**TITLE PAGE**

# 100 cases of Localized Laryngeal Amyloidosis - Evidence for future management

Running title: 100 Cases of Localized Laryngeal Amyloid

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**ABSTRACT**

Objectives:

To update the current understanding of localized laryngeal amyloidosis by analyzing the NHS National Amyloidosis Database and to further clarify the important ongoing management issues.

Methods:

Patients with laryngeal amyloid were identified from the database of the NHS National Amyloidosis Centre, UCL, Royal Free Hospital, London between 2000 and 2017. Patient demographics and disease profile was collated, including exact location of amyloid deposit, treatments if any, and progression of disease.

Results:

103 patients with localized laryngeal amyloid where identified from the database, with a mean age of 54 at diagnosis and female to male ratio of 54:49. Three patients were excluded from further analysis due to limited database information. The majority of amyloid was found in either the supraglottis (44) or glottis (53) but all the laryngeal subsites were involved. One third of the patients (34) had amyloid in more than one laryngeal subsite. No patients were found to progress to systemic amyloid, but many progressed locally to other subsites or further down the LTB tree (29%). Three patients were successfully treated with radiotherapy after other modalities had failed.

Conclusions:

This is the largest case series reported to date of localized laryngeal amyloidosis. It highlights the high incidence of multifocal disease and the significant proportion of patients who progressed, not to systemic amyloidosis but to more extensive localized amyloid. We recommend that in all cases of laryngeal amyloid, patients should undergo a thorough assessment of the upper and lower airways and have ongoing surveillance for at least 15 years.

# 100 cases of Localized Laryngeal Amyloidosis - Evidence for future management

**Keywords**: amyloidosis, laryngeal amyloid, laryngotracheobronchial amyloid, larynx

**Level of Evidence:** Level 4

**Introduction:**

Amyloidosis is a group of diseases characterized by the extracellular deposition of insoluble proteins in tissues. These deposits, first described by Virchow in 1851( 1), are primarily made up of abnormal proteins, known as amyloid fibrils, formed when normally soluble proteins in the body, misfold and aggregate. These deposits can be found in either a localized or systemic distribution.

Modern classification of amyloidosis is biochemically based and depends on the precursor protein ( 2). Amyloidoses are referred to with a capital A (for amyloid) followed by an abbreviation for the fibril protein, such as L for the immunoglobulin light chain, A for serum amyloid A protein, TTR for transthyretin, or ß2M for beta-2 microglobulin. At present there are over 36 different human proteins recognized to misfold and form amyloid fibrils.( 3)

Despite this variability in precursor proteins, all types of amyloid share a number of common features. They all have a similar protein conformation (twisted beta-pleated

sheet) which gives rise to the characteristic binding of Congo red dye (figure 1), and apple-green birefringence when viewed with polarization microscopy ( 4)(figure 2). In their abnormal amyloid confirmation, the fibrils bind serum amyloid P component (SAP) which is thought to contribute to the stability of the amyloid fibril and helps resist proteolysis.( 1)This is the basis for non-invasive imaging of amyloid deposits with SAP scintigraphy.

Localized amyloidosis can be found anywhere within the body( 5) with the larynx one of the most common locations (14-15%). Bladder and cutaneous tissue are also frequent sites of involvement. ( 6, 7 8) When amyloid is localized in the larynx, it is usually the AL type, where the fibril precursor protein is either kappa or lambda light chains, derived from monoclonal immunoglobulins( 7)The amyloid deposits appear as non-specific submucosal swellings, often with a yellow tinge (figure 3)

Aetiology of localized amyloidosis remains unclear. While the vast majority of cases are derived from immunoglobulin light chains, it is unclear why these misfolded proteins accumulate in this localized fashion( 9). Although there is no proven link to smoking, vocal misuse or recurrent infections ( 1 9), one theory suggests a response of circulating precursor proteins, plasma cells and/or immunoglobulins, to localized injury and inflammation. Another more likely theory suggests a localized collection of monoclonal plasma cells( 10 11) and inability of the body to clear the excessive or misfolded immunoglobulins produced by monoclonal plasma cells found in the mucosa (mucosa-associated lymphoid tissue or MALT). Westermark hypothesises further that giant cells, prevalent in localised amyloid deposits but not systemic, are

important in transforming the immunoglobulin light chain into the misfolded amyloid fibrils ( 5).

