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Amyloid goitre

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SYNOPSIS Amyloid goitre is a rare manifestation of amyloidosis; about 50 cases have been recorded and this paper adds a further six cases, the first to be described from Uganda. The condition has to be distinguished from the more common types of goitre, and histological differentiation from medullary carcinoma may be difficult with small biopsies.

Irrespective of an underlying cause, the distribution of amyloidosis in Uganda resembles the classical secondary type, and the findings in 81 cases confirm this. The age of onset of the primary type is earlier than seen elsewhere and it is possible that these variations result from immune depression following malnutrition or endemic infectious diseases.

Amyloid goitre, an enlargement of the thyroid due to widespread amyloid infiltration, is a rare phenomenon. Shapiro, Kohut, and Potter (1971) recorded 47 cases from the world literature. In Uganda, six cases of amyloid goitre have been seen since 1960 and represent a relatively high incidence of this unusual manifestation of systemic amyloidosis.

The distribution of amyloid material in Ugandans suffering from systemic amyloidosis differs from that seen elsewhere (Wright, 1961). A further survey of systemic amyloidosis in Uganda has been carried out to investigate this finding.

Materials and Methods

Five cases of amyloid goitre were seen at necropsy in Mulago Hospital, Kampala, between January 1961 and April 1971; these were discovered only at necropsy and in each case the gland weight exceeded 40 g. During this period 9 274 necropsies were performed. Material from a sixth case was submitted for histological examination following subtotal thyroidectomy.

Sections were cut from the original paraffin blocks, where available, stained with haematoxylin and eosin, Congo red and thioflavine T, and studied to assess the distribution of amyloid. The presence of amyloid was confirmed in all cases by its avidity for Congo red stains, the green-yellow birefringence with Congo red stains viewed by polarized light, and the ultraviolet fluorescence with thioflavine T.

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Clinical Summaries

Three patients were male and three female. The ages at diagnosis ranged from 24 to 70 with a mean of 40. Table I summarizes the relevant findings. In three cases no underlying cause for amyloidosis was found; pulmonary tuberculosis was found in two cases and one patient had a chronic leg ulcer. Three patients presented in congestive cardiac failure, one being secondary to renal hypertension; another presented with the nephrotic syndrome. Pressure symptoms had not been noted in any of the cases where amyloid goitre was discovered at necropsy

Case	*Age*	*Sex*	*Thyroid Weight (g)*	*Presentation*	*Underlying Disease*	*Other Findings*
1	45	F	70	Congestive cardiac failure	None	Severe anaemia
2	49	M	140	Chronic leg ulcer	Chronic leg ulcer	? Tracheal compression
3	24	M	90	Nephrotic syndrome	Pulmonary tuberculosis	None
4	70	M	360	Congestive cardiac failure	None	Chronic glomerulonephritis
5	30	F	50	Congestive cardiac failure, hypertension	None	Acute pancreatitis
6	25	F	145	Dysphagia	Pulmonary tuberculosis	None

