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Case Report
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De Novo AL Amyloidosis in Renal Allograft and Anti-CD38 Monoclonal Antibody Treatment

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Systemic light chain (AL) amyloidosis is characterized by amyloidogenic immunoglobulin light chain (LC) secretion by a usually small clone of plasma cells.[1] Amyloid deposition disrupts normal tissue architecture leading to progressive organ failure. Renal involvement is common, seen in 50%–70% of patients and manifests with nephrotic range proteinuria or nephrotic syndrome. Although recurrence in a renal allograft is a well-described complication of AL amyloidosis, development of de novo AL amyloidosis in renal allografts is rare, and only a few cases are reported.[2,3] In addition, management of the disease in such cases may be challenging due to the concomitant use of immunosuppressive therapies, risk of graft rejection, and increased risk of complications. We hereby present the case of a patient diagnosed with de novo AL amyloidosis in his renal allograft, managed with an anti-CD38 monoclonal antibody-based therapy and who achieved minimal residual disease (MRD) negativity as assessed by next generation flow (NGF) cytometry.[4]

A 70-year-old man was referred to our clinic to be evaluated for monoclonal paraproteinemia, which was first detected in 2014, and gradual development of proteinuria since 2017. He had undergone 2 renal transplants, the first in 1988 from a cadaveric donor and the second in July 2007 from a living donor. The primary underlying renal disease was unknown. He also reported atrial fibrillation and arterial hypertension. He underwent a graft biopsy, which was consistent with AL amyloidosis.

Arterioles and interlobular arteries showed mild to moderate thickening due to deposition of amorphous eosinophilic material stained orange/red with Congo red stain and apple-green birefringence under polarized light, consistent with amyloid. Immunofluorescence was positive for lambda LC (3+) in the vessel walls of arterioles and interlobular arteries. The above findings were consistent with amyloidosis, with segmental amyloid deposits, especially in the vessel walls, AL subtype.

At the time of diagnosis, the patient was on mycophenolate mofetil 750 mg once daily (OD), everolimus 1 mg twice daily, fosinopril 10 mg OD, carvedilol, and apixaban. At initial assessment (Table 1), serum creatinine was 1.0 mg/dL, urea 52 mg/dL, albumin 4.2 g/dL, calcium 9.1 mg/dL, and total urine protein 1722 mg/24 hours with a pattern of albuminuria in urine electrophoresis. Serum immunofixation showed a faint monoclonal IgGλ and the free light chain (FLC) assay revealed abnormal κ (38.20 mg/L) and lambda free light chain (λLC) (56.1 mg/L) but a normal κ/λ ratio (0.68); urine immunofixation was positive for λLC.

Cardiac troponin-T levels were low (<0.05 ng/mL) but N-terminal pro-B-type natriuretic peptide (NT-proBNP) was increased (1566 pg/mL—stage II Mayo). Cardiac echocardiogram did not reveal cardiac wall thickening, there was grade I diastolic dysfunction with preserved left ventricle ejection fraction. No symptoms of peripheral/autonomic neuropathy or orthostasis were reported (blood pressure in sitting position was 128/82 mm Hg), and there was no evidence of soft tissue or gastrointestinal involvement. Whole-body computerized tomography scan did not show organomegaly or bone lesions. The patient was New York Heart Association stage II, and Eastern Cooperative Oncology Group Performance status performance status was 1. A bone marrow biopsy showed 12%–15% monoclonal λLC, CD56+ plasma cell infiltration. NGF detected an abnormal λLC restricted clone. Bone marrow fluorescent in situ hybridization studies did not demonstrate cytogenetic abnormalities.

Treatment with intravenous daratumumab (16 mg/kg weekly cycles 1–2, every 2 wk cycles 4–6), weekly IV cyclophosphamide 500 mg, sc bortezomib 1.3 mg/m^2, and dexamethasone 24 mg, based on the initial data from the ANDROMEDA study, was initiated (Dara-CyBorD).[5] He received prophylaxis with trimethoprim/sulfamethoxazole and valacyclovir. Bortezomib was discontinued after 3 cycles, after sequential dose reductions, due to orthostatic hypotension, peripheral neuropathy, and fatigue. He received a total of 6 cycles of therapy (the 3 last cycles contained only daratumumab). Maintenance immunosuppression (mycophenolate mofetil and everolimus) was ceased, but he received 8 mg of methylprednisolone daily. There were no infectious complications.

The absolute value of the involved FLC normalized after the first cycle of therapy and serum and urine immunofixation became negative after 4 cycles. After the completion of 6 cycles, bone marrow assessment with NGF showed absence of MRD (sensitivity 10^{-5}). A renal response was achieved post the fourth treatment cycle (≥30% decrease in total 24-h urine

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Table 1

Laboratory Assessments During Treatment and Follow-up.

