Amyloidosis in Hodgkin's Disease*

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SUMMARY

A patient with a 13-year history of Hodgkin's disease, who developed the terminal complication of amyloidosis manifesting in a nephrotic syndrome resulting in death, is reported. The incidence of this rare complication is reviewed from reports in the literature; to date only 53 unequivocal cases of amyloidosis, in association with Hodgkin's disease, have been described. The clinical picture is discussed, and the possible pathogenesis of amyloidosis is considered. The importance of intensive combination chemotherapy for preventing long-term complications, is stressed.

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Medical students are well acquainted with the condition of amyloidosis, yet medical practitioners seldom see a patient with amyloidosis. The purpose of this report is to illustrate the clinical appearance of this condition, as well as to draw attention to the fact that amyloidosis may be a fatal complication in a patient with well-controlled malignant disease, and lastly, to consider the pathogenesis and suggest another important immunological effect of neoplastic disease.

Rokitansky, in 1842, first described the disease entity in which many organs exhibited a firm waxy substance, due to the deposition of a homogeneous material. Virchow, in 1854, noted that this substance stained blue-black with iodine and sulphuric acid, almost like starch; he therefore called the substance 'amyloid' and the disease entity 'amyloidosis'. Actually, the substance has no relationship to starch, but is a protein of variable composition, usually associated with a sulphate-bearing polysacchride similar to, if not identical with, chondroitin-sulphuric acid. Wilks, in 1856, was the first to note that this condition may follow chronic suppurative disease.

It has been known that there must be several types of amyloidosis. At first secondary, or more correctly perireticular amyloidosis, completely dominated the picture. This form occurred only in patients who suffered from chronic, mostly suppurating disease. It was therefore regarded as secondary to such primary diseases as tuberculosis, osteomyelitis and neoplastic disease. Waldenström[1] was able to show that this condition was reversible when the primary disease was successfully treated. Primary amyloidosis is not preceded by a discernible cause; increasing knowledge regarding 'primary amyloidosis' or paramyloid that is also pericollagenous, has led to the detection of many different types possibly caused by different mechanisms. From studies in many reported cases, it would appear that primary and secondary amyloidosis have much in common. The primary form with its pericollagenous amyloid depositions mainly in mesechymal organs, affects especially muscular organs such as heart, tongue, gastro-intestinal tract and muscles; whereas the secondary form with perireticular amyloidosis, is more commonly located in parenchymal organs like liver, kidney, spleen and adrenals. However, mesenchymal tissue and parenchymatous organs are often affected in both, and it is maintained by some pathologists that primary and secondary amyloidosis have different histologic pictures.[2]

Amyloidosis as a complication of Hodgkin's disease is a rare, though well-attested complication. As far back as 1856, Wilks reported a case in which gross autopsy material showed the existence of both diseases. However, when 20 standard textbooks of medicine were consulted, it was found that only 6 of these mentioned amyloidosis as a complication of Hodgkin's disease.

A review of the literature reveals only 53 cases of Hodgkin's disease in which the concurrent existence of amyloidosis is either demonstrated by pathologic material obtained at autopsy, or suggested by clinical studies.[3-10] (Equivocal cases, or those with coexistent tuberculosis are excluded.) It is difficult to obtain reliable figures relating to the incidence of amyloidosis in Hodgkin's disease; in the early literature there are no reliable figures at all, because the diagnostic criteria for differentiating Hodgkin's disease from tuberculosis were not adequate, and also because many cases of Hodgkin's disease, in those days, were complicated by tuberculosis. Of the few recorded series, the following incidence is reported: 2%,[5] 4%,[3,6] 8%;[4] only one series showed a surprisingly high incidence, namely, of 20 amyloidosis cases, 4 were diagnosed as secondary to Hodgkin's disease.[10] The words 'rare' and 'occasional' in textbooks and monographs are therefore justified.

The clinical picture of amyloidosis depends upon the organs involved; renal disease is a major component in most patients. The association of Hodgkin's disease and the nephrotic syndrome, due to amyloidosis, is rare.[8] When this association does occur, it is usual for the nephrotic syndrome to appear after the picture of Hodgkin's disease is well established. It is generally accepted that the nephrotic syndrome results from a glomerular abnormality, which has as its cardinal sign massive proteinuria; other features such as hypo-albuminaemia, lipiduria, hypercholesterolaemia and oedema, are more variable.[11]

There has been very little exact knowledge of the source or mode of formation of amyloid. Early studies suggested that amyloid deposits were caused by precipitation of circulating gamma globulin in the tissues, and

