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Impact of Autologous Stem Cell Transplantation on the Incidence and Outcome of Oligoclonal Bands in Patients with Light-Chain Amyloidosis

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The emergence of oligoclonal bands (OB) in patients with multiple myeloma achieving a complete remission (CR) after autologous stem cell transplantation (ASCT) and the use of novel agents is a well-recognized event. The presence of OB is associated with favorable outcome. However, the emergence of OB in light-chain (AL) amyloidosis has never been investigated. The aim of the study was to determine the incidence, natural history, and prognostic impact of OB in 50 patients with AL amyloidosis who achieved at least a partial response either after upfront ASCT (20 patients [40%]) or after conventional treatment in patients ineligible for transplantation (30 patients [60%]). OB were observed in 60% of the patients, with IgG-kappa (30.7%) the most frequently detected isotype. This phenomenon was more prevalent in patients achieving CR than those in other response categories (88% versus 32%, $P = .0001$). The landmark analysis at 1 year after diagnosis demonstrates a significantly longer progression-free survival and an improvement trend in overall survival ($P = .04$ and $P = .06$, respectively). This prognostic impact was also observed in patients who achieved CR and in patients with more advanced stage. In summary, this is the first report of OB in patients with AL amyloidosis. Although its biological meaning remains unclear, it could reflect a more robust humoral immune response.

INTRODUCTION

Systemic immunoglobulin light-chain amyloidosis (AL) is a rare plasma cell (PC) neoplasm, characterized by a clonal population of bone marrow (BM) PC that produces a monoclonal immunoglobulin (Ig) light chain, more frequently of the lambda isotype [1]. The amyloidogenic Ig light chains aggregate and deposit in tissue as amyloid fibrils with a predominant β-pleated sheet structure [2]. The clinical presentation is heterogeneous and its diagnosis requires a high index of suspicion. Amyloid deposition is demonstrated by Congo red staining using crossed polarized light on histological tissue sections. Fibrils can be typified by immunohistochemistry [3], immunoelectron microscopy [4], or mass spectrometry [5]. Prognosis depends on the organ involvement as well as the size and biology of the PC clone [6]. The treatment goal is to suppress the production of the fibril precursor protein by the underlying PC clone, while minimizing the treatment-related toxicity [7]. A good quality of hematologic response (very good partial response [VGPR] or better) is associated with an overall survival (OS) benefit [6].

By contrast, multiple myeloma (MM) is the most common PC neoplasm, characterized by the clonal proliferation of neoplastic PC with the subsequent production of a monoclonal Ig and development of symptoms due to the tumor burden [8]. Emergence of oligoclonal bands (OB), an oligoclonal humoral response different to the original monoclonal immunoglobulin observed at diagnosis by immunofixation (IFE), is a well-recognized event after autologous stem cell transplantation (ASCT) [9-11] and with the use of regimens incorporating novel drugs (bortezomib, thalidomide, and

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lenalidomide) [12,13]. The presence of OB after ASCT is considered a benign phenomenon attributed to a strong immune reconstitution [14,15]. This is apparently associated with greater tumor reduction, higher rate of complete response (CR), and better prognosis in terms of progression-free survival (PFS) and OS [9,11,12,16,17]. However, the frequency and clinical outcome after the emergence of OB in patients with AL amyloidosis who received or did not receive an ASCT have never been described.

The aim of the present study was to determine the incidence, natural history, and prognostic impact of OB in patients with AL amyloidosis achieved at least a partial response (PR) either after upfront ASCT or after conventional treatment in patients ineligible for stem cell transplantation at our institution.

MATERIALS AND METHODS

Patients

The clinical records of 74 newly diagnosed patients with AL amyloidosis at a single institution from January 2006 to December 2015 were reviewed. Those cases who achieved at least a PR after first-line therapy, either ASCT or conventional treatment in patients ineligible for transplantation, were included in the study. Twelve patients were excluded because of lack of hematological response, 9 because of early death, and 3 were lost to follow-up. Fifty patients (26 male, 24 female; median age, 60 years; range, 43 to 83) made up the final study population (Supplementary Figure S1). Initial baseline demographics, clinical, and laboratory data and information concerning treatment and follow-up were collected and are shown in Table 1. The median follow-up for alive patients was 3.3 years. Approval for the review of these records was obtained from the ethics committee of the Hospital Clínic of Barcelona and was in accordance with the Declaration of Helsinki.

