



# AL amyloidosis with a localized B cell neoplasia

Christiane Stuhlmann-Laeisz<sup>1</sup> · Stefan O. Schönland<sup>2</sup> · Ute Hegenbart<sup>2</sup> · Ilske Oschlies<sup>1</sup> · Julius-Valentin Baumgart<sup>1</sup> · Sandra Krüger<sup>1</sup> · Christoph Röcken<sup>1</sup> 

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## Abstract

Immunoglobulin light chain-derived (AL) amyloidosis may occur as a systemic disease usually with dismal prognosis and a localized variant with favorable outcome. We report 29 patients with AL amyloidosis and associated lymphoplasmacytic infiltrate spatially related to amyloid deposits. In 17 cases, the amyloid deposits were classified as AL $\lambda$  and 12 as AL $\kappa$ . Histopathology in all cases showed relatively sparse plasma cells and B cells without tumor or sheet formation by the lymphoplasmacytic infiltrate. The B cells predominantly showed an immunophenotype of the marginal zone. In situ, hybridization revealed 17 cases with  $\lambda$ - and 10 with  $\kappa$  light chain restricted plasma cells, which was concordant with the AL subtype in each case. Clonal immunoglobulin heavy variable gene (IGHV) or  $\kappa$  light chain rearrangement was found in 23/29 interpretable cases. A single case harbored a MYD88<sup>L265P</sup>-mutation. Taken together, we detected 27 (93%) cases of AL amyloidosis with an associated light chain restricted and predominantly molecularly clonal plasma cell population. Clinical data were available in 18 patients. Five patients suffered from systemic lymphoma and two from systemic AL amyloidosis. The remaining cases were classified as localized with regard to both, the AL amyloidosis and the light chain restricted plasma cell population. To the best of our knowledge, we herein present the largest cohort of AL amyloidosis associated with a light chain restricted and predominantly molecularly clonal plasma cell population, which we designate as a distinct disease entity: “AL amyloidosis with a localized B cell neoplasia of undetermined significance”.

**Keywords** Amyloid · Congo red · Light chain · B cell lymphoma

## Introduction

Amyloid is characterized by the pathological deposition of peptides and proteins in diverse tissues and organs, which interferes with normal tissue and organ function. It consists of misfolded, insoluble, toxic proteinaceous aggregates, which are oriented in a  $\beta$ -sheet structure [1–3]. Immunoglobulin-light (AL) chain-derived amyloidosis is the most common amyloidosis in Europe and North America and represents a hematological disorder and

manifests either systemically or locally. Localized AL amyloidosis is rare and may occur at different anatomical locations, including the respiratory and gastrointestinal tract [4, 5]. Both systemic and localized AL amyloidosis are associated with a variety of plasmacytic-differentiated B cell lympho-proliferations. Systemic AL amyloidosis has been linked to a plasma cell dyscrasia, which either resembles a mild increased plasma cell number in the bone marrow [6], an overt plasma cell myeloma, or a lymphoplasmacytic lymphoma (M. Waldenström) [7, 8]; the latter all representing systemic diseases. Recent literature describes smaller cohorts and case reports of localized AL amyloidosis, which are associated with localized plasmacytic-differentiated B cell lympho-proliferations [4, 9–12], where the exact classification of the plasmacytic-differentiated B cell neoplasia often remains an unsolved issue.

We report here on a prospective series of 29 patients with AL amyloidosis, who presented with a sparse lymphoplasmacytic infiltrate within or surrounding the amyloid deposits, some of which we subsequently classified as a “AL amyloidosis with a localized B-cell neoplasia of undetermined significance”.

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✉ Christoph Röcken  
christoph.roecken@uksh.de

<sup>1</sup> Department of Pathology, Christian-Albrechts-University Kiel, Arnold-Heller-Str. 3/14, D-24105 Kiel, Germany

<sup>2</sup> Medical Department V, Amyloidosis Center, University of Heidelberg, Heidelberg, Germany

## Materials and methods

### Patient cohort and study design

Before the study was started, a set of histological (H&E, Congo red), immunohistochemical (antibody panels; see below), and molecular pathological ( $\lambda$ - and  $\kappa$ -light chain in situ-hybridization, IGH-PCR, MYD88-genotype) analyses were defined which should be applied in every case with histological and immunohistochemical ( $\lambda$ - and  $\kappa$ -light chain immunostaining) evidence of a putative clonal lymphoplasmacytic infiltrate. The study was then started in 2015, and until 2017, we collected 29 cases during routine diagnostics of the tertiary referral center (Amyloid Registry Kiel) with biopsy-proven AL amyloidosis and a sparse lymphoplasmacytic infiltrate surrounding the amyloid deposits. Biopsy site, patient age, and gender were documented.

### Histopathology

All specimens had been fixed in formalin and embedded in paraffin (FFPE). Serial sections were cut from each paraffin block and stained with hematoxylin and eosin and Congo red. Amyloid was diagnosed when a typical green-yellow-orange birefringence was found in cross-polarized light in Congo red-stained sections.

### Immunohistochemistry

Immunohistochemical classification of amyloid was carried out and had been validated as described in detail elsewhere [13–17].

The lymphoplasmacytic infiltrate and the light chain restriction of the plasma cells were characterized using commercially available antibodies directed against CD5, CD10, CD20, CD23, CD56 and Cyclin D1, and in situ hybridization  $\kappa$  and  $\lambda$  light chain as listed in Supp. Table 1. Plasma cells were interpreted as  $\kappa$  light chain restricted when the ratio between  $\kappa$ - and  $\lambda$  positive plasma cells was above 8:1. The  $\lambda$  light chain restriction was reported, when  $\lambda$  was expressed in a higher proportion of plasma cells compared to  $\kappa$  positive plasma cells [16].

