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REVIEW PAPER

Localized Nasopharyngeal Amyloidosis: A Clinicopathologic Series of 7 Cases with a Literature Review

Georgios Sakagiannis[1] · **Evangelos Giotakis**[2] · **Lester D. R. Thompson**[3]

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Abstract
Localized nasopharyngeal amyloidosis is an extremely rare entity with only 25 cases described in the English and German literature. We present a case series of seven patients with localized nasopharyngeal amyloidosis and combine the findings with a thorough review the literature.

Keywords Nasopharyngeal amyloidosis · Amyloidosis · Palatine tonsils · Nasopharynx

Introduction

Amyloidosis is a rare clinical entity that represents a group of disorders. It can be broadly classified as systemic or localized disease. Localized nasopharyngeal amyloidosis is an extremely rare entity with only approximately 25 cases described in the English and German literature. A case series of seven patients with localized nasopharyngeal amyloidosis and a thorough review of the literature are presented.

Materials and Methods

A search of the histology records in the University Hospital Attikon in Athens, Greece was performed and combined with the consultation cases of one of the authors (LDRT). All patient records with diagnosis of amyloidosis were retrieved and only patients with localized amyloidosis were included in this case series. A search of PubMed for cases classified as nasopharyngeal amyloidosis, amyloidosis, palatine tonsils, and/or nasopharynx were used to find studies published in English and German. Further reports were identified during the literature review. Duplicate papers were excluded, and the total number of 897 was reduced to 32 relevant papers. The case materials were histologically reviewed, specific studies to confirm amyloidosis evaluated, and a comparison made to the pertinent literature.

Case Reports

Case 1

A 74 year old Caucasian woman presented with a 1 year history of nasal obstruction and a sense of postnasal drip. Flexible nasendoscopy revealed the presence of a diffusely enlarged mass located in the nasopharynx that seemed to partially occlude the eustachian tube orifices and gave the impression of enlarged adenoids. The rest of clinical examination was unremarkable. A head and neck computed tomography scan confirmed the presence of a mass (Fig. 1), with a concurrent negative chest study. Biopsy of the lesion under local anesthesia and endoscopic guidance was followed by a wide excision. Both histopathology samples were diagnosed as amyloidosis (Figs. 2, 3, 4). After thorough clinical and laboratory evaluation, no systematic involvement was identified. Approximately 2 years after initial presentation, she again presented with a 2 weeks history of sense of foreign body in her mouth, mild to moderate dysphagia, and a recent onset of sleep apnea. The clinical exam showed diffusely enlarged palatine tonsils bilaterally. Intraoperatively, an en block resection of the tonsils was not achieved due to

✉ Georgios Sakagiannis
gsakorl@gmail.com

[1] Ear, Nose, Throat and Head and Neck Department, Attikon University Hospital, Athens, Greece

[2] Ear, Nose, Throat, Head and Neck Department, Hippokration University Hospital, Athens, Greece

[3] Department of Pathology, Woodland Hills Medical Center, Los Angeles, CA, USA

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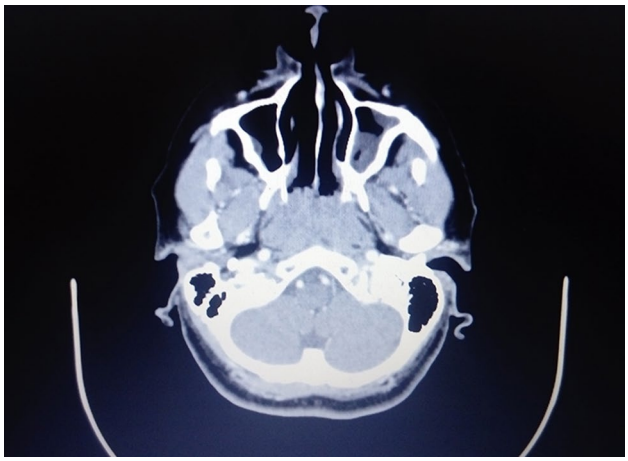

