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Atypical Anti-Glomerular Basement Membrane Nephritis: A Case Series From the French Nephropathology Group

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Atypical Anti-Glomerular Basement Membrane Nephritis: A Case Series From the French Nephropathology Group

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Abstract

Rationale & Objective: Atypical anti-glomerular basement membrane (GBM) nephritis is characterized by a bright linear immunoglobulin staining along the GBM by immunofluorescence without a diffuse crescentic glomerulonephritis nor serum anti-GBM antibodies by conventional ELISA. We characterized a series of patients with atypical anti-GBM disease.

Study Design: Case series.

Setting & Participants: Patients were identified by the French Nephropathology Group as having atypical anti-GBM nephritis between 2003 and 2022.

Findings: Among 38 potential cases, 25 were included. 14 (56%) were female and 23 (92%) had hematuria. Median [interquartile range (IQR)] serum creatinine at diagnosis was 150 [102-203] µmol/L and median [IQR] urine protein to creatinine ratio was 2.4 [1.3-5.2] g/g. 9 (36%) patients had endocapillary proliferative glomerulonephritis (GN), 4 (16%) had mesangial proliferative GN, 4 (16%) had membranoproliferative GN, 2 (8%) had pure and focal crescentic GN, 1 (4%) had focal segmental glomerulosclerosis, and 5 had glomeruli that were unremarkable on histopathology. Nine patients (36%) had crescents, involving a median of 9% of glomeruli. Bright linear staining for IgG was seen in 22 cases (88%) and for IgA in 3 cases (12%). The nine patients (38%) who had a monotypic staining pattern tended to be older with less proteinuria and rarely had crescents. Kidney survival rate at one year was 83% and did not appear to be associated with the light chain restriction.

Limitations: Retrospective case series with a limited number of biopsies including electron microscopy.

Conclusions: Compared to typical anti-GBM disease, atypical anti-GBM nephritis frequently

presents with endocapillary or mesangial proliferative glomerulonephritis pattern and appears to have slower disease progression. Further studies are needed to fully characterize its pathophysiology and associated clinical outcomes.

Keywords: anti-GBM disease; glomerulonephritis; kidney biopsy; renal pathology; atypical anti-GBM nephritis

Plain Language Summary

Atypical anti-glomerular basement membrane (GBM) nephritis is characterized histologically by bright linear immunoglobulin staining along the GBM without diffuse crescentic glomerulonephritis or circulating anti-GBM antibodies. We report a case series of 25 atypical cases of anti-GBM nephritis in collaboration with the French Nephropathology Group. Compared to typical anti-GBM disease, we observed slower disease progression. Patients frequently presented with heavy proteinuria and commonly had evidence of endocapillary or mesangial proliferative glomerulonephritis. About half of the patients displayed a monotypic immune staining pattern, who tended to be older, with less proteinuria and commonly without glomerular crescents in biopsy specimens. No concomitant circulating monoclonal gammopathy was detected. Further studies are needed to fully characterize its pathophysiology and associated clinical outcomes.

1. Introduction

Anti-glomerular basement membrane (anti-GBM) disease is typically characterized by a rapidly progressive glomerulonephritis, with concurrent alveolar hemorrhage in about half of the cases.[1–4] Circulating autoantibodies targeting the non-collagenous (NC1) domain of the α3 chain of type IV collagen, α3(IV)NC1,[5] are typically detected by enzyme-linked immunosorbent assay (ELISA). Renal biopsy typically demonstrates a diffuse crescentic glomerulonephritis, while spared glomeruli are normal. Immunofluorescence study reveals bright and linear polytypic IgG staining along the GBM.[1] Specific treatment relies on aggressive immunosuppressive strategies, based on steroids, plasma exchange and cyclophosphamide. Renal outcome is mainly associated with the severity of renal dysfunction at onset.[6,7] Recurrence is very rare.[8]

Besides typical anti-GBM disease, literature includes numerous small series[9–11] and case reports[12–15] that highlight atypical cases of anti-GBM disease, based on unconventional clinical, biological, histological and/or pathophysiological features.[8] Indeed, atypical published cases encompass recurrent diseases,[16] an absence of renal impairment or crescentic glomerulonephritis despite circulating α3(IV)NC1 autoantibodies and lung hemorrhage,[17] a focal crescentic glomerulonephritis without significant renal dysfunction and low titer of α3(IV)NC1 antibodies,[10,18] IgA staining,[14] IgG staining restricted to the IgG4 subclass[11] and/or anti-GBM antibodies targeting unconventional antigens.[14,19,20] In an effort of standardization, Nasr and colleagues reported in 2016 a well characterized series including 20 cases of unconventional anti-GBM disease, primarily defined from a histopathological perspective.[21] They introduced the term “atypical anti-GBM nephritis”, typified by a bright linear GBM staining for immunoglobulins without a diffuse crescentic phenotype. Compared to typical anti-GBM disease, these cases were characterized by a slower onset and overall chronic course without

detectable circulating α3(IV)NC1 antibodies by commercially available ELISA. Histologically, these cases often displayed an endocapillary or mesangial proliferative glomerulonephritis pattern, with focal or no crescents. Half of the cases were monotypic, but only rarely showed evidence of an associated monoclonal gammopathy. Therapeutic strategies varied from no specific to a treatment similar to typical anti-GBM disease. Since this seminal study, mainly case reports have been reported.[22]

Herein we report the results from a multicenter francophone cohort to bring novel data on atypical anti-GBM disease and attempt to unravel its wide clinico-pathological spectrum.

2. Methods

This retrospective study relied on the contribution of the CFPR - French Nephropathology Group. We asked members to search for an atypical anti-GBM nephritis diagnosis, based on the definition provided by Nasr and colleagues: a bright linear GBM staining for immunoglobulins (≥ 2+) without a diffuse crescentic glomerulonephritis (*i.e.* involving less than 50% of glomeruli). We secondarily excluded all cases with a patent positivity for α3(IV)NC1 antibodies by ELISA, that favors a typical anti-GBM disease diagnosis.

All staining procedures were performed at the time of diagnosis in the corresponding local center, including hematoxylin-eosin-saffron, periodic acid-Schiff, Masson's trichrome and Jones methenamine silver. For immunofluorescence, frozen sections were stained using fluorescein-conjugated anti-human IgA, IgG, IgM, C3, C1q, kappa and lambda light chain (+/- albumin). Determination of the IgG subclass was performed using fluorescein-conjugated antibodies targeting IgG1, IgG2, IgG3, and IgG4. Immunofluorescence staining intensity was graded from 0 to 3+. All light microscopy slides were centralized for a systematic review by BC and MR, either in a digital or physical format. As for the immunofluorescence slides, archived images were

systematically reviewed. Electron microscopy data were based on the initial pathological report.

Demographic, clinical and laboratory data were collected from patients' electronic medical records. For the outcome analysis, the following definitions, based on Nasr *et al.*,[21] were applied: complete remission, remission of proteinuria to <500 mg/g with normal renal function; partial remission, reduction in proteinuria by at least 50% and to < 2 g/g with stable renal function (no more than a 20% increase in serum creatinine); persistent kidney dysfunction, not meeting criteria for complete or partial remission but not reaching end-stage kidney disease; end-stage kidney disease, requiring renal replacement therapy. Patients with initial proteinuria of < 0.5 g/g and who experienced an improvement in the eGFR of > 25%, while still impaired, were considered to have a partial remission.

