Laryngeal amyloidosis, an analysis of 11 cases

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Abstract

Introduction
Amyloidosis is a disease characterized by extracellular deposition of insoluble protein called amyloid. Isolated laryngeal amyloidosis is rare, and accounts for only a few percent of benign laryngeal tumors. In contrast to systemic amyloidosis, local amyloidosis does not appear to affect life expectancy. Men are at a slightly higher risk than women, and the mean age at time of debut is between 40 and 60 years old. Earlier studies have shown that the risk of developing systemic disease is small when isolated laryngeal amyloidosis is diagnosed.

Material and methods
11 patients with histologically verified laryngeal amyloidosis treated at Oslo University Hospital between 1999 and 2013 were studied retrospectively. Different parameters were studied in relation to the anatomical sub site affected.

Results
In our cohort the sub- and supraglottis were the areas most affected. 10 of our 11 patients had dysphonia as part of the presenting symptoms. We found a correlation between anatomical subsite and both presenting symptoms and risk of relapse of symptoms after surgery. We also found a positive correlation between sum of surgical interventions and risk of recurrence, and indications of the disease being more aggressive in patients who were diagnosed when younger than 40 years old. The average follow up of our patients was almost 11 years, and none of our patients developed systemic disease.

Conclusion
Laryngeal amyloidosis is rare. However, most patients will be diagnosed correctly based on the presenting symptoms. The presenting symptoms and risk of residual disease are correlated to anatomical sub site affected, and when diagnosed in patients younger than 40 the disease appears to be more aggressive. Although there is no significant impact on life expectancy, the risk of residual disease is high and long term follow up is needed.
Introduction
Localized amyloidosis is rare, but has been reported in a variety of organ systems [1]. In the head and neck region, the larynx is most often affected [2]. Amyloid deposits account for less than 2% of all benign laryngeal tumors, and the laryngeal ventricles as well as the false and true vocal cords (plica ventricularis et vocalis) are the most frequently affected subsites [2-6]. Previous studies have reported that amyloidosis of the larynx primarily presents among patients aged 40-60 years with a slight predominance among men (M/F-ratio 2:1.4) [1, 5, 7]. A review of the literature conducted by Biewend, M.L., D.M. Menke, and K.T. Calamia in 2006 showed a total of 290 cases of localized amyloidosis with 14 cases (4,83%) localized in the larynx.

Amyloidosis is often associated with impaired organ-function due to an overproduction of insoluble protein and the disease is rarely curable. Earlier studies [8, 9] on localized amyloidosis, however, have shown that it is seldom linked to systemic involvement and does not significantly affect life span [10]. As a localized disease it should be eradicated surgically, however, due to possible residual disease and development of systemic amyloidosis long time follow up is recommended.

The purpose of this study was to examine the presenting symptoms of patients with localized laryngeal amyloidosis; and if presenting symptoms, relapse of symptoms after surgical intervention and likelihood of recovery is correlated to the anatomical sublocalization of the amyloid in the larynx. Furthermore to evaluate whether the course of our cohort evolved into systemic amyloid disease.

Background
The cause of local amyloidosis is presumed to be local synthesis of amyloid, in contrast to the systemic amyloidosis with widespread distribution of amyloid fibrils [11]. There has not been found any association with alcohol use, smoking, vocal abuse or infections [2].

Biochemical nature and histopathology
Amyloidosis is a disease characterized by extracellular deposition of a non-soluble substance known as amyloid. Amyloid consists mainly of protein with an altered tertiary structure, making it organized in fibrils. This fibrillary protein varies with the underlying cause of the disease, but all amyloid fibrils have the same characteristic cross-ß sheet quaternary structure [12].

The typical macroscopical appearance of an amyloid lesion is a firm, non-ulcerating, orange-yellow to gray epithelial nodule [1]. Histologically it usually presents as extracellular amorphous hyaline material that is diffusely scattered in the tissue (picture 1).
The diagnosis of amyloidosis is histological and based on the staining characteristics. When stained with congo red and seen under polarized light, amyloid shows so-called apple-green birefringence (picture 2).

