ANCA related glomerulonephritis

Hey-Chi Hsu, D.D.S., M.S.
（許 輝 吉）
Professor Emeritus
Graduate Institute of Pathology
College of Medicine
National Taiwan University
e-mail: heychi@ntu.edu.tw

ANCA (antineutrophil cytoplasmic antibody)-associated GN can be associated with systemic vasculitis or limited to the kidneys (renal limited vasculitis).

ANCA associated GN often runs a rapid progressive course, leading to ESRF, but may also have a chronic, remitting, and relapsing course.

There are two major types of ANCA antigens.

- **The prevalence of PR3-ANCA (c-ANCA) and MPO-ANCA (p-ANCA) shows geographic variation and is related to types of ANCA vasculitis.**

Aims of this presentation are to show:

- **Protean manifestations and associated conditions**
- **Decisive prognostic factors**
- **Complex histological features and the clinical implication**

The patients came from the multicenters CPCs held in 10 hospitals in Taipei, New Taipei City, and mid-Taiwan (since 1989).

Hence the number of patients is limited.

ANCA associated GN in Taiwan: 51 cases

TP series: bimonthly (15 years) **2.4%**

2001-2007 **2.1% (7/326)**

2008-2015.10 **2.8% (8/288)**

TMU series: monthly (4 years) **2.6%**

2012-2015.08 **2.6% (4/156)**

TC series: bimonthly (15 years) **11.0%**

2001-2007 **8.9% (11/123)**

2008-15.10 **12.5% (21/168)**

ANCAs (+) GN: 51/1062 cases (4.8%)

Table 1. Clinical features of ANCA GN in Taiwan

Age	ANCA: MPO/PR3	Cr ≥4 mg/dL	Hb <8 g/dL	IgG high and/or C' low
<30 (N=7)	5/2	3 (43%)	6 (86%)	3 (43%)
<50 (N=12)	11/2[a]	6 (50%)	3 (25%)	7 (58%)
<65 (N=16)	16/0[a]	8 (50%)	4 (25%)	6 (38%)
≥65 (N=16)	12/4[b]	12 (75%)	7 (44%)	12 (75%)

P-ANCA 44 cases, C-ANCA 6 cases, both 1 case.

[a] MPO-ANCA(+)/anti-GBM (+) in one case each.

[b] MPO-ANCA (+)/PR3-ANCA (+) in one case.

- C-ANCA^{+}: F/M, 6:1; Hyperthyroidism/GD/WG/SS (6/7)

Complex associated conditions in ANCA GN:

Autoimmune diseases:

Graves disease or hyperthyroidism (6)
Wegener's granulomatosis (4)
Sjögren syndrome (2)

Common GN: MN (3); IgAN (3); TMA (1); C3GN (1)

Events preceding disease onset:

- **Drugs and unknown herbs powders (6)**
- **Infections (2)**

ANCA GN in Taiwan: Prognostic factors

Clinical:

Entry Scr level and renal survival at 1 year:

Scr <4 *vs*. ≥4: 96% (22/23) *vs*. 29% (8/28), *P* = 0.0000

Scr <6 *vs*. ≥6: 83% (25/30) *vs*. 24% (5/21), *P* = 0.0000

- **Initial Scr is a decisive clinical prognostic factor.**

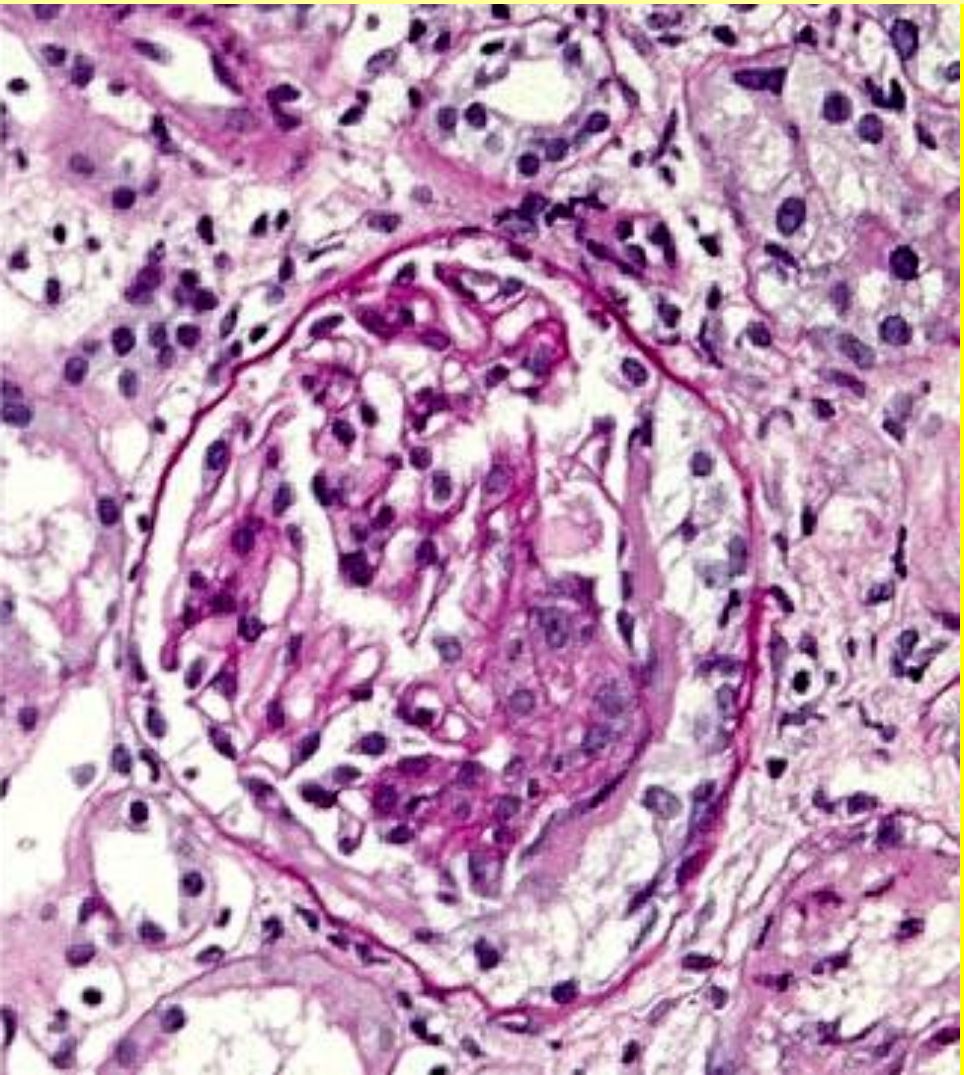
Pathology:

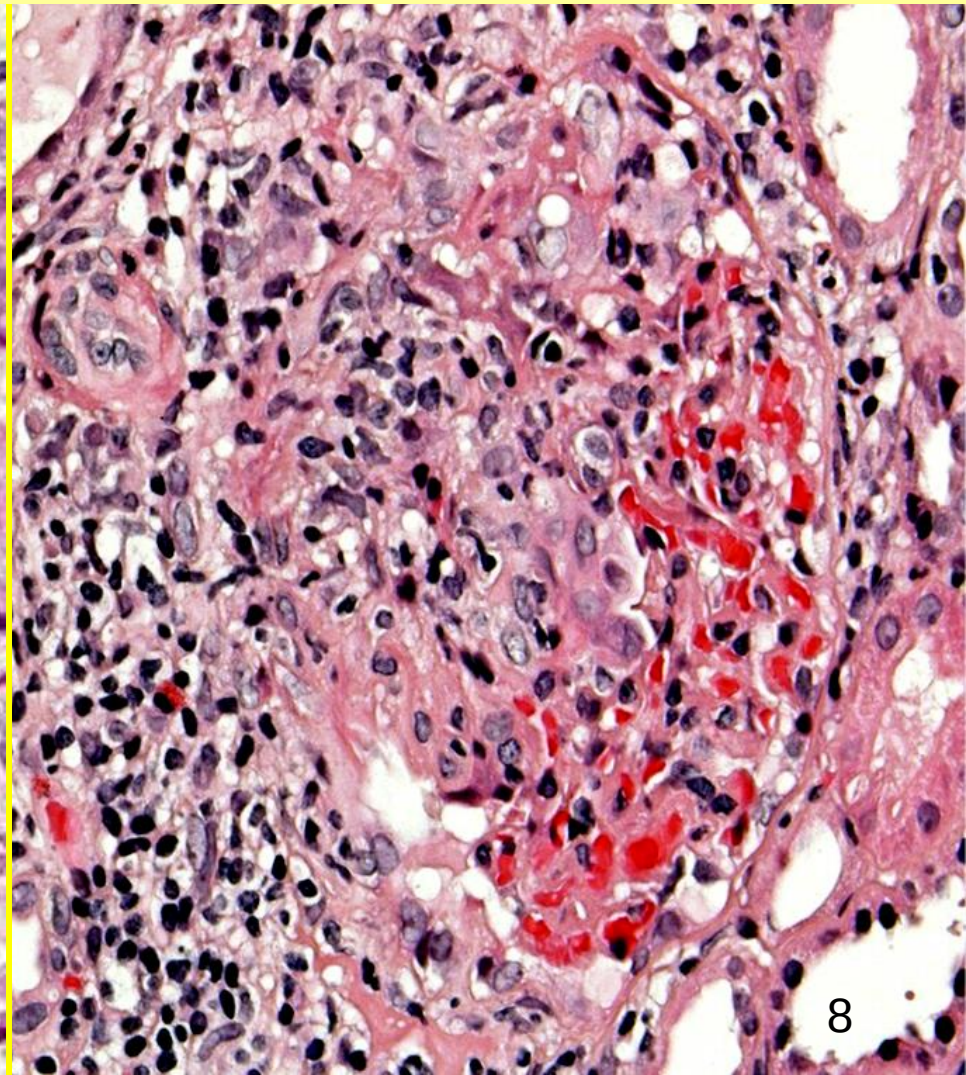
- **Clinical significance: prognosis and beyond**
- **Two basic pathological patterns: crescentic and focal necrotizing GN (together, necrotizing crescentic GN, or NCGN).**

*** Distinct histological fate and clinical significance!**

Two basic pathological patterns of NCGN:

