

Review Article

The pathology and changing epidemiology of dialysis-related cardiac beta-2 microglobulin amyloidosis



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ABSTRACT

Cardiac amyloidosis in the setting of systemic amyloidosis due to β_2 -microglobulin can occur in the setting of long-term dialysis. It has been suggested that newer dialysis techniques may prevent or at least reduce the likelihood of this disorder occurring. Currently, the prevalence and incidence of dialysis-related cardiac β_2 -microglobulin amyloidosis are unclear. The published literature regarding dialysis-related cardiac β_2 -microglobulin amyloidosis ($A\beta_2M$) was reviewed, and a new case of this disorder is reported. The cumulative available data were analyzed for changing patient characteristics over time. Cardiac $A\beta_2M$ was previously a common condition in patients who had undergone dialysis for 9 or more years with traditional low-flow dialysis membranes. Newer dialysis technologies reduce, but do not normalize, serum β_2 -microglobulin levels in chronic dialysis patients. Newer dialysis technologies appear to reduce the risk of developing $A\beta_2M$ compared with traditional low-flow dialysis membranes. New cases of documented dialysis-related cardiac $A\beta_2M$ are uncommon. Analysis of the cases of dialysis-related cardiac $A\beta_2M$ published over the last 3 decades reveals increasing dialysis intervals over time. Thus, new cases of this disorder are typically associated with remote prior dialysis with low-flow membranes. While initially, the majority of cases of dialysis-related cardiac $A\beta_2M$ were reported from Europe and the United States, more recently, the majority of cases were reported from Japan, where there is a relatively large population of patients on very long-term dialysis. In addition, low-flow dialysis membranes continue to be used in many parts of the world, raising the potential for dialysis-related cardiac $A\beta_2M$ to be more common in those countries. Dialysis-related osteoarticular $A\beta_2M$ appears to continue to occur in the setting of chronic dialysis with the use of high-flow membranes. Dialysis-related cardiac $A\beta_2M$ is currently uncommon and typically associated with the use of low-flow dialysis membranes. However, the condition could potentially occur in the setting of long-term dialysis even with the use of high-flow membranes.

Summary: Dialysis-related cardiac β_2 -microglobulin amyloidosis frequently occurred in the past in patients who had undergone dialysis for nine or more years. Currently, the condition is uncommon and typically associated with remote prior dialysis with low-flow membranes. There is potential for this condition to continue to afflict patients receiving chronic dialysis with newer dialysis technologies.

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1. Introduction

β_2 -Microglobulin is a component of the human HLA class I major histocompatibility complex [1]. After release of the complex from the cell surface, β_2 -microglobulin dissociates from the complex and circulates as a monomer with a molecular mass of 11,815 Da. β_2 -microglobulin is normally metabolized in the kidneys, where it is reabsorbed and degraded by proximal tubular cells. Thus, serum levels of β_2 -microglobulin increase in the setting of renal failure and dialysis. The increased levels of circulating β_2 -microglobulin result in the protein depositing in the tissue as amyloid. Since the patients suffering from β_2 -microglobulin amyloidosis ($A\beta_2M$) are usually on dialysis, this form of amyloidosis is often referred to as dialysis-related amyloidosis [2]. Deposition of $A\beta_2M$ in the setting of renal failure and dialysis usually occurs in patients with wild-type β_2 -microglobulin gene sequences. In addition to dialysis-related $A\beta_2M$, there is a hereditary form of $A\beta_2M$ in which mutations in the gene encoding β_2 -microglobulin result in a protein with increased propensity to misfold and form amyloid [3]. This hereditary $A\beta_2M$ often occurs in the absence of chronic renal disease and often in the setting of normal serum β_2 -microglobulin protein levels.

1.1. Dialysis technology and serum β_2 -microglobulin levels

Formation of dialysis-related $A\beta_2M$ is thought to be related to the serum levels of β_2 -microglobulin. In anuric dialysis patients, β_2 -microglobulin is produced at a rate of 150–300 mg/d [1]. The traditional cuprophane and cellulose acetate low-flow dialysis membranes have small pores and do not allow for the passage of β_2 -microglobulin. As a result, serum levels of β_2 -microglobulin increase from the normal level of 1–3 mg/L up to 20–50 mg/L or more in long-term dialysis patients [1]. The newer synthetic high-flow dialysis membranes allow for the removal of β_2 -microglobulin. In patients undergoing long-term dialysis with newer dialysis technologies, serum levels of β_2 -microglobulin can be reduced to 6–20 mg/L, which is less than with the older low-flow membranes but still well above the normal range [1]. In 1997, the introduction of synthetic high-flow hemodialysis membranes coupled with the use of improved dialysate was reported to be associated with an 80% decrease in osteoarticular $A\beta_2M$ [4]. However, the β_2 -microglobulin production rate still exceeds the clearance rate for any dialysis technology currently in use [5].

1.2. Distribution of $A\beta_2M$ deposition

One of the most frequent initial clinical manifestations of $A\beta_2M$ is carpal tunnel syndrome due to amyloid deposition in the synovium of the hands and wrists [6]. These patients may also develop arthralgias of the shoulders, hips, and knees. Later, there may be formation of juxta-articular bone cysts, which can cause pathologic fractures. With time, both the spine and peripheral joints are often involved. Systemic visceral involvement is less common and most often appears histologically as systemic vascular amyloid deposition. Such systemic involvement typically occurs after 9 or more years of dialysis and is usually subclinical. Based on autopsies, systemic visceral $A\beta_2M$ most commonly involves the heart (80% of cases) and gastrointestinal tract (78%), followed by the lungs (59%), liver (41%), and kidneys (33%), with less frequent involvement of the spleen (5%) [7,8].

