The clinicopathologic characteristics and outcome of atypical anti-glomerular basement membrane nephritis

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Classic anti-glomerular basement membrane (GBM) disease presents with rapidly progressive glomerulonephritis (GN) with or without pulmonary hemorrhage. On biopsy typical disease displays bright polytypic linear GBM staining for IgG by immunofluorescence and diffuse crescentic/necrotizing GN on light microscopy. Here, we studied 20 patients with atypical anti-GBM nephritis typified by bright linear GBM staining for immunoglobulins but without a diffuse crescentic phenotype. Patients had hematuria, proteinuria, and mild renal insufficiency, without pulmonary hemorrhage. Light microscopy showed endocapillary proliferative GN in 9 patients, mesangial proliferative GN in 6, membranoproliferative GN in 3, and focal segmental glomerulosclerosis with mesangial hypercellularity in 2. Eight of the 20 showed features of microangiopathy. Crescents/necrosis were absent in 12 and were focal in 8 patients. Bright linear GBM staining for IgG was seen in 17 patients, IgM in 2, and IgA in 1 patient, which was polytypic in 10 patients and monotypic in 10 patients. No circulating α3NC1 antibodies were detected by commercial ELISA. The 1-year patient and renal survival rates were 93% and 85%, respectively. Thus, atypical anti-GBM nephritis is a rare variant of anti-GBM disease characterized clinically by an indolent course, no pulmonary involvement, and undetectable circulating α3NC1 antibodies. Further studies are needed to characterize the molecular architecture of GBM autoantigens in these patients and establish optimal therapy.

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Classic anti-glomerular basement membrane (GBM) nephritis is clinically and pathologically the most aggressive form of glomerulonephritis. Patients typically present with nephritic syndrome and rapidly progressive acute renal failure.[1,2] Lung involvement in the form of alveolar hemorrhage occurs in 34% to 62% of patients.[3,4] Classic anti-GBM disease is due to circulating autoantibodies directed against cryptic epitopes in the NC1 domain of the alpha-3 chain of type IV collagen (α3NC1), also known as the Goodpasture antigen.[5–7] In addition to the classic antibody, autoantibodies against other type IV collagen GBM antigens, including α5NC1, α4NC1, and linear type IV collagen epitopes, are frequent.[6–8] An early critical step in the development of anti-GBM disease is a pathologic conformational change in the α3NC1 and α5NC1 subunits, exposing cryptic epitopes, which in turn can trigger an autoimmune reaction. As such, anti-GBM disease may be considered an autoimmune "conformeropathy."[7] Binding of the autoimmune antibodies to GBM leads to *in-situ* complement activation, recruitment of neutrophils and monocytes, and destruction of the GBM with fibrin extravasation in the urinary space, culminating in crescent formation and rapidly progressive glomerulonephritis.[2]

The pathological *sine qua non* of anti-GBM nephritis is bright linear polyclonal staining of GBM for IgG on immunofluorescence (IF). Focal linear staining of distal tubular basement membranes (TBMs) (which express α3, α4, and α5) occurs in 50% to 79% of patients.[9,10] Most cases show diffuse crescentic and necrotizing glomerulonephritis on light microscopy (LM).[1,2] In one study of 105 patients from the University of North Carolina Nephropathology Laboratory, 97% of anti-GBM nephritis cases show crescents on biopsy, and approximately 85% of cases showed crescents that affected >50% of glomeruli.[2] Glomeruli without crescent formation are typically unremarkable on LM, without mesangial or endocapillary hypercellularity. In this study we describe an atypical form of anti-GBM nephritis characterized clinically by an indolent course, undetectable circulating α3NC1 antibodies by commercially available enzyme-linked immunosorbent assay (ELISA), and histologically by endocapillary proliferative, mesangial proliferative,

