in the nasopharynx. Throughout the literature, only 30 cases [19, 41] (Table 4) are reported within the last 30 years, the largest cohort ($n = 7$) of a study of Sakagiannis et al. published recently in 2017 [41]. Those patients presented with nasal obstruction, recurrent sinusitis, post nasal drip, dysphagia, apnea, Eustachian tube dysfunction, hearing loss, ear plugging or recurrent otitis media. In all cases, a transnasal endoscopy showed an unspecific nasopharyngeal mass leading to a suspected diagnosis of either adenoids or nasopharyngeal cancer, which was ruled out after confirmed biopsy results of amyloidosis. Systemic amyloidosis was found in only one patient who was treated with chemotherapy [52].

Oropharynx and Hypopharynx

In our cohort, one case of amyloidosis in the pharynx was reported. In this patient, the lesions spread from the oropharynx to the hypopharynx (Fig. 1a, c). The patient presented with dysphagia and required resection of the lesions.

In general amyloidosis in the oro- or hypopharynx is extremely rare. Concerning oropharyngeal amyloidosis seven case reports exist so far in the literature within the last 30 years [2] (Table 5). Five patients presented with dysphagia, two were asymptomatic and received a tonsillectomy due to unilateral tonsil enlargement with suspicion of a malignant tumor. In only one patient, a systemic amyloidosis, light chain myeloma III was found and treated with chemotherapy. In the cases of localized amyloidosis, a resection was favored. There is no information about recurrence in those cases.

Regarding localized amyloidosis in the hypopharynx, three cases are reported so far [20, 69, 70]. All patients presented with dysphagia and in two cases a systemic chemotherapy was applied due to development of a systemic amyloidosis. In the other patient, a resection of the lesion was performed (Table 6).

In our patient, a systemic disease was ruled out, but the patient developed a recurrence after the resection a couple

Table 3 Amyloidosis in the oral cavity; *AL* amyloid light chain, *NI* no information

Patient number	Author	Year	No. of patients	Type	Age (years)	Sex	Localization	Treatment	Systemic
1–5	Madani et al. [34]	1991	5	AL	73.2	F (60.0%)	Tongue	NI	Yes (80.0%)
6–24	Kerner et al. [23]	1995	19	AL	71.8	F (52.6%)	Tongue	NI	Yes (52.6%)
25–35	Van der Waal et al. [35]	2002	11	AL	68.5	F (81.8%)	Tongue, lip, buccal mucosa	Chemotherapy	Yes (81.8%)
36–48	Stoopler et al. [36]	2003	13	AL	NI	F (69.2%)	Buccal mucosa	NI	No
49–63	Penner et al. [28]	2006	15	AL	55.7	M (60.0%)	Tongue, lip, buccal mucosa	Resection	Yes (60.0%)
64–68	Angiero et al. [37]	2010	5	NI	59	M (60.0%)	Tongue	NI	Yes (40.0%)
69–71	Elad et al. [33]	2010	3	AL	66.6	M (100,0%)	Tongue	NI	Yes (66.7%)
72–85	Gouvea et al. [38]	2012	14	AL	58	F (71,4%)	Tongue, lip, buccal mucosa	Resection, chemotherapy, no treatment	Yes (50.0%)
86–91	O'Reilly et al. [39]	2013	6	AL	69.3	F (50.0%)	Tongue	Resection, observation	No
92–99	Matsuo et al. [40]	2014	8	AL	56	F (62.5%)	Tongue	Asymptomatic—no treatment Systemic disease—chemotherapy	Yes (50.0%)

Table 4 Amyloidosis of the nasopharynx; *AL* amyloid light chain, *NI* no information, *PND* post nasal drip