Fig. 1 Case 1. Axial CT image of the diffusely enlarged postnasal space mass

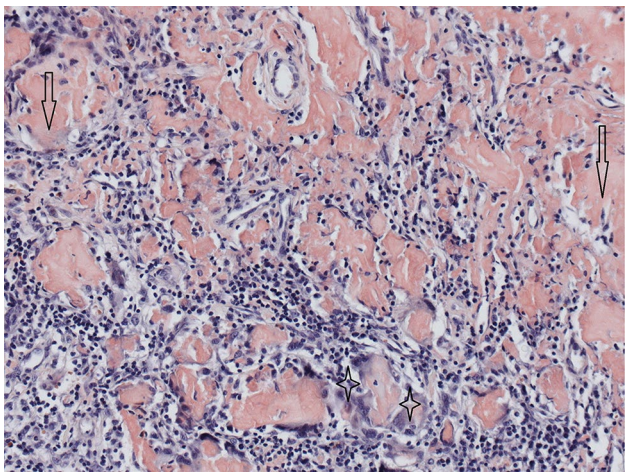

Fig. 2 Case 1. Masses of amyloid deposits (Congo Red positive/arrow) with multinucleated giant cells (star) and secondary inflammatory reaction, magnification ×20, Congo red stain/light microscopy

extreme fragility. The histological examination confirmed amyloidosis. No additional treatment was implemented.

Case 2

A 54 year old Caucasian woman presented with an 8 month history of nasal obstruction. Clinical examination with posterior rhinoscopy revealed the presence of an approximately 1 cm midline mass causing partial nasal obstruction. The rest of clinical examination was unremarkable. No imaging was performed and a biopsy was taken under general anesthesia that was interpreted to be amyloidosis. While lost to follow-up in 2001, there was no clinical disease recurrence in 29 years.

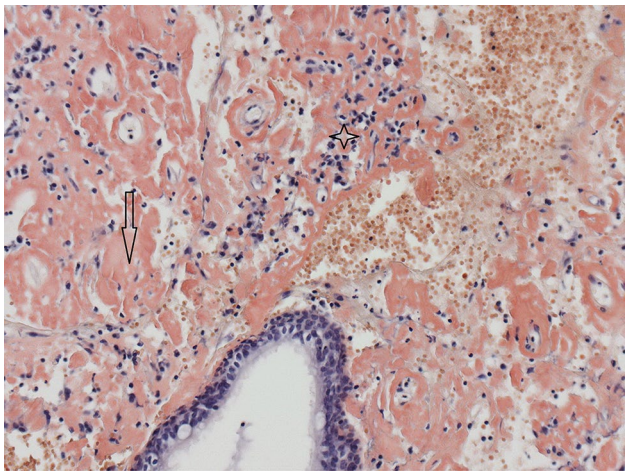

Fig. 3 Case 1. Subepithelial masses of amyloid deposits (Congo red positive/arrow) with few dispersed inflammatory cells (star). Magnification ×20. Congo red stain/light microscopy

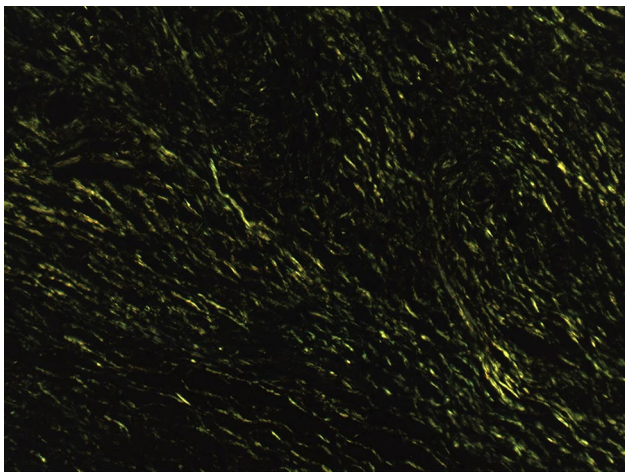

Fig. 4 Case 1. Congo red stain: amyloid deposits showing apple-green birefringence under polarized light, magnification ×20

Case 3

A 7 year old Caucasian female presented with an approximately 1 month history of nasal obstruction. She did not have associated symptoms of otitis media. At surgery, a 1.1 cm midline nasopharyngeal lesion was curetted. Her symptoms improved postoperatively.

