Annals of Case Reports
Narayanan A, et al. Ann Case Rep: 7: 1021.
www.doi.org/10.29011/2574-7754.101021
www.gavinpublishers.com

Case Report

An Unusual Case of Severe Debilitating Arthritis in a Patient with End-Stage Renal Disease

Anand Narayanan[1], Pankti Reid[2], Mary Hammes[1*]

[1]Department of Medicine, Section of Nephrology, University of Chicago Medical Center, Chicago, IL, USA

[2]Department of Medicine, Section of Rheumatology, University of Chicago Medical Center, Chicago, IL, USA

[*]**Corresponding author**: Mary Hammes, Section of Nephrology, University of Chicago, 5841 S. Maryland Ave, MC-5100, and Chicago, IL 60637

Citation: Narayanan A, Reid P, Hammes M (2022) An Unusual Case of Severe Debilitating Arthritis in a Patient with End-Stage Renal Disease. Ann Case Report. 7: 1021. DOI: 10.29011/2574-7754.101021

Received Date: 28 October 2022; **Accepted Date**: 02 November 2022; **Published Date**: 04 November 2022

Abstract

Severe arthropathy can occur in patients with end-stage renal disease (ESRD) receiving hemodialysis. While the general work up for arthritis includes makers of inflammation, serologies and respective joint imaging, for patients with ESRD, it is important to consider arthritis caused by deposition of uremic toxins such as beta-2 microglobulin causing amyloidosis or secondary hyperparathyroidism. We present a unique case of a patient with ESRD who developed a severe, progressive polyarthritis shortly after starting hemodialysis. This prompted a work-up that confirmed the diagnosis of amyloidosis. Arthritis in ESRD requires a careful work-up to establish the underlying etiology that will direct the most effective treatment.

Keywords: Arthritis; End-stage renal failure; Amyloidosis

Introduction

Amyloidosis is a rare condition caused by deposition of fibrils causing numerous systemic manifestations including inflammatory arthritis and organ damage to the kidney, heart, nervous system and gastrointestinal tract. The severity depends on the organs affected and how much amyloid has accumulated. The actual deposition of amyloid fibrils in the synovium of joints is rarely reported [1]. In this case report, we describe a 61-year-old man with end-stage renal failure, presenting with severe arthralgia's and synovitis manifest as localized soft tissue swelling causing marked reduction in use of his hands, shoulders and knees. Inflammatory work-up was negative hence; a synovial biopsy was done which confirmed amyloidosis. Given that he was receiving hemodialysis and met the criteria for the diagnosis of dialysis related amyloidosis, an attempt was made to treat with intensive dialysis and anti-inflammatory agents with poor response. The amyloid biopsy was sent for mass spectrometry, which confirmed the diagnosis of AL amyloid. Although AL amyloidosis is a rare condition, it should be considered while evaluating atypical symptoms in patients presenting with rheumatic complaints. A high index of suspicion is necessary for proper diagnosis, as delay in diagnosis will yield a worse treatment outcome.

Case Presentation

RJ is a 61-year-old male with a history of alcohol and smoking abuse, ESRD secondary to HTN who started dialysis in March of 2018 using a right internal jugular perm-cath. Symptoms of carpal tunnel syndrome (CTS) as manifested by sharp pain in both hands relieved by running them under warm water or dependent position began in December 2018. The hand pain became worse after he had a left upper extremity arteriovenous graft placed with Doppler evaluation showing no evidence of vascular steal. In 2019, he developed olecranon bursitis and worsened CTS requiring bilateral carpal tunnel release.

He established care with rheumatology in 2020 for "*arthralgia*." He complained of "pain all over" mostly in the ankles, bilateral knees, wrists and shoulders. Symptomatically, the joint symptoms were associated with swelling but reported to improve with rest without any predominance of symptoms in the morning hours. Patient denied any extra-articular symptoms

concerning for a systemic rheumatic disease including rashes, sicca, nasal or oral ulcers, upper respiratory symptoms, pleurisy, etc. Initial differential included mechanical joint symptoms from past trauma associated with his work in construction when patient hurt his ankles and hands.

