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The Diagnostic Conundrum of Glomerular Crescents With IgA Deposits

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Introduction: Glomerulonephritis (GN) with crescents and IgA deposits in kidney biopsy poses a frequent diagnostic and therapeutic dilemma because of multiple possibilities.

Methods: Native kidney biopsies showing glomerular IgA deposition and crescents (excluding lupus nephritis) were identified from our biopsy archives between 2010 and 2021. Detailed clinicopathologic features were assessed. One-year clinical follow-up on a subset of cases was obtained.

Results: A total of 285 cases were identified, and these clustered into IgA nephropathy (IgAN, $n = 108$), *Staphylococcus* or other infection-associated GN/infection-related GN (SAGN/IRGN, $n = 43$), and anti-neutrophil cytoplasmic antibody–associated GN (ANCA-GN, $n = 26$) based on a constellation of clinicopathologic features, but 101 cases (group X) could not be definitively differentiated. The reasons have been elucidated, most important being atypical combination of clinicopathologic features and lack of definitive evidence of active infection. Follow-up (on 72/101 cases) revealed that clinicians' working diagnosis was IgAN in 43%, SAGN/IRGN in 22%, ANCA-GN in 28%, and others in 7% of the cases, but treatment approach varied from supportive or antibiotics to immunosuppression in each subgroup. Comparing these cases as "received immunosuppression" versus "non-immunosuppression," only 2 features differed, namely C3-dominant staining, and possibility of recent infection (both higher in the no-immunosuppression group) ($P < 0.05$). Renal loss was higher in the non-immunosuppression subgroup, but not statistically significant ($P = 0.11$).

Conclusion: Diagnostic overlap may remain unresolved in a substantial number of kidney biopsies with glomerular crescents and IgA deposits. A case-by-case approach, appropriate antibiotics if infection is ongoing, and consideration for cautious immunosuppressive treatment for progressive renal dysfunction may be needed for best chance of renal recovery.

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IgAN commonly presents with glomerular hematuria and proteinuria. Kidney biopsies of patients with IgAN display IgA-containing immune complex deposits and may be accompanied by crescent formation. However, other GN such as SAGN, IRGN, IgA vasculitis, and secondary IgAN may also share a similar presentation.[1–8]

Distinguishing between these entities can be clinically challenging but is extremely important because the therapeutic approach varies significantly and ranges from supportive management with SAGN and IRGN to immunosuppression in cases of IgAN.[9,10] The presence of glomerular crescents adds another layer of complexity because it raises the possibility of

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antineutrophil cytoplasmic antibody (ANCA)–associated pauci-immune GN, which despite not being classically associated with immune complex deposition, can present with mild immunofluorescence (IF) staining for IgA and/or IgG, and/or with a few electron-dense deposits (EDDs) on electron microscopy examination.[11–14] In addition, approximately 20% of patients with SAGN/IRGN have positive ANCA serology,[6,15] and infections (including *Staphylococcus aureus* infections) can trigger formation of ANCAs (particularly myeloperoxidase with resultant vasculitis).[16,17]

In our previous work, we highlighted some important histologic features distinguishing SAGN from primary IgAN.[6,10,18] However, crescents were not well studied. Here, we conducted a retrospective clinicopathologic analysis on all biopsy cases that showed glomerular IgA deposits accompanied by crescents. The aims of this study were 2-fold. One was to compare the clinicopathologic features of the 3 groups of cases that had a definitive etiologic diagnosis on biopsy and build statistical prediction models. The second was to better understand the reasons for the ambiguity in histologic diagnosis of the unclassified cases using clinical follow-up and application of the same prediction models.

METHODS

Kidney Biopsy Inclusion

Renal biopsy cases showing crescents with glomerular IgA deposits received at the Ohio State University Wexner Medical Center from January 2010 to December 2021 were retrieved from our Renal Pathology files. These included in-house biopsies and biopsies from multiple outside referring hospitals sent for routine diagnostic work-up. Cases with the diagnosis of lupus nephritis and renal transplant biopsies were excluded.