1.3. Cardiovascular $A\beta_2M$

Between 1986 and 2001, approximately 50 autopsies identifying dialysis-related $A\beta_2M$ involving the heart were reported [9–29]. Since 2001, much fewer cases of dialysis-related cardiac $A\beta_2M$ have been reported, primarily from Japan [30–32]. In most of the published cases, the amyloid was typed as $A\beta_2M$ using immunohistochemistry, but in a few cases, immunoelectron microscopy [9] or immunofluorescence [10]

was employed. In autopsy series published between 1987 and 1997, dialysis-related cardiac $A\beta_2M$ was identified in approximately two thirds of patients who had undergone dialysis for 9 or more years [13, 18,19,23,27] but was not present in patients who had undergone dialysis for less than 9 years [19,22,23,33].

In dialysis-related cardiac $A\beta_2M$, the amyloid most commonly involves small and medium-sized vessels within the myocardium. Other sites of involvement in the heart include the endocardium, subendocardium, myocardial interstitium, perivascular fibrous tissue, atrioventricular node, and aortic and mitral valves [12,17,18,20,24,27, 29,31]. While the degree of cardiac involvement was often mild, diffuse interstitial and nodular involvement has been reported [28], and some cases demonstrated severe involvement with massive amounts of amyloid in the heart [16,30]. In dialysis-related cardiac $A\beta_2M$, the amyloid deposition may be greater in the atria than in the ventricles [29,30]. In some cases, the cardiac amyloid was associated with or undergoing calcification [16,21,29]. Calcification of cardiac amyloid deposits has been seen with other forms of amyloid, and this calcification may cause or contribute to the increased radionucleotide uptake by the heart detected on modified-bone scans in some patients with cardiac amyloidosis [34].

In most of the published cases, the dialysis-related cardiac $A\beta_2M$ was an incidental autopsy finding. However, severe atrial involvement has been associated with atrial dilatation, and diffuse cardiac involvement

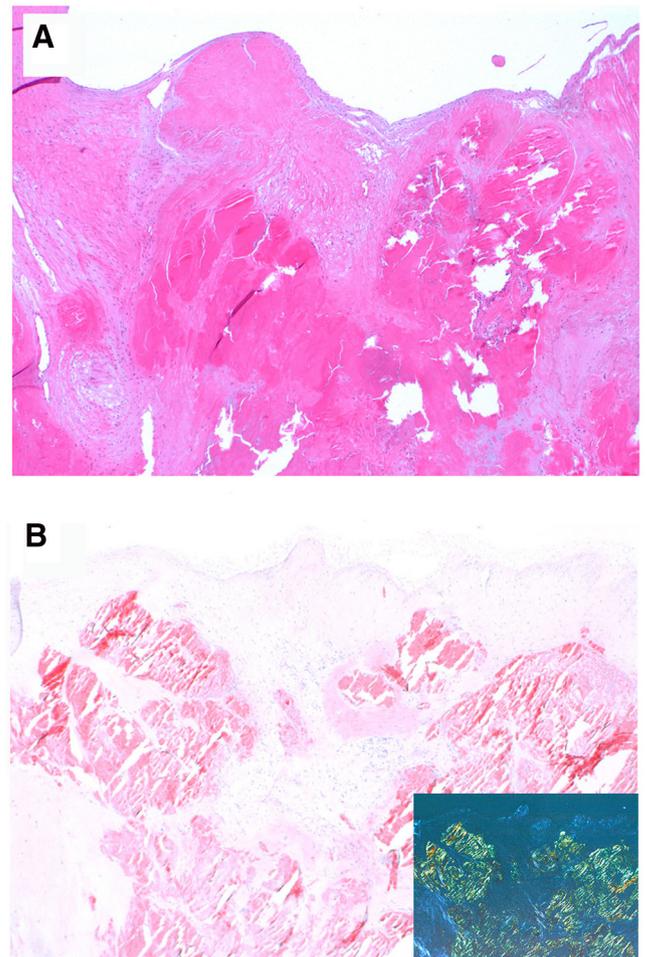


Fig. 1. Amyloid cardiac valvulopathy due to $A\beta_2M$. Depicted are histologic images from the surgically resected mitral valve of a patient who had undergone 41 years of dialysis for Alport syndrome. On hematoxylin and eosin staining (A), there were large nodules of amorphous material which showed characteristic positive staining on Congo red stain (B) characteristic of amyloid, with characteristic green birefringence upon the application of plane polarized light (B inset).