On physical exam RJ is an elderly man, who looks much older than his stated age. At his initial presentation, he had no malar rash, skin ulcerations, nasal or oral ulcerations, pharyngeal exudates or lymphadenopathy. Patient's skin examination raised concern for slight skin thickening with darkening but otherwise, his exam was positive for synovial thickening at bilateral wrists with tenderness to palpation (Figure 1a) and joint effusion identified on ultrasound (Figure 1b). Both knees were tender to palpation and limited flexion due to pain and effusion. Other upper and lower extremities were without increased warmth, swelling or signs of effusion. Given the aforementioned symptoms of polyarticular joint swelling and physical examination as well as ultrasound findings showing joint inflammation, the differential diagnoses included various rheumatic diseases such as rheumatoid arthritis and seronegative spondyloarthropathy among others. Scleroderma was also considered given findings of skin thickening.

Figure 1: Left wrist

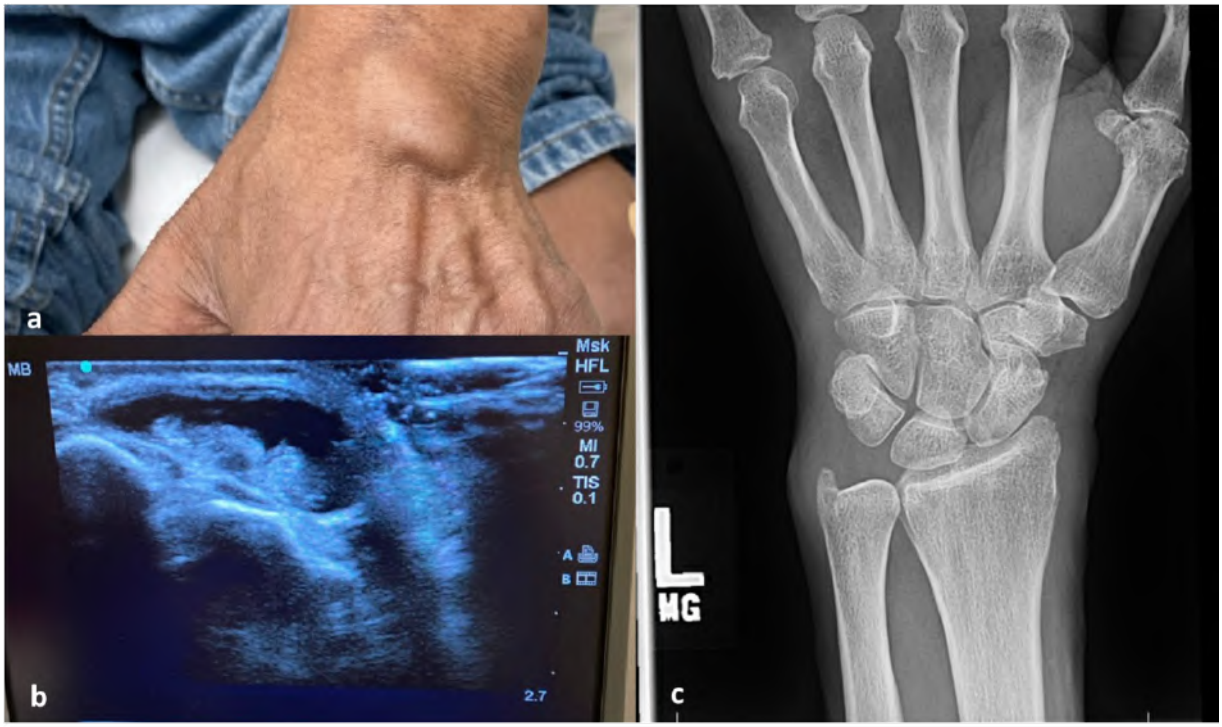

Figure 1: **1a**: Physical exam of the left upper extremity reflecting inflammation and fluid on dorsum of left wrist. **1b**: Bedside ultrasound images demonstrating hypoechogenicity at dorsum of the wrist on longitudinal 2D scan. **1c**: X-ray of left wrist with note of small round lucencies in the distal radius, distal ulna and carpal bones that reflect bony cysts or erosions. First metacarpal with small lucencies indicating cysts or erosions. There is a marginal erosion at first metacarpal head and potential small erosion along the medial base of the fourth and fifth proximal phalanges raising concern for erosive arthritis.

