Amyloid goitre

REPORT OF A CASE AND BRIEF REVIEW OF LITERATURE

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SUMMARY
This paper describes a case of primarily generalized amyloidosis, in which amyloid deposition in the thyroid was so massive as to produce a goitre (amyloid goitre). The relevant literature is briefly reviewed. Neth. J. Med. 17, 115.

INTRODUCTION
Deposition of amyloid in the thyroid gland exists in 15 and 20 per cent of cases of secondary and primary amyloidosis, respectively. The deposition in medullary thyroid carcinoma is well-known, but the existence of an amyloid goitre is very rare and only few observations have appeared in the literature.

AREAN and KLEIN defined 'goitre' as an enlargement of the thyroid gland. Thus 'amyloid goitre' is not merely a deposition of amyloid in the thyroid, but an enlargement of the gland due to deposition of amyloid. A very characteristic feature is the rapid growth of the thyroid in this condition. With their definition, AREAN and KLEIN have found 30 cases of amyloid goitre until 1961, and at least 13 additional accounts of this syndrome have since been given. With the exception of one case, a diagnosis of amyloid goitre has never been made before either operation or biopsy.

We recently saw a patient who was preoperatively suspected to be suffering from amyloid goitre. This diagnosis was confirmed at operation.

CASE HISTORY
A 73-year-old male was seen for the first time in our outpatient department with complaints of recurrent haematemesis, a 'growing' goitre and bruising. A few days later he was admitted to our hospital because of haematemesis and melaena. During his hospital stay of about two months he was operated on because of a non-traumatic splenic rupture due to amyloidosis (which appeared to be primary and generalized) and a concomitant coagulation disorder (Factor V and X deficiency). There was an euthyroid goitre.

Because of the rapid growth of the goitre — in the course of 6 months the circumference of the neck had increased from 34 to 40 cm — the patient was readmitted 7 months later. Physical examination then showed an apparently euthyroid man; blood pressure was 115/70 mm Hg; pulse rate 72/min. The circumference of the neck was 41 cm. The thyroid gland was asymmetrically enlarged: the left lobe was about ten times and the right lobe about twice the normal size. The gland was firm and moved on swallowing. There was a slight inspiratory stridor. Examination of the heart and the lungs showed no abnormalities. There was an upper abdominal scar due to splenectomy; the liver was enlarged to 2 cm below the right costal margin and was firm on palpation. The extremities showed no abnormalities.

Laboratory findings
ESR 20 mm in the first hour. Haemoglobin 12.5 g/100 ml. Leucocyte count 8700/mm³. Differential count: 5% eosinophils, 1% juvenile neutrophils, 30% segmented neutrophils, 47% lymphocytes, 8% monocytes. Creatinine 1.77 mg/100 ml (normal up to 1.45 mg/100 ml); alkaline phosphatase 320 U/l (normal up to 150 U/l); gamma-glutamyltranspeptidase 67.0 U/l (normal 4-23 U/l); SGOT 10 U/l (normal up to 19 U/l); SGPT 11 U/l (normal up to 19 U/l); LDH 119 U/l (normal up to 170 U/l); cholest erol 147 mg/100 ml (normal 150-280 mg/100 ml); calcium 8.8 mg/100 ml (normal 9.0-10.6 mg/100 ml). The total protein content in serum was 61 g/l and distribution was: albumin 51.5%, α₁-globulin 2.8%, α₂-globulin 10.5%, β-globulin 11.2%, and γ-globulin 24.0%. Immunoelectrophoresis (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam): IgA decreased, IgM normal; there was an IgG M component present (light chains of lambda type).

Urinalysis — Average 3 g protein/24 hrs; immunoelectrophoresis (Central Laboratory of the Netherlands Red

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Cross Blood Transfusion Service: some Bence-Jones protein (type lambda), some albumin and other proteins. Excretion of 17-ketosteroids: 5.0 mg/24 hrs (normal 4-26 mg/24 hrs); excretion of 17-ketogenic steroids: 10.3 mg/24 hrs (normal 7.5-19.5 mg/24 hrs). Normal excretion of vanillylmandelic acid (< 8 mg/24 hrs).

