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CASE REPORT

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Progressive liver failure in a patient with adult Niemann-Pick disease associated with generalized AL amyloidosis

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Abstract We report a case in which an adult form of Niemann-Pick disease (type B of NPD) was associated with a rapidly progressive generalized AL amyloidosis of kappa type. Both diagnosis were made by biopsy, the NPD by bone marrow biopsy and fibroblast culture, the amyloidosis by liver biopsy. Malignant non-Hodgkin lymphoma was not found. The patient, a 67-year-old woman, died from hepatic coma subsequent to a progressive liver failure. We discuss possible relations between the lysosomal storage disease and the development and rapid progression of amyloidosis.

Key words Adult Niemann-Pick disease · Generalized AL-amyloidosis · Progressive liver failure · Fibroblast culture · Immunohistochemistry · Electron microscopy

Introduction

Niemann-Pick disease (NPD) comprises a heterogeneous group of autosomal-recessive inherited disorders, all showing an accumulation of sphingomyelin and cholesterol in the nervous system and the visceral organs such as liver and spleen [30]. Two categories are defined by biochemically evaluated sphingomyelinase activity of blood leucocyte or fibroblast culture [29, 34, 36]: the sphingomyelinase-deficient (category I) and non-deficient categories (category II) [9, 30]. While the basic defect of category II of NPD remains unknown [2], several mutations of the gene encoding acid sphingomyelinase in the region p15.1–p15.4 of chromosome 11 were detected in patients with the splingomyelinase-deficient category of NPD [32, 35]. In the most common form of NPD of category I (typeA) [4], severe sphingomyelinase deficiciency causes death from neurological disease in early childhood. The adult type (type B) [4] of the sphingomyelinase-deficient category is characterized by visceral manifestations, with hepato-splenomegaly, foam cells in the bone marrow, diffuse infiltration of the lungs and absence of neurological change [30]. In some cases secondary complications such as portal hypertension [24, 29, 33] or respiratory problems [21, 34] may determine the course of disease. We report an unusual case of a 67-year-old women with biochemically and morphologically identified NPD of the sphingomyelinase-deficient category. The disease process had been complicated by a rapidly progressive generalized AL amyloidosis of kappa type involving almost all visceral organs which finally led to liver failure.

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Case report

A 67-year-old woman presented with post-prandial nausea, a sensation of fullness, aversion for meat, fatique and weight loss of 10 kg within 3 months. Her neurological and psychological status were normal. Historically, 4 years previously a liver biopsy had been performed because of suspected cytomegalovirus hepatitis. In addition, hyperlipoproteinaemia and coronary heart disease were noted. One year prior to death a cardiac pacemaker had been implanted because of sick sinus syndrome.

On physical examination, a generalized slight enlargement of lymph nodes was noticed. CT and ultrasonography demonstrated hepatosplenomegaly, a wide portal vein, minimal ascites and slightly enlarged retroperitoneal and mesenteric lymph nodes. The subsequent cytological examination of a supraclavicular lymph node suggested generalized lymphoma. For further elucidation a liver and a bone marrow biopsy were performed. The histological results of the bone marrow biopsy prompted us to perform a skin biopsy and prepare a fibroblast culture. The serum immunoelectrophoresis showed a slight elevation of the IgG-kappa which was interpreted as a benign monoclonal gammopathy of kappa type.

Since the patient refused an exploratory laparotomy for removal of an abdominal lymph node, chemotherapy with chlorambucil and decortin was initiated after a presumptive diagnosis of a

non-Hodgkin lymphoma. As there were no positive effects within 1 month, the chemotherapy was abandoned. The patient continued to deteriorate and terminaly developed rapidly progressure hepatic dysfunction with icterus, a flapping tremor and foetor hepaticus. The patient died from liver failure about 4 months after her first admission to hospital.

