Virchows Archiv A Pathol Anat (1990) 417:523–528

Virchows Archiv A
Pathological Anatomy and Histopathology

Role of amyloid in dialysis-related arthropathies

A morphological analysis of 23 cases

Manel Solé [1], José Muñoz-Gómez [2], and Josep M. Campistol [3]

Services of [1] Pathology, [2] Rheumatology and
[3] Renal Transplant Unit, Hospital Clínic i Provincial, University of Barcelona, Barcelona, Spain

Received March 14, 1990 / Received after revision May 11, 1990 / Accepted July 4, 1990

Summary. The role of beta$_2$-microglobulin-related amyloidosis in the articular syndromes associated with long-term haemodialysis was analysed in a series of 23 haemodialysed patients from whom 43 amyloid-containing osteoarticular specimens were obtained. Patients with clinical arthropathy had more intense and deep synovial involvement by amyloid than asymptomatic ones. Amyloid proved to be an agent for bone destruction, causing bone cysts and cortical erosions. Amyloid deposition in cartilage was found constantly, leading to fissures and irregularities in the articular surface. From our observations, amyloid seems to be the main pathogenetic factor involved in articular swelling, destructive arthropathies and pathological fractures occurring in haemodialysed patients, although other disturbances related to haemodialysis could play a role.

Key words: Amyloid arthropathy – Beta$_2$-microglobulin – Haemodialysis

Introduction

Since our original description of a series of haemodialysed patients who developed amyloid arthropathy (Muñoz-Gomez et al. 1985), there has been growing interest in this particular complication of chronic renal failure treated with long-term haemodialysis. Clinical and pathological features of the disease have been thoroughly described by ourselves and by others (Bardin et al. 1989; Coggi et al. 1989; Hurst et al. 1989; Muñoz-Gomez et al. 1987; Solé et al. 1989). Beside the most frequent form of amyloid arthropathy, spontaneous fractures and destructive arthropathies have also been related to amyloid deposition. Some authors, however, have been reluctant to admit the predominant role of amyloid in the pathogenesis of the different syndromes described, since other factors deriving from a wide range of metabolic disturbances associated with chronic renal failure and haemodialysis can also cause articular complaints (Bouteiller et al. 1989; Cary et al. 1986; Kuntz and Bardin 1989; McCarthy et al. 1988). The aim of this study is to describe the patterns of amyloid deposition in 42 osteoarticular tissue specimens obtained from 23 haemodialysed patients, in order to explain the mechanisms by which amyloid may produce the different clinical manifestations described.

Offprint requests to: M. Solé, Departament d'Anatomia Patològica, Hospital Clínic i Provincial, Villarroel 170, E-08036 Barcelona, Spain

Patients and methods

The study was based on amyloid-containing osteoarticular specimens obtained from 23 haemodialysed patients. They were 14 males and 9 females, ranging in age from 35 to 77 years (mean 58.75, SD 11.25). They were on a haemodialysis programme for miscellaneous causes other than amyloidosis, for periods ranging from 3 to 18 years (mean 10.71, SD 3.56).

Complaints usually attributed to dialysis amyloidosis were present in 19 patients (mean age 57.93 years; mean time in dialysis 10.71 years). Seventeen of them had articular swelling and pain, 16 presented carpal tunnel syndrome, and 7 had pathological fractures of the femoral neck. Of the remaining 4 patients (mean age 62 years; mean time in dialysis 6.25 years), 1 had a pathological rupture of the tendon of the quadriceps femoris, and 3 did not present relevant osteoarticular symptoms.

In the group of symptomatic patients, nine femoral head specimens were studied; all of them included articular capsule and synovium; six of them were obtained after pathological fracture, one from autopsy, and the remaining two from a patient with bilateral femoral head osteonecrosis attributed to corticoid therapy following renal transplantation. In 1 additional patient with pathological fracture, only small biopsies of bone and capsule were performed in the course of surgery for internal fixation.