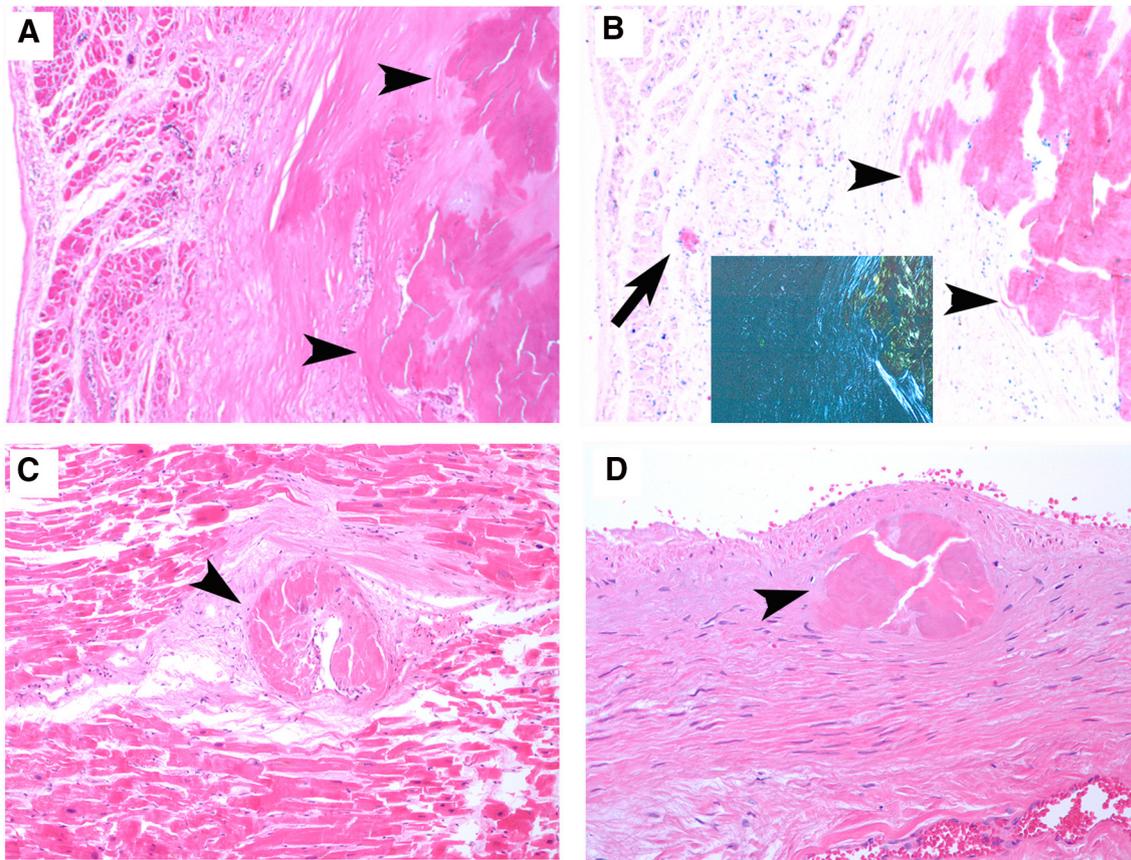


Fig. 2. Cardiac $A\beta_2M$. Autopsy performed 2 years later on the patient from Fig. 1, after 43 years of dialysis, revealed extensive atrial endocardial amyloid (arrowheads) on hematoxylin and eosin (A) and Congo red stains (B), some of which was associated with calcification. There was characteristic green birefringence of the amyloid on Congo red stain upon the application of plane polarized light (B inset). There was also amyloid present in medium-sized vessels of the atria (B, arrow), in medium-sized vessels and perivascular tissue in the ventricles (C), and focally in the epicardial coronary arteries (D).

by $A\beta_2M$ has been associated with heart failure [28,30]. Another major complication of dialysis-related cardiovascular $A\beta_2M$ occurs in the bowel. Intestinal vascular involvement by $A\beta_2M$ can result in intestinal ischemia, infarction, and perforation [23,26,28]. Such end-organ ischemia can also be caused by amyloid vasculopathy resulting from other forms of systemic amyloidosis [35].

1.4. A contemporary case of dialysis-related $A\beta_2M$

A 71-year-old male with end-stage renal disease secondary to Alport syndrome died from pneumonia at Massachusetts General Hospital in 2011. The patient had undergone hemodialysis for 43 years, 3 times per week, starting in 1968. The past medical history also included coronary artery disease, peripheral artery disease, aortic stenosis, atrial fibrillation, secondary hyperparathyroidism, osteopenia, spinal stenosis, esophageal stricture, nephrogenic systemic fibrosis, and seizure disorder. The patient's surgical history included a subtotal parathyroidectomy at age 30, a failed renal transplant at age 33, and distal foot amputation at age 69. Other surgical procedures included multiple hip surgeries and spinal fusions, multiple carpal tunnel releases, esophageal dilations, and a cholecystectomy.

At age 57, he sustained a pathological femoral neck fracture resulting from an amyloid cyst due to dialysis-related $A\beta_2M$. At age 62, an amyloid cyst was resected from the scalp. At age 66, he underwent an incision and drainage of the shoulder joint for removal of an abscess adjacent to amyloid deposits. At age 69, he underwent mitral valve replacement for mixed mitral stenosis and regurgitation. The resected valve was assessed histologically [36], which revealed prominent amyloid deposition and focal calcification (Fig. 1). Prior to the valve surgery, he was diagnosed with New York Heart Association Class III heart

failure, which was felt to be diastolic in nature, and his symptoms persisted after valve replacement. By echocardiography 2 months prior to death, his left ventricular ejection fraction was 53%, which decreased to 38% 1 week prior to death.

At autopsy, amyloid was identified in blood vessels of multiple organs including the lung, liver, spleen, esophagus, stomach, bowel, kidneys, adrenal glands, and prostate. Amyloidomas were present adjacent to the thyroid and esophagus. Amyloid was present in small and medium-sized vessels and perivascular tissue in the ventricles and atria of the heart and was focally present within the coronary arteries (Fig. 2). There was prominent amyloid involvement of the atrial endocardium, which was partially calcified. The amyloid in the left ventricle was typed as $A\beta_2M$ by immunofluorescence (Fig. 3) as described previously [37,38]. Additional findings at autopsy included severe coronary artery disease, nephrogenic systemic fibrosis, end-stage kidneys, and pneumonia, which was the immediate cause of death.

