CLINICAL HISTORY
This 52 year old African American female factory worker was admitted most recently with chest pain/midsternal pressure for one day PTA (10/04).

1.) Past Med Hx: DM type 2 (for a couple of years, most recently started on insulin); uncontrolled hypertension (160-200/100-130), and hypothyroidism; eye grounds said to be normal
2.) PE: bipedal edema/EKG and labs: no evidence of MI
3.) Labs: BUN/serum Cr: 8/0.9 (on 7/04), and on this admission and next few days (10/25-11/10, 2004) was 26-39/2.2-2.8, 4+ proteinuria; remainder normal or negative
4.) Renal Biopsy: (11/09/04) New onset of renal failure and nephrotic syndrome ("thought to be too short a duration of DM as a cause). Other lab tests ordered.
**WHY BIOPSY DIABETIC PATIENTS?**

Most diabetic patients not biopsied at this time
Only biopsied if the clinical/laboratory course not typical:
  e.g., Rapid onset of severe proteinuria
    - Rapid development of acute or chronic renal failure
  Atypical findings: hematuria, normal fundoscopic exam, etc.

---

**DIABETES MELLITUS: PATHOLOGIC CHANGES**

Early:
- Large kidneys/glomeruli; increased GFR
- Microalbuminemia

Advancing:
1. Diffuse Diabetic Glomerulosclerosis
2. Nodular Diabetic Glomerulosclerosis
3. Insudative Changes (Fibrin caps; capsular drops; hyaline arteriolosclerosis)
4. Linear GBM and TBM staining (IgG4; albumin)

---

**Biopsy of a Diabetic Patient**

Step 1  Is it Diabetic Nephropathy?
RENAL BIOPSY IN PROTEINURIC TYPE 2 DIABETICS
(Parving et al)

1.) Three-fourths: Typical diabetic nephropathy

2.) One-fourth: Variety of non-diabetic lesions including MCNS, GN, mixed diabetic-GN lesions.

RENAL BIOPSY IN DIABETICS
(Gambara et al)

1/3: Changes typical of diabetic nephropathy

1/3: Marked increase in the percentage of globally sclerosed glomeruli associated with severe tubulointerstitial lesions, whereas non-sclerosed glomeruli showed only mild diabetic changes

1/3: Changes typical of diabetic nephropathy with superimposed changes of proliferative GN, Membranous GN, and other superimposed diseases.

Biopsy of a Diabetic Patient

Step 1  Is it Diabetic Nephropathy

Step 2  No  Yes
DIABETES AND OTHER SUPERIMPOSED NON-DIABETIC RENAL CONDITIONS

Acute proliferative GN
Cryoglobulinemic GN
Crescentic GN (+/- ANCA)
MPGN I and II (DDO) and III
IgA Nephropathy and HSP (+/- Crescents/ANCA)
Membranous GN (+/- Amyloid) (including Focal/segmental MGN)
Minimal Change Nephrotic Syndrome
Focal Segmental Glomerulosclerosis
SLE (Class IV)
Amyloidosis
Mesangial Proliferative GN
Sarcoidosis
Immune Complex Diseases: Focal GN, OSS and Incidental Postinfectious GN
Anti-GBM Disease (Crescentic)
Churg-Strauss (Crescentic)
Fibrillary GN/Immunotactoid GN
Monoclonal Immunoglobulin deposit disease & Heavy (Immunoglobulin) Chain Nodular Glomerulonephritis
Microscopic polyangitis
Tubulointerstitial Nephritis/Chronic Pyelonephritis
Pre-eclampsia

DUAL GLOMERULONEPHROPATHIES: A Partial List
SLE & Amyloid
Membranous GN & Amyloid
Membranous GN & Anti-GBM
MCNS & Focal segmental Membranous GN
Hereditary Nephropathy & Focal Seg. MGN
Hereditary Nephropathy & Dense Dep. Dis.
Hereditary Nephropathy & SLE
Crescentic GN & Membranous GN
ICD & anti-GBM
Focal segmental MGN & MCNS
Focal segmental MGN & Hereditary Nephropathy