Systemic AL amyloidosis is commonly due to a plasma cell dyscrasia, with circulating monoclonal light chain proteins misfolding and forming amyloid fibrils that deposits throughout the body. It is often associated with high morbidity and mortality due to multiorgan involvement, with cardiac and renal failure the leading causes of death.( 4) The liver as well as  peripheral and autonomic nerves are other organs also commonly affected.( 7 12 13)

Very occasionally, laryngeal amyloid deposits can be part of more widespread systemic disease ( 7) and has been reported as part of the hereditary apolipoprotein A-1 derived amyloid (AApoA1). This very rare hereditary form of amyloidosis is usually, but not always,  systemic and was described by Hazenburg et al as initially presenting in the larynx ( 14). The AApoA1 deposits were soft irregular proliferations of the vocal cord edge rather than the more bulky firm deposits seen with AL.

**MATERIALS AND METHODS:**

The National Amyloid Centre (NAC) located at Royal Free Hospital, part of University College London, is a clinical and research NHS facility that provides diagnostic services and advice on management to all patients in the UK diagnosed with amyloidosis. The NAC database therefore allowed for a unique opportunity to study the largest cohort of patients with localized laryngeal amyloid ever reported.

A retrospective review was performed of the NAC database to identify all the patients diagnosed with localized laryngeal amyloid between 2000 and 2017 after a full clinical evaluation. Approval for analysis and publication was obtained from the National Health Service institutional review board and written consent was obtained from all patients in accordance with the Declaration of Helsinki. Patient demographics and disease profile was collated, including age and sex, presenting symptoms and signs, exact location of amyloid deposit, treatments and progression of disease, if any.

**RESULTS:**

One hundred and three patients were identified from the database for review (54 were female and 49 were male) (table one). The mean age at diagnosis was 54 with a range of 14 to 83 years. Three patients had very limited information in the database and were excluded from further analysis. Of the analyzed patients, 3 had amyloid of ApoA1 type. One patient had a wild type ApoA1 mutation, the second a hereditary A164S mutation and the third was not specified. These patients had dysphonia as their presenting symptom and more systemic disease was excluded after their initial workup at the NAC (table 2).

Dysphonia was by far the most common primary complaint (83%) but other symptoms included cough, shortness of breath, foreign body sensation and wheeze. Four patients were diagnosed after an incidental finding.

Of the subsites involved, the glottis was marginally more common (53 patients) than the supraglottis (44 patients). 26 patients had disease in the subglottis and 11 had evidence of amyloid distally into the tracheobronchial tree. 8% of patients were known to have amyloid in other subsites outside the larynx – 3 nasal cavity, 1 palate, 2 paranasal sinus and 2 in the postnasal space.

Of the 100 patients, two thirds (66) had amyloid localized to one laryngeal subsite with 34 patients having more than one subsite involved. Most amyloid deposits (56/100) were single discrete lesions, however 44 patients were found to have multiple amyloid deposits. Of the 66 patients who had amyloid in only one subsite, 10 had multifocal disease or more than one deposit in that subsite.

Eleven patients had laryngotracheobronchial (LTB) tree amyloid. In at least 9 of these patients, the amyloid was first diagnosed at the glottis before progressing further down the LTB tree while the remaining 2 patients had laryngeal deposits as well as LTB deposits at the initial diagnosis.

65 patients had ongoing follow up data which ranged from one to 365 months (average 39.5 months, median 16 months). 23 patients were followed up for over 3

years and 13 patients were followed for over 5 years. The longest follow up was 30 years in a patient that was first diagnosed at the age of 14.

None of the patients who were diagnosed with laryngeal amyloid were documented to progress to systemic amyloidosis.

Many patients did however, progress locally with further lesions within the same laryngeal subsite (26) or into other subsites (17), either within the larynx, upper aerodigestive tract or inferiorly into the tracheobronchial tree.