Patient number	Author	Year	No. of patients	Type	Age	Sex	Presentation	Treatment	Systemic
1	Gean Marton et al. [42]	1991	1	NI	32	F	Nasal obstruction, glue ear	NI	NI
2	Hegarty et al. [43]	1993	1	NI	NI	NI	Nasal obstruction, postnasal drip	None	No
3	Panda et al. [44]	1994	1	NI	82	M	Bleeding, postnasal drip	NI	NI
4	Dominguez et al. [45]	1996	1	AL	13	F	Nasal obstruction, oral bleeding	Resection	No
5	Lim et al. [46]	1999	1	AL	42	F	Nasal obstruction	NI	NI
6	Pitkaranta et al. [47]	2000	2	NI	14	M	Nasal obstruction	NI	NI
7				NI	41	F	Nasal obstruction	NI	NI
8	Munichor et al. [48]	2000	1	NI	57	F	Nasal obstruction	NI	NI
9	Patel et al. [19]	2002	1	NI	68	M	Serous otitis media, hearing loss	None	No
10	Zhuang et al. [49]	2005	1	NI	81	F	Neck mass	NI	No
11	Motosugi et al. [50]	2006	1	NI	46	F	Nasal obstruction	NI	NI
12	Panda et al. [51]	2006	1	NI	43	M	Nasal obstruction, foreign body sensation of throat	Resection	No
13	Yoshida et al. [52]	2008	1	AL	52	F	Incidental nding on PET/CT	Resection	Yes
14	Chen et al. [53]	2010	1	NI	86	M	Postnasal drip	None	No
15	Karimi et al. [54]	2010	1	NI	56	M	Aural fullness, otitis media with effusion	NI	NI
16	Wu et al. [55]	2011	1	NI	72	M	Orbital symptoms	NI	NI
17	Geller et al. [56]	2011	1	NI	62	M	previous episodes of right dacryocystitis	None	No
18	Durbec et al. [57]	2012	1	NI	59	F	Nasal obstruction, aural fullness	Resection	No
19	Legaza et al. [58]	2012	1	NI	43	M	Nasal obstruction, discharge, epistaxis	NI	NI
20	Mirza et al. [59]	2013	1	NI	31	F	Fluctuating conductive hearing loss	None	No
21	Kumar et al. [60]	2016	1	AL	55	F	Epistaxis, obstruction, hearing loss	Resection	No
22	Luo et al. [61]	2016	1	NI	39	M	Nasal obstruction, hearing loss, epistaxis	Resection, radiotherapy	No
23	Kim et al. [62]	2017	1	NI	73	M	Epistaxis, aural fullness	Resection	No
24	Sakagiannis et al. [41]	2017	7	NI	74	F	Nasal obstruction, dysphagia and apnea	None	No
25				NI	54	F	Nasal obstruction	None	No
26				NI	7	F	Nasal obstruction	Resection	No
27				NI	18	F	Dysphagia	Resection	No
28				NI	13	M	Otitis media with effusion	None	No
29				NI	64	M	Impaired hearing, PND	None	No
30				NI	83	F	Eustachian tube dysfunction	Resection	No

of months later. Recurrence of localized amyloidosis in the oro- or hypopharynx has been not reported in the literature yet.

Parotid Gland

Our cohort did not include a case of localized amyloidosis in the salivary glands. In the literature, only four case

Table 5 Amyloidosis of the oropharynx; *AL* amyloid light chain, *NI* no information

Patient number	Author	Year	No. of patients	Type	Age	Sex	Presentation	Treatment	Systemic
1	Lopez et al. [63]	1996	1	NI	72	M	Unilateral tonsil enlargement, asymptomatic	Resection	No
2	Finsterer et al. [64]	1997	1	NI	53	M	Dysarthria, dysphagia	NI	light chain myeloma III
3	Metternich et al. [65]	1998	1	NI	63	M	Dysphagia	Resection	No
4	Passerotti et al. [2]	2008	1	NI	55	F	Dysphagia	Resection	No
5	Green et al. [66]	2000	1	NI	47	M	Foreign body sensation throat	Resection	No
6	Grindle et al. [67]	2011	1	AL	29	F	Odynophagia	NI	No
7	Chiesa Estomba et al. [68]	2015	1	AL	73	M	Unilateral tonsil enlargement, asymptomatic	Resection	No

