



# Renal Amyloidosis in Behçet's Disease

## *Clinicopathologic features of 10 cases*

Kemal Kösemehmetoğlu, MD and Dilek Baydar, MD  
*Department of Pathology, Hacettepe University Hospital, Ankara, Turkey*



# Behçet's Disease

- Multi-systemic inflammatory disorder
- Young adults
- Incidence: 0.64-421/100000
- Distinct geographic distribution
- Mucocutaneous lesions
  - Oral and genital ulcers
  - Skin lesions (erythema nodosum, acneiform lesions, i.e)
- Multiple organ involvement as a result of vasculitis
  - Uveitis
  - Arthritis
  - GI ulcers, CNS and renal involvement
- No single diagnostic test!



Hulusi BEHÇET  
(1889-1948)



# Renal amyloidosis in Behçet's Disease

- Rare (0.01-4.8%) and late onset (10 years) complication
- AA amyloidosis
- Male predominance
- 5-year survival of 46%

Type of Renal Involvement	No. of Cases	References for Newly Published Cases*
Amyloidosis	108	(9-20)
Glomerulonephritis	88	(11-12,19,21-27)
Renal vascular disease		
Macroscopic vascular disease		
Renal artery aneurysm	18	(28-34)
Renal artery stenosis/occlusion	16	(9,35-37)
Renal vein thrombosis	14	(38-40)
Microscopic vascular disease	7	(41)
Interstitial nephritis	5	(42)
Total	253†	

Akpolat, T., et al. Semin Arthritis Rheum, 2008

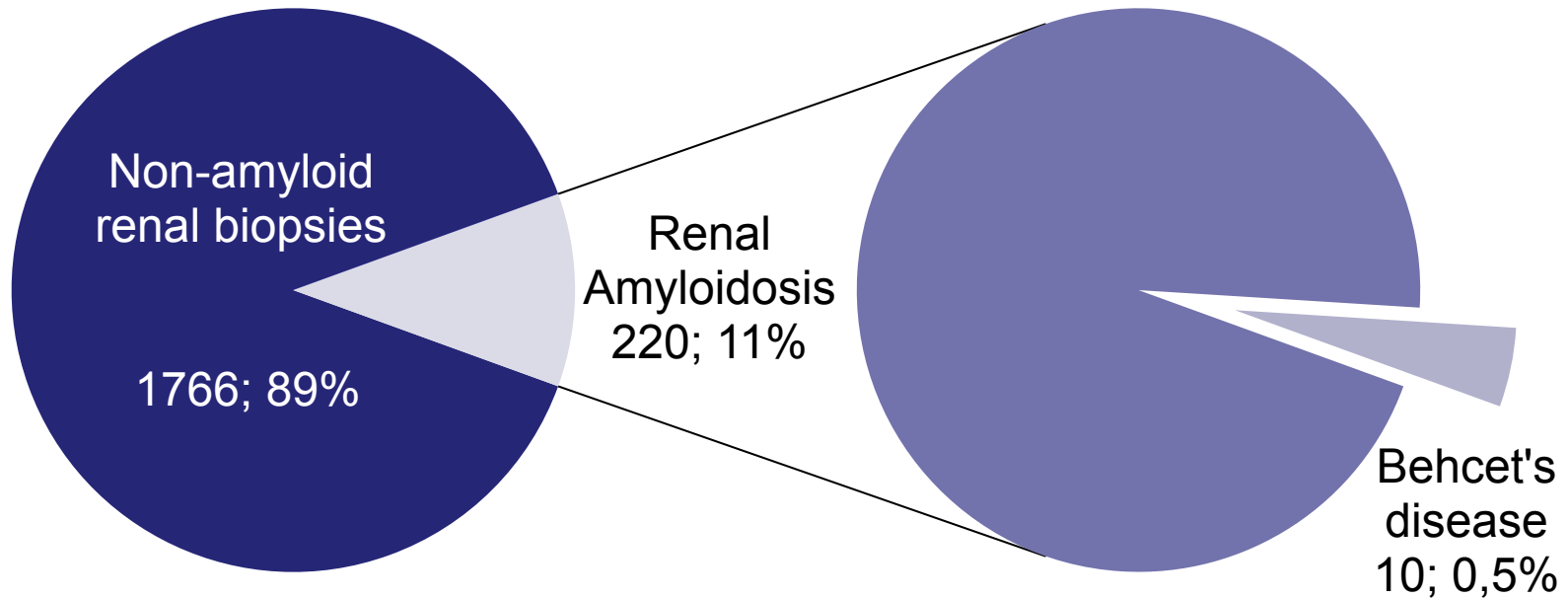


# Material and Methods

- Hacettepe University Hospital, Department of Pathology
- Available clinical information was gathered from hospital records and computer-based patient data system
- For the diagnosis of Behcet's disease, classification criteria of International Study Group were used
- Amyloid typing is performed using immunohistochemistry
  - Amyloid P, Amyloid A, Lambda, Kappa



# Case Selection



10 (5.1% of all renal amyloidosis) cases  
between 1981-2009



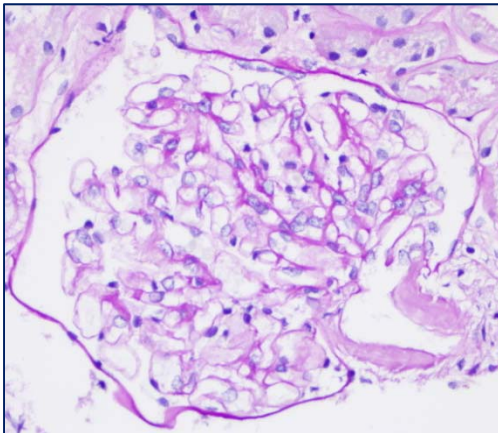
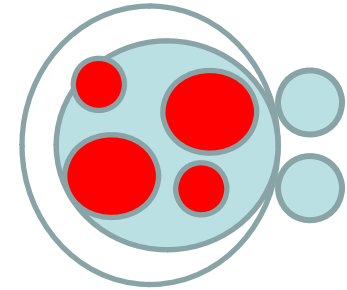
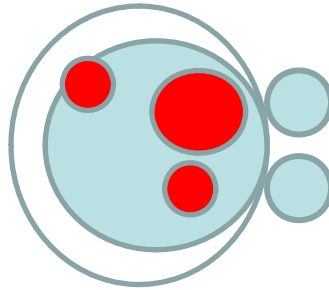
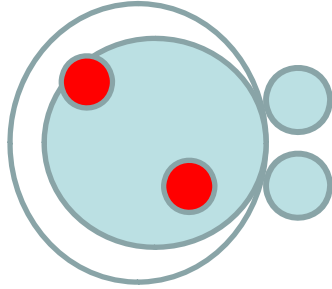
# Glomerular Compartment

1. Severity of glomerular amyloid deposition
2. Glomerular deposition pattern
3. Glomerular size



# Glomerular Compartment

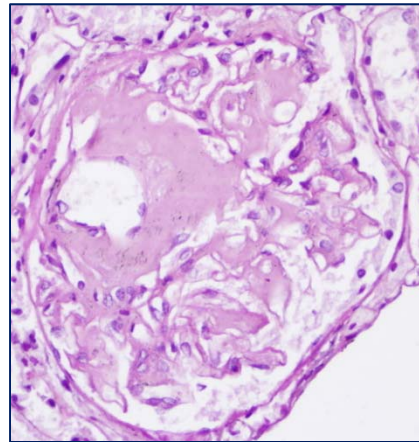
## 1. Extent of glomerular amyloid deposition