Oligoclonal Bands Definition

We performed a retrospective and systematic review of serum and urine IFE studies. OB was defined as the presence of a serum and/or urine IFE monoclonal spike that was different from the original M-protein either in heavy and/or light chains or with a different IFE migration pattern. Response, relapse, and progression were defined according to the Consensus Opinion from the X International Symposium on Amyloid and Amyloidosis [18] but also including the recent consensus update that allows VGPR category definition [6]. IFE was performed every 3 to 6 months in patients throughout their follow-up.

Statistical Analysis

Baseline characteristics and differences among the subgroups of patients were analyzed by using Student's *t*-test for continuous variables and the chi-square test for categorical variables or nonparametric tests when required. Time-to-event analysis were performed by the Kaplan-Meier method and survival curves were compared using the log-rank test. PFS was defined as survival from a landmark-time of 1 year after diagnosis until hematological relapse or death from any cause. OS was calculated from the same landmark time to the date of death from any cause or the date of last follow-up [19,20]. All statistical test values were 2-sided, with statistical significance evaluated at the .05 alpha level. All analyses were performed using SPSS 20.0 for Windows.

Table 1
Patient Characteristics according to the Presence or Absence of OB

Variable	Baseline (n = 50)	Without OB (n = 20)	With OB (n = 30)	*P*
Age, years, median (range), yr	60 (43 - 83)	61 (43 - 82)	60 (49 - 83)	.92
Gender (m/f)	26/24	9/11	17/13	.42
Immunological subtype				.48
Light chain	29 (58)	10 (34.5)	19 (65.5)	
IgG	16 (32)	9 (56.2)	7 (43.8)	
IgA	3 (6)	1 (33.3)	2 (66.7)	
IgM	1 (2)	0 (0)	1 (100)	
Biclonal	1 (2)	0 (0)	1 (100)	
Light chain subtype				.27
Kappa	11 (22)	6 (54.5)	5 (45.5)	
Lambda	39 (78)	14 (35.9)	25 (64.1)	
PC clone, median (range)				
BM PC	12 (1 - 79)	13 (1 - 64)	11 (1-79)	.50
dFLC* (mg/L)	337 (0 - 7823)	390 (75 - 6792)	276 (0 - 7823)	.15
Organ involvement				
Heart	37 (74)	15 (40.5)	22 (59.5)	.90
Kidney	35 (70)	13 (37.1)	22 (62.9)	.53
Liver	8 (16)	3 (37.5)	5 (62.5)	.88
Gastrointestinal	12 (24)	5 (41.7)	7 (58.3)	.89
Autonomic nervous system	8 (16)	4 (50)	4 (50)	.53
Soft tissues	15 (30)	8 (53.3)	7 (46.7)	.21
Other	5 (10)	2 (40)	4 (60)	.99
No. of organs involved				.96
1	11 (22)	5 (45.5)	6 (54.5)	
2	18 (36)	6 (33.3)	12 (66.7)	
3 or more	21 (42)	9 (42.8)	12 (57.2)	
Mayo Risk Stratification System 2004†				.66
1	16 (35.6)	5 (31.2)	11 (68.8)	
2	15 (33.3)	7 (46.7)	8 (53.3)	
3	14 (31.1)	5 (35.7)	9 (64.3)	
Type of treatment				
ASCT	20 (40)	5 (25)	15 (75)	.07
Novel drugs	29 (58)	11 (37.9)	18 (62.1)	.73
Hematologic response				**.0001**
CR	25 (50)	3 (12)	22 (88)	
VGPR	10 (20)	6 (60)	4 (40)	
PR	15 (30)	11 (73.3)	4 (26.7)	

Data presented are n (%) unless otherwise indicated.
Bold typeface indicates statistical significance.
M indicates male; f, female; dFLC, difference between involved and uninvolved serum free-light chain.
* Only available in 41 patients with dFLC.
† Only available in 45 patients with cardiac biomarkers.