Classification of systemic amyloidoses

Amyloidosis-Type	Precursor Protein	Clinical Association
Acquired		
AA	SAA	Rheumatoid arthritis, chronic-inflammatory bowel diseases, bronchiektasia, tuberculosis, leprosis, lues, Mucoviscidosis
AL	**light chain**	**Multiple Myeloma, monoclonal gammopathy, Waldenstrom´s Disease**
Aβ2M	β2-Mikroglobulin	Dialysis
ATTR	Transthyretin	Senile systemic amyloidosis
Inherited		
ATTR	Transthyretin	FAP: Familiar Amyloid-Polyneuropathy, FAC: Familiar Cardiomyopathy
AFib	Fibrinogen	
Apo A1/2	Apolipoprotein	
ALys	Lysozyme	
AGel	Gelsolin	

Adapted from Westermark, *Amyloid* 2002

UniversityHospital Heidelberg

Light chain (AL) amyloidosis

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Amyloidosis Center
University Hospital Heidelberg

Opening Symposium; Heidelberg, 02.05.09

Clinical manifestation

Site	AL	AA	ATTR	AApoAI	AApoAII	ALys	AFib	AGel
Kidney	++	++	(+)	++	++	++	++	(+)
Heart	++	(+)	++	++	+	–	–	(+)
PNS	+	–	++	+	–	–	–	++
ANS	+	+	++	–	–	–	–	(+)
Liver/spleen	+	+	–	++	–	++	(+)	–
GI	+	+	–	–	–	+	–	–
CNS	–	–	+*	–	–	–	–	–
Skin	+	–	–	+	–	+	–	++
Eye	–	–	++	–	–	–	–	++
Testis	–	+	–	++	–	–	–	–

Merlini, *Blood* 2007

Light chain amyloidosis (AL)

- Monoclonal plasma cell disorder
  - lambda predominance
- Multiple myeloma or Waldenstrom´s disease is the underlying diasease in about 10%
- Incidence: 5-13 new diagnoses / 1 mio. / year
  (Falk, NEJM 1997)
- Median age at diagnosis about 65 years
- Predominance of males

Light chain amyloidosis (AL)

- Bad prognosis due to fast developing organ failure

- Median Survival:
  - 13 months after diagnosis
  - Cardiac failure present: 5 month

(Kyle, Semin Hematol 1995)

Diagnostic algorhythm

Amyloidosis suspected:

- Biopsy / Kongo-Red staining
- Typing of amyloidosis
  - Evaluation of gammopathy
  - Immunohistology
  - Germ-line mutation analysis
- Organ involvement / Performance Status
- Treatment recommendation

Amyloidosis suspected

- Myocardial hypertrophy without hypertension
- Orthostatic dysregulation and dizziness without vascular cause
- Nephrotic syndrom
- Chronic diarrhea
- Hepatomegaly / AP elevation
- Spontaneous skin bleedings without anticoagulation
- Fast worsening polyneuropathy
- PNP without diabetes, positive family history
- Carpaltunnel syndrome
- Ongoing hoarseness
- Weight loss

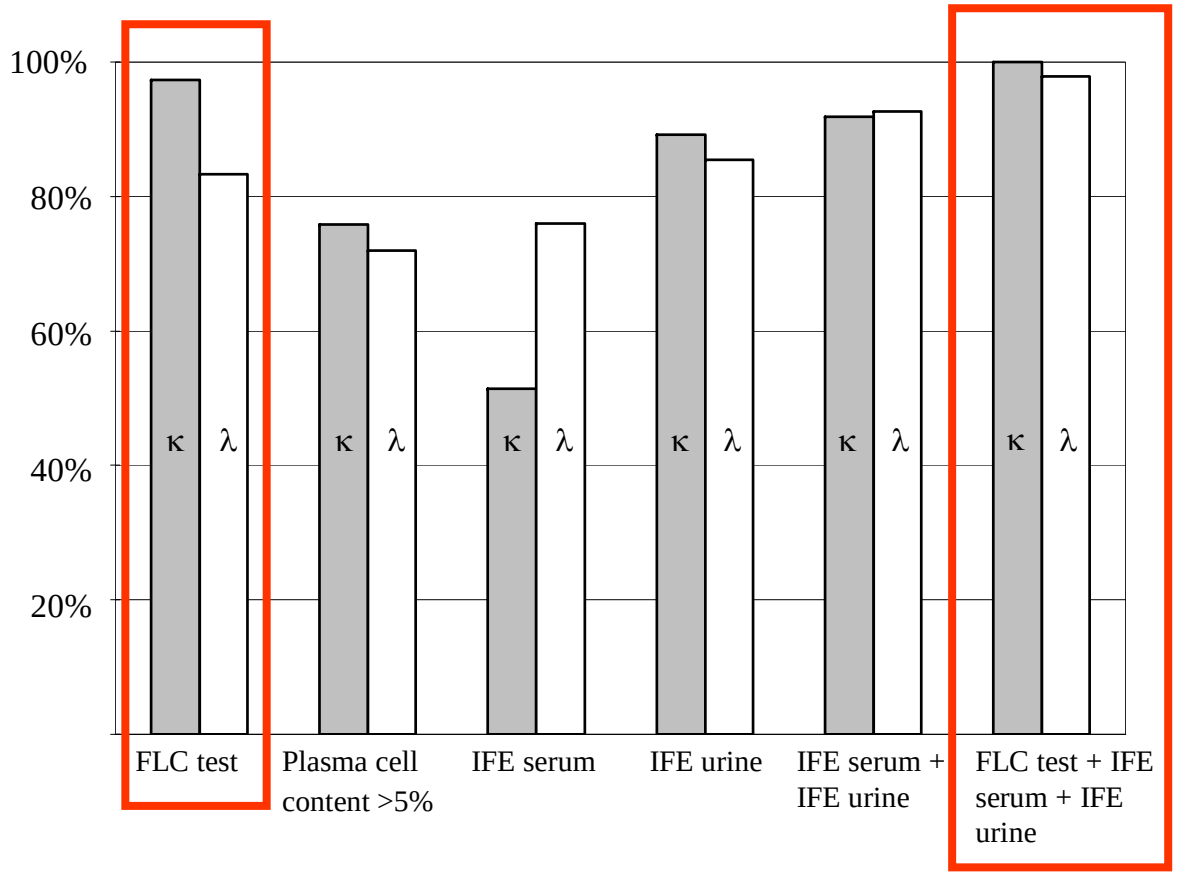
Typing of amyloidosis
Gammopathy

- Serum electrophoresis
- Immunfixation
  - Serum
  - Urine
- Presence of monoclonal light chain
  - **Serum (free light chains)**
  - Urine (24h collection)
- Bone marrow cytology / biopsy

