frontiers | Frontiers in Hematology

TYPE Case Report
PUBLISHED 11 October 2022
DOI 10.3389/frhem.2022.997262

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Blood Cancer, a section of the journal Frontiers in Hematology

RECEIVED 18 July 2022
ACCEPTED 26 August 2022
PUBLISHED 11 October 2022

CITATION
Puertas B, Rey-Búa B, Eiros R, Martín-Arribas A, Montero-Mateos E, Hernández-Sánchez A, Gómez-Úbeda S, Alejo-Alonso E, Martín-López AA, Antúnez P, Villacorta-Argüelles E, Gallego-Delgado M, Puig N, Mateos M-V and González-Calle V (2022) Case Report: Renal relapse after heart transplantation, induction, and autologous stem cell transplantation in a patient with AL amyloidosis with exclusive cardiac involvement.
Front. Hematol. 1:997262.
doi: 10.3389/frhem.2022.997262

Case Report: Renal relapse after heart transplantation, induction, and autologous stem cell transplantation in a patient with AL amyloidosis with exclusive cardiac involvement

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There is no recommendation on what salvage therapy is optimal in the solid organ recipient with AL amyloidosis, such as a heart transplant. With this case, we illustrate how treatment with daratumumab may be effective and safe in a patient with AL amyloidosis with renal involvement at the relapse after heart transplantation and autologous stem cell transplantation.

KEYWORDS

amyloidosis therapy, amyloidosis diagnosis, heart transplantation, autologous stem cell transplantation, daratumumab

10.3389/frhem.2022.997262

Introduction

AL amyloidosis is a systemic disease characterized by the tissue deposition of pathological light chain produced by a small clone of plasma cells (PC). The clinical features are heterogeneous and depend on the location and severity of organ involvement, with heart failure and nephrotic syndrome being common, with dismal outcomes when severe cardiac involvement is present (1). The therapy based on daratumumab, cyclophosphamide, bortezomib, and dexamethasone is the only treatment approved by the Food and Drug Administration and the European Medicines Agency for the first line of AL amyloidosis due to the results of phase III of the study Andromeda (2). The goal of therapy is achieving a fast and deep hematologic response because it is associated with organ response and overall survival. Although a high proportion of AL amyloidosis patients will relapse, there is no consensus for the treatment of relapsed/refractory cases, and this should be treated in the context of a clinical trial when possible (3). Furthermore, there are no existing data to recommend an optimal regimen for transplant recipient, such as heart transplant patients.

We herein describe the renal relapse of a patient with AL amyloidosis and exclusive heart involvement at diagnosis after induction, autologous stem cell transplantation, and heart transplantation. The patient was successfully treated with intravenous daratumumab in monotherapy.

Clinical case

A 49-year-old man without comorbidities was diagnosed with lambda AL amyloidosis in February 2016, with exclusive heart involvement stage IV of Mayo [2012 review Mayo Clinic criteria (4)] [NT-proBNP 7839 ng/L, cardiac troponin T 131 pg/ml, and serum lambda free light chains (sFLC) 1,254.6 mg/L] with high tumor burden and t(11;14) (15% of pathological PCs). Other biochemical diagnostic data were as follows: 24-h proteinuria of 0.12 g with immunofixation negative, creatinine clearance of 0.83 mg/dl, alkaline phosphatase of 208 IU/L, and serum albumin of 3.2 g/L. It is worth noting that the patient did not meet any of the CRAB criteria for active multiple myeloma.

Once the AL was diagnosed, the patient underwent a heart transplant because of cardiac function that could limit the antitumoral treatment and potential autologous stem cell transplantation (ASCT). Thereafter, at 6 weeks after the heart transplant, he received the regimen bortezomib, cyclophosphamide, and dexamethasone (as shown in Figure 1) and reached hematologic complete response (CR) with positive measurable residual disease (MRD) by next-generation flow and heart response. In this scenario, the watch-and-wait approach was observed.

At 3 years later, the patient presented asymptomatic non-nephrotic proteinuria (1.5 g/24 h) with negative immunofixation, with sFLC ratio and normal kidney function.