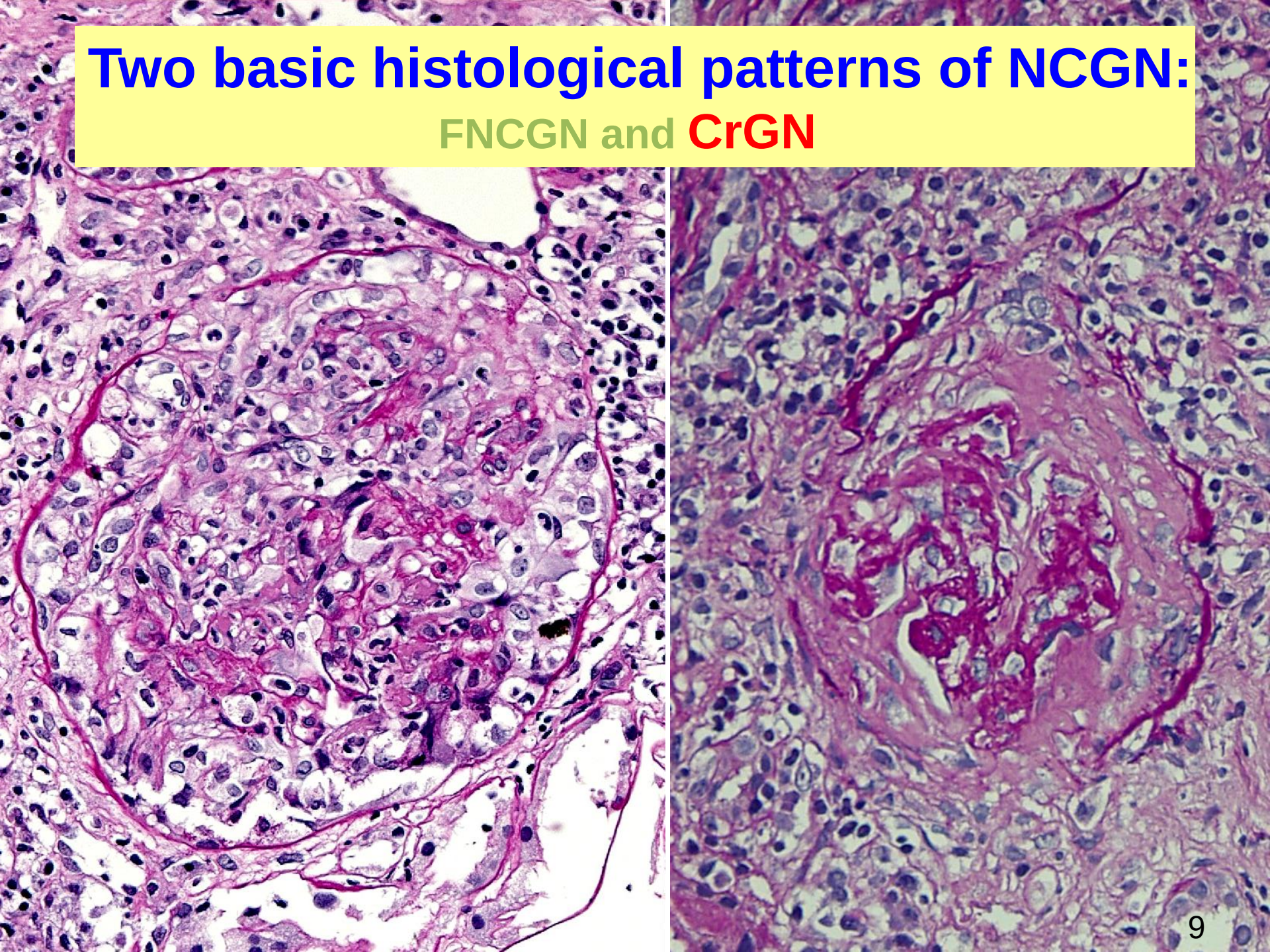
FNCGN and CrGN



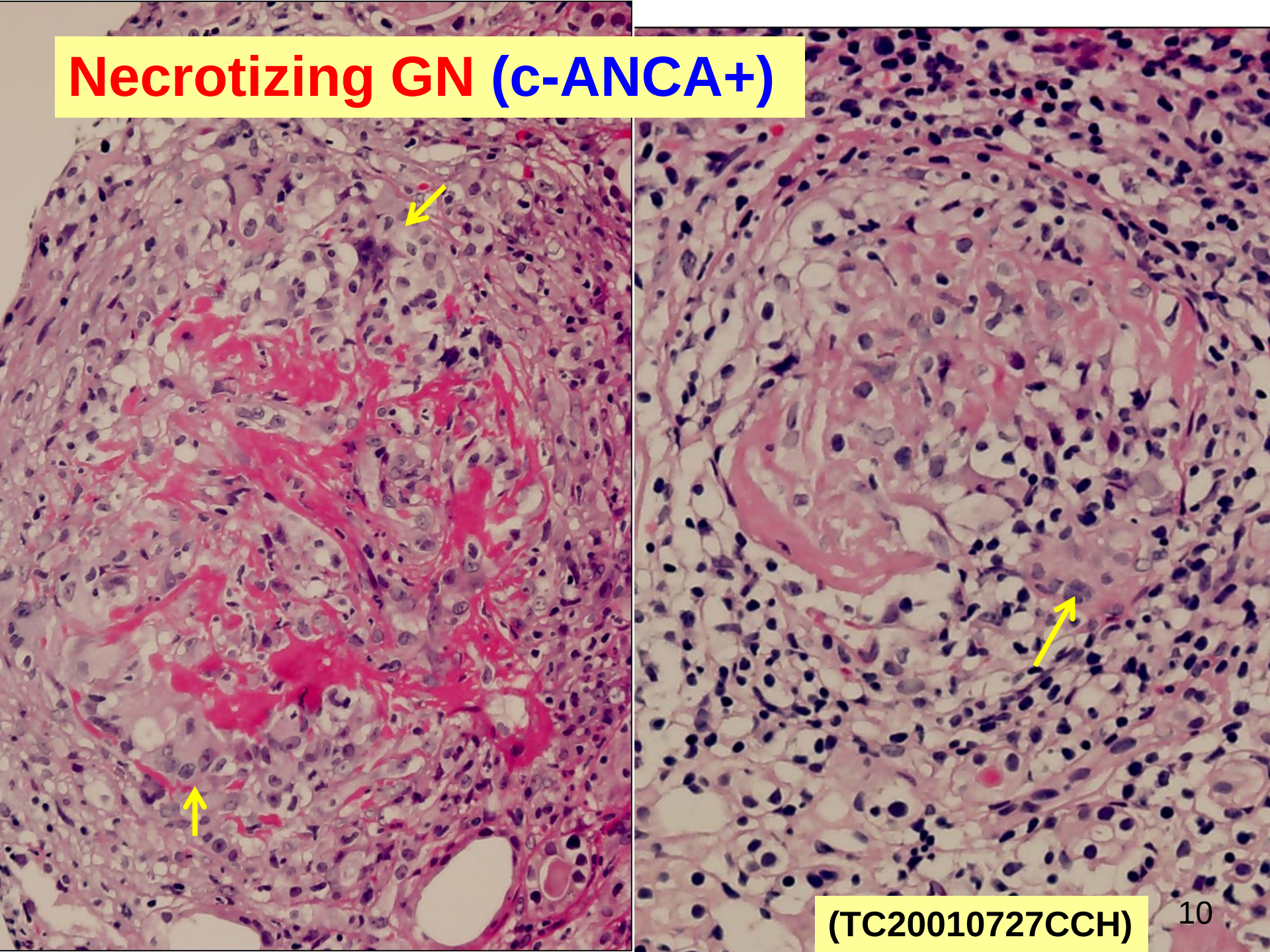


Two basic histological patterns of NCGN:

FNCGN and CrGN



Necrotizing GN (c-ANCA+)



(TC20010727CCH)

Necrotizing GN without any crescents accounts for 13 out of 123 patients with WG or MPA with renal involvement.

(Westman KWA, et al. J Amer Soc Nephrol 1998;9:842-852)

It is therefore important to note that the severity of glomerular tuft destruction (necrosis) is the basis of NCGN.

Case illustration

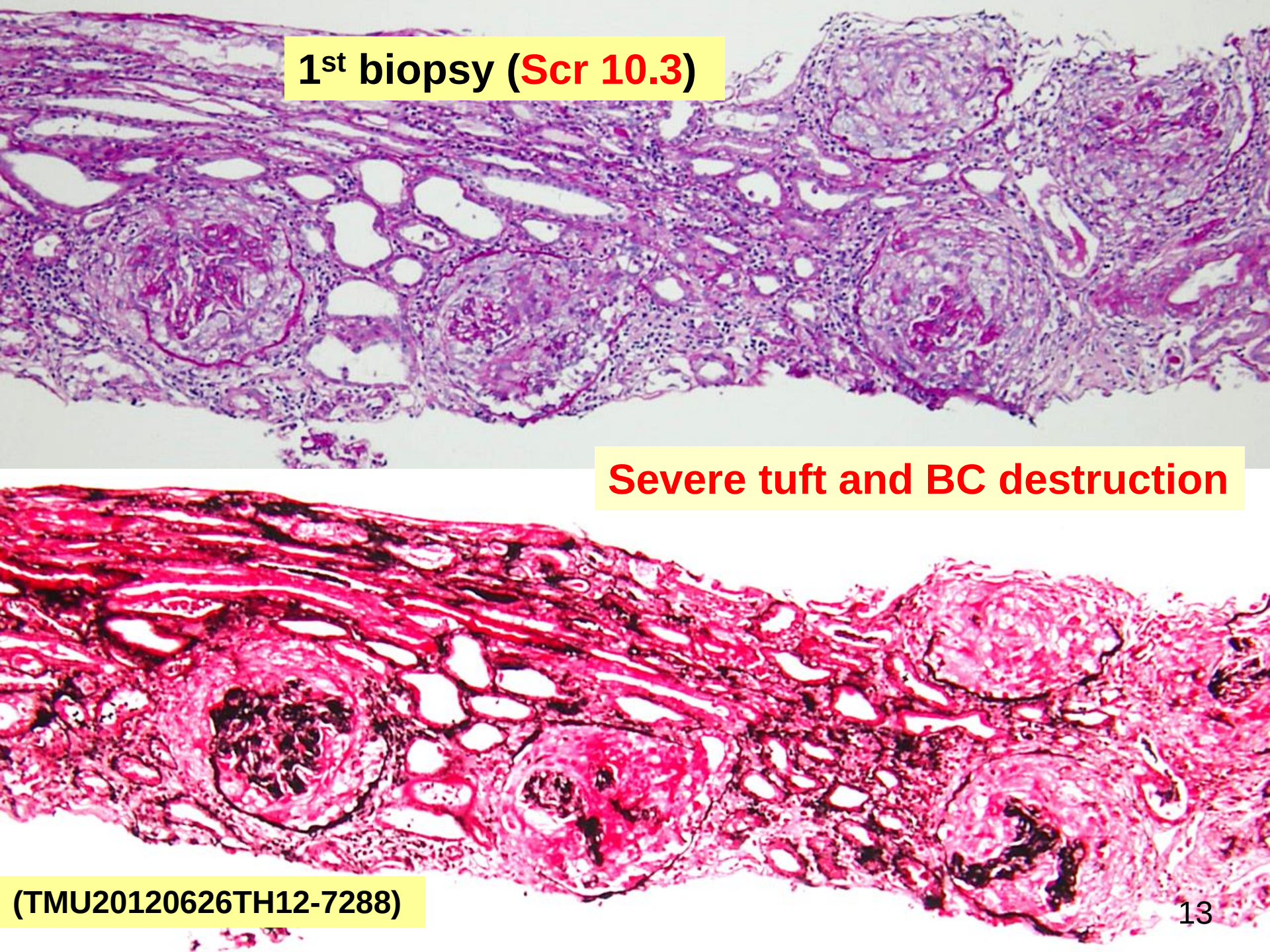
RPGN following exposure to pesticide spray: ANCA/anti-GBM (-) CrGN

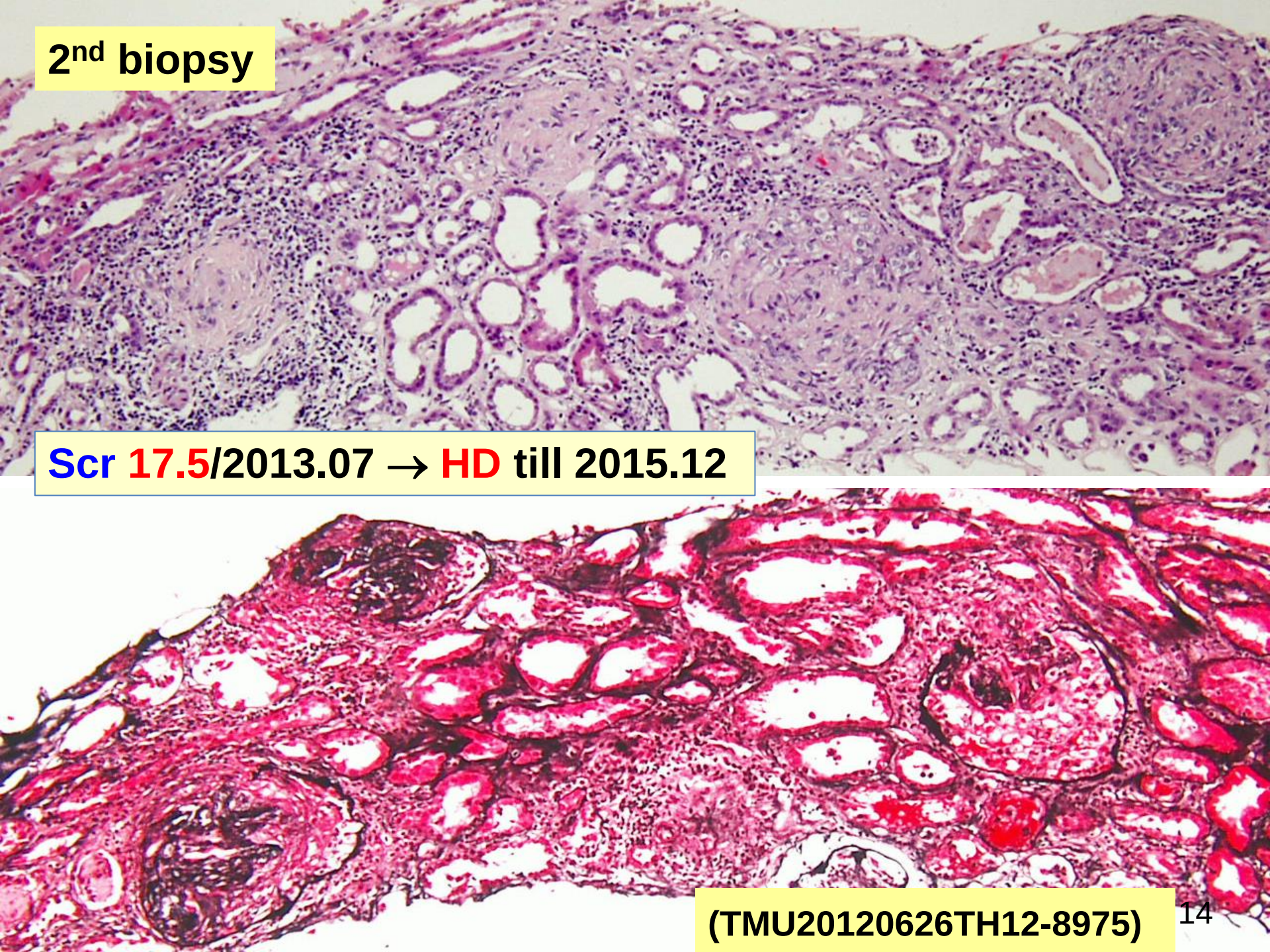
(55M) Back to 南投 from Taipei for farming. Fever (38℃) for 3 days after pesticide spray. WBC 12170; proteinuria, hematuria

Scr: 5.9/20120515 → 10.3/0521 (1st biopsy) → Plasma exchange x12, compesolone and cyclophosphamide → 7.9/0621 (2nd biopsy) → Renal outcome?