- Sceletal X-ray / CT bone scan / MRI

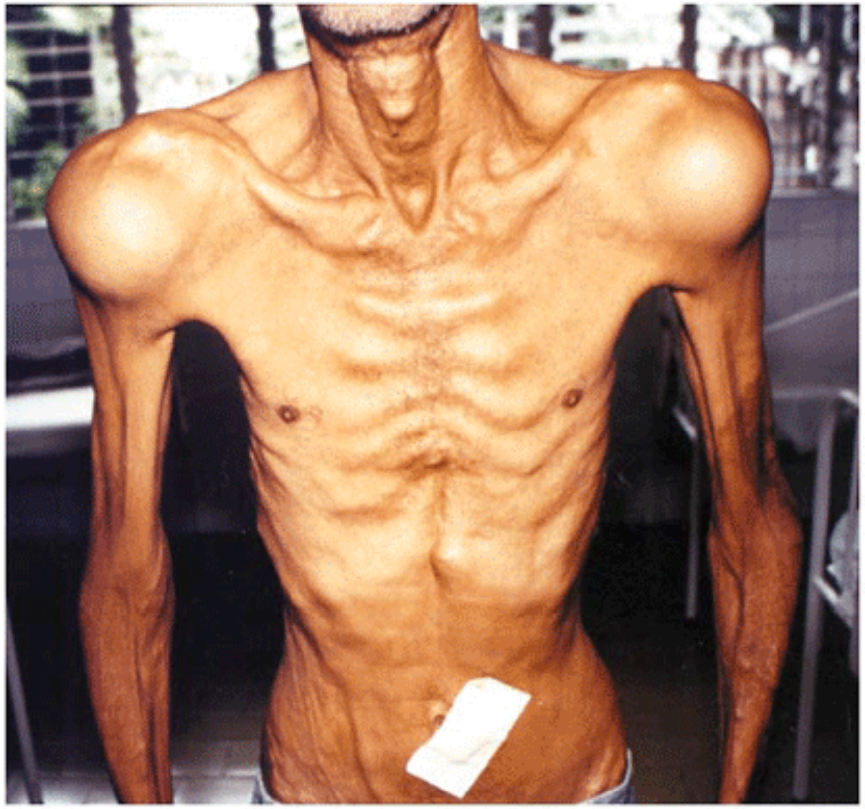
Gammopathy in AL amyloidosis

Sensitivity of FLC



Bochtler, *Haematologica* 2008

Pathognomonic symptoms of AL amyloidosis



NEJM, 2005

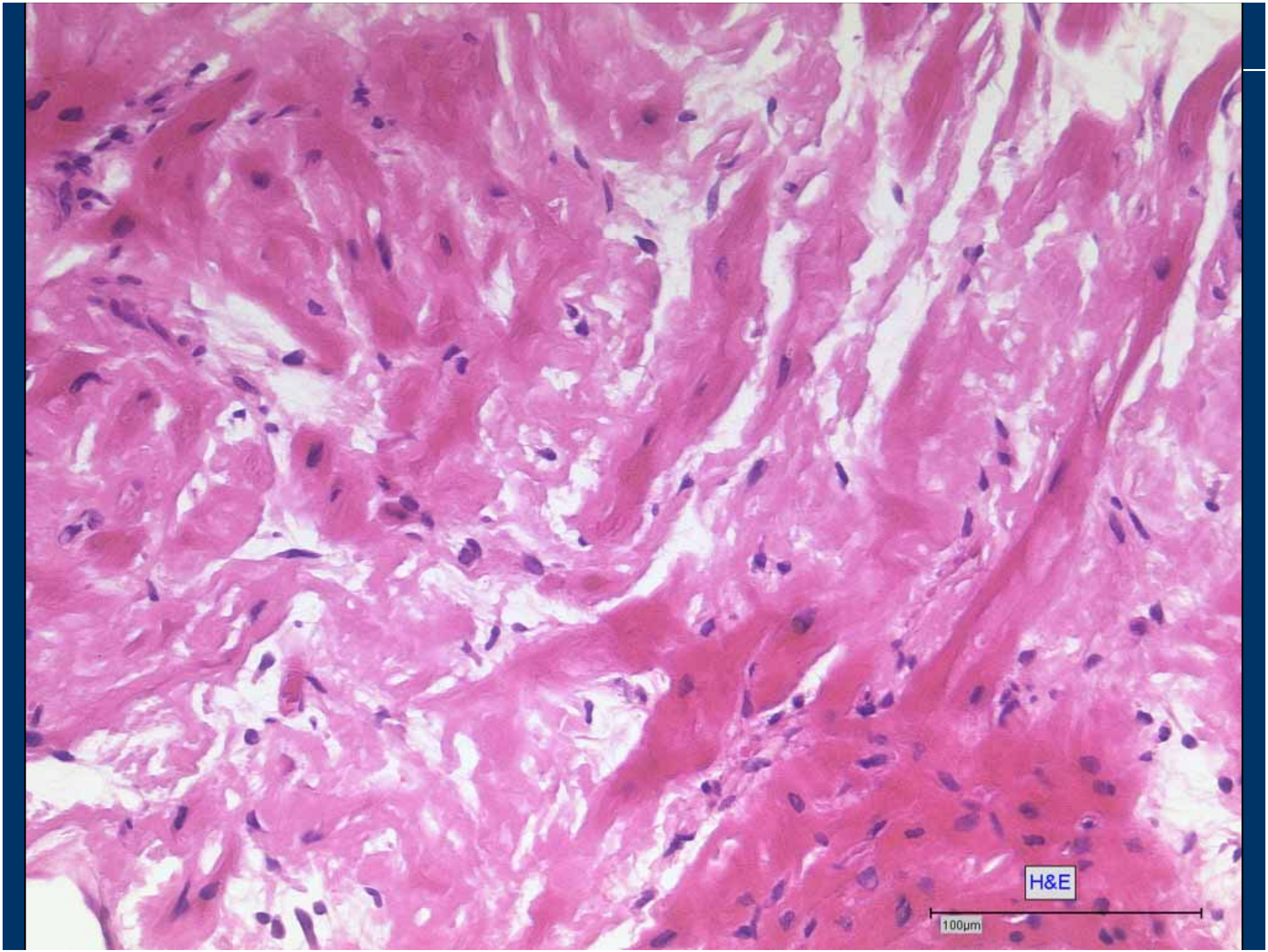
Typing of amyloidosis
Immunhistology and mutation analyses