Data Collection

Demographic data (age, sex, and ethnicity); clinical history of infection; laboratory parameters at the time of biopsy (serum creatinine level, serum complement levels [C3 and C4], urine protein, presence or absence of hematuria, blood culture results, and/or other specimen culture results); and serologic data (ANCA testing result) were collected from electronic medical charts and biopsy pathology reports. The Ohio State University clinical laboratory uses normal cutoffs of >80 mg/dl for C3 and >12 mg/dl for C4.[19] In some cases, only qualitative results for C3 and C4 (low/normal) were available.

Histopathologic features on light microscopy, IF staining, and electron microscopy were assessed using the biopsy pathology reports. Exudative glomerular lesions were assessed as previously described.[20,21] IF staining was assessed semiquantitatively (trace = 0.5+, mild = 1+, moderate = 2+, strong = 3+). The presence or absence of immune-type EDDs on ultrastructural examination was also recorded. When present, the distribution pattern of EDDs was evaluated as mesangial only, mesangial with capillary wall deposits (subendothelial, subepithelial), presence of subepithelial humps, or absence of EDDs.

Based on the pathology reports, the cases were grouped as follows: group 1: IgAN, group 2: SAGN/IRGN (only included cases with culture-proven infection at the time of GN), group 3: ANCA-GN, and group X: could not be definitively differentiated into any of the 3 groups based on the biopsy findings and clinical information available to the pathologist at the time of biopsy evaluation. The diagnostic criteria for IgAN, SAGN/IRGN, and ANCA-GN included a combination of clinical, laboratory, and pathologic features as described in reference texts.[6,7,22–26]

For group X, a follow-up to understand the management approach used and the status of the renal function at 1-year postbiopsy was performed using electronic charts for the cases managed at the Ohio State University Wexner Medical Center and by telephone conversations with nephrologists for cases receiving care at outside institutions. Detailed treatment regimens were not available, and renal outcomes were based on the serum creatinine values 1 year after biopsy and/or the need for dialysis. This study was not meant to be a prospective longitudinal outcomes study, but more directed toward addressing the difficulties in biopsy diagnoses.

Statistical Analysis

Categorical variables were expressed as numbers (percentages), whereas continuous values were expressed as mean ± standard deviations or median (interquartile range). Wilcoxon rank sum test, Kruskal-Wallis, and χ^2 test were used to assess differences between groups as appropriate. A P value <0.05 was considered statistically significant. *Post hoc* analyses for multiple comparisons were done using the Bonferroni correction. Statistical analyses were performed using the JMP Pro 15 (SAS Institute Inc., Cary, NC).

Prediction Model

Multinomial logistic regression model using a combination of parameters (out of 10 candidate parameters; Supplementary Table S1) was constructed using groups 1 to 3 (R version 4.1). Four predictors could be used before the model failed due to excessively wide standard errors. Three best combinations were chosen. A random forest model with 1000 trees was fit to the

Table 1. Demographic data of patients in all groups and statistical comparisons for groups 1–3

Variable	IgAN (group 1) (n = 108)	SAGN/IRGN (group 2) (n = 43)	ANCA-GN (group 3) (n = 26)	P value	Unclassified (group X) (n = 101)
Age (yr)[a]	40 ± 16	53 ± 15[b]	59 ± 18[b]	<0.001	60 ± 14
Age range	(7–86)	(24–83)	(24–87)		(24–91)
Male:female	69:39	31:12	16:10	0.56	69:32
Caucasian	80, 83% (n = 96)	34, 94% (n = 36)	17, 81% (n = 21)	0.17	73, 86% (n = 85)
History of diabetes	10, 9%	13, 30%[b]	6, 23%	0.005	27, 27%
History of infection (excluding UTI, and URTI)	0, 0%	43, 100%[b] (all culture positive)	1, 5%[c]	<0.001	29, 29%
ANCA+	1, 2% (n = 56)	4, 15% (n = 26)	26, 100%[b,c] (n = 26)	<0.001	24, 33% (n = 73)
sCr (mg/dl)[a]	3.1 ± 3.1	4.6 ± 2.1[b]	5.6 ± 4.1[b]	<0.001	4.7 ± 2.8
Low C3 (yes)	3, 5% (n = 57)	14, 39%[b] (n = 36)	0, 0%[c] (n = 20)	<0.001	12, 14% (n = 85)
Low C4 (yes)	1, 2% (n = 57)	3, 8% (n = 36)	0, 0% (n = 20)	0.16	6, 7% (n = 85)
Proteinuria (yes)	96, 94% (n = 102)	35, 100% (n = 35)	18, 100% (n = 18)	0.08	81, 100% (n = 81)
Nephrotic proteinuria or ≥3+ (dipstick)	49, 48% (n = 102)	21, 60% (n = 35)	3, 17%[c] (n = 18)	0.008	50, 62% (n = 81)
Hematuria (yes)	86, 91% (n = 94)	34, 94% (n = 36)	22, 96% (n = 23)	0.70	79, 96% (n = 82)