<25%



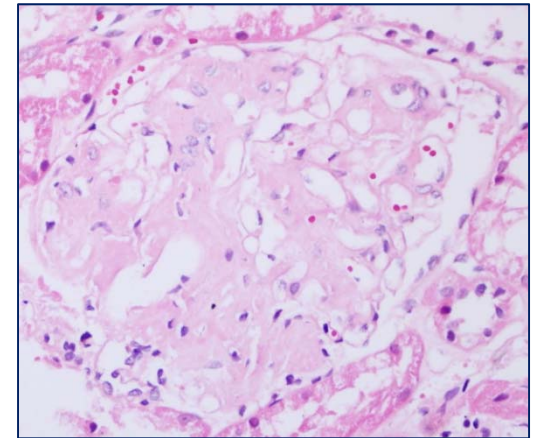
Grade 1



25-50%



Grade 2



>50%

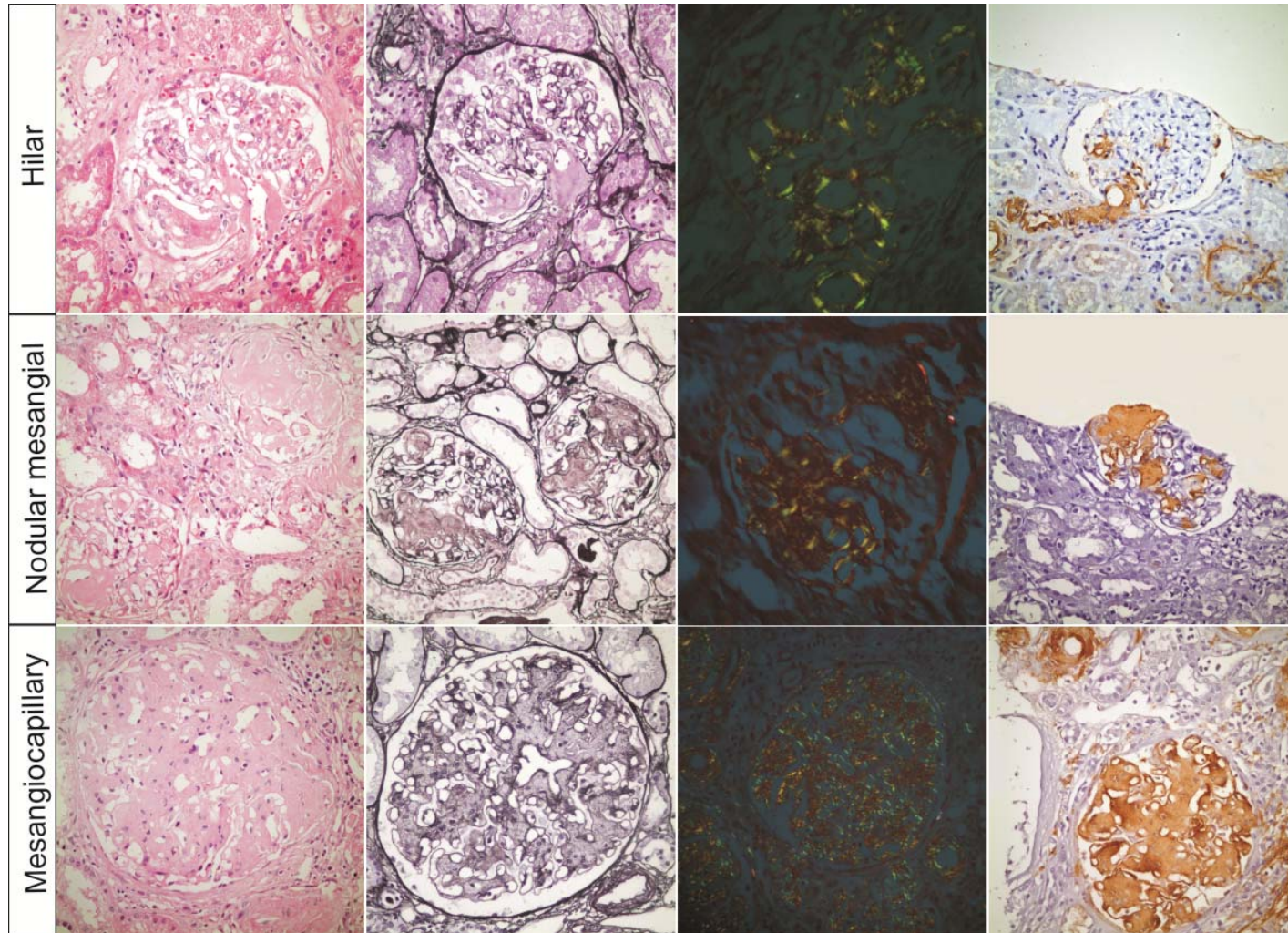


Grade 3



# Glomerular Compartment

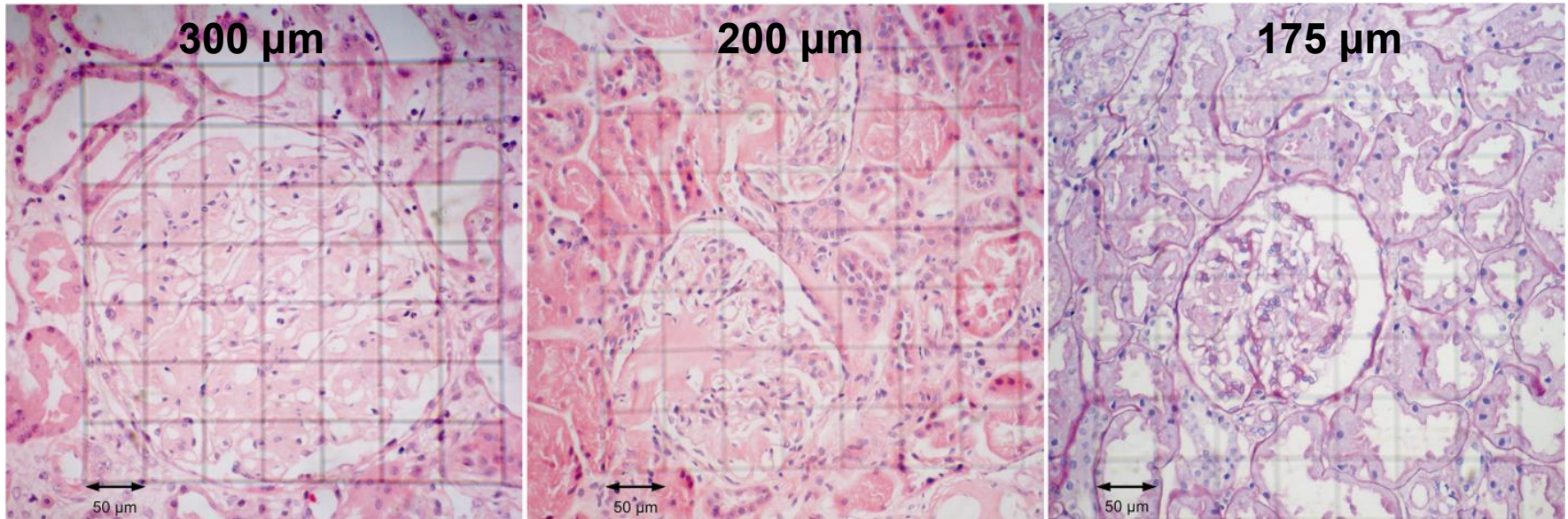
## 2. Glomerular Amyloid Deposition Patterns