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later work raised the possibility that specific antibodies to the inducing agent may play a causative role.[12,13] These concepts lost favour when it was noted that patients with severe hypogammaglobulinaemia sometimes develop amyloidosis, and when it was shown that amyloid fibrils do not react with antisera to human IgG and its subunits. Teilum[14] propounded a so-called 'two-phase cellular theory of local secretion', where the common fundamental lesion in various forms of amyloidosis is a failure of normal differentiation and maturation of plasmocytoid and other pyroninophilic reticular cells, under the stress of protracted stimulation. He suggested that the effects of cortisone, ACTH and nitrogen mustard, through suppression of the reticulo-endothelial cells, wou'd be acceleration of the amyloid process. Lately, attention has been directed to a closer temporal relation between amyloid formation and impaired cellular immunity.[15] Conditions which favour the depletion of small lymphocytes can all accelerate, or enhance, the development of amyloid. Cathcart and co-workers[16] suggest that experimental amyloidosis (and possibly other amyloidotic states), is the end-product of a specific clone of inactivated lymphocytes. As long as the specific antigenic challenge is sustained, amyloid production would be enhanced, but once the antigenic stimulus is removed, amyloid production would cease. Non-specific factors such as blood supply and renal clearance, might also influence the rate and site of deposition of newly-formed amyloid.

CASE REPORT

Thirteen years ago, a 30-year-old White woman presented with severe pruritus, weight loss and a swelling in the neck. Biopsy of the left supraclavicular lymph glands confirmed the diagnosis of Hodgkin's disease. Treatment with radiotherapy and cyclophosphamide gave a partial remission. Four years later, she developed a large mass in the right fossa iliaca, as well as enlarged inguinal glands. Radiation over the affected area resulted in improvement, but within a year she was very ill with anaemia, weakness, weight loss and a very large abdominal mass. Her disease was then fully controlled with vinblastine injections. She remained in complete remission for 4 years, but then had a relapse, with weakness, weight loss, fever, night sweat and the mass in the right fossa iliaca again enlarged. At this stage, her sedimentation rate was 54 mm in the 1st hour (Westergren), serum albumin was 3,6 g/100 ml, globulin 4,5 g/100 ml and gamma globulin 1,2 g/100 ml, her serum copper was 306 μg, and Reed-Sternberg cells were found in the bone marrow. Treatment with procarbazine, vincristine, chlorambucil and prednisone procured a complete remission, lasting one year. Her serum calcium content was normal except for a period of 5 months when increased values were recorded. No reason for these increased values could be found, and strontium uptake and roentgenologic examination of the skeleton showed no bone lesions.

The patient relapsed again, with enlargement of the same glands in the right fossa iliaca, as well as hepatomegaly; she complained of severe pruritus and lost an appreciable amount of weight. She was found to be anaemic, with a haemoglobin of 8,5 g/100 ml, her sedimentation rate was 53 mm/h, the alkaline phosphatase was increased to 26 IU, the serum copper was 366 g, her serum albumin was 1,7 g/100 ml, the globulin 2,4 g/100 ml and the gamma globulin 0,4 g/100 ml. Combination chemotherapy with *bis*-chlorethyl-nitrosourea (BCNU), vincristine and a prednisone procured a complete remission, and after a 6-month induction treatment period, she was given maintenance treatment with chlorambucil *per os* and periodic reinduction injections of vincristine. The hepatomegaly had disappeared, the glands in the fossa iliaca had virtually disappeared and symptomatically the patient was quite well. Her haemoglobin had now increased to 13,6 g/100 ml; the sedimentation and serum copper, however, remained high throughout this asymptomatic period. Her serum albumin varied between 2,8 and 4,0 g/100 ml, the globulin from 3,0 to 5,2 g/100 ml and the gamma globulin from 0,2 to 2,4 g/100 ml. Five months after the start of this intensive combination therapy an abnormal serum electrophoretic macroglobulin was recorded; this was noted only once and never recurred.

This remission lasted for 2 years; she then relapsed with the following symptoms: febrile attacks up to 40°C, cold shivers, an extensive maculopapular rash (histologically this was an allergic vasculitis), severe pruritus and malaise to the point of exhaustion. A gallium scan showed increased retention, therefore Hodgkin's involvement of para-aortic glands was suspected; however, there was no other indication of reactivation of the Hodgkin's disease. The patient's urine showed a 4 + proteinuria, but no organisms. Serological tests for schistosoma, salmonella, rickettsia and brucellosis were all negative. The patient's complaints of tiredness and febrile attacks lasted for one month, then her condition rapidly deteriorated and she developed a serious diarrhoea. She was then admitted to hospital in an exhausted state. Physical examination showed puffy oedema of the face, as well as oedema of both legs; there were no respiratory or cardiovascular abnormalities, except for a rather low range of systolic and diastolic blood pressure (systolic 80—70 and diastolic 50—30), the abdomen was distended, but no ascites or organomegaly were detected. Her alkaline phosphatase at this stage was 57,5 IU, SGOT was 69 Transac IU, blood urea was 50 mg/100 ml, blood creatinine was 1,0 mg/100 ml, blood uric acid was 8,8 mg/100 ml, the total serum protein was now only 3,2 g/100 ml, the albumin was 0,7 g/100 ml, globulin was 2,5 g/100 ml and gamma globulin was 0,3 g/100 ml. Symptomatic treatment gave little relief, and she died 10 days after admission.