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained at the initial diagnosis for the research use of biopsy remnants.

All statistical analyses were performed using the R software, version 4.1.1.[23] Quantitative data are presented as median [first quartile-third quartile]. Qualitative data are presented as number (%). Comparisons between continuous variables were conducted by non-parametric tests (Mann-Whitney for two groups and Kruskall-Wallis for more than 2 groups). Differences between qualitative data were analyzed using the Fisher's exact test. The significance level was considered at 0.05.

3. Results

Population

Thirty-eight cases were initially submitted from 14 centers located in France, London (United-Kingdom), Montreal (Canada) and Brussels (Belgium). Two cases were primarily

excluded based on the pathological report and clinico-biological parameters and one case due to insufficient clinical data. Thirty-five cases were then submitted for centralized review. Ten cases were secondarily excluded, notably 4 cases not matching the above-mentioned criteria and 6 cases due to a highly suspected alternative diagnosis (especially diabetic nephropathy and a questionable membranous nephropathy). We finally retained 25 cases. The detailed flow-chart is displayed in **Figure S1**.

Clinico-biological characteristics at diagnosis

The cohort consisted of 25 adults, ranging from 18 to 85 years-old with a median age of 49 and including 14 women (56%) and 11 men (44%), diagnosed between June 2003 and February 2022. Five patients (20%) had a recent infection prior to the diagnosis, including one prostatitis, one tooth abscess, two upper airway infections and one SARS-Cov2 infection. No patient had alveolar hemorrhage: one had hemoptysis at onset, but no alveolar hemorrhage on the chest CT scan (patient #22). One patient had a diffuse interstitial pneumonia (patient #12), interpreted as sodium retention and smoking-induced. Sixteen of 23 patients (70%) had hypertension and 11 of 25 (44%) had edema at diagnosis. Significant coexistent medical conditions are detailed in **Table S1**.

At the time of diagnosis, median serum creatinine was 150 µmol/L (range 65-900) and median urine protein to creatinine ratio was 2.4 g/g (range 0-11.7). Four patients (17%) required dialysis at diagnosis or at an early time of their medical care. Nearly all patients had hematuria (23/25, 92%), including 3 patients with gross hematuria. A nephrotic syndrome was present in 9 patients (36%). Conventional anti-GBM ELISA was negative in 19 of 22 tested patients (86%). Three patients (14%) had an equivocal/weakly positive result, and repeat testing was carried out in two patients with a negative result. Indirect immunofluorescence for anti-GBM testing was

performed in 11 patients and was positive in 2: one patient with a weakly positive ELISA test and one with a negative ELISA test (patient #12 and #22, respectively). Western blot was performed in four patients and was negative (patients #5, #6, #8 and #9). Anti-nuclear antibody was positive in 4 of 22 tested patients, 2 with anti-SSA and 2 without specificity. Antineutrophil cytoplasmic antibodies and testing for hepatitis B, hepatitis C and HIV were negative (n=24 and n=20, respectively). Complement levels (C3 and C4) were normal (n=21). Only one patient had a serum monoclonal gammopathy (IgM kappa) of the 22 tested patients (including all monotypic cases), without diagnosed hematologic malignancy (patient #10, with a monotypic IgG1 lambda glomerular staining). The kappa to lambda ratio was normal in 11 patients and mildly abnormal in 1 (2.5, patient #15 with a polytypic staining pattern). None of the 15 tested patients, including 6 of the 9 monotypic cases, had a urine monoclonal protein. A bone marrow aspiration was performed in 3 patients with a monotypic staining pattern, without any anomaly. Main clinico-biological characteristics of the cohort are summarized in **Table 1** and specified for each patient in **Table 2**.

Pathological characteristics at diagnosis

Light microscopy

Main pathological characteristics are displayed in **Table 3**. Nine cases (36%) had focal cellular crescents, with a median percentage of glomeruli with crescents of 9% (range 0-46). Besides crescents, the pattern of glomerular injury was an endocapillary proliferative glomerulonephritis (EPGN, **Figure 1**) in 9 (36%), a mesangial proliferative glomerulonephritis (MesPGN) in 4 cases (16%) and a membranoproliferative glomerulonephritis (MPGN, **Figure 2**) in 4 (16%). Two patients (8%) had a focal crescentic glomerulonephritis, while other non-affected glomeruli were optically normal. Glomeruli were unremarkable in 5 cases (20%) and

one case showed one lesion of focal segmental glomerulosclerosis with otherwise unremarkable glomeruli. Red cell casts were seen in 9 cases (36%). Arteriolar thrombotic microangiopathy (TMA) was seen in 1 patient (patient #3), and one other case showed glomerular features of TMA (2 glomerular thrombi, patient #5, no crescent). Five cases (20%) showed at least moderate arteriolar hyalinosis, whereas 5 cases showed at least moderate arteriosclerosis.

Immunofluorescence

All cases displayed bright linear immunoglobulin staining along the GBM, with IgG in 22 cases (88%) and IgA in 3 cases (12%). One case showed a co-dominance of IgG and IgA and two cases a dominant IgG staining (3+) associated with a linear IgA (2+). One case (patient #9) also showed granular mesangial deposits of C3 (2+). Light chain restriction was seen in 9 of 24 cases (38%, 5 kappa and 4 lambda). IgG subclass assessment was performed in 17 cases, with a predominance of IgG1 in 7 cases (41%), IgG4 in 5 (29%) or both in 2 cases. All monotypic cases with available data (5/9) stained for only one IgG subclass: IgG1 kappa in 3 cases, IgG1 lambda in one case and IgG3 lambda in one case. DNAJB9 immunohistochemistry was negative in the five tested patients (#5 to #9).

Electron microscopy

Electron microscopy was performed with an adequate sample in 10 cases, including 3 monotypic cases. None of these cases showed glomerular capillary wall electron-dense deposits that would have matched the linear staining for Ig seen by immunofluorescence or favored a differential diagnosis. Segmental podocyte foot process effacement was seen in 5 patients (50%), with a vacuolization of podocytes in one. Segmental widening of the subendothelial zone was seen in one case, but no features of thrombotic microangiopathy were seen otherwise.

Treatment and outcome

Median follow-up was of 38.3 [9.3-54.8] months. Twelve out of the 25 cases (48%) received at least one immunosuppressive therapy, including corticosteroids only (either oral or intravenous) in 3 patients and corticosteroids associated with cyclophosphamide and plasma exchange in 4 patients. Two patients were treated by rituximab alone and 1 by mycophenolate mofetil. Patients with histological crescents were more frequently treated by plasma exchange and cyclophosphamide compared to non-crescentic patients (P = 0.002 and 0.01, respectively).

At one year, median creatinine was 152 [103-168] µmol/L (n=12) and median urine protein to creatinine ratio was 1.3 [0.4-1.9] g/g (n=11). Five of 15 (33%) patients had partial remission (including 2 patients who received an immunosuppressive therapy), 7/15 (47%) persistent renal dysfunction (4 received an immunosuppressive therapy) and 3/15 (20%) had end-stage kidney disease (ESKD).