# Glomerular Compartment

## 3. Glomerular Size

- The largest glomerule was identified for each biopsy and its diameter was measured by 20.4CM10/100SQ ocular micrometer
- Mean human glomerule diameter: 201  $\mu\text{m}$  (110-276  $\mu\text{m}$ )



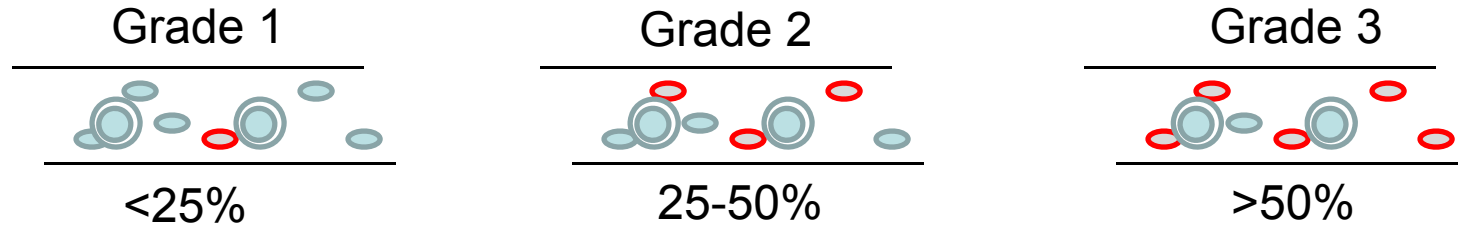


# Interstitial Compartment

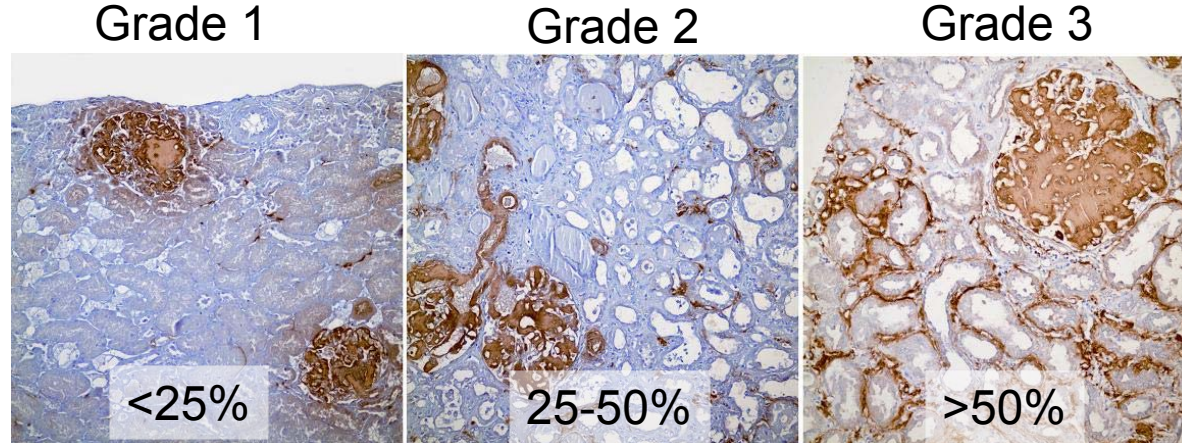
1. According to the extent of tubular atrophy and fibrosis, chronic tubulointerstitial damage was graded as
  - <25% —————> Grade 1
  - 25-50% —————> Grade 2
  - >50% —————> Grade 3
2. Presence of interstitial amyloid fragments
3. Presence of amyloid in tubular basal membrane
4. Presence of interstitial inflammatory cells

# Vascular Compartment

## 1. Extent of arteriolar amyloid deposition



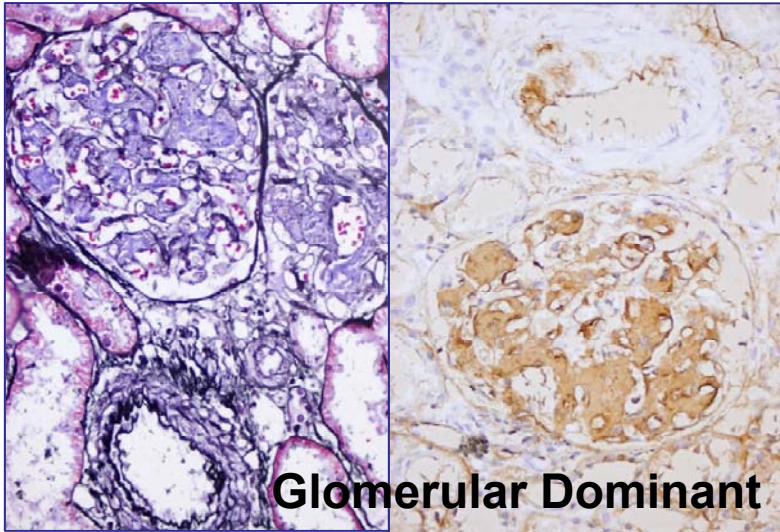
## 2. Extent of peritubular capillary involvement



## 3. Presence of amyloid deposition in the wall of arteries

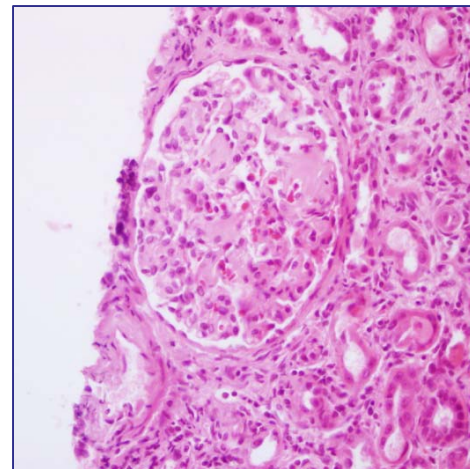
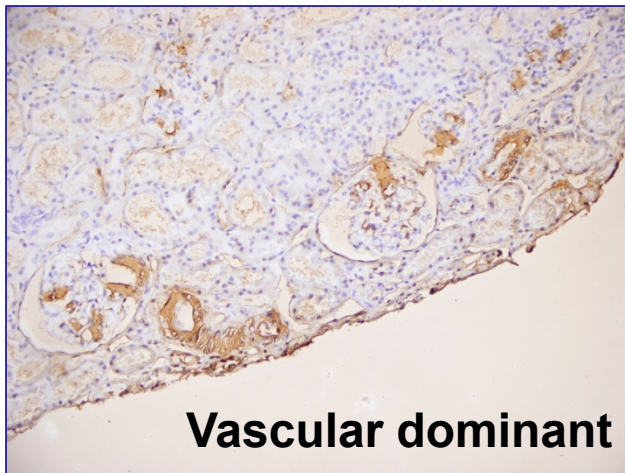
## 4. Presence of vasa rekta involvement

# Form of amyloid deposition



1. Glomerular Dominant
2. Vascular Dominant
3. Co-dominant

Verine, J., et al., Hum Pathol, 2007





# Clinical Findings

- All patients were male
- Mean age: 41±10 (27-56)
- Nephrotic syndrome in ¾ of cases
- None presented with end stage kidney disease

