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Laryngeal amyloidosis

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LARYNGEAL amyloidosis is a very rare disease, accounting for less than 1 per cent of all benign laryngeal tumours (Hellquist *et al.*, 1978), characterized by the deposition of a homogeneous eosinophilic extra-cellular material in the laryngeal tissues. This material is of a proteinaceous nature. It was first described by Rokitansky in 1842 and given the term amyloidosis by Virchow in 1851. Reports of laryngeal amyloidosis have appeared since 1875. Amyloidosis can be either generalized (and then be primary or secondary), or localized. The nature of amyloidosis is still unknown. It occurs slightly more often in males, usually between the ages of 40 and 60.

According to some reports the sites are, in descending order of frequency: the false cords, aryepiglottic folds and subglottic region, but the report from the Mayo Clinic gives the vocal cords as the most common location (Hellquist *et al.*, 1979). There was also a review by McAlpine *et al.* (1936).

Over the past four years we have had six cases of laryngeal amyloidosis.

Case Reports

Case 1.

S.Z., a black male, aged 54. Presented on 9 March 1976 complaining of pedal oedema, dyspnoea for a month, abdominal swelling for six weeks and hoarseness. He had previously been admitted in 1967 for haemoptysis and claimed that his voice had always been hoarse. On examination he was found to be in congestive cardiac failure and on ear, nose and throat examination he was found to have a large left tonsil with an ulcer on the surface of the tonsil with a whitish slough.

Direct examination of the larynx showed a smooth globular mass arising from the base of the epiglottis on the left side and from the adjacent aryepiglottic fold. The tumour mass obscured the view of the glottis. Initial biopsy of the tonsil revealed a plasmacytoma.

Direct laryngoscopy was performed. The tumour was found to be solid, with a broad base. Biopsy of the laryngeal lesion revealed laryngeal amyloidosis with no evidence of plasmacytoma.

At this stage, a full blood count with differential count was normal. Urea and electrolytes were normal. Alkaline phosphatase was normal. Protein electrophoresis was normal. Bence-Jones protein was not isolated. The electrophoresis pattern was not typical of myeloma although the globulin was raised. Skeletal survey failed to reveal any other evidence of myeloma.

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Treatment: The patient was treated with radiotherapy for the plasmacytoma of the tonsil, had local removal of the amyloid lesion of the larynx, and was treated for his congestive cardiac failure.

E.C.G. did not suggest cardiac amyloidosis.

He presented again in 1978 with a recurrence of the original tumour and, at the same time, was found to have multiple amyloid masses in the larynx with a fixed left cord. There was subglottic extension on the anterior and posterior walls of the larynx. Biopsies at this stage of both the tonsil and the larynx were consistent with a myelomatous infiltrate.

The myeloma has since been treated with chemotherapy and the patient is alive and well, with no evidence of recurrence at present.

This patient is interesting in that the amyloidosis of the larynx preceded direct infiltration of the larynx by plasmacytoma.

Case 2.

S.M., a black male, aged 40. He was first admitted on 8 February 1977 complaining of hoarseness for one year and dysphagia with pain for one week. He also complained of nasal obstruction.

On examination of the nose there were multiple nasal polyps, with mucopus on the right side, and the postnasal space was full of polyps.

Indirect laryngoscopy: There was marked oedema of the arytenoids with marked swelling of the false cords. No supraglottic opening was visible. There was oedematous ballooning of the mucosa on the mucosal aspect of the arytenoids and aryepiglottic folds. The lower limit could not be seen.

Direct laryngoscopy: The arytenoids were found to be free and normal. The glottic opening could not be seen. A large laryngeal cyst was found which was excised and a vocal nodule was present which was removed.

The biopsy result showed amyloid of both the postnasal space and the larynx (Fig. 1).

Investigations: X-rays of the sinuses showed extensive opacity of all sinuses. The bone marrow was normal. Urea and electrolytes were normal. Full blood count and differential count were normal. Urine investigation revealed no Bence-Jones protein. C-reactive protein was positive. Protein electrophoresis was within normal limits. L.E. cells were not shown. WR was negative. There was no other evidence of amyloidosis in any other organ. No cause for the amyloid could be identified.