At the end of the follow-up (n=24), median serum creatinine was 103 [82-113] µmol/L and median urine protein to creatinine ratio was 1.2 [0.3-2.3] g/g. Three patients (13%) had complete remission, including 2 treated by immunosuppressive strategies. Five patients (21%) had partial remission, of whom 3 received an immunosuppressive therapy. Five patients (21%) had ESKD at the end of the follow-up, of whom three displayed severe interstitial fibrosis at diagnosis. One patient was transplanted, without known recurrence. Eleven patients (46%) had persistent renal dysfunction. None of the patients died during the follow-up period. From the 4 patients requiring dialysis at diagnosis onset, one patient (#22) had complete remission at the end of the follow-up (21 months) and three had ESKD.

Repeat biopsies

Eight patients (31%) had at least a second renal biopsy during follow-up (patients #5, 6, 7, 9,

13, 20, 21 and 22). All cases showed a persistent bright linear staining of Ig along the GBM, including similar light chain restriction if initially present (n=4). Yet, two cases showed a more discontinuous staining. One patient (#7) had a focal crescentic GN at diagnosis without other glomerular alterations and had a focal membranoproliferative pattern 14 months later. Otherwise, cases showed a similar glomerular pattern with increased chronicity (FSGS +/- enhanced mesangial matrix) and tended to have more interstitial fibrosis.

Characteristics of monotypic versus polytypic cases

We next compared monotypic to polytypic cases of anti-GBM nephritis (**Table 1**). Patients with monotypic staining were older, with a median age of 55 [53-67] compared to 44 [28-52] (P = 0.05). They tended to have a higher serum creatinine level at diagnosis (P = 0.06). Only one of 9 monotypic cases (11%) had crescents as opposed to 8 of 15 (53%) in polytypic cases (P = 0.08). There was no overt difference in terms of glomerular pattern of injury. There were no overt differences in outcome, with regards to the rate of progression to ESKD and other outcome parameters at one year and at the end of the follow-up.

Description of the characteristics depending on the glomerular pattern of injury

While the number of cases remains small, focal crescentic GN and MPGN patterns of injury were associated with a higher serum creatinine at diagnosis (P = 0.03) and encompassed 3 of 4 cases requiring dialysis at onset. MPGN and MesPGN patterns were associated with a higher rate of nephrotic syndrome (P = 0.002). Focal crescentic GN cases and crescentic MPGN were treated more aggressively, combining methylprednisolone, plasma exchange and/or cyclophosphamide (P from <0.001 to 0.006). At the end of the follow-up, ESKD occurred in 3 of 4 cases with an MPGN pattern, while other patterns were much less associated with ESKD. Main clinicopathological characteristics depending on the glomerular pattern of injury are detailed in

Table S2.

Literature-based clinicopathological characteristics of atypical anti-GBM nephritis

To explore more deeply the clinicopathological spectrum of atypical anti-GBM nephritis, we combined our data with the series published by Nasr and colleagues.[21] Relevant clinicopathological characteristics are summarized in **Table 1**.

The merged cohort consisted of 45 patients, with a median age of 52 [43-64], including 22 men and 23 women. Monotypic cases represented 19 of 45 patients (42%). Monotypic cases were significantly associated with an older age, with a median age of 59 [52-66] as compared to 45 [32-56], $P = 0.03$. Moreover, monotypic cases had a lower urine protein to creatinine ratio at diagnosis, with a median of 1.4 g/g [0.4-4.9] compared to 4.2 [2.0-8.8], $P = 0.02$. They also rarely had a crescentic phenotype: 2 of 19 (11%) compared to 14/25 (56%), $P = 0.004$. There was no overt light chain restriction predominance (11 lambda and 8 kappa), but most cases showed IgG1 staining. When segregating patients based on their histopathological glomerular pattern, similar findings as reported in our cohort were found (see also **Table S3**).

4. Discussion

Our understanding of atypical anti-GBM disease remains sparse, notably because the "atypical" nature of the reported cases is highly variable, whether it be on a clinical, biological, histological and/or pathophysiological perspective. Herein we report a francophone cohort of "atypical anti-GBM nephritis" and describe our understanding of the wide clinicopathological spectrum of atypical anti-GBM disease.

Similar to the Nasr series,[21] our cohort of atypical anti-GBM nephritis mainly displayed a more chronic disease course, essentially characterized by a "slowly" progressive renal insufficiency, hematuria and a quite heavy proteinuria compared to "typical" anti-GBM disease.

No case had alveolar hemorrhage and anti-GBM testing by conventional ELISA was negative (or equivocal/weakly positive in a minority of cases). By light microscopy, glomeruli frequently showed endocapillary or mesangial proliferation, with focal crescents in about one-third of cases. However, we did not see an overrepresentation of thrombotic microangiopathy features, a finding described in the Nasr series.[21] We confirmed the better patient outcome than in typical anti-GBM disease, without any reported death after a median follow-up of nearly three years. Overall renal survival was of 83% at one-year and 79% at three years. Therapeutic strategies varied between cases, with more aggressive immunosuppressive strategies when crescentic features were histologically present. A membranoproliferative pattern seemed to be associated with a poorer renal prognosis.

Monotypic atypical anti-GBM nephritis accounted for nearly 40% of the cohort and our results further support that they share some distinctive clinicopathological features. Patients tended to be older, with less proteinuria and were histologically less frequently crescentic. No serum or urine monoclonal gammopathy matching the staining seen by immunofluorescence was present, similar to the study of Nasr.[21] These monotypic cases would benefit from sensitive techniques, such as serum immunoblot and bone marrow molecular studies, to reveal a possible B-cell disorder and support the hypothesis of a monoclonal gammopathy-induced renal injury.

While literature contains numerous cases of described “atypical” anti-GBM disease, the term “atypical anti-GBM nephritis”, introduced by Nasr *et al.*, converges towards four main aspects: a bright linear GBM staining for immunoglobulin (≥ 2+ on a scale 0-3), no circulating α3(IV)NC1 antibodies, no lung involvement and no diffuse crescentic glomerulonephritis.[21] Still, 3 cases of our cohort had equivocal/weakly positive α3(IV)NC1 antibodies, while two of them displayed a MesPGN pattern, not typical of anti-GBM disease. This could suggest low-affinity and/or low-

titer antibodies, especially in one case with a positive indirect immunofluorescence. Moreover, the boundary between diffuse and focal crescentic glomerulonephritis remains rather empirical. In fact, one case of our cohort had crescents in about half of the glomeruli, and rare cases have been reported with a diffuse crescentic phenotype in the literature.[24,25] Besides, Ohlsson *et al.* reported 4 cases of atypical anti-GBM disease with alveolar hemorrhage and a characterized IgG4 anti-GBM activity, with a diffuse crescentic glomerulonephritis in two of them.[11] Liang *et al.* also reported 3 cases with pulmonary involvement out of 19 published cases of anti-GBM disease without detectable serum anti-GBM antibodies.[25] Finally, in both the cohort of Nasr and ours, some cases showed unremarkable glomeruli or FSGS lesions, which question the use of the term "nephritis". Indeed, Rosales and Colvin proposed the designation "glomerular disease with idiopathic linear immunoglobulin deposition", as alternative mechanisms of linear immunoglobulin deposition in the GBM are possible outside a characterized anti-GBM activity.[26] Indeed, the heterogeneous nature of atypical anti-GBM nephritis supports that different antibodies could be causal depending on the cases, with immunoglobulin deficient in inducing inflammation and/or alternative targeted GBM antigens, which could ultimately explain the more indolent course of atypical anti-GBM nephritis.[26] Nevertheless, while some previously published atypical anti-GBM cases clearly revealed an anti-GBM activity,[14,20,27] most cases do not provide such demonstration and we cannot exclude that in some cases the immunoglobulin staining is independent of the antibody specificity, but possibly due to the physiochemical properties of either the antibody or the GBM, like in monoclonal immunoglobulin deposition disease (MIDD) and diabetes, respectively.[26] Care must be taken as the use of the term "atypical anti-GBM nephritis" implies a characterized anti-GBM activity, which could be misleading and justify aggressive immunosuppressive therapies from a clinician's perspective.