Table 1 | Pathologic findings in patients with atypical anti-GBM nephritis

Pt #	Glomerular pattern of injury	# of gloms/% global sclerosis/ % crescents/ % necrosis	TA/IF	Immunofluorescence	IgG subclass staining by immunofluorescence	Electron microcopy
1	MPGN with focal crescents	15/20/40/7	Mild	Lin GBM and focal TBM IgG (2+), κ (2+), and λ (2+); neg IgA, IgM, C1q, and C3	3+ IgG4; neg IgG1, IgG2, and IgG3	No electron-dense deposits; global FPE
2	MPGN with diffuse endocapillary proliferative features and focal crescents	13/0/23/15	None	Lin GBM and focal TBM IgG (3+), κ (3+), λ (3+), and IgA (+/−); +/− gran mes IgM (+/−) and C3 (+/−); neg C1q	3+ IgG4; +/− IgG1; neg IgG2 and IgG3	No electron-dense deposits; GBM gaps; seg FPE
3	EPGN with focal crescents and mild TMA features	25/4/8/12	Mild	Lin GBM and focal TBM IgG (3+), κ (3+), and λ (3+); gran GBM C3 (1+) and IgM (+/−); neg IgA and C1q	Bright IgG2 and IgG4; neg IgG1 and IgG3	Rare minute mes deposits; GBM gaps; TMA features; seg FPE
4	EPGN with focal crescents and TMA features	16/19/19/0	Mild	Lin GBM and focal TBM IgG (3+), κ (3+), λ (3+), C3 (+/−); neg IgA, IgM, and C1q	2+ IgG1; 1+ IgG2; 1+ IgG4; neg IgG3	No electron-dense deposits; TMA features; seg FPE
5	MesPGN with TMA features	16/0/0/0	Mild	Lin GBM IgG (3+), κ (2+), and λ (1+); neg IgA, IgM, C1q, and C3	Not done	One subepi deposit; TMA features; global FPE
6	EPGN with focal necrosis	20/0/0/5	None	Lin GBM IgG (3+), κ (3+), λ (3+); gran mes IgA (+/−), IgM (+/−), and C3 (+/−); neg C1q	3+ IgG2; 1+ IgG1; neg IgG3 and IgG4	Seg subepi deposits (<10% of loops); seg FPE
7	MPGN with TMA features	24/0/8/0	Mild	Lin GBM and focal TBM for IgG (3+), κ (2+), and λ (2+); gran GBM C3 (1+); neg IgA, IgM, C1q	3+ IgG1; 3+ IgG4; trace IgG3; neg IgG2	Rare mes and subendo deposits; TMA features; global FPE
8	MesPGN with segmental scars and TMA features	10/0/0/0	Moderate	Lin GBM and focal TBM for IgG (3+), κ (2+), and λ (3+); gran mes C3 (+/−); neg IgA, IgM, and C1q	2+ IgG2; 2+ IgG4; neg IgG1 and IgG3	No electron-dense deposits; TMA features; seg FPE
9	FSGS	18/33/0/0	Moderate	Lin GBM for IgG (3+), κ (3+), and λ (3+); gran mes IgM (+/−); FSGS lesions C3 (2+) and IgM (2+); neg IgA and C1q	3+ IgG4; +1 IgG2; neg IgG1 and IgG3	Rare mes deposits, global FPE
10	EPGN with TMA features	8/25/25/0	Moderate	Lin GBM and focal TBM for IgG (3+), κ (3+), and λ (3+); gran mes and GBM C3 (1+); neg IgM, IgA, C1q	2+ IgG1; +/− IgG4; neg IgG2 and IgG3	No electron-dense deposits; TMA features; seg FPE
11	MesPGN with segmental burnt-out membranous nephropathy	18/22/0/0	None	Lin GBM IgG (3+) and λ (3+); neg κ, IgA, IgM, C1q, and C3	3+ IgG2; 1+ IgG4; neg IgG1 and IgG3	Seg reabsorbed subepi deposits; seg FPE
12	MesPGN	16/25/0/0	Mild	Lin GBM and focal TBM for IgG (3+) and λ (3+); gran GBM IgA (+/−); gran mes IgM (1+), C1q (1+), and C3 (+/−); neg κ	Not done	No electron-dense deposits; seg FPE
13	EPGN with TMA features	13/0/0/0	Mild	Lin GBM and focal TBM IgG (2+) and λ (2+); gran mes C3 (+/−); neg κ, IgA, IgM, and C1q	Neg IgG1, IgG2, IgG3, and IgG4 (2 gloms only)	No electron-dense deposits; TMA features; global FPE
14	EPGN	5/20/0/0	None	Lin GBM and focal TBM IgG (3+) and λ (3+); gran mes IgM (+/−); neg κ, IgA, C3, and C1q	Trace IgG1; neg IgG2, IgG3, and IgG4	No electron-dense deposits; seg FPE
15	EPGN	28/0/0/0	Mild	Lin GBM IgG (3+) and λ (3+); gran mes IgM (+/−); neg κ, IgA, C3, and C1q	Trace IgG1; neg IgG2 and IgG4; no glom for IgG3	No electron-dense deposits; seg FPE
16	EPGN with mild TMA features	35/43/0/0	Moderate	Lin GBM IgG (3+) and κ (3+); gran mes C3 (2+); neg λ, IgA, IgM, and C1q	1+ IgG1; neg IgG2, IgG3, and IgG4	No electron-dense deposits; GBM gaps; TMA features; seg FPE
17	EPGN	16/6/0/0	None	Lin GBM IgG (3+) and λ (3+); gran mes IgM (+/−); neg κ, IgA, C3, and C1q	IgG1; neg IgG2, IgG3, and IgG4	No electron-dense deposits; global FPE
18	MesPGN	13/15/0/0	Moderate	Lin GBM IgM (3+) and κ (1+); neg λ, IgG, IgA, C3, and C1q	Not applicable	No electron-dense deposits; seg FPE
19	FSGS	34/9/0/0	None	Lin GBM IgM (3+) and κ (2+); gran mes C3 (+/−); neg λ, IgG, IgA, C3, and C1q	Not applicable	No electron-dense deposits; global FPE
20	MesPGN with segmental scars and focal crescents/necrosis	24/42/3/4	Moderate	Lin GBM IgA (2+), λ (3+) and IgG (+/−); neg IgM, C3, C1q, and κ	Not applicable	No electron-dense deposits; seg FPE

EPGN, endocapillary proliferative glomerulonephritis; FPE, podocyte foot process effacement; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; glom, glomeruli; gran, granular; Lin, linear; mes, mesangial; MesPGN, mesangial proliferative GN; MPGN, membranoproliferative glomerulonephritis; neg, negative; seg, segmental; subendo, subendothelial; subepi, subepithelial; TA/IF, tubular atrophy and interstitial fibrosis; TBM, tubular basement membrane; TMA, thrombotic microangiopathy.