The patient then underwent repeated operations for local removal of the amyloid in the larynx and from the nose. Intranasal antrostomy was performed.

He also presented with serous otitis media and had grommets inserted on two occasions.

At the last examination his larynx was normal but there was still evidence of some amyloid deposits in the postnasal space which were removed.

Case 3.

P.G., a black male, aged 35. This patient presented on 11 October 1977 with severe respiratory distress and stridor. An emergency tracheostomy was performed.

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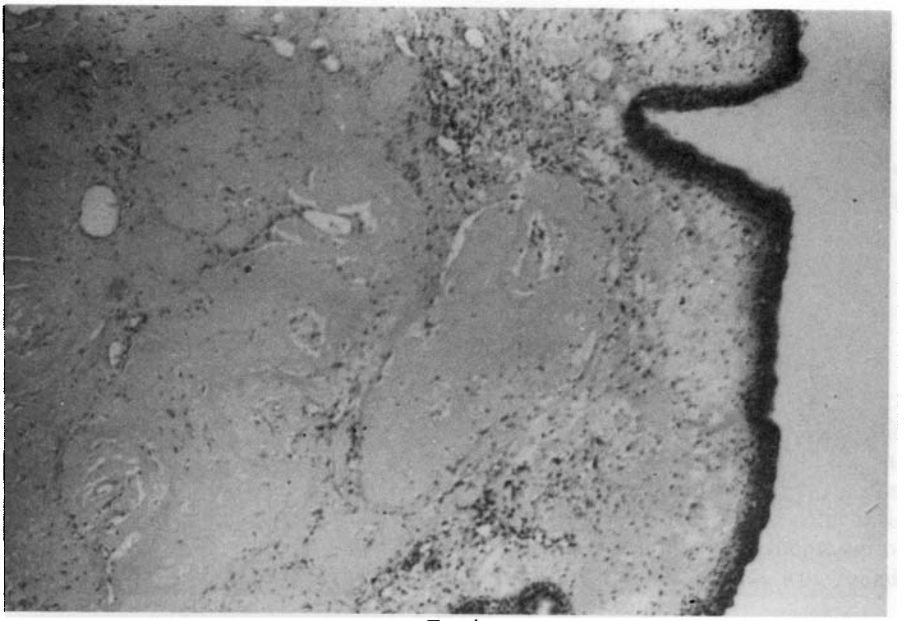


FIG. 1

Amorphous extracellular deposition of eosinophilic material consistent with amyloid and confirmed on special staining (Case No. 2).

Indirect laryngoscopy showed a subglottic narrowing. He had a 3f hepatomegaly and splenomegaly but otherwise all systems were normal. X-rays and tomograms revealed diffuse glottic and subglottic infiltration (Figs. 2 and 3).

Biopsy of the laryngeal masses revealed amyloidosis.

Investigations: Bence-Jones protein was negative. Urea and electrolytes were normal. Rectal biopsy was negative for amyloidosis. Full and differential blood counts were normal. L.E. cells were not seen. Barium swallow was normal. Bone marrow and protein electrophoresis were normal. Liver biopsy was non-contributory.

The patient had repeated removals of the amyloid and on 16 November 1977 had a laryngofissure, with excision and curettage of the amyloid of the trachea and subglottis, down to the level of the third tracheal ring.

A silastic keel was inserted between the thyroid laminae and the cartilage was sutured in place with dermalon. The stent was left in place for four months and then removed. Despite the removal of the stent, subglottic oedema and amyloid persisted and continued to grow, necessitating repeated endoscopic removals.

He was finally extubated in May, 1979, and on last examination in February, 1980, the larynx had settled and there was no evidence of any active amyloid. No primary cause for the amyloidosis was found.

Case 4.

S.C., an Indian male, aged 35. He presented with hoarseness for one year and dryness of the throat. He had been a singer in the past but there was nothing else of note.

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FIG. 2

Right lateral view of the glottic and subglottic deposition of amyloid in Case No. 3.

