Dr. Jacob Churg
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.
IgM
kappa
null
WHY BIOPSY DIABETIC PATIENTS?

Most diabetic patients not biopsied at this time

Only biopsied if the clinical/laboratory course not typical:

- Rapid onset of severe proteinuria
- Rapid development of acute or chronic renal failure
- Atypical findings: hematuria, normal fundoscopic exam, etc.
Biopsy of a Diabetic Patient

Step 1  Is it Diabetic Nephropathy?
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

Step 2  No       Yes
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
Among 1715 renal biopsies investigated by means of light microscopy, immunofluorescence, and/or electron microscopy, 20 cases of various glomerulopathies (GP) were found to be superimposed on diabetic glomerulosclerosis (DGS). The most frequently superimposed GPs were acute GN (nine cases) and cryoglobulinemic GN (six cases). Although the former association is known to occur, the latter has not so far been reported. In the other patients DGS was associated with crescentic GN (two cases), membranoproliferative GN, membranous GN, and IgA nephropathy (one case each). 

41), we are dealing with small series of cases (3, 6, 20, 42, 43), or even with case records.

The present study reports on the occurrence of the superimposition of different types of GN on DGS in patients admitted to the nephrology units of ...
DIABETES AND OTHER SUPERIMPOSED NON-DIABETIC RENAL CONDITIONS

Acute proliferative GN
Cryoglobulinemic GN
Crescentic GN (-/+ ANCA)
MPGN I and II (DDD) 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
Immobile Complex Diseases: Focal GN, OSS and Incidental Healed Postinfectious GN
Anti-GBM Disease (Crescentic)
Churg-Strauss (Crescentic)
Fibrillar GN/Immunotactoid GN
Monoclonal Immunoglobulin deposition disease & Heavy (Immunoglobulin) Chain Nodular Glomerulosclerosis
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
DUAL GLOMERULOPATHIES?  
THE SAME DISEASE OR TWO DIFFERENT DISEASES?

IgA Nephropathy (with Minimal Change Nephrotic Syndrome)
IgA Nephropathy (with Membranous GN pattern)

Focal Segmental Sclerosis in Diabetic Nephropathy, or Membranous GN, or Hypertension

Others
<table>
<thead>
<tr>
<th>Author</th>
<th>% Diabetic Nephropathy</th>
<th>% Other</th>
</tr>
</thead>
<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>Ruggenenti</td>
<td>46%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>(35% Nephroscl.)</td>
<td></td>
</tr>
<tr>
<td>Suzuki</td>
<td>73%</td>
<td>27%</td>
</tr>
<tr>
<td>Mazzucco</td>
<td>29% and 51%</td>
<td>33% and 57%</td>
</tr>
<tr>
<td>(2 Protocols)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castellano</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Author</td>
<td>%Diabetic Nephropathy</td>
<td>%Other</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Serra</td>
<td>74%</td>
<td>9% DN+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17% Other</td>
</tr>
<tr>
<td>Hironaka</td>
<td>71%</td>
<td>29% DN + (1/2 DN also)</td>
</tr>
<tr>
<td>Richards</td>
<td>86% (I) 50% (II)</td>
<td>9% DN+/4% Not DN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48% Not DN</td>
</tr>
<tr>
<td>Waldherr</td>
<td></td>
<td>2% ICD</td>
</tr>
<tr>
<td>Amoah</td>
<td>88% (1) 72% (2)</td>
<td>12% (1) ±DN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28% (2) ±DN</td>
</tr>
<tr>
<td>Hommel (Hematuria)</td>
<td></td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>69% ±DN</td>
<td></td>
</tr>
<tr>
<td>Yum</td>
<td>56%</td>
<td>44%</td>
</tr>
</tbody>
</table>
Concomitant Presence of Three Different Glomerular Diseases in the Same Patient

Report of a Case and Review of the Literature

T. Bertani, L. Olesnicky, S. Abu-Regiaba, S. Glasberg, C. L. Pirani

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Key Words. Diabetic glomerulosclerosis · Amyloidosis · Membranous glomerulopathy · Nephrotic syndrome

Abstract. A 51-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 diseases 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?