Needle biopsies of the knee were performed in 7 patients with articular swelling and pain. Synovial tissue from the wrist was obtained in 6 patients in the course of surgery for carpal tunnel syndrome. Synovial tissue of the knee joint was obtained from 1 patient in the course of surgery for an epidermoid cyst located over the knee.

In the asymptomatic group, one femoral head and two sternoclavicular joints were obtained from 3 patients on autopsy; all three

specimens contained articular capsule and synovium. Synovial and tendinous biopsies were performed in the patient suffering rupture of the quadriceps tendon.

All tissue specimens were fixed in 10% buffered formalin and embedded in paraffin by the usual method. Osseous tissue was previously decalcified in a solution of formic acid and HCl for 24 h. Sections were stained with alkaline Congo red for demonstration of amyloid. In synovial tissue, iron deposition was investigated using Perls' stain.

Immunohistochemical detection of beta$_2$-microglobulin was performed in sections from all cases using the avidin-biotin-peroxidase complex method (Hsu et al. 1981). Beta$_2$-microglobulin antiserum (Dako, Copenhagen, Denmark) was used at a dilution of 1/600. In some cases antisera against amyloid A, prealbumin, kappa and lambda chains, and P component (Dako) were also applied.

Results

The pattern of deposition of amyloid in the 42 specimens included in the study was analysed, considering the different articular structures separately (synovial membrane and subsynovial capsule, articular cartilage, and bone). The presence and extent of amyloid deposition in the different tissues and its relation with the existence or not of symptoms attributed to beta$_2$-microglobulin amyloidosis is showed in Table 1.

Amyloid deposition in synovial membrane was found in all patients independently of their symptoms. The extension of the deposition was larger in the symptomatic patients, especially in the subsynovial capsule (Table 1). Macroscopically, some alteration of synovial membrane was seen only in the larger specimens. Synovium appeared slightly hyperplastic and villous, its colour varying from yellow to brownish. A thick capsule was noted in all six surgical specimens of femoral head obtained after fracture. Microscopically, the overall structure of synovium was usually disturbed, but its morphology varied from one field to another within the same specimen. Usually, synovial hyperplasia with villi formation and multilayering of superficial cells was observed, alternating with zones of more or less normal appearance. Similarly, amyloid deposits varied in extent and morphology from one area to another. Small dense amyloid deposits were observed scattered in the synovial tissue, without distortion of the synovial structure. A macrophage response was observed in two instances, both with presence of foreign body giant cells engulfing small amyloid fragments (Fig. 1). Extensive deposits were looser, frequently containing blood vessels and stromal cells, and sometimes lying like a band underneath the superficial synovial cell layer (Fig. 2). Both types of deposits were found in symptomatic as well as in asymptomatic patients, but large nodules replacing the full extent of a synovial villus were observed only in synovial biopsies obtained from the knee and wrist of patients with clinical arthropathy (Fig. 3). In surgical specimens of fractured bone and in the hip joint studied on autopsy from a patient with clinical arthropathy, more intense deposition was observed in deeper layers, with massive infiltration and thickening of the subsynovial capsule. Massive amyloid deposition was also seen in the round ligament. Congo-red-positive deposits showed a strong positive reaction both with beta$_2$-microglobulin and P-amyloid-component antibodies. Occasionally, Congo red and beta$_2$-microglobulin stains showed cytoplasmic positivity both in superficial synovial cells and in deeper histiocytes. Reaction with beta$_2$-microglobulin antibodies could be observed in synovial cells far from Congo-red-positive deposits; this reaction, however, had a predominant membrane pattern, raising the possibility of a passive diffusion of normal membrane-related beta$_2$-microglobulin.