BIOPSY OF DIABETICS

<table>
<thead>
<tr>
<th>Author</th>
<th>% Diabetic Nephropathy</th>
<th>% Other</th>
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<tbody>
<tr>
<td>Gambara</td>
<td>~ 33%</td>
<td>33% DN +</td>
</tr>
<tr>
<td>Zukowska-</td>
<td>78% (European)</td>
<td>22%</td>
</tr>
<tr>
<td>(Meta Analysis)</td>
<td>73% (Asian)</td>
<td>27%</td>
</tr>
<tr>
<td>Tone</td>
<td>36%</td>
<td>17% DN +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48% Other</td>
</tr>
<tr>
<td>Parving</td>
<td>~ 75%</td>
<td>25%</td>
</tr>
<tr>
<td>Ruggerenti</td>
<td>46% (35% Nephrosis)</td>
<td>19%</td>
</tr>
<tr>
<td>Suzuki</td>
<td>73%</td>
<td>27%</td>
</tr>
<tr>
<td>Mazzucco</td>
<td>29% and 51% (2 Protocols)</td>
<td>33% and 57%</td>
</tr>
<tr>
<td>Castellano</td>
<td>45%</td>
<td>55%</td>
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</tbody>
</table>
Concomitant Presence of Three Different Glomerular Diseases in the Same Patient
Report of a Case and Review of the Literature

T. Nessar, L. Ozer, M. S. Ahuja, R. S. Clarke, C. L. Prasad

*Department of Pathology, Columbia University, College of Physicians and Surgeons, and *Department of Medicine and Pathology, Lenox Hill Hospital, New York, NY, USA

Key Words: Diabetic glomerulosclerosis - Amyloidosis - Membranous glomerulopathy - Nephrotic syndrome

Abstract. A 35-year-old man with diabetes mellitus and the nephrotic syndrome on renal biopsy was found to have diabetic glomerulosclerosis, amyloidosis and membranous glomerulopathy. The presence of three distinct glomerular diseases in the same patient is unique. Possible factors involved in their pathogenesis are discussed and the literature on concomitant glomerular disease is reviewed.

TRIPLE RENAL DISEASES: A PARTIAL LISTING INCLUDING DIABETIC NEPHROPATHY

IgA Nephropathy/Crescentic/ANCA (Lai)
Amyloid, Membranous GN (Bertani/Pirani)

Biopsy of a Diabetic Patient

Step 1  Is it Diabetic Nephropathy

Step 2  No

Step 3  Then What? That's all DM Plus (Dual Disease)

A B C Etc
PROMINENT PARITIAL EPITHELIUM:  
A Common Sign of Renal Glomerular Injury

Egon F. Gaffney, MB, BCh, BAO

Materials and Methods

Seventy-seven consecutive renal biopsy specimens obtained at Grady Memorial Hospital in 1970-1980 were examined. Biopsy specimens that included less than ten glomeruli were excluded from the study. All renal tissue was obtained by percutaneous needle biopsy or by open surgical biopsy. Each specimen was subsectioned into portions for light, immunofluorescence, and electron microscopy. 

Crescents in Diabetic Glomerulopathy  
Incidence and Clinical Significance

I. B. Elfenbein, M.D., and J. W. Reeves, M.D.

Department of Pathology, Temple University Hospital and Health Sciences Center, Philadelphia, Pennsylvania 19140

Crescents, defined as any proliferative or fibrous space occupying reaction of the parietal layer of Bowman's capsule, occur as a regular and integral feature of the glomerular changes of diabetes mellitus. The frequency of crescents and their relationship to the capsule increase with increasing total severity of diabetic glomerular and vascular disease in glomeruli with mild-moderate diffuse glomerulosclerosis (DS), severe diffuse DS, and nodular DS. The high frequency (40-90%) of crescents and infarctions in glomeruli with extensive lesions is unrelated to over-all severity of diabetic renal disease. The 9.25% percent of glomerular with crescentic lesions had 45 per cent of the total crescents observed. The mechanism of crescent formation in diabetes is probably similar to the proposed pathogenesis of crescents in other renal diseases. The underlying injury in the glomerular capillaries in diabetes is mainly the "crescentic lesion." The percentage of diabetic crescents with crescents correlated better with blood urea nitrogen and creatinine than did the percentage of end stage glomeruli (a measure of severity of vascular disease). The occurrence of diabetic crescents was...
IS IT A CRESCENT?