_Congo red test_ – 51 per cent retention (49 per cent extraction; this result is not diagnostic for amyloid).

_Rectal biopsy_ (microscopy) – Amyloid deposit in submucosal capillary walls (Congo red stain).

_Thyroid analysis_ – $T_4$ 58 mmole/l (normal 50-130 mmole/l, anion exchange chromatography); no antibodies against colloid and cytoplasm could be detected (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service). Normal calcitonin (< 25 pg/ml, radio-immunoassay, M. Frölich, University Hospital, Leiden). $^{131}$I tracing: uptake after 24 hrs 24.0 per cent (normal 20-40 per cent); uptake after 48 hrs 31 per cent (normal 25-40 per cent). Scanning of the thyroid with $^{99m}$Tc as pertechnetate: multinodular goitre.

_Bone marrow_ (Dr P. Lopes Cardozo, University Hospital, Leiden) – Erythropoiesis normal, leucopoiesis focally shifted to the left, slight increase of eosinophils. Megakaryopoiesis normal; some plasmocytosis; some increase of lymphatic elements.

_Coagulation studies_ – Bleeding time 120 sec. Thrombocytes 247,000/mm³. Prothrombin time (Quick) 15 sec (control 15 sec). Recalcification time 195 sec (control 180 sec). Thrombin time 16 sec (normal 13 sec). Fibrinogen 790 mg/100 ml (normal 250-400 mg/100 ml).

_X-ray examination_ – Bone series showed no myelomatous lesions and chest films showed displacement of the trachea to the right, demonstrating the substernal extent of the goitre.

_ECG_ – No evidence of amyloid deposit in the myocardium.

The spleen (removed at operation during first period in hospital) and the rectum (biopsy) showed marked deposits of amyloid material. Moreover, amyloid deposits were suspected in the liver at laparotomy, but biopsy was not performed because of the coagulation disorder at that time (the elevated alkaline phosphatase and gamma-glutamyltranspeptidase are probably a reflection of this deposition). The slightly elevated serum creatinine and
proteinuria indicated the possibility of amyloid deposits in the kidney.

Since the growth of the thyroid was so rapid and was giving rise to pressure symptoms, and because of the possibility of malignancy, surgical exploration was carried out. A total left-sided thyroidectomy was performed, after frozen section (Dr H. L. Kalsbeek).

Pathology (M. Voortman) - Macroscopic examination: left thyroid lobe 195 g. Two nodules with a firm consistency, each surrounded by a thick fibrous layer (Fig. 1). Microscopic examination: in the interstitium there was a very extensive deposit of a hyaline material (Fig. 2). This material showed the staining characteristics of amyloid in Congo red- and toluidin blue staining. The follicles were stretched and flattened with broadened interstitium; locally there was some fibrosis and calcification.

The postoperative period was uneventful, and the patient was dismissed on the 7th day.

DISCUSSION
Amyloid is a material deposited in tissue, which shows birefringence when examined by polarization microscopy after staining with Congo red. When studied in the electron microscope the material has a fibrillar appearance; the fibrillae have a diameter of 75-100 Å. Various investigations have shown the close relationship between immunoglobulins and amyloid and it seems likely that the major protein component of the amyloid fibril may consist of fragments of the light chain of the immunoglobulin, as discussed by Glenner et al.18. Cohen11 in his articles on amyloid, reviews some classifications of amyloidosis. One of the most useful classifications, in our opinion, is the one given by Cathcart et al.9 This classification is reproduced in Table I.

Because no underlying disease and no malignancy (even no myeloma) was found, our patient could belong to group Ia: primary systemic non-familial amyloidosis. This group seems to be
characterized by: 1) low serum levels of M component; 2) slightly depressed serum levels of polyclonal immunoglobulins; 3) rarely Bence-Jones proteinuria; 4) no osteolytic lesions; 5) no blastic plasmocytes, no sheets of immature cells.

Our patient had a serum M component and some Bence-Jones proteinuria; no osteolytic lesions and no blastic plasmocytes were shown.