DM Plus (Dual Disease)

That’s all
CRESCENTS IN DIABETIC NEPHROPATHY
Prominent Parietal Epithelium: A Common Sign of Renal Glomerular Injury

Eoin F. Gaffney, MB, BCh, BAO

Reported abnormalities of the normally inconspicuous renal glomerular parietal epithelium include tubular metaplasia, adenomatoid transformation, columnar metaplasia, and embryonal hyperplasia of Bowman's capsular epithelium. In this study, glomerular parietal epithelium was analyzed in 77 consecutive renal biopsy specimens representing a spectrum of renal diseases. In 57 biopsy specimens, prominent parietal epithelium (PPE) (ten or more enlarged parietal cells with hyperchromatic or vesicular nuclei and discernable vacuolated cytoplasm in at least two glomeruli) was identified and graded according to its severity in the specimen. Extensive PPE was present in all five cases of

Materials and Methods

Seventy-seven consecutive renal biopsy specimens obtained at Grady Memorial Hospital in 1979–1980 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 subdivided into portions for light, immunofluorescence, and electron microscopy. Tissue
Crescents in Diabetic Glomerulopathy
Incidence and Clinical Significance

I. B. ELFENBEIN, M.D., AND J. W. REYES, 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 adhesions to the capsule increases with increasing total severity of diabetic glomerular and vascular disease in glomeruli with mild-moderate diffuse glomerulosclerosis (GS), severe diffuse GS, and nodular GS. The high frequency (>90 per cent) of crescents and adhesions in glomeruli with exudative lesions is unrelated to over-all severity of diabetic renal disease. The 8.73 per cent of glomeruli with exudative 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 "exudative lesion." The percentage of diabetic glomeruli 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 percentage of diabetic glomeruli with
Epithelial crescent in diabetic glomeruli. A case report.

Toth T.

Department of Pathology, County Hospital, Szolnok, Hungary.

The kidney as a target organ for secondary microvascular complications of diabetes mellitus represents a major problem. The pathology of diabetic glomerulopathy is well known. The coexistence of immunocomplex-mediated glomerulonephritis and diabetes mellitus has rarely been reported. The presence of crescents in glomerular disease of diabetes mellitus has been usually ignored in the literature. The present study describes one patient with epithelial crescentic diabetic glomerulopathy with rapidly progressive renal failure.
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 2  Yes
       
Step 3  That’s all
       
Step 4  DM Plus (Dual Disease)
       
Step 5  What in excess of DM

Crescents  GN  Etc
CRESCENTIC GN: Mechanisms

A.) Immune Complex Deposition
B.) Anti-GBM disease
C.) ANCA-associated (pathogenic)
Rapidly progressive crescentic glomerulonephritis

Principal discussant: J. Charles Jennette

The University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

pulmonary edema. Hemodialysis was initiated and continued throughout her admission. Renal ultrasound showed normal kidney size with echogenicity consistent with parenchymal disease. Serologic tests were ordered and a renal biopsy was performed.

The renal biopsy demonstrated involvement of essentially all glomeruli by necrosis, sclerosis, or both. Approximately 90% of glomeruli had cellular or fibrocellular crescents (Fig. 1A). There was focal disruption of Bowman’s capsule. Most glomeruli had prominent adjacent periglomerular inflammation, including occasional multinucleated giant cells. A few small foci of granulomatous inflammation were present but were centered on identifiable glomeruli (Fig. 1C). Arteries and arterioles had moderate sclerosis as well as focal necrotizing vasculi-
Table 3. Frequency of glomerular crescents, necrosis, and endocapillary hypercellularity in different types of glomerular disease evaluated by the University of North Carolina Nephropathology Laboratory

