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Case report

Generalized amyloidosis from β_2-microglobulin, with caecal perforation after long-term haemodialysis

H. Zhou[1], U. Pfeifer[1], and R. Linke[2]

[1] Pathologisches Institut der Universität, Postfach 2120, W-5300 Bonn, Federal Republic of Germany
[2] Max-Planck-Institut für Biochemie, W-8033 Martinsried, Federal Republic of Germany

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Summary. A 73-year-old man with chronic renal failure of undetermined aetiology had received haemodialysis for 12 years when he died of acute purulent peritonitis due to caecal perforation. Amyloid deposits detected in a cystic bone lesion in the left hip had caused a pathological fracture 17 days before death. At autopsy, extensive amyloid deposits were found in the osteoarticular system, in the cartilaginous surface and the capsular tissue of joints, ligaments, vertebral discs and bone. In addition, vascular amyloid deposits were diagnosed in the heart, kidneys, testes, lungs, skin and in the gastrointestinal tract. A special feature of this case were interstitial amyloid deposits forming a fine-meshed structure in the myocardium and plate-like deposits in the gastrointestinal tract. Immunohistochemically, all these deposits reacted strongly with antibody to human β_2-microglobulin but showed no reaction with antibodies to AA, A-lambda, A-kappa and AF. The present case demonstrates that extra-osteoarticular manifestations of AB-amyloidosis can cause serious complications.

Key words: Long-term haemodialysis – β_2-Microglobulin – Derived amyloidosis – Caecal perforation – Pathological hip fracture – Immunohistochemistry

Introduction

Since the first published reports on the carpal tunnel syndrome in patients with long-term haemodialysis by Warren and Otieno (1975), further amyloid-related lesions have been identified, especially in the osteoarticular system (Assenat et al. 1980; Clanet et al. 1981; Bardin et al. 1985; Huaux et al. 1985). Biochemical examinations proved the major constituent of this amyloid fibril to be a β_2-microglobulin (β_2m) derivate (Geyjo et al. 1985). Amyloidosis from β_2m (AB-amyloidosis) most commonly affects the carpal tunnel, joint capsules, intervertebral discs and the juxta-articular bones. Only in a few cases were amyloid deposits found outside the osteoarticular system; in the myocardium (Fuchs et al. 1987; Noel et al. 1987; Ogawa et al. 1987; Theaker et al. 1987), lungs, liver (Noel et al. 1987; Ogawa et al. 1987; Theaker et al. 1987), kidneys (Theaker et al. 1987), gastrointestinal tract (Fuchs et al. 1987; Noel et al. 1987; Ogawa et al. 1987; Takahashi et al. 1988; Shinoda et al. 1989), tongue (Guccion et al. 1989) and subcutaneous adipose tissue (Floege et al. 1989; Sethi et al. 1990). The possibility that other types of amyloid were present in addition to AB-amyloid was not always ruled out in those cases. The present autopsy report demonstrates that generalized AB-amyloidosis in patients undergoing long-term haemodialysis can cause life-threatening complications.

Offprint requests to: H. Zhou

Case report

Seventeen years before his death, a 73-year-old male patient was hospitalized after experiencing gouty complaints. At that time the onset of renal failure was observed and chronic pyelonephritis or gouty kidney was suspected (but not proved) as the cause. Suffering from an increasing impairment of renal function, the patient started haemodialysis 12 years before his death. A papillary carcinoma of the urinary bladder grade I was found and resected 2 years after the initiation of regular haemodialysis. No relapse of this tumour occurred.

Seventeen days before his death the patient sustained a pathological fracture of the left femoral neck after a fall. Subsequent to the insertion of a total endoprosthesis he developed circulatory insufficiency from which he did not recover. An anergic sepsis was suspected to have caused the circulatory failure.

Methods

The soft-tissue specimens obtained at operation and at autopsy were fixed in 10% buffered formalin and embedded in paraffin. All paraffin sections were stained with haematoxylin and eosin, Sirius red and van Gieson. Amyloids were identified by positive reaction with Congo red staining according to Puchtler et al. (1962) and by apple-green birefringence typical of amyloid when viewed

under polarized light. Immunohistochemical examinations were performed in order to determine their chemical nature. The following antibodies against amyloid protein were applied: AA, β_2m (Dakopatts, Hamburg, FRG), A-lambda, A-kappa and AF (Max-Planck Biochemistry Institute, Martinsried, FRG). The antigen antibody binding was visualized by means of the avidin-biotin method using 3-amino-9-ethylcarbazol as the chromogen.