<b>Kidney Function (GFR)</b>	<b># of cases</b>
Normal (≥90 ml/min)	5
Mild dysfunction(60-89 ml/min)	1
Moderate dysfunction (30-59 ml/min)	3
Severe dysfunction (15-29 ml/min)	1
Renal failure (<15 or dialysis)	0

- In majority, sedimentation rate >100 mm/hr



# Presenting Sign&Symptoms for Renal Disease

Edema	90%	(9/10)
Hepatomegaly	63%	(5/8)
Nocturia	42%	(3/7)
Fatigue	40%	(4/10)
Hypertension	33%	(2/6)
Neuropathy	30%	(3/10)
Nephromegaly	30%	(3/10)
Anemia	22%	(2/9)



## Signs for Behçet's Disease

Complete form	63%	(5/8)
---------------	-----	-------

Incomplete form	38%	(3/8)
-----------------	-----	-------

---

Oral ulcer	100%	(8/8)
------------	------	-------

Genital ulcer	88%	(7/8)
---------------	-----	-------

Skin lesions	63%	(5/8)
--------------	-----	-------

Eye involvement	38%	(3/8)
-----------------	-----	-------

Thrombophlebitis	38%	(3/8)
------------------	-----	-------

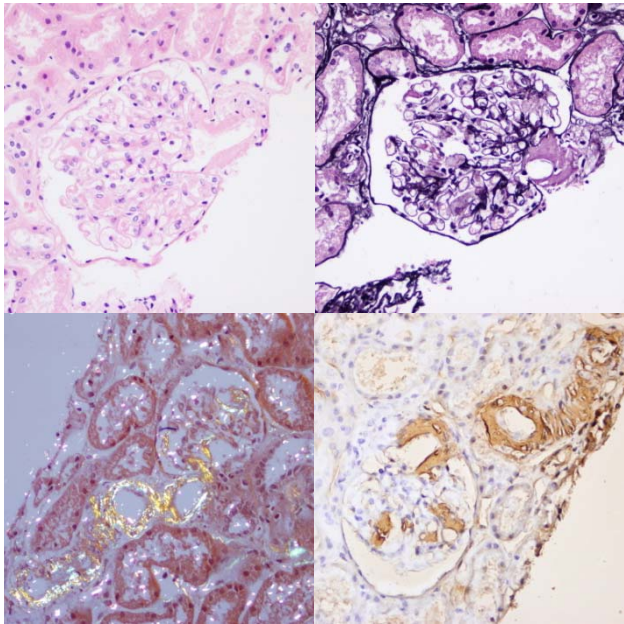


# Morphological Findings

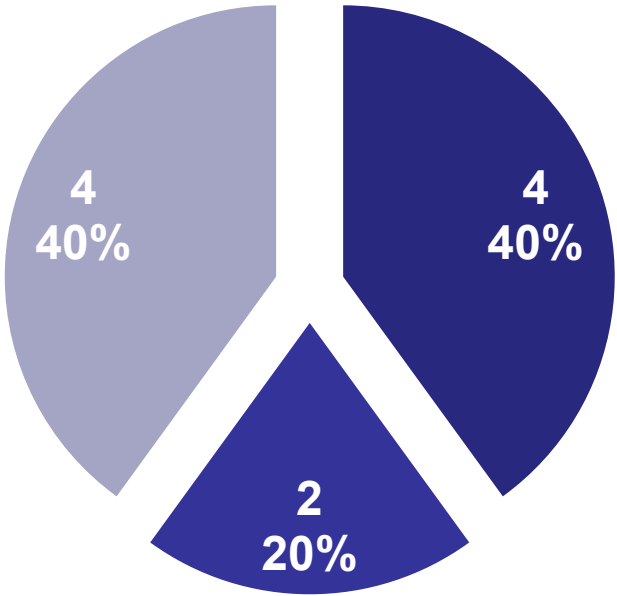
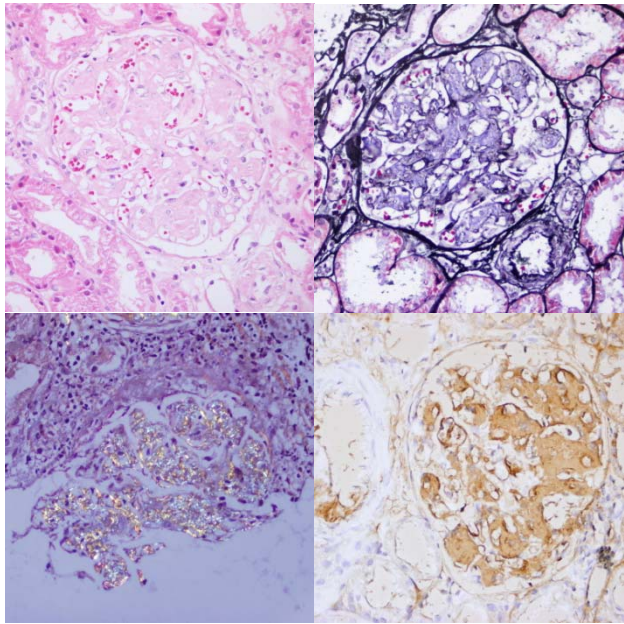
- All of the cases were AA amyloidosis
- $18 \pm 10$  (4-48) glomerules/biopsy
- 7% global sclerosis