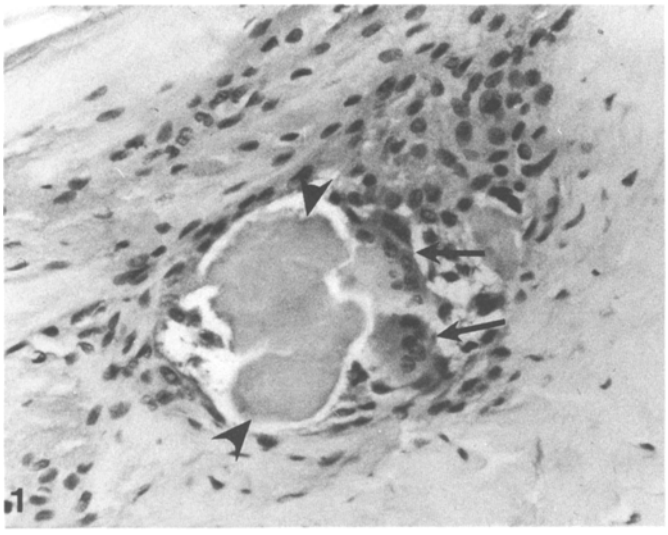
Table 1. Extent of amyloid deposition in articular tissues

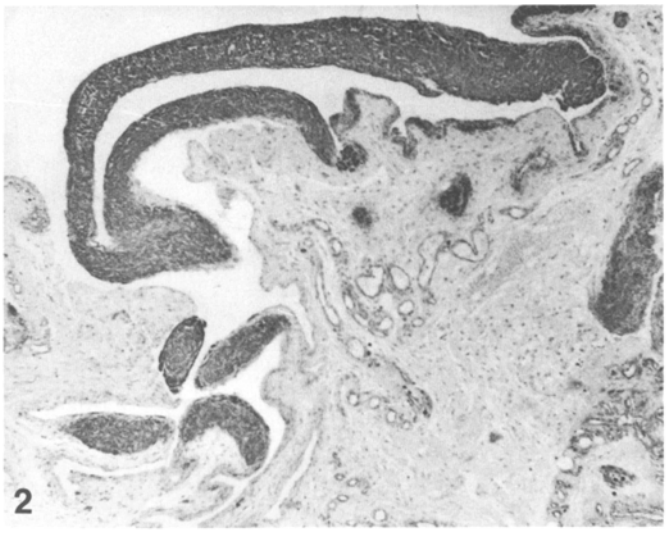
	Synovium	Capsule	Cartilage	Bone
Symptomatic patients ($n=19$)				
Number of specimens	21	9	8	8
Extent of amyloid +	12	1	4	2
++	9	8	4	3
Asymptomatic patients ($n=4$)				
Number of specimens	4	3	3	3
Extent of amyloid +	4	2	0	0
++	0	0	3	0

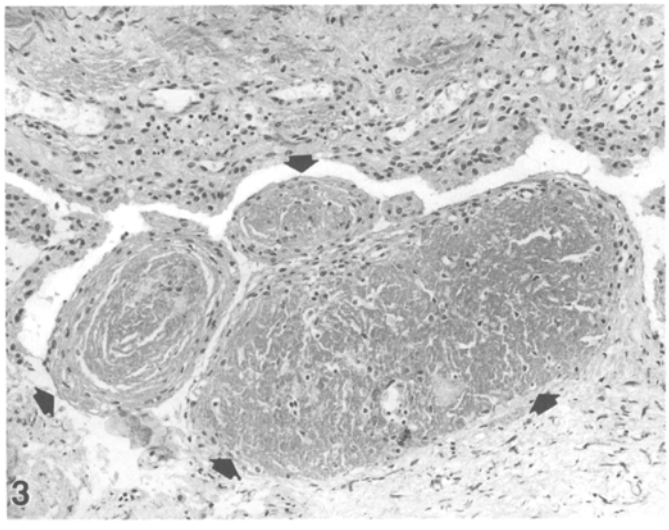
Iron deposition was found in only two of six needle biopsies, but it was more frequently found in larger specimens. Deposits were usually visible only with Perls' stain, and they were limited to the synovial cell layer and superficial macrophages. Only 4 patients, including 1 case with needle biopsy, had significant deposition acceptable as synovial haemosiderosis. One was the case presenting with bilateral necrosis of the femoral head, in which similar amounts of iron were found in the synovium of both surgical specimens and in a synovial biopsy of the wrist performed 2 years later.

