Rare dual-clone phenomenon: concurrent λ AL amyloidosis and κ restricted B-cell lymphoproliferative disorders

Systemic light chain (AL) amyloidosis and light chain deposition disease (LCDD) are disorders in which misfolded immunoglobulin light chains accumulate in tissues - either as amyloid fibrils in AL amyloidosis or as non-fibrillar, amorphous deposits in LCDD - leading to progressive organ dysfunction.[1] These disorders most often arise from an underlying plasma cell clone, occasionally in association with multiple myeloma, and less commonly from B-cell lymphoproliferative disorders (LPD) such as chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia (WM), and marginal zone lymphoma.[2-4] In rare cases, they occur in the setting of both a plasma cell clone and a concurrent B-cell LPD; instances in which the two clones express discordant light chain restriction are even more unusual.[3,5-7] Such dual-clone presentations pose distinct diagnostic and therapeutic challenges.

Here, we describe six patients evaluated at the Boston University Amyloidosis Center who presented with λ-type AL amyloidosis or LCDD alongside a κ-restricted B-cell LPD. The study was approved by the Institutional Review Board and conducted in accordance with federal regulations and the Declaration of Helsinki. We outline their clinical presentations, pathologic features, treatments, and outcomes, highlighting the implications of this unusual dual-clone overlap.

In all six cases, the pathogenic light chains were traced to an underlying plasma cell clone, as evidenced by concordant light chain restriction between the plasma cells and the amyloid or LCDD deposits. Five patients had λ-type AL amyloidosis-confirmed by immunohistochemistry, immunogold electron microscopy, or mass spectrometry-based typing of an affected-organ biopsy-and one patient had λ LCDD.[8] The co-existing κ-restricted B-cell LPD included two cases of CLL, two cases of monoclonal B-cell lymphocytosis (MBL), one case of WM, and one CD5-positive low-grade B-cell lymphoma; all were identified by bone marrow biopsy and aspirate. Baseline characteristics are summarized in Table 1. All patients were diagnosed with both clones concurrently, except for one patient in whom the B-cell LPD was identified at a later time. Four patients had single-organ involvement, whereas two patients had multiorgan involvement - both of whom had CLL as their co-existing B-cell LPD. Although the pathogenic λ free light chain level was higher than the non-pathogenic κ free light chain level in four cases, only two demonstrated a difference between involved and uninvolved free light chains (dFLC) >50 mg/L. Cytogenetic and fluorescence *in situ* hybridization (FISH) data were available in a subset of patients and revealed abnormalities limited to the B-cell LPD clone, including trisomy 12 (patient 1), deletion 13q (patient 2), and trisomy 9 (patient 5). No history of autoimmune disease, immunosuppression, or hematologic malignancies was identified.

Frontline treatment regimens and longer-term outcomes - including progression/relapse events, subsequent therapies, and survival status - are summarized in Table 2. All patients received plasma cell-directed therapy, most commonly daratumumab- or bortezomib-based regimens, and two patients underwent high-dose melphalan with autologous stem cell transplantation (HDM/SCT). Treatment strategies fell into two broad categories. In three patients (patients 1, 3, and 4), treatment was directed exclusively at the plasma cell clone, as the accompanying B-cell LPD did not meet criteria for therapy. Notably, patient 1 later required CLL-directed therapy during surveillance after completing plasma cell-directed therapy, prompted by rapidly rising κ light chains, progressive lymphocytosis, and bulky lymphadenopathy. Meanwhile, patient 3 achieved a complete hematologic response to plasma cell–directed treatment, after which the previously detectable κ-restricted MBL clone was no longer present on repeat bone marrow evaluation. These observations raise the possibility that plasma cell-directed therapy - or perhaps interactions between the plasma cell clone and the B-cell compartment - may influence the course of the coexisting LPD, though causality cannot be established.

In the remaining three patients (patients 2, 5, and 6), treatment was directed at both clones, either from the outset or at some point during the disease course. Regimens with activity against both plasma cell and B-cell clones were used, including proteasome inhibitors combined with anti-CD20 monoclonal antibodies, and HDM/SCT. Patient 2, who presented with symptomatic AL amyloidosis and CLL requiring treatment, received rituximab-cyclophosphamide for CLL cytoreduction prior to HDM/SCT. Patient 5 initially received bendamustine-rituximab for neuropathy attributed to WM; persistent symptoms prompted further evaluation, which revealed co-existing AL amyloidosis diagnosed 2 years after the WM diagnosis. This patient subsequently underwent HDM/SCT to target both disorders. Patient 6, who had λ LCDD and a CD5-positive low-grade B-cell lymphoma, was treated with bortezomib-dexamethasone-rituximab, chosen for dual-clone activity.

