

Amyloidosis Associated with Neoplastic Diseases

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SUMMARY

In a series of 78 patients with secondary amyloidosis, associated neoplastic diseases were found in 13 (17%). Included are 5 cases of multiple myeloma, 3 cases of lymphoma, and the rest were carcinomas. Cases are reported of patients with carcinoma of the stomach, gall bladder, urinary bladder, kidney or colon, illustrating the various associated neoplasms. The literature concerning the incidence of the two conditions in relation to each other is reviewed.

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Amyloidosis is known to be associated with neoplastic disease. The association is particularly well documented for multiple myeloma,¹⁻³ and Hodgkin's disease.^{2,4,5} The association of amyloidosis with neoplastic diseases other than multiple myeloma and Hodgkin's disease has also been noted, but the incidence and documentation in the literature appear to be smaller.^{2,6-8} Medullary carcinomas of the thyroid gland are known to contain varying amounts of amyloid in the stroma.⁹ However, the amyloid is confined to the tumour,¹⁰ while we are dealing with cases of generalised amyloidosis.

The present article reports the incidence of amyloidosis associated with neoplastic diseases, and includes case reports of patients with neoplastic diseases other than multiple myeloma or lymphoma.

SOURCE OF PATIENTS AND INCIDENCE OF AMYLOIDOSIS

The patients in this study form part of a current series of patients with amyloidosis diagnosed in the 3 general hospitals in Jerusalem since 1949, and include 78 cases with systemic amyloidosis. Thirteen patients (17%) are cases of amyloidosis associated with neoplastic diseases. Of the 13 patients, 5 had multiple myeloma (4 females), 3 had lymphomas (2 females), and the remaining 5 patients, having other kinds of neoplastic diseases, are the subjects of the following reports.

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CASE REPORTS

Case 1

A female, born in Syria, was first diagnosed at the age of 75 years as having hypothyroidism and myxoedema, and treatment with thyroid preparations was initiated. Five years later, chronic congestive heart failure gradually developed and was treated, but at the age of 85 years she was admitted to hospital because of severe congestive heart failure.

On examination her blood pressure was found to be 95/50 mmHg, the skin dry and of parchment-like consistency, the face swollen and the tongue enlarged, and the neck veins were engorged. The chest was emphysematous and râles were heard at both lung bases. Heart sounds were normal, and a mild systolic murmur was heard over the base. The liver was enlarged to 15 cm below the right costal margin, with many nodules palpable over its surface. There was pitting oedema of the legs. Circulation time (arm-to-tongue) was 21 seconds. The ECG showed an old myocardial infarction. A compressed fracture of the ninth dorsal vertebra was noted on X-ray film. On urinalysis 4+ protein was found. The haemoglobin was 10.3 g/100 ml and blood glucose was 118 mg/100 ml. Total serum proteins were 5.1 g/100 ml (albumin 1.8 g/100 ml, uric acid 11.3 mg/100 ml, cholesterol 190 mg/100 ml). The bilirubin, calcium and phosphorus were normal. Protein-bound iodine was 2.2 µg/100 ml. In the ward the patient was oliguric and died after 4 days.

At autopsy, the immediate cause of death was discovered to be multiple recent and old pulmonary emboli. The autopsy also revealed carcinoma of the gall bladder invading the liver. Amyloidosis was found in the kidneys, adrenals, pancreas, a salivary gland, in a small scar in the myocardium, and in many arteries.

Case 2

A male, born in Morocco, underwent right nephrolithotomy at the age of 25 years. A year later he underwent resection of a Meckel's diverticulum, and at that time traces of protein were found in the urine. At the age of 35 years he underwent right hernioplasty, and 3 years later was admitted to hospital because of urinary tract infection and an elevated blood urea.

