Phagocytosis of dialysis-related amyloid deposits by macrophages

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Case

A 24-year-old man started haemodialysis in 1975. He had presented with proteinuria and microscopic haematuria in 1971, and developed severe hypertension and renal impairment in 1973. His kidneys were of a small size but no cysts were seen, despite a strong family history of autosomal dominant polycystic kidney disease. He had a subtotal parathyroidectomy for secondary hyperparathyroidism in 1982. He developed a typical dialysis-related amyloidosis with bilateral carpal tunnel syndrome, which was operated on in 1986 and 1988, as well as bilateral popliteal cysts limiting knee flexion, bilateral scapulohumeral periarthritis, and cervical spondyloarthropathy. In 1999 he underwent tenosynovectomy of the flexors and was operated on again for right carpal tunnel syndrome.

Small blocks (approximately 1 mm³) of the tissue obtained surgically from his right carpal tunnel were fixed in 4% (w/v) paraformaldehyde and 0.1% (v/v) glutaraldehyde in PBS. Ultrathin sections (60–90 nm) were immuno-labelled with anti-β2-microglobulin (Nordic, Tilburg, The Netherlands) and anti-amyloid P component (APC) (Dako, Glostrup, Denmark) antibodies. Specific immuno-labelling was assessed with 10 nm gold particles coupled with protein A, and observed with a Hitachi H-600 AB transmission electron microscopy (Hitachi, Tokyo, Japan).

Figure 1 shows an electron micrograph of a macrophage in contact with fibrillar material (an amyloid) mainly in the extracellular space (EC). Amyloid material was labelled with both the antibodies used. Labelling was much more dense with anti-β2-microglobulin antibodies (Figure 1A, C and D) than with anti-APC antibodies (Figure 1B), confirming that, although APC is present, it occurs far less commonly in amyloid fibrils than β2-microglobulin does. It can be seen that the cell developed protrusions to surround the amyloid fibrils. The figure shows different stages of encircling the amyloid material: the protrusion (thin arrows) grows from (A) to (B) and bilaterally encompasses the labelled fibrils in (C). Figure 1(D) shows the incorporated gold-labelled amyloid fibrils in the intracellular space in a patchy distribution (wide arrows) along with the remaining EC amyloid material diffusely labelled.

Discussion

The present ultrastructural study of β2-microglobulin amyloidosis shows, in a sequential motion-like manner, the process of phagocytosis by infiltrating macrophages. The role played by monocytes in amyloid deposits is controversial. Several studies assessing the timing of appearance of intracellular amyloid fibrils in experimental amyloidosis, have concluded that macrophages synthesize the amyloid fibrils [1–3]. A similar conclusion was reported by Garbar et al. [5] following a post-mortem histological study showing that macrophage infiltration is a late phenomenon in β2-microglobulin amyloid deposits. Elucidating the role played by macrophages in β2-microglobulin amyloidosis is important both to understand the
Fig. 1. Different stages of phagocytosis by macrophages are shown. Amyloid fibrils are immuno-labelled with gold particles. Anti-β2-microglobulin antibodies were used in (A), (C) and (D), and anti-amyloid P component antibodies in (B). Amyloid fibrils are in close contact with the cell, which develops protrusions (thin arrows) that grow from (A) to (B) and encompass amyloid material in (C). Internalized immuno-labelled amyloid material can be observed within the cell in a patchy distribution in the lysosomes in (D) (wide arrows), along with amyloid fibrils remaining outside the cell, not yet phagocytosed. IC, intracellular; EC, extracellular space.
mechanisms resulting in the appearance of amyloidosis, and to guide our efforts in preventing or treating it [reviewed in 6]. Indeed, it has been suggested that advanced glycation end product (AGEP) modification of β2-microglobulin would attract macrophages, which would then participate in the formation of β2-microglobulin amyloid fibrils [7]. However, if macrophage infiltration is a secondary phenomenon, the chemotactic activity of AGEP-modified β2-microglobulin is unlikely to participate in the genesis of amyloid fibrils. Nevertheless, AGEPs may still influence some of the characteristics of dialysis-related amyloidosis, such as the particular tissue distribution or deposit enlargement, but not participate in the conformational changes leading to amyloids [8].

The present report is a clear, graphical illustration of phagocytosis in β2-microglobulin amyloidosis. These images strongly suggest that the infiltrating cells attempt to remove the amyloid fibrils already formed. Therefore, to progress with the understanding of β2-microglobulin amyloidosis we will have to focus on the physicochemical properties of the components of amyloid deposits rather than on the cellular participation.

References