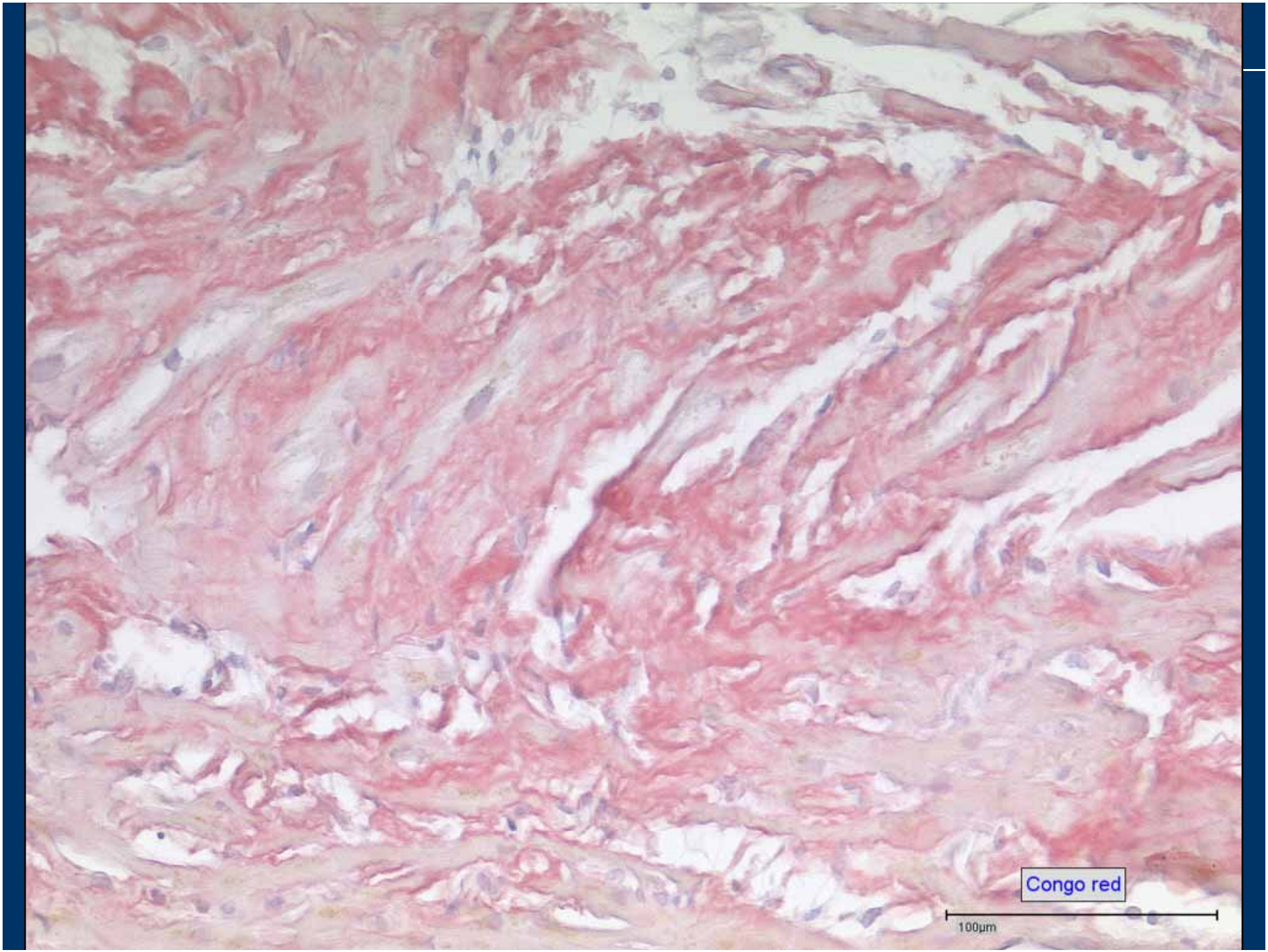
- Amyloid typing on tissue biopsies
- Presence of hereditary forms
  - Genotyping (TTR, Apo A, Fib-alpha)