### DNA extraction and analysis of clonal immunoglobulin rearrangements

Genomic DNA was extracted from FFPE tissue with QIAamp DNA Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions. DNA was used as template for amplification of immunoglobulin heavy chain (*IGH*) and light chain (*IGK*) gene rearrangements according to the BIOMED-2 multiplex protocol [18]. PCR products were subjected to GeneScan analysis for characterization of Ig gene

rearrangement patterns on an ABI 3500 genetic analyzer (Applied Biosystems, Darmstadt, Germany). Data analysis was performed with GeneMapper Software v4.1. Interpretation of GeneScan results was performed according to standard guidelines [19].

### MYD88 L265P mutation analysis

A 76 basepair-fragment spanning codon 265 of the human *MYD88* gene was amplified from genomic DNA by PCR using the primers MYD88-F2 (5'-gcaggtgccatcagaagc-3') and MYD88-R2 (5'-acctcagatgctggggaact-3'). The amplified PCR products were controlled by agarose gel electrophoresis and directly sequenced by pyrosequencing on a PyroMark Q24 sequencer (Qiagen) using the sequencing primer MYD88-S1 (5'-cccatcagaagcgac-3'). The sequencing results were analyzed using the PyroMark Q24 software. The detection limit of the applied assay accounts for 5% tumor DNA.

### Clinical data

Clinical data were obtained by interrogation of the treating physicians using a standardized questionnaire, focusing on the following items: were the amyloid depositions systemically or localized; was the patient suffering from a systemic lymphoma; and was there a monoclonal gammopathy in the serum immunofixation electrophoresis?

### Disease classification

Systemic disease was assumed, when systemic amyloidosis was diagnosed clinically and/or when there was evidence for lymphoma infiltration in the bone marrow and/or if the medical history of the patient showed evidence for a systemic lymphoma.

A localized disease was signed out in patients with evidence of local amyloid deposits associated with a clonal plasma cell infiltration without clinical data and/or negative clinical staging were designated as: "AL amyloidosis with a localized B-cell neoplasia of undetermined significance (AL-LBN)". All cases are categorized in Table 1 and Supp. Table 2. Cases with systemic disease or missing clonality of the lymphoplasmacytic infiltrate are categorized as "others" in Supp. Table 2.

## Results

### Histopathology and immunohistochemistry

Between 2015 and 2017, we collected prospectively a cohort of 29 referral cases of histomorphologically and immunohistochemically proven AL amyloidosis of diverse

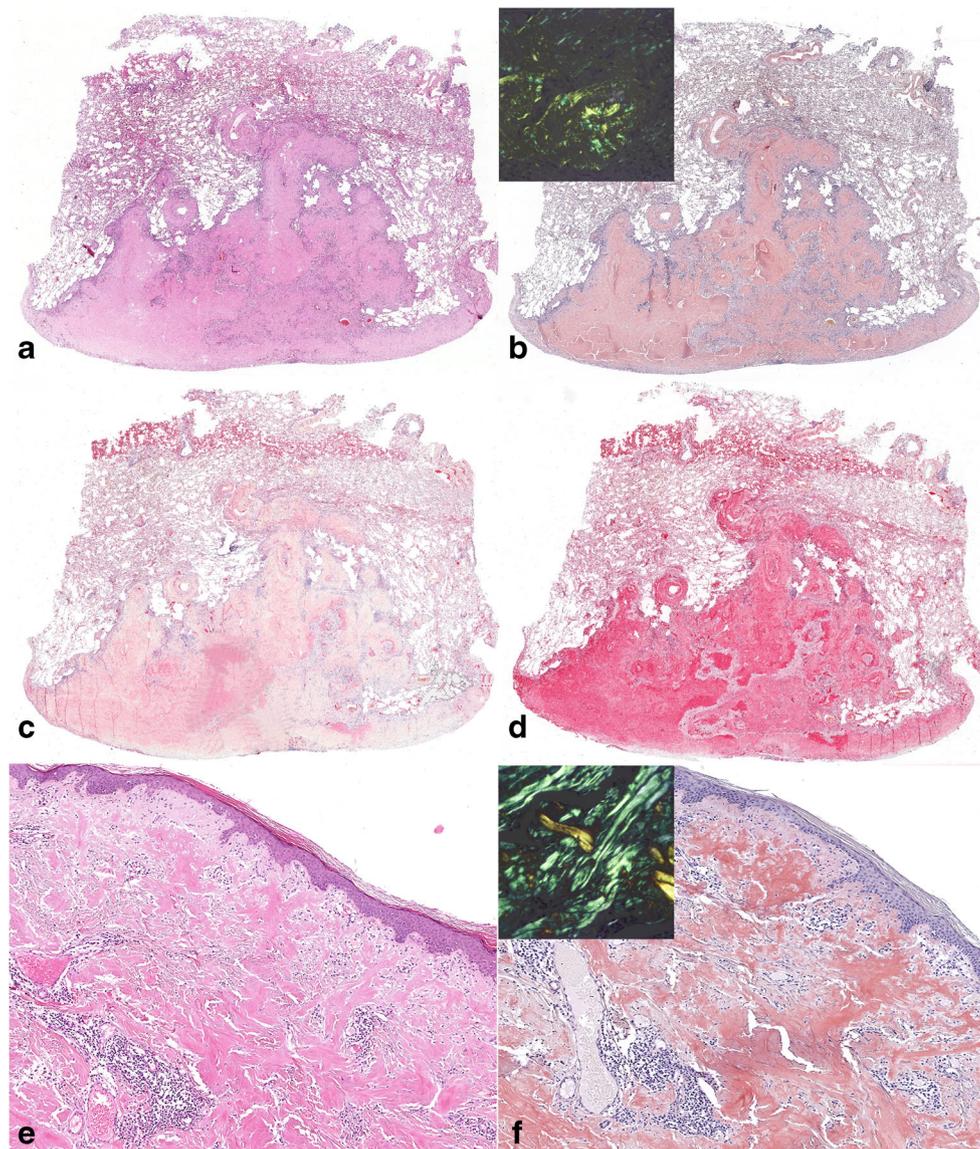
**Table 1** Characteristics of a cohort of 29 patients with AL amyloidosis and an overt lymphoplasmacytic infiltrate (for further details see Suppl. Table 2, MgZL, marginal zone lymphoma; *n.a.*, not available, *AL-LBN*, AL amyloidosis with localized B cell neoplasia of undetermined significance)