Types of amyloidosis and nomenclature
Previously amyloidosis was classified based on the clinical picture of the disease. The current classification of amyloidosis is based on the nature of the fibrillar protein. There are numerous proteins that can make amyloid, and therefore many forms of amyloidosis. We know of 30 human amyloid proteins [13] and many of these proteins circulate as normal constituents of plasma.

The two major forms of amyloidosis are AL and AA amyloidosis. AL amyloidosis is a monoclonal plasma cell disease where there is an overproduction of immunoglobulin light chains and these are deposited in different organs. Localized amyloidosis in the larynx is most often AL amyloidosis [15].

AA amyloidosis is perceived as a complication to chronic inflammation leading to
an overproduction of serum amyloid A (SAA). Currently we cannot explain why some people with chronic inflammation develop AA amyloidosis, and others do not.

Local vs. systemic
Whether amyloid is accumulated locally or widespread, we classify the disease as local or systemic.
   Localized amyloidosis accounts for 9 - 15% of all amyloid cases [16] and has been described in nearly every organ system [1].
   The organs most often affected by systemic amyloidosis are liver, kidneys, heart, spleen and pancreas.

Clinical manifestations and diagnostics of laryngeal amyloidosis
The pathology of amyloidosis is due to amyloid displacement of normal tissue, obstructed blood flow and direct toxic effects [17]. Thus, the symptoms of laryngeal amyloidosis are correlated to the size and sub site of the tumor [18].

Patients may present with cough, globulus, hemoptysis or stridor, but the most frequent symptom is dysphonia [1, 19, 20]. The symptoms often lead to a laryngoscopy where amyloid lesions may have the typical macroscopical appearance as mentioned in the section ‘Biochemical nature and histopathology’. However, the diagnosis of amyloidosis is histological, and a biopsy is needed. To this day we have no way of telling which organ manifestations a patient has or will get by examining the protein.

Laryngeal amyloidosis does not seem to have a significant impact on life expectancy [10], whereas patients diagnosed with systemic amyloidosis have a median survival time of less than two years [16]. Nevertheless, death caused by laryngeal amyloidosis has been reported [21].

According to UpToDate’s guidelines per December 31 2013, an investigation of systemic amyloidosis is only recommended when there is more than one organ involved. The preferred way of investigating for systemic disease is through a fine needle aspiration of abdominal fat, with a sensitivity of 70-80% [22].

Treatment of laryngeal amyloidosis
Treatment of laryngeal amyloidosis ranges from observation to hemilaryngectomy [23]. Extirpation of the amyloid tumor with maintenance of functional anatomy is the goal of treatment [23-25]. Currently, the most popular and recommended approach is transoral endoscopic microlaryngoscopy with a carbon dioxide laser, which is the standard treatment at our Department.

Prognosis of laryngeal amyloidosis
As reported by Ma et al [2], Pribitkin et al [25] and Talbot et al [26] the likelihood of relapse of symptoms after primary surgical resection is prominent. Often the surgery has to be repeated due to growth of residual disease or as a two-step procedure due to bulky tumors [2]. Regular and long-term follow-up is required [2, 25, 26].
In the above mentioned literature review done by Biewend, M.L., D.M. Menke, and K.T. Calamia in 2006, 286 of the 290 cases (98 %) of localized amyloidosis remained free of systemic disease. 4 of the patients had systemic involvement diagnosed during follow-up, but this might have been a result of failing to diagnose systemic involvement initially [1].

**Materials/Methods**

We undertook a retrospective analysis of all primary cases of histologically verified laryngeal amyloidosis treated at the Department of Otorhinolaryngology, Division of Surgery and Clinical Neuroscience at Oslo University Hospital during 1999 to 2013.

Information concerning the patient's previous and current medical condition was obtained from our hospital records, through regular feedback from the local hospital or family physician, autopsy records, telephone interview of patients themselves or from the next of kin.