Materials and methods

Biopsy specimens and samples obtained at autopsy were fixed in 10% buffered formalin and embedded in paraffin. All paraffin sections were stained with H&E, Giemsa and van Gieson. Amyloid was identified by positive reaction with Congo red staining according to Puchtler et al. [23] and by apple-green birefringency typical of amyloid when viewed under polarized light. Immunohistochemical examinations were performed in order to determine the chemical nature of the amyloid. The following antibodies were applied: AA, AL-lambda, AL-kappa, AB(β_2M), AF (TTR) (all from the Max-Planck-Institut für Biochemie, Martinsried, Germany). Antigen antibody binding was visualized by means of the avidin-biotin method using 3-amino-9-ethylcarbazol (Dako, Hamburg, Germany) as chromogen.

For transmission electron microscopy the formalin-fixed specimens were washed in cacodylate buffer, postfixed in 1.25% osmium tetroxide, dehydrated in graded alcohols and embedded in Epon 812. Thin sections were cut with an LKB Ultratome III, stained with uranyl acetate and lead acetate, and examined with a Siemens Elmiscop 101 at 80 kV.

Results

Biopsy findings

Both liver biopsies were examined by the authors. The first liver specimen obtained 4 years prior to death had shown a minimal portal fibrosis. Amyloid deposits were excluded by Congo red staining. A second liver biopsy performed 4 months prior to death revealed atrophy of parenchymal cells due to diffusely extended amyloid depositions which showed positive reaction with antibody against AL-kappa. A minimal erythropoietic and granulopoietic bone marrow hyperplasia associated with a high-grade plasmocytosis (10%) as well as lipid storage of reticular cells (sea-blue histiocytes) were found at bone marrow biopsy. On the basis of these findings NPD was suspected.

The biochemical analysis of fibroblast culture showed largely reduced sphingomyelinase activity to 5% of the normal value, which confirmed our presumptive diagnosis of an adult NPD (Institute for Brain Research, University of Tübingen, Germany).

Autopsy findings

At autopsy, a marked generalized icterus was detected. Yellow-tan ascites (450 ml) was found in the abdomen. The grossly enlarged liver (weighing 2850 g) and spleen (560 g) showed weakly shining glassy cut surfaces. The heart had a firm consistency and was hypertrophic. The mesenteric and retroperitoneal lymph nodes reached a size of 3.5 cm and were of firm consistency.

Histologically, generalized amyloidosis was found. As seen on the biopsy, extensive sinusoidal and portal vascular amyloid deposits were identified, which had led to marked atrophy of the liver cell plates (Figs. 1, 2). There was marked canalicular cholestasis. The splenic parenchyma was almost completely replaced by amyloid deposits. Extensive vascular and interstititial amyloid depositions were also detected in the heart, gastrointestinal tract, pancreas, kidneys, lungs, adrenals, thyroid gland, lymph nodes and other visceral organs. Apart from the choroid plexus, the brain was devoid of amyloid deposition.

Immunohistochemical examination of amyloid by means of a panel of antibodies confirmed the previous diagnosis of a severe AL amyloidosis of kappa type (Fig. 3). A moderate positive reaction with antibodies against AL-lambda light chains, however, was also observed.

A notable finding was the large number of foamy macrophages in the residual splenic parenchyma (Fig. 4). Numerous sea-blue histiocytes could be visualized, in particular in the bone marrow, liver and lymph nodes (Fig. 5). At electron microscopy, they showed typical lysosomal inclusions of lamellar structures (Fig. 6). Similar to the bone marrow biopsy, a marked plasmacytosis with a predominant expression of kappa-light chain was observed in the bone marrow, spleen and lymph nodes. A plasmacytoma was excluded.