1st biopsy (D7): NCGN, crescentic, or CrGN (>90%)
2nd biopsy (D37): NCGN, sclerotic

(TMU20120626T)


1st biopsy (Scr 10.3)
Severe tuft and BC destruction
(TMU20120626TH12-7288)


2nd biopsy
Scr 17.5/2013.07 → HD till 2015.12
(TMU20120626TH12-8975)

In 2010, the international histopathological classification of ANCA-associated GN was proposed and divided into four classes: Focal, crescentic, mixed and sclerotic.
(Berden AE, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010; 21:1628–1636)

The histopathological classification has been validated in over 10 studies, confirming its predictive value for renal outcome for patients with focal or sclerotic-class. But, the crescentic and mixed classes showed conflicting results.
(Rahmattulla C, et al. Histopathological classification of antineutrophil cytoplasmic antibody-associated glomerulonephritis: an update. Curr Opin Nephrol Hypertens 2014, 23:224–231)

Classification schema for ANCA GN

Class	Inclusion Criteria	Cases (%)
Focal	≥50% normal glomeruli	16
Crescentic	≥50% glomeruli with cellular crescents, segmental or global	55
Mixed	<50% normal, <50% crescentic, <50% global sclerotic glomeruli	16
Sclerotic	≥50% global sclerotic glomeruli	13

Whether crescents are segmental or circumferential is irrelevant. The amount of fibrinoid necrosis is irrelevant. (Berden AN, et al. J Am Soc Nephrol 21: 1628–1636, 2010. 100 patients from 32 centers in 9 European countries)

*** Glomerular necrosis is the basis of crescents (segmental or global). Irrelevant?**
*** 55% crscentic class: Discriminatory value?**

Basic Concept for the Modification of Histological Classification of ANCA GN:

How much glomerular function still can be saved?

- **Glomerular function is at least partly rescuable: Focal segmental necrosis or crescents irrespective of percentage.**

- **Complete destruction and loss of function: Total glomerular necrosis or circumferential crescents (cellular to fibrous) – the basis of CrGN, and global sclerosis – the basis of Sclerotic class.**

- **Using the schema of the International Histological Classification**

Comparison among evaluations of GN histological categories with clinical background in Europe, China and Japan

	Europe	Italy	China	Japan	Taiwan
Patients (N)	100	93	121	87	51
Centers (N)	32	1	1	3	10
ANCA test					
PR3-ANCA	45		13	0	7
MPO-ANCA	47		108	76	44
Pathological classfication number (%)					
Focal	16 (16)	21%	33 (27.3)	40 (46)	13 (25.5)
Crescentic	55 (55)	30%	53 (43.8)	7 (8)	17 (33.3)
Mixed	16 (16)	39%	24 (19.8)	26 (29.9)	12 (23.5)
Sclerotic	13 (13)	10%	11 (9.1)	14 (16.1)	9 (17.6)

(modified from: Muso et al. Clin Exp Nephrol 2013;17:659-62; Moroni G, et al. Clin Exp Rheumatol 2015;33:S-56-63 – Italy)

Probability of renal survival: (1-year renal survival, %)

100 European patients (Berden AE, et al. 2010):

Focal (93) > crescentic (84) > mixed (69)> sclerotic (50)

181 Dutch patients (Hilhorst et al. 2013): 5-year

Focal (91) > mixed (69) > crescentic (64) (sclerotic 1 case)

121 Chinese patients (Peking): (Chang DY, et al. 2012).

Focal (100) > mixed (83) > crescentic (73) > sclerotic (29)

87 Japanese patients (Muso et al. 2013)

Focal (100), mixed (96) > crescentic (86) > sclerotic (35)

93 Italian patients (Moroni et al. 2015): 5-year (patient?)

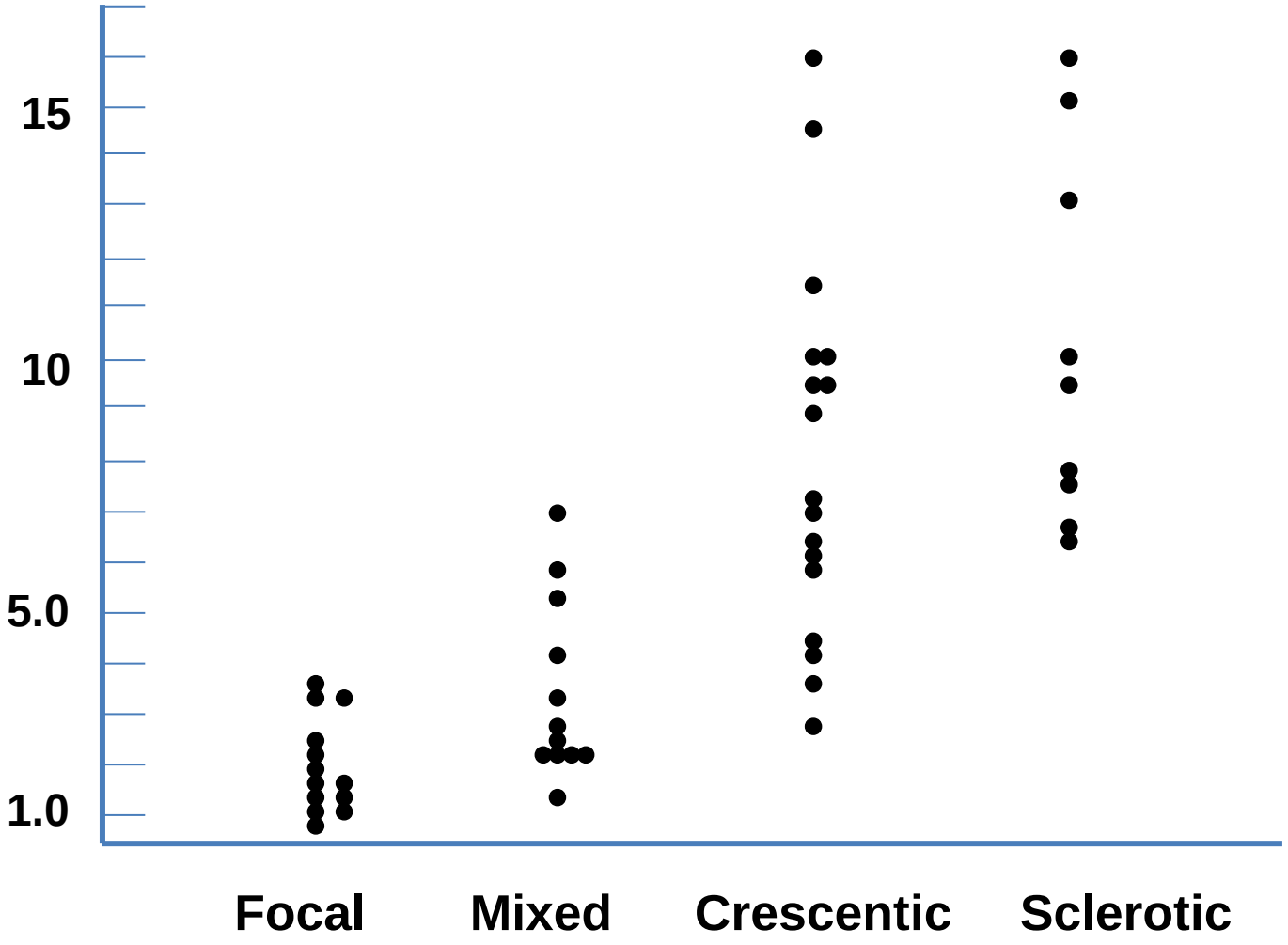
Focal (82), mixed (81) >> crescentic (37), sclerotic (51)

(The proposed histological classification was not predictive of renal prognosis. Clin Exp Rheumatol 2015;33:S-56-63)

51 patients: Taiwan

Focal (100), mixed (92)[a] >> crescentic (24)[b] , sclerotic (11)

([a] One died: pneumonia; [b] Three died: cancer, sepsis, uremia)



Serum creatinine distribution and histological classes in 51 cases of ANCA associated GN in Taiwan

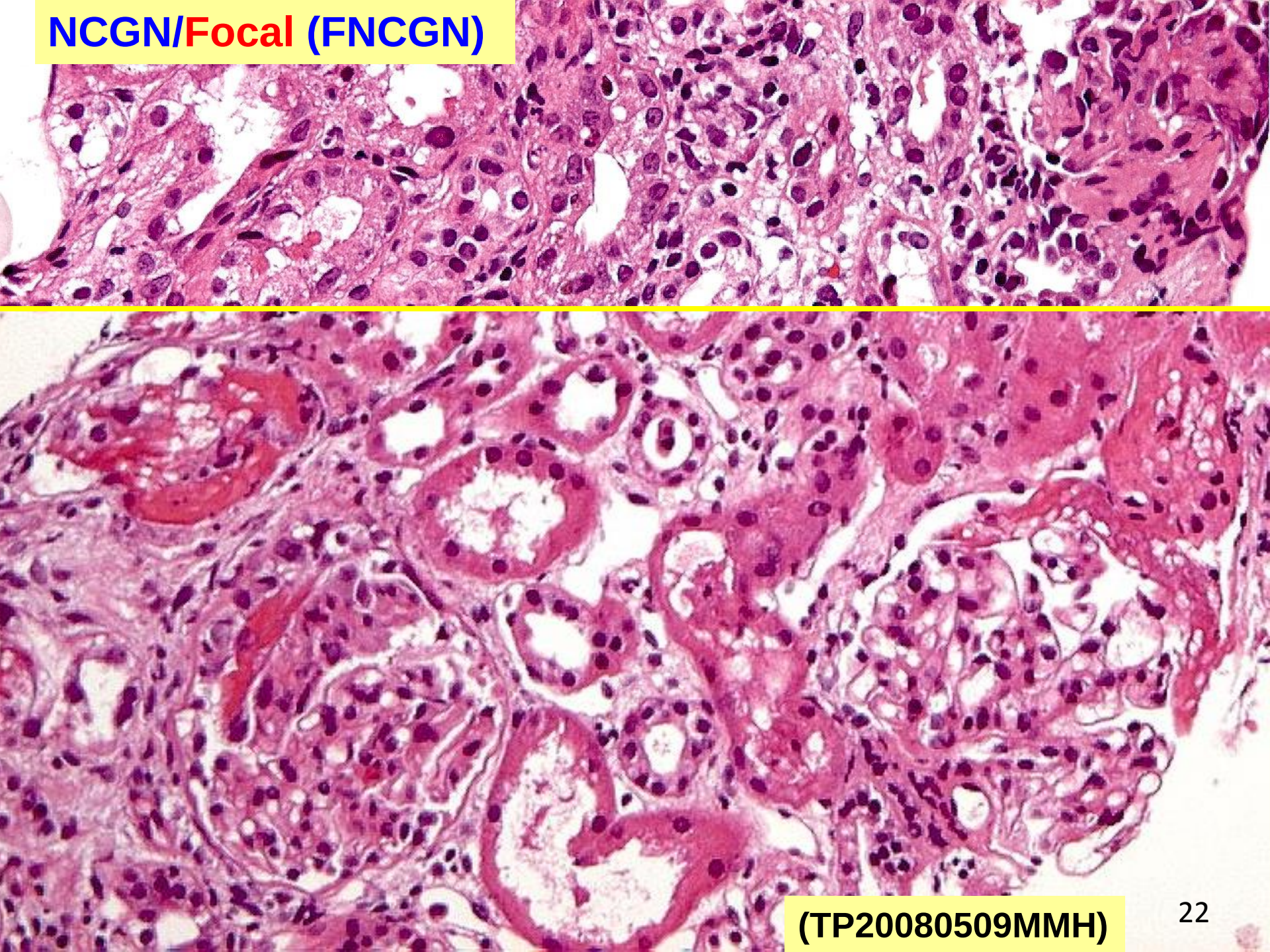
Impact of histology upon clinical course and prognosis