# Glomerular amyloid deposition patterns

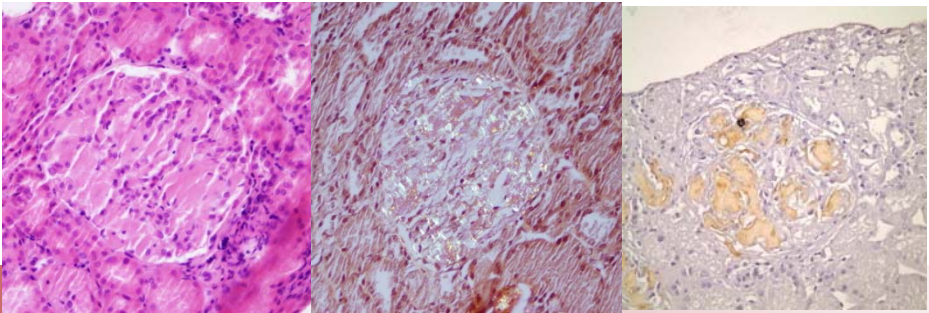
**Hilar**



**Mesangiocapillary**



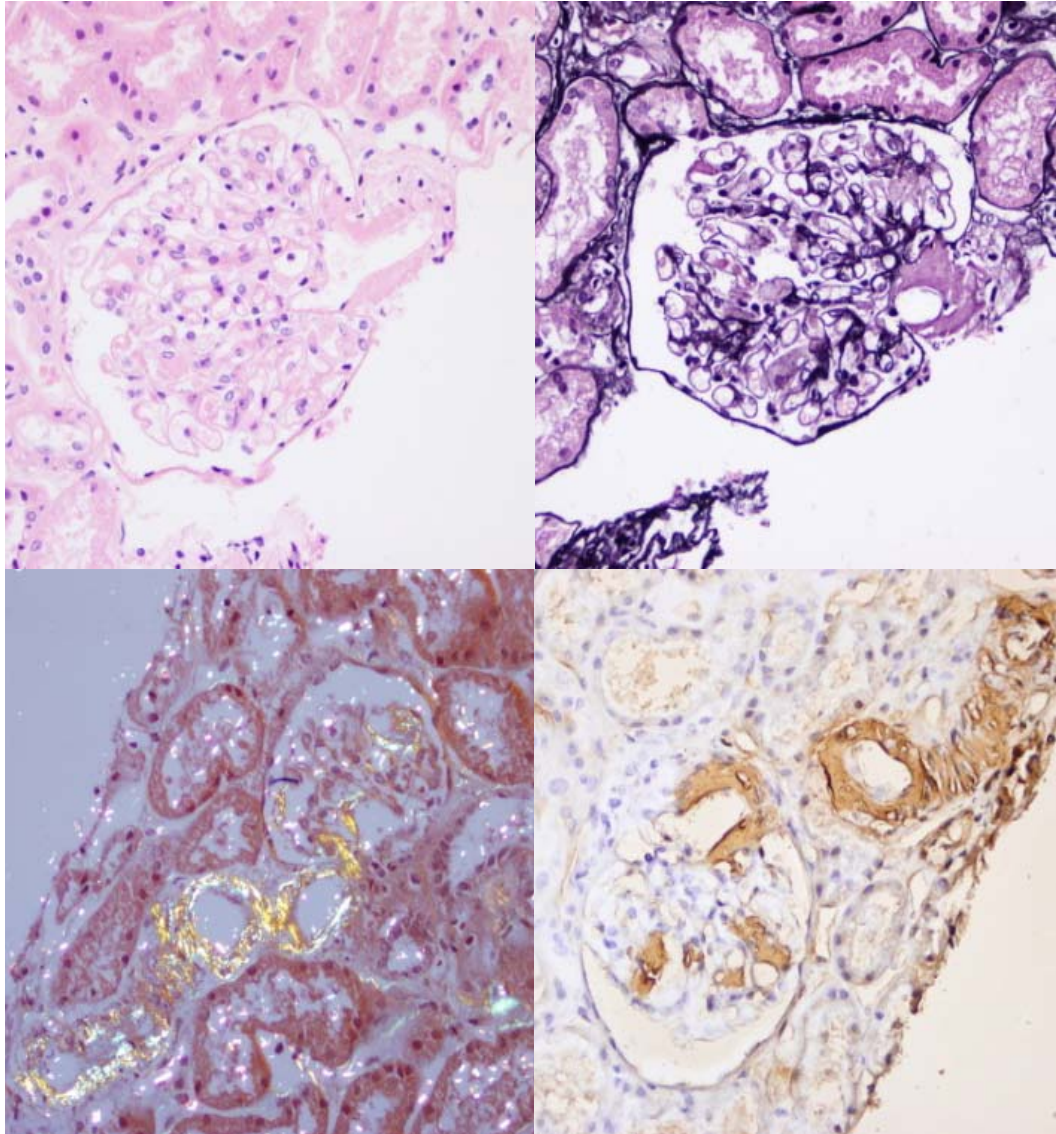
**Mesangial nodular**





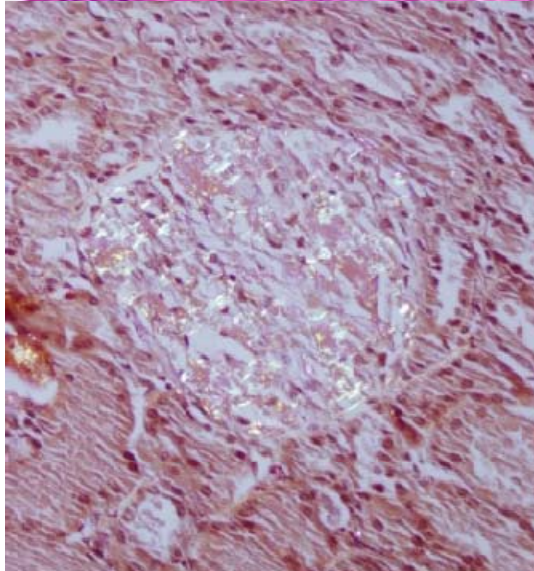
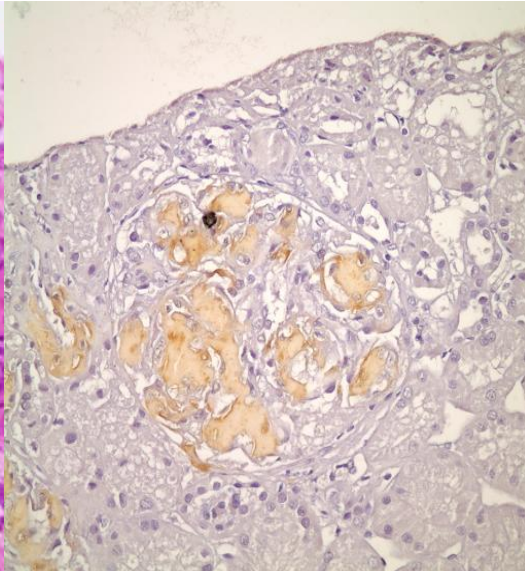
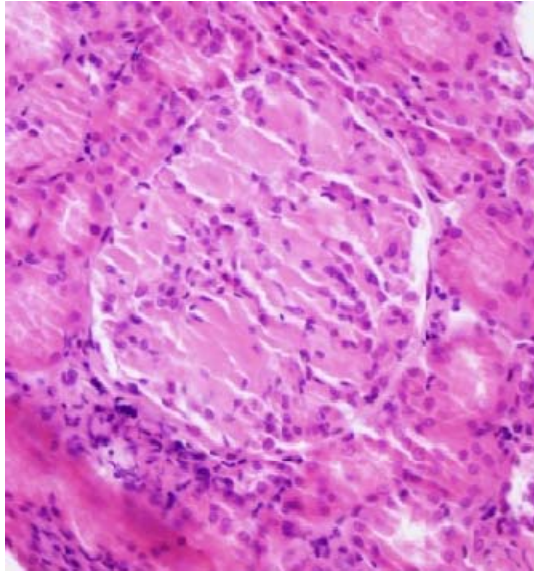
	Age (yrs)	Duration of Behcet's disease (mo)	Serum Creatinin (mg/dl)	Creatinin clearance (ml/min)	Urine protein (mg/day)
<b>Hilar</b>	44±8	92±77	0.97±0.55	91±58	3.2±2.6
<b>Mesangial nodular</b>	37±13	162±42	0.70±0.00	71±44	2.8±0.0
<b>Mesangiocapillary</b>	39±13	90±70	0.83±0.40	80±56	5.9±2.8

- 4 cases had severe proteinuria (>5 g/day)
  - 3 of 4 cases (75%) showed mesangiocapillary pattern
  - All revealed glomerular dominant or co-dominant form of amyloidosis
  - Verine et al. demonstrated that mesangiocapillary pattern and glomerular form are associated with proteinuria



