


Does dialysis-related amyloidosis regress after transplantation?

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Introduction

Do amyloid deposits regress after successful therapy of their aetiological factors? The issue is of great clinical relevance as more and more efficient treatments are developed. It remains hotly disputed as illustrated by the fate of dialysis-related (or β2M) amyloidosis. After a successful renal transplantation has fully corrected the β2M excretory defect, some studies suggest that β2M amyloidosis regresses [1,2], whereas others hold the opposite view [3–7]. A recent report of Tan et al. [2], claiming regression after renal transplantation, rekindles this debate.

Two contradictory views

Two contradictory views are expressed at the present time. The first holds that β2M amyloidosis regresses after transplantation. It relies mainly on changes in focal uptake of labelled serum P component (SAP), a protein co-deposited with amyloid fibrils. Scintigraphy is used to detect as well as to assess, semiquantitatively, amyloid deposits. Tan et al. [2] report that after a median post-transplant delay of 4.5 years, labelled SAP uptake decreases at least one initially positive site in eight of nine transplanted patients, falling below detection limits in six sites from three patients. They conclude that β2M amyloidosis may regress several years after the restoration of a normal renal function.

The alternative view claims that there is at present no conclusive evidence that β2M amyloid regressions after transplantation. It is based mainly upon morphological evidence. β2M amyloid deposits form bone cysts readily identified by X-rays. Provided that strict criteria are adhered to, these bone cysts are characteristic of amyloid deposition [8]. Thus several studies have examined their evolution after renal transplantation [3,5–7] and demonstrated that they neither disappear nor even regress in size even after 10 years. Tan et al. [2] report similar results but claim that cyst size regresses ‘not substantially’ without providing quantitative criteria for regression. The persistence of β2M amyloidosis is further corroborated by histological evidence of β2M amyloid deposits up to 10 years after transplantation [4–6,9].

The validity of SAP scintigraphy to quantify β2M amyloid deposits

The validity of each view hinges upon the quantitative significance of the chosen marker, either scintigraphy or morphological evidence.

Let us first consider the value of SAP scintigraphy to detect and quantify amyloid deposits. Hawkins et al. [10] pointed out a few years ago the difficulties of an
‘… accurate estimation of tissue amyloid content because histological examinations cannot reasonably sample more than a very small proportion of the involved organs and, even then, light microscopy examination of green birefringent areas may not reflect quantitatively the absolute amount of amyloid fibril deposits’. In mice with casein-induced, massive amyloidosis of the spleen and liver, there is little variation in the proportion of the injected dose of labelled SAP that localizes; correlation is thus excellent, but the range of amyloid deposit size is rather narrow. By contrast, in the amyloid-enhancing factor induced model, amyloid deposition varies markedly between mice; correlation between histological score and localized labelled SAP proves ‘imperfect’ [10].

In man, correlation between SAP accumulation and quantitation of amyloid is even less clear. In their recent paper, Tan et al. [2] quote six references from their own group addressing this critical issue. Interestingly, only two provide original data. The first [11] concerns a single patient with AL amyloidosis. At autopsy, the percentage of injected tracer expressed per 100 g of tissue is weakly correlated with a semiquantitative histological assessment of amyloid deposits. For tissues with similar amyloid involvement, uptake varies fivefold. The second reference is an extended abstract published in the proceedings of a 1993 international symposium on amyloidosis [12]. Autopsy material was harvested in 15 patients with various types of amyloidosis, 8 h to 5 months after a labelled SAP study. Amyloid deposits were quantitatively graded by two experienced assessors in tissue sections stained with Congo red. Results were compared with labelled SAP uptake, the amount of native unlabelled SAP extracted from available organs, and when possible the residual quantity of labelled SAP within them. In spleen and liver, correlation between histological assessment and scintigraphic estimates is said to be excellent (r = 0.90 and 0.95 respectively). For other organs, however, correlation is not assessed but should be rather poor as a result of poor sensitivity (50% for the kidneys and 25% for the heart). Native SAP extracted from liver, spleen, kidneys and heart ‘correlates with histological score’ (no r value given). In the four patients given radioactive SAP 1–118 days beforehand, residual radioactivity in various (undefined) tissues is proportional to the amount of native SAP extracted from them. In the absence of detailed methodological, clinical, and individual information, these results are not convincing.

