ful for 32 cycles and revealed a lambda 3a sequence. There were 6 amino acid substitutions compared with the germ line sequence (Figure 2).

We report systemic AL amyloidosis affecting a father and his son. A possible genetic predisposition for AL amyloidosis would be complex, since all light chains have different amino acid sequences, depending both on the existence of about 50 different light chain variable domain genes and on somatic mutations. The light chain is composed of three segments, the variable (V) domain which is attached to the constant (C) chain via the joining (J) segment. Most of the variation is found in the variable region and in the area around the joining of this domain to the constant part. The literature has documented that the light chain involved in amyloidosis usually consists of the N-terminal part of a monoclonal protein. On the other hand, there have been three cases described where the amyloidogenic protein was from the C-terminal part.[10-12] A missense mutation leading to AL amyloidosis is theoretically possible if it occurs in the gene for the constant or joining segment. This could lead to an amyloidogenic constant or joining region and affect the aggregation propensity of the variable domains. In this scenario, our material should consist of several different variable domains combined with one specific pair of lambda J segment and constant domain. Instead, we found two different monoclonal variable regions. Therefore, other factors are probably involved in the pathogenesis of the disease and may be responsible for the inheritance.

In summary, we report a patient who originally was believed to suffer from familial TTR amyloidosis since his father had died from systemic amyloidosis two decades earlier. However, biochemical analysis of the fibril protein of both individuals showed AL amyloidosis. These patients underline the importance of a direct determination of the amyloid type in all individuals with systemic amyloidosis.

Stina Enqvist,[1] Ulf-Henrik Mellqvist,[2] Johan Mölne,[3] Knut Sletten,[4] Charles Murphy,[5] Alan Solomon,[5] Fred J Stevens,[6] and Per Westermark[1]

[1]Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden; [2]Department of Hematology, Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Department of Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden; [4]Biotechnology Centre of Oslo, University of Oslo, Oslo, Norway; [5]Human Immunology and Cancer Program, Department of Medicine, University of Tennessee Graduate School of Medicine, Knoxville, USA; [6]Biosciences Division, Argonne National Laboratory, Argonne, USA

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Correspondence: Per Westermark, MD, PhD, Rudbeck Laboratory, C5, SE-751 85 Uppsala, Sweden. E-mail: Per.Westermark@genpat.uu.se

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Donor lymphocyte infusions in amyloid light chain amyloidosis: induction of a "graft-versus-plasma cell-dyscrasia effect"

Systemic amyloid light chain (AL) amyloidosis is a rare protein folding disorder with poor prognosis due to multiple organ impairment (mainly heart and kidney). Underlying disease is a monoclonal gammopathy in most patients, only a small portion has symptomatic multiple myeloma. Treatment results in AL amyloidosis have improved in recent years. Apart from high-dose chemotherapy with melphalan supported by autologous stem cells (HDM)[1] and melphalan-dexamethasone combination therapy[2] new drugs active in multiple myeloma (MM) have become available.[3-5] The main goal of treatment is to improve or at least preserve the function of the affected organs by elimination or control of the monoclonal plasma cell disorder.[1] Long-term survival (>10 years) in about 20% of patients with complete remission (CR) after HDM could be shown recently.[6] However, more than 50% of the patients do not achieve CR or relapse after initial therapy. Treatment of these patients has not been well investigated. It was recently shown that allogeneic stem cell transplantation (allo-SCT) could be an option for eligible patients leading to sustained CR.[7] However, allo-SCT is a clinical challenge in this fragile patient group. Donor lymphocyte infusion (DLI) might be an approach to further increase CR rate after allo-SCT using reduced-intensity conditioning (RIC) as shown in MM.[8] However, there are no data about application of DLI in this rare and fatal disorder.

Two patients with systemic AL amyloidosis were treated with allo-SCT in both centers until 2007. We administered DLI in both patients because they did not reach CR after allo-SCT. Patient characteristics and

Table 1. Patients' characteristics.