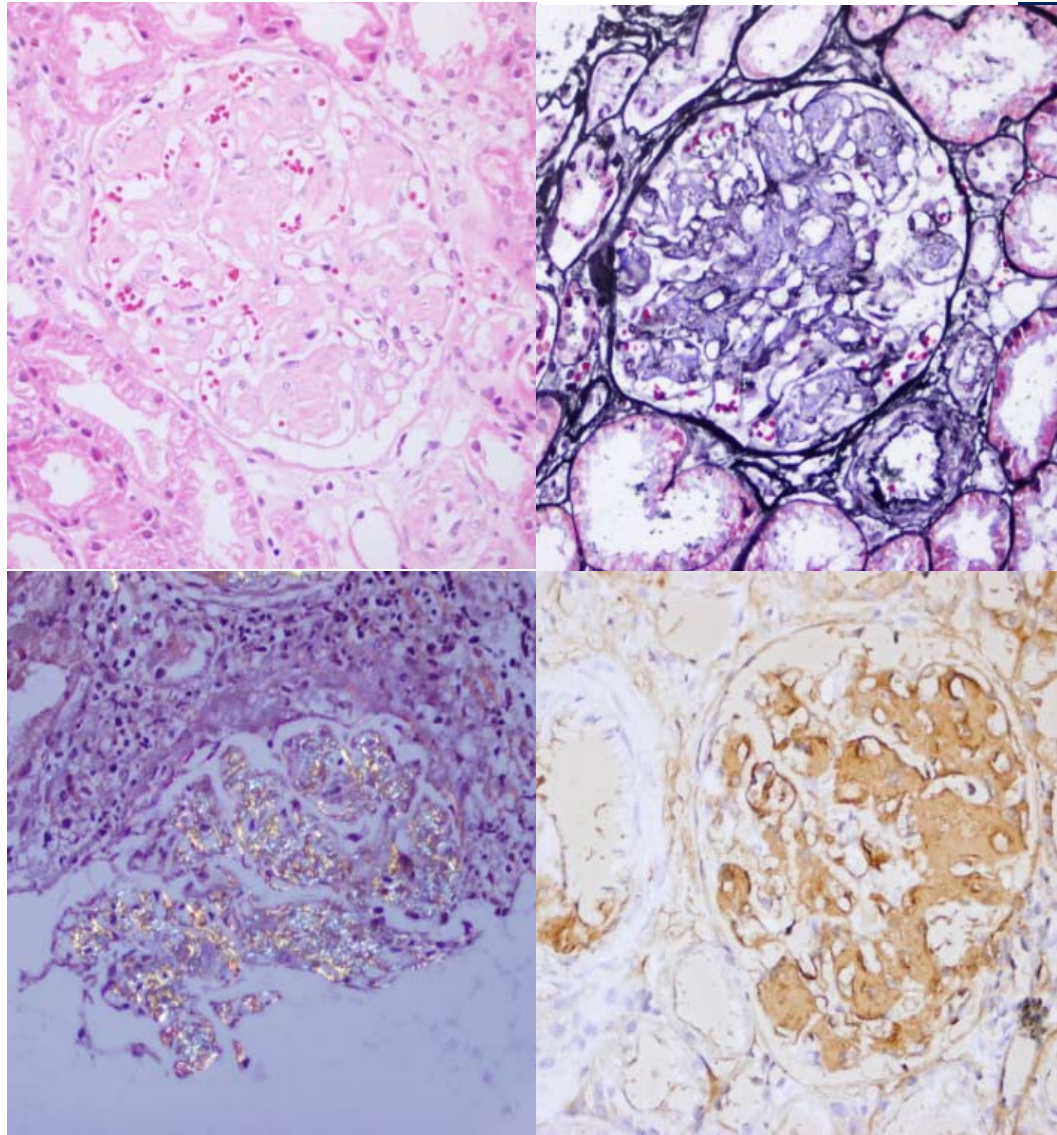
## Hilar pattern (4 cases)

- Older age group
- Hypertension in 1 case
- Grade 1-2 glomerular and chronic tubulointerstitial damage
- Arteriolar involvement (instead of peritubular capillaries) is predominant
- Vascular dominant form



## Mesangial nodular pattern (2 cases)

- Long duration of disease
- Less proteinuria
- Grade 2 glomerular damage
- Co-dominant form



## Mesangiocapillary pattern (4 cases)

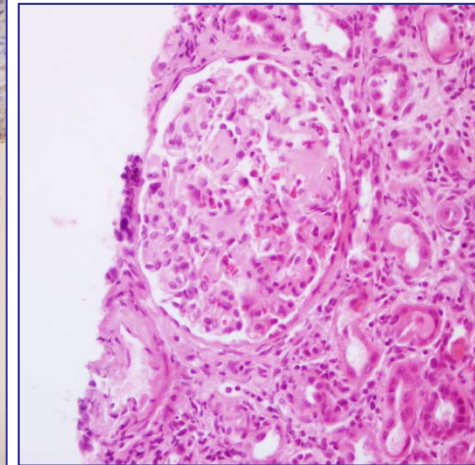
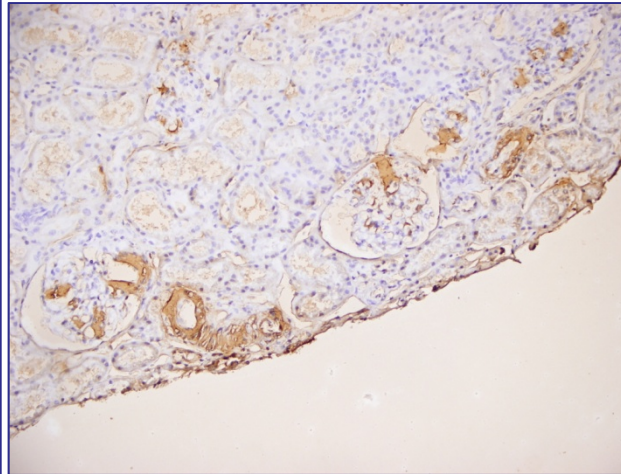
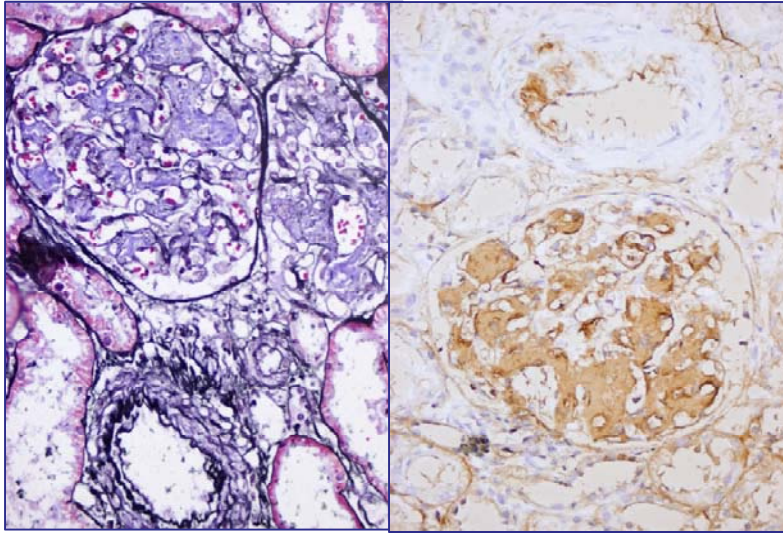
- 75% showed severe proteinuria (proteinuria >5 g/day)
- Peritubular capillary (instead of arterioles) involvement is predominant
- Usually grade 2-3 chronic tubulointerstitial damage
- Glomerular dominant form