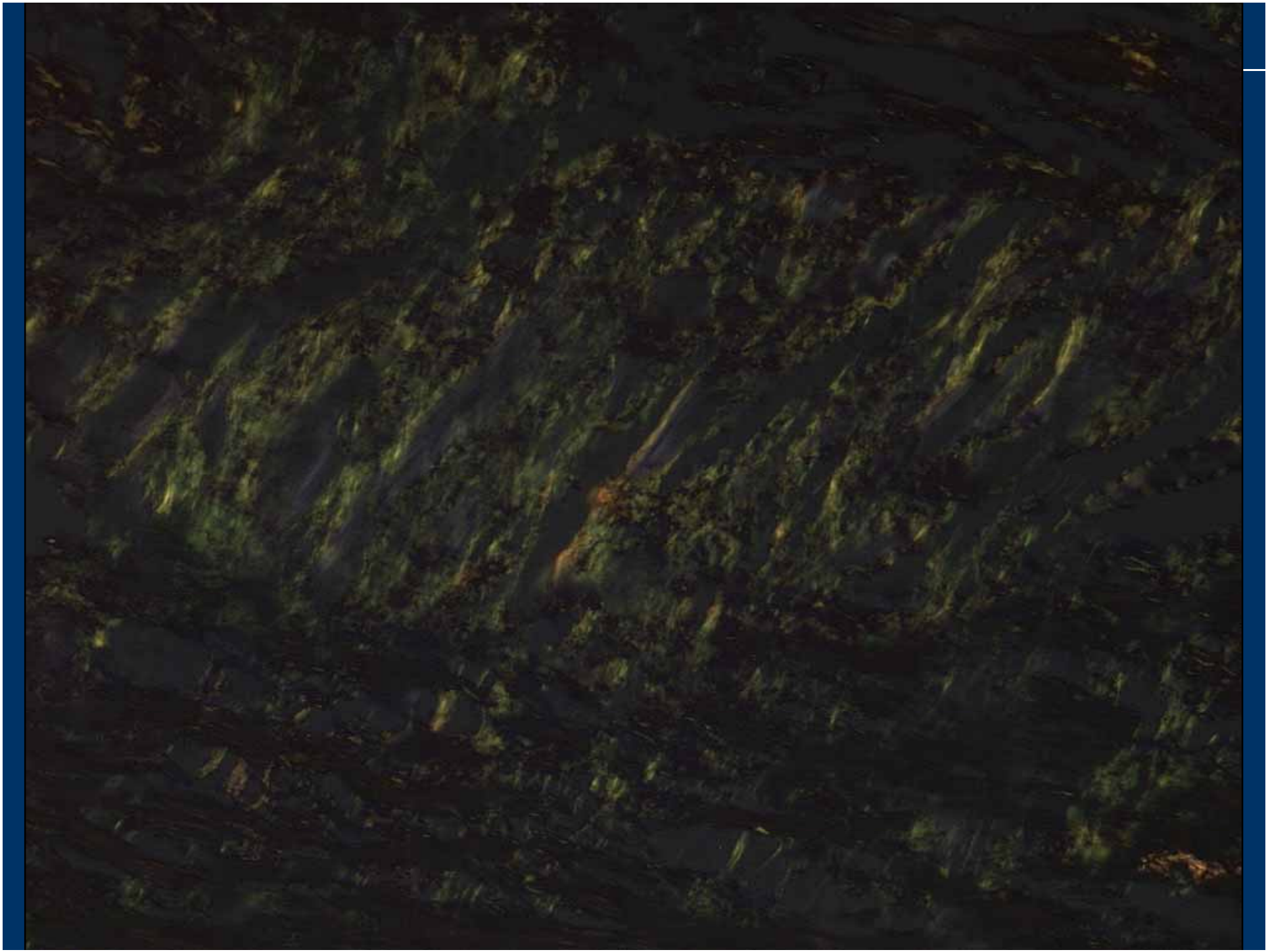
- **<u>Cave misdiagnosis</u>**
  - In older patients (senile TTR amyloidosis)
  - Concomitant presence of monoclonal gammopathy and a hereditary amyloidosis