1.5. The changing epidemiology of cardiac $A\beta_2M$

While, initially in the mid 1980s, the majority of reports of cardiac $A\beta_2M$ were from Europe and North America [9,10,12,13,15,33], after 1995, the majority of cases of cardiac $A\beta_2M$ were reported from Japan [26–31]. One possible explanation for this change may be the differences in cultural views toward brain death and solid organ transplantation from deceased donors in Japan compared with Europe and North America [39]. As a result, kidney transplantation, which can prevent the deleterious effects of long-term dialysis, is not as common in Japan as in Europe and North America, and subsequently, there are relatively large numbers of patients in Japan on long-term dialysis. At the end of

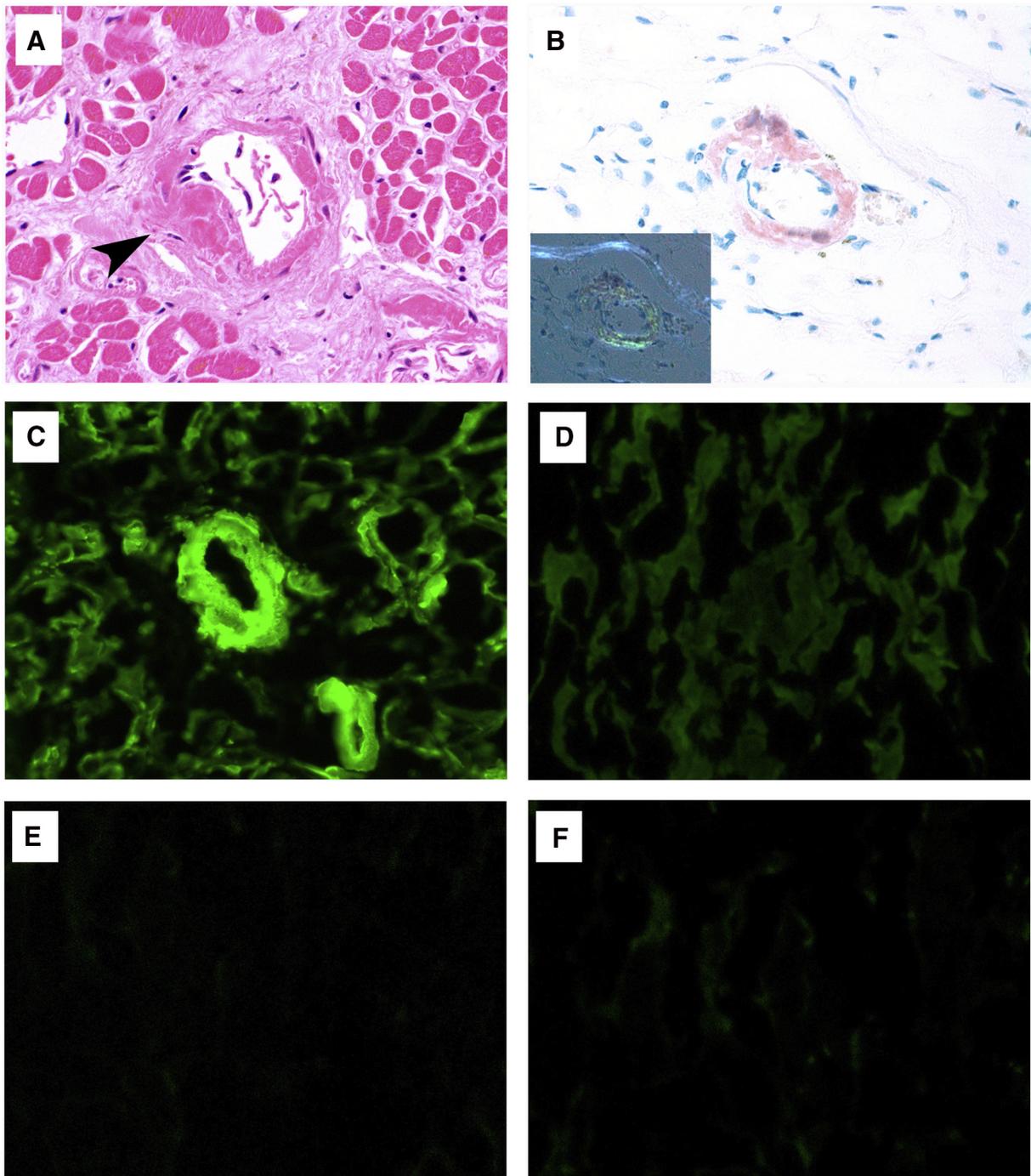


Fig. 3. Typing cardiac $A\beta_2M$ by immunofluorescence. Fresh-frozen left ventricular myocardium from the patient in Fig. 2 was utilized to type the amyloid by immunofluorescence as described previously [37,38]. Shown are histologic images with hematoxylin and eosin stain (A) and Congo red stain (B) showing vascular amyloid deposition, with characteristic green birefringence upon the application of plane polarized light (B inset). Also shown are immunofluorescence stains for β_2 -microglobulin (C), transthyretin (D), kappa immunoglobulin light chain (E), and lambda immunoglobulin light chain (F). There was specific staining of the amyloid for β_2 -microglobulin.