“A buildup of several cell layers in a crescentic shape, caused by proliferation of parietal cells and probably also of the visceral epithelial cells of the glomerulus. The cells rest in a framework of fibrin, basement membrane, and collagen.”

A Handbook of Kidney Nomenclature and Nosology
International Committee for Nomenclature and Nosology of Renal Disease, 1975

DEFINITION OF A CRESCENT

“Extracapillary (glomerular) hypercellularity other than the epithelial hyperplasia of collapsing variant of focal segmental glomerulosclerosis”

TRUE CRESCENTS FROM FOUR OTHER CASES
(Next 4 slides)
“Non-Crescent Crescents”
i.e., Prominent Cells in Bowman’s Space: Are all so-called “Crescents” created equal or really crescents?

1.) “Tubularization”: ATN, etc
2.) “Cellular Caps” in FSGS
3.) Cellular Lesions in FSGS; marked extracapillary hypercellularity (as in Virulent, recurrent FSGS)
4.) Marked Extracapillary hypercellularity in HIVAN, collapsing GN.
5.) Hypercellular tubular-like structures in Bowman’s Space in ESRD (adenomatoid lesions/pseudotubules; etc)
6.) ? ETC

GLOMERULAR EPITHELIAL HYPERPLASIA FROM OTHER CASES (NOT THIS ONE) : NOT TRUE CRESCENTS

1.) Next two slides: Case of Chronic Sclerosing Lupus GN/approaching ESRD
2.) Other/Next 4: Recurrent (Virulent) Focal segmental sclerosis in a transplant
1.) Classic global collapsing FSGS from a nephrotic woman with SLE who had no deposits by IF or EM: not a cellular crescents but just marked hypercellularity in Bowman’s Space (one slide).

2.) Next 2 slides: Nephrotic woman with no deposits by EM or IF. Good example of a lesion that looks like segmental necrosis with a crescent, but with the silver stain shows endocapillary foam cells and capillary collapse without breaks.
“ADENOMATOID HYPERPLASIA”
SEEN IN ESRD, ETC. (HUGHSON, HENNIGAR X2, MACMANUS, ETC)

OUR PATIENT
I interpreted initially as definite crescents
Biopsy of a Diabetic Patient

Step 1 Is it Diabetic Nephropathy

Step 2 No

Step 3 Then What? (A B C etc.)

Step 4 What in excess of DM

Step 5 Crescents GN Etc.

CRESCENTIC GN: Mechanisms

A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (?pathogenic)

<table>
<thead>
<tr>
<th>Type of glomerular disease</th>
<th>Number</th>
<th>% with any crescents</th>
<th>% with 1+ crescents</th>
<th>Average % glomerular crescents</th>
<th>Glomerular crescents (1+ to +++)</th>
<th>Glomerular hypereosinophilia (++)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GBM glomerulonephritis</td>
<td>182</td>
<td>92.1</td>
<td>86.4</td>
<td>37</td>
<td>1.3</td>
<td>0.8</td>
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<tr>
<td>ANCA glomerulonephritis</td>
<td>181</td>
<td>90.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>LN glomerulonephritis (II &amp; IV)</td>
<td>764</td>
<td>90.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>AIP glomerulonephritis</td>
<td>205</td>
<td>90.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>ANCA glomerulonephritis</td>
<td>181</td>
<td>90.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>Renal infection glomerulonephritis</td>
<td>178</td>
<td>96.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>Type I membranoproliferative glomerulonephritis</td>
<td>178</td>
<td>96.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>Type II membranoproliferative glomerulonephritis</td>
<td>178</td>
<td>96.3</td>
<td>83.5</td>
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<td>1.9</td>
<td>0.8</td>
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<tr>
<td>Type III membranoproliferative glomerulonephritis</td>
<td>178</td>
<td>96.3</td>
<td>83.5</td>
<td>49</td>
<td>1.9</td>
<td>0.8</td>
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<tr>
<td>Membranous nephrotic syndrome</td>
<td>54</td>
<td>3.6</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>54</td>
<td>3.6</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Glomerulosclerosis</td>
<td>648</td>
<td>3.2</td>
<td>0.3</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CRESCENTIC GN: Mechanisms