No.	Sex	Age [years]	Anatomical site	Amyloid type	Amyloidosis local (l)/systemic (s)	Systemic lymphoma yes (y)/no (n)	Diagnosis
1	F	62	Orbita	AL $\kappa$	n.a.	n.a.	<i>AL-LBN</i>
2	M	68	Epipharynx	AL $\kappa$	l	<i>n</i>	<i>AL-LBN</i>
3	F	56	Lung	AL $\kappa$	n.a.	n.a.	<i>AL-LBN</i>
4	F	57	Lung	AL $\kappa$	l	n.a.	<i>AL-LBN</i>
5	M	63	Lung	AL $\kappa$	n.a.	n.a.	<i>AL-LBN</i>
6	M	56	Lung	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
7	F	68	Lung	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
8	M	37	Lung	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
9	M	80	Lung	AL $\lambda$	l	<i>n</i>	<i>AL-LBN</i>
10	F	71	Lung	AL $\lambda$	l	n.a.	<i>AL-LBN</i>
11	M	73	Lung	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
12	M	69	Lung	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
13	F	72	Lung	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
14	M	74	Skin	AL $\lambda$	l	n.a.	<i>AL-LBN</i>
15	M	70	Skin	AL $\lambda$	l	<i>n</i>	<i>AL-LBN</i>
16	M	67	Lymph node	AL $\lambda$	l	n.a.	<i>AL-LBN</i>
17	F	38	Lymph node	AL $\lambda$	l	<i>n</i>	<i>AL-LBN</i>
18	M	57	Ureter	AL $\lambda$	l	<i>n</i>	<i>AL-LBN</i>
19	M	36	Bladder	AL $\lambda$	l	<i>n</i>	<i>AL-LBN</i>
20	M	72	Bladder	AL $\lambda$	l	<i>n</i>	<i>AL-LBN</i>
21	F	66	Soft tissue	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
22	M	82	Colon, mesenterium, lymph node	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
23	F	66	N. ischiadicus	AL $\lambda$	n.a.	n.a.	<i>AL-LBN</i>
24	M	67	Lung	AL $\kappa$	l	y (suspicious for MgZL)	Systemic MgZL with associated tumorous AL $\kappa$ amyloidosis
25	M	60	Lung	AL $\kappa$	l	<i>n</i>	AL $\kappa$ amyloidosis with an associated predominant $\kappa$ light chain expressing plasma cell population without evidence for clonality
26	M	77	Lung	AL $\lambda$	s	y	Systemic B-cell lymphoma with associated AL $\lambda$ amyloidosis
27	M	56	Lymph node	AL $\kappa$	s	y (no diagnosis)	Systemic B-cell lymphoma with associated AL $\kappa$ amyloidosis
28	F	64	Soft tissue	AL $\kappa$	l	y	Systemic plasmacytic-differentiated MgZL
29	M	81	Bone marrow, small bowel	AL $\kappa$	n.a.	y	Plasma cell myeloma and vascular and interstitial AL $\kappa$ amyloidosis

anatomical origin with a sparse lymphoplasmacytic infiltrate surrounding the amyloid deposits (Figs. 1 and 2). Twelve out of 29 (41%) cases presented with tumor-like amyloid deposits; 6/29 (21%) cases with vascular and interstitial deposits; 4/29 (14%) cases with tumor-like, vascular, and interstitial; 4/29 (14%) cases with interstitial; 1/29 case (3%) with tumor-like and endoneural; 1/29 case (3%) with tumor-like and vascular; and 1/29 case (3%) with tumor-like and interstitial amyloid deposits. The lymphoplasmacytic infiltrate was in all

cases composed of clusters and partially follicular-arranged small B cells and groups of mature plasma cells. B cells presented with dense nuclear chromatin and a small cytoplasmic rim. The typical morphology of monocytoid B cells and lympho-epithelial lesions was not present in any case.