Results

Serological evaluation included rheumatoid factors, CCP, ANA, scleroderma 70 antibody, anti-centromere antibody, SSA and SSB antibody, which were all negative. Infectious work up was negative for hepatitis, GC/Chlamydia, HIV, TB, CMV, EBV. SPEP/UPEP showed monoclonal free kappa present in the gamma globulin region with concentration of 0.15 mg/dL and immunoglobulin A at 0.47 mg/dL with immunoglobulin G and M within range. ESR was 61mm/Hr and CRP was 39 mg/dl. CBC showed a normocytic anemia, creatinine was elevated and estimated GFR was low as expected with ESRD. PTH was drawn monthly and ranged from 111-320 pg/mL, phosphorus 5.2 mg/dl and corrected calcium of 9.9 mg/dl (Table 1).

X-Rays were ordered of the hand, wrist, knee which suggested inflammatory arthropathy. X-ray of the wrists showed multiple bony cysts, metacarpophalangeal erosions and periosteal reactions along the metatarsal diaphysis bilaterally that developed over 1.5 years (Figure 2a). MRI showed severe tenosynovitis bilaterally in the wrists (Figure 2b).

Figure 2: MRI with and without contrast of the left wrist

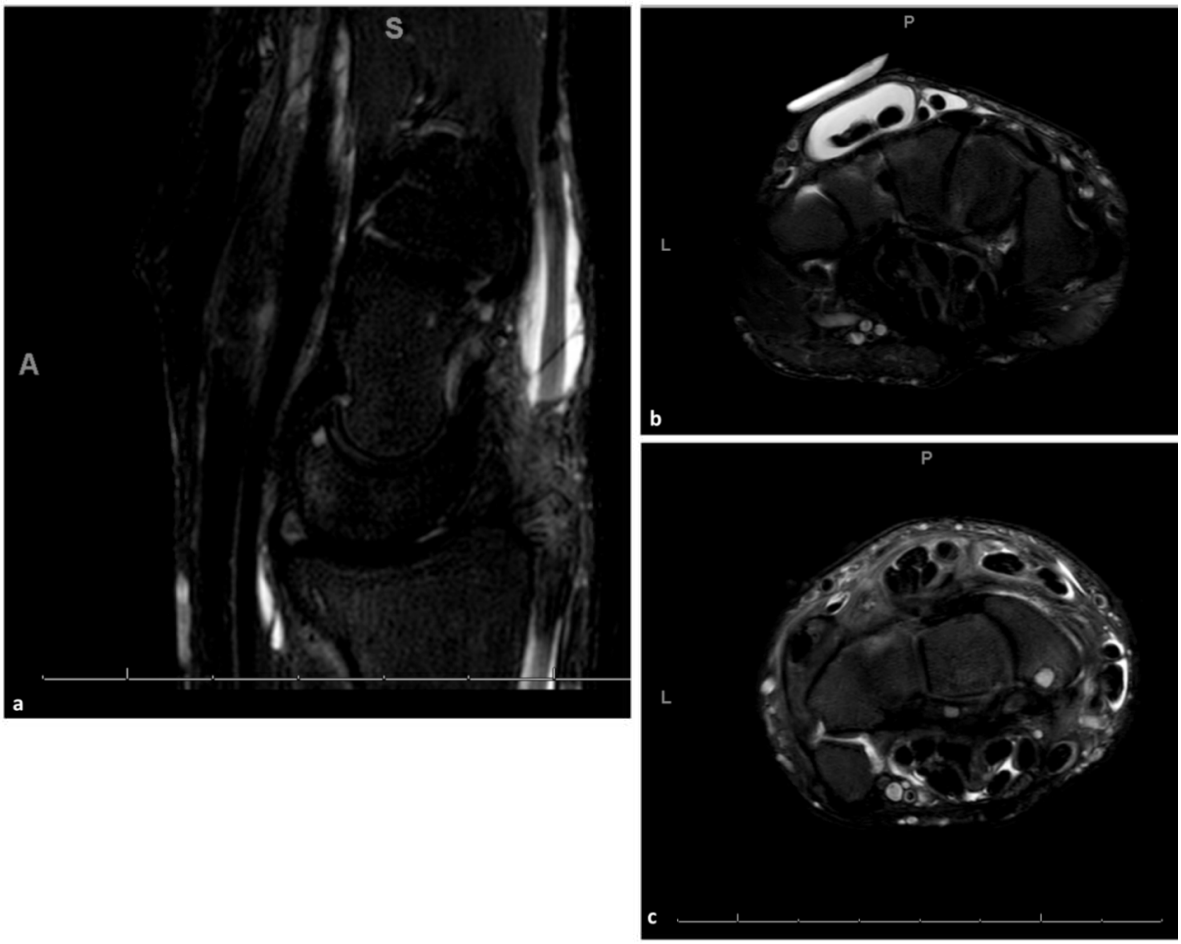

Figure 2: MRI with and without contrast of the left wrist demonstrating tenosynovitis, most severely affecting the extensor digitorum longus tendons on sagittal view (hyperintensity seen in panel a) but also impacting flexor digitorum longus and flexor pollicis longus tendons as demonstrated by the circumferential fluid within the tendon sheaths on axial view (panel b). Rounded foci of hyperintense signal on the fluid sensitive sequence (panel c) within the distal radius, scaphoid, and lunate likely reflect bony cysts. This is fluid around the radioulnar and ulnotriquetral recess which does not enhance and is consistent with amyloid deposition.

Aspiration of the synovial fluid in the right and left wrist showed 178/uL WBC and 1013/uL WBC respectively with macrophage and neutrophils predominance, no organisms or crystals seen. Knee arthrocentesis also showed 1000/uL WBC predominance with macrophages and neutrophils predominance.

In June 2021, the patient had a biopsy of a left dorsal extensor mass from the wrist that was positive for amyloid deposition in a background of synovial fluid and Congo red staining was positive. B2M level was elevated at 14.6 mg/dl. The specimen was sent for amyloid typing by liquid chromatography tandem mass spectrometry (LC MS/MS) which detected a peptide profile consistent with AL (kappa)-type amyloid. A bone marrow biopsy was done which showed plasma cell neoplasm with 12-15 kappa light chain restricted, CD19- CD56+, plasma cells involving normocellular marrow (10-20% cellular). Plasma IgG, IgA and IgM were low and free kappa light chains and ratio was elevated (Table1).