Age at diagnosis/sex	49/male	60/female
Underlying plasma cell disorder	MM stage I	Monoclonal gammopathy
Monoclonal light chain	κ	λ
Monoclonal protein in serum	IgG 8.8 g/L	Unknown
Monoclonal light chain in urine	1780 mg/day	Unknown
FLC ratio	106 (κ 1300 mg/L)	Unknown
Major involved organ at dx	Kidney	Heart
Chemotherapy before allo-SCT	HDM, Bortezomib	M-Dexa, HDM
Pre-transplantation baseline parameters		
Serum albumin	35 g/L	
Urine total protein	12.5 g/die	
Serum creatinine	1.9 mg/dL	
EF		Normal
IVS		11 mm
Troponin ug/L / BNP in ng/L	<0.01/193	Not done
Karnofsky Index	80	80
Remission prior allo-SCT	PR	PR
Monoclonal protein in serum	2.9 g/L	3.9g/L
Monoclonal light chain in urine	432 mg/die	n.d
FLC ratio	15 (κ 144 mg/L)	0.1 (λ 61 mg/L)
Time dx to allo-SCT	20 months	28 months
Donor/sex	HLA identical sibling/ male	MUD (10/10)/ female
Stem cell source	PB	PB
Conditioning	2 Gy/fludarabine	2 Gy/fludarabine
Donor Chimerism day +30/+100	95% / 100%	99% / 100%
GvHD prophylaxis	CSA, MMF	MTX, ATG
Acute GvHD grade (organ)	1 (gut), day +29	2 (gut), day +85
Treatment of aGvHD, response	None, resolved	Steroids, resolved
Chemotherapy before DLI	Bortezomib	None
Remission prior to DLI	PR	PR
Monoclonal protein in serum	3.3 g/L	4.2 g/L
Monoclonal light chain in urine	400 mg/die	n.d
FLC ratio	2 (κ 30 mg/L)	0.1 (λ 81)
cGvHD prior to DLI	None	None
Time between allo-SCT and DLI	day +207	day +275
cGvHD after DLI	skin and mouth mucosa	skin
Time DLI to CR	41 days	182 days
Remission after DLI	CR	CR
Monoclonal protein in serum	VIFE neg	VIFE neg
Monoclonal light chain in urine	VIFE neg	VIFE neg
FLC ratio	1.1 (κ 37 mg/L)	0.9 (λ 88 mg/L)
Observation since allo-SCT	25 months	27 months
Observation since DLI	18 months	18 months
Current status	alive in CR with limited cGvHD	alive in CR without GvHD
Organ response	yes (kidney)	Clinical improvement (soft tissue, gut)
Current Karnofsky index	100	80

aGVHD: acute graft-versus-host disease; ATG: anti-thymocyte globulin; cGvHD: chronic graft-versus-host disease; CR: complete remission; dx: diagnosis; DLI: donor lymphocyte infusion; Gy: Gray; HDM: high-dose melphalan; HLA: human leucocyte antigen; M-Dexa: melphalan/dexamethasone; MM: multiple myeloma; MUD: matched unrelated donor; PB: peripheral blood; PR: partial remission; VIFE: immunofixation.

treatment results are summarized in Table 1. They received HDM as upfront therapy. Dominant organs involved were kidney in Patient 1 and heart in Patient 2. Patient 2 had further involvement of gut (diarrhea) and macroglossia. Indication for allo-SCT was organ progression due to persistent amyloidogenic light chain production after HDM. RIC was performed with 2 Gy of total body irradiation and fludarabine. Donors were HLA-identical sibling in Patient 1 and HLA-matched (10/10 loci) unrelated donor in Patient 2. The indication for DLI in both patients was persistent amyloidogenic light chain production (without further organ progression) after allo-SCT. A dosage of 5×10^6 and 1×10^6 CD3 positive cells per kilogram body weight was applied respectively. Toxicity was graded according to the Common Toxicity Criteria (*http://ctep.info.nih.gov/reporting/index.html*). Standard criteria were used for grading of acute and chronic GvHD. Response to treatment was defined according to the amyloidosis Consensus Criteria.[9] Organ response of soft tissues and gut (which is not included in the Consensus Criteria) was judged by clinical evidence. Hematologic response to DLI was investigated by free-light chain assay, immunofixation as well as by chimerism analysis of plasma cells as recently described.[10] Written informed consent from the patients and approval from the ethics committee were obtained. Data were analyzed as of August 1st, 2008. The time from allograft to DLI was +207 days for Patient 1 and +275 days for Patient 2 after withdrawal of immunosuppression on day +141 and +190 respectively. No hematologic toxicity and no infections after DLI were observed. Patient 1 experienced limited chronic GvHD of the skin and mouth mucosa and was treated with topical steroids. Patient 2 experienced extensive chronic GvHD and received cyclosporine and prednisone for a short period of time. In Patient 1, CR of MM stage I was induced two months after occurrence of chronic GvHD (Figure 1A). At this timepoint the incomplete plasma cell chimerism converted into a full donor plasma cell chimerism. Organ response of the kidney occurred 15 months later (Figure 1B). Patient 2 achieved CR 5 months after occurrence of cGvHD and full donor plasma cell chimerism followed by reduction of the size of the tongue and frequency of diarrhea (Table 1). The criteria for cardiac response were not yet fulfilled (septum thickness unchanged, cardiac improvement only by one NYHA stage).