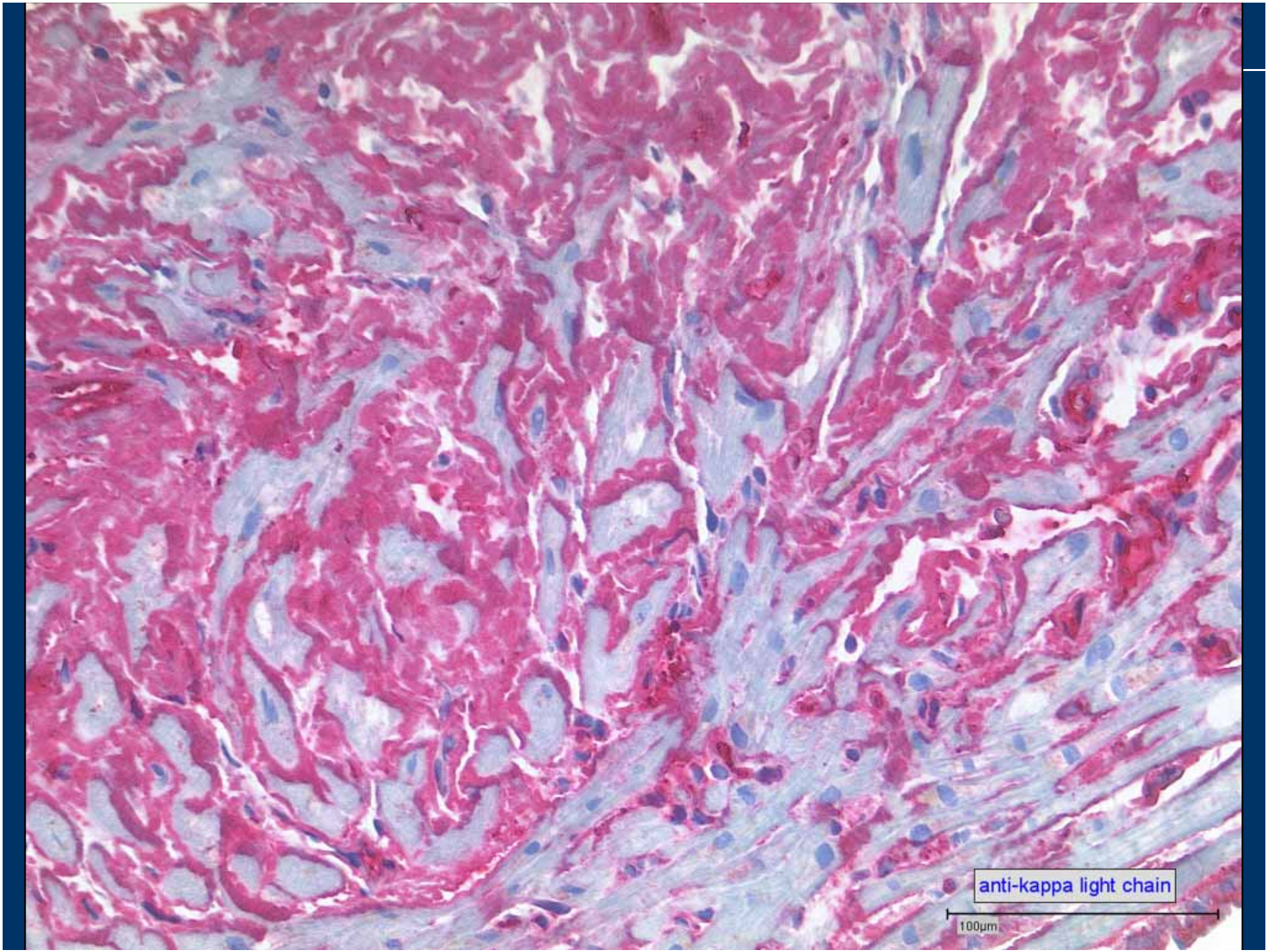
Immunohistology

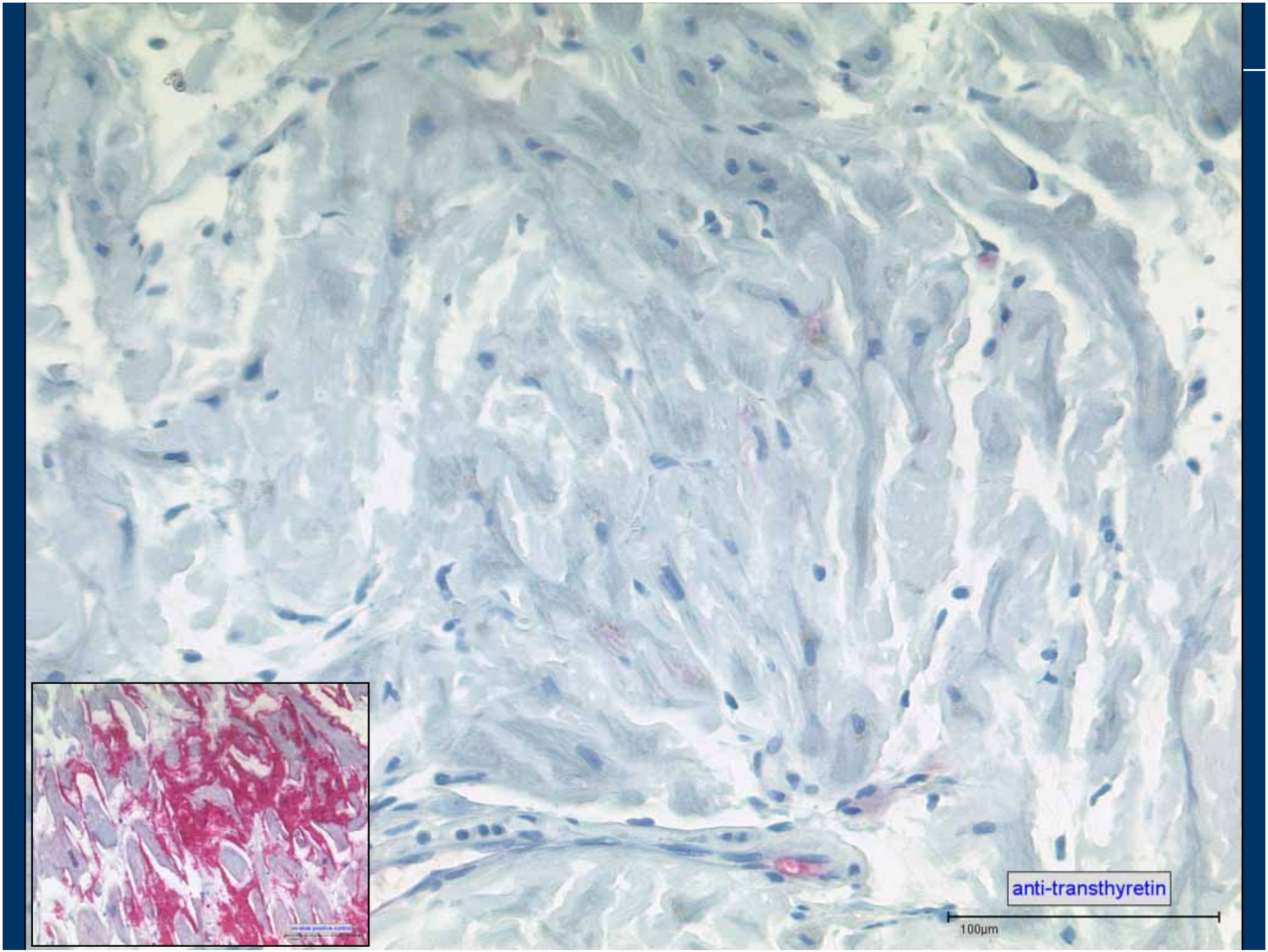
- Patient with kappa AL (Heart Biopsy)
  - Prof. C. Röcken, Kiel