A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (?pathogenic)

Nephrology Forum

Rapidly progressive crescentic glomerulonephritis
Principal discussant: J. Charles Jennette
The University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

CRESCENTIC GN: Mechanisms

A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (?pathogenic)

Table 3. Frequency of glomerular crescents, arrows, and mesangial hypercellularity in different types of glomerular disease evaluated by the University of North Carolina Nephrology Laboratory.

CRESCENTIC GN: Mechanisms

A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (?pathogenic)

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A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (?pathogenic)
CRESCENTIC GN: Mechanisms

A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (?pathogenic)
D.) None of the above (non A, non B, non C)

10-20% of Pauci-Immune Crescentic Glomerulonephritis

What is that?


**DIABETES AND CRESCENTS: One Disease or Two?**

1.) A severe form of progressive diabetic nephropathy?

2.) Two diseases for the price of one: i.e., diabetic nephropathy and a proliferative GN

---

**EVOLUTION OF ONE RENAL DISEASE INTO ANOTHER**

Membranous GN into Anti-GBM (Klassen)

---

**RECENT NEPHNPPPT: SUPERIMPOSED GN’S ?: IGA & SLE**

Two thirds of the responders indicated that they believed Occam’s Razor (i.e., one disease, not two).

---

**DOES ONE RENAL DISEASE LEAD TO OR ACCENTUATE THE PRODUCTION OF ANOTHER**

Could it be Autoimmune?

- Release previously sequestered antigen
- Alteration of Self Antigen (Molecular mimicry)
- Can autoimmunity wax and wane in a single patient
Case 1: My Diagnosis

Diffuse (and early/slight focal/segmental nodular) diabetic glomerulosclerosis with 20% crescent formation (? With superimposed glomerulonephritis) – see Above (order anti-GBM and ANCA: please be positive!)

Interstitial Inflammation & Fibrosis and Tubular Degeneration

Dr. Clarke Stout

“I think she does have mild diffuse and nodular diabetic glomerulosclerosis in that several small typical KW nodules are present, and the EM photos are consistent with mild diffuse lesion. It is hard to say how much of the non-nodular mesangial expansion is due to diabetes, and how much is due to the nephritic process, but I suspect most of it is due to the later”.

Dr. Clarke Stout

“Crescents are not rare in diabetic glomeruli, and in my experience are almost always associated with an underlying focal mesangiolysis or KW nodule… I have never seen crescents as exuberant as the ones in the present case in a diabetic glomerulus, and none of the photos show nodules under the crescents.

She appears to have some type of superimposed non-immune mediated glomerulonephritis which I suspect you have a name for…”
Biopsy of a Diabetic Patient

Step 1: Is it Diabetic Nephropathy

Step 2: No →

Step 3: Then What? That’s all DM Plus (Dual Disease)