Results

The autopsy revealed that the patient had died of a faecal peritonitis resulting from a perforation of the caecum, which was distended with faeces. Bilateral atrophic kidneys with complete loss of glomeruli and with atrophy and partial cystic transformation of the tubules were found as the cause of the renal failure. Signs of gouty kidney or interstitial nephropathy due to drug abuse were not observed. An additional finding was a non-metastatic renal cell carcinoma in the right kidney, measuring about 30 mm in diameter.

The surgically resected femoral head showed rarefication of the spongiosa and a rough articular surface. Within the fracture area of the femoral neck a well-defined cystic lesion, 30 mm wide and filled with a red soft mass, was detected. Histologically, this material consisted of a loose connective tissue with scattered amyloid deposits. The articular surface showed signs of arthrosis and revealed a linear deposit of amyloid (Fig. 1a–c). At autopsy, disseminated focal amyloid deposits of the osteoarticular system were seen, especially in the joint capsules, in the ligaments of the vertebral column, and in the intervertebral discs.

In addition, generalized extra-osteoarticular amyloid deposits were identified. Vascular amyloid was found predominantly in the heart, greater omentum, lungs, urinary bladder, skin, kidneys, testes, adrenal glands and other organs (Fig. 2a, b), sometimes leading to considerable stenosis of the vascular lumen. Liver, spleen and brain were devoid of amyloid.

A significant finding in this case was interstitial amyloid deposits. They were encountered as plate-like formations in the gastrointestinal tract, where both the lamina muscularis propria and the lamina submucosa were affected (Fig. 2c, d). Extensive deposition was seen close to the gastric ulcers. Numerous giant cells were seen in some of the plate-like amyloid deposits. In the myocardium, fine-meshed as well as focal interstitial amyloid deposits were found (Fig. 2e).

Immunohistochemically, all of the amyloid deposits irrespective of their localization (osteoarticular system, blood vessels or interstitial tissue of other organs) reacted strongly with antibody against β_2m, whereas the reactions with antibodies against amyloid proteins AA, AF, A-lambda and A-kappa were negative.

At autopsy, the examination of Congo-red-stained sections of small pelvic kidney stones revealed a characteristic apple-green birefringence under polarized light. These concretions showed positive reaction with antibody against β_2m. Subsequently, examination of concretions detected in the urinary bladder carcinoma also demonstrated a positive reaction with Congo red staining. As with the previously described pelvic kidney stones these tumour-bound concretions reacted positively with antibody against β_2m (Fig. 2f).

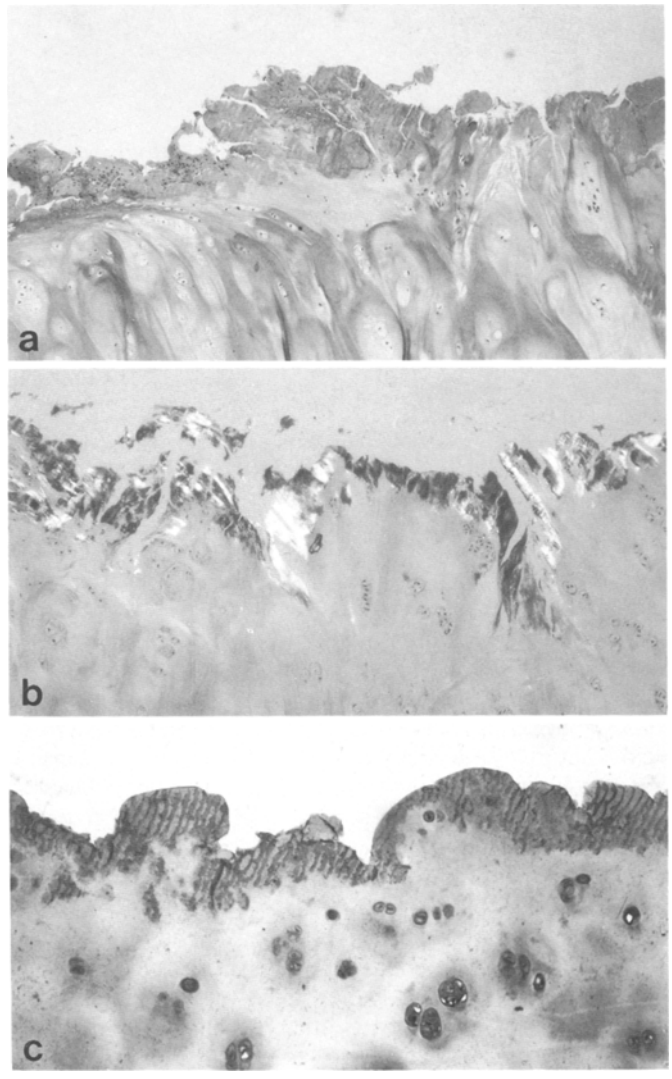

Fig. 1a–c. Joint surface of the surgically resected head of the femur. **a** Marked arthrotic lesions of the cartilaginous surface. van Gieson, ×64. **b** Cartilaginous surface after Congo-red staining, under partially polarized light. There are linear amyloid deposits at the arthrotically altered joint surface. ×64. **c** Immunohistochemical staining of the joint surface with antibody to β_2-microglobulin (β_2m). The amyloid shows strongly positive reaction with the antibody. ×160