Table I *Summary of case findings in six patients with amyloid goitre*

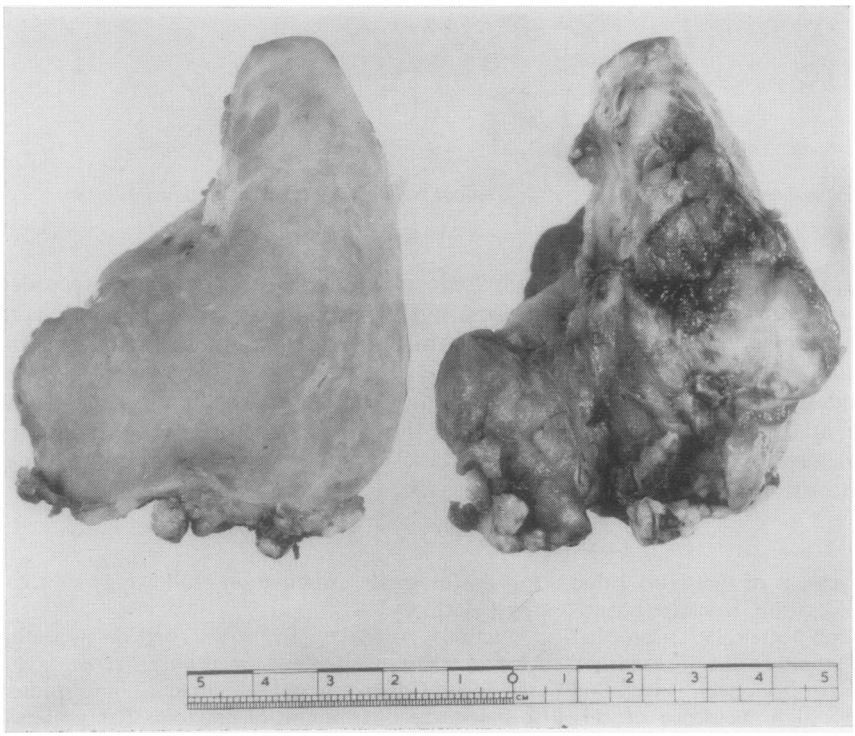

Fig. 1 *Partial thyroidectomy specimen showing cut surface and medial surfaces with tracheal indentation in case 6 (scale in cm).*

but sudden enlargement of the gland may have contributed to death in case 2. Case 6 was a 25-year-old female who complained of dysphagia. On examination she was noted to have a smooth, symmetrical goitre without retrosternal extension; partial thyroidectomy was performed. The specimen received in the laboratory weighed 145 g and on cross section was a yellow-white colour with a glassy appearance (Fig. 1).

Case[1]	*Liver*	*Kidney*	*Spleen*	*Adrenals*	*Tongue*	*Alimentary Tract*	*Heart*
1	V	V	++	V	+	V	+
2	V	+	V	+	+	–	+
3	V	++	+	–	–	–	–
4	V	+	V	–	–	–	+
5	V	+	V	V	–	–	+

Table II *Distribution of amyloid material in five necropsied cases of amyloid goitre*

[1]Case numbers are the same as for Table 1
V = infiltrate predominantly perivascular
\+ = perivascular and parenchymatous infiltrate
++ = perivascular and marked parenchymatous infiltrate
– = no material available for examination.

There was no significant tribal distribution.

The distribution of the amyloid in the five necropsied cases is summarized in Table II.

Microscopic Findings

Microscopic examination of the thyroid shows complete or near complete replacement of the thyroid parenchyma by amyloid in all cases. The infiltrate originates between the acini which are stretched, attenuated, and the lining epithelium flattened. Occasional islands of more normal thyroid tissue are seen (Fig. 2). A patchy, chronic inflammatory infiltrate of plasma cells and lymphocytes is often present but is seldom prominent. Occasional foci of foreign body giant cells and epithelioid cells occur at the periphery of amyloid deposits (Figs. 3 and 4).

Amyloid was present in all organs studied microscopically. Infiltration of the liver was minimal in all five cases and extensive infiltration of the spleen was found only in two cases. By contrast, the kidney showed extensive perivascular, glomerular and interstitial infiltration in four cases. The heart showed perivascular and some interstitial infiltration in all four cases examined.

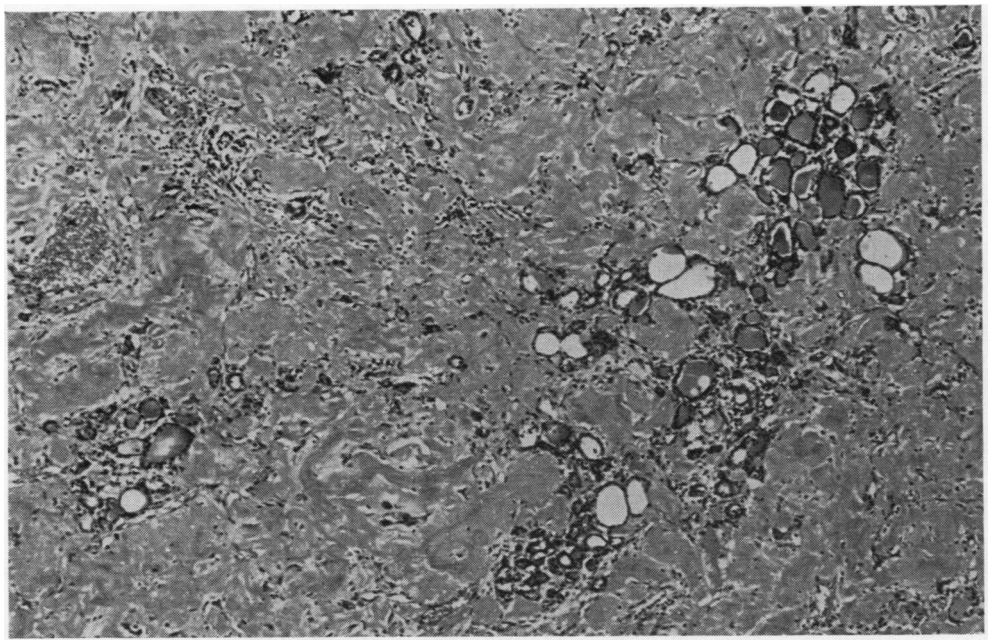

Fig. 2.

