Head and neck manifestations of amyloidosis

Abstract

Objective: To review the manifestations of amyloidosis relevant to otorhinolaryngology and head and neck surgery.

Method: A literature review was undertaken following a Medline search of articles pertaining to amyloidosis, otolaryngology and head and neck surgery.

Results: 42 articles were critically reviewed. Manifestations in the head and neck included amyloidosis of the larynx, thyroid, nose and paranasal sinuses, oropharynx and hypopharynx, and the salivary glands.

Keywords

Amyloid, Amyloidosis, Head and Neck, Otolaryngology, ENT, Otorhinolaryngology.

Introduction

Amyloidosis is a disease characterised by the extracellular deposition of proteinaceous material, causing damage to tissues. It may be localized or systemic, and hereditary or acquired, the most common forms of the latter being associated with underlying chronic inflammatory or haematological disorders. The phenomenon was originally described by Virchow in the mid-19th century, and the deposited material named ‘amyloid’ due to its starch-like tinctorial properties at autopsy. Deposits of amyloid in the structures of the head and neck are among the more common manifestations of amyloidosis. This article reviews the literature surrounding the most common manifestations of amyloidosis relevant to otolaryngology and head and neck surgery.

Method

A review of the literature on amyloidosis related to the head and neck was performed. Articles were retrieved using a Medline search; articles not in English, or older than 30 years were generally excluded unless of historical significance. The search terms used were (singly or in combination): “amyloid”, “amyloidosis”, “ENT”, “otolaryngology”, “head and neck”, “ear”, “nose”, “throat”, “goitre”, “pharynx” and “larynx”. In total, 179 articles were obtained. The results were then reduced to 42 articles of particular relevance for the purpose of the literature review.

Amyloidosis

Amyloidosis refers to a heterogeneous group of diseases caused by deposition in the extracellular space of proteins in a characteristic insoluble fibrillar form. Amyloid deposits can occur in any tissue, and histologically give characteristic apple-green birefringence under polarised light when stained with Congo Red (Figure 1).1

Amyloid deposits may be derived from any one of a diverse, unrelated group of plasma precursor proteins. These proteins, through a mechanism that is not fully understood, mis-fold and autoaggregate to form deposits with a common fibrillar structure in the extracellular space.

The incidence of amyloidosis is approximately 5-10 per million per year, with up to 20% of these cases involving the head and neck.2 Amyloidosis is classified according to the type of protein of which the fibrils are composed, and more than 20 subtypes have been described. Amyloid of different fibril types are associated with differing and sometimes very characteristic clinical manifestations, which overlap to some extent; the reasons for tissue tropism of amyloid proteins are unclear.3

AL amyloid fibrils are derived from either kappa or lambda monoclonal immunoglobulin light chains, associated with a B-cell dyscrasia. AL amyloidosis can be localised to a single anatomical site or epithelial type, or is more commonly systemic, in which it frequently involves the heart, kidney, gastrointestinal tract and tongue.4 Systemic AL amyloidosis was formerly known as primary amyloidosis, since the underlying cell dyscrasia, usually a low grade intramedullary plasma cell disorder, does not itself cause symptoms. Systemic AL amyloidosis can however develop in patients with overt multiple myeloma and other
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Whilst the prognosis of localised AL amyloidosis is often very good, that of systemic AL amyloidosis is often very poor indeed.

AA amyloid fibrils are derived from the acute phase reactant serum amyloid A protein, which is synthesised in the liver under regulation of pro-inflammatory cytokines. AA amyloidosis is associated with chronic inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease, and was formerly known as secondary amyloidosis.

AA amyloidosis predominantly involves the kidneys from a clinical point of view, although deposits in the liver, spleen and gastrointestinal tract are common.

β2-microglobulin is a minor plasma protein that is catabolised in the kidney in health, and accumulates in the serum in patients with chronic renal failure. Deposition of β2-microglobulin amyloid occurs in the synovium, joints, tendon sheaths, heart, gastrointestinal tract, liver, lungs, prostate, adrenals, and tongue, but usually presents with musculoskeletal symptoms.

Diagnostic tests

The diagnosis of amyloidosis is made on the basis of clinical features along with characteristic Congo red staining of a biopsy of an involved organ or tissue. The sensitivity of histology depends on the site biopsied. In suspected systemic amyloidosis, subcutaneous fat and rectal biopsies have quite a high yield, and may be safer than biopsy of a clinically affected organ such as the kidney or heart.