Immunostaining classified 17/29 (59%) cases as AL $\lambda$  and 12/29 (41%) cases as AL $\kappa$  amyloid. All cases presented with CD20<sup>+</sup> B cells arranged in a reactive like manner forming small clusters and naive follicles and harboring a marginal



**Fig. 1** Localized AL amyloidosis in lung and skin specimens. **a** Tumor-like, mass-forming amyloid deposits are present in the lung and are associated with a sparse lymphoplasmacytic infiltrate within and surrounding the deposits. **b** The amyloid deposits stain red in bright light and show the typical green-yellow-orange birefringence in cross-polarized light after Congo-red (B-insert). The amyloid deposits are immunonegative for  $\kappa$  light chain (**c**) and strongly immunoreact with an antibody directed

against  $\lambda$  light chain (**d**). **e** A dense subepidermal amyloidosis of the skin with a concomitant, sparse, predominantly perivascular localized lymphoplasmacytic infiltrate. **f** After Congo red-staining, the amyloid deposits show typical green-yellow-orange birefringence in cross-polarized light (f-insert). Hematoxylin and eosin (**a**, **f**), Congo red-staining (**b**, **h**), anti- $\kappa$ -light chain immunostaining (**c**), anti- $\lambda$ -light chain immunostaining, original magnifications 0.5-fold (**a–d**) and 4-fold (**f**, **h**)

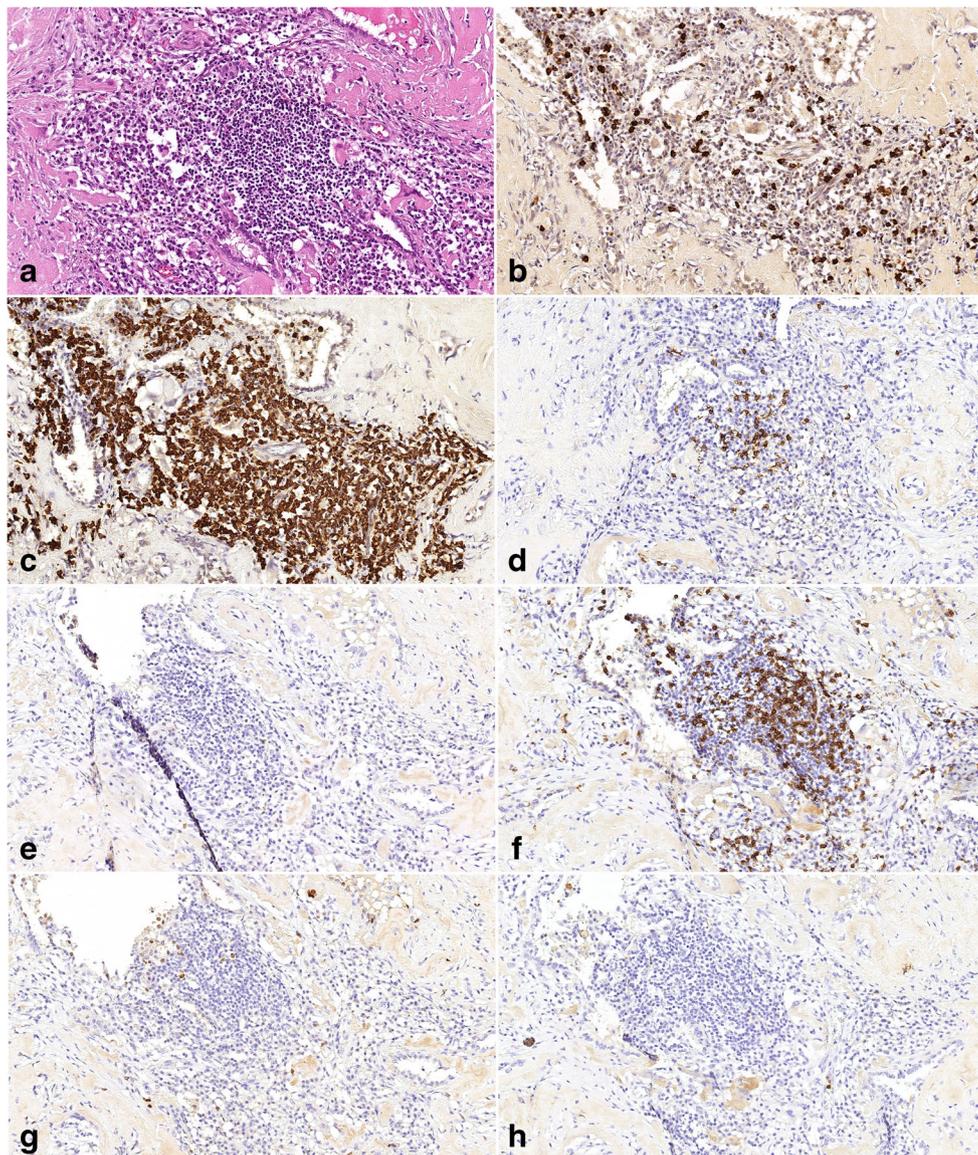
zone immunophenotype ( $CD5^-$ ,  $CD23^-$ ,  $CD10^-$  and Cyclin  $D1^-$ ; Fig. 2). Tumor forming diffuse sheets of B-cells or plasma cells, the former described for extranodal marginal zone lymphomas and the latter described for extramedullary plasmacytomas, were not observed.

With  $\kappa$ - and  $\lambda$  in situ hybridization 17 (59%) cases showed a  $\lambda$  light chain restricted and 10 (34%) a  $\kappa$  light chain restricted plasma cell population ( $\kappa$ : $\lambda$ -ratio > 8:1). Two (7%) of the  $\kappa$  light chain restricted cases presented with a  $\kappa$ : $\lambda$  ratio < 8:1. A light chain restriction on the B cells was not found in any case

(Fig. 2). The light chain detected in the plasma cells was concordant with the AL amyloid-type.