None of these studies included patients with $\beta_2M$ amyloidosis. In this group of patients, the limited specificity of labelled SAP scans is a further cause of concern when its ability to monitor amyloid deposits is discussed. Labelled SAP accumulation in the spleen has been reported by Nelson et al. [1] in eight of 22 patients (36%) dialysed for more than 10 years. However, detailed autopsy studies [13] in 18 patients dialysed for 10–23 (mean 13.5) years have revealed histological evidence of spleen amyloidosis in only one case (5%). Such a discrepancy suggests that in $\beta_2M$ amyloidosis, the specificity of the SAP scan might be wanting [4]. It is as yet unknown whether the probable aspecific splenic uptake also regresses after renal transplantation; such information might cast new light on the significance of changes in labelled SAP uptake. Only inadequate specificity is relevant to the present discussion. Still, it should be remembered that the sensitivity of SAP scintigraphy is also limited. The technique fails to identify $\beta_2M$ amyloid deposits in 63% of clinically symptomatic shoulders whereas SAP does not accumulate in the hips, a frequent site of $\beta_2M$ amyloid depositation [1]. In other types of amyloidosis, sensitivity falls to 50% in the kidneys and to 25% in the heart [12].

A last cause of concern stems from the variability of the observations made in transplanted patients. In a first study of five patients with clinical and histological (n = 4) evidence of amyloidosis while on dialysis, Nelson et al. [1] did not observe labelled SAP uptake 0.8 to 2.4 years after a successful graft, a finding interpreted as evidence of $\beta_2M$ amyloid regression. By contrast, 5 years later, the same group [2] describes a significant uptake of labelled SAP in eight of 9 patients, despite a longer delay after transplantation (median 4.5 years). This discrepancy raises the issue of the technical problems inherent to quantitative assessments of external scintigraphy.

The difficulty of a histological quantitation of systemic amyloid deposits, the questionable correlation between SAP labelling and quantity of deposited amyloid both in mice and man, the limited specificity and sensitivity of the technique, taken together with the apparent variability of external scan results in transplanted patients call thus for a very cautious interpretation of post-transplantation changes of the SAP scan.

The validity of morphological method

The alternative view that $\beta_2M$ amyloidosis does not regress significantly after renal transplantation relies mainly upon morphological evidence.

The significance of bone amyloid cysts hinges upon the quantitative relationship between their size and their actual amyloid content. The demonstration of persistent $\beta_2M$ amyloid deposits in some cysts [6] or in synovia [4,5] does not rule out the possibility that the deposits were initially larger and that fibrous tissue progressively replaces amyloid in bone cysts, thus preventing cyst regression. Furthermore the relevance of amyloid bone deposits to the total amount of precipitated $\beta_2M$ amyloid remains to be demonstrated. For instance Tan et al. [2] have suggested that bone amyloid might mobilize more slowly from bone cysts than from other sites, a hypothesis still to be tested. These various limitations have to be kept in mind whenever the post-transplantation regression of $\beta_2M$ amyloidosis is discussed.
Conclusion

We have yet to conceive a meaningful protocol capable of evaluating the relationship between the amount of deposited amyloid and either radiological abnormalities or labelled SAP uptake. We remain thus faced with two apparently irreconcilable views in the absence of a gold standard for amyloid quantitation. Such a dilemma remains provocative: its solution might emerge from as yet unknown approaches. Interestingly, it has been recently reported in abstract form [14] that macrophages infiltrating β2M amyloid deposits are able to degrade amyloid P component but not β2M. These results, if confirmed, are compatible with the hypothesis that P component and therefore labelled SAP accumulation may regress after transplantation while β2M fibrils persist unmodified.

Whatever the final answer, the defendants for both points of view agree on one central, clinically relevant conclusion: renal transplantation cures rapidly the sometimes crippling symptoms of dialysis-related arthropathy. Although high doses of steroids certainly account for this benefit in the short term it is noteworthy that symptoms do not recur as long as graft function is adequate, even when steroid therapy is eventually withheld.

References


The impact of vascular access for haemodialysis on patient morbidity and mortality

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Introduction

A letter to the editor of Nephrology Dialysis Transplantation in this issue (p. 850) suggests that haemodialysis patients with a history of vascular access failure are at higher risk of death. The analysis compares patient survival between patients who had only one access during follow-up and those who have multiple accesses and therefore seems to rely on a post hoc definition of the group at highest risk. It is plausible that a first access failure predicts future failures and poor outcomes, and therefore that the primary focus of research on vascular access should be directed at factors leading to a first access failure in order to prevent this first event. Potential risk factors for poor outcomes may include (1) failure to place a permanent vascular access prior to dialysis, and (2) the type of permanent vascular access initially placed.