Scintigraphy following administration of radio-labelled serum amyloid P component (SAP) is a specific imaging technique, which also enables serial quantification of amyloid deposits throughout the body, but is only available in a few centres including the National Amyloidosis Centre.

MR imaging is occasionally useful in imaging affected tissues to assist in surgical approach, but is non-specific for amyloidosis. Amyloid deposits typically have similar T1 and T2-weighted appearances to skeletal muscle. The appearance of amyloid on CT imaging is also non-specific and similar to any inflammatory tissue. Amyloid lesions have a characteristic appearance on dynamic contrast-enhanced MRI, which is a promising advanced imaging technique.

Management of systemic amyloidosis

The aim of treatment in AL amyloidosis is suppression of the underlying amyloid-producing plasma cell clone using various chemotherapy regimens derived from the treatment of multiple myeloma. Such treatment can substantially improve the otherwise dismal prognosis but is associated with significant morbidity and mortality. The best outcomes are associated with the most complete haematological responses. Treatment of AA amyloid comprises anti-inflammatory therapies to suppress production of serum amyloid A protein associated with the underlying inflammatory disorder. Eprodisate is a new therapy which may preserve renal function in these patients.

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Larynx

Laryngeal amyloidosis is rare, accounting for 0.5-1% of benign laryngeal tumours. However, the larynx is one of the more common sites in the head and neck for amyloid deposition. It was first described in 1873 by Borrow and Neuman. In contrast with tongue amyloidosis, laryngeal involvement is usually due to a localised deposition of AL amyloid, and is only rarely a manifestation of systemic amyloidosis. The most common presenting symptom is slowly progressive dysphonia; acute airway compromise is rare. Amyloid deposition may cause diffuse thickening of the true or false cords. Discrete lesions take the form of smooth, non-ulcerative swellings around 1.5 cm across, and may occur anywhere in the supraglottis, glottis or subglottis. The disease occurs most often in adults, but has been reported in paediatric patients. Diagnosis is by microlaryngoscopy and biopsy.

Management of laryngeal amyloidosis is by surgical removal of affected tissue. Excision with carbon-dioxide laser is favoured by most reviewers, reporting improvements in speech and low rates of recurrence. Due to the very low percentage of patients with laryngeal amyloid deposits who go on to develop systemic amyloidosis, some authors believe that extensive investigation in this group of patients is unwarranted.

Figure 1: Renal biopsy in a patient with systemic AL amyloidosis stained with Congo red and viewed a) under bright light demonstrating pink staining of glomerular and vascular amyloid deposits, and b) under crossed polarised light demonstrating the characteristic apple-green birefringence. Figure reproduced with kind permission of Prof P Hawkins.
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Thyroid gland
Amyloid goitre is an occasional manifestation of systemic amyloidosis, most commonly in AA amyloidosis. Amyloid is also occasionally forms local deposits in the thyroid in association with medullary carcinoma of the gland, but significant deposition is rare. In systemic amyloidosis, a large proportion of patients have microscopically detectable amyloid deposition in the thyroid gland. However, in the absence of thyroid malignancy, the presence of amyloid deposition to the extent that the gland becomes enlarged is very rare. It is most often associated with amyloidosis secondary to a chronic inflammatory disease or neoplasm, but is also seen in primary amyloidosis (Figure 2).

Patients typically present with a diffusely enlarged, non-tender goitre, with or without impingement of the airway. Enlargement may occur rapidly over the course of a few weeks. Despite the usually substantial infiltration of the thyroid parenchyma, patients are generally euthyroid. Macroscopically, the gland is firm, appears pale, and tests positively for the presence of amyloid when stained with Congo red. Lobular or diffuse adipose tissue is sometimes observed microscopically, as is lymphocytic infiltration.

Obstructive symptoms such as dyspnoea or dysphagia indicate surgical intervention by total/subtotal thyroidectomy. As the patient is most commonly euthyroid, the only other indication for surgery is to improve cosmesis. Removal of the thyroid gland does not appear to affect prognosis; mortality is affected by the involvement of vital organs by systemic amyloidosis. Thyroidectomy is also indicated if the diagnosis is uncertain, particularly if there is suspicion of malignancy of the gland.