### Glomerular Dominant

### Vascular dominant

### Co-dominant

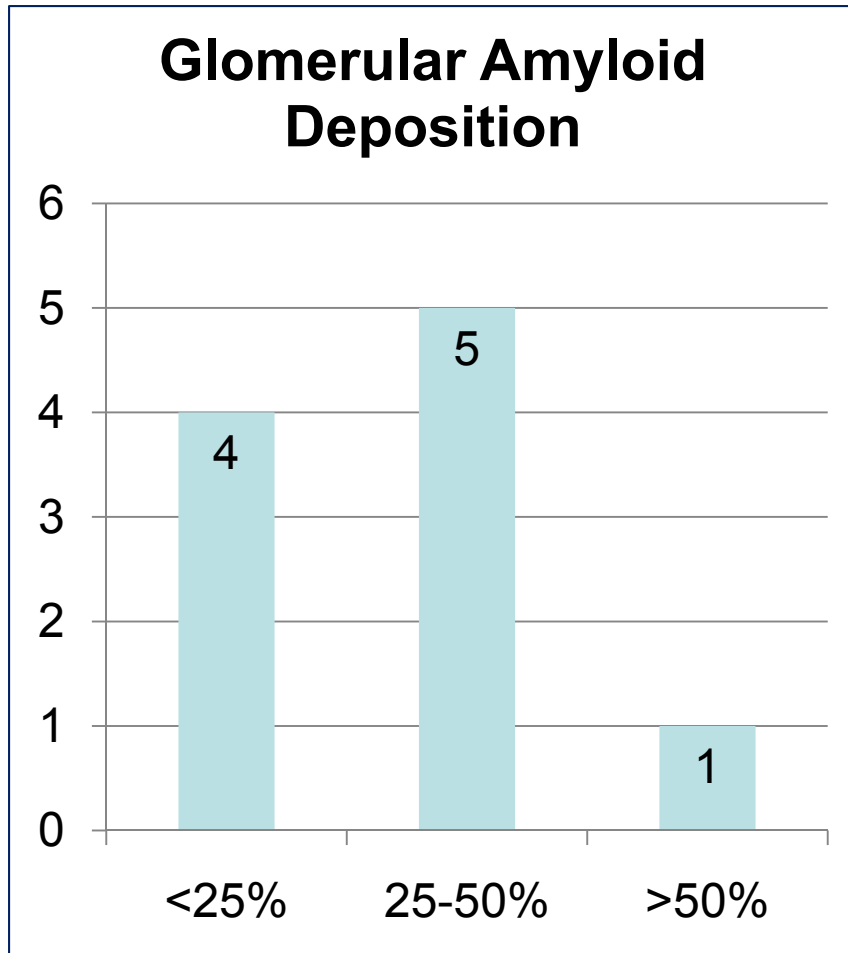


	Hilar	Mesangial nodular	Mesangiocapillary
<b>Glomerular Dominant</b>			3 (75%)
<b>Vascular Dominant</b>	2 (66%)		
<b>Co-Dominant</b>	1 (33%)	2 (100%)	1 (25%)

In 1 case, form of amyloid deposition could not be assessed



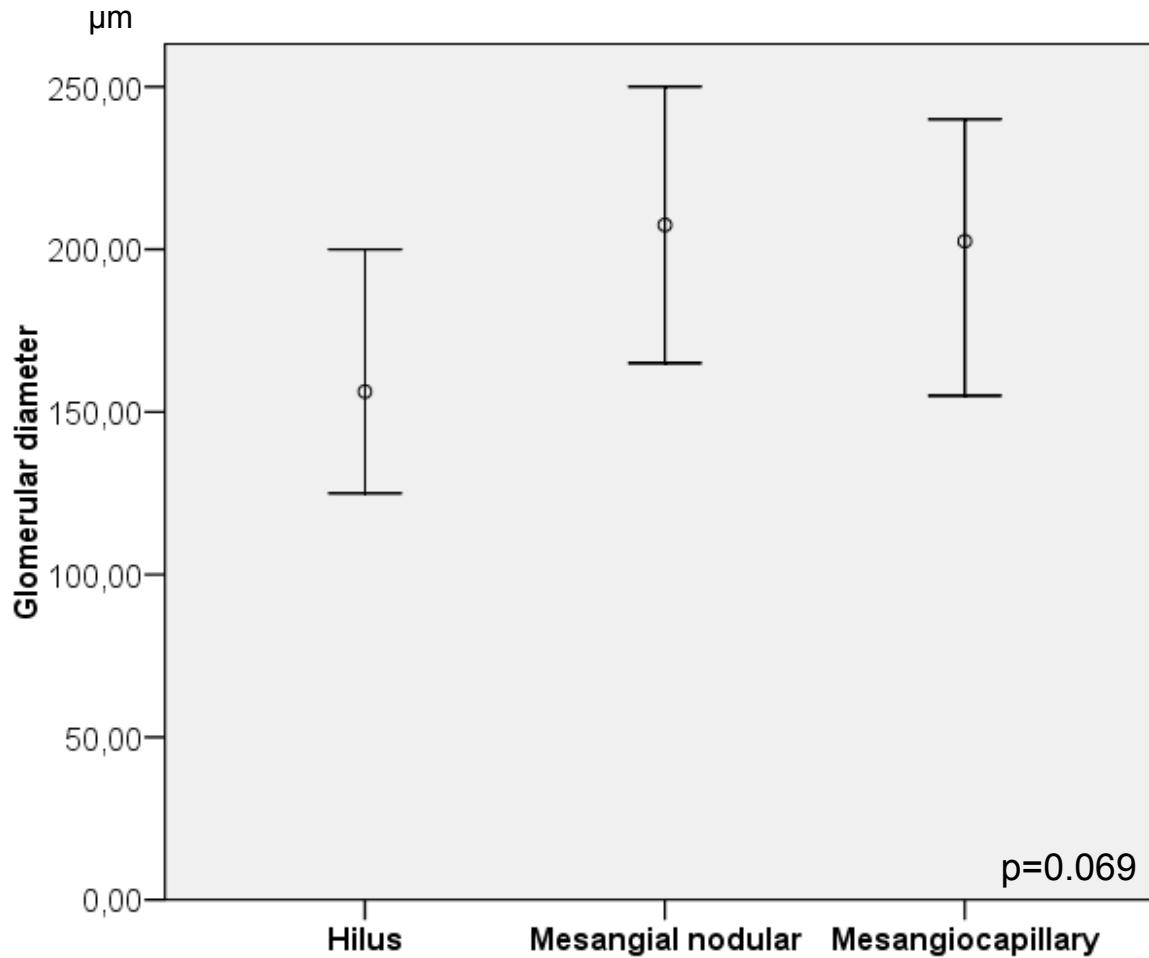
# Extent of glomerular amyloid deposition



	Glomerular Size	Proteinuria
Grade 1	155 $\mu\text{m}$	5.8 g/day
Grade 2	201 $\mu\text{m}$	3.9 g/day
Grade 3	225 $\mu\text{m}$	2 g/day



