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Real-life experience on light chain cardiac amyloidosis: delay in diagnosis is still a major issue

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Background

Amyloidosis represents a heterogeneous group of misfolding protein disorders characterized by the deposition of amyloid fibrils in various tissues and organs. More than 36 different amyloidogenic proteins have been identified, with light chain (AL) and mutant or wild-type transthyretin (ATTR) being the most common forms. In systemic AL amyloidosis, clonal plasma cells produce amyloidogenic light chain fragments causing organ damage including the heart and kidneys. It remains a rare and life-threatening disease, with patient morbidity and mortality strongly associated with the severity of cardiac involvement. Early diagnosis and identification of the amyloid protein involved are therefore critical. However, the diagnosis of AL is often delayed due to the non-specific nature of presenting symptoms. Awareness of the disease and a high index of suspicion are key elements for early diagnosis to allow timely initiation of appropriate therapy to prevent further organ damage.

We retrospectively analyzed data on cardiac involvement in 114 consecutive patients with AL amyloidosis diagnosed at 2 academic institutions between 2007 and 2024.

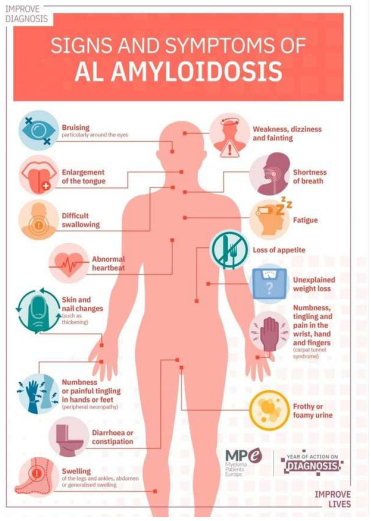
Results

The median time from initial presentation to diagnosis was 6 months. Patients with bilateral carpal tunnel syndrome, arthritis and neuropathy experienced the longest diagnostic delay (up to 156 months), highlighting missed screening opportunities.

One or more biopsy specimens were obtained from each patient to confirm the clinical diagnosis, most commonly from abdominal fat, skin, salivary gland, bone marrow, less commonly from kidney, heart, liver or GI tract. Clinical diagnosis could not be confirmed histologically in only one patient. As expected, lambda monotypy was predominant, and a marrow infiltration over 10% was seen in 50% of patients.

More than half of the patients had 3 or more organs involved at the time of diagnosis. The heart was involved in 83 (73%) of them. Fifty-two (50%) had a severe heart disease (European stage IIIa/IIIb), with nearly one-third of them dying prematurely in the first six months after diagnosis.

Over the past decade, daratumumab has been added to the traditional regimen of VCD offering faster and deeper hematological responses. Achieving hematological CR/VGPR (in 43%) was an important determinant of outcome in our series. Given in later lines, the impact of daratumumab was less clear (role of prior lines of therapy or refractoriness to treatment).



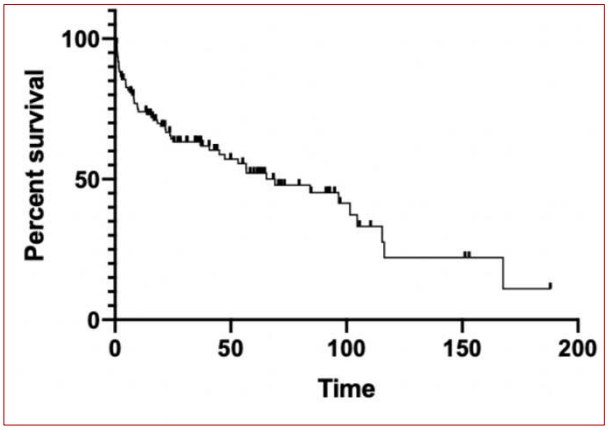


Fig. 1. Overall survival of the whole cohort; the median OS is at 60,1 months.

Characteristics		n (%)
Number of patients		114 (100)
Sex, male		61 (53)
Median age at diagnosis, years [range]		65 [32-88]
Median time from first symptom to diagnosis, months [range]		6 [0-156]
	Symptoms at diagnosis,	61 (53)
	Fatigue	34 (30)
	Weight loss	69 (61)
	Dyspnea	67 (59)
	Oedema	12 (11)
	Syncope	21 (18)
	Macroglossia	17 (15)
	Purpura	29 (25)
	Polyneuropathy	28 (45)
	Nephrotic syndrome	39 (34)
	Carpal tunnel syndrome	34 (30)
	GI symptoms	
Number of organ involved,	1, 2, ≥3 (%)	35 (31), 31 (27), 48 (42)
Underlying B-cell malignancy	myeloma	59 (52)
Ligh chain,	lambda (%)	80 (70)

Heart involvement, number of patients (%)		83 (73)
US/MRI features, *only in 88/108 patients*		
	LVEF <50%	22 (25)
	median septum thickness, mm [range]	13,5 [5-26]
Mayo2004/European Cardiac Stage,	I	22 (19)
	II	21 (18)
	IIIa	28 (25)
	IIIb	22 (19)
	NA	21 (18)

Kidney involvement, number of patients (%)		89 (78)
Renal staging system (Palladini),	I	33 (29)
	II	43 (38)
	III	13 (11)
	NA	25 (22)

Outcomes		n (%)
Number of patients with >6 months FU (%)		99 (86)
Vital status,	alive/dead	57/57
Early death < 6 months from diagnosis		21 (18)
Early death according to cardiac stage,	I	1
	II	4
	IIIA	4
	IIIB	11
	NA	1

Conclusions

Despite growing awareness about AL amyloidosis, nonspecific symptoms and varied manifestations continue to pose a significant issue to prompt recognition and treatment. In any case, time to diagnosis remains around 6 months, whether we refer to the period before 2020 or after 2020.

Questions and challenges remain also for patients with very advanced disease, but treatment with daratumumab-based regimens clearly offers the chance to reach deep responses in the remaining patients with less advanced disease, translating into organ responses and improved quality of life and, most likely, better OS.

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