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REVIEW ARTICLE

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Aβ-2M-amyloidosis and related bone diseases

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Abstract Aβ-2M-amyloidosis is a type of systemic amyloidosis that is specifically seen in patients with chronic kidney diseases. The precursor protein of Aβ-2M-amyloid fibril is β2-microglobulin, and its elevated serum level is the main cause of Aβ-2M-amyloidosis in patients with kidney failure. However, the precise mechanism of Aβ-2M-amyloidogenesis remains unclear. In vitro analyses of Aβ-2M amyloidogenesis are still being actively conducted. Osteolytic lesions are often found around synovial membrane with Aβ-2M-amyloid deposition. Both evident osteoclastogenesis and active osteoclastic bone resorption are found, while osteoblastic bone formation is absent in the lesion most likely associated with the inflammation caused by infiltrating macrophages/monocytes into Aβ-2M-amyloid deposition. The precise cell biological mechanism of this inflammatory change is unknown. Further studies are needed to establish specific treatments against this as yet unsolved problem with long-term dialysis therapy.

Key words Aβ-2M-amyloid · β2-microglobulin · macrophage · osteolysis

Introduction

Aβ-2M-amyloidosis is a type of systemic amyloidosis which is specifically seen in patients with chronic kidney diseases [1]. Aβ-2M-amyloid fibrils are often deposited on synovial membranes around large joints, and therefore this type of amyloidosis characteristically induces severe bone/joint complications.

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Amyloid formation and deposition around a bone/joint

The precursor protein of Aβ-2M-amyloid fibrils is β2-microglobulin [2]. An extremely elevated serum β2-microglobulin level is definitely the main cause of Aβ-2M-amyloidosis [3], since its speed of elimination from the circulation is severely prolonged in patients with kidney failure.

However, serum β2-microglobulin levels are comparable between dialysis patients with and without Aβ-2M-amyloidosis. Moreover, its level in synovial fluid is not elevated in patients with Aβ-2M-amyloidosis [4]. Thus, the precise mechanism of Aβ-2M-amyloidogenesis remains unclear.

Recent studies confirmed that the formation of Aβ-2M-amyloid fibrils conformed to the nuclei-dependent polymerization model. The elongation of Aβ-2M-amyloid fibrils was observed in certain conditions in vitro, and factors such as glycosaminoglycans, apolipoprotein E, and phospholipids contribute to the stabilization of these elongated fibrils [5–7]. Glycosaminoglycans may also play a critical role in the deposition of β2-microglobulin on cartilage.

The roles of infiltrating macrophages/monocytes in the initial amyloidogenesis are unknown. However, the infiltrating cells around synovial tissues may contribute to the further development of Aβ-2M-amyloidosis, since they assimilate circulating β2-microglobulin monomers [8].

Bone lesions associated with Aβ-2M-amyloidosis

Bone lesions are often found around synovial membrane with Aβ-2M-amyloid deposition [9].

Histological observations have shown synovial tissues with Aβ-2M-amyloid deposition invading bone. There are

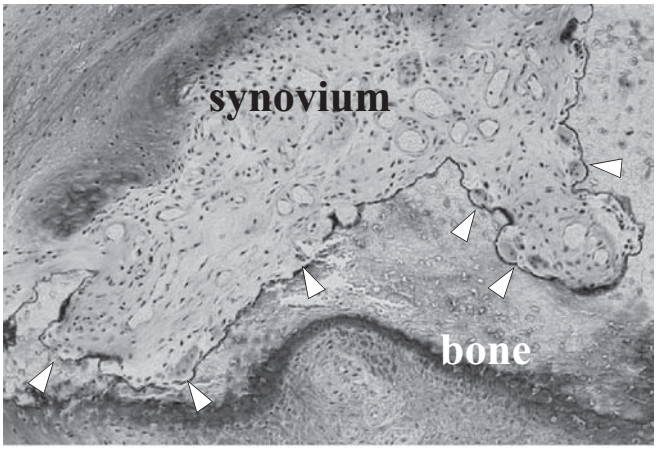


Fig. 1. Synovial invasion into bone. A great number of macrophages infiltrate the sinovial fibrous tissue. Many osteoclasts can be seen on the bone surface confronting the sinovium (*arrowheads*)