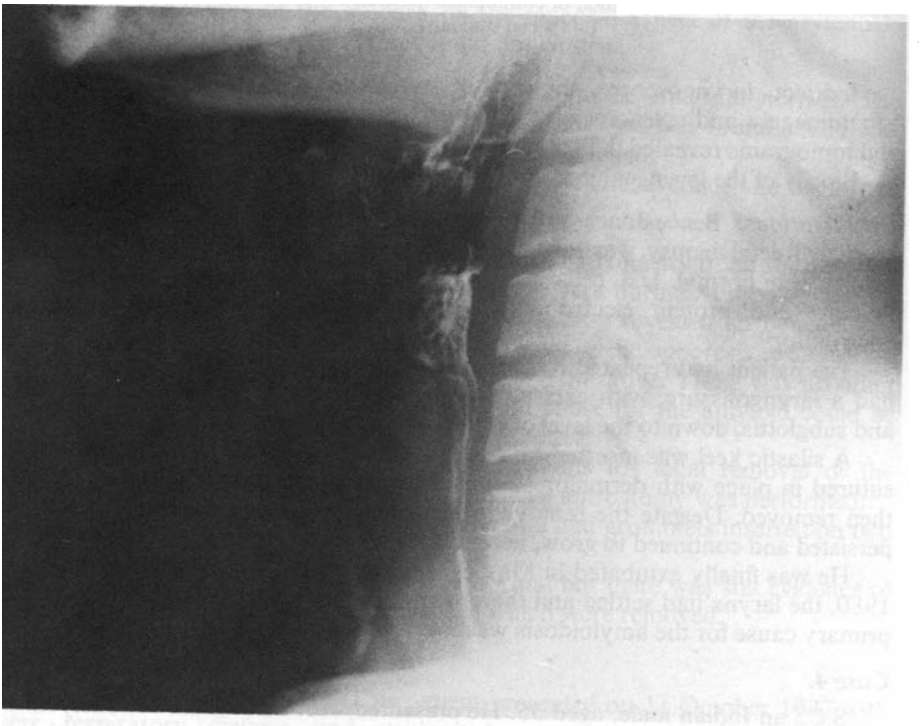


FIG. 3

Left lateral view of glottic and subglottic deposition of amyloid in Case No. 3.

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On indirect examination he was found to have a swelling of the left false cord extending across to the opposite cord. The left true cord was not seen.

Direct laryngoscopy showed a polypoid lesion of the left false cord with thickening and a polypoid lesion of the left vallecula. Biopsies were taken.

The patient was also found to be diabetic.

Histology revealed amyloidosis, the amyloid being laid down in a nodular pattern around vessels and glands, and a foreign body reaction was evident around some deposits.

Investigations: The patient was found to be diabetic. All other investigations, i.e., full blood count with differential, Bence-Jones protein, L.E. cells, urea and electrolytes, and protein electrophoresis, were all normal.

Case 5.

W.N., a black male, aged 48. Date of admission 11 September 1980. His main complaint was one of hoarseness for two years. On indirect examination he was found to have ulceration of the anterior commissure, congestion of both cords, and swelling in the posterior commissure. X-rays revealed diffuse subglottic extension (Figs. 4 and 5). On direct laryngoscopy a lesion involving the posterior commissure with congestion of the posterior third of both cords was found. Ulceration was present as well as mild subglottic narrowing.

Histology revealed deposits of amyloid in the sub-epithelial tissues (Fig. 6). Protein electrophoresis, IGG levels were normal, light chain and Bence-Jones protein were not found. Full blood count revealed a normal differential.

Tomography of the larynx revealed very little movement of the cords. There was marked thickening of both cords, possibly due to oedema.

The lesion was removed endoscopically. The patient is at present being followed up.

Case 6.

A.M., an Indian male, aged 50. Admitted 24 February 1981. History of hoarseness and dysphagia for three months. On indirect examination, a fleshy, polypoid mass, about 2 mm. in diameter, was found in the anterior commissure. This was removed by direct laryngoscopy.

The histology was consistent with amyloidosis.

Investigations: Full blood count with differential was normal; there was no Bence-Jones protein; no light chains in the urine; electrophoresis was normal; liver function tests were normal; the sedimentation rate was normal; chest X-ray was normal.

No cause for amyloid could be found.

This patient is being followed up at present.