### Molecular analysis

Analysis of the Ig-gene rearrangement identified a clonal rearrangement in 19 (66%) cases. Eight (28%) cases displayed numerous amplification products and were interpreted as “not clonal.” Two (7%) cases showed no amplification products within the expected sizes due to



**Fig. 2** Morphological and immunohistochemical characterization of the lymphoplasmacytic infiltrate. Magnified illustration of the lymphoplasmacytic infiltrate in the lung presented in Fig. 1a–d. The generally sparse lymphoplasmacytic infiltrate was composed of small lymphocytes with dense nuclear chromatin and a small cytoplasmic rim and mature plasma cells with excentric localized nucleus and wide cytoplasm with a perinuclear halo (a). Using in situ hybridization, only few  $\kappa$ -positive reactive plasma cells were found (b) among a predominantly  $\lambda$  light chain restricted plasma cell population (c).

Intermingled few CD20 positive small B-cells (d), which were immunonegative for CD23 (e), CD5 (f), cyclin D1 (g), and CD10 (h). CD5 highlights intermingled reactive T cells (f). Cyclin D1 staining shows few intermingled histiocytes (g). Hematoxylin and eosin (a);  $\kappa$ - (b), and  $\lambda$  light chain (c) in situ hybridization; anti-CD20- (d), anti-CD23- (e), anti-CD5- (f), anti-Cyclin D1 (g), and anti-CD10-antibodies (h); Original magnifications  $\times 200$ , overall presentation of the identical field of view (a–g)

the limited DNA quality obtained from FFPE material (Suppl. Table 2). In seven cases (no.1; no. 3; no. 5; no. 25; no. 27; no. 28, no. 29), which either presented with an ambiguous  $\kappa$  light chain restriction of the plasma cells or with a polyclonal or ambiguous result in the Ig-rearrangement analysis, we additionally performed  $\kappa$ -light chain PCR. Five (71%) cases showed a clonal rearrangement of the  $\kappa$  light chain (data not shown). Collectively, the Ig- and the  $\kappa$  light chain rearrangement

analyses classified 23 cases as molecularly clonal. Among the remaining six cases, five presented with numerous amplification products, and one case showed no amplification products within the expected sizes, probably due to low DNA quality.

Finally, the somatic  $MYD88^{L265P}$ -mutation status was analyzed in all cases. A single case (no.16; Table 1; Suppl. Table 2) displayed a  $MYD88^{L265P}$ -mutation. The remaining 28 cases had no mutation.

## Clinical characteristics

Ten (34%) patients were female and 19 (66%) were male. The average age was 64 years (median 66 years; range 36–82 years). A lesional mass was found in the upper respiratory tract and lung [15 (52%) patients], the urogenital tract [3 (10%)], the skin [2 (7%)], the soft tissues [2 (7%)], the gastrointestinal tract [2 (7%)], the N. ischiadicus [1 (3%)], the lymph node [3 (10%)], and the orbita [1 (3%)].

Further, clinical data were obtained from 22 different referring pathologists and hence different clinics. The latter and the retrospective analysis of the clinical data might explain that, despite an extensive interrogation of the treating physicians, we received clinical data only from 18 (62%) patients. Nevertheless, 7/18 patients with available clinical data were screened and treated in the Amyloidosis Center Heidelberg (Table 1 and Suppl. Table 2). Fourteen (78%) patients had evidence of a localized and two (3%) of a systemic AL amyloidosis. No data was available from two (11%) patients. As detailed below, three (17%) patients presented with a systemic lymphoma in the bone marrow biopsy. Six (33%) had no evidence of a systemic lymphoma. In four (22%) patients, a bone marrow biopsy was not taken and in five (28%), data were unavailable. A monoclonal gammopathy IgG- $\kappa$  in the serum immunofixation electrophoresis was detected in three (17%) patients; the latter was corresponding with the amyloid subtype and the light chain restriction of the plasma cells. Thirteen (72%) patients had no evidence of a monoclonal gammopathy in the serum immunofixation electrophoresis. No data were obtained from two (11%) patients. At the time point of interrogation ten (56%) patients were alive, two (11%) were dead (both died of other concomitant underlying diseases), and six (33%) were lost to follow-up.

Among the three patients with bone marrow involvement, one had a simultaneously diagnosed plasma cell myeloma (case no. 29; Table 1). The second patient had a lymphoma compatible with a marginal zone lymphoma (case no. 24; Table 1). In the third patient, the histological classification of the lymphoma remained obscure, while he presented with a systemic AL amyloidosis and a monoclonal gammopathy (case no. 27; Table 1 and Suppl. Table 2).

One patient without bone marrow involvement suffered from a metachronous plasmacytic-differentiated marginal zone lymphoma with histological evidence of orbital and nodal involvement and thus has to be interpreted as a systemic disease (case no. 28; Table 1). Yet, another patient without bone marrow involvement suffered from a metachronous diffuse large B cell lymphoma, which due to the available clinical information developed from a cytologically indolent B cell lymphoma. Although the exact histological classification of the cytological indolent lymphoma component and information about a plasmacytic differentiation remained

obscure, we interpreted this case as a systemic disease (case no. 26; Table 1).

## Discussion

The current WHO-classification of Tumors of Hematopoietic and Lymphoid Tissue 2017 [6] classifies localized plasmacytic-differentiated B cell lymphoproliferations (e.g., in the skin, in the stomach, and in the salivary glands) as plasmacytic-differentiated marginal zone lymphomas, presupposing that a small B cell component is detectable within the biopsy specimen. Some authors claim that plasmacytic-differentiated marginal zone lymphomas have to be classified as pure plasma cell neoplasms, because they exhibit the immunophenotype of plasma cells rather than the immunophenotype of mature B cells in flow cytometry analysis [20]. The question whether a relatively small B cell component in localized amyloidosis is part of the neoplastic clone or not is currently unknown, and the classification of a lymphoproliferation associated with localized AL amyloidosis is an unsolved issue. The main challenge is the differentiation between a pure localized plasmacytic-differentiated B cell lymphoma and a secondary infiltration by a systemic plasmacytic-differentiated B cell lymphoma.