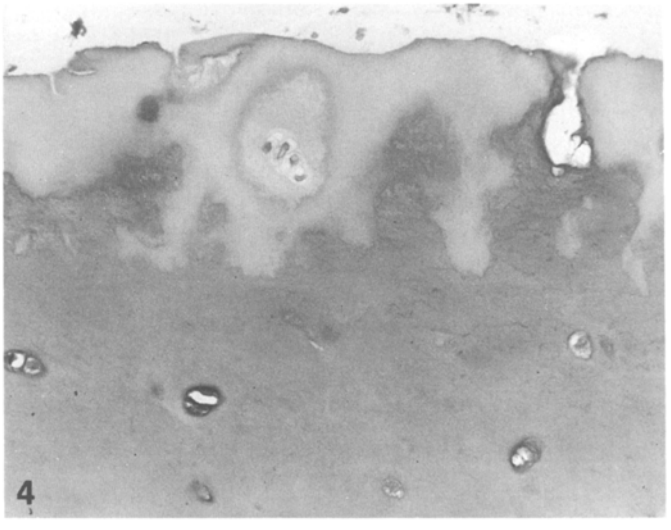
The involvement of articular cartilage was evaluated on femoral head and sternoclavicular joint specimens. The cartilage showed amyloid infiltration in all the cases, no differences being noted in relation to the presence or absence of articular symptoms. In femoral head specimens the articular surface appeared smooth, and a slight brownish coloration could be appreciated, mainly in basal areas. Microscopically, amyloid formed a narrow dense band along the cartilaginous surface, surrounding the condrocytes without affecting them (Fig. 4). The amyloid band was wider near the insertion of the articular capsule and synovium and around the insertion of the round ligament in the fovea capitis, merging imperceptibly with the synovial amyloid deposits. In four of the spontaneously fractured femoral heads, the amyloid line was continuous, affecting the entire articular surface, while in the remaining cases, areas far from the capsulo-ligamentary insertion zones were free of amyloid.

Amyloid deposition often showed irregular surface, with frequent cracks and fissures (Fig. 5), but deep penetration into cartilage was limited. Only in 1 patient with no recorded articular symptom, whose femoral head was obtained on autopsy, was amyloid found to extend deeply along a vertical fissure of the cartilage. In sternoclavi-









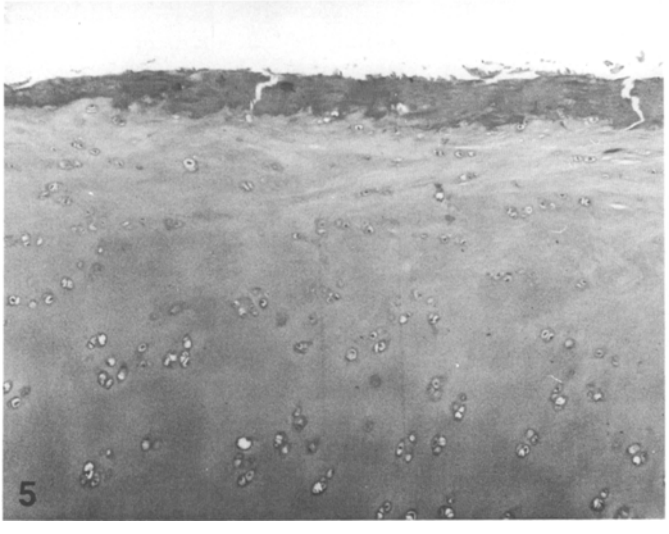


Fig. 1. Small dense amyloid deposits in synovial tissue (*arrowheads*), partially surrounded by foreign body giant cells (*arrows*). H & E, × 300

Fig. 2. Dark-stained deposits of beta$_2$-microglobulin amyloid forming bands and nodules along the synovial membrane. ABC-beta$_2$-microglobulin, × 30

Fig. 3. Nodular amyloid deposition in the synovial membrane (*arrows*). Nodules are partially covered by synovial lining cells. Stromal cells can be seen scattered within the amyloid substance. Congo red, × 120