32 patients required only one treatment while 34 had a more progressive disease that required multiple treatments over many years. Of these patients with progressive disease, only 27 patients had documented further surgical interventions with data that was able to be analyzed. Time to further surgical intervention ranged from 3 months to 14 years with an average of 4.6 years and a median of 3 years. 4 patients did not need surgical intervention until 10 years after their initial diagnosis. Surgical interventions ranged from laser resection and debulking, balloon dilatation and cold steel resection. This was dependent on the referring surgeon and was not performed at NAC.

Three patients had such significant disease that radiotherapy was offered and used as a successful treatment option. These patients had progressive multifocal amyloid disease in the supraglottis, subglottis and LTB tree. They were offered radiotherapy when the frequency of surgery to alleviate their symptoms was too high for the

patient or surgery was no longer safe to perform due to the extent of disease into the LTB tree.

**Discussion:**

We describe the largest reported cohort of patients with localized laryngeal amyloidosis. Amyloidosis is a very rare group of diseases, with the larynx involved in only 9% - 15% of all cases ( 15 16 ) Due to the paucity of localized laryngeal amyloidosis, the literature contains mostly case reports and small case series ( 3 9 17), leaving the disease poorly understood and management decisions lacking in any high level of evidence.

Previously, the largest cohort of localised laryngeal amyloid was a subset of Mahmood et al's long-term observational study( 7). This was taken from the same NAC database from 1980 to 2011 and their 92 patients also included those with tonsillar amyloid. This paper analyses in further detail, 100 cases of localized amyloid of the larynx which were seen at NAC between 2000 and 2017.

Localized laryngeal amyloidosis, accounts for 0.2 to 1.2 per cent of all benign laryngeal tumors( 3) It typically presents with dysphonia, but other symptoms, such as foreign body sensation, cough or shortness of breath, can be the primary complaint and depends on the exact site of fibril deposition. Some patients are

asymptomatic and diagnosed after an incidental finding as occurred with four of our cohort.

Similar to the larger case series( 1 6 15 18) already in the literature, we found no clear male or female predominance (54F, 49M). This is similar to localized (AL) amyloid disease found elsewhere in the body ( 7) Localized laryngeal amyloid can present at any age with our patient cohort ranging from 14 to 83 years of age. While it does appear to have a peak incidence in the 5$^{th}$ decade, patients as young as 8 have been reported( 3)

Although the data suggests that the glottis and supraglottis where the more common subsites (53% and 44% respectively), we suggest the more important message is the multifocal nature of localized laryngeal amyloidosis. Over a third of the patients (34%) had amyloid deposits in more than one laryngeal subsite, and 19% of patients had amyloid deposits outside the larynx (8% superiorly in the upper airway and 11% inferiorly into the tracheobronchial tree). Even if only one laryngeal subsite is involved with amyloid deposits, there can often be more than one deposit in that one area.

**This highlights the need for comprehensive examination of the entire airway looking for multiple amyloid deposition**. The upper airway should be visualised with camera, either with a video nasendoscope or in theatres, and a high level of suspicion maintained for other amyloid deposits. We would also recommend a HRCT chest to assess the lower airway.

The larynx can be involved with systemic amyloidosis ( 19) so it is important to determine if the laryngeal deposits are truly localized disease or part of more widespread systemic disease. Table 2 summarizes the recommended workup for these patients which is usually done in conjunction with a rheumatologist. This starts with serum and urine immunofixation and electrophoresis and serum assessment of organ function with imaging including SAP scan where available and CT/MRI chest, abdomen and pelvis if indicated. MRI is the modality of choice when evaluating for cardiac amyloidosis.

Abdominal fat aspirate is a well-tolerated investigation and may be safer than taking a biopsy from a suspected organ with amyloid deposit. Abdominal fat aspirate has a sensitivity approaching 80% for those with systemic disease. ( 19) Scintigraphy following administration of $I^{123}$ labelled SAP is a nuclear scanning technique that was developed at the NAC and used to identify amyloid deposits within solid organs. With a sensitivity of 90% for systemic AA and AL amyloid ( 20), it can also be used to rule out systemic disease in these patients. Unfortunately, SAP scintigraphy is not widely available, and its main role is in monitoring patients with systemic disease.