Still, regardless of the terminology, the presence of the four main features of atypical anti-GBM nephritis seems to be associated with similar clinicopathological cohorts, while still being heterogeneous. It remains to date the best way to standardize the diagnosis, even towards a possibly temporary entity, in which the pathophysiology should be thoroughly explored in further studies. **Figure 3** summarizes our current understanding of the spectrum of atypical anti-GBM disease.

Care must be taken to exclude the main differential diagnoses before performing a diagnosis of atypical anti-GBM nephritis. Outside of classical anti-GBM nephritis, MIDD must be ruled out when a monotypic staining pattern is observed. A diffuse linear staining along GBM and tubular basement membranes (TBM) by immunofluorescence, finely granular deposits by electron microscopy and an abnormal ratio of kappa or lambda free light chains in serum will favor a diagnosis of MIDD. As for polytypic cases, diabetic glomerulosclerosis displays an absence of GBM-restricted linear staining for immunoglobulin by immunofluorescence, with a similar staining of albumin and immunoglobulin along GBM and TBM.

Our study has some limitations. First, we could not provide an estimate of the incidence of atypical anti-GBM nephritis, due to the multicentric and retrospective nature of the inclusion method. Secondly, electron microscopy was available in just under half of the cases. Yet, we did not see, in any case without informative electron microscopy, features that could have favored a differential diagnosis such as MIDD and only one case without electron microscopy had diabetes, but with positive indirect immunofluorescence, at least suggesting an anti-GBM activity. Thirdly, we acknowledge that we do not provide insights about the pathophysiological mechanisms underlying atypical anti-GBM nephritis.

To conclude, we detailed a francophone cohort of “atypical anti-GBM nephritis”, confirming

its slower onset and more chronic, yet not indolent, renal course compared to typical anti-GBM disease, a lack of lung involvement and the absence of patent α3(IV)NC1 antibodies by ELISA. By light microscopy, a frequent mesangial and/or endocapillary proliferative glomerulonephritis was seen, while being occasionally and focally crescentic. Monotypic cases involved older patients with lower proteinuria and rarely a crescentic phenotype. It must be stressed that anti-GBM nephritis remains to date a histopathological description rather than a pathophysiology-based entity. We hope that these data will pave the way for a better standardization of the diagnosis, a better pathophysiological characterization of the anti-GBM activity and ultimately guidelines for personalized therapeutic strategies.

Supplementary Material
Supplementary File (PDF)
Figure S1: Flow-chart of the study.
Table S1: Main clinico-pathological characteristics of the cohort depending on the glomerular pattern
Table S2: Main clinico-pathological characteristics of the merged cohort depending on the glomerular pattern
Table S3: Main clinico-pathological characteristics of the merged cohort depending on the glomerular pattern

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Table 1: Main clinico-pathological characteristics of the cohort

	Current cohort (n=25)	**Polytypic (n=15)**	**Monotypic (n=9)**	**P-value**	**Nasr's and current cohorts (n=45)**	**Polytypic (n=25)**	**Monotypic (n=19)**	**P-value**
Clinico-biological characteristics								
Male gender	11/25 (44%)	6/15 (40%)	4/9 (44%)	1.0	22/45 (49%)	10/25 (40%)	11/19 (58%)	0.4
Age, median [IQR]	49 [35-55]	44 [28-52]	55 [53-67]	**0.05**	52 [43-64]	45 [32-56]	59 [52-66]	**0.03**
Serum creatinine at diagnosis (µmol/L)	150 [102-203]	115 [68-191]	176 [142-368]	0.06	168 [106-230]	168 [88-203]	160 [117-250]	0.5
Need for dialysis at onset	4/24 (17%)	2/14 (14%)	2/9 (22%)	1.00	4/44 (9%)	2/24 (8%)	2/19 (11%)	1.0
Urine protein to creatinine ratio (g/g), median [IQR]	2.4 [1.3-5.2]	2.8 [1.6-5.6]	1.5 [0.4-4.9]	0.2	2.8 [1.2-6.6]	4.2 [2-8.8]	1.4 [0.4-4.9]	**0.02**
Nephrotic syndrome	9/25 (36%)	6/15 (40%)	2/9 (22%)	0.7	16/45 (36%)	11/25 (44%)	4/19 (21%)	0.2
Hematuria	23/25 (92%)	13/15 (87%)	9/9 (100%)	0.5	42/45 (93%)	22/25 (88%)	19/19 (100%)	0.3
History of smoking	15/25 (60%)	9/15 (60%)	5/9 (56%)	1.0	26/44 (59%)	15/24 (63%)	10/19 (53%)	0.6
Diabetes	2/25 (8%)	2/15 (13%)	0/9 (0%)	0.5	6/45 (13%)	4/25 (16%)	2/19 (11%)	0.7
Overweight or obesity	16/24 (58%)	10/15 (67%)	5/8 (63%)	1.0	NA	NA	NA	NA
Alveolar hemorrhage	0/25 (0%)	0/15 (0%)	0/9 (0%)	NA	0/45 (0%)	0/25 (0%)	0/19 (0%)	NA
Recent infection	5/25 (20%)	5/15 (33%)	0/9 (0%)	0.1	NA	NA	NA	NA
History of autoimmune disease	6/25 (24%)	3/15 (20%)	2/9 (22%)	1.0	10/45 (22%)	4/25 (16%)	5/19 (26%)	0.5
Anti-GBM by conventional ELISA								
Negative	19/22 (86%)	10/13 (77%)	9/9 (100%)	0.2	37/40 (93%)	19/22 (86%)	18/18 (100%)	0.2
Equivocal/weakly positive	3/22 (14%)	3/13 (23%)	0/9 (0%)		3/40 (7%)	3/22 (14%)	0/18 (0%)	
Pathological findings								
Glomerular pattern of injury								
MesPGN	4/25 (16%)	4/15 (27%)	0/9 (0%)	0.3	10/45 (22%)	6/25 (24%)	4/19 (21%)	1.0
EPGN	9/25 (36%)	4/15 (27%)	5/9 (56%)	0.2	18/45 (40%)	8/25 (32%)	10/19 (53%)	0.2
MPGN	4/25 (16%)	2/15 (13%)	1/9 (11%)	1.0	7/45 (16%)	5/25 (20%)	1/19 (5%)	0.2
FCGN	2/25 (8%)	2/15 (13%)	0/9 (0%)	0.5	2/45 (4%)	2/25 (8%)	0/19 (0%)	0.5
Unremarkable/FSGS	6/25 (24%)	3/15 (20%)	3/9 (33%)	0.6	8/45 (18%)	4/25 (16%)	4/19 (21%)	0.7
Crescents and/or fibrinoid necrosis	9/25 (36%)	8/15 (53%)	1/9 (11%)	0.08	16/45 (36%)	14/25 (56%)	2/19 (11%)	**0.004**
Light-chain restriction by IF	9/24 (38%)	0/15 (0%)	9/9 (100%)	NA	19/44 (43%)	0/25 (0%)	19/19 (100%)	NA
Features of thrombotic microangiopathy	2/25 (8%)	1/15 (7%)	1/9 (11%)	1.0	10/45 (22%)	7/25 (28%)	3/19 (16%)	0.5
Moderate and severe IF/TA	8/25 (3%)	3/15 (20%)	4/9 (44%)	0.4	14/45 (31%)	6/25 (24%)	7/19 (37%)	0.5
Immunosuppressive treatment								