2012, there were over 12,000 patients in Japan who had been on dialysis for more than 25 years [40].

Eleven previously published autopsy cases of dialysis-related cardiac $A\beta_2M$ with clearly defined dates of death and dialysis time frames were identified in the literature [9,12,14–16,18,24,26,28,30]. Plots of the dialysis time frame and date of death for these 11 cases and the current case are shown in Fig. 4. All of these patients started dialysis before or during 1980, indicating at least some use of low-flow dialysis membranes. By linear regression, there was a highly statistically significant correlation between the duration of dialysis and the year of death, indicating that

cardiac $A\beta_2M$ is being seen in the setting of progressively longer dialysis durations.

1.6. Contemporary development of cardiac $A\beta_2M$

Considering that newer high-flow dialysis filter technology results in lower circulating β_2 -microglobulin levels compared with older low-flow dialysis filters, an important question is whether cardiac $A\beta_2M$ is still occurring. While high-flow dialysis membranes, which may help to prevent the formation of dialysis-related $A\beta_2M$, are now standard

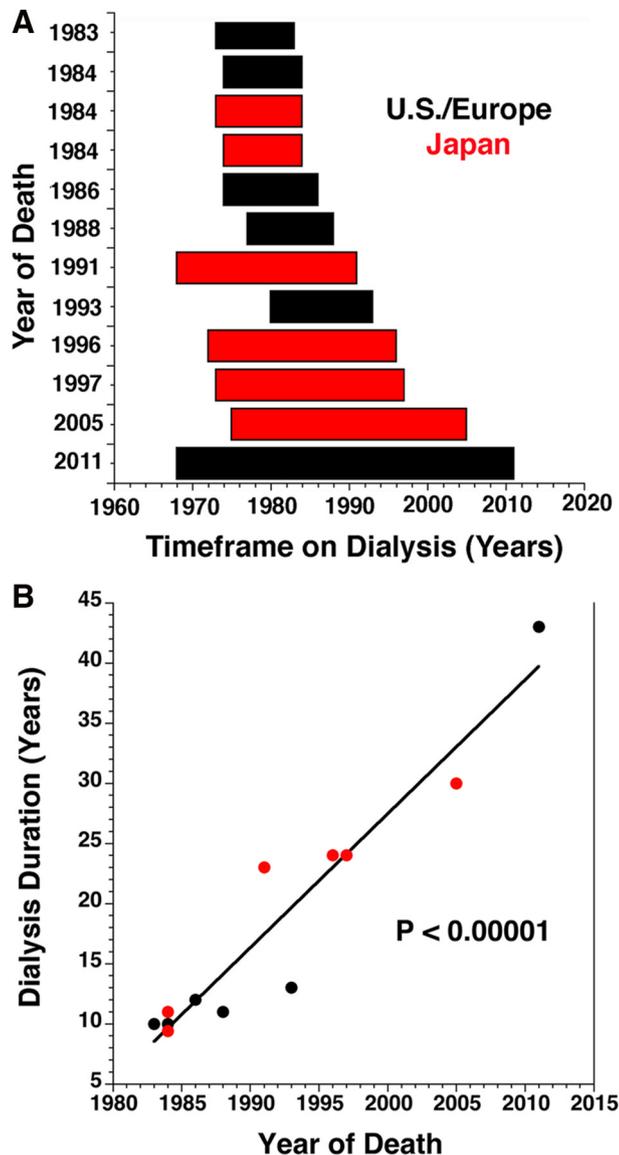


Fig. 4. The changing epidemiology of cardiac $A\beta_2M$. (A) Bar graph depicting dialysis interval and year of death for 12 patients with cardiac $A\beta_2M$ with clearly defined dialysis time frames and years of death. The cases include 11 previously published cases [9,12,14–16,18,24,26,28,30] and the current case (bottom). The time frame for the dialysis for each patient is represented by the bar with the year of death indicated on the y-axis. Cases from the United States and Europe are indicated in black, and cases from Japan are indicated in red. All of these patients had started dialysis before or during 1980. The majority of cases with dates of death prior to 1990 are from the United States and Europe, while the majority of cases with dates of death after 1990 are from Japan. (B) A plot of the relationship between dialysis relation and year of death shows a marked positive correlation ($P < 0.00001$) by linear regression indicating progressively longer dialysis intervals over time.

in the United States and Europe, many countries continue to utilize low-flow dialysis membranes [41–44]. Thus, in assessing a patient's risk for dialysis-related $A\beta_2M$, it is important to consider not only the length of the dialysis period but also the country in which the dialysis occurred and the types of dialysis filters utilized.

Since even the newer high-flow dialysis filters reduce but do not completely normalize serum β_2 -microglobulin levels in dialysis patients, is dialysis-related cardiac $A\beta_2M$ still occurring with the newer dialysis filter technologies? These newer dialysis membranes might delay the onset of $A\beta_2M$ deposition but not entirely prevent it [45,46]. However, multiple recent large surgical pathology series from Europe and North America, which totaled over 1000 visceral organ biopsies with amyloid primarily involving heart, kidney, and gastrointestinal tract,

together reported no cases of $A\beta_2M$ [37,38,47–54]. This would suggest that new development of systemic $A\beta_2M$ is either not occurring in these geographic regions or is at most very rare and/or largely subclinical. However, many of these studies utilized immunohistochemistry for typing the amyloid without inclusion of antibodies to β_2 -microglobulin in the antibody panel. Such practice has been reported to result in the misclassification of amyloid that is in fact $A\beta_2M$ [55].