None of our cohort of patients with localized laryngeal amyloid had documentation of progression to systemic disease. A clear limitation of our study however is that patients, especially those diagnosed with localized disease, are often followed up by the referring doctor once they have been assessed. While we would suspect that any progression to systemic disease would be referred back to the NAC, long term follow up data is lacking.

Due to the significantly higher morbidity and mortality of systemic amyloidosis, the possibility of localized amyloid progressing to systemic disease has always been a concern for treating physicians. If we look at localized amyloid disease in other areas of the body, the literature suggests that it is exceedingly rare . The Mayo Clinic recently published their experience of localized AL amyloid found throughout the body ( 6), and they did not find any progression into systemic disease in their cohort of 413 patients. They went further to suggest that most cases of systemic AL progressing from localized disease were likely missed diagnoses to begin with.

In the previous study of the NAC database looking at all patients with localized AL amyloid ( 7) seven of the 606 patients (1%) with localized disease progressed to systemic disease, but none of these patients had laryngeal disease initially. 5 of these patients were initially diagnosed with localized lymph node amyloid and another had localized amyloid of the bone. Lymph node involvement has been shown in one study ( 21) to be a risk factor for progressing to systemic AL amyloidosis. These seven patients progressed to systemic disease between 20 months and 7 years after initial diagnosis.

In the more recent review by Basset et al ( 10,) they observed systemic progression in 1% of their overall cases of localized amyloid (293 cases) as well. Neither of these three patients had amyloid in the larynx (lung and nasopharynx) and the progression did not involve the heart, kidneys or liver.

One recent review ( 22) suggested a patient from a previous series by Rudy et al had developed systemic amyloid 10 years after initial diagnosis of laryngeal amyloid.

This series however discusses a 67yo male who had amyloidosis involving heart, colon, orbit and sinuses and *then* developed laryngeal amyloid 10 years after this initial diagnosis ( 15). Interestingly there was one 37yo female with laryngeal amyloid who was found to have colon involvement one year later. There is no discussion however about the extent of initial workup for these patients and again raises the possibility that more extensive amyloid disease was missed at the original presentation.

Bartels et al reported a patient who developed systemic disease after an 8-year period of localized laryngeal amyloidosis ( 23). The patient's diagnosis and initial treatments were done at another hospital and details of the initial diagnosis and workup were not provided. In communications with the author, it is suggested that this patient may have had systemic amyloid from the beginning, supporting Kourelis et at. Apart from these two cases that may have been systemic disease to begin with, **we have not been able to find any well documented cases in the literature of localized laryngeal amyloidosis progressing to widespread systemic disease.**

Although we did not have any patients that developed systemic disease, 43 per cent of the patients were found to progress locally, either within the same laryngeal subsite (26) or into a different site (17). While our follow up data is incomplete, it does suggest that some patients will progress slowly with at least 4 of our patients undergoing surgical intervention over 10 years after their initial diagnosis was made. In Dedo's report on 10 patients with laryngeal amyloid, one patient returned with recurrence 16 years after initial treatment ( 24)

**Therefore long term follow up is necessary for all patients with localized laryngeal amyloid.** This should include regular comprehensive examination of the upper airway with video nasendoscope as a minimum, as well as HRCT chest if there is any suggestion of progression into the LBT.

34% of our cohort had documentation of more than one surgery to the laryngeal amyloid. This high rate of recurrence and need for ongoing surgery is well documented in the literature with Hazenburg et al suggesting that up to two thirds may need revision surgery, half of them within one year after initial surgery (20).

While previous open procedures such as laryngofissure have been described ( 25 26), endoscopic surgery is now the main stay of treatment. Numerous techniques have been described ( 12 22 24 27) including cold steel, coblation and laser without any clear superiority.  In an organ such as the larynx, preserving function needs to be prioritized given the benign nature of this disease.  The aim of any surgery therefore, should be to debulk and reduced the symptoms attributed to the amyloid disease without significantly impacting the function of the larynx, rather than completely clearing the amyloid deposits. This is likely to impact on the rate of recurrence and need for further surgery.