Fig. 4. Dense, pale amyloid substance in the articular surface of the cartilage. Penetration through the cartilaginous matrix spares the chondrocytes. H & E, × 250

Fig. 5. Superficial band of beta$_2$-microglobulin amyloid along the cartilaginous surface of the femoral head. Small fissures can be seen. ABC-beta$_2$-microglobulin, × 100

Fig. 6. Eroded laminar bone limiting a large lytic lesion of the femoral neck. Amyloid is seen as a dark-stained substance in the upper half of the figure. *Arrows* indicate the scalloped margins of the eroded bone. ABC-beta$_2$-microglobulin. Polarized light microscopy, × 80)

cular joints, the pattern of amyloid deposition was similar, with marked superficial deposition near the synovial insertion and extension as an incomplete irregular band over the articular surface. Similarly, the cartilaginous disc was affected by wide deposits at the periphery, with the central areas tending to be clear.

Congo-red-positive deposits reacted strongly with $beta_2$-microglobulin and P-component antibodies. No reaction was observed using other amyloid antibodies. Chondrocytes were always non-reactive.

Involvement of bone was observed only in 5 patients, all of them with amyloid-related symptoms. Foci of osteolysis were identified in three of the six fractured femoral heads. In two of them, such pseudocysts were located at the level of the fracture in the femoral neck, ranging from 2.5 to 3 cm in diameter. Both were partially occupied by reddish, elastic material, which corresponded to loose haemorrhagic fibrovascular tissue diffusely infiltrated by amyloid. Bone trabeculae limiting the lytic areas appeared eroded, with scalloped borders, and slightly increased osteoclastic activity (Fig. 6). Remains of necrotic trabeculae could be found within the intracystic tissue. There were no signs either of osteoblastic regeneration or of sclerosing reaction of surrounding bone. Continuity between the deeply amyloid-infiltrated capsulo-synovial tissue and the intracystic tissue, without intervening bone, was evident in one of the cases. In the third specimen, a small lytic lesion measuring 0.5 cm in diameter was found near the insertion of the round ligament; this lesion was filled by amyloid-infiltrated tissue similar to that of the larger lesions. Erosion of the cortical bone related with a highly amyloid-infiltrated capsulo-synovial insertion zone at the femoral neck level was observed in this third case, and microscopic amyloid deposits were also found along the line of fracture.

In 1 patient the femoral head was obtained 2 months after unsuccessful fixation of the fracture. The specimen had been fragmented during the extraction. No lytic lesions were identified. Areas with avascular necrosis and regenerative changes were prominent. Small nodular amyloid deposits were found in fibrosed medullary spaces. Similar deposits were present in both specimens from the patient with bilateral femoral head necrosis following corticoid therapy.

A bone biopsy of the femur was performed in 1 additional patient in the course of surgery for internal fixation of a femoral neck fracture. Dense amyloid deposits were found to fill medullary spaces in this small specimen (Fig. 7).

In all cases, amyloid deposits reacted strongly with $beta_2$-microglobulin and P-component antibodies. No reaction was observed with other amyloid antibodies when tested. Background staining for $beta_2$-microglobulin was noted in haemorrhagic areas. $Beta_2$-microglobulin also stained the haematopoietic marrow.

Amyloid deposits were not found in bone in the rest of the osseous specimens (two femoral heads after fracture, and one femoral head and two sternoclavicular joints from autopsy). Although some degree of osteodystrophy was frequently observed in bone specimens, prominent changes of hyperparathyroidism were found in only 2 cases.