(13F) C-ANCA (+) NCGN/Focal
Graves' disease, PTU 3 years

(2008.04) Fever, productive cough, hemoptysis, gross hematuria, proteinuria, Scr 0.7 mg/dL → (biopsy) → (MTP pulse, prednisolone, endoxan) → U/A (-), cANCA (-)/2015.09 (7 yrs)

(TP20080509MMH)

NCGN/Focal (FNCGN)



(TP20080509MMH)

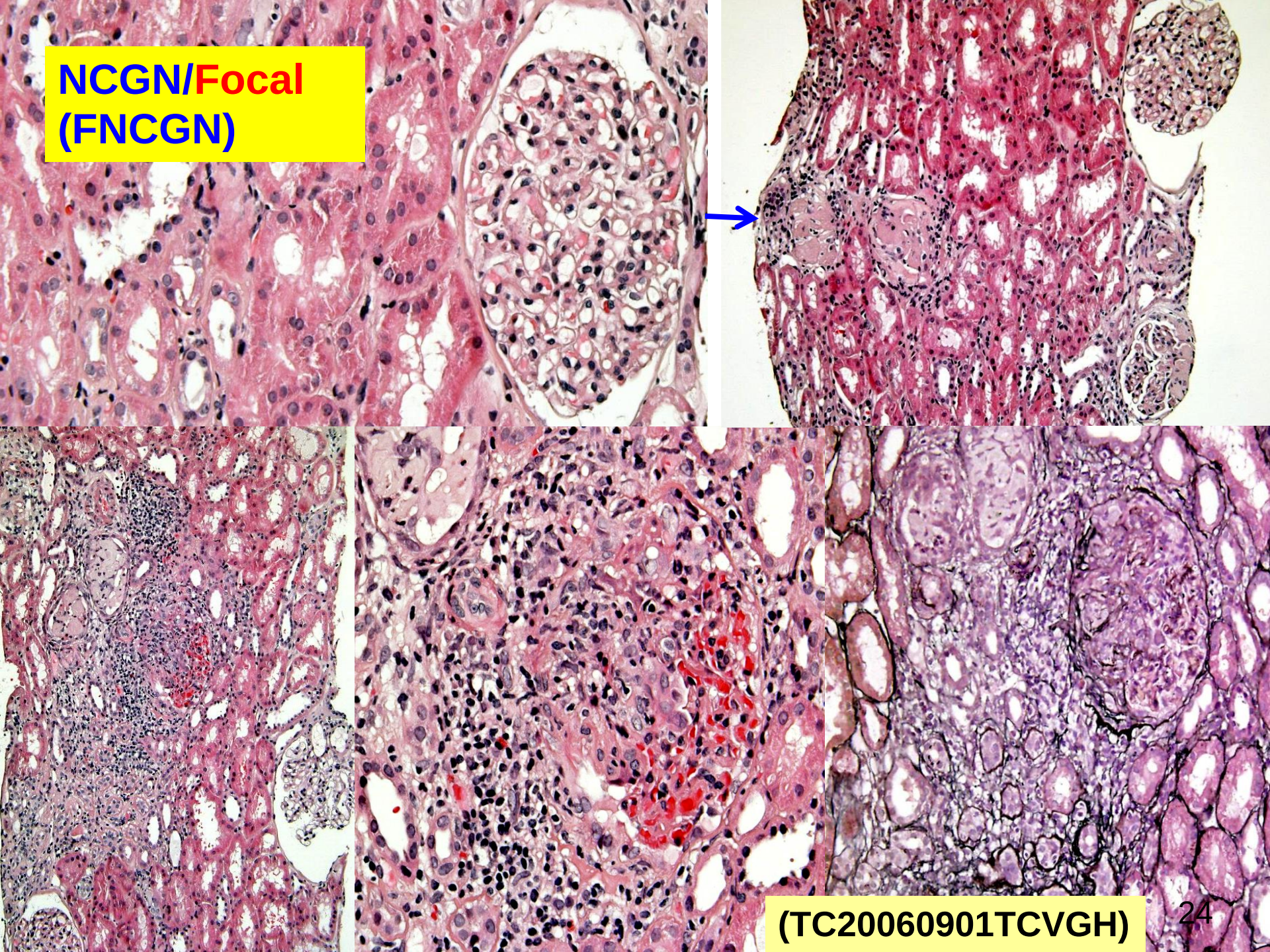
(53F) pANCA (+) NCGN/Focal (chronic smoldering)

Mild persistent proteinuria 5 yrs, with microhematuria

Scr: 1.0/2006 (biopsy) → **1.1**/2007.11 → **1.8**/2008.02 → **1.5**/2009.09 → **1.7**/2011.06 → **1.36**/2014.10 → **1.29**/**2015**.07
(Prednisolone/2006.05-2010.11; Endoxan/2008.06, 2009.09, x2)

- **Scr levels elevated, but stable for 9 years**
- **ANCA (+): 2006.08 - 2012.02 (>5 years)**

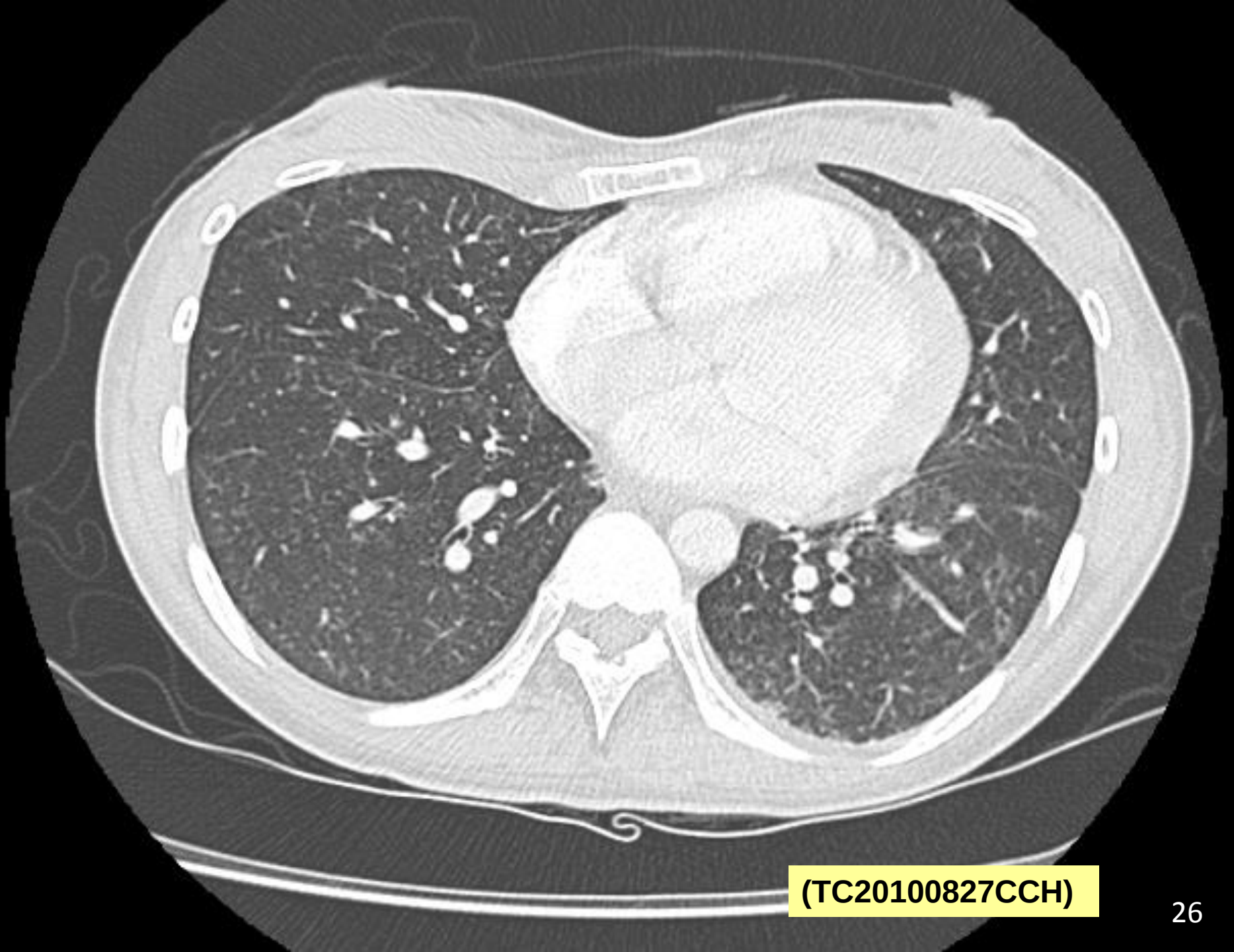
(TC20060901TCVGH)


NCGN/Focal
(FNCGN)
(TC20060901TCVGH)

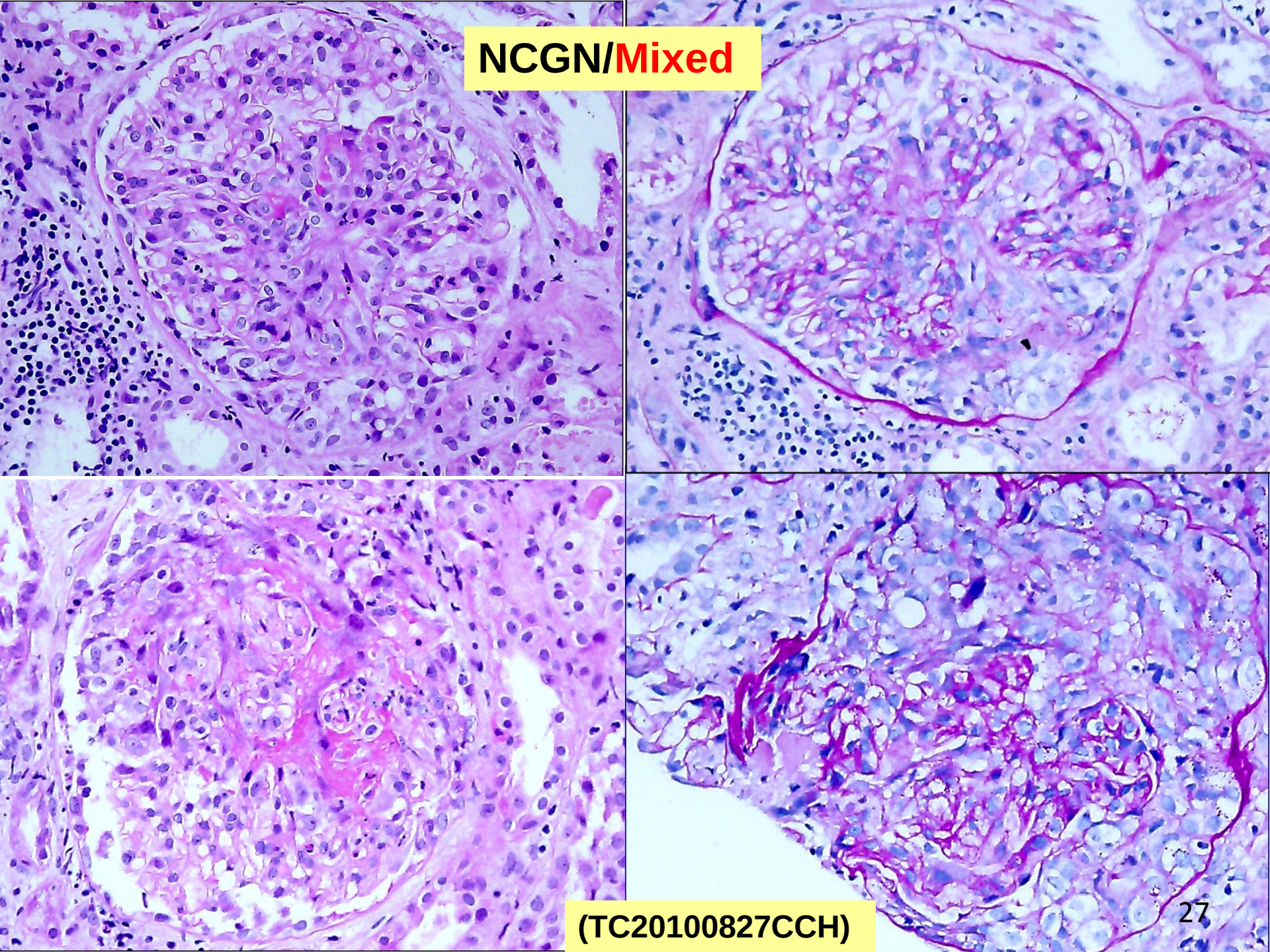
(20F) C-ANCA(+) NCGN/Mixed
Graves disease, PTU, 12 yrs
WG triad