A transthoracic echocardiogram showed normal left ventricular performance and was negative for restrictive pericarditis with no speckled pattern. A skeletal survey of the spine and upper and lower extremities showed no discrete myelomatous lesions. An abdominal wall fat pad biopsy was negative for Congo red.

Variable	Reference Range, Adults	Patient Value
	This hospital *	
Hemoglobin (g/dl)	13.5-17.5	11.6
Hematocrit (%)	41-53	36.3
White-cell count (per mm^3)	3.5-11.0	8.6
Platelet count (per mm^3)	150-450	287
Urea nitrogen (mg/dl)	Jul-20	72
eGFR(ml/min)	>59	7
Calcium (mg/dl)	8.4-10.2	8.8
Phosphorus (mg/dl)	2.5-4.4	4.8
PTH (pg/mL)	15-75	111
SCL-70 AB	< 1.0	< 0.2
Anti-centromere antibody	< 1.0	< 0.2
Rheumatoid factor	<14	< 10
CCP (U/mL)	< 1.0	< 0.5
ANA	<1:80	<1
SSA AB	< 1.0	< 0.2
SSB AB	< 1.0	< 0.2
IgG (mg/dl)	800-1700	524
IgA (mg/dl)	100-490	44
IgM (mg/dl)	50-320	14
Kappa free light chain (mg/dl)	0.3300-1.94	272
Lambda free light chain (mg/dl)	0.5700-263	2.53
Kappa/Lambda ratio	0.2600-1.65	108
*Reference range for adults from the University of Chicago Hospital.		

Table 1: Laboratory Data.

Treatment Plan

After evaluation by Rheumatology, the prevailing diagnosis was dialysis-related amyloidosis (DRA) given characteristic triad of scapulohumeral arthritis, CTS and flexor tenosynovitis of the hand and rapidly enlarging bone cysts. The patient had an evaluation from Hematology/Oncology and initially there was low suspicion of primary amyloidosis given patient's preliminary cancer screening work up had been negative. There was minimal evidence of other forms of amyloidosis, specifically AL amyloidosis, with the exception of a slight increase in a serum kappa light chain (0.15 g/dL), which can also be seen in the setting of DRA [2]. The patient was started on a systemic corticosteroid course along with intra-articular steroid injections for certain medium and large joints. However, the patient experienced only temporary relief and had recurrence of joint pain and swelling soon after the corticosteroid taper. Methotrexate was avoided given the history of ESRD and the patient was started a course of leflunomide as a steroid-sparing agent along with doxycycline 100 mg twice a day based on evidence that it can alleviate joint pain from DRA [3]. The patient received hemodialysis three times a week with excellent urea clearance and a Kt/V of over 1.2 on a high efficacy, flux dialyzer. After one month of doxycycline 100 mg BID, leflunomide 10