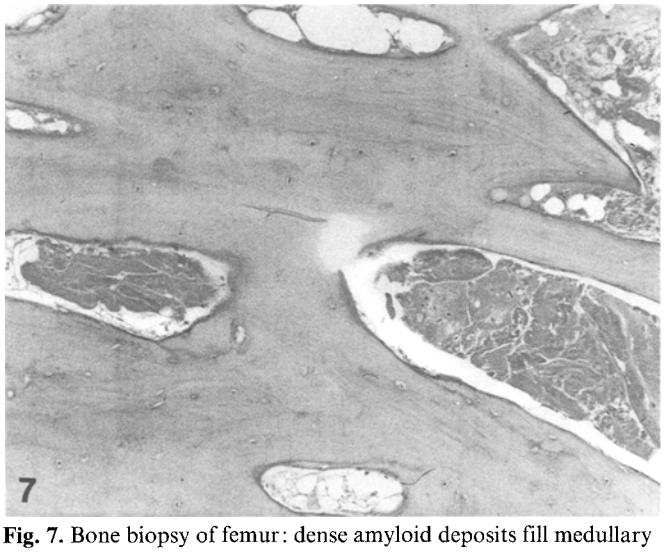


Fig. 7. Bone biopsy of femur: dense amyloid deposits fill medullary sapces. H & E, ×100

Discussion

The role of amyloid in the most usual clinical complaints of $beta_2$-microglobulin-related amyloid arthropathy (articular swelling and pain in an oligoarticular distribution, along with articular effusions in large joints), seems to be well established. The notable clinical and pathological similarities between this disease and AL-amyloid arthropathy lead one to consider amyloid as the main common pathogenetic factor (Bardin et al. 1989; French 1980; Kavanaugh 1978; Mohr 1984; Muñoz-Gomez et al. 1987; Wiernik 1972). Moreover, other disturbances associated with haemodialysis that have been alternatively proposed, such as hyperparathyroidism (McCarthy et al. 1988), iron deposition (Cary et al. 1986) and apatite crystals (Kuntz and Bardin 1989), have been substantiated only as minor findings in our study. Amyloid is constantly found in synovial biopsies taken from the involved joints (Muñoz-Gomez et al. 1985). Although deposits are occasionally quite small in such biopsies, this fact can be explained by the irregular distribution of amyloid in the synovial membrane that we have found in larger specimens. The occurrence of effusions is fully justified by the disturbances in the synovial fluid turnover caused by amyloid infiltration of the membrane. Massive amyloid deposition in deeper structures would account for articular swelling. Asymptomatic patients also have amyloid in their synovium, but it is mainly in a superficial location, and usually less extensive. Thus, the amount of amyloid deposition, possibly related to the duration of dialysis and its immunological events, would be the main factor determining the onset of clinical complaints. The link between amyloid deposition and fractures is even clearer, since bone erosions and cysts are found in relation to the line of fracture (Di Raimondo et al. 1986; Huaux et al. 1985). From our findings, amyloid seems to have a special ability to produce bone destruction. So-called bone cysts probably

originate by penetration of amyloid from heavily infiltrated tissues at the capsulo-synovial insertion and at the insertion of the round ligament on the fovea capitis. An additional mechanism of osseous infiltration exists, as illustrated in 3 patients of our series with amyloid deposition in medullary spaces. Both types of osseous amyloid deposition have also been described in AL-amyloidosis (Cary 1985; Kavanaugh 1978; Kramer et al. 1986). Not all the cases, however, have conspicuous amyloid deposits at the site of fracture. Bone fragility caused by concomitant factors such as hyperparathyroidism and aluminium deposition may be an additional and/or alternative mechanism in such cases.