The patients were registered according to gender, age, symptomatology, laryngeal subsite affected, type and number of treatments and complete follow-up. The anatomical subsites were defined as either glottic, supraglottic or subglottic respectively.

Patients who after surgery presented with relapse of symptoms returned to our department for further examination and repeated surgical intervention. Accordingly, the number of surgical procedures reflects the number of relapses for each individual, whether as a result of new amyloid lesions or growth of residual disease.

Follow up was set from the date of the primary diagnosis to the last date of recorded follow-up and/or to death of either cause.

We also conducted a review of the literature, by searching in Pubmed with the search phrase "amyloi* AND laryn*". The selection of literature was based on the availability of full text articles, language and the subjective quality of the article.

**Results**

A total of 11 patients with primary amyloid lesions in the larynx were found. None of the patients had evidence of systemic rheumatic or hematological disease. All 11 cases were histologically verified through histological examinations done by a pathologist. None of the patients had systemic amyloidosis at the time of debut.

**Table 1: Summary of cohort**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex and age</th>
<th>Debut symptom</th>
<th>Sub site</th>
<th>Clinical correlation</th>
<th>Treatment</th>
<th>Times operated</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M 38</td>
<td>Dysphonia, dyspnoea</td>
<td>Subglottis</td>
<td>Primary localized amyloidosis</td>
<td>Surgery: Co2-laser</td>
<td>5</td>
<td>NED, being followed-up, follow-up time: 12 years</td>
</tr>
<tr>
<td>2</td>
<td>M 42</td>
<td>Stridor</td>
<td>Subglottis</td>
<td>Primary localized amyloidosis</td>
<td>Surgery: Co2-laser</td>
<td>1</td>
<td>NED, being followed-up, follow-up time: 7 years</td>
</tr>
<tr>
<td>3</td>
<td>M 54</td>
<td>Dysphonia</td>
<td>Subglottis</td>
<td>Primary localized amyloidosis</td>
<td>Surgery: Co2-laser</td>
<td>3</td>
<td>Follow-up discontinued after 12 years, mild stable symptoms</td>
</tr>
</tbody>
</table>
Table 2: Parameters in relation to sub site. The numbers reflect patient number shown in table 1

<table>
<thead>
<tr>
<th></th>
<th>Subglottis</th>
<th>Glottis</th>
<th>Supraglottis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>6, 7</td>
<td>8, 9, 10</td>
</tr>
<tr>
<td>Male</td>
<td>1, 2, 3, 4</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td>1</td>
<td>5, 6</td>
<td>8</td>
</tr>
<tr>
<td>40-49 years</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td>3</td>
<td>9, 10, 11</td>
<td></td>
</tr>
<tr>
<td>60-69 years</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;69 years</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1, 2, 3, 4</td>
<td>6, 7</td>
<td>8, 9, 10</td>
</tr>
<tr>
<td><strong>Symptom of debut</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td>3</td>
<td>5, 6, 7</td>
<td>8, 9, 10</td>
</tr>
<tr>
<td>Stridor</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Dysphonia and dyspnoea</td>
<td>1, 4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Developed systemic amyloidosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1, 2, 3, 4</td>
<td>5, 6, 7</td>
<td>8, 9, 10, 11</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exirpation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>1, 2, 3, 4</td>
<td>5, 6, 7</td>
<td>8, 9, 11</td>
</tr>
<tr>
<td><strong>Follow up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td></td>
<td>7</td>
<td></td>
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<tr>
<td>5-10 years</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>10-15 years</td>
<td>1, 3, 4</td>
<td>5</td>
<td>10, 11</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still in follow-up</td>
<td>1, 2, 4</td>
<td>5, 6</td>
<td>11</td>
</tr>
<tr>
<td><strong>Times operated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1, 2</td>
<td>5, 6</td>
<td>11</td>
</tr>
</tbody>
</table>
We found a male/female ratio of 1:2:1. The mean age at diagnosis was 48.2 years (range 32-72.5 years). No significant difference in age was found between males and females. 9 out of 11 patients were non-smokers.