Plasma cell-directed therapy was effective in all six cases.

Table 1. Baseline features in amyloid light chain amyloidosis or light chain deposition disease with concurrent κ-restricted B-cell lymphoproliferative disorders.

Patient	Age at diagnosis, years	Sex	Deposition disorder	Pathogenic light chain	Organ involvement	Bone marrow plasma cell %	LPD	LPD light chain	λ/κ/dFLC at deposition disorder diagnosis, mg/L	SPEP/ SIFE / UIFE	Timing of diagnoses
#1	71	M	AL	λ	Renal, cardiac	5	CLL	κ	48/42/6	SPEP: M-spike - SIFE: none UIFE: none	Synchronous
#2	47	M	AL	λ	Renal, cardiac, gastrointestinal	5-10	CLL	κ	41/10/31	SPEP: M-spike + SIFE: IgG λ UIFE: IgG λ	Synchronous
#3	72	F	AL	λ	Cardiac	15-20	MBL	κ	97/15/82	SPEP: M-spike - SIFE: none UIFE: none	Synchronous
#4	71	M	AL	λ	Soft tissue	<5	MBL	κ	1,997/13/1,984	SPEP: M-spike - SIFE: free λ UIFE: Bence-Jones λ	Synchronous
#5	74	M	AL	λ	Peripheral nerve	<5	WM	κ	17/27/<0	SPEP: M-spike + SIFE: IgM κ UIFE: none	AL diagnosed 2 years after WM
#6	58	M	LCDD	λ	Renal	5-10	B-cell lymphoma*	κ	21/149/<0	SPEP: M-spike + SIFE: IgM κ UIFE: Bence-Jones κ	Synchronous

*CD5-positive low-grade B-cell lymphoma (MYD88-), IgM κ. AL: amyloid light chain amyloidosis; BM: bone marrow; CLL: chronic lymphocytic leukemia; dFLC: difference between involved and uninvolved free light chains; F: female; κ: kappa, λ: lambda; LCDD: light-chain deposition disease; LPD: lymphoproliferative disorder; M: male; MBL: monoclonal B-cell lymphocytosis; SIFE: serum immunofixation electrophoresis; SPEP: serum protein electrophoresis; UIFE: urine immunofixation electrophoresis; WM: Waldenström macroglobulinemia.

Table 2. Treatment approaches and responses in amyloid light chain amyloidosis or light chain deposition disease with concurrent κ-restricted B-cell lymphoproliferative disorders.

Patient	Frontline therapy	Clone targeted by frontline therapy	Hematologic response*	Major organ response**	LPD treatment response	Any progression/ relapse	Subsequent therapy	Survival status
#1	CyBorD → Daratumumab maintenance	PC$^{\phi}$	CR	KidCR CarCR	CR	LPD progression	Obinutuzumab-venetoclax	Alive
#2	Cyclophosphamide-Rituximab → HDM/SCT	PC & LPD	CR	Kidney not evaluable¶ CarCR	CR	PC disease multiple relapse	IMiDs → relapse → kidney transplant → relapse → daratumumab	Alive
#3	Dara-CyBorD	PC	CR	Not evaluable§	No residual clone in BM	None	None	Alive
#4	Radiotherapy to solitary plasmacytoma	PC	CR	Not evaluable	Persistent MBL in BM	None	None	Alive
#5	Bendamustine-Rituximab → HDM/SCT	PC & LPD	Not evaluable†	Not evaluable	CR	None	None	Alive
#6	Bortezomib-Dexamethasone-Rituximab → HDM/SCT	PC & LPD	Not evaluable†	KidCR	PR	None	None	Alive