Discussion

The generalized AL amyloidosis is also referred to as immunocyte-derived amyloidosis [14]. Accordingly, it occurs as the result of an overproduction of immunoglobulins in diverse proliferative disorders of the B-lymphocytes (multiple myeloma, Bence-Jones plasmacytoma, Waldenströms macroglobulinaemia, non-Hodgkin lymphoma, heavy chain disease, monoclonal gammopathies, etc.) or idiopathic [1, 11, 13, 14, 31]. In our case none of these proliferative diseases was found. The minimal increase of kappa light chains identified serologically together with the plasmacytosis of the bone marrow may be suggestive of a non-overt plasma cell dyscrasia underlying the development of AL amyloidosis of kappa type. The moderate reaction of the amyloid deposits with

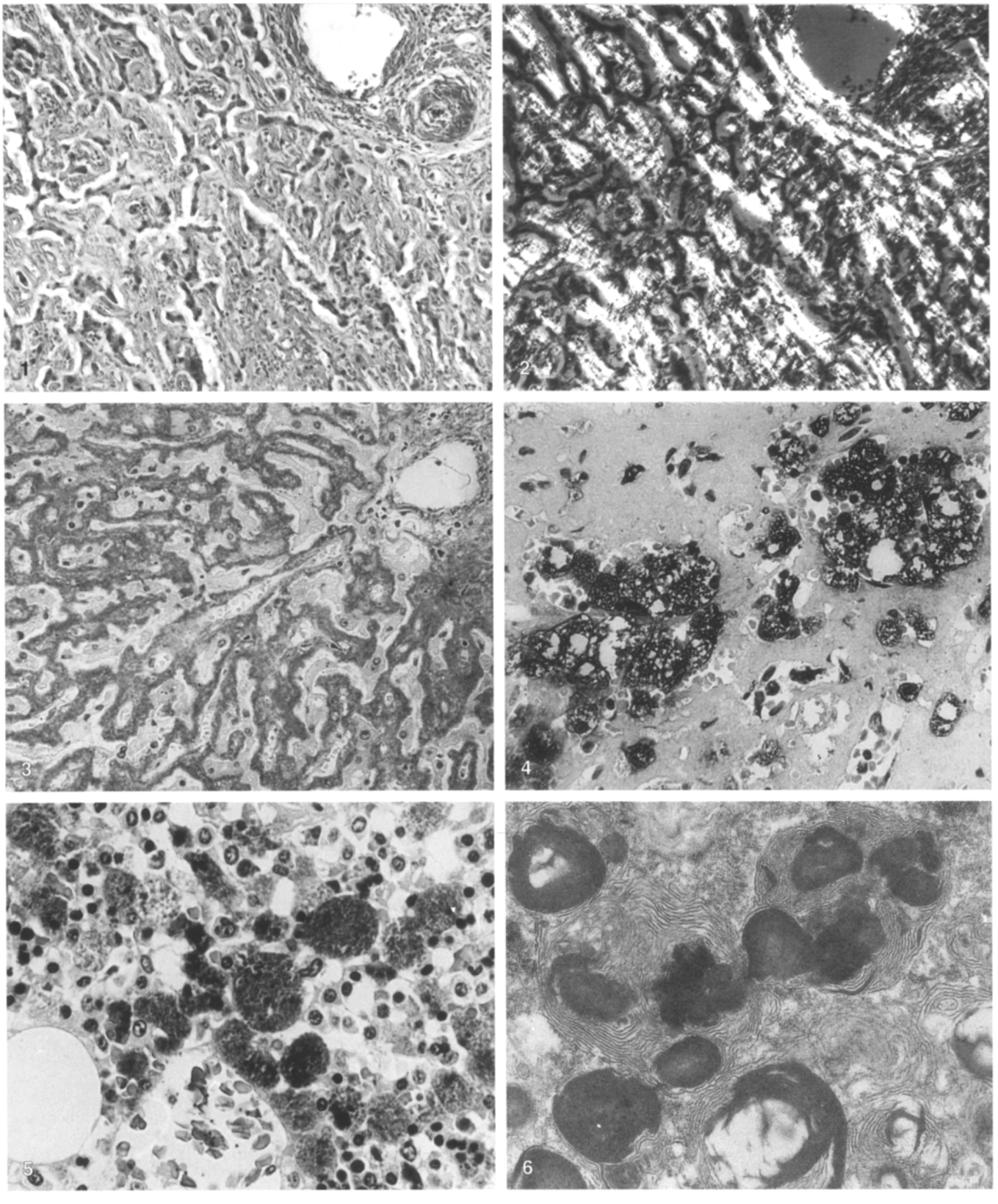
Fig. 1, 2 Severe amyloid deposits in the liver sinusoids with concomitant atrophy of the hepatocytes. **Fig. 1** Congo red, ×140. **Fig. 2** Congo red, ×140, polarized light