Step 4: What in excess of DM

Step 5: No → Crescentic GN

Step 6: Yes → ICD, Anti-GBM, ANCA, Something else

Step 7: ?Severe rare/Post infectious

Step 8: Atypical DM (viral) GN

SEVERITY OF DIABETIC NEPHROPATHY

SEVERITY OF GN/CRESCENTIC GN

Crescentic GN in DM

DN + Crescentic GN

DN + Crescentic GN

DN + Crescentic GN

2 Diseases

DN + Crescentic GN

DN + Crescentic GN

DN + Crescentic GN

DN + Crescentic GN

? One or Two Diseases or a Continuation of Changes

Mild DN

Moderate DN

Moderate to Severe DN

Severe DN

1+ 2+ 3+ 4+
COGNITIVE DIAGNOSTIC ERRORS (Acad.Med.Aug03)
1.) Anchoring: Lock-in too early/fail to adjust to later information
2.) Confirmation: Look for confirming evidence to support Dx/not looking for refutation
3.) Diagnosis Momentum: One Dx label attached: stickier and stickier
4.) Ascertainment Bias: Thinking shaped by prior expectations/stereotyping
5.) Availability: If things rapidly come to mind/recent experience—more likely to occur
6.) Base rate neglect: Ignore prevalence of a disease
7.) Commission bias: tendency toward action
8.) Overconfidence: Universal tendency to believe we know more than we do

COGNITIVE ERRORS (CONT'D)
9.) Premature Closure: “when the diagnosis is made, the thinking stops”
10.) Fundamental Attribution Error: comorbid medical conditions overlooked
11.) Representativeness Restraint: Looking for prototypical manifestations of disease; leads to missing atypical variants
12.) Search Satifying: Call off search once something is found
13.) Sutton’s Slip: When possibilities other than the obvious are not given sufficient consideration
14.) Sunk Costs: The more you invest in a Dx, less likely to release it, and consider alternatives
15.) Vertical Line Failure: Thinking in Silo’s: inflexible: what else could it be?

COGNITIVE DEBIASING STRATEGIES TO DECREASE DIAGNOSTIC ERRORS
1.) Be aware of bias/approach/experience
2.) Consider alternatives
3.) Metacognition: Step back/reflect on thinking process
4.) Decrease reliance on memory
5.) Training bias/simulations
6.) Strategies to avoid bias
7.) Get more information
8.) Minimize time pressures
9.) Accountability
10.) Feedback

WHY PRESENT THIS CASE?
1.) I had it available! (and it intrigued me!)
2.) The Epidemic/Pandemic of Diabetes Mellitus (we’re likely to see many more biopsies)
3.) The Differential Diagnosis & Occam’s Razor: One or two diseases? (Dr. Pirani’s interest and suggestions)
4.) Algorithmic steps/approach
5.) Maybe all “crescents” are not created equal
6.) Heurism/Missteps/Getting it Right and how will we know?
7.) I’d like to know: What do you think it is?
Case 1 Expert Panel Diagnoses

- Diabetic GS with concurrent ANCA-disease or possibly anti-GBM (2)
- LCDD with early diabetic change
- Non-diabetic nodular sclerosis complicated by crescents (vs chronic TMA)

FOLLOWUP OF THIS PATIENT

12/04: ANCA and anti-GBM (Mayo Med. Labs): Both Negative

9/16/05: Urine protein: 9.03 grams/24 hrs
9/25/05: Serum creatinine 1.1; BUN 22
         Serum albumin 2.7

She was noted to be noncompliant with essentially all her medications due to financial constraints.

THIS PATIENT

1.) No evidence (clinical or via renal biopsy) of an Immune Complex GN
2.) Anti-GBM: negative (Mayo Labs)
3.) ANCA: negative (Mayo Labs)

(Cost of #3 & #4): $400.00 plus shipping
ACKNOWLEDGEMENTS

1.) Drs. Conrad L. Pirani and Jacob Churg
2.) The Renal Pathology Society, Inc.
3.) Dr. Rory R. Dalton, Dept. of Pathology/MCG
4.) Drs. Clark Stout, Patrick Walker, Charles Jennette, Arthur Cohen, Vivette D'Agati, Charles Alpers, Melvin Schwartz, Randy Hennigar, and others
5.) Dr. Agnes Fogo

IN HONOR OF DR. CONRAD L. PIRANI AND JACOB CHURG

“And gladly wolde he lerne, and gladly teche”

Geoffrey Chaucer
The Canterbury Tales (1387)