Necropsy

There was serous fluid in both pleural cavities (150 ml left and 300 ml right), both lungs exhibited some congestion and oedema. The heart weighed 250 g and except for moderate atherosclerosis, no other gross abnormalities were noted. There were enlarged lymph glands in the

area of the pulmonary aorta. Several superficial ulcers were seen in the oesophagus and stomach. The liver weighed 2 000 g, looked pale and as though there might have been tumour infiltration. The kidneys weighed 150 g (right) and 110 g (left) with no visible abnormalities. There was haemorrhagic cystitis, with a deep ulcer in the superior surface of the bladder. Both adrenals weighed 7 g and some enlarged gland masses surrounded them. The spleen weighed 400 g and infiltration masses were visible; enlarged lymph glands were found in the mediastinum and para-aortic area. No other noteworthy changes were present in the body.

Histology

The enlarged lymph glands showed typical lesions of nodular sclerosing Hodgkin's disease. Extensive amyloid deposits were present in the kidneys, spleen, liver, adrenals and stomach. Sections of all other organs showed no Hodgkin's disease or amyloidosis; a moderate amount of interstitial fibrosis was present in the myocardium, and there was some pulmonary congestion, with centrilobular emphysema.

Comment

This is a typical case of Hodgkin's disease, with a long history of disease control with radiotherapy and chemotherapy; it should be noted that this patient was never treated with nitrogen mustard. She enjoyed years of clinical remission, although a persistently high sedimentation rate and serum copper level, as well as a positive gallium scan, suggested disease activity even during the remissions. A month before exitus, she relapsed with tiredness and spiking fever; at this stage an extensive search for any form of infection was negative. Her serum albumin started to drop, while the serum globulin was higher than normal. Two weeks before death, she was admitted in an exhausted state with 4 + albuminuria and oedema. The total serum protein had dropped at this stage to 3,2 g/100 ml with a hypo-albuminaemia of 0,7 g/100 ml. The blood urea remained within normal limits till a preterminal raise of 50 mg/100 ml. The patient was too ill for a renal biopsy or other special investigations to determine the cause of the nephrotic syndrome. Amyloidosis of kidneys, adrenals, liver, spleen and stomach was found at autopsy.

DISCUSSION

Amyloidosis as a complication of Hodgkin's disease is considered to be rare. From a survey of the literature it appears that only a small number (53) of such cases has been reported throughout the years. The incidence of this complication could hardly be more than 1%, it is most likely still less. Renal disease usually dominates the picture in perireticular amyloidosis, but the association of Hodgkin's disease and the nephrotic syndrome, due to amyloidosis, is unusual. In the case presented here, the diagnosis of amyloidosis was not made antemortem. It was suspected that her nephrosis could be based on pressure by retroperitoneal glands, or even by the direct infiltration of the kidneys, which is very rare. The treatment of secondary perireticular amyloidosis is mainly that of the primary causative disease.

From the case report it will be evident that the therapeutic armamentarium had been exhausted in this individual; attention is drawn to the fact that this patient was not initially treated with current combination chemotherapy. Not only is the incidence of remissions in extensive and advanced Hodgkin's disease, as well as the quality of these remissions, so infinitely better with modern intensive combination chemotherapy, but it is also aimed at avoiding long-term complications, such as amyloidosis. Although early reports implicated injections of nitrogen mustard as an enhancing factor in amyloidosis,[14,16] modern therapy of Hodgkin's disease has not been implicated as accelerating amyloid formation.

In the investigation of the relationship between amyloid formation and impaired cellular immunity, a great number of factors which can enhance the development of amyloid have been implicated: thymectomy,[17] splenectomy,[18] ionizing radiation,[19] antimetabolites,[20] cortisone,[14] parabiosis[21] and other conditions which favour the depletion of small lymphocytes.[22] It appears that amyloidosis is an expression of immunological tolerance. The fact that immunology is concerned in the development of tumours, the rate of growth and metastasis, and the clinical state of patients with neoplastic disease, is generally accepted. The occurrence of amyloidosis as a complication of Hodgkin's disease, points to another immunological facet in malignant disease.

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