Fig. 3 Immunohistochemical staining of the liver with an anti-body against AL-kappa. ×224

Fig. 4 Foamy macrophages in the spleen surrounded by extensive amyloid deposits. Stained with an anti-body against CD-68 (macrophage), ×350

Fig. 5 Bone marrow containing some sea-blue histiocytes. Giemsa, ×490

Fig. 6 Part of a sea-blue histiocyte with numerous membrane-bound sphingomyelin accumulations (finger print patterns). Electron micrograph, uranyl acetate and lead acetate, ×22250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the antibody against AL-lambda light chains may be non-specific because such a reaction is not uncommon in various amyloid syndromes [19].

In the present case the diagnosis of a NPD was established by enzymatic analysis of cultured fibroblasts. With its late manifestation, our case represents the adult non-neuronopathic form of NPD, which is often only identified incidentally during physical examination [30].

The association of NPD with a generalized amyloidosis is extremely rare. To our knowledge there exists only one similar case in the literature. Castleman and McNeely [3] reported a 78-year-old woman with a clinically observed monoclonal gammopathy. She died of congestive heart failure. At autopsy, extended generalized primary amyloidosis was identified together with a biochemically established NPD. With regard to the rarity of the adult form of NPD it is impossible to be certain whether the simultaneous appearance of a generalized amyloidosis and NPD represents an accidental coincidence of two rare and unrelated diseases or whether there exists a causal relation on account of statistical data. The striking similarity between the case reported by Castleman and McNeely [3] and our case nevertheless suggests a possible mutual influence.

The adult type and NPD of the sphingomyelinase-deficient category belongs to the lysosomal storage diseases which concern the reticuloendothelial system predominantly [10, 30]. Remarkably, there have been several descriptions of the co-existence of Gaucher's disease and plasma cell dyscrasias manifesting as diffuse, monoclonal or oligoclonal gammopathies, multiple myeloma and rarely as amyloidosis [6, 15, 18, 20, 22, 26], although it should be noted that in monoclonal gammopathies macrophages which store crystallized globulins may be mistaken for Gaucher cells (author H.E.S., unpublished observations). It has been proposed that the large amount of stored lipid in macrophages acts as a chronic antigenic stimulus leading to an early diffuse and later monoclonal gammopathy, a precondition for the development of immunocyte-derived amyloidosis [6, 28]. Decreased antigen clearance secondary to an overloaded reticulo-endothelial system may precede the development of plasma cell dyscrasias [20]. Whether or not the lipid-laden macrophages in Gaucher's disease play a role in the processing of a light-chain precursor into tissue amyloid deposits remains speculative [1, 8].

It is noteworthy that in the present case the generalized amyloidosis developed within 4 years, as demonstrated by two successive liver biopsies, although only a minimal monoclonal gammopathy had been observed clinically. This suggests, in line with the genesis of gammopathy by Gaucher's disease, that abnormal function of the reticuloendothelial system due to storage of sphingolipids and cholesterol might have favoured the development and accelerated the course of the amyloidosis.

The cause of the progressive liver failure that predominated in the final period of disease was not identified. Individuals with NPD may show a mild increase of liver transaminases which is not accompanied by a significant liver dysfunction [30]. Liver failure due to intrahepatic block of blood flow by excessive lipid-laden Kupffer's cells has only rarely been reported in patients with the adult form of NPD [17, 24]. In our case the rapidly developing amyloidosis of the liver must be considered to be the underlying cause of the progressive liver failure, although this is a rarely encountered complication of amyloidosis [5, 7, 12, 16, 25, 27].

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