n (%)	12/25 (48%)	7/15 (47%)	5/9 (56%)	1.0	26/41 (63%)	15/23 (65%)	11/17 (65%)	1.0
Cyclophosphamide	4/25 (16%)	4/15 (27%)	0/9 (0%)	0.3	10/41 (24%)	8/23 (35%)	2/17 (12%)	0.1
Plasma exchange	5/15 (20%)	4/15 (27%)	1/9 (11%)	0.6	7/41 (17%)	6/23 (26%)	1/17 (6%)	0.2
Prednisone	5/25 (20%)	3/15 (20%)	2/9 (22%)	1.0	17/41 (41%)	11/23 (48%)	6/17 (35%)	0.5
Methylprednisolone	5/25 (20%)	3/15 (20%)	2/9 (22%)	1.0	7/41 (17%)	5/23 (22%)	2/17 (12%)	0.7
Rituximab	3/25 (12%)	1/15 (7%)	2/9 (22%)	0.5	5/41 (12%)	2/23 (9%)	3/17 (18%)	0.6
MMF/Mycophenolic acid	1/25 (4%)	1/15 (7%)	0/9 (0%)	1.0	5/41 (12%)	4/23 (17%)	1/17 (6%)	0.4
Follow-up								
Duration of follow-up in months, median [IQR]	38.3 [9.3-54.8]	21 [5.5-54]	39 [26-57]	0.26	27 [12-52]	21 [5.5-49.5]	38 [18-51]	0.2
1-year rate of patient survival	18/18 (100%)	9/9 (100%)	8/8 (100%)	1.00	31/32 (97%)	15/16 (94%)	15/15 (100%)	1.0
1-year rate of renal survival (in surviving patient)	15/18 (83%)	8/8 (100%)	7/9 (78%)	0.47	26/31 (84%)	12/14 (86%)	14/16 (88%)	1.0
3-year rate of renal survival (in surviving patient)	11/14 (79%)	6/6 (100%)	5/7 (71%)	0.46	16/22 (73%)	9/11 (82%)	7/10 (70%)	0.6
End stage kidney disease with replacement therapy	5/24 (21%)	1/14 (7%)	3/9 (33%)	0.26	9/40 (23%)	3/22 (14%)	5/17 (29%)	0.3

Main characteristics are displayed for the current French cohort as well as the merged cohort (Nasr's and the current one). Values are provided as number (%) or median [IQR], both for the whole cohorts and depending on the light chain restriction status. Mann-Whitney tests were performed for quantitative variables and Fisher's exact tests for categorical variables to compare characteristics of monotypic from polytpic cases. Statistical significance ($P \leq 0.05$) is highlighted using bold fonts. The term "crescents" is used here for active extracapillary proliferation (*i.e.* cellular and/or fibro-cellular crescent) and the number of cases with crescents is provided. Fibrous crescents are excluded. Proteinuria is expressed as the urine protein to creatinine ratio (g/g), where proteinuria was reported in g/day in the cohort of Nasr *et al*. When analyzing the merged cohort, corresponding values were converted to g/g. Abbreviations: IQR, interquartile range; IF, immunofluorescence; IF/TA, interstitial fibrosis and tubular atrophy; EPGN, endocapillary proliferative glomerulonephritis; MesPGN, mesangial proliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FCGN, focal crescentic glomerulonephritis; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; TMA, thrombotic microangiopathy; MMF, mycophenolate mofetil.

Table 2: Main clinical and biological characteristics of each patient

Patient #	Age	Gender	Smoker	Diabetes	Anti-GBM by ELISA	Indirect IF (anti-GBM)	SCr at biopsy (μmol/L)	Pro at biopsy (g/g)	Hematuria	Nephrotic syndrome	Treatment	Duration of f/u (month)	Outcome
1	55	M	No	No	Negative	Not done	111	1.5	Yes	No	Nephroprotection	39.1	Persistent renal dysfunction (last SCr 112, Pro 1.5)
2	22	M	Yes	No	Not done	Negative	115	4.2	Yes	No	Nephroprotection	6.2	Persistent renal dysfunction (last SCr 117, Pro 3.0)
3	47	M	Yes	No	Not done	Negative	400	5	Yes	Yes	Nephroprotection	53.7	ESKD, peritoneal dialysis initiated 3 months after the diagnosis
4	67	F	Yes	Yes	Not done	Not done	69	6	Yes	Yes	Nephroprotection	0.0	Lost to follow-up
5	67	M	Yes, former	No	Negative	Negative	176	2	Yes	No	Nephroprotection	156	ESKD, hemodialysis initiated 10 years after diagnosis
6	43	F	Yes	No	Negative	Negative	202	5	Yes	No	Nephroprotection	53.1	Persistent renal dysfunction (last SCr 171)
7	43	M	No	No	Weakly positive	Not done	194	2.4	Yes, gross	No	MP/CYC/PLX	74.4	Persistent renal dysfunction (Pro 2.5, no hem, subnormal SCr 103)
8	31	M	Yes	No	Negative	Negative	187	7.1	Yes	Yes	Nephroprotection	41.8	Persistent renal dysfunction (last SCr 265, Pro 2)
9	24	F	No	No	Negative	Negative	203	10	Yes	Yes	Pred/CYC/PLX	9.3	Partial remission (normal SCr, Pro 1g/d, hem)
10	65	F	Yes, former	No	Negative	Negative	160	0.06	Yes, gross	No	Nephroprotection	66	Persistent renal dysfunction (last SCr 134, hem without Pro)
11	35	M	No	No	Negative	Not done	425	4.9	Yes, gross	No	None	57	Normal kidney function
12	60	F	Yes	Yes	Weakly positive	Positive	66	1.5	Yes	Yes	Ritux	54.8	Subnormal kidney function
13	68	F	No	No	Negative	Not done	270	0	Yes	No	Pred	51.1	Partial remission (last SCr 160, no Pro)
14	18	M	No	No	Weakly positive	Not done	81	2.2	Yes	No	Nephroprotection	35	Partial remission (persistent Pro 0.6, normal SCr)
15	44	M	No	No	Negative	Negative	150*	10.5	Yes	Yes	Pred/CYC/PLX	98.5	ESKD, Transplantation
16	25	F	Yes	No	Negative	Not done	66	5.2	Yes	Yes	Pred 6 months	73.9	Partial remission (Pro 0.5, hem, normal SCr 66)
17	82	F	No	No	Negative	Not done	764*	1.2	Yes	No	MP	38.3	ESKD, hemodialysis initiated two weeks after diagnosis
18	53	F	Yes	No	Negative	Not done	368*	5.7	Yes	Yes	MP/PLX	8.3	ESKD, hemodialysis initiated two months after diagnosis
19	54	F	No	No	Negative	Not done	102	2.8	No	No	Nephroprotection	3.9	Partial remission (last SCr 102, Pro 1,2 without hem)