Some recent studies, primarily from Japan, have suggested that $A\beta_2M$ is continuing to afflict patients even with the use of modern dialysis technologies. In long-term dialysis patients, continued improvements in dialysis technologies have reduced, but not eliminated, the burden of carpal tunnel syndrome, which is a clinical surrogate for $A\beta_2M$ [56]. In a recent study from Japan, $A\beta_2M$ was identified in surgically resected intervertebral disk tissue from patients who had undergone long-term dialysis with high-flow membranes [57]. In a cardiac imaging study from Japan, serum β_2 -microglobulin levels independently correlated with left ventricular hypertrophy by echocardiography [58], although it is not known if the hypertrophy in these patients was actually due to $A\beta_2M$ deposition in the heart. In another recent study from Japan, $A\beta_2M$ was detected in 71% of calcified aortic valves obtained as either surgical specimens or autopsies [59]; however, the years during which the patients received dialysis and the types of dialysis membranes utilized were not specified. It has long been recognized that focal amyloid deposits are present in calcified valves even in the absence of dialysis; in a previous study from Germany, this “dystrophic” amyloid was attributed to apolipoprotein A-I [60]. Overall, these studies indicate that in patients currently on long-term dialysis with high-flow membranes, $A\beta_2M$ is likely depositing in the osteoarticular tissue and potentially in the heart as well.

2. Conclusions

Cardiac $A\beta_2M$ was previously a common condition in patients who had undergone dialysis for 9 or more years with traditional low-flow dialysis membranes. Newer dialysis technologies reduce, but do not normalize, serum β_2 -microglobulin levels in chronic dialysis patients. The newer dialysis technologies appear to reduce the risk of developing $A\beta_2M$ compared with traditional low-flow dialysis membranes. New cases of documented cardiac $A\beta_2M$ are uncommon and are associated with increasing dialysis intervals, consistent with remote prior dialysis with low-flow membranes. Low-flow dialysis membranes continue to be used in many parts of the world, raising the potential for dialysis-related cardiac $A\beta_2M$ to be more common in those countries. Dialysis-related osteoarticular $A\beta_2M$ and potentially cardiac $A\beta_2M$ appear to occur in the setting of chronic dialysis even with the use of high-flow membranes.

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References

- [1] Druke TB, Massy ZA. Beta2-microglobulin. *Sem Dial* 2009;22:378–80.
- [2] Westermarck P, Benson MD, Buxbaum JN, Cohen AS, Frangione B, Ikeda S, et al. A primer of amyloid nomenclature. *Amyloid* 2007;14:179–83.
- [3] Valleix S, Gillmore JD, Bridoux F, Mangione PP, Dogan A, Nedelec B, et al. Hereditary systemic amyloidosis due to Asp76Asn variant β_2 -microglobulin. *N Engl J Med* 2012;366:2276–83.
- [4] Schwalbe S, Holzhauser M, Schaeffer J, Galanski M, Koch KM, Floege J. Beta 2-microglobulin associated amyloidosis: a vanishing complication of long-term hemodialysis? *Kidney Int* 1997;52:1077–83.
- [5] Scarpioni R, Ricardi M, Albertazzi V, De Amicis S, Rastelli F, Zerbin L. Dialysis-related amyloidosis: challenges and solutions. *Int J Nephrol Renovasc Dis* 2016;9:319–28.
- [6] Jadoul M, Druke TB. β_2 microglobulin amyloidosis: an update 30 years later. *Nephrol Dial Transplant* 2016;31:507–9.
- [7] Jadoul M, van Ypersele de Strihou C. β_2 -microglobulin amyloidosis. *Complications of Long-term Dialysis*, Brown EA, Parfrey PS; 1999. p. 121–44.
- [8] Hoshii Y, Takahashi M, Ishihara T, Uchino F. Immunohistochemical classification of 140 autopsy cases with systemic amyloidosis. *Pathol Int* 1994;44:352–8.