Regarding sub site, only 27% was localized to the glottic region whereas the subglottic and supraglottic region represented more than one third (36%) respectively. 7 of our 11 patients had dysphonia as their only presenting symptom, and 10 out of 11 patients had dysphonia as part of their symptoms.

All 11 patients were treated surgically and primarily in terms of endoscopic CO2-laser resection, except one case managed with cold instruments. 8 of the 11 patients underwent surgery more than once and each patient was operated 2.7 times on average.

During the study period, the follow-up ranged from 4 to 18 years with an average of 10.73 years. The 4 patients excluded from further follow up due to no or only modest symptoms, had follow up at an average of 10.8 years, whereas the rest has been under continuous follow up (11.8 years). Some patients with no evidence of disease are still under follow up.

None of our 11 patients developed systemic amyloidosis. Unfortunately, we were not able to obtain information on which subtype of localized amyloidosis our patients had. This would be an interesting parameter to study with relation to symptoms and recurrence rate.

Involvement of the glottic region correlated strongly to the debut symptoms, as all our patients with lesions in the glottic area had dysphonia as their only symptom. 3 out of 4 patients with supraglottic located amyloid also had dysphonia as their debut symptom. None of the patients with lesions in the glottic area had dyspnoea as part of their presenting symptom, whereas 50% reported dyspnoea among the subglottic group.

The number of surgical interventions showed an uneven distribution in relation to laryngeal subsite. Patients with lesions in the glottic area had surgery at an average of 2.33 times, whereas surgery was performed 2.75 times among lesions in the subglottic area. Patients with lesions in the supraglottic area were operated at an average of 4 times, which could reflect a greater risk of aggressive disease in case of supraglottic involvement, though no statistical significance was found (p>0.05).

During follow-up 3 out of 4 patients in the subglottic group had either no symptoms or were withdrawn from further follow-up because of clinically unaffected anatomy by laryngoscopic evaluation.

In the glottic group, two-thirds still had their laryngeal lesions when evaluated laryngoscopically; one was lost to follow up. The cases with glottic amyloidosis had the least extent of surgery, but were subjected to greater degree of symptoms.
In terms of symptoms, 3 out of 4 among the supraglottic group were considered mildly affected and follow up was passed on to the referring entity or the patients’ general practitioner.

Of the 8 patients who were operated more than once, 4 patients had residual disease indicating that one did not achieve radicality during the primary intervention. 3 patients presented with both residual disease as well as new lesions in other areas of the larynx. In one patient we were not able to obtain information about the localization of the second surgical procedure.

Discussion
Most articles on this field are case reports, and there are few cohorts of more than 10 patients. Nevertheless, the findings in our 11 patients will not be statistically significant. Still, it may be a contribution to the growing understanding of this disease.

The patients we present in our study were all examined, diagnosed, treated and had their first post-operative follow-up at the same department. This means that each patient was subjected to a standardized clinical evaluation as well as surgical intervention and follow-up, which may eliminate potential bias.

In consistence with earlier reports we found a slight predominance of men in our material [1, 5, 7]. The average age among our cohort supports previous observations showing that people aged 40-60 years are more prone to get the diagnose [1, 5, 7]. However, only 5 of our patients were aged between 40 and 60 years at the time of symptom debut.

The anatomical subsites with highest predominance of lesions are known to be the laryngeal ventricles as well as the false and true vocal cords [2-6]. This correlates to our glottic and supraglottic area. In our study we found an equal number of patients with lesions in the subglottic and supraglottic area, whereas glottic lesions represented a minority.

Earlier findings have shown that the most frequent symptom is dysphonia [1, 19, 20]. This is also our finding, with 10 of 11 patients having dysphonia as part of their debut symptom. In Norway prolonged dysphonia (> 3 weeks) typically leads to a laryngoscopic evaluation by an ENT-specialist, and if relevant a biopsy is taken. This will in most cases lead to the correct diagnosis. One of our patients had stridor as the primary symptom and no affection of the voice. Stridor will normally also lead to laryngoscopy as one of the early examinations, and therefore also represents an important prognostic symptom that leads to the diagnosis. With this finding, few patients will have undiagnosed laryngeal amyloidosis as long as they seek medical attention for their symptoms and a referral to an ENT department is made.