While endoscopic surgery is the main stay of treatment, our cohort highlights the need to explore other options with three patients undergoing radiotherapy treatment.

Our three patients had progressive multifocal amyloid disease and were either unable to tolerate the frequency of the surgery required to improve their symptoms, or were unable to have surgery as the extent of disease into their LBT meant surgical risk was too high. They received radiotherapy at different institutions (20G in 10 fractions), and all responded well with no further progression of their disease.

Indications for considering radiotherapy should include rapidly progressive or recurring disease that remains localized but threatens the patient's airway, swallowing or voice, should surgical debulking continue to proceed. More extensive disease would also be an indication, when surgical resection is not possible due to the large area involved, or the possible morbidity is too high. These decisions should take into account the patient's ability to receive multiple surgical treatments, on grounds of health or inability to travel to specialist medical facilities.

While not first line, treatment of localized amyloidosis with radiotherapy has been reported with good outcomes and absence of progression, presumed by targeting the clonal proliferation( 28 29 30 31) Doses range from 20 – 45 Gy fractioned over 10-20 fractions and treatment is aimed at arresting the progression of disease rather than cure. Patients with LTB disease, can be very symptomatic and difficult to treat due to the higher morbidity and mortality from surgical interventions 27 32 33. Radiotherapy, especially for this subgroup, may be an underutilized treatment option.

As a retrospective database review, this study had a large proportion of patients that were either discharged back to their treating otolaryngologist after review or lost to

follow up. Therefore, data on progression and surgical interventions is incomplete and likely to have been underestimated.

**Conclusion:**

With 103 patients, this is the largest case series reported to date of localized laryngeal amyloidosis. There is no gender predominance or typical anatomical distribution. More importantly, this review highlights the high incidence of multifocal disease and the significant proportion of patients who progressed, not to systemic amyloidosis but to more extensive localized amyloid. These findings lead us to recommend that in all cases where laryngeal amyloid is identified, patients should undergo a thorough assessment of the upper and lower airways and have ongoing surveillance for at least 15 years.

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Table one

| DEMOGRAPHICS | n=103 |
|---|---|
| Male | 49 |
| Female | 54 |
| Age range | 14-83 |
| Median | 53 |
| Mean | 54 |
| SITE INVOLVED | |
| One subsite only † | 66 |
| Multiple subsites | 34 |
| Supraglottis | 44 |
| Glottis | 53 |
| Subglottis | 26 |
| LTB | 11 |
| Other | 8 |
| No data available | 3 |
| LOCAL PROGRESSION ‡ | |
| Same site | 26 |
| Different site | 17 |
| Discharged or no data available | 60 |

† 10 patients had more than one deposit in that single subsite (multifocal)

‡ incomplete data as some patients followed up with local otolaryngologist

| MANAGEMENT [§] | |
|---|---|
| Surgery | 32 |
| Multiple surgeries | 34 |
| Discharged or no data available | 37 |
| Radiotherapy[¶] | 3 |

Table 2

[§] incomplete data as some patients followed up with local otolaryngologist

[¶] radiotherapy as well as previous surgery

| Workup for systemic disease |
| --- |
| • Serum and urine electrophoresis and immunofixation<br>• Assessment of organ function: serum biochemistry, proteinuria, cardiac function by imaging and biomarkers<br>• SAP scintigraphy if available<br>• Abdominal fat aspirate<br>• Bone marrow aspirate and trephine if circulating monoclonal immunoglobulin detected<br>• CT chest/abdomen/pelvis if clinically indicated<br>• Cardiac MRI if clinically indicated |

**Figure legend**

Figure 1 – congo red dye binding to amyloid deposits

Figure 2 – apple-green birefringence when viewed under polarization microscopy

Figure 3A – note the yellow appearance of the submucosal amyloid deposits on the left arytenoid and vocal process as well as under the right vocal cord.

Figure 3B – subglottic amyloid deposits extending into the upper trachea