Table 6 Amyloidosis of the hypopharynx, *AL* amyloid light chain

Patient number	Author	Year	No. of patients	Type	Age (years)	Sex	Presentation	Treatment	Systemic
1	Chadwick et al. [20]	2002	1	AL	56	F	Dysphagia	Six-episode course of chemotherapy for myeloma	Yes
2	Ghekiere et al. [69]	2003	1	AL	76	F	Dysphagia, dysphonia	CO_2-laser resection	No
3	Hammami et al. [70]	2010	1	AL	60	F	Dysphagia	Chemotherapy associated melphalan (14.5 mg/day) and prednisone (116 mg/day).	Yes

reports of amyloidosis in the salivary glands are known (16, 781-73) (Table 7). Three cases presented with asymptomatic swelling in the parotid region. After resection, the pathological results revealed amyloidosis. In all of those cases, a systemic amyloidosis was ruled out. Only one case so far is known to develop a recurrence.

Diagnosis

The majority of our cases presented with unspecific symptoms of the upper aerodigestive tract without a suspected diagnosis of amyloidosis upon clinical findings. In order to rule out a malignancy, a biopsy was performed. In general, on histological examination, a specific Congo red staining was performed (Fig. 2). When viewed under polarized light, it demonstrates the characteristic apple-green birefringence, which is pathognomonic of

Table 7 Amyloidosis in the parotid gland; *AL* amyloid light chain, *NI* no information

Patient number	Author	Year	No. of patients	Type	Age	Sex	Presentation	Treatment	Systemic
1	Myssiorek et al. [71]	1992	1	NI	NI	NI	Sicca symptom	NI	No
2	Vavrina et al. [72]	1995	1	NI	NI	NI	Asymptomatic swelling in the left parotid region	Resection.	No
3	Nandapalan et al. [16]	1998	1	NI	NI	NI	Asymptomatic swelling	NI	No
4	Gareb et al. [73]	2018	1	AL	70	F	Asymptomatic swelling in the right parotid region	Resection	No

amyloidosis [25]. In the past, especially concerning laryngeal amyloidosis, different imaging modalities were applied. Computed tomography scan [74] has been found to be a non-specific diagnostic modality for localized amyloidosis [75], whereas Magnetic Resonance Imaging is believed to play an important role in forming the differential diagnosis of laryngeal calcified masses, in particularly in differing between amyloidosis and cartilaginous tumors [75].

Workup

A routine workup for amyloidosis is recommended in order to rule out a systemic disease. In our cohort, two patients (localization: larynx and tongue) developed a systemic disease. A recent study of Rudy et al. 22 cases of laryngeal amyloid reported of a 18%-rate of second-organ involvement, which should have ramifications on the workup of patients with newly diagnosed amyloid in the head and neck [13]. Therefore, an interdisciplinary collaboration with the department of internal medicine or a specialist in amyloidosis in order to rule out a systemic disease is highly recommended. The workup includes a routine blood work (electrolytes, bilirubin, creatinine, alkaline, phosphatase, search for monoclonal proteins, serum free light chain testing, WBC, RBC, thrombocytes, hemoglobin; Table 8), urinary examination including immunoelectrophoretic studies, urine Bence-Jones protein, investigation of the cardiopulmonary system (ECG, cardiac ultrasound, chest X-ray), assessment for hepatosplenomegaly and a biopsy of one other site, in general the rectum or abdominal fat pad [13, 26, 76]. One study of Philipps et al. suggests the assessment of serum amyloid P [26]. After injection of radio-labeled 123 iodine serum amyloid P (SAP), a scan localizes the amyloid depositions depending on the amount of the amyloid. In AL serum amyloid A amyloidosis [77], the reported sensitivity is fairly high with 90%, and therefore is considered to be the best modality in clinical use for evaluating a systemic distribution of amyloid in the body, regardless which amyloid type [78, 79].