Nasal bleeding, oral ulcers, hemoptysis, gastric ulcers, lung infiltration, Hb 6.5; hematuria, proteinuria for 1 m → Scr 2.2; BMI 17.2 (biopsy/2010**) → Prednisolone, Azathioprine → (40 d later) 1.37: ANCA (-) →**
(**ANCA: P+ ↔ C+/2011-2012**)
0.87/2013.04 → **1.06**/2014.04 → **alive/**2015.11 (**>5 years**)

(TC20100827CCH)



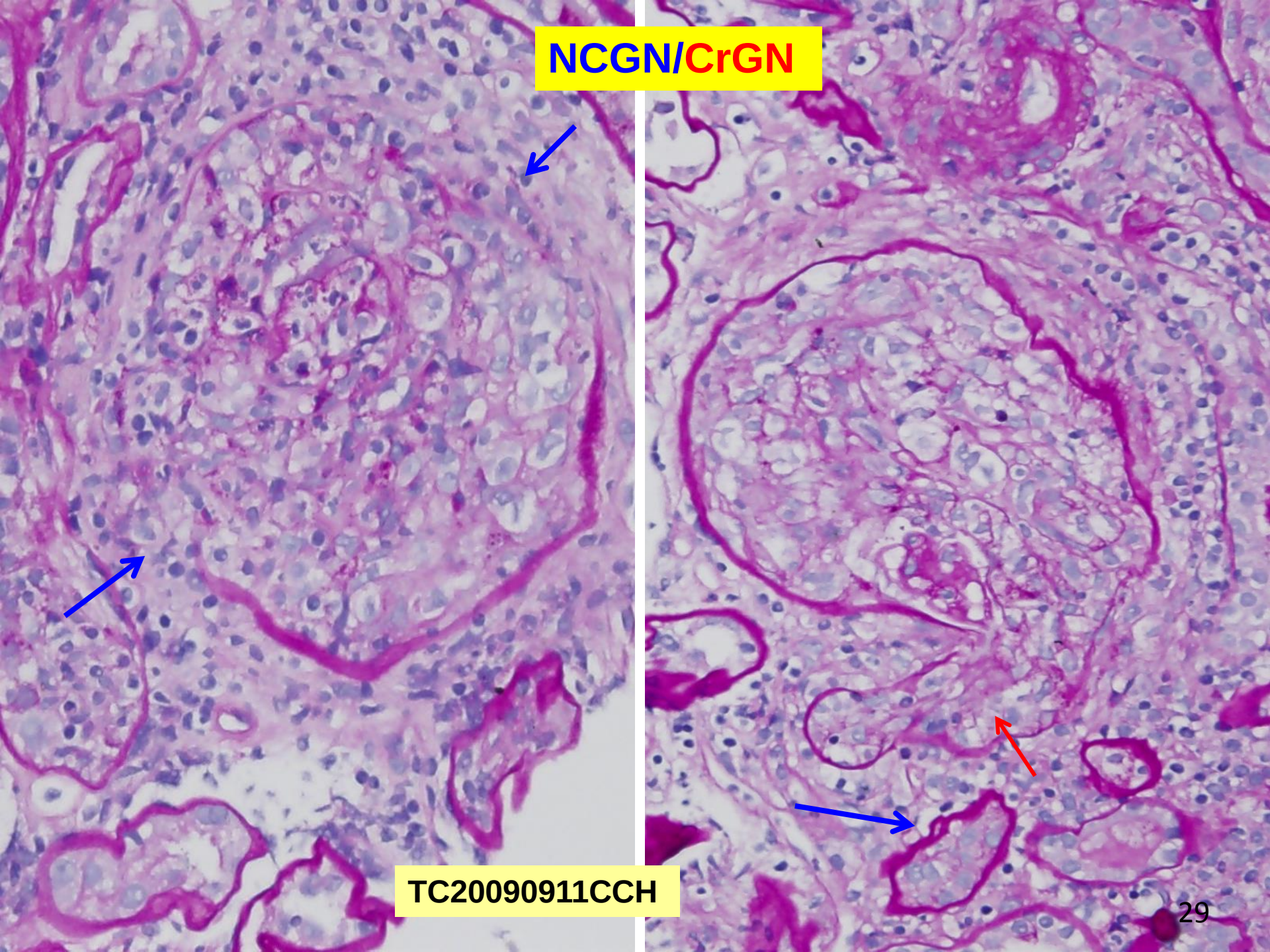
(TC20100827CCH)

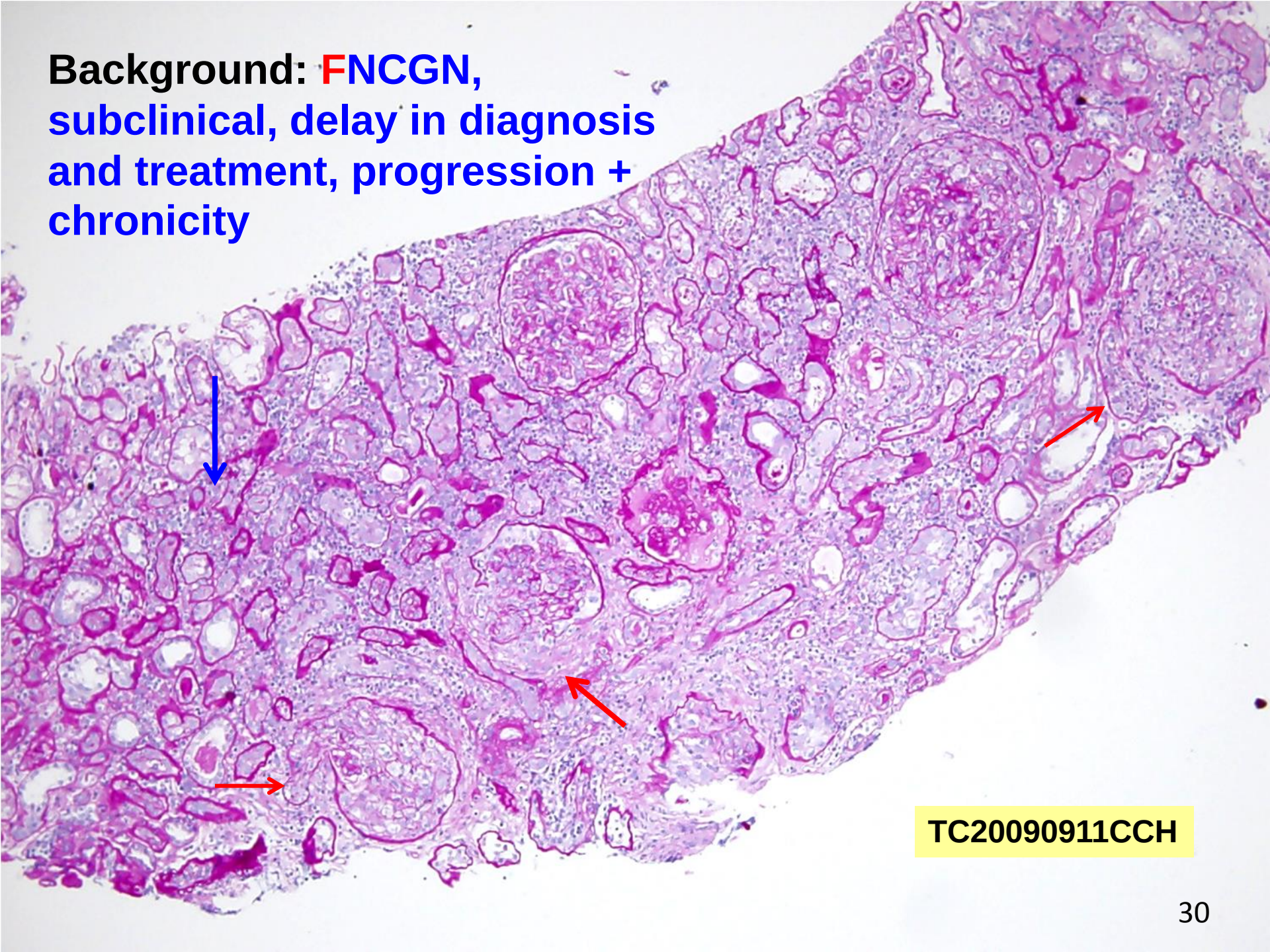

NCGN/Mixed
(TC20100827CCH)

(59F) MPO-ANCA (+) NCGN/CrGN (?)

(2009**0418) At ER for back pain** (lumbar spondylosis with spur): **Scr 2.1, proteinuria, hematuria** → **2.88/0615 (biopsy/**0616 **– 2 m)** → (Prednisolone, Pulse therapy, endoxan) → **2.26/0615** → **3.67/0626** → **3.75/0702** → **(infection)** → **5.3/0717** → **HD** → **severe UTI**/2009.08 → **Expired**/0722

(TC20090911CCH)


NCGN/CrGN
TC20090911CCH


Background: FNCGN,
subclinical, delay in diagnosis
and treatment, progression +
chronicity
TC20090911CCH

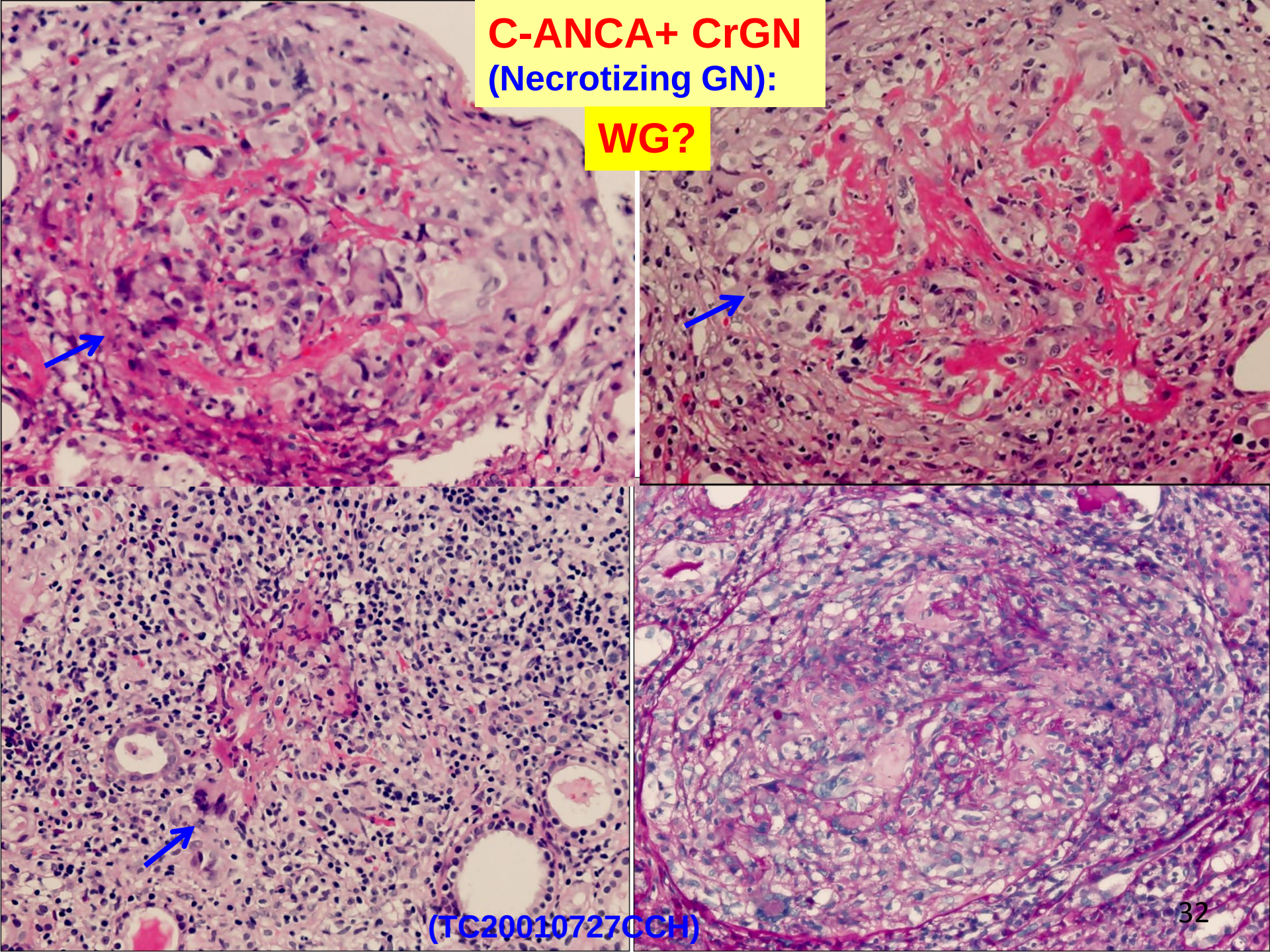
(74F) c-ANCA+ NCGN/crescentic (CrGN)