Considering the medical history of the patient, we proposed the differential diagnosis of three entities: transplant-associated microangiopathy favored by immunosuppression (tacrolimus), novo glomerulonephritis, or kidney relapse of AL amyloidosis. Microangiopathy was dismissed because of no evidence of hemolysis (bilirubin, lactate dehydrogenase, haptoglobin, and hemoglobin were normal) and no evidence of schistocytes in the blood smear. The proteinuria progressed in 1 month to nephrotic range (4.5 g/24 h), together with an increase of sFLC lambda from 40 to 80 mg/L and dFLC (difference between involved and uninvolved free light chain concentration) from 18 to 31 mg/L. Since kidney involvement was not documented at the moment of diagnosis of AL, a kidney biopsy was performed. A homogeneous, acellular, and amorphous substance was observed in hematoxylin–eosin-stained sections in the glomeruli, mesangium, and capillary walls, with green birefringence with Congo red stain (Supplementary Figure 1) and positive immunofluorescence for lambda, confirming lambda AL amyloid deposition. Heart graft involvement was ruled out (the cardiac magnetic resonance and cardiac biomarkers were normal); thus, an exclusive kidney relapse of lambda AL amyloidosis was confirmed, stage I (proteinuria <5 g/24 h and without kidney failure). Besides this, the persistence of a small clone with the same immunophenotypic pattern, as previously identified, was detected within the bone marrow (51% of pathological PCs within 0.09% of the total BM PC compartment).

Once relapse was confirmed, intravenous daratumumab was started according to the protocol of our center (90 min of infusion after two uneventful infusions). The response to treatment was fast, and hematological CR was achieved after the second cycle of daratumumab (Figure 2). Partial renal response was observed after 6 months of treatment, and complete renal response was documented subsequent to the 12th cycle [graded renal response published in 2021 American Society Hematology (5)]. In this situation, a bone marrow aspirate was performed, observing undetectable MRD (with sensibility of 10^{-5}) by next-generation flow. The therapy with daratumumab was discontinued after that, and close follow-up was established. Cardiac function was monitored by cardiologists together with the periodic monitoring of cardiac biomarkers and tacrolimus levels, which remained stable throughout the treatment. The regimen was well tolerated, the patient did not present any relevant adverse event, and he only had to discontinue daratumumab during 1 month because of mild SARS-CoV2 infection.

At the last follow-up, the patient continues with complete hematologic and renal response 12 months after daratumumab discontinuation, with an excellent quality of life, working actively, and treatment free.

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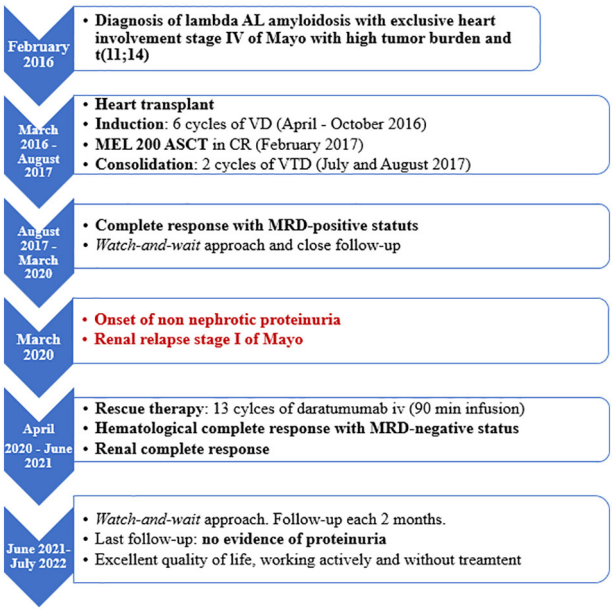

FIGURE 1
Cronopathology of the patient until the presentation of the case. VD, Bortezomid and dexamethasone; MEL, Melphalan; ASCT, Autologous stem cell transplantation; CR, complete response; VTD, Bortezomib, thalidomide and dexamethasone.

Discussion and conclusions

We present here a patient with AL amyloidosis who relapsed 3 years later after achieving CR with induction, ASCT, and consolidation treatment. Despite recent therapy advantages, AL amyloidosis is still an incurable disease. Indeed the Mayo Clinic (6) and the Pavia Amyloidosis Study group (7) have demonstrated that the presence of any residual plasma cell after treatment is associated with inferior progression-free survival, and this is the case of our patient, who had positive MRD after consolidation as well as severe cardiac involvement at diagnosis, another well-known prognosis factor (1).