20	18	F	Yes	No	Negative	Negative	123	0.4	Yes	No	Ritux	18	Persistent but mild renal dysfunction (last SCr 109)
21	53	M	Yes	No	Negative	Not done	142	11.7	Yes	Yes	Pred/Ritux	26.2	Persistent renal dysfunction (last SCr 108, Pro 8,4 without hem)
22	48	M	Yes	No	Negative	Positive, 1:80	900*	1.6	Yes	No	MP/PLX/CYC/Pred	21	Normal kidney function
23	52	F	Yes	No	Negative	Not done	65	1.2	No	No	Nephroprotection	15.2	Persistent Pro 1.28, normal SCr, trace of hem
24	49	F	Yes	No	Not done	Not done	66	1.3	Yes	No	Nephroprotection	5.6	Persistent Pro 0.9, hem, normal SCr
25	51	F	No	No	Negative	Not done	124	0.8	Yes	No	MMF	1.4	Persistent renal dysfunction (last SCr 109, Pro 1.34, hem)

Three patients displayed a weakly positive anti-GBM testing by conventional ELISA. Patient #7 had a first weakly positive assay (14 IU/mL) and the second performed was negative. Patient #12 had a first weakly positive assay (12 IU/mL) and several others that remained negative. Indirect immunofluorescence was performed and positive with human kidney but not primate kidney. Patient #14 had several weakly positive ELISA (15 and 16 IU/mL, normal <7), and the value decreased during follow-up (8.5 at 6 months, 8 à 12 months and was negative, 4.8 at 24 months). Patients with serum creatinine at diagnosis marked with an asterisk required dialysis at onset (patients #17 and 22) or within the first two months of medical care (patients #15 and 18). Proteinuria is displayed as the urine protein/creatinine ratio. Patients #11[28] and #22[29] were already published as case reports. Abbreviations: IF, immunofluorescence; SCr, serum creatinine; Pro, proteinuria; f/u, follow-up; MP, methylprednisolone; CYC, cyclophosphamide; PLX, plasma exchange; Ritux, rituximab; Pred, prednisone; MMF, mycophenolate mofetil; hem, hematuria; ESKD, end-stage kidney disease.

Table 3: Main pathological characteristics of each patient

Patient #	Glomerular pattern of injury	Number of glomeruli	Global sclerosis, %	Active crescents, %	Fibrinoid necrosis, %	IF/TA	Immunofluorescence	IgG subclass staining by immunofluorescence	Electron microscopy
1	EPGN	11	9	0	0	Mild	Lin GBM IgG (3+) and κ (3+)	2+ IgG1; neg IgG2, IgG3 and IgG4	No electron-dense deposits; no TMA features; no FPE
2	EPGN	18	17	0	0	Moderate	Lin GBM IgG (3+), IgA (2+), IgM (1+), κ (3+) and λ (3+)	3+ IgG4; neg IgG1, IgG2 and IgG3	Not done
3	MPGN	15	40	0	0	Severe	Lin GBM and TBM IgG (3+) and segmental IgM, C3 and C1q	3+ IgG2; 2+ IgG4; neg IgG1 and IgG3	Non-informative
4	MesPGN	11	0	0	0	Mild	Lin GBM and TBM IgG (3+), κ (2+) and λ (2+)	3+ IgG2; neg IgG1, IgG3 and IgG4	No electron-dense deposits
5	EPGN	11	36	0	0	Moderate	Lin GBM IgG (2+) and κ (2+)	Not done	No electron-dense deposits
6	EPGN with focal crescents	13	8	8	0	Mild	Lin GBM IgG (3+), IgM (1+), κ (2+) and λ (2+)	3+ IgG4; 1+ IgG1; neg IgG2 and IgG3	No electron-dense deposits; no TMA features; no FPE
7	FCGN	12	17	30	0	Mild	Lin GBM IgG (3+), κ (2+) and λ (2+)	3+ IgG1; 1+ IgG2; neg IgG3 and IgG4	No electron-dense deposits; seg widening of the subendothelial zone; seg FPE
8	EPGN with focal crescents	13	8	8	8	Moderate	Lin GBM IgG (3+), κ (3+), λ (3+), IgM (+/-) and C3 (+/-)	3+ IgG4; 2+ IgG1; neg IgG2 and IgG3	Not done
9	MPGN and crescentic GN	13	0	46	0	None	Lin GBM IgG (3+), κ (3+) and λ (3+), C3 (mes gran 2+), IgA (1+)	3+ IgG4; 2+ IgG1; 1+ IgG2; neg IgG3	No electron-dense deposits; no TMA features; seg FPE
10	EPGN	14	7	0	0	Mild	Lin GBM IgG (2+) and λ (2+)	+ IgG1; neg IgG2, IgG3 and IgG4	Not done
11	Unremarkable	17	0	0	0	None	Lin GBM IgG (3+), κ (3+), C3 (+/-)	+ IgG1; neg IgG2, IgG3 and IgG4	Not done
12	MesPGN	13	8	0	0	None	Lin GBM IgG (3+), κ (3+) and λ (3+)	3+ IgG4; 1/2+ IgG2; neg IgG1 and IgG3	Not done
13	EPGN	12	25	0	0	Moderate	Lin GBM IgG (3+), κ (2+)	3+ IgG1; neg IgG2, IgG3 and IgG4	Not done
14	MesPGN	29	7	0	0	Mild	Lin GBM and TBM IgG (2+), κ (1+) and λ (1+)	Not done	Not done
15	MPGN with focal crescents	22	5	38	10	Mild	Lin GBM IgG (2+), κ (1+) and λ (1+)	Not done	No electron-dense deposits; no TMA features
16	MesPGN with focal crescents	15	7	7	0	Mild	Lin GBM IgG (2+), κ (2+) and λ (2+)	Not done	Not done