As reported by others [18], we also found a strong correlation between locus of the tumor and the presenting symptoms. Furthermore it seems that the location of the amyloid deposits also reflects the risk of relapse of symptoms. The patients with supraglottic amyloid lesions received repeated surgical intervention in a greater extent than the glottic and subglottic lesions. This may indicate that the anatomical sub site involved should determine the intensity of follow up. However, our finding was not statistically significant and further studies should be conducted on this topic.
When studying the rate of surgical interventions in relation to prognosis of the disease, we found a positive relation between sum of surgical interventions and likelihood of surgery-requiring relapse. Two patients became free of signs of amyloidosis by laryngoscopic evaluation, and these two patients were operated 1 and 2 times respectively. A total of 4 patients were withdrawn from further follow up due to mild or no symptoms, and these were operated on average 2.25 times. The patients who were alive with disease, and still under follow up, had been operated an average of 4 times. These findings may indicate that relapse is decided by qualities of the disease itself. Whether it is due to laryngoscopic accessibility, proximity to vital structures or histological qualities we do not know.

We also found an inverse relation between patient age at time of symptom debut and sum of surgical interventions. 4 of our patients were diagnosed younger than 40 years old, and the average times of surgery for these patients were 3. The patients in our cohort diagnosed at age higher than 40 were operated at an average of 2.6 times. This may indicate that patient age at time of symptom debut is correlated to the level of aggressiveness of the disease.

It is a consistent finding that there is a high risk of relapse of symptoms after surgical management of laryngeal amyloidosis [2, 25, 26], and our findings support this. 3 of our 11 patients were operated only once, and the overall average times of surgery was almost 3.

The majority of the relapses seem to be caused by growth of residual tumor of the primary lesion and may be explained by lack of radicality during the initial management. We can not, however, exclude that new amyloid is deposited at the same location as earlier, maybe due to amyloidogenic factors at that particular site. Whether the newly discovered lesions are in fact new lesions or that these lesions were overlooked at the first endoscopic evaluation, we cannot know.

In our material, we were not able to obtain exact histological confirmation on whether the removed amyloid had free margins. It would be interesting to study the recurrence rates of tumors that were removed radically at the primary intervention, as it could indicate the prognostic value of the extent of the surgical procedure.

Others have recommended different surgical methods for the different sites of the larynx [19], and there have been reports of full remission with the use of radio-therapy [5]. At our hospital, all but one were treated with laser as this is the standard treatment.

There is a lot of evidence pointing towards a low risk of developing systemic amyloidosis after having diagnosed a certain isolated laryngeal amyloidosis [8, 9], and none of our patients developed systemic disease. This finding supports the hypothesis of locally synthesized amyloid in the cases of localized amyloidosis. Again, a histological evaluation of the margins might increase our knowledge on the outcome in localized amyloidosis.

We recommend prolonged follow-up primarily to evaluate symptoms and the need for re-excision of amyloid deposits. We emphasize the importance of a standardized
examination and treatment at high-volume institutions, both to reduce the degree of recurrent disease as well as ensuring an optimal postoperative voice outcome.

**Conclusion**

Localized amyloidosis of the larynx is a rare disease and it is unlikely to develop into systemic disease. However, rare, the symptoms often lead to an endoscopic evaluation with a biopsy to confirm the diagnosis. The debut symptoms depend on the laryngeal subsite affected, and our findings may suggest that also the risk of residual disease and the likelihood of eradicating symptoms correlate to the anatomical subsite affected. We also found a positive correlation between sum of surgical interventions and risk of relapse of symptoms, as well as an increased risk of aggressiveness of the disease when diagnosed in patients younger than 40 years old. The overall risk of residual disease is high, which emphasizes the value of long term follow up.

**References**