Our study on a cohort of 29 patients with tumor-like AL amyloidosis showed a concomitant light chain restricted and predominantly molecularly clonal plasma cell population. Considering the clinical presentation, most of the herein analyzed cases presented as localized processes, in which a sparse local clonal plasmacytic infiltration causes a localized amyloid deposition within the tissue in an otherwise healthy patient without overt lymphoma. The final classification as a localized disease is solely possible ruling out a secondary infiltration by an underlying systemic plasmacytic-differentiated B cell lymphoma by appropriate staging as proposed for comparable entities like primary cutaneous lymphomas [21–23].

In our cohort, AL $\lambda$  amyloid (59%) was slightly more prevalent than AL $\kappa$  amyloid (41%). The type of amyloid was 100% concordant with the detected light chain in the plasma cells. A clonal Ig-gene or  $\kappa$ -light chain rearrangement was found in 23 patients. Four (14%) cases presented with an unambiguous light chain restricted plasma cell population without detectable clonal Ig-rearrangement. Putative explanations might be that the underlying clone was undetectable by the used primer systems due to somatic hypermutation in the Ig-gene locus, as it has been described in follicular lymphomas [24], or the underlying clone was undetectable due to pauci-cellularity. Collectively, we identified 27 (93%) cases with an AL amyloidosis and an associated light chain restricted and predominantly molecularly clonal plasma cell population.

The accompanying lymphoplasmacytic infiltrate revealed a marginal zone-immunophenotype of the B cells in all cases. This finding excluded the diagnoses of a plasmacytic-differentiated chronic lymphocytic leukemia (CD5 and CD23 co-expression) [25], rare variants of plasmacytic-differentiated follicular lymphoma (germinal center immunophenotype) [26, 27], and a plasmacytic-differentiated mantle cell lymphoma (Cyclin D1 expression) [28, 29].

Further, we were unable to find evidence for a lymphoplasmacytic lymphoma (M. Waldenström) using *MYD88*-genotyping, since we found only a single case (no. 16; Supp. Table 2) exhibiting a *MYD88*<sup>L265P</sup>-mutation. The patient presented with local  $\kappa$ -light chain AL amyloidosis in the lymph node and an associated  $\kappa$ -light chain restricted and molecularly clonal plasma cell population. Eighty-six to 100% of lymphoplasmacytic lymphomas harbor the *MYD88*<sup>L265P</sup>-mutation [30–33]. Further, 10–87% of IgM monoclonal gammopathy of undetermined significance (MGUS) shows the *MYD88*<sup>L265P</sup>-mutation [30–35]. Finally, the most likely differential diagnoses in our *MYD88*<sup>L265P</sup>-mutated case are either a secondary infiltration of the lymph node by a lymphoplasmacytic lymphoma (M. Waldenström) or an IgM-MGUS. Unfortunately, data on clinical presentation and serum immunofixation electrophoresis were unavailable and no final diagnosis could be reached in this case.

In consideration of the additional clinical information, five patients (case no. 24, no. 26, no. 27, no. 28, no. 29) suffered from a systemic lymphoma, and one patient (case no. 25) presented with an AL $\kappa$  amyloidosis with an associated predominant  $\kappa$ -light chain expressing plasma cell population without evidence for clonality. With regard to the remaining 23 (79%) cases, which had a light chain-restricted lymphoplasmacytic infiltrate without evidence of a systemic lymphoma and systemic amyloidosis, there are two open differential diagnoses: a localized plasmacytic-differentiated marginal zone lymphoma and a pure plasma cell-derived neoplasia. For the diagnosis of a plasmacytic-differentiated marginal zone lymphoma, we missed the more extended sheet-like infiltrate of a small B cell component, which was generally sparse in our cohort. For the diagnosis of an extramedullary plasmacytoma, we missed sheets of neoplastic plasma cells.

We believe that the herein described light chain restricted clonal plasma cell population is more appropriately described with the proposed term “AL-LBN”, sharing features with MGUS in the bone marrow as described in the current WHO-classification of Tumors of Hematopoietic and Lymphoid Tissue 2017 [6].

Our study results point out that the final diagnosis of an AL-LBN presumes a detailed elaboration of the following decision tree by answering the given questions: (1) Is there evidence for clonality of the lymphoplasmacytic infiltrate; (2) are the amyloid deposits localized or systemically; (3) is there evidence for

a systemic lymphoma; and (4) is the final disease classification according to the histological pattern, i.e., (a) localized extranodal plasmacytic-differentiated marginal zone lymphoma (histological pattern: sheets of clonal B cells and intermingled clonal plasma cells), (b) localized extramedullary plasmacytoma (histological pattern: sheets of mature clonal plasma cells), or (c) AL-LBN (histological pattern: sparse lymphatic infiltrate and sparse clonal plasma cells)?

In view of the proposed AL-LBN, we believe that the classification of the underlying disease of AL amyloidosis can be amended [3]. Table 2 outlines in detail, which different forms of plasmacytic-differentiated B cell neoplasms are potentially causing either localized or systemic amyloidosis. Systemic AL amyloidosis may be associated with a systemic clonal plasma cell population in the bone marrow either resembling a frank multiple myeloma or a plasmacytic-differentiated B cell lymphoma [7, 36, 37]. Localized AL amyloidosis may be associated with a localized clonal plasma cell population either resembling a plasmacytoma, a localized plasmacytic-differentiated B cell lymphoma (different possible subtypes), or a clonal infiltrate not meeting the criteria of a plasmacytic-differentiated marginal zone lymphoma or an extramedullary plasmacytoma, i.e., AL-LBN.