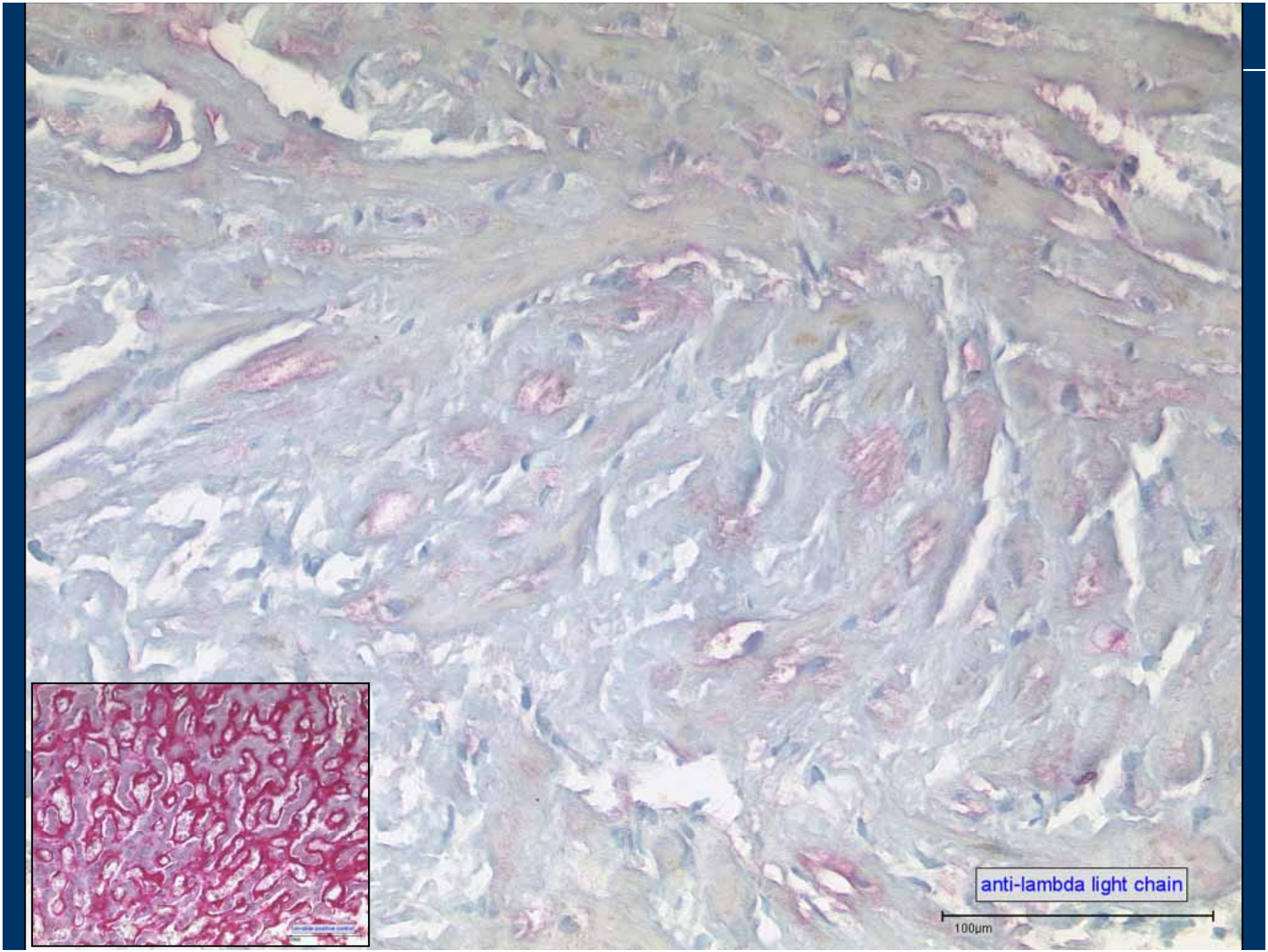

H&E
100µm


Congo red
100µm




anti-kappa light chain
100µm

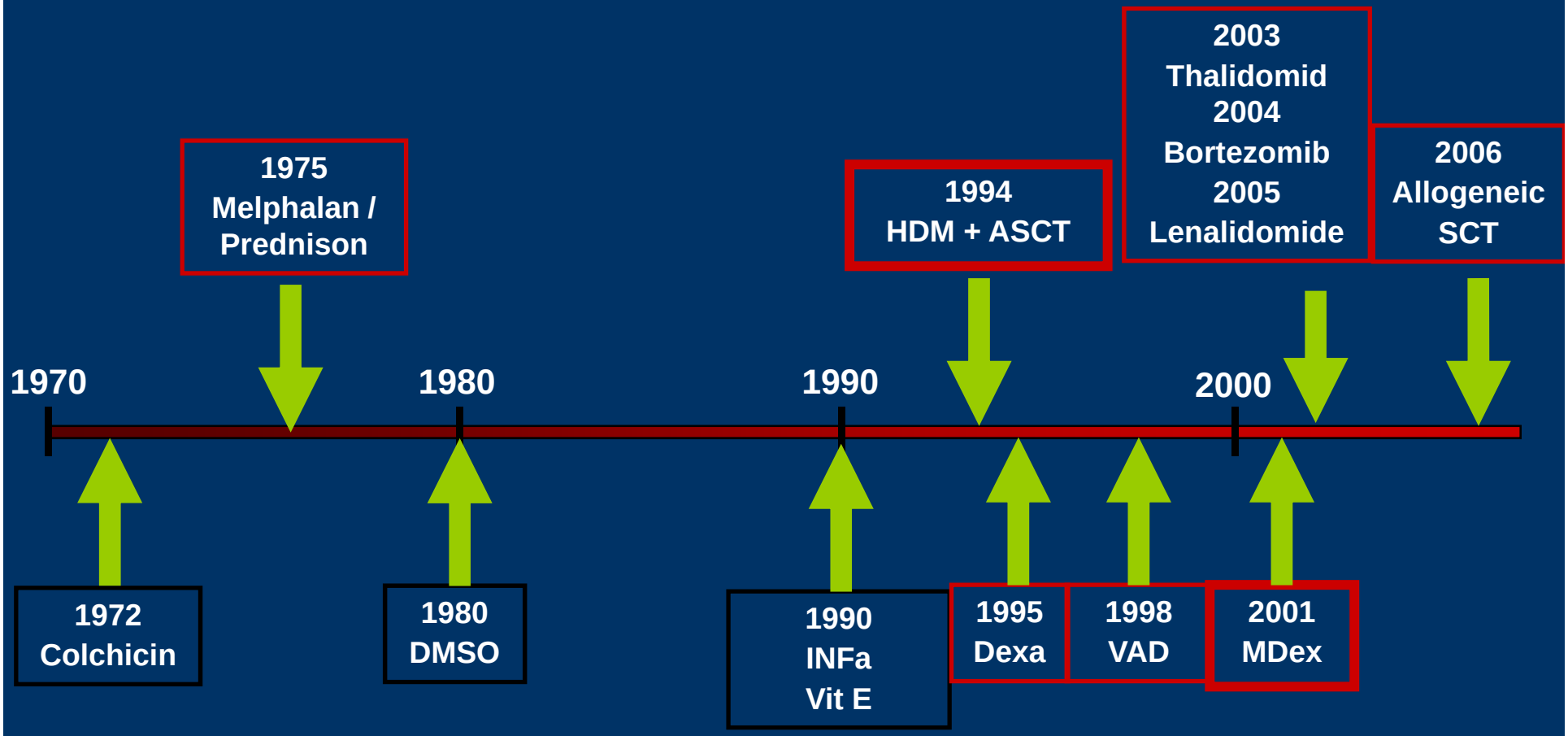

anti-transthyretin
100µm


anti-lambda light chain
100µm

Therapeutic goal

- Reduction / Elimination of the plasma cell clone
  - Sustain or improve function of involved organs
  - Avoid new organ involvement