In Table II we have listed the cases of amyloid goitre found in the literature (using the classification of Table I). Most cases should be classified as secondary amyloidosis. In 3 cases no deposits of amyloid were shown outside the thyroid; these are classified as primarily localized amyloidosis.

The amyloid goitre is usually a rapidly enlarging nodular or diffuse goitre, firm on palpation and often giving rise to symptoms due to pressure. One of the most striking features of amyloid goitre is the rapidity of growth. The goitre usually develops within 4 months to 3 years, with an average of one year. A malignant growth of the thyroid or thyroiditis is usually suspected. The patients are euthyroid as a rule. So far as we know there has not been a case of amyloid goitre in which hyperthyroidism has been diagnosed with any certainty (by means of PBI, T4, tracing, etc.). Some cases have been recorded with an increased BMR, possibly caused by the underlying disease. Macroscopically the goitre is smooth or nodular, with an average weight of 150-200 g. The cut surface is usually homogeneous grey-yellow-to-brown in colour and has a waxy appearance. Microscopically the thyroid tissue seems to be replaced by the amyloid material. The follicular epithelium is flattened, and there is little colloid. Often there are masses of lymphocytic and plasmocytic infiltrates. Amyloid deposits are sometimes seen in the walls of blood vessels; large amounts of adipose tissue in amyloid goitre have been described. The amyloid goitre must be distinguished from the medullary (solid, amyloidotic) carcinoma of the thyroid. This is a neoplasm of the thyroid in which solid masses of polygonal tumour cells usually are separated by an abundant hyaline stroma, containing a variable amount of amyloid; the tumour cells probably arise from the C-cells (or parafollicular cells) of the thyroid, the cells that are known to produce calcitonin. Calcitonin in serum may be increased in this type of thyroid carcinoma. For this reason calcitonin in serum was determined in our patient preoperatively. To our knowledge there is no association between systemic amyloidosis and medullary carcinoma of the thyroid. Amyloid in the medullary carcinoma seems to be formed by the neoplastic cells. The case recorded by BRANDENBURG (one of the review of AREAN and KLEIN) had, in our opinion, a medullary carcinoma, and therefore this case cannot be accepted as an amyloid goitre.

Amyloidosis of the thyroid gland is not so exceptional as might have been thought originally. BATTAGLIA describes it to be present in 15 per cent of the cases of secondary amyloidosis.

TABLE I: CLASSIFICATION OF AMYLOIDOSIS

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Description</th>
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<tr>
<td>I</td>
<td>primary amyloidosis</td>
<td>a) systemic non-familial, b) familial, c) localized</td>
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<tr>
<td>II</td>
<td>lymphoproliferative disorders with amyloid</td>
<td>a) myeloma, b) plasmocytoma, c) other lymphoproliferative disorders</td>
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<tr>
<td>III</td>
<td>secondary amyloidosis</td>
<td>a) chronic infections, b) chronic inflammations (no infection), c) non-lymphoproliferative malignancies</td>
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TABLE II: CASES OF AMYLOID GOITRE IN THE LITERATURE

<table>
<thead>
<tr>
<th>Classification*</th>
<th>Number of cases</th>
<th>Reference (no)</th>
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<tr>
<td>I a</td>
<td>8</td>
<td>3, 6, 13, 16, 33, 36, 42, 46</td>
</tr>
<tr>
<td>b</td>
<td>2</td>
<td>24 (2×)</td>
</tr>
<tr>
<td>c</td>
<td>3</td>
<td>2, 12, 38</td>
</tr>
<tr>
<td>II a</td>
<td>23</td>
<td>5, 8, 10, 14, 15, 17, 20, 21, 22, 26, 29, 30, 31, 32, 34 (2×), 37, 40, 41, 43, 44 (2×), 48</td>
</tr>
<tr>
<td>b</td>
<td>3</td>
<td>19, 23, 25</td>
</tr>
<tr>
<td>c</td>
<td>Unclassifiable</td>
<td>3</td>
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<tr>
<td></td>
<td>3</td>
<td>28, 39, 45</td>
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*See Table I.
Amyloid goiter in a case of generalised primary amyloidosis. Amer. J. Med. 43, 604.

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