It is worthy to mention that the relapse confirmation could have been delayed due to the absence of kidney involvement at baseline. To the best of our knowledge, there has not been any report in the literature of any case of R/R AL amyloidosis with

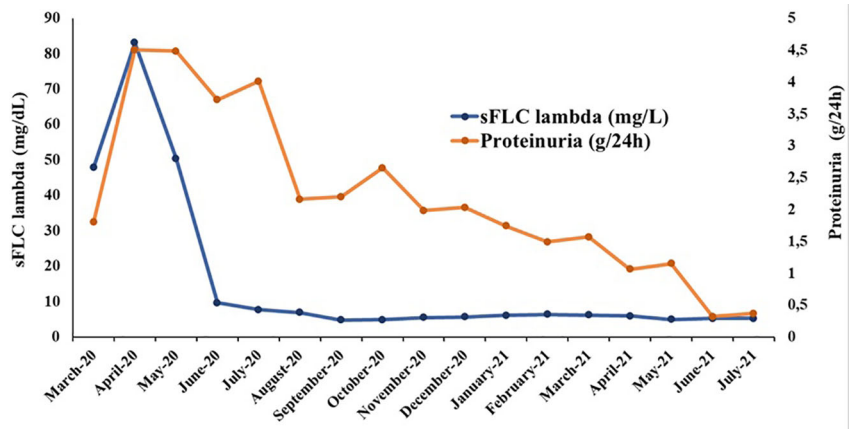

FIGURE 2
Biological evolution after daratumumab. sFLC, Serum free light chain.

involvement of a new organ not previously affected, the kidney in this case, and after heart transplant. We could not explain how amyloid did not affect heart graft at the moment of relapse. We hypothesize that the human leukocyte antigen donor had to play a role in the "capricious" disposition of amyloid.

In addition, there are some controversies regarding when to start the rescue treatment in R/R AL amyloidosis. On the one hand, it is known that a period exists between hematologic relapse and organ progression in AL amyloidosis patients. This period could be highly variable, as reported by a study from the Mayo Clinic (8). Therefore, treatment might be delayed (9). On the other hand, it had been demonstrated that a low concentration of pathological light chain is enough to feed the amyloid process and cause organ damage. In the present case, there was no question of restarting the treatment in a patient with AL amyloidosis with renal involvement and nephrotic-range proteinuria.

Furthermore, there is not any rescue therapy approved for the treatment of R/R AL amyloidosis, and the decision has to be guided by disease, patient, and treatment-related factors. In our patient, the increased risk of heart graft failure was the main concern for initiating an antitumoral therapy. Accordingly, the second line of treatment was subjected to a multidisciplinary committee composed of cardiologists, nephrologists, and hematologists. First, our patient was a heart transplant recipient with R/R AL amyloidosis; thus, an effective drug to rapidly prevent progressive organ damage related to amyloid deposits, together with an acceptable safety profile, was required. First of all, to avoid the risk of increasing graft failure, toxicity, and myelosuppression, especially with renal involvement, we discarded the immunomodulators used in the relapse setting, like lenalidomide or pomalidomide. With respect to disease-related factors, the presence of t(11;14) made us avoid retreatment with bortezomib-based regimens (10). In this scenario, the combination of venetoclax and dexamethasone plus/minus proteasome inhibitor could be a suitable treatment for this patient (11). However, limited experience with this scheme and its myelosuppressive profile were the reasons to avoid it. Finally, daratumumab emerged as a potential rescue treatment because it could cover both needs (2, 12–14). In the prospective phase II trial of Boston Medical Center (12), 86% of R/R AL amyloidosis patients achieved at least very good partial response (VGPR), the median time to initial response was 1 month, and renal response occurred in 67% of patients, with median time to initial organ response of 18 weeks. In the Spanish multicentric retrospective study published in 2020 (15), the overall hematologic response rate was 72%, and daratumumab yielded a ≥VGPR in 65% of patients. The organ response rates were also high, especially in patients with kidney involvement, with a very short time of response. This early renal response, not shown with other drugs, could be the consequence of a rapid hematologic response that was achieved after the first cycle in the reported series. The second reason for the use of daratumumab in monotherapy was because of its safe myelotoxic and tolerability profile, the main problems being the infusion-related adverse event (AE), which can be minimized with premedication of infusion, and mild respiratory tract infections. In the two phase 2 studies that evaluated the safety of daratumumab in R/R AL patients (12, 13), only one patient stopped the treatment due to severe AE, and grade 3 or 4 hematologic toxicities were not frequently reported. Finally, the third reason was the potential cardioprotective effect of daratumumab. Although the underlying physiopathology is not well known, CD38 expression mediates endothelial dysfunction induced by hypoxia–reoxygenation in the heart; so, the pharmacological inhibition of CD38 could exert a cardioprotective effect by reducing damage post-ischemia (16). Actually, in the prospective randomized phase 3 CANDOR study (17) comparing the regimen daratumumab, carfilzomib, and dexamethasone (DaraKd) *versus* carfilzomib and dexamethasone (Kd) in myeloma patients, a slightly lower rate of cardiac failure was documented in the DaraKd arm (7 *versus* 10%). In addition, recently, the data from a prospective study (16) was published, which suggests that daratumumab attenuates the cardiotoxic effect of carfilzomib. Some cases of steroid-refractory or steroid-dependent cardiac rejections that were successfully treated with daratumumab have also been reported (18). It is worth noting that the treatment with intravenous daratumumab was chosen instead of the subcutaneous formulation because the latter was not available in our institution at the moment of the relapse.