Laboratory Assessments	February 2019 Baseline	May 2019 C2	June 2019 C3	July 2019 C4	August 2019 C5	October 2019 EOT	January 2020 Follow-up	June 2020 Follow-up	October 2020 Follow-up	March 2021 Follow-up
Total urine protein (g/24 h)	9.6	6.8		4.1		3.8	2.6	3.5	2.1	0.718
Serum Cr (mg/dL)	1.0	1.22	1.03	0.86	0.88	0.97	0.96	1.13	1.0	1.13
eGFR (mL/min/1.73 m^2)	78.52	62.42	75.88	93.44	91	81.32	82.3	67.9	78.29	67.8
κLC (mg/L) (3.3–19.4)	38.2	12.0	24.0	21.2	19.3	17.61	27.5	34.6	29.3	19.8
λLC (mg/L) (5.71–26.3)	56.1	8.09	15.8	11.4	12.6	10.3	16.4	18.9	19.0	16.5
κ/λ (0.26–1.65)	0.68	1.48	1.52	1.86	1.53	1.71	1.68	1.83	1.54	1.20
dFLC	18.1	N/E	N/E	N/E	N/E	N/E	N/E	N/E	N/E	
Serum IFx	IgGλ	IgGλ	IgGλ	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Urine IFx	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
NGF clone detection—MRD	+					(–)				
NT-proBNP (pg/mL)	2192	1566	2183	1664	2652	1488		1976	1722	1320

Cr = creatinine; dFLC = difference between involved and uninvolved free light chain; eGFR = estimated glomerular filtration rate; EOT = end of treatment; IFx = immunofixation; MRD = minimal residual disease; N/E = non evaluable; NGF = next generation flow for the assessment of minimal residual disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide; κLC = kappa serum free light chain; λLC = lambda free light chain.

protein, without decline in estimated glomerular filtration rate), which has been sustained; at the time of last follow-up, proteinuria was ~0.7 g/24 h.[6] Regarding cardiac response, a reduction of NT-proBNP was observed, which reached at times a >30% decline. Clinically the patient has mild residual peripheral neuropathy, his functional status has improved slightly with no symptoms of orthostatic hypotension. He remains in complete response (CR) 18 months following therapy completion (Fig. 1).[7]

Recurrence of AL amyloidosis in the renal allograft is a well-documented complication, but de novo amyloidosis in the renal allograft following renal transplantation after nonamyloidosis-related end-stage renal disease is highly unusual. Most cases in the literature concern secondary (AA) amyloidosis in the context of ongoing active chronic inflammatory/autoimmune disorders. There are very few cases of 4 patients with de novo AL amyloidosis in their renal allografts in the literature.[2,3] The original renal pathology varies, as does the type of allograft received and the timing at which AL amyloidosis developed post-transplant. Treatment administered includes bortezomib, corticosteroids, melphalan, and autologous stem cell transplant.

The second important point of the case that we present here is the use of anti-CD38-based therapy (daratumumab) in a setting of immunosuppression but also of the urgent need to salvage the renal graft and prevent the potential complications of cardiac amyloidosis. Our choice of therapy was based on the need for rapid and deep hematologic response, avoiding potential toxicity to the renal graft.[8] At the time of treatment initiation, the results of the ANDROMEDA study had not been available; however, the initial data indicated that his combination could be extremely effective and rapidly acting.[5] Dara-CyBorD has become recently the first Food and Drug Administration-approved therapy for AL amyloidosis; the addition of sc Daratumumab to CyBorD increased the rate of hematologic responses with no additional safety signals.[9]

The case presented points out some very important diagnostic issues in the management of patients with AL amyloidosis. To set the diagnosis, it is necessary to detect the circulating