mg and prednisone 5 mg, symptoms improved slightly from severe (rated 10/10) to moderate (rated 6/10). Due to ongoing swelling and pain most noted in the left knee with an exam consistent with tenosynovitis and synovitis, treatment with adalimumab was started [4]. Given the poor response to aggressive anti-inflammatory agents, the biopsy specimen was sent for LC MS/MS with findings of ALkappa-type amyloid deposits. A bone marrow was done which was confirmed multiple myeloma and the patient was started on chemotherapy (daratumumab-cyclophosphamide, bortezomib and dexamethasone (Dar-CyBorDex) [5].

Discussion

Amyloidosis can have multi-organ involvement with varied presentations in different patients, making efficient diagnosis often difficult. Currently 36 different insoluble proteins are recognized to have amyloidogenic potential and it is important to identify the protein as it directs treatment options [6]. In the past, little effective treatment could be offered to amyloidosis patients. Consequently, relying on characteristic clinical findings of the different amyloid types was often sufficient for supportive patient management [6]. However, more selective therapies have evolved rapidly and accurate determination of the amyloid protein type has become mandatory [6]. As exemplified by the case we presented, the most commonly recognized amyloid type is systemic AL amyloidosis due to deposition of immunoglobulin light chains produced by a bone marrow–based monotypic plasma cell population. Primary AL amyloidosis most commonly affects the heart, kidney, liver nervous system and GI tract . This disease requires systemic chemotherapy directed at the bone marrow plasma cells, which the patient is now receiving with a future option of a stem cell transplantation pending his response.

Inflammatory polyarthritis is a rare manifestation of AL amyloidosis but can occur mimicking primary rheumatic diseases such as rheumatoid arthritis or seronegative spondyloarthropathy [7]. A careful clinical exam including symptom onset, joint involvement and symmetry along with serologic, tissue and imaging studies should be done. Radiographic signs of amyloid arthropathies are often absent or nonspecific [8]. When they exist, the findings are diverse and may include bone erosions and cysts, bone demineralization, or thickening of the soft tissues [9].

Dialysis-related amyloidosis (DRA) is a serious complication of long term dialysis therapy and a debilitating disease characterized by the deposition of amyloid fibrils of Beta-2 microglobulins (B2M) in the bone, osteoarticular structures and viscera of patients [10]. B2M are normally cleared by glomerular filtration with reabsorption and catabolism in the proximal tubules [11]. Consequently, B2M is inversely related to glomerular filtration rate (GFR) and residual renal function is the best determinant of B2M levels [12]. For this reason, one of the therapeutic goals in treatment of patients with chronic kidney disease is to maintain the GFR as long as possible. For patients who develop end-stage renal disease (ESRD), microglobulins accumulate in the plasma and may result in slow but extensive tissue deposition with resultant arthropathy with synovial thickening [13]. B2M levels can increase up to 60-fold in patients on dialysis [14]. However, it has been demonstrated that high plasma B2M level is not a reliable predictive marker of DRA [15] and tissue biopsy of the affected areas remains the gold standard for the diagnosis [14]. Despite some guidance regarding diagnostic tools for DRA, the pathologic triggering events that causes DRA remain in question. Pathogenicity has been attributed to several factors including inadequate clearance by high flux dialyzers, intradialytic B2M production, advanced glycation end products and elevated levels of cytokines [16]. Common clinical symptoms and findings are carpal tunnel syndrome (CTS), bone cysts, scapula-humeral periarthritis, peripheral joint arthropathy, and destructive spondyloarthropathy similar to symptoms on the case presented [17-19]. In regard to incidence, postmortem studies have showed 21% of patient develop amyloid deposition <2 years after starting on dialysis, 50% in 4-7 years post-dialysis initiation, and up to 100% in >13 years [19]. European studies have suggested that DRA can be seen in as many as 20% of patients after 2-4 years on dialysis [14]. The criteria for the diagnosis of DRA includes at least two or more major findings of: multiple joint involvement, carpel tunnel syndrome, trigger finger, spinal lesions and bone cysts [17]. While DRA was considered in the differential for amyloidosis and the patient met the criteria, the diagnosis was excluded as the LC MS/MS did not detect the B2M peptide [6].