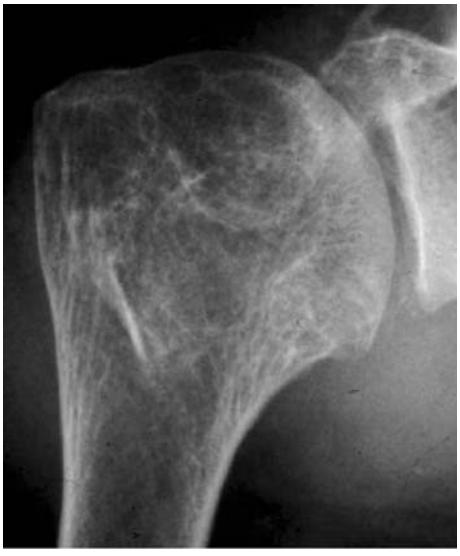
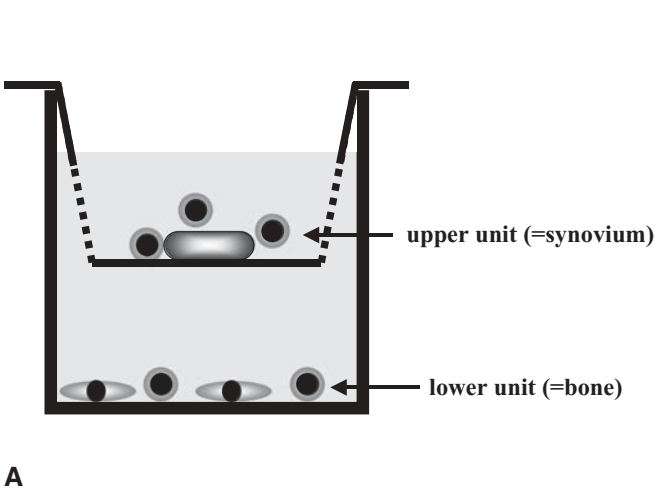
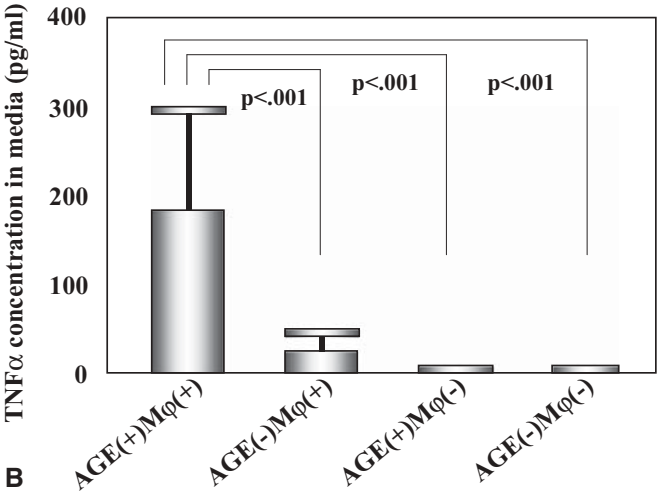