<table>
<thead>
<tr>
<th>Type of glomerular disease</th>
<th>Number</th>
<th>% with any crescents</th>
<th>% with &gt;50% crescents</th>
<th>Average % glomerular crescents&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Glomerular necrosis (0 to 4+)</th>
<th>Glomerular hypercellularity (0 to 4+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GBM glomerulonephritis</td>
<td>105</td>
<td>97.1</td>
<td>84.8</td>
<td>77</td>
<td>1.7+</td>
<td>0.8+</td>
</tr>
<tr>
<td>ANCA glomerulonephritis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>181</td>
<td>89.5</td>
<td>50.3</td>
<td>49</td>
<td>1.2+</td>
<td>0.8+</td>
</tr>
<tr>
<td>Lupus glomerulonephritis (III &amp; IV)</td>
<td>784</td>
<td>56.5</td>
<td>12.9</td>
<td>31</td>
<td>1.7+</td>
<td>2.2+</td>
</tr>
<tr>
<td>H-S purpura glomerulonephritis</td>
<td>31</td>
<td>61.3</td>
<td>9.7</td>
<td>27</td>
<td>0.4+</td>
<td>1.5+</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>853</td>
<td>32.5</td>
<td>4.0</td>
<td>21</td>
<td>0.1+</td>
<td>1.4+</td>
</tr>
<tr>
<td>Post-infectious glomerulonephritis</td>
<td>120</td>
<td>33.3</td>
<td>3.3</td>
<td>19</td>
<td>0.3+</td>
<td>2.7+</td>
</tr>
<tr>
<td>Type I membranoproliferative glomerulonephritis</td>
<td>307</td>
<td>23.8</td>
<td>4.6</td>
<td>25</td>
<td>0.2+</td>
<td>2.8+</td>
</tr>
<tr>
<td>Type II membranoproliferative glomerulonephritis</td>
<td>16</td>
<td>43.8</td>
<td>18.8</td>
<td>48</td>
<td>0.2+</td>
<td>1.8+</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis</td>
<td>101</td>
<td>22.8</td>
<td>5.0</td>
<td>26</td>
<td>0+</td>
<td>0.6+</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin deposition disease</td>
<td>54</td>
<td>5.6</td>
<td>0</td>
<td>13</td>
<td>0+</td>
<td>0.3+</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>251</td>
<td>5.6</td>
<td>0.9</td>
<td>26</td>
<td>0.4+</td>
<td>0.3+</td>
</tr>
<tr>
<td>Diabetic glomerulosclerosis</td>
<td>648</td>
<td>3.2</td>
<td>0.3</td>
<td>20</td>
<td>0+</td>
<td>0.3+</td>
</tr>
<tr>
<td>Nonlupus membranous glomerulopathy</td>
<td>1092</td>
<td>3.2</td>
<td>0.1</td>
<td>15</td>
<td>0.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>ANCA glomerulonephritis was defined as glomerulonephritis with 2+ or less staining of glomeruli for any immunoglobulin in a patient who is positive for MPO-ANCA or PR3-ANCA by ELISA

<sup>b</sup>Average % of glomeruli with crescents when crescents were present

<sup>c</sup>Endocapillary (not extracapillary) hypercellularity

Carstens SA, Hebert LA, Garancis JC, Piering WF, Lemann J Jr.

Two patients with long-standing diabetes mellitus and diabetic retinopathy were evaluated for declining renal function and heavy albuminuria. Initially, diabetic glomerulosclerosis was suspected as the cause of progressive glomerulopathy. However, in both patients the rate of loss of glomerular filtration rate was greater than that usually seen in diabetic glomerulosclerosis, and the urine sediment contained many RBC casts. These findings led to renal biopsy, which demonstrated crescentic glomerulonephritis superimposed on diabetic glomerulopathy. Both patients were treated with prednisone and cyclophosphamide and both experienced substantial improvement in renal function. These experiences demonstrate the importance of searching for evidence of a superimposed treatable glomerulopathy in the diabetic patient with glomerulopathy and advancing renal insufficiency.
Diabetic nephropathy with anti-GBM nephritis.