On admission he appeared pale, blood pressure was 125/70 mmHg, and a blowing systolic murmur was heard over the heart. The liver and spleen were not palpable, nor was there leg oedema. On urinalysis 3+ protein was found, with many red and white blood cells. Culture of the urine

revealed *Pseudomonas aeruginosa*. In the blood, haemoglobin was 7,4 g/100 ml, haematocrit 24%, leucocyte count 15 700/mm³, blood urea 188 mg/100 ml and glucose 106 mg/100 ml. Total serum proteins were 4,7 g/100 ml, (albumin 1,1 g/100 ml), and cholesterol 140 mg/100 ml. The bilirubin and alkaline phosphatase were normal. A chest X-ray film was normal. The ECG demonstrated left heart strain. A cytосcopy was performed and many tumours were observed on the urinary bladder wall. The patient died in terminal renal failure.

At autopsy anaplastic carcinoma of the urinary bladder was found, stenosing the ureteral orifices. Bilateral hydro-ureters and hydronephrosis with bilateral chronic pyelonephritis were also noted. Generalised amyloidosis was found, involving kidneys, intestine, spleen, liver and adrenals.

Case 3

A female, born in Iraq, complained of dyspnoea on effort and palpitations at the age of 58 years. A year later atrial fibrillation developed. At the age of 60 years she was first admitted to hospital and thyrotoxicosis was diagnosed. Urinalysis was negative, and the haemoglobin was 10,2 g/100 ml. The blood chemistry tests, including urea, glucose, proteins and cholesterol, were normal. Eight months later she was readmitted because of increasing difficulties in swallowing, nausea, and loss of weight.

On examination severe cachexia and pallor were found. The blood pressure was 110/80 mmHg and the pulse irregular. The haemoglobin was 7,9 g/100 ml, total serum proteins 5,6 g/100 ml (albumin 1,6 g/100 ml), cholesterol 114 mg/100 ml, serum iron 34 µg/100 ml, and on urinalysis 1+ protein was found. Lymphadenopathy was found in the neck. A 7-cm tumour was palpated in the epigastrium, but the liver and spleen were not palpable nor was leg oedema noted. A barium meal revealed a 5-cm filling defect in the mid-oesophagus, and the gastric mucosa appeared irregular. On ECG, atrial fibrillation was noted. The patient was treated symptomatically and died after 77 days.

At autopsy, carcinoma of the stomach of the ulceroinfiltrative type was found, involving the lesser curvature, with metastases to the oesophageal wall, causing stenosis of the oesophagus, and with metastases to the pancreas and lymph nodes. Amyloidosis of the kidneys was found. Colloid hyperplasia was noted in the thyroid gland.

Case 4

A female born in Yugoslavia was first hospitalised at the age of 43 years because of increasing weakness. A left renal cell carcinoma was found, nephrectomy was performed, and for the next 2 years the patient was asymptomatic. At that time a metastasis was found, first in the left parotid gland area and later in the lungs. At the age of 46 years the patient was readmitted because of fever.

On admission dyspnoea was noted, and a swelling was seen at the left parotid gland causing partial paralysis of

the facial nerve with regional lymphadenopathy. Blood pressure was 130/90 mmHg. The liver was palpable 4 cm below the right costal margin. The ECG was normal, but two metastatic lesions were noted on X-ray film in the right lung and one round lesion in the left lung. On urinalysis traces of protein were found, with few leucocytes. The haemoglobin was 9,5 g/100 ml, and the sedimentation rate increased to 110 in the first hour. The blood biochemistry was normal. The patient's condition gradually deteriorated and she died after 3 months.

At autopsy, recurrence of the carcinoma was found in the site of the nephrectomy, with metastases in the lung, thyroid, liver, pancreas, right kidney, right adrenal, left ovary, uterus, right breast, and right axillary, mediastinal, carinal, peripancreatic and mesenteric lymph nodes. Generalised amyloidosis was also found.

