Eröffnungssymposium des
Amyloidose-Zentrums Heidelberg
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UniversityHospital Heidelberg

Amyloid: Der fokussierte Blick
Die Sicht des Nephrologen

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Renal Amyloidosis

Kidney Biopsy

frequent renal involvement: kidney biopsy = diagnosis

Cave: frequently hemorrhage, fragility of vessels (endothelial deposition)

renal amyloidosis mainly glomerular lesions

heavy proteinuria

renal insufficiency without heavy proteinuria possible

especially vessels, interstitium

Renal Amyloidosis

Clinical Course

Most common initial manifestation in (AL)-amyloidosis:
nephrotic syndrome, refractory edema

renal involvement is likely: proteinuria> 500 mg/24h
(interdisciplinary guidelines 2006, DGAK)

renal involvement 50-80%
65% > 1 g/24h, 44% nephrotic (up to 30 g/die)

rarely progressive renal insufficiency at diagnosis
rarely nephrogenic diabetes insipidus (collecting duct)
rarely Fanconi syndrome (proximal tubulus)

Renal Amyloidosis

Clinical Course

Progressive loss of GFR: AL > AA > fam. A. ?

Bergesio et al. Renal involvement in systemic amyloidosis. NDT 2008; 23: 941

Renal involvement at diagnosis: 1/3 dialysis-dependent

Median to dialysis: 13,8 month

Survival at dialysis: 8,5 month

Gertz et al. Arch Intern Med 2002; 152: 2245

Higher mortality: sepsis, vessels, cardiovascular

Treatment of Renal Amyloidosis

remission of nephrotic syndrome ?
normalisation / improvement of renal function ?
persistence of renal AL amyloid ?

renal response in 18% of patients
(= reduction proteinuria ≥ 50% c/o progressive RI)
Kyle et al. (N Engl J Med 1997; 336: 1202-1207)

reduction of proteinuria in about 10% of patients
Skinner et al. (Am J Med 1996; 100: 290-298)

Treatment of Renal Amyloidosis

renal response in 36% of surviving patients (12 mo.)
(> 50% reduction proteinuria + < 25% reduction creatinine clearance)

hematological remission = reduction of proteinuria
(9,6 g/24h to 1,6 g/24h after 12 months)
no change in proteinuria if disease persistence

hematological remission = renal response (71%)

86% of surviving patients ≥ 75% baseline Krea-Clear.
8% dialysis-dependent

Dember et al., Ann Int Med 2001; 134: 746-753
Skinner et al. Ann Int Med 2004; 140: 85-93

Renal Amyloidosis

Clinical Course

Regression of Amyloid ?

2 patients with biopsy-proven renal AL amyloidosis (7g/24h)

after successfull HDCT + PBSCT < 2 g/24h, but Re-Bx c/o regression

Zeier et al. NDT 2003; 18: 2644

Why is reduction of proteinuria possible ?

no correlation between amount of amyloid and function

structural changes influence selective permeability of glomeruli

direct (reversible) toxic effect of light chains ?

precursor proteins, folding intermediates, protofilaments ?

Rapid improvement of function after elimination of light chains

similar effect with AA amyloidosis

HD-Melphalan + PBSCT in AL-Amyloidosis + ESRD

25 patients with ESRD (∅ dialysis 7 Mo.) / 180 patients c/o ESRD
15/25 HDT + PBSCT, mortality peri-SCT 13% (2/15)

hematological CR (ESRD) 53% (8/15), 6/8 CR alive after 4,5 years

Hematological response + mortality comparable !

ESRD: more mucositis, blood products (Ery/Thrombo)
Renal transplantation in individual patients possible!

Casserly et al, Kidney Int 2003; 63: 1051-57

Melphalan / Dexamethason

HDM/SCT vs. Mel/Dex

69/100 with renal involvement (proteinuria 6,7/7,7 g/24h)

Renal response in 8/11 patients (n=73; 13/29 + 17/44)

3 year survival 37 vs. 70%

1/3 Pat. dialysis-dependent

Jaccard et al. NEM 2007; 357: 11

Who can receive a kidney transplant ?

experiences especially in AA amyloidosis

Recurrence, perioperativ mortality (pneumonia, sepsis)

Living Kidney Transplantation + PBSCT

goal: stable (sufficient) kidney function

chance to give high-dose chemotherapy

better chance to reach remission ?

Leung et al, AJT 2005; 5: 1660

kidney transplantation can´t prevent complications after SCT !

stable kidney function during SCT

ARF during HDCT / PBSCT

„postconditioning renal insufficiency“ (> 50% Crea ⇧ /48h)
typical in amyloidosis (compared to multiple myeloma)

ARF in 20% of patients with AL amyloidosis
dialysis in 13,8% of cases with ARF

recovery of kidney function in 45% of patients (n=173)

Fadia et al. Kidney Int 2003; 63: 1868

recovery of kidney function in 1/11 of patients / 8/11 died (n=80)

Leung et al. Am J Kidney Dis 2005; 45: 102

early refferral to dialysis treatment ? (Crea > 3 mg/dl)

Fallbericht

Pat. ♀, 66 years

AL amyloidosis, kappa: diagnosis 2001

Organ involvement: kidney, colon, heart (*tongue, liver*)

VAD / HD-Ifosfamid / Melphalan 100 mg/m^2 + PBSCT

complete remission (FLC, IFE, cytology) 2002

Dialysis-dependent since 06/2001

Traumatic splenic rupture + splenectomy 2001

→ Kidney transplantation 02/2008

highly immunized, PRA 99%, 2 MM (0-1-1), AM, 4x PPh

Krea 04/09 0,78 mg/dl, no proteinuria

Renale Amyloidose

Weshalb ist die Niere betroffen ?

Häufige Nierenbeteiligung bei AL, AA, Fibrinogen, ApoAII, weniger ApoAI, Lysozym

Position der Mutation des ApoAI-Proteins ?
→ Amino-terminaler Anteil = Nierenbeteiligung ?

„Kidney tropism“ spezifischer Leichtketten ?

Aufnahme amyloidogener Proteine durch Mesangialzellen ?

Negative Ladung bzw. hoher Glykosaminglykananteil der glomerulären Basalmembran ?

Renale Amyloidose

Wie schädigt Amyloid die Niere ?

Zerstörung der Gewebearchitektur

→ fehlende Korrelation zwischen Amyloidmenge und Funktion

Nephrotoxizität

→ Vorläuferproteine, „folding intermediates“ oder Protofilamente ?

→ rasche Reduktion der Proteinurie bzw. Verbesserung der Nieren-funktion nach Reduktion der Leichtketten

→ ähnlicher Effekt bei AA-Amyloidose beobachtbar

→ keine Regression des Amyloids in Bx trotz klin. Besserung