- [9] Casey TT, Stone WJ, DiRaimondo CR, Brantley BD, DiRaimondo CV, Gorevic PD, et al. Tumoral amyloidosis of bone and beta₂-microglobulin origin in association with long-term hemodialysis: a new type of amyloid disease. *Hum Pathol* 1986;17:731–8.
- [10] Bardin T, Shirahama T, Noel LH, Voisin MC, Druke T, Dryll A, et al. Hemodialysis-associated amyloidosis and beta-2 microglobulin. clinical and immunohistochemical study. *Am J Med* 1987;83:419–24.
- [11] Campistol JM, Cases A, Torras A, Soler M, Munoz-Gomez J, Monttoliu J, et al. Visceral involvement of dialysis amyloidosis. *Am J Nephrol* 1987;7:390–3.
- [12] Fuchs A, Jagirdar J, Schwartz IS. Beta 2-microglobulin amyloidosis (AB2M) in patients undergoing long-term hemodialysis. *Am J Clin Pathol* 1987;88:302–7.
- [13] Noel LH, Zingraff J, Bardin T, Atienza C, Kuntz D, Druke T. Tissue distribution of dialysis amyloidosis. *Clin Nephrol* 1987;27:175–8.
- [14] Ogawa H, Saito A, Hirabayashi N, Hara K. Amyloid deposition in systemic organs in long-term hemodialysis patients. *Clin Nephrol* 1987;28:199–204.
- [15] Theaker JM, Raine AEG, Rainey AJ, Heryet A, Clark A, Oliver DO. Systemic amyloidosis of beta₂-microglobulin type: a complication of long term haemodialysis. *J Clin Pathol* 1987;40:1247–51.
- [16] Gejyo F, Homma N, Maruyama H, Ohara K, Arakawa M. In: Amyloid and Amyloidosis, Isoe T, Araki S, Uchino F, Kito S, Tsubura E eds, editor. Coexistence of beta₂-microglobulin-derived amyloid deposits and ectopic calcification in the heart of a chronic hemodialysis patient; 1988. p. 617–22.
- [17] Ullian ME, Hammond WS, Alfrey AC, Schultz A, Molitoris BA. Beta-2-microglobulin-associated amyloidosis in chronic hemodialysis patients with carpal tunnel syndrome. *Medicine (Baltimore)* 1989;68:107–15.
- [18] Campistol JM, Solé M, Muñoz-Gomez J, Lopez-Pedret J, Revert L. Systemic involvement of dialysis-amyloidosis. *Am J Nephrol* 1990;10:389–96.
- [19] Athanasou NA, Ayers D, Rainey AJ, Oliver DO, Duthie RB. Joint and systemic distribution of dialysis amyloid. *Q J Med* 1991;78:205–14.
- [20] Zhou H, Pfeifer U, Linke R. Generalized amyloidosis from beta₂-microglobulin, with caecal perforation after long term hemodialysis. *Virchows Archiv A Pathol Anat Histopathol* 1991;419:349–53.
- [21] Mazanec K, McClure J, Bartley CJ, Newbould MJ, Ackrill P. Systemic amyloidosis of beta₂ microglobulin type. *J Clin Pathol* 1992;45:832–3.
- [22] Ohashi K, Hara M, Kawai R, Ogura Y, Honda K, Nihei H, et al. Cervical discs are most susceptible to beta₂-microglobulin amyloid deposition in the vertebral column. *Kidney Int* 1992;41:1646–52.
- [23] Gal R, Korzets A, Schwartz A, Rath-Wolfson L, Gatfer U. Systemic distribution of beta₂-microglobulin-derived amyloidosis in patients who undergo long-term hemodialysis. Report of seven cases and review of the literature. *Arch Pathol Lab Med* 1994;118:718–21.
- [24] Lutz AE, Schneider U, Ehlerding G, Frenzel H, Koch KM, Kühn K. Right ventricular cardiac failure and pulmonary hypertension in a long-term dialysis patient – unusual presentation of visceral beta₂-microglobulin amyloidosis. *Nephrol Dial Transplant* 1995;10:555–8.
- [25] Athanasou NA, Puddle B, Sallie B. Highly sulphated glycosaminoglycans in articular cartilage and other tissues containing beta₂ microglobulin dialysis amyloid deposits. *Nephrol Dial Transplant* 1995;10:1672–8.
- [26] Araki H, Muramoto H, Oda K, Koni I, Mabuchi H, Mizukami Y, et al. Severe gastrointestinal complications of dialysis-related amyloidosis in two patients on long-term hemodialysis. *Am J Nephrol* 1996;16:149–53.
- [27] Ohashi K, Takagawa R, Hara M. Visceral organ involvement and extracellular matrix changes in beta₂-microglobulin amyloidosis – a comparative study with systemic AA and AL amyloidosis. *Virchows Arch* 1997;430:479–87.
- [28] Kawano M, Muramoto H, Yamada M, Minamoto M, Araki H, Koni I, et al. Fatal cardiac beta₂-microglobulin amyloidosis in patients on long-term hemodialysis. *Am J Kidney Dis* 1998;31:1–5.
- [29] Takayama F, Miyazaki S, Morita T, Hirasawa Y, Niwa T. Dialysis-related amyloidosis of the heart in long-term hemodialysis patients. *Kidney Int* 2001;78:S172–6.
- [30] Kodama T, Takemura T, Shiraiishi J, Kunogi J, Aoyagi T. A case of almost-exclusively atria-dominant cardiac amyloidosis related with hemodialysis. *Int J Cardiol* 2008;127:e69–72.
- [31] Koda R, Yamazaki H, Kazama J, Ito T, Saeki T, Emura I, et al. A case report of severe visceral beta₂-microglobulin-derived amyloidosis without obvious joint symptoms or radiological findings in a chronic hemodialyzed patient with systemic lupus erythematosus. *Ther Apher Dial* 2009;13:232–7.
- [32] Seki T, Hattori A, Yoshida T. Hemodynamic deterioration after aortic valve replacement in a patient with mixed systemic amyloidosis. *Gen Thorac Cardiovasc Surg* 2017;65:470–3.
- [33] Fennes AZ, Emmett M, White GM, Greenway G, Michaels DB. Carpal tunnel syndrome with cystic bone lesions secondary to amyloidosis in chronic hemodialysis patients. *Am J Kidney Dis* 1986;7:130–4.
- [34] Stats MA, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. *Cardiovasc Pathol* 2016;25:413–7.