Oral cavity
Amyloid deposition in the oral cavity is almost always a manifestation of primary systemic amyloidosis, and typically results in diffuse macroglossia with or without lip swelling. Single or multiple deposits on the hard or soft palate have also been described (Figure 3). The tongue is enlarged and firm to palpation, classically with a scalloped edge caused by indentation by the teeth. Localised nodular deposition of amyloid in the tongue has also been described, but is limited to a small number of case reports.

Patients with amyloid-related macroglossia typically present with a variable combination of oropharyngeal symptoms: subjective enlargement of the tongue, dyspnoea, obstructive sleep apnoea, speech difficulties and swallowing problems, together with symptoms of amyloid involvement at other sites, and symptoms of the underlying cause (e.g. multiple myeloma).

Tongue enlargement occurs progressively over years, and may be severe, having profound and disabling cosmetic effects in addition to functional impairment. Due to the very poor prognosis of the systemic amyloidosis that usually underlies amyloid macroglossia, the aim of intervention is palliative. Surgical resections reported in the literature take the form of V-shaped partial glossectomy, giving temporary but nevertheless worthwhile alleviation of symptoms. Some reporters advocate avoiding surgical intervention altogether in favour of elective tracheostomy, especially considering difficulties with general anaesthesia, bleeding encountered at operation and the likelihood of recurrence.

Ear
Involvement of the ear in amyloidosis is very rare. Two forms of amyloid deposition have been described. A small number of case reports describe polypoid or “heaped-up” mass lesions with the appearance of benign tumours in the external canal, causing narrowing of the meatus. This has been found in both systemic and localised amyloidosis. The pinna may also be affected, causing pruritic scaling of the auricular skin.

Nasal cavity and paranasal sinuses
Discrete amyloid masses may arise in the nasal cavity, nasopharynx and paranasal sinuses. They present similarly to more common tumours of this region, with nasal blockage, discharge or recurrent epistaxis; the mass is usually seen on nasendoscopy. Nasopharyngeal amyloid deposits may arise in the fossa of Rosenmüller and present as otitis media with effusion due to Eustachian tube orifice blockage. Most case...
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Amyloidosis is a rare disease which may involve the structures of the head and neck in around 20% of cases. This article reviews and collates the literature, including the most recent case reports, on head and neck manifestations of amyloid deposition, and underlines the importance of this condition in the knowledge base of otolaryngologists.

Discussion

Amyloidosis is a chronic disease that can present with diverse symptoms according to the predominant site(s) of amyloid protein deposition. A significant number of these manifestations are in the structures of the head and neck, and as such are of relevance to otolaryngologists. The likelihood of systemic disease can be inferred from the location of the deposits - for instance tongue infiltration is strongly associated with AL amyloidosis secondary to multiple myeloma.

Features consistent with localised amyloidosis may sometimes represent the presenting features of systemic amyloidosis. Therefore, further evaluation for systemic disease is essential in these patients, as it has serious ramifications for their prognosis. In the reviewed articles this was generally accomplished by clinical examination, full blood count, renal and liver function testing, serum immunoglobulin assays, protein electrophoresis and urine testing for Bence Jones protein, chest X-ray, abdominal fat aspiration and bone marrow aspiration. Additional testing for inflammatory conditions (ANA/ENA, rheumatoid factor, ESR) was also part of the workup in some cases. Some teams also elected to perform imaging to exclude organomegaly, and cardiac testing to detect cardiomyopathy.

Evaluation of discrete lesions is challenging: imaging may be non-specific and clinical appearances similar to other benign or malignant lesions. Biopsy may not be feasible, and results may not be reliable, as discussed above; fine-needle aspiration is of low yield.40–42 The diagnosis is therefore only made reliably on excision of the lesion.

When head-and-neck deposits are associated with systemic amyloidosis, the prognosis is not generally dictated by the nature of the lesion unless the airway is compromised.

In the absence of systemic disease, localised deposits in the head and neck can be treated conservatively or by resection. With a few exceptions resection is associated with a low recurrence rate and a good prognosis. Some teams continue to observe these patients at regular intervals for disease progression.20,21,33

Despite the rarity of amyloid deposition in the head and neck, it remains an important differential diagnosis in cases where diagnostic uncertainty exists in a patient with symptoms and signs, especially where patient comorbidities make systemic amyloidosis a possibility.

Summary

Amyloidosis of Waldeyer’s ring and hypopharynx is very rare, but is usually diagnosed after excision of the parotid lesion.