Case 5

A male, born in Hungary, suffered rectal bleeding at the age of 60 years. A year later a compressed fracture of the third lumbar vertebra was found. Hepatomegaly was noted with elevated blood alkaline phosphatase. On barium enema examination, a constriction was demonstrated 10 cm above the rectum. A course of radiotherapy was initiated to the lumbar area. Five months later the patient was readmitted. His condition had deteriorated, and he was pale, with blood pressure 130/70 mmHg. The liver was palpable 5 cm below the right costal margin. In the urine 2+ protein was found, but Bence-Jones protein was absent. Blood haemoglobin was 8,7 mg/100 ml, and blood biochemistry was normal except the alkaline phosphatase, which was 15 units (Bessey-Lowry). Serum protein electrophoresis was normal. In the bone marrow an increased number of plasma cells was present, but this was not diagnostic of multiple myeloma.

Biopsy specimens obtained through colonoscopy demonstrated the presence of malignant polypoid carcinoma of the rectum. On the same biopsy specimen amyloidosis of the colon was demonstrated. The patient underwent laparotomy and partial colectomy, but died 2 months later with septic shock. Autopsy was not performed.

DISCUSSION

The purpose of the present article is to draw attention to the appearance of secondary amyloidosis in the presence of carcinomatous neoplastic disease. The present series as well as a review of the literature demonstrate that many neoplastic diseases can be complicated by secondary amyloidosis,^{2,8,11,12} and the incidence of such cases, as reflected in some of the larger series published, is compiled in Table I. The percentage runs from as low as 2,4%⁶ to the highest incidence of 32%.³

Attempts to examine the situation from the other point of view, that is, the incidence of amyloidosis in series of cases of neoplastic diseases, brought a less fruitful yield. Much attention was given to multiple myeloma. In this

TABLE I. INCIDENCE OF CASES OF AMYLOIDOSIS ASSOCIATED WITH NEOPLASTIC DISEASES IN SERIES OF CASES OF AMYLOIDOSIS

Author	No. of cases			Total No. of cases with neoplastic diseases	Total No. of cases of amyloidosis	% of cases with neoplastic diseases
	Multiple myeloma	Lymphomas*	Carcinomas			
Higuchi ⁶	—	—	—	12	506	2,4
Dahlin ¹²	3	2	5	10	44	23
Calkins and Cohen ¹	4	0	0	4	21	19
Briggs ¹¹	0	3	1	4	73	5,5
Cardell ⁴	3	4	0	7	22	32
Blum and Sohar ¹⁹	5	0	9	14	200	7
Present series	5	3	5	13	78	17

* Including Hodgkin's disease.

disorder the incidence of amyloidosis varies from 6% to 15%.¹⁻³ Among 234 patients with Hodgkin's disease examined at necropsy, amyloidosis was found in 5 cases (2,1%).²³ Renal cell carcinoma is another example where a methodical trial was carried out in order to find the true incidence of secondary amyloidosis. In a series of 273 cases with renal cell carcinoma, 8 cases (2,9%) were found to be associated with amyloidosis.⁸ Of 93 instances of carcinoma of the uterus, amyloid involvement of the kidneys was found in 4 cases.⁷ A most instructive analysis was published by Kimball,² who in a series of 4033 cases of cancer, found amyloidosis in 16, establishing an incidence of 0,4%. Hodgkin's disease and multiple myeloma comprised a significantly higher percentage of the amyloidosis group than was expected from their frequency in the total autopsy series.² In this last series 6 cases out of 16 were neoplastic diseases other than multiple myeloma and Hodgkin's disease.

The problem exists as to why amyloidosis appears in greater proportion among patients with multiple myeloma and lymphomas. Work done by Glenner and associates¹⁴⁻¹⁶ indicates that amyloid fibrils may be of immunoglobulin origin, and formation of amyloid fibrils by intralysosomal digestion of light polypeptide chains of immunoglobulins was suggested. Other work done by Ben-Ishay and Zlotnick,^{17,18} demonstrated the presence of amyloid fibrils in the reticulo-endothelial cells and suggested that those cells are implicated in amyloid production.

All these observations may provide a possible explanation of the higher incidence of amyloidosis in neoplastic

disorders related to the reticulo-endothelial system. It still leaves unexplained the appearance of a variety of carcinomas in association with amyloidosis. Possibly, the alleged altered immunity in these disorders may be connected to appearance of amyloid.

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