Allo-SCT might be a curative approach for AL amyloidosis patients who failed melphalan based chemotherapy,[7] but is restricted to patients having a suitable donor and good performance status. In recent years, the introduction of RIC has allowed also patients with impaired organ functions to receive allo-SCT. It is known that the risk of TRM after RIC is reduced compared to conventional conditioning.[11]

This is the first report of donor lymphocyte infusions in AL amyloidosis. The procedure was safe and successful. Our patients achieved a sustained CR for the first time in their disease course (followed by organ response in Patient 1 and clinical improvement in Patient 2). The conversion to a full donor plasma cell chimerism might be a surrogate marker for a molecular complete response.[10] The efficacy of DLI to induce CR in HDM refractory patients with AL amyloidosis provides strong evidence that potent immunological effects can also be induced in clonal plasma cell disorders other than MM. It might be even more effective in these because the

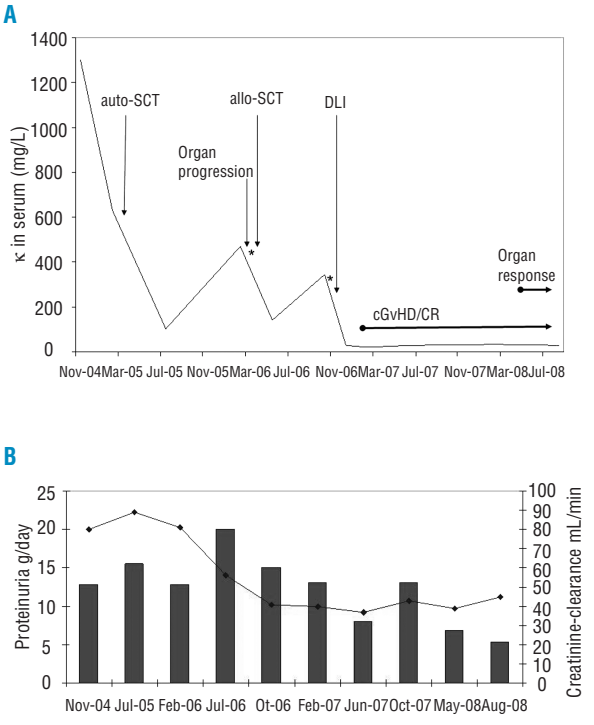

Figure 1. Description of hematologic and organ response in Patient 1 (AL κ+). (A) FLC κ during treatment course. *2 cycles of bortezomib were administered for re-induction before allo-SCT and DLI. (B) Illustration of kidney response. Bars denote proteinuria and the line the creatinine-clearance. A 50% reduction of proteinuria was achieved since May 2008. cGvHD: chronic graft-versus-host-disease; CR: complete remission with conversion to 100% donor plasma cell chimerism; DLI: donor lymphocyte infusion; FLC: free-light chain.

clonal plasma cell burden is not as high and the plasma cells are considered to be more indolent in AL amyloidosis.[12] However, as shown in MM this potent graft-versus-plasma-cell-dyscrasia-effect is also associated with the occurrence of chronic GvHD.

In summary, our report provides the rationale to further investigate allo-SCT and post-transplant immunotherapeutic strategies in systemic AL amyloidosis.

Stefan O. Schonland,[1] Nicolaus Kröger,[2] Christine Wolschke,[2] Peter Dreger,[1] Anthony D. Ho,[1] and Ute Hegenbart[1]

[1]Department of Internal Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg; [2]Department of Stem Cell Transplantation, University Hospital Eppendorf, Hamburg, Germany

Key words: AL amyloidosis, multiple myeloma and other Plasma Cell Dyscrasias; allogeneic transplantation, donor lymphocyte infusion, plasma cell chimerism.

Correspondence: Ute Hegenbart, MD, Amyloidosis Clinic Department of Internal Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Im Neuenheimer Feld 410 D-69120 Heidelberg, Germany. Phone: international +49.6221568001. Fax: international +49.6221564659. E-mail: ute.hegenbart@med.uni-heidelberg.de

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In HPA 1a-immunized women the decrease in anti-HPA 1a antibody level during pregnancy is not associated with anti-idiotypic antibodies

A large screening and intervention study, aimed at reducing morbidity and mortality associated with severe anti-HPA 1a antibody induced neonatal alloimmune thrombocytopenia (NAIT), has recently been carried out in Norway.[1] Recently, it was shown that the anti-HPA 1a levels surprisingly decreased in 92 of 147 women who had been pregnant previously and who carried an HPA 1a positive fetus ($P_{92 \text{ or more of } 147}=0.003$).[2]