Discussion

The nature of the proteinaceous amyloid substance remains obscure.

Several classifications of amyloid have been proposed, none of which is entirely satisfactory. The most useful clinically was given by Barnes and Zafar (1977), and is as follows:

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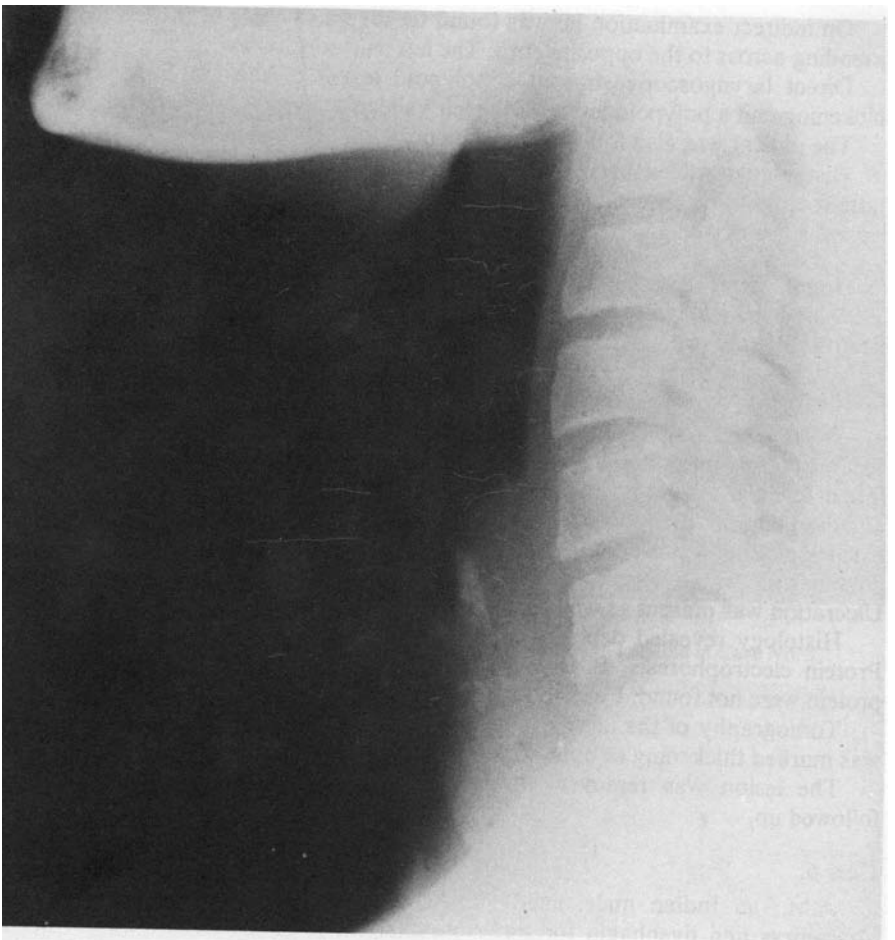


FIG. 4

Left lateral view showing glottic and subglottic deposition of amyloid in Case No. 5.

1. Primary amyloidosis (a) Localized;
   (b) Generalized.
2. Secondary amyloidosis (a) Localized;
   (b) Generalized.
3. Amyloidosis associated with multiple myeloma.
4. Hereditary or familial amyloidosis.

Primary amyloidosis is a deposition of amyloid principally in the mesenchymal tissues, tongue, heart, gastro intestinal tract, etc., without an underlying predisposing disease. Secondary amyloidosis is associated with a chronic destructive tissue process, such as tuberculosis or rheumatoid arthritis. In this variety, amyloid is deposited primarily in the organs rich in reticulo-endothelial tissue, i.e., spleen, liver, etc.