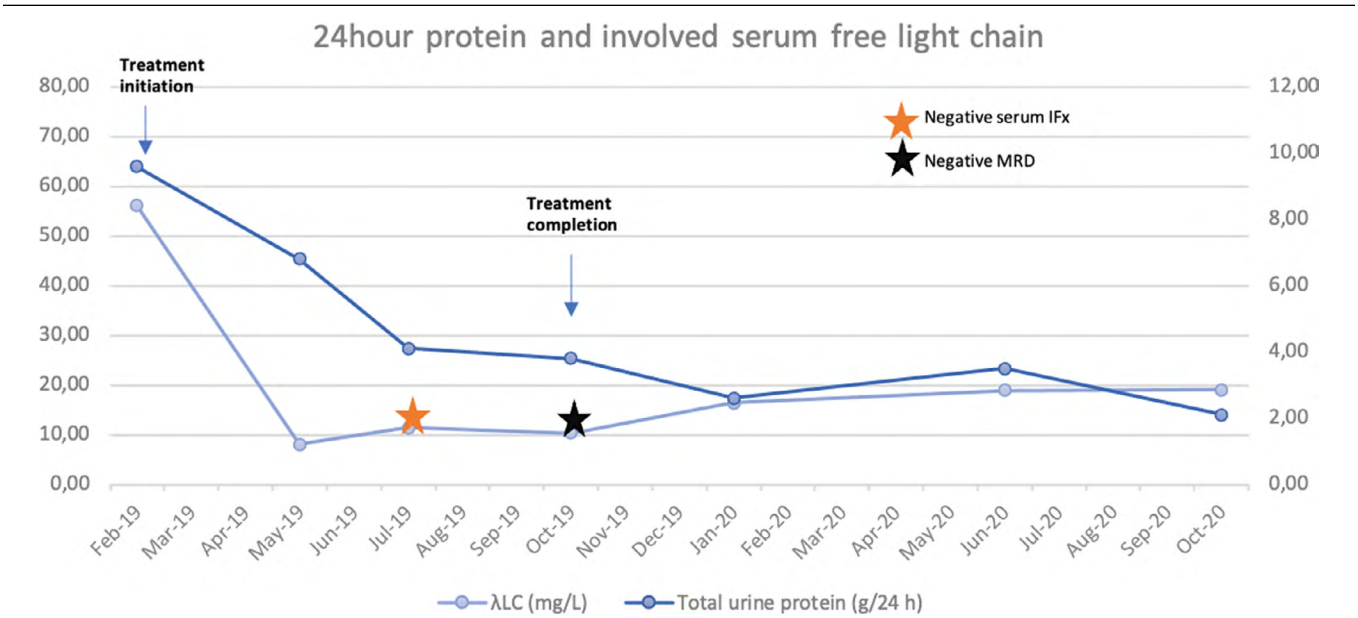

Figure 1. Graphical illustration of laboratory assessments during the treatment course. IFx = immunofixation; MRD = minimal residual disease; λLC = lambda free light chain.

plasma cell clone however small this may be and to identify and type correctly the amyloid deposits in target tissues. Amyloid typing requires adequate technology; specialized centers utilize currently immunohistochemistry with custom-made antibodies, immunoelectron microscopy or mass spectrometry that is antibody independent.[10] When there is high degree of clinical suspicion and urine and serum immunofixation are negative, FLC ratio and absolute levels normal and bone marrow biopsy negative, NGF or next generation sequencing should be used to rule out the presence of a small plasma cell clone.

In addition, the assessment of hematological response in patients with low baseline FLC is complicated; very good partial response cannot be assessed (baseline difference between involved and uninvolved free light chain might be less than 40 g/dL prior to treatment initiation), and CR requires a normal FLC ratio that can be skewed by discordant suppression of LC levels. Indeed our patient achieved CR, with undetectable MRD at a level of $<10^{-5}$. MRD assessment by NGF has been introduced in the management of AL amyloidosis in recent years. Recent data demonstrated the association between MRD negative CR and more rapid and sustained organ responses.[11] The MRD status of AL amyloidosis patients following treatment completion can be used to tailor the therapeutic approach and also as surrogate endpoint in clinical trials.

Regarding the safety of therapy, bortezomib has been well tolerated in patients with renal allografts and can at times be effective in cases of humoral rejection.[12] Our patient developed the well-known complications of neurotoxicity and fatigue, leading to early discontinuation. The experience with daratumumab in patients with solid organ transplantations is however limited. Daratumumab targets CD38 and causes plasma cell depletion.[13] There is a theoretical concern that there is also CD38+ T-reg depletion, leading to the activation of cytotoxic CD-8+ T-cells.[14] T-cell clonal expansion and clonal drift, with renewal of the pretreatment T-cell receptor clonotype repertoire, may cause expansion of low-frequency pretreatment T-cell clones that could pose a risk for the renal allograft.[15] Specific recommendations for modifications of immunosuppression in kidney transplant recipients with plasma cell disorders do not exist. Reduction or discontinuation of maintenance immunosuppression is the common practice in an effort to achieve disease regression and reduce infectious complications. A multidisciplinary approach is always mandatory. In our case, the decision to stop maintenance therapy was based on the low risk of graft rejection and the myelosuppressive effects of the long-term use of immunosuppressives particularly when combined with chemotherapeutic agents like cyclophosphamide.

Of course, more data are needed, and a single case cannot provide proof of safety. Our experience with other patients with renal allografts who have received daratumumab is also positive, with no concerns regarding renal graft rejection. Daratumumab has also been shown to be effective in the treatment of chronic active antibody-mediated kidney allograft rejection.[16]

In conclusion, we described a rare case of de novo AL amyloidosis in a renal allograft recipient, treated with the most contemporary regimen. Our experience supports the efficacy, but most importantly, the safety of this therapy and especially daratumumab in patients with renal allografts.

Patient consent statement

Informed consent has been obtained from the patient. Written and signed document can be provided if required.

Disclosures

EK received honoraria from Amgen, Genesis Pharma, Janssen, Takeda, and Pfizer; he received research funding from Amgen and Janssen. All the other authors have no conflicts of interest to disclose.

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