- [35] Lin JR, Wang H, Collins AB, Stone JR. Tongue necrosis and systemic vascular amyloidosis. *Human Pathol* 2011;42:734–7.
- [36] Stone JR, Basso C, Baandrup UT, Bruneval P, Butany J, Gallagher PJ, et al. Recommendations for processing cardiovascular surgical pathology specimens: a consensus statement from the Standards and Definitions Committee of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology. *Cardiovasc Pathol* 2012;21:2–16.
- [37] Collins AB, Smith RN, Stone JR. Classification of amyloid deposits in diagnostic cardiac specimens by immunofluorescence. *Cardiovasc Pathol* 2009;18:205–16.
- [38] Halushka MK, Eng G, Collins BA, Judge DP, Semigran MJ, Stone JR. Optimization of serum immunoglobulin free light chain analysis for subclassification of cardiac amyloidosis. *J Cardiovasc Transl Res* 2015;8:264–8.
- [39] Aita K. New organ transplant policies in Japan, including the family oriented priority donation clause. *Transplantation* 2011;91:489–91.
- [40] Kazama JJ, Yamamoto S, Wakasugi M, Narita I. A hip fracture in a dialysis patient with Aβ₂M amyloidosis. *Kidney Int* 2014;85:214–5.
- [41] Lombardi R, Rosa-Diez G, Ferreira A, Greloni G, Yu L, Younes-Ibrahim M, et al. Acute kidney injury in Latin America: a view on renal replacement therapy resources. *Nephrol Dial Transplant* 2014;29:1369–76.
- [42] Andreoli MCC, Dalboni MA, Watanabe R, Manfredi SR, Canziani MEF, Kallas EG, et al. Impact of dialyzer membrane on apoptosis and function of polymorphonuclear cells and cytokine synthesis by peripheral blood mononuclear cells in hemodialysis patients. *Artif Organs* 2007;31:887–92.
- [43] Shayanpour S, Shahbazian H, Mohammadshahi M, Baqaii S, Abaforush F. Evaluating the effect of N-acetylcysteine on residual renal function in chronic hemodialysis patients treated with low-flux dialysis membrane; a randomized clinical trial. *J Renal Injury Prevent* 2018;7:269–74.
- [44] Han S, Yang K, Zhu H, Liu J, Zhang L, Zhao J. Proteomics investigation of the changes in serum proteins after high- and low-flux hemodialysis. *Ren Fail* 2018;40:506–13.
- [45] Dember LM, Jaber BL. Dialysis-related amyloidosis: late finding or hidden epidemic? *Sem Dial* 2006;19:105–9.
- [46] Labriola L, Jadoul M. Dialysis-related amyloidosis: is it gone or should it be? *Sem Dial* 2017;30:193–6.
- [47] Keibel A, Rocken C. Immunohistochemical classification of amyloid in surgical pathology revisited. *Am J Surg Pathol* 2006;30:673–83.
- [48] Bergesio F, Ciciani AM, Santostefano M, Brugnana R, Manganaro M, Palladini G, et al. Renal involvement in systemic amyloidosis – an Italian retrospective study on epidemiological and clinical data at diagnosis. *Nephrol Dial Transplant* 2007;22:1608–18.
- [49] von Hutten H, Mihatsch M, Lobeck H, Rudolph B, Eriksson M, Rocken C. Prevalence and origin of amyloid in kidney biopsies. *Am J Surg Pathol* 2009;33:1198–205.
- [50] Kieninger B, Eriksson M, Kandolf R, Schonland P, Kristen A, Hegenbart U, et al. Amyloid in endomyocardial biopsies. *Virchows Arch* 2010;456:523–32.
- [51] Schonland S, Hegenbart U, Bochtler T, Mangatter A, Hansberg M. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. *Blood* 2012;119:488–93.
- [52] Maleszewski JJ, Murray DL, Dispenzieri A, Grogan M, Pereira NL, Jenkins SM, et al. Relationship between monoclonal gammopathy and cardiac amyloid type. *Cardiovasc Pathol* 2013;22:189–94.
- [53] Freudenthaler S, Hegenbart U, Schonland S, Behrens H, Kruger S, Rocken C. Amyloid in biopsies of the gastrointestinal tract – a retrospective observational study on 542 patients. *Virchows Arch* 2016;468:569–77.
- [54] Garcia Y, Collins AB, Stone JR. Abdominal fat pad excisional biopsy for the diagnosis and typing of systemic amyloidosis. *Human Pathol* 2018;72:71–9.
- [55] Linke R, Oos R, Wiegel N, Nathrath W. Classification of amyloidosis: misdiagnosing by way of incomplete immunohistochemistry and how to prevent it. *Acta Histochem* 2006;108:197–208.
- [56] Hoshino J, Yamagata K, Nishi S, Nakai S, Masakane I, Iseki K, et al. Significance of the decreased risk of dialysis-related amyloidosis now proven by results from Japanese nationwide surveys in 1998 and 2010. *Nephrol Dial Transplant* 2016;31:595–602.
- [57] Tsai TT, Kaliya-Perumal AK, Jenq CC, Niu CC, Ho NY, Lee TY, et al. The unresolved problem of beta₂-microglobulin amyloid deposits in the intervertebral discs of long-term dialysis patients. *J Orthop Surg Res* 2017;12:194.
- [58] Masuda M, Ishimura E, Ochi A, Tsujimoto Y, Tahara H, Okuno S, et al. Serum beta₂-microglobulin correlates positively with left ventricular hypertrophy in long-term hemodialysis patients. *Nephron Clin Pract* 2014;128:101–6.
- [59] Kurita N, Fujii A, Kotera N, Tanaka M, Tanaka S, Miyairi T, et al. Dialysis amyloid deposition in the aortic valve and its association with aortic stenosis. *Blood Purif* 2015;40:146–54.
- [60] Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, et al. High prevalence of amyloid in 150 surgically removed heart valves – a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions. *Cardiovasc Pathol* 2010;19:228–35.