In summary, amyloidosis is a rare, complex disease, which requires a high index of suspicion for diagnosis. Technical advances have developed mass spectroscopy based proteomics to identify the amyloid fibrils implicated in the disease process. As amyloid disease continues to have a toll on the quality of life, we need to utilize these diagnostic methods to make a timely diagnosis and prevent further disease. Finally, given the rarity of this disease, to best identify the underlying biologic pathways, collaborative efforts across institutions will be necessary.

References

1. Glenne G (1980) Amyloid deposits and amyloidosis: the beta-fibrilloses (first of two parts). N Engl J Med 302: 1283-1292.

2. Koch KM (1992) Dialysis-related amyloidosis. Kidney Int 41:1416-1429.

3. Piccoli GB, Hachemi M, Molfino I, et al (2017) Doxycycline treatment in dialysis related amyloidosis: discrepancy between antalgic effect and inflammation, studied with FDG-positron emission tomography: a case report. BMC Nephrol 18: 285.

4. van de Putte LBA, Atkins C, Malaise M, et al (2004) Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 63:508-516.

5. Palladini G, Kastritis E, Maurer MS, et al (2020) Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood; 136:71-80.

6. Dasari S, Theis JD, Vrana JA, et al. (2020) Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples. Mayo Clin Proc. 95: 1852-1864.

7. Alpay-Kanıtez N, Çelik S, Bes C (2018) Polyarthritis and its differential diagnosis. Eur J Rheumatol 1:167-173.

8. Majumder MSM, Ahmed S, Shazzad MN, et al. (2021) AL amyloidosis presenting as inflammatory polyarthritis: a case report. Mod Rheumatol Case Rep 5: 391-398.

9. Georgiades CS, Neyman EG, Barish MA et al. (2000) Amyloidosis. A Review and CT Manifestations. Radiographics 24: 405-416.

10. Eiichiro Kanda, Daniel Muenz, Brian Bieber, et al. (2021) Beta-2 microglobulin and all-cause mortality in the era of high-flux hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study. Clinical Kidney Journal 14: 14361-1442.

11. Winchester JF, Salsberg JA, Levin NW (2002) Beta-2 microglobulin in ESRD: an in-depth review. Adv Ren Replace Ther 10:279-309.

12. Sedighi O, Abediankenari S, Omranifar B (2019) Association between plasma Beta-2 microglobulin level and cardiac performance in patients with chronic kidney disease. Nephrourol Mon 7: doi: 10.5812/numonthly.23563.

13. Fenves AZ, Emmett M, White MG, et al. (1986) Carpal tunnel syndrome with cystic bone lesions secondary to amyloidosis in chronic hemodialysis patients. Am J Kidney Dis 7: 130-4.

14. Scarpioni R, Ricardi M, Albertazzi V, et al. (2016) Dialysis-related amyloidosis: challenges and solutions. Int J Nephrol Renovasc Dis 9: 319-328.

15. Argyropoulos CP, Chen SS, Ng Y-H, et al. (2017) Rediscovering Beta-2 Microglobulin As a Biomarker across the Spectrum of Kidney Diseases. Front Med 4: 73.

16. Laura M. Dember (2006) Amyloidosis-Associated Kidney Disease. J Am Soc Nephrol 17: 3458-3471.

17. Nishi, S., Yamamoto, S., Hoshino, J. et al. (2019) The features of bone articular lesions in dialysis-related amyloidosis (DRA) and criteria for the clinical diagnosis of DRA. Ren Replace Ther 5.

18. Kopeć J, Gadek A, Drozdz M, et al. (2011) Carpal tunnel syndrome in hemodialysis patients as a dialysis-related amyloidosis manifestation--incidence, risk factors and results of surgical treatment. Med Sci Monit 17:CR505-CR509.

19. Ignacio Portales-Castillo, Jerry Yee, Hiroshi Tanaka, et al. (2020) Beta-2 Microglobulin Amyloidosis: Past, Present, and Future. Kidney360 1: 1447-1455.