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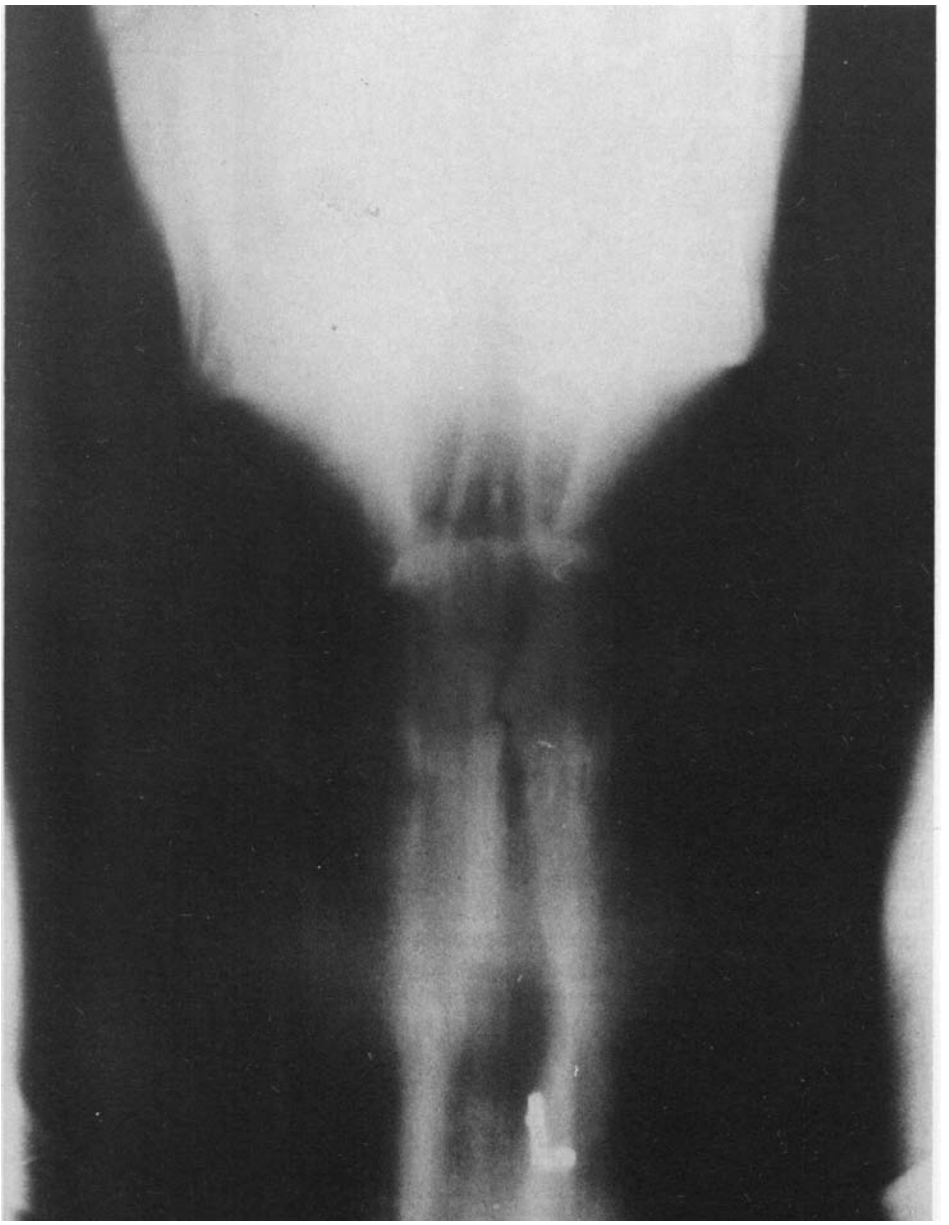


FIG. 5

A.P. tomography demonstrating diffuse laryngeal involvement by amyloid in Case No. 5.

The larynx is rarely involved in generalized secondary amyloidosis and very infrequently in generalized primary amyloidosis.