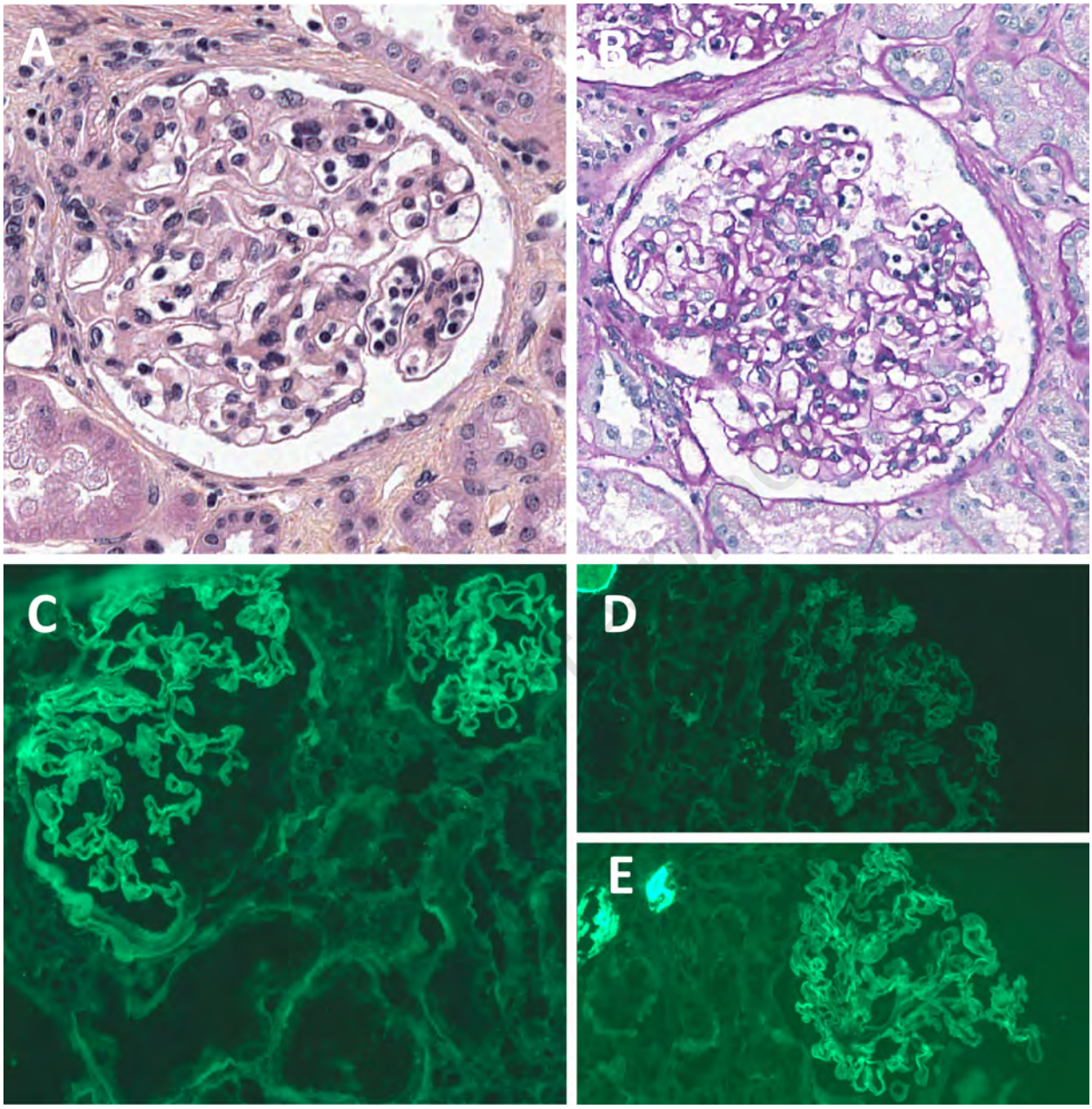
17	Unremarkable	9	22	0	0	Severe	Lin GBM IgG (2+) and λ (2+)	Not done	Not done
18	MPGN with focal crescents	10	20	25	0	Severe	Lin GBM IgG (3+), IgA (2+), λ (3+), κ (+/-)	Not done	Not done
19	FSGS	12	50	0	0	Moderate	Lin GBM IgA (2+), κ (+/-) and λ (1+)	Not done	Not done
20	Unremarkable	8	25	0	0	None	Lin GBM IgG (3+) and κ (2+)	3+ IgG1; neg IgG2, IgG3 and IgG4	Not done
21	EPGN	11	9	0	0	None	Lin GBM IgG (2+) and λ (2+)	2+ IgG3; neg IgG1, IgG2 and IgG4	No electron-dense deposits; no TMA features; seg FPE and cytoplasmic vacuolisation of podocytes
22	FCGN	12	0	8	8	Mild	Lin GBM IgG (3+), κ (3+) and λ (3+)	3+ IgG4; 1+ IgG2; neg IgG1 and IgG3	Not done
23	Unremarkable	22	5	0	0	Mild	Lin GBM IgG (2+), IgA (2+), κ (2+) and λ (2+)	2+ IgG1; neg IgG2, IgG3 and IgG4	No electron-dense deposits; seg FPE; no TMA features
24	Unremarkable	19	11	0	0	Mild	Lin GBM IgG (2+), κ (2+) and λ (1+)	2+ IgG4; neg IgG1, IgG2 and IgG3	Not done
25	EPGN with focal crescents	25	12	9	0	Mild	Lin GBM IgA (2+), κ (1+) and λ (1+)	Not done	No electron-dense deposits; seg FPE; no TMA features

Cortical interstitial fibrosis and tubular atrophy were semi-quantitatively graded as: none/negligible (0-5%), mild (6-25%), moderate (26-50%) or severe (>50%). Immunofluorescence results are semi-quantitatively displayed on a scale from 0 to 3+. The term "crescents" is used here for active extracapillary proliferation (*i.e.* cellular and/or fibro-cellular crescent). Fibrous crescents are excluded. Patient #19 had one FSGS lesion, but all other glomeruli were unremarkable. As for patients #7 and #22, outside of crescentic lesions, glomeruli were unremarkable. Patients with mesangiocapillary features were included in the EPGN category. Abbreviations: IF/TA, interstitial fibrosis and tubular atrophy; EPGN, endocapillary proliferative glomerulonephritis; MesPGN, mesangial proliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; FCGN, focal crescentic glomerulonephritis; lin, linear; gran, granular; seg, segmental; GBM, glomerular basement membrane; TBM, tubular basement membrane; neg, negative; TMA, thrombotic microangiopathy; FPE, foot process effacemen

Figure 1: Illustrative case of a monotypic atypical anti-glomerular basement membrane nephritis with an endocapillary proliferative pattern of glomerular injury (patient #21). (A) Several glomerular capillary loops are completely or partially occluded by leukocytes. There is no patent mesangial matrix increase. (Hematoxylin-Eosin-Saffron, original magnification x400). (B) Similarly, segmental endocapillary hypercellularity is seen in this glomerular section. This case had no crescentic features (Periodic Acid-Schiff, original magnification x400). (C, D, E) A moderate (2+) and linear staining along the glomerular basement membrane is seen by immunofluorescence with the antibody targeting IgG (C) and lambda (E), while kappa light chain is negative (D), original magnification x400.

Figure 2: Illustrative case of a polytypic atypical anti-glomerular basement membrane nephritis with a membranoproliferative and focally crescentic pattern of glomerular injury (patient #9). (A) A prominent mesangial matrix expansion is seen with a segmental cellular crescent at the top (Masson's trichrome, original magnification x400). (B) A lobulated flocculus by mesangial matrix expansion is seen with several double contours of the glomerular basement membrane (Jones methenamine silver, original magnification x400). (C, D, E) A strong and linear staining along the glomerular basement membrane is seen by immunofluorescence with the antibody targeting IgG (C), kappa (D) and lambda light chains (E), original magnification x400.