*Hematologic response reflected the best response post-frontline therapy. **Organ response was assessed per multicenter-validated graded organ response criteria for amyloid light-chain (AL) amyloidosis. $^{\phi}$Because the lymphoproliferative disorder (LPD) did not initially meet treatment indications, frontline therapy targeted only the plasma cell clone; obinutuzumab-venetoclax was initiated once the patient met criteria for chronic lymphocytic leukemia treatment later in the disease course. ¶Due to advanced involvement at diagnosis requiring renal transplantation. §Due to baseline NT-proBNP <650 pg/mL. †Due to free light chain measurements being confounded by the concurrent κ-restricted LPD, resulting in κ predominance. AL: amyloid light chain; BM: bone marrow; CarCR: cardiac complete response; CR: complete response; Dara-CyBorD: daratumumab, cyclophosphamide, bortezomib, dexamethasone; HDM/SCT: high-dose melphalan and autologous stem cell transplantation; IMiD: immunomodulatory drug; KidCR: kidney complete response; MBL: monoclonal B-cell lymphocytosis; PC: plasma cell; PR: partial response.

Four patients achieved a complete hematologic response by consensus criteria.[9] Bone marrow flow cytometry and minimal residual disease (MRD) assessment at the time of best hematologic response were available in three patients: patients 1 and 2 achieved MRD negativity with clearance of the plasma cell clone despite persistence of the κ-restricted B-cell clone, whereas in patient 3 both clones were undetectable. In two additional patients, hematologic response could not be reliably assessed because free light chain measurements were confounded by the concurrent κ-restricted LPD, resulting in κ predominance. Despite this, both patients experienced substantial clinical improvement, and no additional plasma cell-directed therapy was required. These two cases highlight an important limitation of standard free light chain-based response criteria in the setting of dual-clonal disease. When the uninvolved light chain is driven by a second clonal process rather than background production, free light chain ratios and dFLC values may be unreliable, and treatment benefit is better assessed by organ responses and overall clinical course. Over a median follow-up of 72 months (range, 25-190), most patients remained progression-free without need for additional therapy. Subsequent treatment was required in patient 1 (delayed CLL-directed therapy) and patient 2 (recurrent plasma cell–driven disease), while all patients were alive at last follow-up (Table 2).

Previous reports of discordant abnormal light chain expression have been most thoroughly described in multiple myeloma, where detailed assessments using flow cytometry, FISH, and immunoglobulin gene rearrangement analyses have established that co-existing plasma cell and B-cell LPD clones often reflect biologically distinct neoplasms.[10,11] In AL amyloidosis, such dual-clone presentations are considered rare; however, this rarity must be interpreted in the context of disease prevalence. Although B-cell LPD such as MBL and CLL are relatively common in older adults, AL amyloidosis is rare; therefore, their co-occurrence is inherently uncommon. Only two published cases have described λ-type AL amyloidosis co-existing with κ-restricted CLL, both with renal involvement attributable to AL amyloidosis, while the CLL remained clinically silent.[5,6] In a large four-decade cohort of AL amyloidosis, 14 patients (0.6%) had co-existing CLL, with discordant light chain restriction reported in only two cases.[3] Our case series expands this limited literature by presenting additional examples of discordant light chain biology and by including cases

associated not only with CLL but also with WM and other low-grade B-cell lymphomas. To our knowledge, this is the largest series of λ-type AL amyloidosis or LCDD co-existing with κ-restricted B-cell LPD and the first to describe this phenomenon in the era of contemporary plasma cell-directed therapies, including daratumumab-based regimens. Whether this co-existence reflects coincidence or shared biology remains uncertain given the small sample size. Larger studies integrating genomic characterization, clonal evolution, and microenvironmental analyses will be needed to clarify the mechanisms underlying this dual-clone presentation.

In conclusion, our findings highlight three practical considerations for clinicians managing dual-clone hematologic disorders. First, precise typing of amyloid or LCDD deposits is essential to identify the pathogenic light chain and guide therapy selection. Second, treatment decisions should account for the relative clinical impact and activity of each clone, with regimens of overlapping efficacy used when both clones require therapy. Third, dual clonality complicates response assessment, and standard free light chain–based response criteria may be limited in this setting; treatment benefit is often better evaluated through organ responses and overall clinical course. Early recognition of dual-clone biology and its integration into diagnostic and therapeutic planning may help optimize outcomes in this uncommon but clinically important overlap between plasma cell and B-cell disorders.

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Contributions

OC, AS, and VS designed the study, performed data analysis, and wrote manuscript. OC, AS, LM, and TJ collected the data. OC, AS, LM, TJ, and VS performed the research and provided clinical care to the patients. All authors critically reviewed and approved the manuscript.

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Data-sharing statement

The datasets, including individual participants' data supporting the results reported in this article will be available 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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