Right hip replacement 5 years ago
Drugs including herbs powder for hip pain for years

Decreased UO to anuria and generalized edema for 2 weeks. Lab: proteinuria, hematuria

Scr: 11/0323 → 14/0325 → 16/0327 (biopsy 0408) → HD/0426

(TC20010727CCH)

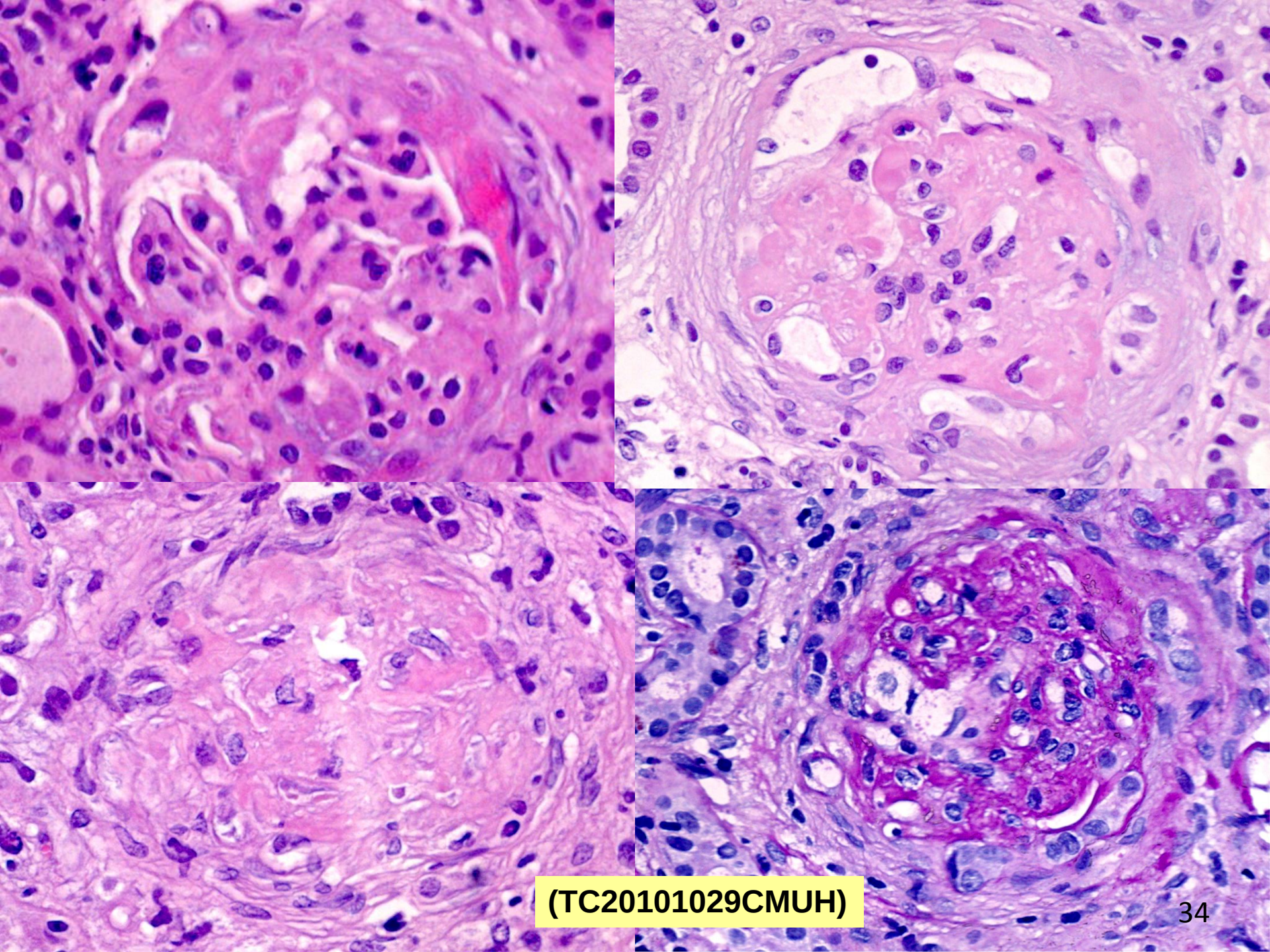

C-ANCA+ CrGN
(Necrotizing GN):
WG?
(TC20010727CCH)

(44M) P-ANCA (+) NCGN, sclerotic (>5 m)

(2010.04, 上海):
Exertional dyspnea, hemoptysis, rash, anemia, Scr elevated (vasculitis?) → prednisolone

(2010.08, Taiwan):
Scr: 5.2 → 7.61/2010.09 (biopsy >5 m) → (MTP, prednisolone, endoxan, plasmapheresis, PE) → 7.51/2010.10 → PD/2010.12

(TC20101029CMUH)



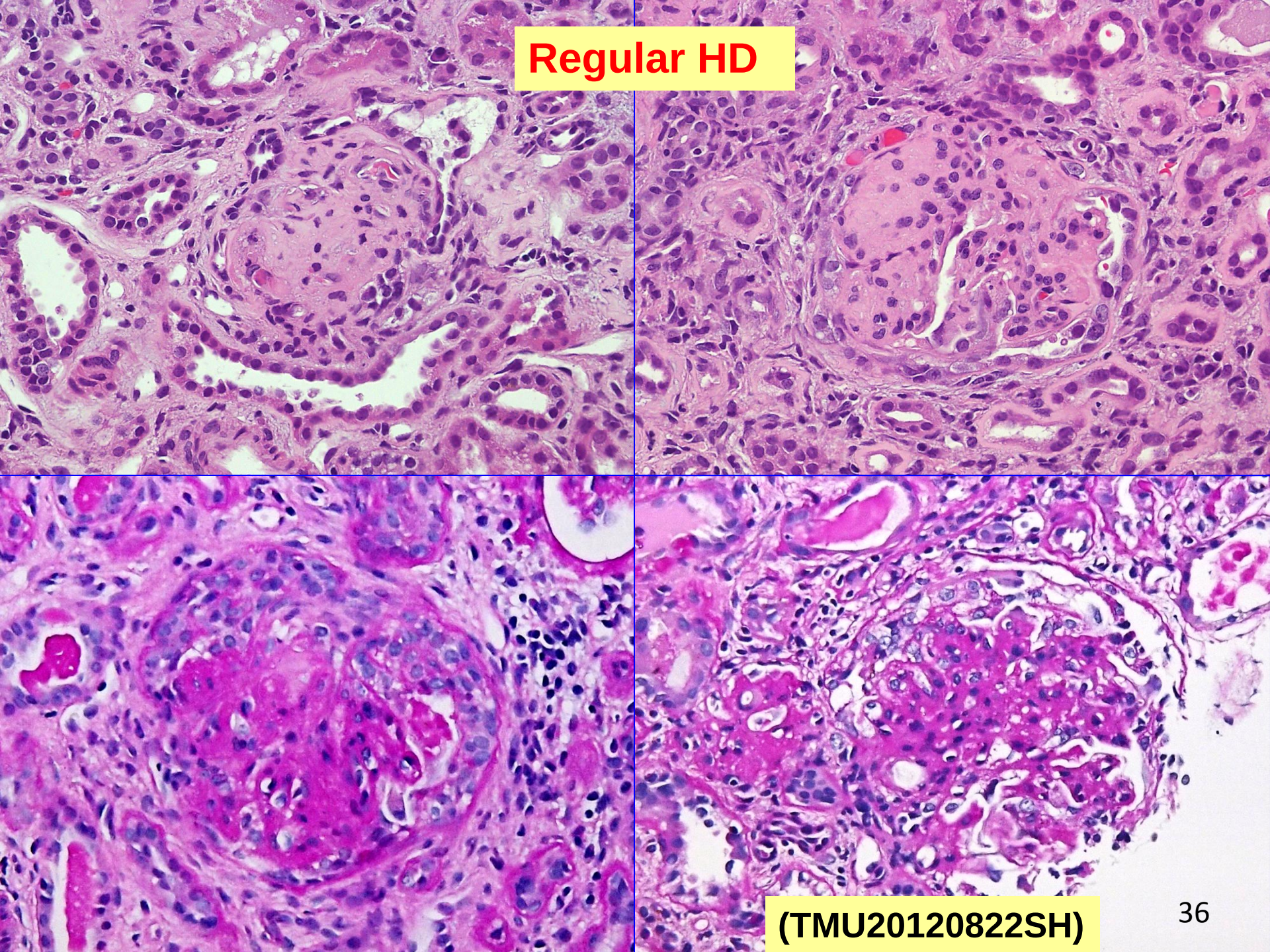
(TC20101029CMUH)

(15F: student) P-ANCA(+) NCGN/sclerotic (>10 m)

(2011) Routine health exam: Cr 1.2 mg/dL
(20120720) Hb 5.9 g/dL, Cr 9.66; hematuria, proteinuria
→ HD → biopsy/0726 **(Pulse steroid, MTP, MMF)**
→ Renal outcome?