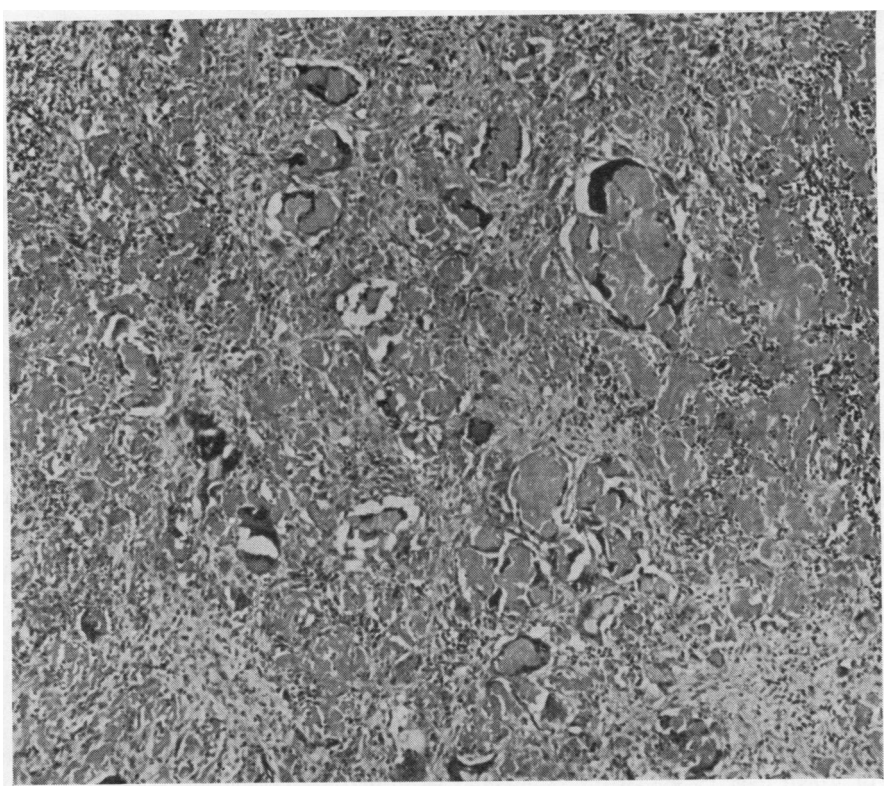

Fig. 3.

Fig. 2 *The normal thyroid architecture is almost completely replaced by amyloid except for a few surviving acini in case 6 (haematoxylin and eosin* × *50).*

Fig. 3 *Another area with a marked giant cell reaction around the deposits of amyloid (haematoxylin and eosin* × *50).*