Fig. 2. Bone cysts in the head of the humerus



A



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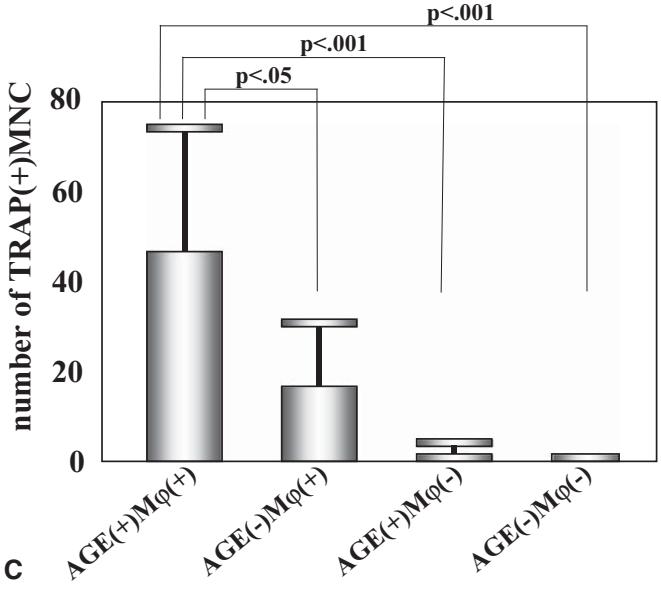

C

Fig. 3. Osteoclast formation study simulating synovial tissue. **(A)** Peripheral blood-derived monocytes/macrophages were cultured with heat-agglomerated albumin with or without advanced glycation end products (AGEs) modification (*top*). Osteoblasts and spleen cells were cocultured (*bottom*). The units are separated by a semipermeable membrane. The lower unit simulates bone, while the upper unit simulates invading synovium. **(B)** The TNFα concentration in the culture media. **(C)** Number of TRACP-positive multinucleated cells in the lower unit

numerous infiltrating cells in the sinovial tissue, and many of them are CD46-positive macrophage/monocytes [10]. Both evident osteoclastogenesis and active osteoclastic bone resorption have been found on the bone surface, while osteoblastic bone formation is absent (Fig. 1). As a result, large osteolytic lesions are formed. Bone cysts are often observed around joints as a consequence of osteolysis (Fig. 2). In spinal bones, discitis occurs around Aβ-2M-amyloid deposition, and spinal osteolysis develops from the side of such discs. Since many of these lesions appear in weight-bearing joints, they often lead to further destruction that largely limits the activity of daily living.

Cause of inflammatory cell infiltration around Aβ-2M-amyloid deposition

The cause of these osteolytic lesions is most likely the inflammation around the Aβ-2M-amyloid deposition. Aβ-2M-amyloid seems to attract inflammatory cells.

Inflammation is a common finding around amyloid depositions [11]. Nevertheless, it is more evident around Aβ-2M-amyloid depositions than that found with any other form of amyloidosis. In the 1990s, β2-microglobulin modified with advanced glycation end products (AGEs) was intensively examined as a candidate for an inflammation inducer around amyloid deposition [12,13]. However, we have to be aware that the natures of β2-microglobulin and Aβ-2M-amyloid fibrils are quite different. For example, while β2-microglobulin is a water-soluble substance, Aβ-2M-amyloid fibrils are absolutely insoluble in water. Therefore, experiments in which β2-microglobulin monomers, or chemically modified β2-microglobulin monomers, are put into culture media do not simulate the pathophysiological conditions of Aβ-2M-amyloidosis.

The role of AGEs has not been neglected, since modification with AGEs is often documented on Aβ-2M-amyloid depositions [14]. Figure 3 shows the results of an osteoclast formation study specially modified to simulate synovial tissue with amyloid deposition. For this purpose, heat-agglomerated albumin was applied as a substitute for Aβ-2M-amyloid. AGE-modified heat-agglomerated albumin promoted inflammatory cytokine production in the surrounding macrophages/monocytes, and a greater number of osteoclasts were formed in the coculture system nearby. Thus, the modification of Aβ-2M-amyloid deposition with AGEs is still a likely candidate for the inflammation inducer, if not the only one.

Conclusion

Aβ-2M-amyloidosis and related osteopathy are unsolved problems associated with long-term dialysis therapy. The disease involves protein misfolding, amyloid deposition and elongation, inflammation, and osteoclastic bone resorption. Each step could be a possible target of therapy against Aβ-2M-amyloidosis. Further investigations are needed to establish specific treatments.

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