The biopsy showed amyloidosis. Further clinical exam failed to disclose systemic disease. She is alive without evidence of disease 35 years after initial evaluation.

Case 4

An 18 year old Caucasian female was seen with a 2 month history of difficulty swallowing. No other symptoms were noted and her past medical history was unremarkable. A subtotal oropharyngeal obstruction was found upon clinical examination with a firm, mucosal covered 3 cm polyp attached to her left nasopharynx, identified as the source of her symptoms. The polyp was excised via a transoral approach under general anesthesia and was diagnosed as amyloidosis. Diagnostic work up did not identify systematic disease. She was disease free at last contact, 34 years after initial presentation.

Case 5

A 13 year old Caucasian boy was seen with a 3 month history of left ear plugging and recurrent episodes of left otitis media. No other clinical history was significant. Due to unilateral symptoms, he underwent flexible endoscopy revealing a 1.1 cm lesion of left nasopharynx. The subsequent MRI revealed left asymmetry in the soft tissues compared to right with partial occlusion of the eustachian tube. A biopsy under endoscopic guidance was found to be amyloidosis. Clinical evaluation showed no evidence of systemic disease, and he is free of disease without recurrence (4 years).

Case 6

A 63 year old Caucasian male, a previous surfer, was seen with a 4 year history of postnasal drip and some hearing difficulties. Clinical examination revealed the presence of bilateral external auditory canal exostoses, occluding about 80% of the canal, a likely cause of the hearing changes. While the nasal mucosa was mildly edematous, nasal endoscopy revealed the presence of a right 1.4 cm nasopharyngeal mass, which on biopsy revealed localized amyloidosis. After 4 years of follow-up he is disease free, without ever developing systemic manifestations of amyloidosis.

Case 7

An 81 year-old Afrocarribbean female presented with an almost 3 years history of chronic rhinosinusitis and eustachian tube dysfunction. The patient has a known history of sarcoidosis. Her symptoms in the sinonasal tract were interpreted to be part of systemic sarcoidosis. During workup, she noted reduced hearing, which was attributed to age related hearing loss although with an element of conductive loss. Flexible nasoendoscopy disclosed a 2.8 cm left nasopharyngeal mass causing partial airway obstruction and mild to moderate left eustachian tube occlusion. The mass was excised transnasally, interpreted as amyloidosis. While residual disease in the nasopharynx was noted 3 months later, intervening working failed to disclose systematic disease.

Discussion

Amyloidosis is a rare clinical entity. It is characterized by the extracellular presence of proteinaceous material comprised of various proteins subunits [1]. Virchow initially believed that the main component resembled starch (Greek word: amylon) and therefore the condition was misleadingly called amyloidosis in 1854. While more formally documented in 1843, there are reports from the seventeenth century of possible amyloidosis. The Congo red stain helped to characterize the extracellular deposits and was initially used by Benhoff in 1922. The introduction of electron microscopy years later further expanded the understanding of the disease by describing the fibrillary nature of the deposits in 1959 by Cohen and Calkins [2].

Clinical manifestations of amyloidosis vary and depend on the presence of localized or systemic disease. Systemic amyloidosis can be clinically classified as primary, secondary or familial but this classification, while helpful because of its simplicity, is considered obsolete. Amyloid deposits result from a precursor protein, which is misfolded resulting in the eventual deposition of fibrils [2]. If the amyloid deposition is limited to the tissue where its precursor protein is produced, then the disease is considered localized. Amyloid will be considered systemic if the precursor protein is produced in a different part of the body and thereafter transported to a site where the amyloid deposition is found [3].

Biochemically, there are four main types of systemic amyloidosis and 11 less frequently occurring ones. Nomenclature of amyloidosis starts with A (for amyloid) followed by an abbreviation for the dominant fibril protein. For example if the dominant fibril protein is an immunoglobulin (abbreviated L), patients are said to have light chain amyloidosis (AL). Other common biochemical forms of amyloidosis are AA amyloidosis where serum amyloid A protein (SAA), an acute phase reactant, is the precursor protein of this type and ATTR amyloidosis in precursor protein transthyretin (TTR) is the characteristic protein. This classification describes the protein but not necessarily the clinical expression of disease.