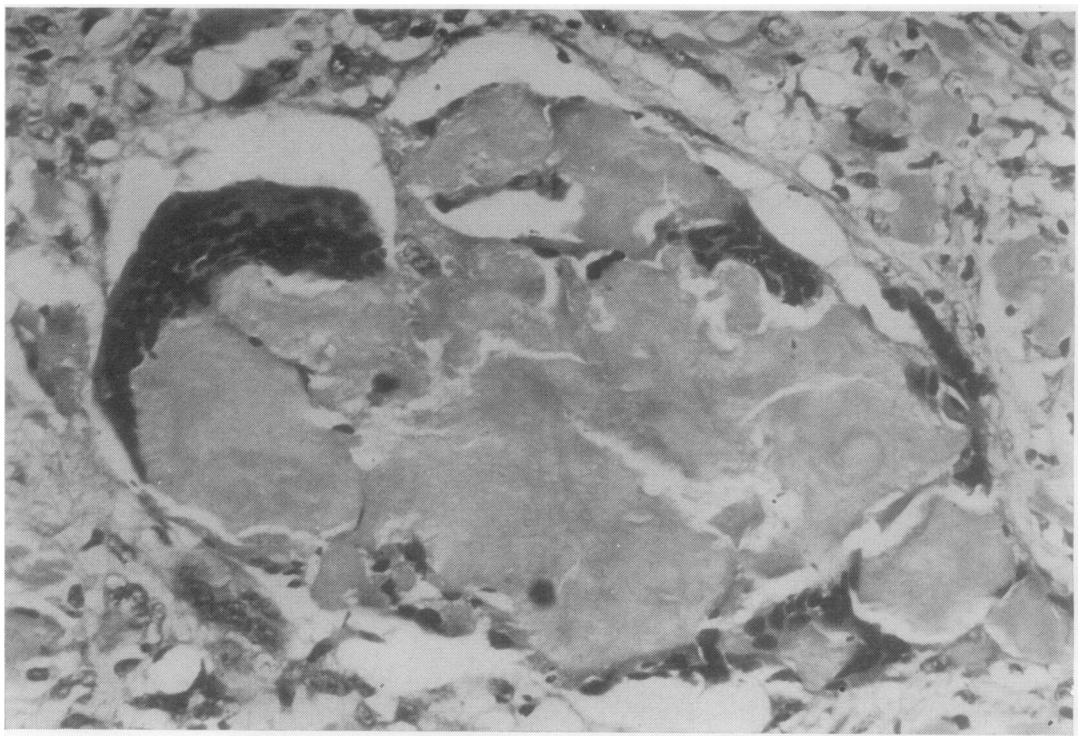

Fig. 4 *A foreign body giant cell associated with deposits of amyloid in case 6 (haematoxylin and eosin × 300).*

In addition, the kidneys in cases 4 and 5 showed the changes of chronic glomerulonephritis.

Discussion

Some degree of microscopic infiltration of the thyroid is found in most cases of systemic amyloidosis, the distribution usually being strictly perivascular (minor involvement). Enlargement due to widespread infiltration (major involvement or amyloid goitre) is rare.

Amyloid infiltration of the thyroid was first described in 1855 (von Rokitansky), and the first recorded example of amyloid goitre in 1858 (Beckmann). Walker (1942) reports two cases of amyloid goitre with a review of 56 cases from the literature. Arean and Klein (1961) point out that some earlier cases included as amyloid goitre were merely examples of amyloid infiltration of the thyroid found incidentally at necropsy, and, with their stricter criteria, accept only 29. Recently Shapiro, Koluit, and Potter (1971) recorded 47 cases from world literature, to which may be added the cases recorded by Hunter, McDougall, and Winston Evans (1968) and by Abraham, Damodaran, and Sharma (1967).

In Caucasian subjects microscopic involvement of the thyroid gland by amyloid can be found in 50% of primary systemic amyloidosis and 80% of the secondary type (Arean and Klein, 1961); such infiltration is usually confined to the walls of blood vessels and is clinically unsuspected.

Amyloid infiltration of the thyroid sufficient to produce a clinically detectable goitre is rare but when it occurs the enlargement of the gland is rapid. In recorded series the history ranges from four months to three years with an average of about one year. The gland is firm to hard in consistency although a few are soft; the cut surface varies in colour from white, grey to yellow, with occasional areas of haemorrhage.

Clinical evidence of myxoedema is uncommon despite the widespread infiltration of the gland. It occurred in none of the 29 cases reviewed by Arean and Klein (1961) but it did, after thyroidectomy, in their own case. In the present series, none of the necropsy cases or the case diagnosed clinically had any evidence of thyroid hypofunction.

The histological diagnosis of amyloid goitre is straightforward if adequate material is available. However, amyloid goitre may show small groups of distorted cells separated by an amyloid stroma that could lead in a needle biopsy to a mistaken diagnosis of medullary carcinoma. Two cases of medullary carcinoma were found in the 80 Ugandan cases of thyroid carcinoma recorded in the Kampala Cancer Registry (Templeton, 1970).

The distribution of the amyloid deposits in the other organs of the five necropsied patients is shown in Table II. All five cases showed only perivascular involvement of the liver and only two had extensive splenic involvement. However, widespread perivascular, glomerular, and interstitial involvement was noted in the kidneys of four of the five cases. The relatively severe involvement of the kidney compared with the predominantly perivascular infiltration in other organs has already been noted in Uganda (Wright, 1961). The same author recorded 40 cases of amyloidosis from the Mulago Hospital necropsy records over a 10-year period up to 1960; in 26 cases no associated chronic disease was found. The thyroid had been examined histologically in seven cases of primary amyloidosis and one case of the secondary type and only two cases in the former group showed involvement; this was reported as being insignificant in both cases.