Therapy of AL Amyloidosis



High-dose melphalan / autologous stem cell transplantation (HDM)

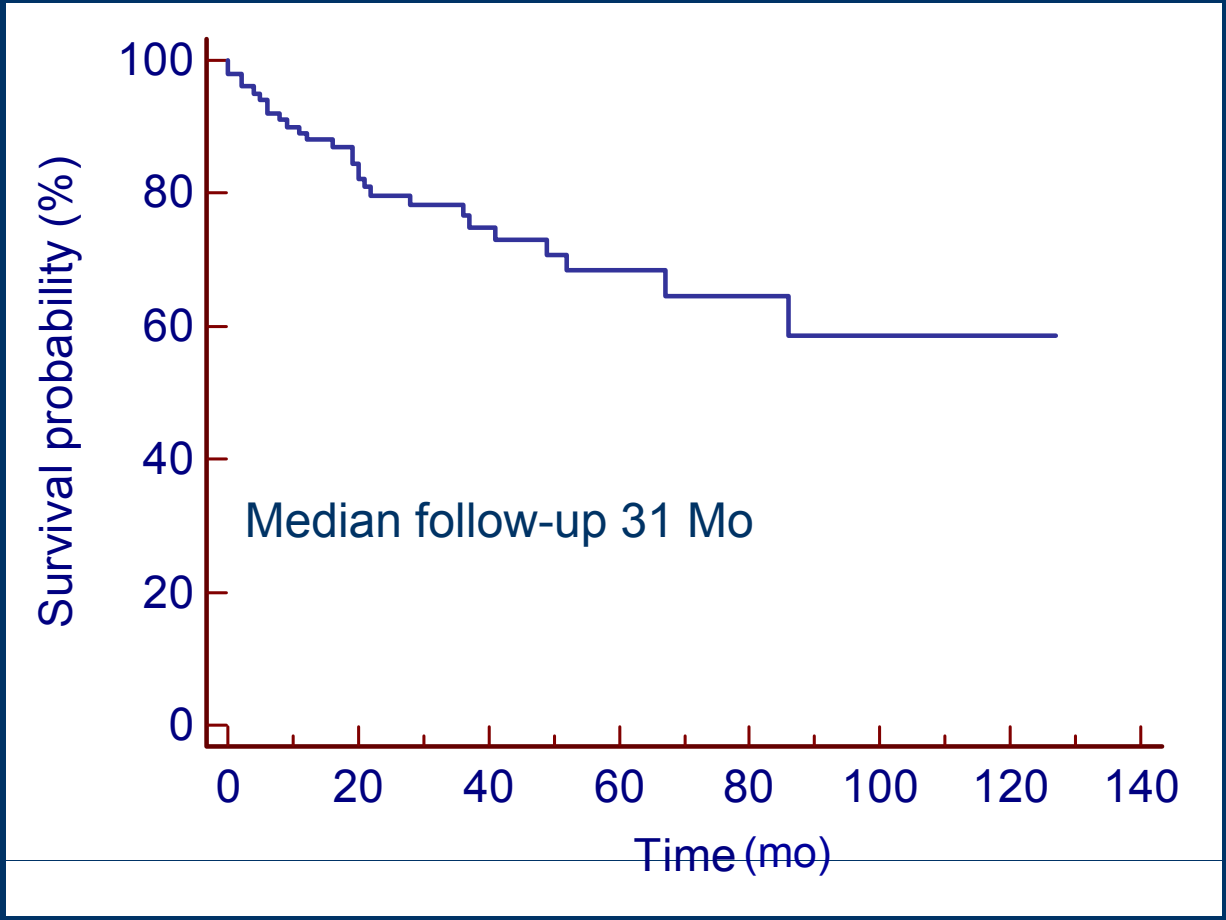
Patient selction (at Heidelberg)

- Age < 70 years
- NYHA Stage < III
- WHO PS < 3
- Systolic RR ≥ 90 mm Hg
- no symptomatic effusions

High-dose melphalan

Age at Tx, years	57 (35-69)	
Males / Females	56 / 44	
Results		
Complete remissions	42 / 95	44%
Partial remissions	32 / 95	34%
Organ response	40 / 92	43%
Mortality	3 / 100	3%