Ahuja TS, Velasco A, Deiss W Jr, Indrikovs AJ, Rajaraman S.

Department of Medicine, University of Texas Medical Branch at Galveston 77555, USA. tahuja@utmb.edu

Immune complex glomerulonephritis can be superimposed on diabetic glomerulosclerosis. Idiopathic membranous glomerulonephritis, immunoglobulin (Ig) A glomerulonephritis, Henoch-Schönlein nephritis, membranoproliferative glomerulonephritis, minimal change glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, amyloidosis, focal segmental glomerulosclerosis, and rarely crescentic glomerulonephritis can all occur with diabetic nephropathy. We describe for the first time an unusual case of diabetic nephropathy coexistent with anti-glomerular basement membrane (GBM) nephritis. The renal function of this patient improved with plasmapheresis and immunosuppressives. We also review the literature on coexistent rapidly progressive glomerulonephritis (RPGN) and diabetic nephropathy.
Myeloperoxidase-antineutrophil cytoplasmic antibody-associated glomerulonephritis superimposed on biopsy-proven diabetic nephrosclerosis.


Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

We present a case of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis with diabetic nephrosclerosis, diagnosed by serial renal biopsies within a short period. A 78-year-old man with renal insufficiency, who had been diagnosed with diabetic nephrosclerosis by renal biopsy 9 months earlier, was admitted to the hospital for dyspnea and rapid deterioration of renal function. The titer of serum MPO-ANCA was high, and the second renal biopsy confirmed the presence of necrotizing glomerulonephritis with crescents. Methylprednisolone pulse therapy followed by oral administration of prednisolone led to resolution of respiratory symptoms and reversal of MPO-ANCA. Renal function did not improve, however, necessitating hemodialysis. A review of the literature showed several cases of necrotizing glomerulonephritis superimposed on diabetic nephropathy but only a few reported cases of MPO-ANCA glomerulonephritis associated with diabetic nephrosclerosis. Diabetic patients who show rapid deterioration of renal function should undergo renal biopsy to determine the concomitant presence, if any, of other glomerular diseases and to prevent life-threatening

Satko SG, Freedman BI, Iskandar SS.

Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1053, USA. ssatko@wfubmc.edu

A 73-year-old white man with slowly progressive chronic renal failure and nephrotic-range proteinuria was found to have antineutrophil cytoplasmic antibody in a perinuclear pattern (p-ANCA) at a titer of 1:800. Renal histologic findings revealed an advanced scarring glomerulopathy with diffuse and nodular mesangial sclerosis. Light, electron, and immunofluorescence microscopic findings were highly suggestive of diabetic glomerulosclerosis. Interestingly, this patient had no history of diabetes mellitus or diabetic retinopathy. The presence of p-ANCA positivity can be found in patients with a broad range of renal histologic findings, and does not necessarily imply the existence of pauci-immune necrotizing crescentic glomerulonephritis. For this reason, we urge caution in the empiric cytotoxic treatment of p-ANCA-associated renal disease in stable patients. When possible, a tissue diagnosis should be made.
ANCA-negative pauci-immune renal vasculitis: histology and outcome

Ute Eisenberger\textsuperscript{1,2}, Fadi Fakhouri\textsuperscript{2}, Philippe Vanhille\textsuperscript{3}, Hélène Beaufs\textsuperscript{4}, Alfred Mahr\textsuperscript{5}, Loic Guillemin\textsuperscript{5}, Philippe Lesavre\textsuperscript{1,6} and Laure-Hélène Noël\textsuperscript{6}

\textsuperscript{1}Department of Nephrology, University Hospital, Bern, Switzerland, \textsuperscript{2}Department of Nephrology, \textsuperscript{4}INSERM U574, \textsuperscript{6}INSERM U507, and AP-HP, Necker Hospital, \textsuperscript{5}Department of Internal Medicine, Cochin Hospital, Paris and \textsuperscript{3}Department of Internal Medicine, Valenciennes Hospital, France

Abstract
Background. Pauci-immune renal vasculitis with focal glomerular necrosis and crescent formation is usually associated with anti-neutrophil cytoplasmic antibodies (ANCA). However, ANCA's are absent in up to 10% of cases, which constitutes a rarely studied variant of renal vasculitis.