# Glomerular Diameter



Hilar type:  $156.3 \pm 31.5$

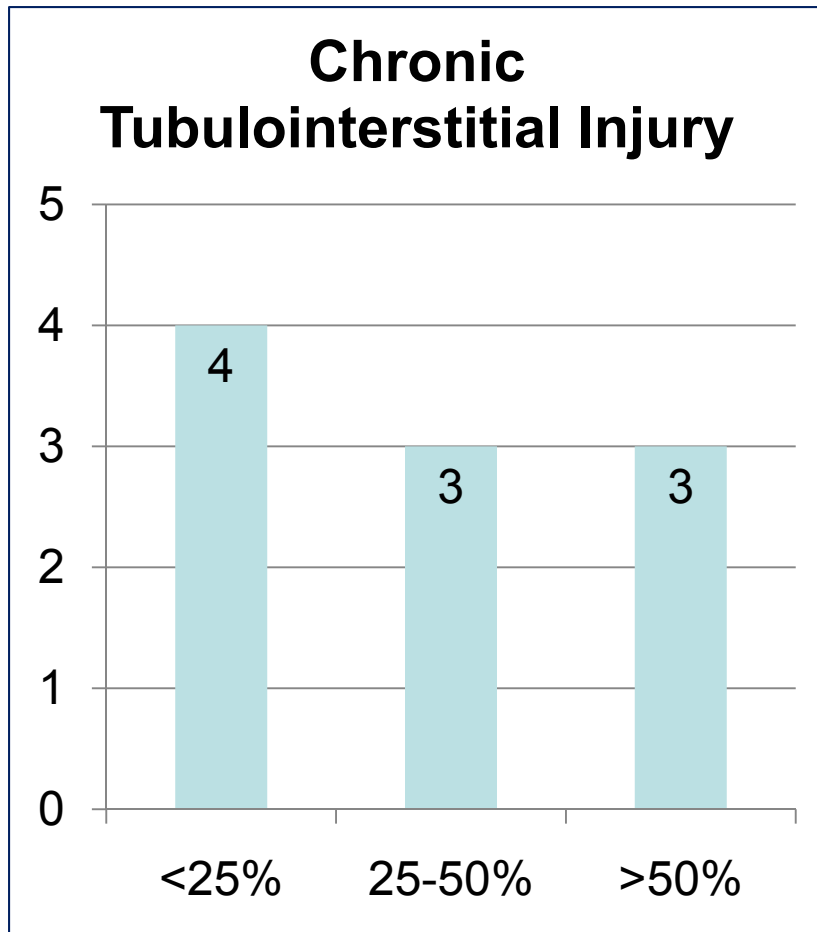
Mesangial nodular type:  $207.5 \pm 60.1$

Mesangiocapillary type:  $202.5 \pm 38.0$

Mean glomerular diameter:  $185.00 \pm 42.75$  µm (125-250 µm)

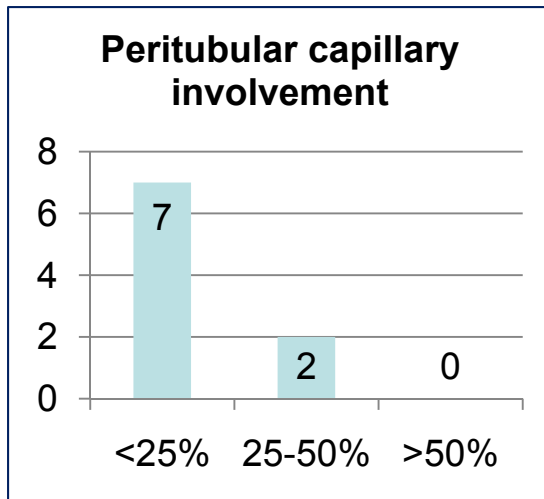
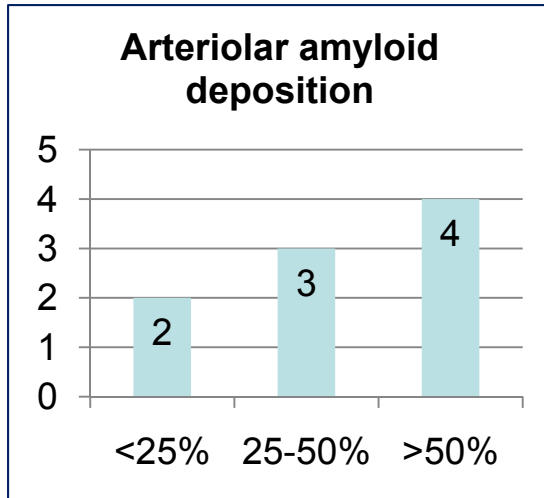


# Interstitial Compartment

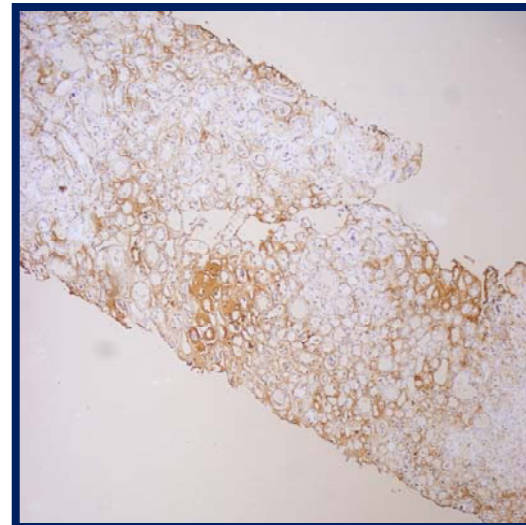


- 2 cases showed interstitial amyloid deposition
- 3 cases had interstitial inflammation regardless of chronic tubulointerstitial injury
- No amyloid deposition on tubular basal membrane

# Vascular Compartment



- In 4 cases there was no peritubular capillary amyloid deposition
- In 5 cases, biopsy contained a large arteriole/artery
  - One has segmental amyloid staining
- All 4 cases containing renal medulla have various degrees of vasa recta involvement.



In 1 case, arteriolar or peritubular capillary involvement could not be assessed



# Treatment

- Colchisin (5 patients)
- Steroid (4 patients)
- Cyclophosphamide (2 patients)
- Methotrexate and Etanercept (1 patient)



# Follow-up data

- Interval between diagnosis of Behcet's disease and renal amyloidosis:  
108 mos. (24-192)
- Mean follow-up:  
59.5 mos. (median, 39; range, 0-250)
- Prognosis
  - 2 patients (20%): progressed to end stage renal disease within 52 and 250 mos.
  - 1 patient (10%): remission (esbach level declined during 52 mos.)
  - 5 patients (50%): persistent proteinuria (mean follow-up 57 mos.)
  - 2 patients (20%): lost to follow up



	<b>AA Amyloidosis</b>	<b>FMF</b>	<b>Rheumatoid arthritis</b>	<b>Behçet's disease</b>		
	<b>Lachman et al.</b>	<b>Akse-Onal et al.</b>	<b>Chevrel et al.</b>	<b>Dilsen et al.</b>	<b>Akpolat et al.</b>	<b>Our study</b>
<b>Median duration of primary disease (yrs)</b>	17 (0-68)	4 (1-16)	19 (5-38)	16 (7-27)	12 (1-36)	9 (2-16)
<b>Frequency among AA amyloidosis</b>			28.3%			5.1%
<b>Mean age</b>	50	13	60	39	45	41
<b>Sex (M:F)</b>	1.3:1	1.23:1	1:1	8:0		10:0
<b>Proteinuria (g/day)</b>	3.9		4.4	5		4



# Conclusions

- Renal amyloidosis in Behçet's disease has a diverse pathology in terms of preferential location of amyloid deposition and its intensity and therefore patients follow variable clinical courses accordingly
- In the etiology of AA amyloidosis, Behçet's disease should be investigated in young male adults with nephrotic syndrome
- Configuration of amyloid deposition in renal biopsies may address some of the clinical findings



# Acknowledgements

- This study is a part of a larger study granted by Hacettepe University Scientific Research Unit, Grant number: 08D01101003
- We thank to Orhan Başhan, Özlem Bektaş, Melike Denişik, Faruk Köksal and Lokman Kale for their critical technical assistance and Dr Ali Akdoğan for his help on clinical inference.