Localized AL amyloidosis with a localized clonal plasma cell population has been described in single case reports and in smaller cohorts [11, 12, 38, 39]. Table 3 provides an overview of the literature with larger case series. Thompson et al. [43] presented 11 cases of laryngeal AL amyloidosis and a concomitant sparse lymphoplasmacytic infiltrate with a reactive distribution pattern. None of the cases had evidence of a systemic plasmacytic-differentiated B cell lymphoma. Clonality was demonstrated by the light chain restriction of the plasma cells in 3/11 cases, which were subsequently categorized as localized AL amyloidosis with an associated lymphoplasmacytic disorder within the spectrum of marginal zone lymphomas. Ryan et al. [9] described 20 cases of diverse anatomical origin with AL amyloidosis and an associated light chain restricted lymphoplasmacytic infiltrate, which was designated to be within the spectrum of extranodal marginal zone lymphomas. Two histological patterns were described: Firstly, samples that presented with a dense lymphoplasmacytic infiltrate with sparse amyloid deposits and, secondly, those which presented with tumorous amyloid deposits with a surrounding sparse lymphoplasmacytic infiltrate. Furthermore, clinicopathological characteristics concerning the distribution pattern of the lymphoma and amyloid deposits were given. Molecular analyses, e.g., Ig-rearrangement analysis, were done only in two cases. Walsh et al. [42] presented ten cases obtained from the skin with a localized AL amyloidosis and an associated light chain restricted plasma cell population, without evidence of a systemic involvement. Two patterns of AL amyloidosis were described: Firstly, systemic amyloidosis with an additional systemic B cell lymphoma and, secondly, localized

**Table 2** Systematic delineation of the different presentation forms of AL amyloidosis

	Plasma cell myeloma	Systemic plasmacytic-differentiated marginal zone lymphoma (MgzL)	Lymphoplasmacytic lymphoma (M. Waldenström)	Other plasmacytic-differentiated B-cell lymphomas	Extrametullary plasmacytoma	Localized plasmacytic-differentiated marginal zone lymphoma (MgzL)	Localized B-cell neoplasia of undetermined significance	Tumor-like/localized AL amyloidosis
AL amyloid-deposition	Systemic	Systemic	Systemic	Systemic	Localized	Localized	Localized	Localized
Histology of lympho-plasmacytic infiltrate	Intermingled reactive B-cells possible infiltration of densely packed tumor forming plasma cells often with a more immature appearance	Variable dense B-cell infiltrate with a plasma cell component	Variable dense B-cell infiltrate with a plasma cell component	CLL: Diffuse infiltration of small lymphocytes	Intermingled reactive B-cells possible predominant infiltration of densely packed tumor forming mature plasma cells	Variable dense B cell infiltrate with a plasma cell component	Intermingled single or cluster forming B cells, predominantly loosely packed infiltrating plasma cells	Unspecific inflammatory infiltrate without evidence of clonality
Immunopheno-type of B cells	Reactive B-cells	CD20+, CD23, CD5, CD10 and Cyclin D1 negative	CD20+, CD23, CD5, CD10 and Cyclin D1 negative	CLL: CD20+, CD23+, CD5+	Reactive B-cells	CD20+, CD23, CD5, CD10 and Cyclin D1 negative	CD20+; CD23, CD5, CD10 and Cyclin D1 negative	Reactive B-cells
Immunopheno-type of plasma cells	CD20, CD23, CD5, CD10 negative. Occasionally Cyclin D1+ and CD56+, light chain restriction.	CD20, CD23, CD5, CD10 and Cyclin D1 negative and light chain restricted	CD20, CD23, CD5, CD10 and Cyclin D1 negative and light chain restriction.		CD20, CD23, CD5, CD10 and Cyclin D1 negative and light chain restriction.	CD20, CD23, CD5, CD10 and Cyclin D1 negative and light chain restriction	CD20, CD23, CD5, CD10 and Cyclin D1 negative and light chain restriction	Polytypic
Genotype of neoplastic cells	Often Cyclin D1 and occasionally <i>MYC</i> rearrangements	Occasionally t(14;18)(q32;q21)	<i>MYD88</i> mutation (> 90%)	CLL: No specific genetic markers	Lack of Cyclin D1 translocation, lack of <i>MYC</i> rearrangement	Occasionally t(14;18)(q32;q21)	Unknown	No aberrations
Clinics/staging	Evidence for systemic plasma cell myeloma (bone marrow involvement)	Evidence for systemic lymphoma e.g. bone marrow involvement, lymphadenopathy	Bone marrow involvement mandatory, loose clusters of lymphocytes and plasma cells with intermingled mast cells	Systemic involvement e.g. bone marrow involvement, lymphadenopathy or end organ involvement	No evidence for systemic plasma cell myeloma (no bone marrow involvement)	No evidence for systemic lymphoma (no bone marrow involvement, no lymphadenopathy)	No evidence for systemic lymphoma (no bone marrow involvement, no lymphadenopathy)	No evidence for systemic lymphoma (no bone marrow involvement, no lymphadenopathy)
Monoclonal gammopathy*	Measurable	Measurable	Measurable (IgM)	Measurable	Negative or weakly positive	Negative or weakly positive	Negative or weakly positive	negative