- **MPO-ANCA (+)/2012.08**

(TMU20120822SH)


Regular HD
(TMU20120822SH)

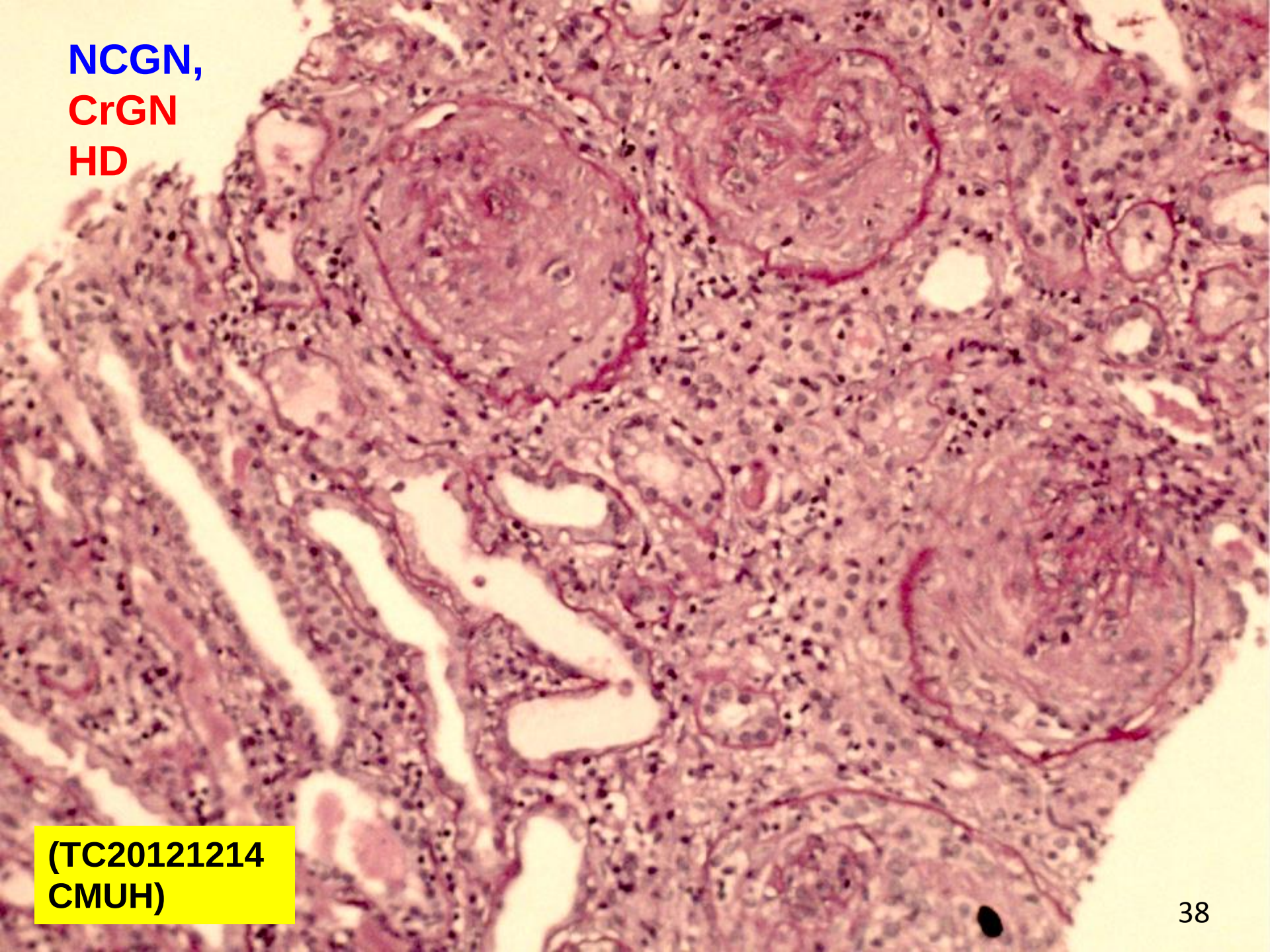
ANCA GN following infections

(47M) P-ANCA (+) NCGN/class?

(0205) Fever for several days. OSSA bacteremia
(0214) Vegetation on TV and AV, infective endocarditis
(0220) AKI with oliguria, hematuria, proteinuria.

Scr: (0.85/0208) → 3.52/0220 → 9.53/0228 → HD → 8.6/0305 → biopsy/0404 (45 d) → Renal outcome?

(TC20121214CMUH)


NCGN,
CrGN
HD
(TC20121214
CMUH)

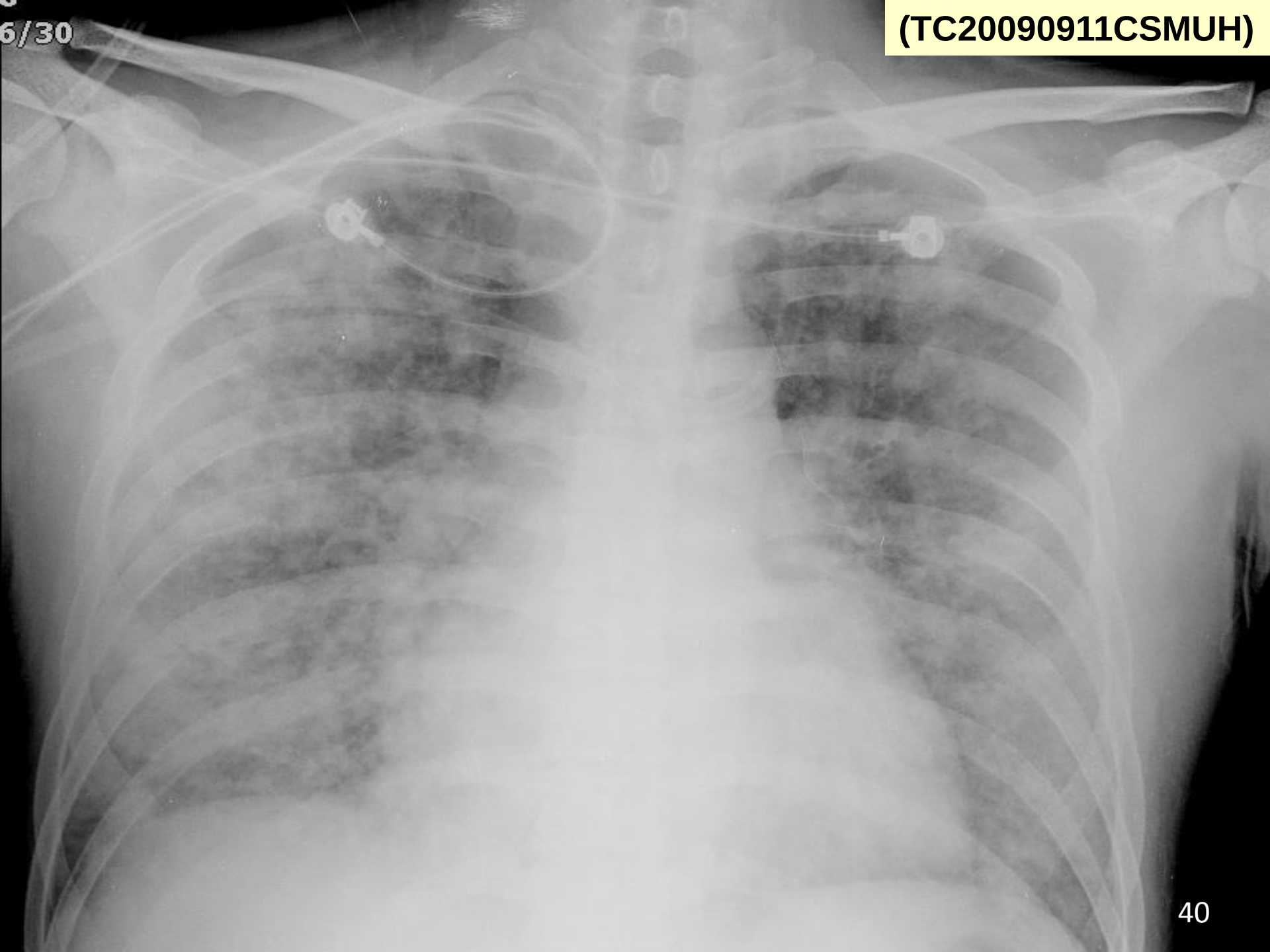
(29M) P-ANCA (+) FNCGN/Mixed

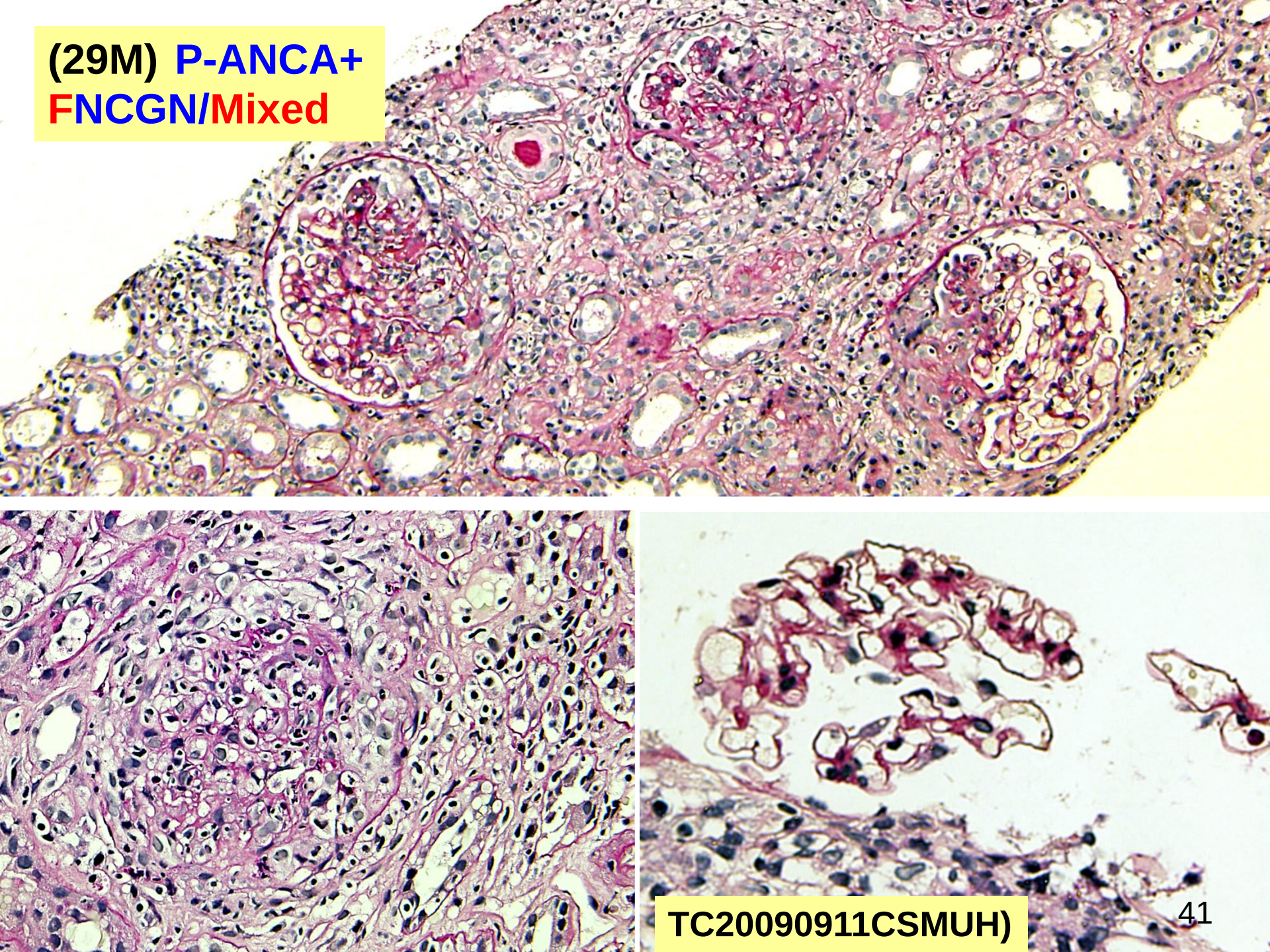
Mycoplasma infection (antibody+) with acute motor axonal neuropathy 2 months ago, treated with plasma exchange; then bilateral pneumonia with acute respiratory failure developed.

Scr: (0.8/2009.**05)** → **2.9**/0630 → **3.3**/0702 **(biopsy/0716) (PE, DFPP, corticosteroids)** → **1.5-1.4/**2009.12-**2010.08;**

- **ANCA (-)/since 2009.12**

(Acta Neurol Taiwan 2013;22:26-31)


6/30
(TC20090911CSMUH)


(29M) P-ANCA+
FNCGN/Mixed
TC20090911CSMUH)