Electromicroscopy showed all amyloid to have a similar basic fibrillar structure with rigid, unbranched fibrils measuring 50–150 (5–15 nm.) Ångströms

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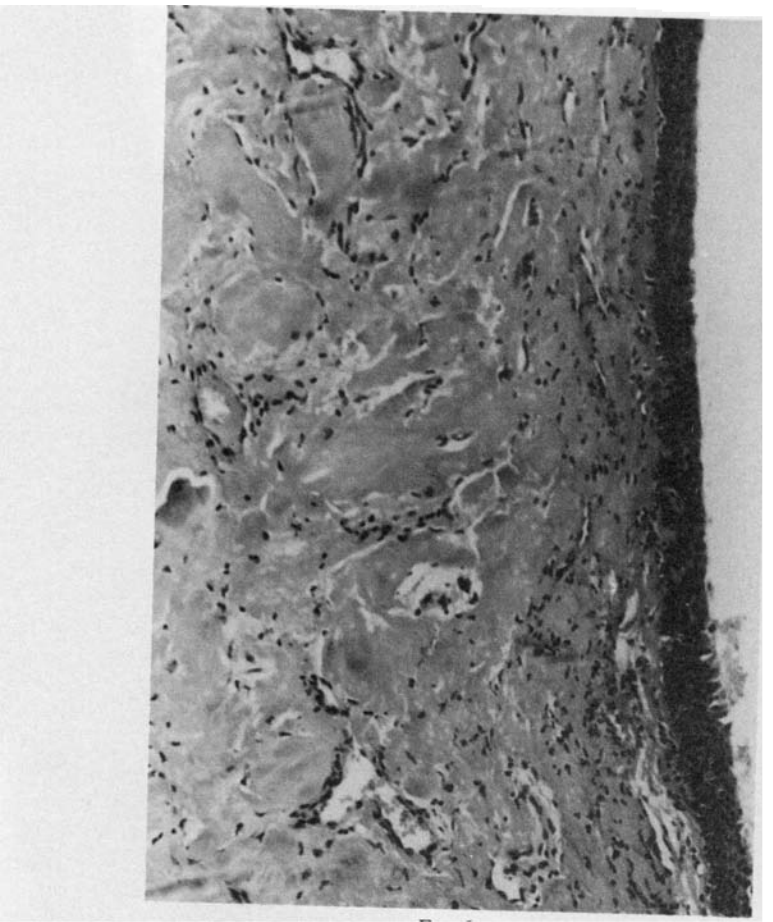


FIG. 6

Amorphous extracellular deposition of eosinophilic material consistent with amyloid and confirmed on special staining (Case No. 5).

in diameter. The length of the fibrils has been estimated at 8,000 Ångströms (800 nm.). They are arranged in an anti-parallel fashion in sheets.

A fibril is the major component accounting for 90–95 per cent of the composition of amyloid. The rod structure with pentagonal sub-units accounts for 5–10 per cent of the make-up of the amyloid and these pentagonal sub-units are called 'doughnuts' because of their hollow centre. The rod is thought to represent an alpha-one globulin.

Clinical analysis has distinguished three chemical types of amyloid:

(1) of immunoglobulin origin;
(2) of unknown origin;
(3) apudamyloid.

The amyloid fibrils associated with generalized primary amyloidosis, some forms of localized amyloidosis and those associated with plasma cell dyscrasias are derived primarily from the aminoterminal-variable region of the light chain of

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TABLE I
LARYNGEAL AMYLOID

Case	Age	Sex	Race	Duration of Symptoms	Site of Lesion	Underlying Cause
1.	54	M	A	9 yrs.	Tonsil, epiglottis aryepiglottic fold	Plasmacytoma
2.	40	M	A	1 yr.	Nose, P.N.S., glottic subglottic	Nil
3.	35	M	A	2 yrs.	Glottic, subglottic	Nil
4.	35	M	I	1 yr.	L. false cord and vallecula	Nil
5.	48	M	A	2 yrs.	Ant. and Post. commissure, subglottic	Nil
6.	50	M	I	3 mths.	Ant. commissure	Nil

A = African
I = Indian

a homogenous immunoglobulin. The amyloid of unknown origin has fibrils not derived from immunoglobulin. This type of amyloid is also found in secondary amyloidosis and familial Mediterranean fever.

The third type, apudamyloid, is associated with endocrine polypeptide tumours.

The immunoglobulin type is found to consist of intact immunoglobulin light chains or fragments of them. Either kappa or lambda light chains may form amyloid although lambda light chains are more amyloidogenic. Heavy chains have not been reported as forming amyloid.