CLL chronic lymphocytic leukemia, *MgzL* marginal zone lymphoma

\*Immunofixation in serum/urine and free light chain in serum

**Table 3** Review of the literature

Reference	Number of cases (n)	Anatomical site of involvement	Characterization of B- $\gamma$ -plasma cell infiltrates		Additional analysis	Clinical data		Classification of the lymphoplasmacytic infiltrate
			Arrangement and phenotype of B-cells	Phenotype of plasma cells (pc)		Bone marrow staging	Follow up data	
Grogg et al. [4]	18	Lung	- Variable degree of lymphoplasmacytic infiltrate particularly arranged in a reactive like pattern - No further subtyping of the B-cells	Monotypic 14/18 (78%) $\kappa$ predominant, additional staining for heavy chain expression	- MGUS 3/12 (25%; SPEP) - None (n = 14) t(14;18)(q32;q21) - Mass spectroscopy: co-deposition of heavy and light chains in localized AL amyloidosis	ND	- None of the patients developed systemic amyloidosis - 6/14 (43%) had recurrence (either MgzL or amyloidosis)	Lymphoplasmacytic disorder within the spectrum of MgzL
Dacic et al. [40]	11 6/11 NA 5/11 primary ML; either MgzL or CLL	Lung	Primary ML: all cases with a predominant infiltrate of small B-cells	0/6 cases light chain restriction in NA 4/5 light chain restriction in ML (2/5 $\kappa$ ; 2/5 $\lambda$ )	ND	ND	ND	No statement about the further classification of the infiltrate
Lim et al. [41]	6	primary pulmonary MgzL with secondary pulmonary amyloidosis	All cases presented with dense lymphoplasmacytic infiltrate	3/3 $\kappa$	0/6 MGUS (SPEP)	5/6 without evidence of lymphoma	- 2/6 dead (one with progress to DLBCL) - 4/6 alive	Lymphoplasmacytic disorder within the spectrum of MgzL
Walsh et al. [42]	10	Skin	All cases with predominant amyloid deposits and a sparse lymphoplasmacytic infiltrate	7/10 $\kappa$ 3/10 $\lambda$	ND	All except one no evidence of lymphoma	- 4/10 local recurrence - 1 dead	Lymphoplasmacytic disorder within the spectrum of MgzL
Ryan et al. [9]	20	Diverse anatomical sites	8/20 dense B-cell infiltrate (marginal zone immunophenotype) with sparse amyloid deposits 12/20 with dominant amyloid deposits with a sparse lymphoplasmacytic infiltrate	12/19 $\lambda$ 7/12 $\kappa$ shown either by FACS analysis or by in situ hybridisation or by IHC	- 3/11 negative- 8/11 IgM or IgG MGUS (SPEP)	1/5 MgzL lymphoma	- 7/15 AWED - 6/15 AWD - 1 alive (without information) - 1 dead	Lymphoplasmacytic disorder within the spectrum of MgzL
Thompson et al. [43]	11	Larynx	Predominant amyloid deposits with sparse lymphoplasmacytic infiltrate	2/11 $\kappa$ 1/11 $\lambda$ 7/11 no light chain restriction	ND	ND	- 3/11 AWED - 1/11 AWRD - 5/11 DWED - 2/11 DWD	Lymphoplasmacytic disorder within the spectrum of MgzL
Current study	29	Diverse anatomical sites	All cases with predominant amyloid deposits and a sparse lymphoplasmacytic infiltrate, B-cells were arranged in a reactive-like pattern	12/29 $\kappa$ 17/29 $\lambda$	- 2/17 IgG $\kappa$ (SPEP) - 2/17 systemic amyloidosis	3/17 systemic lymphoma	- 9/17 alive - 2/17 DWED	AL-LBN

NA nodular amyloidosis, ND not determined, SPEP serum protein electrophoresis, ML malignant lymphoma, MgzL marginal zone lymphoma, CLL chronic lymphocytic leukemia, DLBCL diffuse large B-cell lymphoma, AWED alive without evidence of disease, AWD alive with disease, DWED dead without evidence of disease, DWD dead with disease, AWRD alive with recurrent disease, MGUS monoclonal gammopathy of undetermined significance, FACS fluorescence-activated cell scanning, IHC immunohistochemistry

AL amyloidosis with a localized B cell lymphoma, which was proposed to be within the spectrum of cutaneous marginal zone lymphomas. Ig-rearrangement analyses were not done in any of the cases. Single case reports and studies with smaller cohorts present localized AL amyloidosis with an associated light chain restricted plasma cell population at different anatomical sites [12, 38, 39]. In all these studies, molecular analyses and assessment of the light chain restriction of the plasma cells have been carried out inconsistently or only in few cases, and a precise classification of the concomitant clonal plasma cell population, especially focusing on the differentiation between an extremely plasmacytic-differentiated marginal zone lymphoma and a pure plasma cell neoplasia, is largely missing (Table 3).

Further, molecular analyses are warranted to differentiate between an extremely plasmacytic-differentiated localized extranodal marginal zone lymphoma and a pure plasma cell neoplasia to shed further light on the diverse etiologies and histoanatomical manifestations of AL amyloidosis.

**Author contributions** Study concept and design was done by CSL and CR. Clinical data were provided by UH and SOS. Surgical pathological data were acquired by CSL and CR. The data were analyzed and interpreted by CSL, JB, and IO. Drafting of the manuscript and critical revision of the manuscript for important intellectual content were done by all authors. Administrative, technical, or material support was provided by UH, SOS, SK, and CR. The study was supervised by CR.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics statement** This project was approved by the local ethics committee of the University Hospital in Kiel conforming to the Declaration of Helsinki (D 581/15-D585/15).

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