Figure 3: Comprehensive view of the clinico-pathological landscape of atypical anti-GBM disease. Atypical anti-GBM diseases encompass a wide range of clinical, biological and histological phenotypes, which ultimately limits the emergence of therapeutic guidelines. First introduced by Nasr and colleagues, the term "atypical anti-GBM nephritis" is defined by a bright linear immunoglobulin staining pattern along the GBM by immunofluorescence without a diffuse crescentic glomerulonephritis or patent anti-GBM antibodies by conventional ELISA. Compared to typical anti-GBM disease, it is characterized by a more chronic disease course, a better renal outcome and a lack of lung involvement. By light microscopy, a mesangial and/or endocapillary proliferative glomerulonephritis is frequently seen. Around 40 to 50% of anti-GBM nephritis show a monotypic staining pattern. These cases tend to affect older patients, with a lower proteinuria and have more rarely a crescentic phenotype by light microscopy, while no corresponding monoclonal gammopathy is found in most patients. In all disease phenotypes, no specific electron-dense deposits are seen by electron microscopy. While some reports confirmed the pathogenesis of the linear immunoglobulin deposition (Ohlsson et al[1]; Olaru et al[2], Borza et al[3], Kuang et al[4], and Ho et al[5]), this remains an exception. Thus, Rosales and Colvin proposed the term "glomerular disease with idiopathic linear immunoglobulin deposition", which does not imply a direct anti-GBM activity of the immunoglobulin staining and probably reflects more our current lack of knowledge about the pathophysiology of this disease. Besides conventional ELISA, alternative techniques, like indirect immunofluorescence or Western Blot, can be useful to confirm the presence of an anti-GBM activity (*). Abbreviations: GBM, glomerular basement membrane; MesPGN, mesangial proliferative glomerulonephritis; EPGN, endocapillary proliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; AKI, acute kidney injury; CKD, chronic kidney disease.


A
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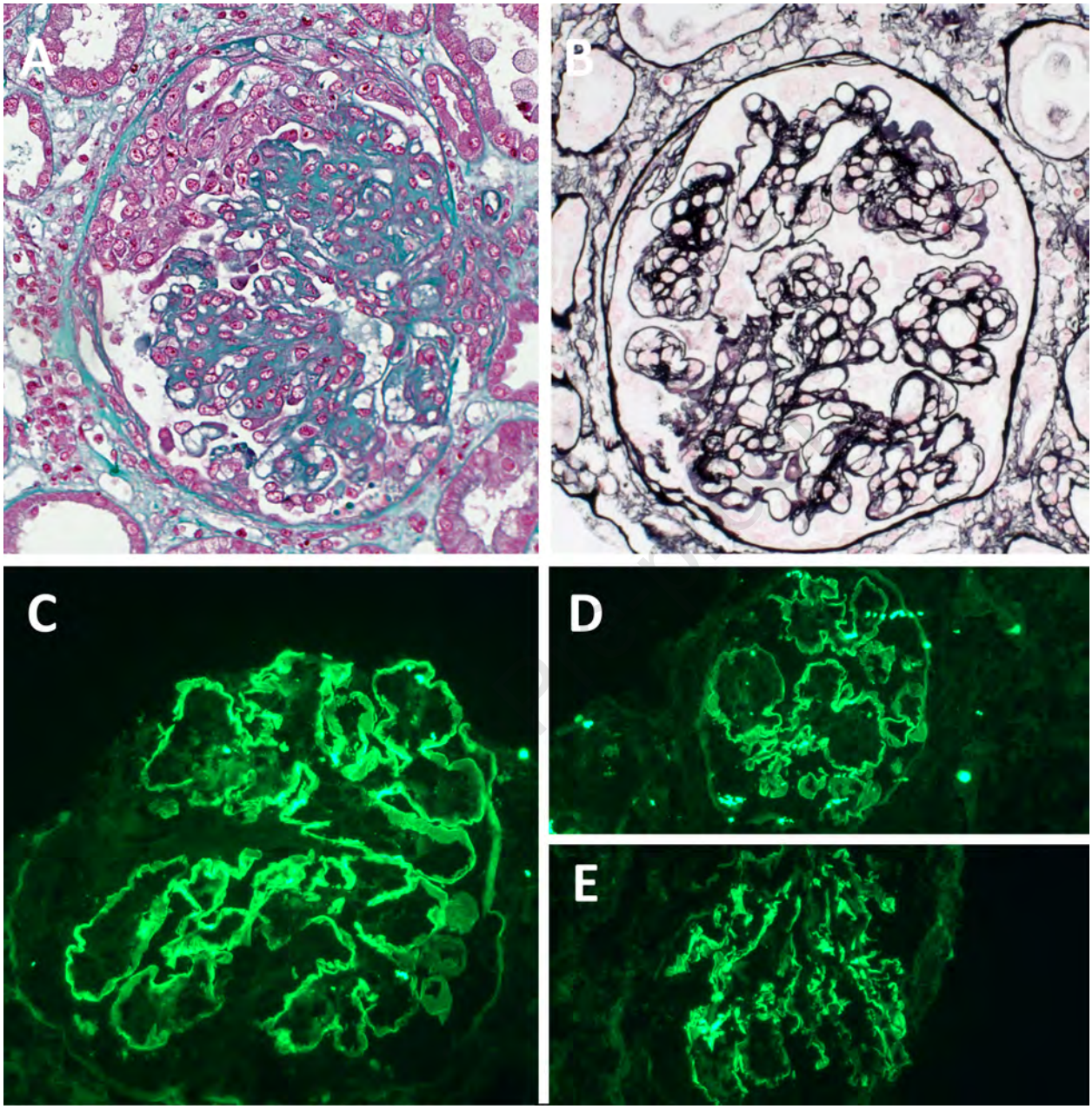
A
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Level of atypia

	Typical anti-GBM nephritis		Atypical anti-GBM nephritis		
				Glomerular disease with idiopathic linear immunoglobulin deposition	
Crescentic glomerulonephritis	Diffuse	Focal	Diffuse or Focal	Mostly focal if present Fibrous crescents possible	Absence
Glomeruli without crescent	Usually normal		Usually normal	Frequent MPGN/focal EPGN/ MesPGN	Unremarkable, +/- FSGS, +/- slight MesPGN
IF pattern	Linear IgG along GBM		Linear IgG along GBM, more rarely IgA	Linear IgG along GBM, rarely IgA or IgM	Linear IgG along GBM, more rarely IgA or IgM
IgG subclass (if applicable)	IgG 1or IgG3 predominant		Variable, mostly IgG1 or IgG4		IgG1 or IgG4
Light-chain restriction	Rare		Possible[1,2]	Around 50%, although rare in crescentic forms	Around 50%
Electron microscopy	No significant electron-dense deposits		No significant electron-dense deposits		
Clinical presentation	AKI, hematuria +/- pulmonary hemorrhage	Variable AKI and hematuria +/- pulmonary hemorrhage	AKI, hematuria +/- pulmonary hemorrhage	AKI +/- CKD but slower onset Hematuria, proteinuria (mostly heavy) No pulmonary involvement	Proteinuria, +/- CKD and hematuria No pulmonary involvement
Anti-GBM detection by ELISA targeting α3(IV)NC1	Yes		No or weakly positive	Usually no, rarely equivocal/weakly positive	No
Pathogenesis of the Ig linear staining	Undoubtful		Undoubtful*	Most likely*	Uncertain*
Pathogenesis explanation	Characterized autoantigen: α3(IV)NC1		Characterized autoantigen - α3(IV)NC1 with « *less aggressive* » *Ig subclass (IgG4)*[1] - Alternative antigens like hexamer α345(IV)NC1[2], α1/2(IV)[3] or LM521[4] *+/- different isotype (IgA)*[5]	Unknown	
		- Early renal biopsy - Weak concentration of antibodies			
Recurrence	Rare		Possible	Possible, chronic course	