The amyloid associated with secondary amyloidosis and familial Mediterranean fever appears to be a protein derivative of non-immunoglobulin origin. Some individuals believe that the source of the amyloid of unknown origin is the pentagonal structure observed under the electron microscope in all cases of amyloid, whereas others believe the most likely source is the proteins associated with the immunoglobulins, e.g., the J-piece, or secretory piece, or components of complement. The third biochemical class of amyloid is that associated with endocrine polypeptide tumours, i.e., medullary carcinoma of the thyroid, pancreatic islet cell tumours which produce apudamyloid which differs from other forms by the absence of tryptophane and tyrosine. The origin of an apudamyloid might be a polypeptide produced at the same time as the hormone. Amyloid is clearly seen as extracellular eosinophilic deposits (Fig. 6).

The most commonly used special stain for the diagnosis of amyloid is Congo Red which gives it a bright red colour. In polarising light an apple-green birefringence is obtained. This is due to the presence of beta-pleated sheet fibrils. The presence of these fibrils has been revealed by low-angled X-ray diffraction which is another method for identifying the amyloid substance.

There are other methods of diagnosing amyloidosis which are more sensitive than Congo Red, although Congo Red has very few false positives and negatives. Still more sensitive, however, is the Phorwhite BBU, with even fewer false staining reactions. Sulphated Alcian Blue and Methyl Violet stains are commonly used.

Crystal violet gives a positive metachromatic reaction. Potassium Permanganate technique for distinguishing between the chemical types of amyloid has been introduced.

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The larynx is the most common site for amyloidosis of the respiratory tract. Amyloidosis of the larynx can have one of two forms: it can produce tumourous masses, or display diffuse infiltration, as in our cases.

Barnes and Zafar (1977) found that amyloid of the larynx can be distinguished into four patterns:

1. amorphous random masses;
2. deposits in vessel walls;
3. in the basement membrane of seromucinous glands;
4. as hyaline rings in adipose tissue.

The treatment of laryngeal amyloidosis is surgery, consisting of endoscopic removal with the aid of the operating microscope. Extensive cases may necessitate laryngofissure. Repeated excisions are necessary in cases of diffuse amyloid. Good results have been described with laser excision (Gaillard *et al.*, 1979).

Patients presenting with amyloid of immunoglobulin origin, in other words, plasmacytoma, should have chemotherapy and radiotherapy as well as repeated local removal. In view of the dangers of stenosis of the larynx, and also in view of the recurrence of the lesion before it can be controlled, conservative local surgery is to be advocated.

Steroid treatment is in general unsuccessful and in fact, in animal experiments, steroids have accelerated amyloid formation (Barnes and Zafar, 1977).

Our cases are interesting in that one patient presented with plasmacytoma of the tonsil and larynx; plasmacytomas may be associated with amyloidosis.

In this particular patient the laryngeal amyloid pre-dated by two years the active involvement of the larynx by myeloma.

Of the other patients, two patients presented with amyloidosis of the extralaryngeal tissues: one patient had gross destruction of the nasal cavities, gross infiltration of the nasal cavities, and gross infiltration of the postnasal space; the other patient had a vallecular deposit. None of our patients had systemic deposits.

All our patients were male; we had no females with amyloidosis and all our patients were between 35 and 50 years of age. The most common symptom was hoarseness, and dysphagia was a common complaint.

In our environment patients present late and they presented with very large lesions, one patient requiring tracheostomy. Although the mucosa was normally intact, our fifth patient presented with ulceration and inflammation, and our fourth patient had evidence of a foreign body reaction to the amyloid. In the other cases there was no reaction to the amyloid.

Treatment in all cases consisted of local removal which, in cases 1, 2 and 3, had to be done on repeated occasions. Case 1 was treated with chemotherapy for the plasmacytoma.

Summary

A series of six cases of laryngeal amyloid is presented (Table I). One patient had amyloid associated with a plasmacytoma. Three patients had multiple sites in the upper respiratory tract involved. The symptoms and signs were discussed, with the majority of patients presenting with hoarseness, stridor and dysphagia. No case of generalized amyloid was found.

Treatment consisted of local removal, three cases requiring repeated removals. The one case with a plasmacytoma was treated with chemotherapy. The nature of amyloid is also discussed.

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