A form of destructive arthropathy involving the spine and large joints may occur in haemodialysed patients (Bouteiller et al. 1989; Hurst et al. 1989; Kuntz and Bardin 1989; Kuntz et al. 1988; Muñoz-Gomez et al. 1987). It is defined by a progressive narrowing of the articular space, with erosions in the cartilaginous plates and presence of osseous cysts. The role of amyloid as the cause of such an arthropathy is under debate (Bouteiller et al. 1989; Hurst et al. 1989; Kuntz and Bardin 1989). AL-amyloidosis is seldom associated with destructive arthropathy, but this complication has also been described in some cases (Kramer et al. 1986; Leonard et al. 1985). Both $beta_2$-microglobulin and AL-amyloidosis show similar patterns of amyloid deposition in articular cartilage (Bywaters and Dorling 1970). However, the relevance of this finding has been debated, since deposition of amyloid in articular cartilage occurs also in age-related asymptomatic articular amyloidosis (Cary 1985). The demonstration of strong $beta_2$-microglobulin reactivity in all of our cases of dialysis-related arthropathy rules out the possibility of it being an innocuous unrelated finding. Moreover, most reports on age-related amyloidosis usually describe minute deposits in the capsule and cartilage (Egan et al. 1982; Goffin et al. 1981; Ladefoged and Christensen 1980; Mohr 1976), although larger deposits have been reported in the sternoclavicular cartilaginous disc, mainly in a central location (Goffin et al. 1981). In contrast, in our cases, deposition was massive in the articular capsule and predominated in the peripheral areas of the articular cartilage, including the sternoclavicular cartilaginous disc. Thus, whereas in age-related amyloidosis amyloid would form locally as a degenerative change, in $beta_2$-microglobulin amyloidosis amyloid could spread from capsulo-synovial insertions, along the superficial layers of cartilage, favoured by the disposition of collagen fibers in this zone, which are parallel to the articular surface. This explanation would be more satisfactory than an eventual imbibition of amyloid proteins present in the synovial fluid by cartilage, since permeability of cartilage seems to be restricted to smaller molecules (Bywaters and Dorling 1970). Moreover, this mechanism could account also for the presence of amyloid in cartilage devoid of synovial fluid, such as the intervertebral disc (Hurst et al. 1989; Kuntz et al. 1988; Sebert et al. 1986). Deposition of amyloid in the superficial layers of cartilage produces fibrillation and surface irregularities, debilitating the resistance of the articular plate. The next step in this destructive process would be the formation of deep fissures filled with amyloid, as observed in one of our patients, similar to those described by Bywaters and Dorling (1970) in AL-amyloid arthropathy. Amyloid deposition in the cartilage, together with the presence of amyloid-filled subchondral cysts, can explain the cartilaginous destruction both in AL and $beta_2$-microglobulin-related amyloidosis, although an adjuvant role of additional debilitating factors such as aluminium deposition cannot be totally ruled out in our cases.

In conclusion, the similarities in clinical and pathological presentations of osteoarticular involvement both in $beta_2$-microglobulin and in AL-amyloidosis support the predominant role of amyloid in this type of arthropathy. The pattern of amyloid deposition can explain most clinical complaints and radiological signs, and although the existence of additional factors cannot be excluded, the actual relevance of such factors is yet to be demonstrated.

References

Bardin T, Zingraff J, Drüeke T, Kuntz D (1989) Clinical aspects of beta-2 microglobulin amyloidosis. In: Gejyo F, Brancaccio D, Bardin T (eds) Dialysis amyloidosis. Wichtig, Milan, pp 79–90

Bouteiller G, Ton That H, Goudable C, Orfila C, Durand D (1989) Arthropathies destructices et ostéonécroses au cours de l'hemodialyse chronique. Etude chez 87 malades. Rev Rhum 56:453–458

Bywaters EGL, Dorling J (1970) Amyloid desposits in articular cartilage. Ann Rheum Dis 29:294–305

Cary NRB (1985) Clinicopathological importance of deposits of amyloid in the femoral head. J Clin Pathol 38:868–872

Cary NRB, Sethi D, Brown EA, Erhardt CC, Woodrow DF, Gower PE (1986) Dialysis arthropathy: amyloid or iron? Br Med J 293:1392–1394

Coggi G, Maiorano E, Braidotti P, Dell'orto P, Viale G (1989) Beta-2 microglobulin amyloidosis in synovial membranes: histopathology, immunocytochemistry and electron microscopy. In: Gejyo F, Brancaccio D, Bardin T (eds) Dialysis amyloidosis. Wichtig, Milan, pp 57–78

Di Raimondo CR, Casey TT, Di Raimondo CV, Stone WJ (1986) Pathologic fractures associated with idiopatic amyloidosis of bone in hemodialysis patients. Nephron 43:22–27