Table 8 Workup for systemic amyloidosis

Workup for systemic amyloidosis
Renal system
Bloodwork
Electrolytes
Creatinine
Urine examination
Immunoelectrophoretic studies
Urine Bence-Jones protein
Hepatic system
Blood work
Bilirubin
Alkaline phosphatase
GGT
Liver transaminase
Abdominal ultrasound
Blood count
CBC
RBC
WBC
Cardiopulmonary system
Blood Work
Serum BNP
ECG
Cardiac ultrasound
Chest X-ray
Biopsy of another site: e.g., rectum, abdominal fat pad

Treatment

In general, localized amyloidosis is regarded as a benign disease, not necessarily requiring removal of the lesions. Management of localized amyloidosis in the upper aerodigestive tract depends on the symptoms each patient experiences. Therefore, the localization of the amyloidosis lesion is crucial. In our study, most of the patients suffered severely from the amyloid masses. The resection of the lesions was performed with cold steel in the larynx and pharynx, with CO_2 laser in the tongue. In bulky disease, the application of cold instruments, CO_2 laser or microdebrider for resection of laryngeal amyloidosis is recommended [6, 29, 75, 76]. In cases of recurrence, repeated resections are required. In particularly in laryngeal amyloidosis, the maintenance of an adequate airway is an issue. Thus, even small amyloid depositions may cause symptoms and are handled with endoscopic excisions or balloon dilatation [8]. In systemic amyloidosis, a treatment of high-dose Melphalan followed by autologous stem cell transplantation is favored [25]. It carries a high risk of mortality and, however, promises an improved median overall survival with up to 8.2 years, a 5-year survival rate of 63.9%, and 10-year survival rate of 43.4% [80].

Prognosis and Follow-Up

Concerning localized diseases, the prognosis is fairly well. In our cohort, most of the patients had a very short follow-up (mean 23.02 ± 51.17 months) or were lost to follow-up due to being asymptomatic. Two patients (13.3%) developed a systemic disease and were treated with chemotherapy. In systemic amyloidosis, the prognosis is in

general poor depending on the extent of organ involvement. When left untreated, the median survival is around 1–2 years [5]. Since it is known that amyloidosis, in particular in the larynx, can have a long latency, follow-up up to 10 years is recommended [25]. A recurrent amyloidosis war found in one of our patients (6.7%). Recurrence in laryngeal amyloidosis is reported up to 8–14 years, whereas some lesions are reported to remain unaltered for up to 17 years [29, 81]. Besides that, amyloidosis in the larynx is fairly frequent with one study reporting nearly half of the cohort developing localized recurrence of requiring subsequent resection of large lesions [82]. Therefore, a close collaboration with the treating general practitioner and education of the patient about the disease is crucial.

Conclusion

Amyloidosis in the upper aerodigestive tract remains a very rare disease. Nonetheless, every otorhinolaryngologist should be aware of this disease, when detected it is a straight forward to treat illness (Fig. 3). The appearance of a systemic amyloidosis needs to be ruled out, and thus there is a chance to develop a multiple myeloma. Given the slow progressive character of amyloidosis, a long-term follow-up up to 10 years is inevitable.

Acknowledgements The authors would like to thank Thore Thiesler, MD (Department of Pathology, UKB Bonn, Germany) and Julia Kitz, MD (Department of Pathology, UMG Goettingen, Germany) for performing the histological examination.

Author Contributions TS collected data, wrote parts of the manuscript. JS collected and analyzed data and wrote the manuscript. GS, AP, and AO recruited and examined the patients, provided graphical material and proof read the manuscript. FB and MC analyzed data and proof read the manuscript. MJ initiated the project, collected data and wrote parts of the manuscript.

Conflict of interest The authors declare no conflict of interest.

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