The optimal duration of therapy at relapse in AL amyloidosis also remains unclear yet. In the French Network for AL/Intergroup Francophone du Myélome trial (13), the duration of daratumumab was six cycles, 55% reached hematologic response, and cardiac and renal response, respectively, were obtained in 25 and 31% of cases. In the other phase 2 trial with daratumumab (12), where the patients received up to 24 cycles, 96% attained hematologic response, which was VGPR or better in 86% of patients, and cardiac and renal response, respectively, were observed in 50 and 67%. Based on the results of the trials, it could be argued that the longer the duration of daratumumab treatment, the better. However, these results may be interpreted with caution because these are indirect comparisons between studies, and in the last trial, there was no improved response after the third cycle of daratumumab.

In addition, the achievement of undetectable MRD is associated with a significantly better outcome and a very low risk of hematologic relapse (19). In the study of Kastritis *et al.* (19), hematologic relapse did not occur in MRD-negative patients, whereas 20% of MRD-positive patients had a documented hematologic progression. This prognostic value of MRD, added to the need to avoid toxicity and the state of sustained immunosuppression in a heart transplant patient, especially during the COVID-19 pandemic, finally supports our clinical decision to discontinue daratumumab after 1 year

of treatment. Thus, clinical trials to address the optimal duration of treatment at relapse in AL amyloidosis are needed. Until that moment, the integration of MRD assessment in the decision-making process could be of help, as this case illustrates.

In summary, we report here the treatment decision-making for a patient with AL amyloidosis at relapse with kidney involvement after a first line of therapy including heart transplantation, induction, autologous stem cell transplantation, and consolidation. The selection of the monoclonal antibody daratumumab was based on efficacy, safety, and trying to prevent heart rejection. The patient achieved complete hematological response and undetectable measurable disease as well as organ response.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

BP and VG-C wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

EV-A has received honoraria derived from lectures and participation in advisory boards from Takeda, Amicus Therapeutics, Novartis, and Ferrer. NP has received honoraria for consulting or advisory role from Amgen, Celgene, Janssen, Takeda, The Binding Site, GSK, and Sanofi. M-VM has received honoraria derived from lectures and advisory boards from Janssen, BMS-Celgene, Amgen, Takeda, Abbvie, Sanofi, Oncopeptides, Adaptive, Roche, Pfizer, Regeneron, GSK, Bluebird Bio, and Sea-Gen. VG-C has received honoraria from Janssen and Celgene and research funding from Janssen and has a consulting or advisory role for Prothena and Janssen. BP has received honoraria from Janssen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frhem.2022.997262/full#supplementary-material

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