Egan MS, Goldenberg DL, Cohen AS, Segal D (1982) The association of amyloid deposits and osteoarthritis. Arthritis Rheum 25:204–208

French BT (1980) Amyloid arthropathy in myelomatosis – intracytoplasmic synovial deposition. Histopathology 4:21–28

Goffin YA, Thoua Y, Potvliege PR (1981) Microdeposition of amyloid in the joints. Ann Rheum Dis 40:27–33

Hsu SM, Raine L, Fanger H (1981) Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC an unlabeled antibody (PAP) procedures. J Histochem Cytochem 29:577–580

Huaux JP, Noel H, Bastien P (1985) Amylose articulaire, fracture du col femoral et hémodialyse périodique chronique. Rev Rhum 52:179–182

Hurst NP, Van Den Berg R, Disney A, Alcock M, Albertyn L, Green M, Pascoe V (1989) Dialysis related arthropathy: a survey of 95 patients receiving chronic haemodialysis with special reference to beta-2 microglobulin related amyloidosis. Ann Rheum Dis 48:409–420

Kavanaugh JH (1978) Multiple myeloma, amyloid arthropathy, and pathological fracture of the femur. J Bone Joint Surg [Am] 60:135–137

Kramer MR, Van Dijk JM, Hados I, Hershka C (1986) Destructive bone lesions in primary amyloidosis. Postgrad Med 62:1037–1041

Kuntz D, Bardin T (1989) Dialysis destructive arthropathy. In: Gejyo F, Brancaccio D, Bardin T (eds) Dialysis amyloidosis. Wichtig, Milan, pp 101–109

Kuntz D, Bardin T, Cornelis F, Flippo RM, Duquenoy B, Delcambre B, Delacroix C, Sebert JL, Tourliere P, Benhamou C (1988) Les arthropathies destructices des insuffisants renaux dialysés. Rev Rhum 55:842

Ladefoged C, Christensen HE (1980) Congophilic substance with green dichroism in hip joints in autopsy material. Acta Pathol Microbiol Scand Sect A 88:55–58

Leonard PA, Clegg DO, Lee RG (1985) Erosive arthritis in a patient with amyloid arthropathy. Clin Rheumatol 4:212–217

McCarthy JT, Dahlberg PJ, Kriegshauser JS, Valente RM, Swee RG, O'Duffy JD, Kurtz SB, Johnson WJ (1988) Erosive spondylarthropathy in long term dialysis patients: relationship to severe hyperparathyroidism. Mayo Clin Proc 63:446–452

Mohr W (1976) Amyloid deposits in the periarticular tissue. Z Rheumatol 35:412–417

Mohr W (1984) Arthropathien bei systemischen Krankheiten. In: Mohr W (ed) Gelenkkrankheiten. Thieme, Stuttgart, pp 231–235

Muñoz-Gomez J, Bergada-Barado E, Gomez-Perez R, Llopart-Buisan E, Subias-Sobrevia E, Rotes-Querol J, Sole-Arques M (1985) Amyloid arthropathy in patients undergoing periodical haemodialysis for chronic renal failure: a new complication. Ann Rheum Dis 44:729–733

Muñoz-Gomez J, Gomez-Perez R, Llopart-Buisan E, Sole-Arques M (1987) Clinical picture of the amyloid arthropathy in patients maintained on haemodialysis using cellulose membranes. Ann Rheum Dis 46:573–579

Sebert JL, Fardellone P, Marie A, Deramond H, Lambrey G, Legars D, Galibert P, Smajda A, Fournier A (1986) Destructive spondyloarthropathy in hemodialysed patients: possible role of amyloidosis. Arthritis Rheum 29:301–303

Sole M, Cardesa A, Palacin A, Muñoz-Gomez J, Campistol JM (1989) Morphological and immunohistochemical findings in dialysis-related amyloidosis. An analysis of 16 cases. Appl Pathol 7:350–360

Wiernik PH (1972) Amyloid joint disease. Medicine 51:465–479