Methods. This retrospective multicentre cohort study underline the importance of the exact diagnosis in an active vasculitic disease process even in the absence of ANCA.

Keywords: ANCA-negative; microscopic polyangiitis; neutrophils; pauci-immune renal vasculitis; renal biopsy; renal outcome; Wegener's granulomatosis
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?
DO CRESCENTS MAKE IT A CRESCENTIC GN?

What percentage of glomerular involvement is needed?

20-80% or more?
50% or more?
80% or more?
Biopsy of a Diabetic Patient

Step 1  Is it Diabetic Nephropathy

Step 2  No

Step 3  Then What?

- A
- B
- C
- Etc

Step 3  Yes

- That’s all
- DM Plus (Dual Disease)

Step 4  What in excess of DM

- Crescents
- GN
- Etc

Step 6  No

- ICD
- Anti-GBM
- ANCA

Step 6  Yes

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

?–1347
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
**Biopsy of a Diabetic Patient**

**Step 1**  
**Is it Diabetic Nephropathy**
- **No**
- **Yes**

**Step 2**  
**No**

**Step 3**  
**Then What?**
- A
- B
- C
- Etc

**Step 4**  
**What in excess of DM**
- Crescents
- GN
- Etc

**Step 5**  
**Yes**

**Step 6**  
**ICD**
- Anti-GBM
- ANCA
- Something else

**Step 7**  
**Severe rare/Atypical DM**

**Step 8**  
**Post infectious (viral) GN**
- Stress
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
          Yes

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

Step 4  What in excess of DM

Step 5  Crescents
          GN
          Etc

Step 6  No
          Yes

Step 7  ICD
          Anti-GBM
          ANCA
          Something else

Step 8  ?Severe rare/Atypical DM
          ?Post infectious (viral) GN
          ?Stress
Biopsy of a Diabetic Patient

Step 1: Is it Diabetic Nephropathy
- No
- Yes

Step 2: No

Step 3: Then What?
- A
- B
- C
- Etc

Step 4: What in excess of DM

Step 5: Crescents
- GN
- Etc

Step 6: No

Step 7: ICD Anti-GBM ANCA Something else

Step 8: ?Severe rare/Atypical DM

?Post infectious (viral) GN ?Stress
FUZZY THINKING
THE NEW SCIENCE OF FUZZY LOGIC
<table>
<thead>
<tr>
<th>SEVERITY OF GN/CRESCENTIC GN</th>
<th>Crescentic GN in DM</th>
<th>DN + Crescentic GN</th>
<th>DN + Crescentic GN</th>
<th>DN + Crescentic GN</th>
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<tr>
<td>4+</td>
<td>2+</td>
<td>3+</td>
<td>4+</td>
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<tr>
<td>3+</td>
<td>DN w/ Crescents</td>
<td>DN + Crescents</td>
<td>DN + Crescents</td>
<td>DN + Crescents</td>
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<tr>
<td>2+</td>
<td>2 Diseases</td>
<td>2 Diseases</td>
<td>2 Diseases</td>
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<td>1+</td>
<td>? One or Two Diseases or a Continuation of Changes</td>
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<td>? One or Two Diseases or a Continuation of Changes</td>
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<th>SEVERITY OF DIABETIC NEPHROPATHY</th>
<th>Mild DN</th>
<th>Mod. DN</th>
<th>Mod. to Severe DN</th>
<th>Severe DN</th>
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<tbody>
<tr>
<td>1+</td>
<td>2+</td>
<td>3+</td>
<td>4+</td>
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</tbody>
</table>

- GN: Glomerulonephritis
- DN: Diabetic Nephropathy
- Crescents: Crescent formation
- DM: Diabetes Mellitus
- Mod.: Moderate
- Severe: Severe
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
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)
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
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.
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)