Treatment of systemic disease is usually very challenging as a result of systemic complications. Thus, management becomes quite specialized, requiring a multidisciplinary approach to include internal medicine, cardiology, nephrology, oncology or hematology input in decision making. Amyloidosis may be associated with malignancy, and thus proper workup and a step by step approach is important even when isolated lesions are discovered [4].

Localized amyloidosis in the head and neck area is rare and most cases described manifest themselves within the larynx (60%) and thyroid gland (amyloid goiter or a product of medullary thyroid carcinoma), followed by the trachea (9%), orbit (4%), and nasopharynx (3%). Amyloid deposits, of course, may be seen in literally any head and neck site (tongue, oral cavity, gingiva, parathyroids, skin, eyelid, lymph nodes, bone, nasal cavity and paranasal sinuses, salivary glands, external auditory canal, pinna and pharynx) [5, 6]. The majority of these lesions represent isolated amyloidosis, which is not correlated with increased morbidity and mortality or the sequelae (kidney, heart) associated with the systemic form. Generally speaking, treatment of local disease is typically excision followed by routine surveillance for recurrence.

Nasopharyngeal amyloidosis is extremely rare. Panda et al. described in their review in 2007 only 13 cases in over 70 years (1935–2007) [7]. There has been an increase in the number of reported cases, perhaps as a result of advancements in endoscopy techniques and imaging technology possibilities [8]. A summary table of all English published cases between 1935 and 2017 is presented in Table 1, while a second table with the biochemical characteristics of our seven cases is presented in Table 2.

Table 1 A summary of nasopharyngeal amyloidosis from literature and current series

#	Authors	Year published	Age/sex	Site	Main symptom(s)
1	Kramer and Som [9]	1935	nr	Nasopharynx	Nasal obstruction
2	Johner et al. [10]	1972	nr	Nasopharynx	Nasal obstruction
3	Simpson et al. [11]	1984	29/F	Nasopharynx	Postnatal discharge, glue ear
4	Zack Zong [12]	1984	14/M	Nasopharynx	Decreased hearing, glue ear
5	Gean-Marton et al. [13]	1991	32/F	Nasopharynx	Nasal obstruction, glue ear
6	Hegarty and Rao [14]	1993	nr	Nasopharynx/skull base	Nasal obstruction, postnasal drip
7	Panda et al. [15]	1994	82/M	Nasopharynx, oral cavity	Bleeding, postnasal drip
8	Dominguez et al. [16]	1996	13/F	Nasopharynx and soft palate	Nasal obstruction, oral bleeding
9	Lim et al. [17]	1999	42/F	Nasopharynx	Nasal obstruction
10	Pitkaranta and Malmberg [18]	2000	14/M	Nasopharynx	Nasal obstruction
11			41/F	Nasopharynx	Nasal obstruction
12	Munichor et al. [19]	2000	57/M	Nasopharynx, neck mass	Nasal obstruction
13	Patel et al. [20]	2002	nr	Nasopharynx	Serous otitis media, hearing loss
14	Zhuang et al. [21]	2005	81/F	Nasopharynx and neck	Neck mass
15	Motosugi et al. [22]	2006	46/F	Nasopharynx	Nasal obstruction
16	Panda et al. [7]	2006	43/M	Nasopharynx with oropharyngeal extension	Nasal obstruction, foreign body sensation of throat
17	Yoshida et al. [8]	2008	52/F	Nasopharynx	Incidental finding on PET/CT
18	Chen et al. [23]	2010	86/M	Nasopharynx	Postnasal drip
19	Wu et al. [24]	2011	72/M	Orbit-nasopharynx protrusion	Orbital symptoms
20	Karimi and Chheda [25]	2010	56/M	Nasopharynx	Aural fullness, otitis media with effusion
21	Durbec et al. [26]	2012	59/F	Nasopharynx	Nasal obstruction, aural fullness
22	Legaza et al. 27]	2012	43/M	Nasopharynx	Nasal obstruction, discharge, epistaxis
23	Mirza et al. 28]	2013	31/F	Nasopharynx	Fluctuating conductive hearing loss
24	Kumar et al. 29]	2016	55/M	Bilateral nasal cavity, nasopharynx, skull base	Epistaxis, obstruction, hearing loss
25	Luo et al. 30]	2016	39/M	Nasopharynx	Nasal obstruction, hearing loss, epistaxis
26	Present case 1	2017	74/F	Nasopharynx and Palatine tonsils	Nasal obstruction, dysphagia and apnea
27	Present case 2	2017	54/F	Nasopharynx	Nasal obstruction
28	Present case 3	2017	7/F	Nasopharynx	Nasal obstruction
29	Present case 4	2017	18/F	Nasopharynx extending to oropharynx	Dysphagia
30	Present case 5	2017	13/M	Nasopharynx	Otitis media with effusion
31	Present case 6	2017	63/M	Nasopharynx	Hearing difficulty and postnasal drip
32	Present case 7	2017	83/F	Nasopharynx	Eustachian tube dysfunction