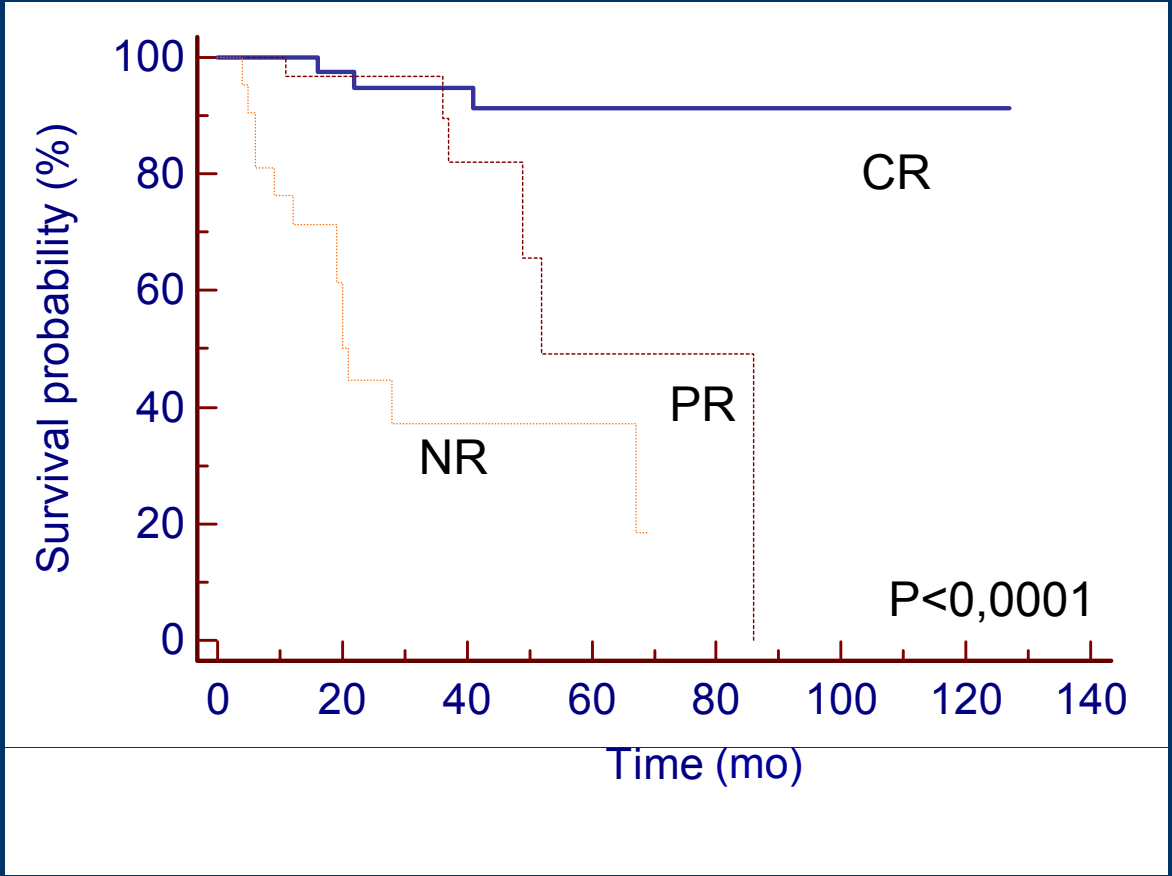
High-dose Melphalan
Overall survival, N=100



High-dose melphalan

Importance of CR achievement

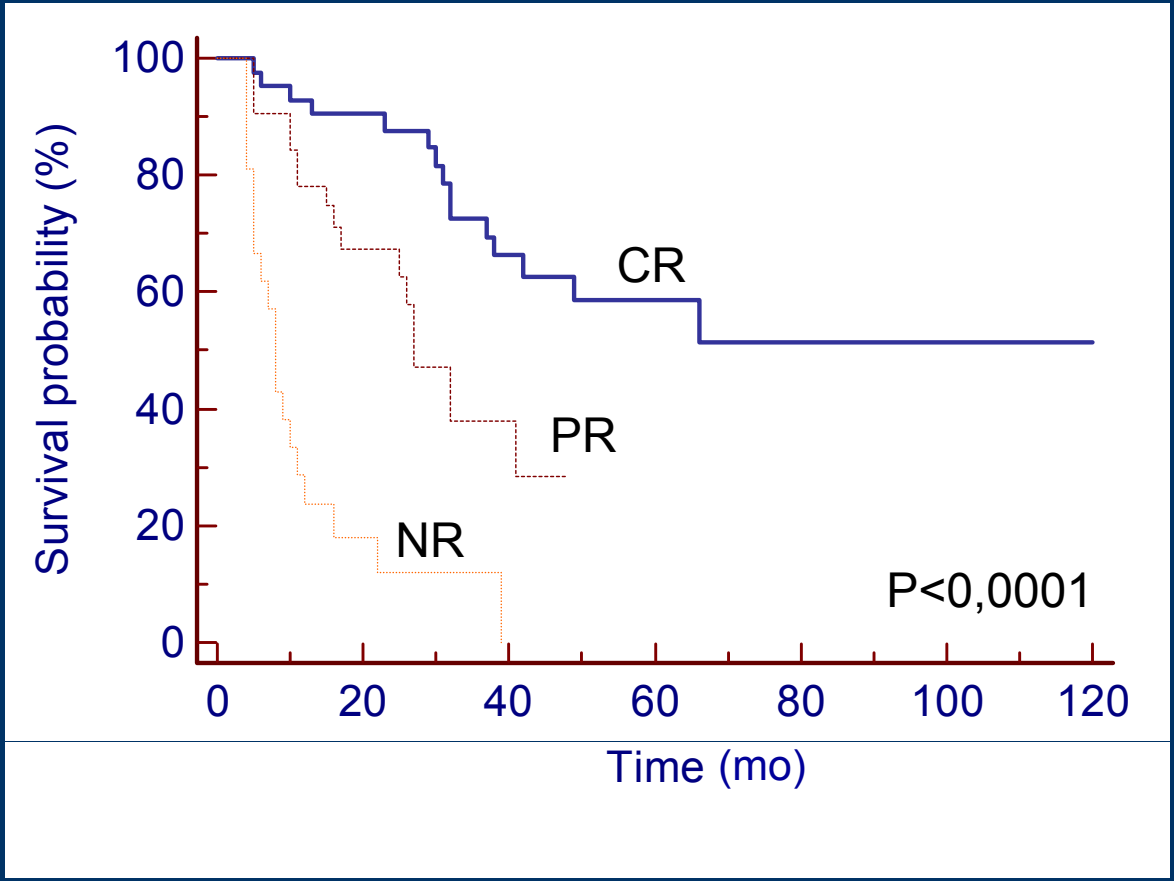
Overall Survival (N=95)



High-dose melphalan

Importance of CR achievement

Event-free-Survival



Event def.:
- Death
- Organ progression
- Haem. progression
- Second chemotherapy

Summary

- Diagnostic tools have improved.
- Chemotherapeutic spectrum has importantly widened in the last 10 years.
- HDM ist currently treatment of choice for eligible patients in experienced centres.
- Solid organ transplantation is possible in selected patients.

Perspective

- Conventional chemotherapy in combination with new drugs is currently being tested in clinical trials (L-MD, B-MD)
- Development of new Anti-Amyloid-Treatment

Thanks to

- Martha Skinner and her team

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Medizinische Klinik V

Direktor A.D. Ho

Alle Ärzte und Pflegekräfte, die Amyloidose-Patienten seit 1998 versorgen

Alle Kolleg/innen, die uns Patienten überwiesen haben

UniversityHospital Heidelberg

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