Oropharynx, hypopharynx and oesophagus

Amyloid protein may be deposited in single or multiple locations in Waldeyer’s ring, including the tongue base, and is a rare differential in asymmetric tonsillar enlargement. Patients typically present with throat discomfort, with or without dysphagia.10,36

Amyloid deposition in the hypopharynx is very rare, but has been reported to masquerade as a post-cricoid tumour.37 It may occur in systemic amyloidosis.35

Massive deposition of amyloid in the nasal cavity has recently been described in association with multiple myeloma.38

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Conflicts of Interest

All authors have no conflict of interest to declare. No extraneous funding was obtained.

References


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**Head and Neck Manifestations of Amyloidosis**

**CPD Questions**

1. **With regard to the pathophysiology of amyloidosis, select the single TRUE answer**
   a. Systemic AL amyloidosis has a relatively good prognosis.
   b. AA amyloid protein accumulates as a result of chronic inflammation.
   c. Amyloid deposition leads to cell cytoplasm staining avidly with Congo Red.
   d. AL amyloidosis is most commonly localised to a single anatomical area.
   e. \( \beta_2 \)-microglobulin is plasma protein synthesised in the kidneys.

2. **With regard to investigation of amyloidosis, select the single best option**
   a. Random subcutaneous fat biopsy has a low yield in systemic amyloidosis.
   b. Nuclear-medicine isotope scanning is widely used in the diagnosis of amyloidosis.
   c. CT allows delineation of discrete amyloid deposits.
   d. Amyloid deposits appear similarly to skeletal muscle on T1 MRI.
   e. Biopsy of the affected site or organ is ideal in systemic amyloidosis.

3. **Match the following presentations to the most appropriate treatment modality:**
   a. Amyloidoma of right thyroid lobe
   b. Systemic AL amyloidosis
   c. AA amyloidosis
   d. Amyloidoma of true vocal cord
   e. Macroglossia in advanced systemic amyloidosis
   f. Amyloid infiltration of the thyroid is strongly associated with Familial Mediterranean Fever.
   g. Glottic
   h. Parotid
   i. Tongue
   j. Thyroid
   k. Supraglottis

4. **With regard to multiple myeloma, select the single FALSE answer:**
   a. Bence-Jones proteins are freely filtered by the kidney.
   b. AL-amyloidosis develops in up to 15% of patients with multiple myeloma.
   c. The tongue is a common site of involvement in multiple myeloma-associated amyloidosis.
   d. A majority of patients are treated with autologous bone marrow transplant.
   e. Serum protein electrophoresis reveals a monoclonal increase in serum globulin.

5. **Which of the following statements regarding amyloid goitre is FALSE?**
   a. Total thyroidectomy in diffuse amyloid goitre improves prognosis.
   b. Diffuse involvement of the thyroid with amyloid rarely results in hypothyroidism.
   c. Amyloid deposition is associated with medullary thyroid carcinoma.
   d. Amyloid goitre occurs most commonly in AA amyloidosis.
   e. AA amyloidosis is associated with
      a. Waldenström’s macroglobulinaemia
      b. Colorectal carcinoma
      c. Bronchiectasis
      d. Hypothyroidism
      e. Chronic renal failure

6. **The most common site of amyloid deposition in the head and neck is the**
   a. Glottic
   b. Parotid
   c. Tongue
   d. Thyroid
   e. Supraglottis

7. **AA amyloidosis is associated with**
   a. Dialysis-associated amyloidosis
   b. Senile cardiac amyloidosis
   c. AL amyloidosis
   d. Alzheimer’s disease
   e. Secondary systemic amyloidosis (AA)

8. **Match the following forms of amyloidosis to their protein types:**
   a. Dialysis-associated amyloidosis
   b. Senile cardiac amyloidosis
   c. AL amyloidosis
   d. Alzheimer’s disease
   e. Secondary systemic amyloidosis (AA)
   f. Apolipoprotein A
   g. Cystatin C
   h. \( \beta_2 \)-microglobulin

   Options:
   a. Beta-amyloid (\( \beta_2 \)A)
   b. Serum amyloid A protein
   c. C-reactive protein
   d. Transthyretin
   e. Kappa immunoglobulin light chains
   f. Apolipoprotein A
   g. Cystatin C
   h. \( \beta_2 \)-microglobulin