Discussion

For so far unknown reasons AB-amyloid is generally located in the osteoarticular system. Symptoms due to AB-amyloidosis range from the carpal tunnel syndrome (Assenat et al. 1980; Bardin et al. 1985), destructive arthropathy (Goldstein et al. 1985; Munoz-Gomez et al. 1985), subchondral bone cysts with ensuing pathological bone fracture (Huaux et al. 1985; Scheumann et al. 1989; Campistol et al. 1990), destructive spondylarthropathy (Kuntz et al. 1984; Sebert et al. 1986; Bindi and

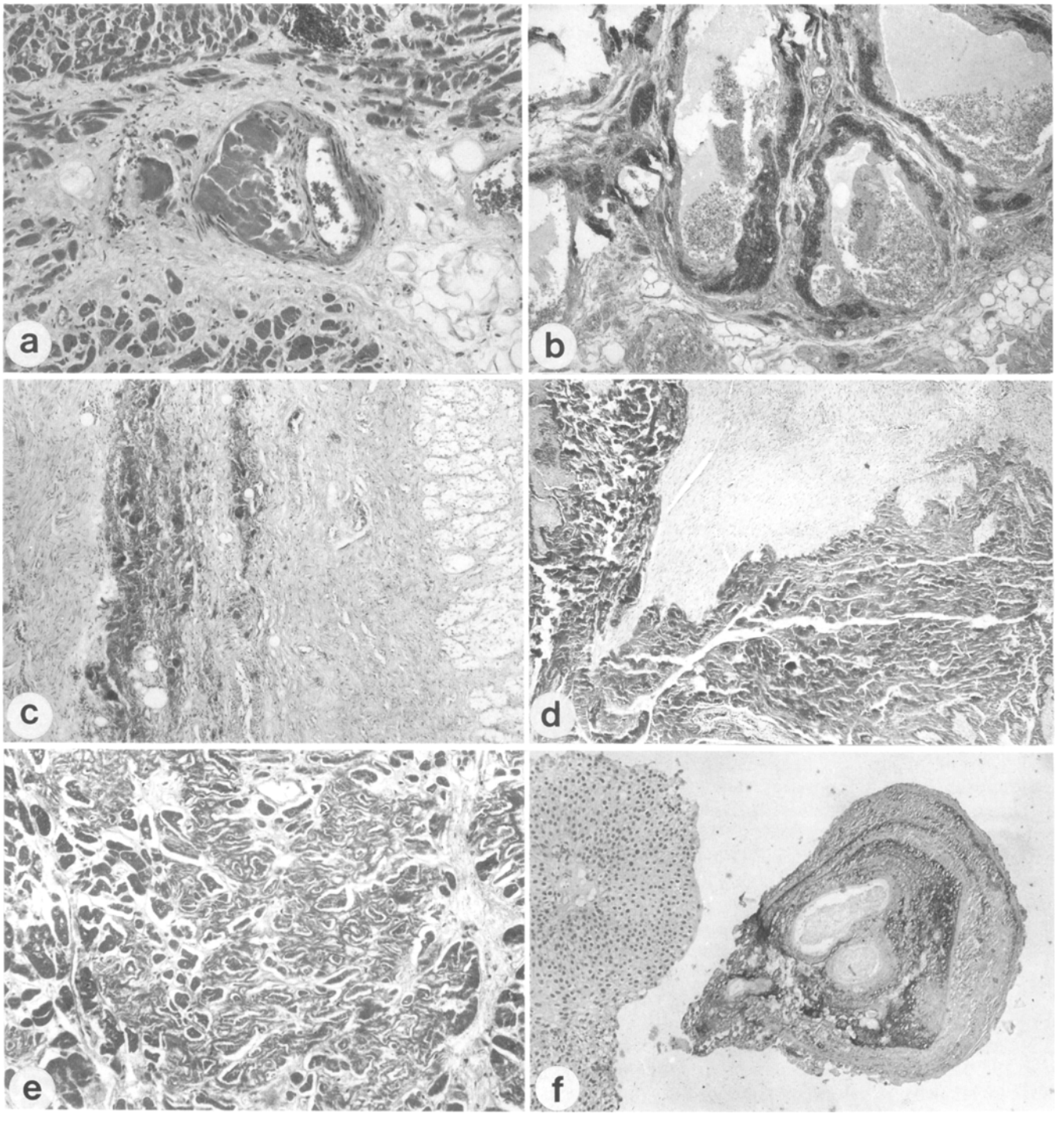

Fig. 2a, b. Vascular amyloid deposits. **a** Intramural amyloid deposits in the wall of a myocardial artery showing marked narrowing of the vascular lumen H&E, ×120. **b** Vascular amyloid deposits in venous vessels of the testis showing a positive reaction with antiserum to β_2m. ×48 **c–e** Interstitial amyloid deposits. **c** Focal interstitial amyloid deposits in the muscle layer of the stomach. Congo red, ×48. **d** Plate-like interstitial amyloid deposits in the lamina muscularis mucosae of the stomach. Congo red, ×30. **e** Interstitial amyloid deposits in the myocardium (H&E, ×160. **f** Immunohistochemical examination of a concretion embedded in the urinary bladder carcinoma with antiserum to β_2m. A marked concentric lamination of the concretion can be seen that strongly reacts with antiserum to β_2m. ×120

Chanard 1990) to spondylodiscopathy partially with consequent quadriparesis (Allain et al. 1988; Schober et al. 1990). We report a case in which amyloid deposits from the osteoarticular system were generalized. The linear amyloid deposits on the cartilaginous surface of great joints were at least partly responsible for the severe arthrosis that had been diagnosed clinically. A degenerative arthropathy, however, can not be excluded. No evidence has been provided for the initially suspected gout and gouty arthropathy.

A more serious complication is the intraosseous amyloid deposits. These apparently led to the resorption of the bone substance and finally to the pathological fracture of the left femoral neck. The pathogenesis of this bone lesion, generally termed as bone cysts, remains to be defined. They clearly differ from cystic bone lesions associated with arthrosis which are exclusively located in the subchondral region (Mohr 1984).

Recently, studies on extra-osteoarticular deposits of AB-amyloid have been presented (Fuchs et al. 1987; Noel et al. 1987; Ogawa et al. 1987; Theaker et al. 1987). Most cases demonstrate vascular amyloid deposits, occasionally concurring with clinical symptoms such as melaena and diarrhoea (Maher et al. 1988). Complications such as infarction of the intestine (Choi et al. 1989) or perforation of the colon due to ischaemic colitis (Takahashi et al. 1988) with amyloid deposits in the intestine have been reported rarely.