nr not reported

Table 2 A summary of biochemical characteristics of our current series of nasopharyngeal amyloidosis

Case #	Age (years)	Sex	Kappa	Lambda	Transthyretin	Amyloid type
1	74	F	N	N	N	AA
2	54	F	n/a	n/a	n/a	AA
3	7	F	n/a	n/a	n/a	AA
4	18	F	N	N	N	AA
5	13	M	N	N	N	AA
6	63	M	N	N	N	AA
7	81	F	N	N	N	AA

M male; *F* female; *N* negative, *AA* acute phase protein, *n/a* not available

Based on the available information and the testing done, they are all AA cases, since there are no light chains or transthyretin identified.

There does not seem to be a sex predilection (13 males and 15 females) with a broad age range at initial presentation (7–86 years), although localized nasopharyngeal amyloidosis seems to affect mainly people older than 40 years of age (18 cases over 40 and 10 cases younger than 40 years).

As expected, localized amyloidosis mainly manifests with nasal obstruction (18 cases, 56%), while hearing changes, otitis media and eustachian tube dysfunction is also frequently reported in unilateral lesions (11 cases, 35%). Postnasal drip is seen less frequently (n = 4, 13%), with other symptoms less commonly identified (epistaxis, 9%; dysphagia or globus symptoms, 9%; bleeding, 6%). Depending on extent of disease, orbital or neck symptoms may also be seen. Rarely, incidental discovery is noted.

Imaging studies may help to define the extent of the disease and when calcifications are seen, suggest the possibility of amyloidosis, but no imaging findings are characteristic [13, 31]. Curiously, by MRI, early enhancement on dynamic contrast-enhanced MR may suggest the diagnosis [22]. Congophilia with associated green birefringence when viewed with polarized light remains the most widely used study to confirm the diagnosis [1, 2]. As techniques improve, determination of the protein structure or sequence may add to the diagnosis [1].

Surgery is the treatment of choice for localized head and neck amyloidosis and it should be employed when amyloid deposits cause morbidity. At present, there is no literature to support that non-treated localized amyloidosis progresses to systematic disease [32]. In cases of extensive amyloid deposits where an excision would cause more significant morbidity than the disease itself, a watchful waiting approach would be suggested, as disease progression is slow in many of the reported cases. A single case report reported that surgery with radiation led to complete remission [30], an approach suggested when surgical extirpation may be technically difficult to impossible. In all our cases where an excision rather than only a biopsy was performed, there was no residual or recurrent disease.

Conclusion

In summary, nasopharyngeal amyloidosis is a rare, slow progressive disease. Clinical recognition of this disease entity is difficult primarily as a result of its rarity, with histopathology confirmation required. In some cases, CT and MRI can contribute to the diagnosis before biopsies are obtained. As in any head and neck amyloid deposits, nasopharyngeal amyloidosis necessitates further assessment to exclude systemic disease, managed by a multidisciplinary team. In localized cases, excision would be the first treatment option. However, as this is usually a slowly progressing, benign process, maintenance of functional status must be considered. Adjuvant radiotherapy is a promising treatment option. Otolaryngologists need to include amyloidosis in their differential diagnosis despite its rarity.

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Compliance with Ethical Standards

Conflict of interest All authors declare that he/she has not conflict of interest as it relates to this research project.

Ethical Approval All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board, which did not require informed consent.

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