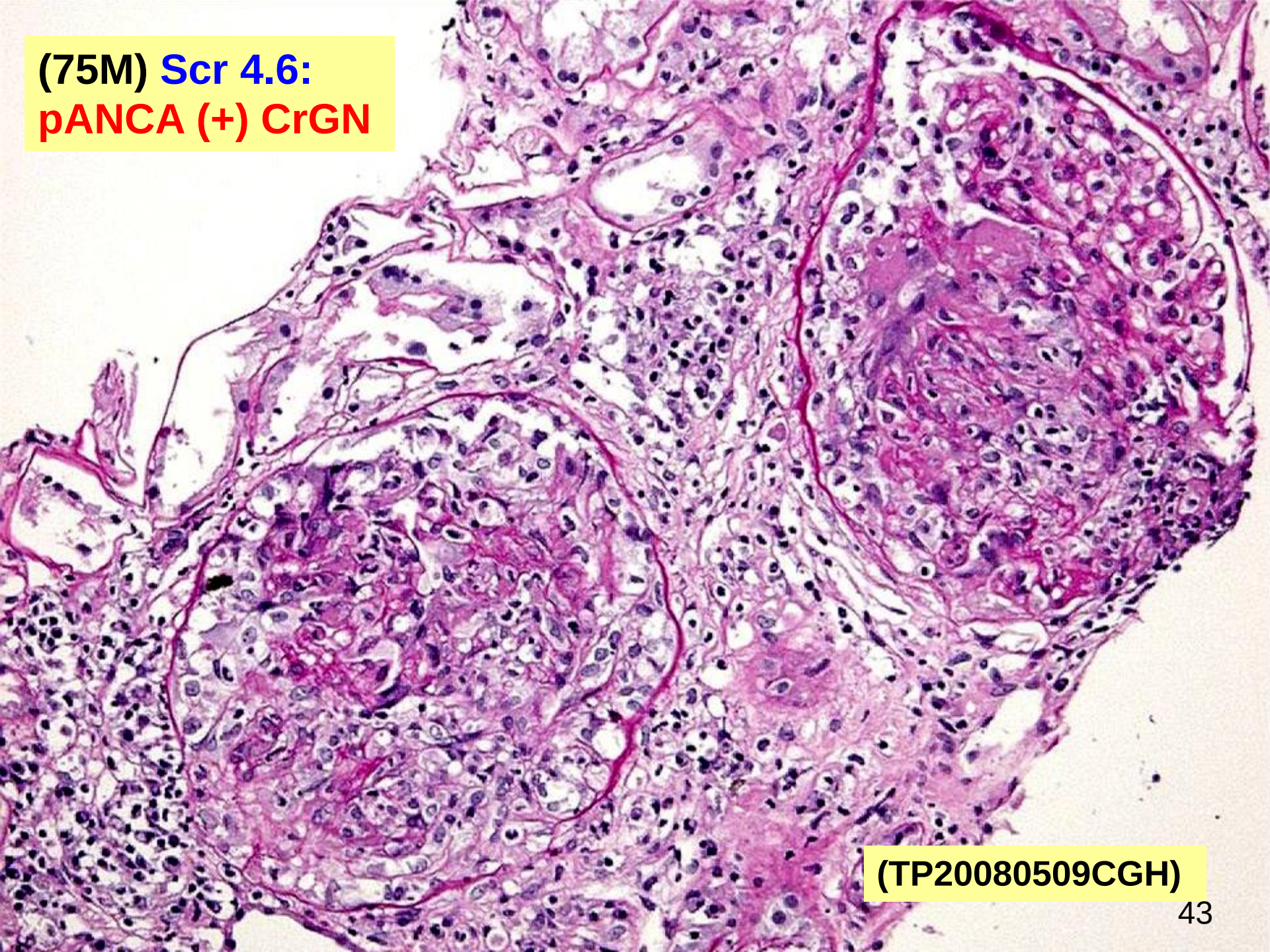
(75M) P-ANCA (+) NCGN/CrGN + TMA

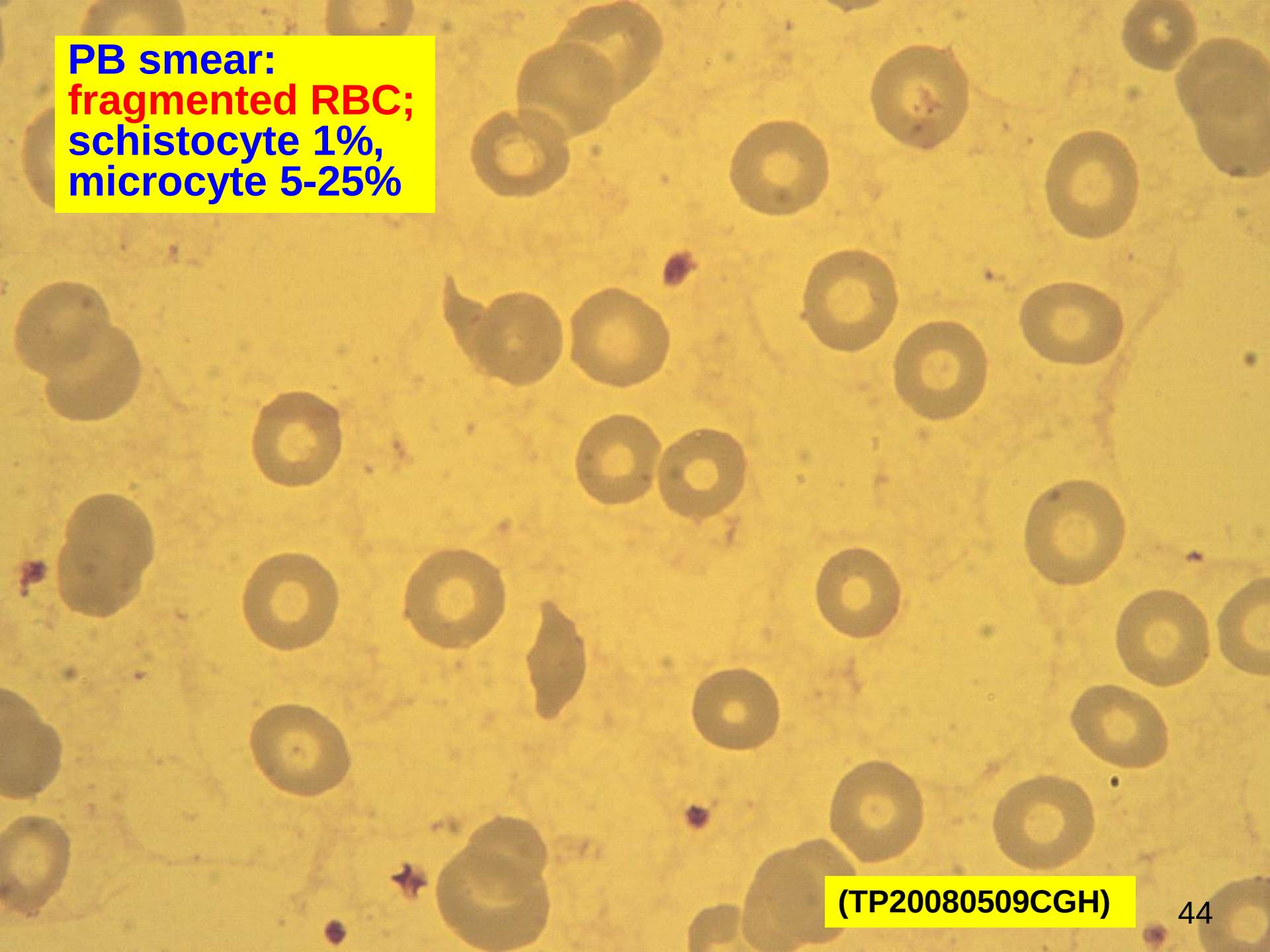
(20080328): Epigastric pain and tarry stool after medication (celecoxib, COX-2 inhibitor) for rhinorrhea.
PES: multiple esophageal/gastric ulcers, duodenal ulcer.
Lab: Hb 7.2; hematuria, proteinuria

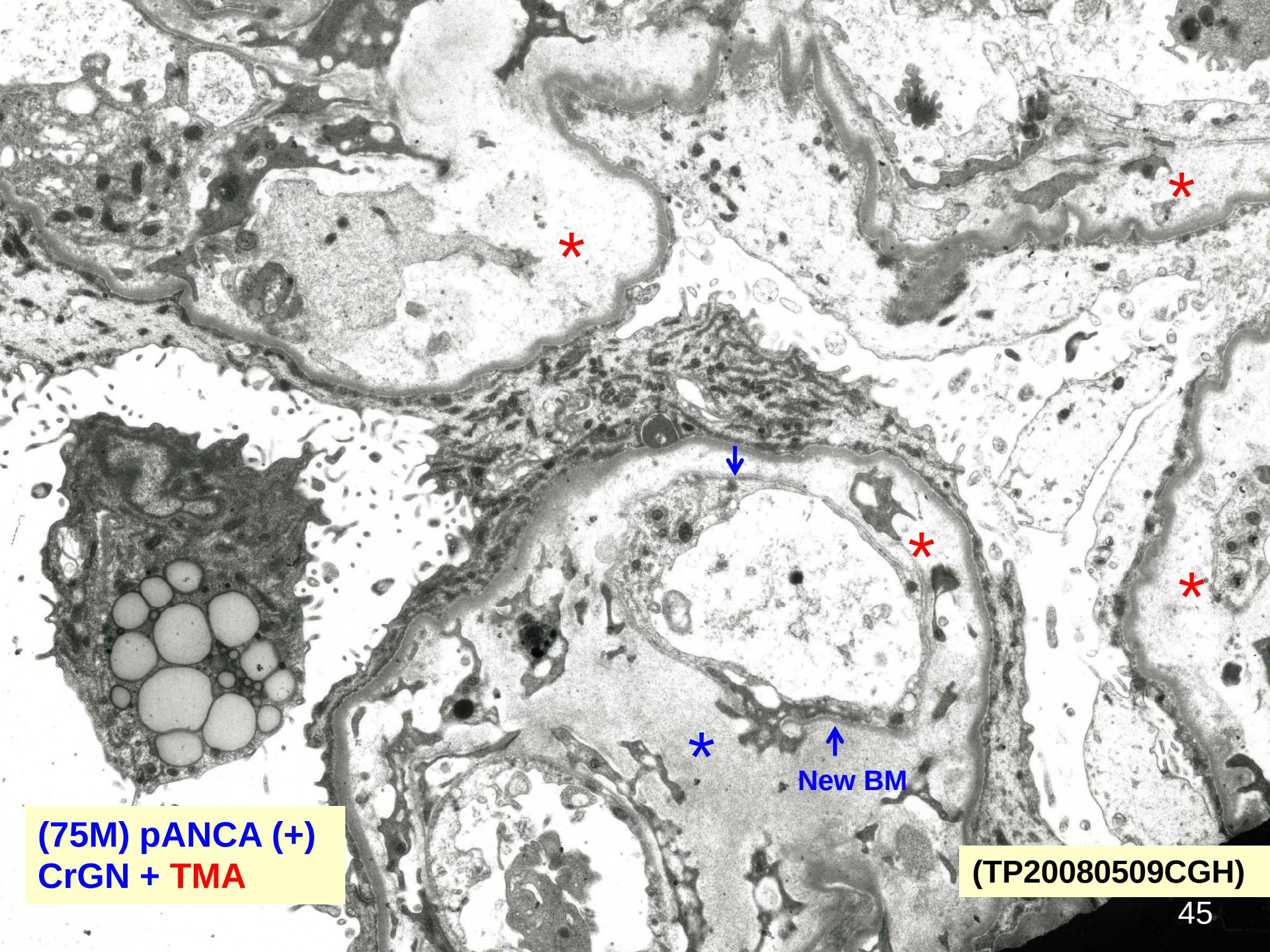
Scr: 1.3/2008.03→4.6/2008.04 (biopsy/38d) → 5.1/2008.05
(1215) Hemoptysis, Lung SCC, brain metastasis → 6.0/2009.02 → Expired (10 m)

- **Heavy smoker 40+ yrs, COPD and lung SCC**

(TP20080509CGH)


(75M) Scr 4.6:
pANCA (+) CrGN
(TP20080509CGH)


PB smear:
fragmented RBC;
schistocyte 1%,
microcyte 5-25%
(TP20080509CGH)



(75M) pANCA (+)
CrGN + TMA

(TP20080509CGH)

Summary

ANCA GN is a heterogeneous group of destructive GN, with complex histology and clinical course, and often associated with various disease conditions and environmental factors.

The histological changes are closely related to clinical manifestations, disease course, therapeutic efficacy and ultimately renal outcome.

知道臨床，知道病理；知道病理，知道臨床。

There are two decisive prognostic factors:

- **Clinical: Entry Scr level**
- **Pathology: Extent of irreversible glomerular destruction**

Some suggestions

- **It is preferred to differentiate FNCGN from CrGN (RPGN) to better understand the disease course and renal outcome.**

- **Looking beyond the histological diagnosis, pathology report can reveal clues for better prediction of disease course and the potential to the disease progression via therapy, and ultimately to achieve optimum recovery.**

- **Hope: Nephrologist is at least an amateur renal pathologist!**

Acknowledgements:

Special thanks to the nephrologists and renal pathologists for their contribution and participation:

TP (Taipei): CGH (國泰綜合醫院), MMH (馬偕紀念醫院)

TMU (臺北醫學大學): TMUH (附設醫院), WFH (臺北市立萬芳醫院), SHH (衛生福利部雙和醫院 – 新北市)

TC (臺中、彰化): CMUH (中國醫藥大學附設醫院), CSMUH (中山醫藥大學醫院), TCVGH (臺中榮民總醫院), KTGH (光田綜合醫院), CCH (彰化基督教醫院醫)

Thanks and Have a Nice Meeting with Great Success!