In the present case the extra-articular amyloid deposits played a significant role in the fatal outcome of the disease. The vascular amyloid manifestations can be assumed to have caused local circulatory disturbances. Such a local ischaemia has to be considered as one factor for cardiac insufficiency. But an even more relevant factor are the interstitial amyloid deposits which were a noteable finding in this case and which are well known, in all other types of amyloidosis, to lead to cardiac insufficiency when present in the myocardium. The perforation of the caecum was mainly the consequence of local ischaemia (due to vascular amyloid deposits) and generalized ischaemia due to cardiac insufficiency. It may even be assumed that faecal stasis promoted the perforation of the caecum. In addition the plate-like interstitial amyloid deposits may have possibly created a disturbance of the motility of the intestinal tract, as was suggested by Shinoda and his colleagues (1989). It is of interest that in our case amyloid masses were located proximately to the gastric ulcers, which possibly indicates involvement of the amyloid deposits during the development of the gastric ulcer.

A frequently observed complication in patients undergoing long-term dialysis is the development of renal amyloid concretions which contain β_2m-derived protein fibrils (Linke et al. 1986). Other components like lysozyme and amyloid-p component can also occur (Ozasa et al. 1989). In our report the urinary concretions found in the renal pelvis at autopsy and those previously resected from the urinary bladder carcinoma exhibited characteristic staining features for amyloid and reacted with antibody against β_2m. This confirms the assumption that AB-amyloid, plays an important part in the development of urinary concretions. Having developed as early as 2 years after the initiation of the haemodialysis, they may be considered to be an early sign of increasing AB-amyloidosis. Further examination will show whether this finding applies to other cases (Linke et al. 1986).

In conclusion, AB-amyloidosis can be a generalized disease. Beginning with a topical affinity for the osteoarticular system it can later involve other organs and cause severe extra-osteoarticular complications, which influence the disease process and the chances of survival of dialysis patients.

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