III.3  HEMODIALYSIS-ASSOCIATED AMYLOID OF $\beta_2$-MICROGLOBULIN NATURE

Tsuranobu Shirahama, Alan S. Cohen and Martha Skinner

The Arthritis Center, Boston University School of Medicine,
the Thorndike Memorial Laboratory,
and the Division of Medicine,
Boston City Hospital,
Boston, Massachusetts 02118, U.S.A.

1. Introduction

With the widespread use of long-term hemodialysis to maintain patients with end-stage renal disease, a number of complications have been recognized. Among them, carpal tunnel syndrome (CTS) and osteoarthropathy have received increasing attention recently because of their persistence, severe disabling effects and unclarified etiology. Recently, amyloid has been implicated in a possible cause of these phenomena (1-13). The type (biochemical nature) of the amyloid had not been elucidated. Early in 1984 we instituted studies of hemodialysis-associated amyloid (AH), analyzed the clinical and pathologic picture, successfully identified the chemical nature of the amyloid through histochemical, immunohistochemical and biochemical analyses, and carried out some additional studies in order to elucidate its etiology (14-16). We were fortunate in the development of the chain of events that led to our conclusions and will describe them in a personal chronologic fashion.

2. Clinical and pathological aspects

Although we had been aware of the complication of CTS and osteoarthropathy in maintenance hemodialysis and the implication of amyloid in these conditions through published literature and personal communications (1-13), our intense study on this subject started in 1984 after having a series of discussions with Dr. F. Gejyo of Niigata University, Japan that led to our collaboration. As the person in charge of hemodialysis program at the university's Kidney Center (one of the oldest and largest hemodialysis centers in Japan), he was facing a serious problem in that an increasing number of their patients under chronic hemodialysis developed CTS. Carpal release operations had been performed on 7 patients until then (June, 1984), and amyloid deposits were found in all surgical tissues examined.
Based on the information available at the time, we assessed the circumstances with regard to amyloid as follows:

1. The association of amyloid deposition in this hemodialysis-associated CTS is quite high, and therefore amyloid may have a significant etiologic role.

2. The issue as to whether the amyloidosis associated with chronic hemodialysis be systemic or localized has not been clearly settled.

3. This amyloidosis develops as a complication of chronic hemodialysis which is an aggressive treatment in a sense, and therefore may turn out to be secondary (acquired) amyloidosis. In addition, the cuprophan membrane used in hemodialysis evokes interleukin-1 production and subsequently an acute phase reaction (17) which in turn creates high levels of SAA. These conditions tend to support the hypothesis that this amyloid may be of AA-type. On the other hand, while CTS is known to associate with amyloidosis, there have been no proven cases of CTS associated with secondary AA amyloidosis reported so far (18-23). Therefore, the clinical picture of this amyloidosis does not fit well that of any known type of amyloidosis. We set the goals of our study to answer these questions.

3. Histologic aspects in regard to distribution of amyloid

Using Congo red and hematoxylin staining, we initially examined the tissues collected at carpal release operation from 5 patients who all also underwent diagnostic rectal biopsy. Substantial amyloid deposits were observed in all the carpal tissues, i.e. synovia and perineural connective tissue. Deposition of amyloid was also found in rectal biopsies from three of the five patients. Amyloid deposition was however minute in all three cases, and was restricted in the walls of small rectal blood vessels (16). Besides CTS, destructive osteoarthropathy was recently added to the list of prominent manifestations caused by deposition of amyloid associated with chronic hemodialysis. Many different joints can be affected. Large cystic lesions have been noted in the humerus at the shoulder joint, in the femur adjacent to the hip and in the carpal bones at the wrist joint. Arthralgias in other joints suggest they may also be involved. Clinical symptoms can widely vary from acute and chronic articular and para-articular inflammatory episodes in multiple joints to femoral neck fracture as the results of destructive osteoarthropathy (3,7,8,10).

Our finding of amyloid deposits in the rectal biopsies in three of five cases (16) and the involvement of multiple joints (1-13) indeed support the possible systemic involvement of this type of amyloidosis. While systemic amyloid deposition was indeed observed in a few cases, there are also reports that extensive examination of cases with hemodialysis-associated amyloidosis did not reveal visceral amyloid deposition (1,6,7,9,10, and personal communications). In our own more recent experience, among 5 autopsy cases whose records we had access to