In this subsequent 10-year study on consecutive material up to the end of 1970, 41 cases of amyloidosis were recorded from 9 038 necropsies; this represents an incidence of 0·45%. Table III shows the distribution of amyloid in these cases. There was a greater incidence of tongue, heart, and thyroid infiltration than previously reported (Wright, 1961) but otherwise the findings are similar. The kidney is involved in most cases and is usually the most severely affected organ, amyloid being found in the glomeruli, arteries, and to a lesser extent around the tubules. Minor involvement of the thyroid is present in most cases. Three cases of amyloid goitre were found in this 10-year period (the two additional cases reported came to necropsy in 1971), which is a higher relative incidence of this form of the disease than in other parts of the world. In Caucasians the distribution of amyloid in primary and secondary amyloidosis is regarded by some as very different whereas in Uganda both resemble the classical secondary type. Table IV shows the distribution of amyloid in 81 cases from Uganda (the figures are compounded from the present series and a previous study (Wright, 1961)) and compares it with primary

	13 Cases of Primary Amyloidosis		*28 Cases of Secondary Amyloidosis*	
	No. Examined	*No. Positive*	*No. Examined*	*No. Positive*
Tongue	6	5 (83%)	8	6 (75%)
Heart	12	7 (58%)	16	6 (37%)
Liver	13	10 (77%)	25	18 (72%)
Pancreas	11	7 (64%)	13	6 (46%)
Spleen	13	11 (85%)	24	22 (92%)
Kidney	11	10 (91%)	27	26 (96%)
Adrenal	9	7 (77%)	13	9 (70%)
Thyroid	5	4 (80%)	10	7 (70%)

Table III *Distribution of amyloid in 41 cases of systemic amyloidosis seen from 1961 to 1970*

	39 Cases of Primary Amyloidosis from Uganda			*Minimal Percentage Involvement in Primary Amyloidosis*[2]	*42 Cases of Secondary Amyloidosis from Uganda*			*Percentage Involvement in Secondary Amyloidosis*[3]
	No. Examined	*No. Positive*	*Percentage Involvement*		*No. Examined*	*No. Positive*	*Percentage Involvement*	
Tongue	8	5	62	40	10	7	70	—
Heart	24	9	38	90	24	8	33	43
Liver	31	21	68	35	35	24	69	87
Pancreas	20	10	50	—	18	9	50	63
Spleen	28	23	82	40	30	28	93	100
Kidney	37	35	95	35	40	37	92	93
Adrenal	26	19	73	25	22	14	64	93
Thyroid	12	6	50	—	11	7	64	59

Table IV *Distribution of amyloid in 81 cases*[1] *of systemic amyloidosis from Uganda compared with those in primary and secondary amyloidosis from outside Africa*

[1]These figures are a combination of a previous 10-year study (Wright, 1961) and the present series.
[2]Minimal percentage involvement in 145 cases of primary amyloidosis (Symmers, 1956).
[3]Percentage involvement in secondary amyloidosis (Dahlin, 1949).

(Symmers, 1956) and secondary amyloidosis (Dahlin, 1949) from outside Africa).

The age of patients with secondary amyloid is dependent upon the time at which the underlying disease begins. In this series the range was 4 to 60 with a mean at 33; this is not significantly different from outside Africa (Dahlin, 1949). In the primary group the age range was 12 to 70 with a mean of 43; half the patients were under 50. Wright (1961) records an age range in 26 cases of primary amyloid of 14 to 65: 85% were under 40 and 50% were less than 30. Rukavina, Block, Jackson, Falls, Carey, and Curtis (1956) from America recorded one third of their cases of primary amyloid as under 50. The age of presentation of primary amyloid in Uganda is significantly earlier than that seen outside Africa.

In West Africa, Edington and Mainwaring (1964) found 11 cases of amyloidosis in a necropsy population of 3 806. In two cases no underlying cause was detected and in one of these the distribution of amyloid was that described in the classical secondary type. They found the kidney to be the organ most frequently showing heavy deposits of amyloid but commonly the adrenals and spleen were also heavily infiltrated. Other organs were rarely severely affected and in 10 cases where the thyroid was examined eight were found to have minor involvement. These findings are in general agreement with those from Uganda.

The differences in distribution suggest that some factors are operative in Ugandans which induce deposition of amyloid material in a similar fashion to that associated with chronic infectious diseases. Certainly malaria and filariasis are widespread in Uganda, many of the population contracting these diseases at an early age. The unusual levels of serum proteins in the Africans (McFarlane, Talerman, and Steinberg, 1970) are possibly a manifestation of continual bombardment by such infective agents, coupled perhaps with immunological defects as a result of malnutrition (Mugerwa, 1971). In addition, evidence seems to be accumulating that amyloidosis is often associated with deficiency of delayed hypersensitivity reactions (Muckle, 1968; Cathcart, Mullarkey, and Cohen, 1970; Lehner, Cameron, and Ward, 1970).

Thus we might suggest that early and prolonged exposure to infections and infestations, possibly complicated by defects in cellular immunity, could be responsible for the different distribution and earlier onset of primary amyloidosis in Ugandans.

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