ANCA-GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; IgAN, immunoglobulin A nephropathy; SAGN/IRGN, *Staphylococcus* infection–associated glomerulonephritis/infection-related glomerulonephritis; URTI, upper respiratory tract infection; UTI, urinary tract infection.
[a]Numerical variable. Continuous values are shown with mean ± SD or median (interquartile range). Continuous values were analyzed using Kruskal-Wallis test. Categorical values were analyzed using χ^2 test with *post hoc* Bonferroni correction ($P < 0.017$ would be significant).
[b]$P < 0.017$ vs. IgAN.
[c]$P < 0.017$ vs. SAGN/IRGN.
This is a 3-group analysis (group X is not included in the statistical analysis).

Table 2. Pathologic findings of patients in all groups and statistical comparisons for groups 1–3

Variable	IgAN (group 1) (n = 108)	SAGN/IRGN (group 2) (n = 43)	ANCA-GN (group 3) (n = 26)	P value	Unclassified (group X) (n = 101)
Light microscopy					
M-hypercellularity present	91, 84%	34, 79%	3, 12%[a,b]	<0.001	52, 51%
E-hypercellularity present	48, 44%	32, 74%[a]	2, 8%[a,b]	<0.001	38, 38%
Segmental sclerosis present	62, 57%	1, 2%[a]	8, 31%[a,b]	<0.001	12, 12%
Sclerotic glomeruli (%)	18 (5–39)	6 (0–26)[a]	27 (7–41)[b]	0.02	17 (5–30)
C-crescents (%)	2 (0–7)	13 (6–28)[a]	7 (0–38)	<0.001	15 (5–30)
FC + F-crescents (%)	6 (0–24)	0 (0–0)[a]	20 (6–46)[b]	<0.001	0 (0–11)
Total crescents (%)	12 (6–25)	13 (6–29)	48 (24–69)[a,b]	<0.001	23 (9–39)
≥5 neutrophils per glomerulus present	1, 1%	11, 26%[a]	1, 4%	<0.001	12, 12%
Necrotizing lesions present	12, 11%	21, 49%[a]	15, 58%[a]	<0.001	56, 56%
IF/TA grade (0–3)[c]	1.7 ± 1.0	1.1 ± 0.9[a]	1.7 ± 0.9	0.006	1.3 ± 0.9
ATN present	41, 38%	38, 88%[a]	18, 69%[a]	<0.001	75, 74%
RBC casts present	31, 29%	29, 67%[a]	13, 50%	<0.001	58, 57%
Immunofluorescence					
IgG (0–3)[c]	0.5 ± 0.6	0.9 ± 0.8[a]	0.6 ± 0.6	0.02	0.7 ± 0.7
IgA (0–3)[c]	2.4 ± 0.6	1.5 ± 0.6[a]	1.1 ± 0.6[a,b]	<0.001	1.6 ± 0.7
C1q (0–3)[c]	0.3 ± 0.4	0.4 ± 0.6	0.2 ± 0.3	0.29	0.2 ± 0.4
C3 (0–3)[c]	1.6 ± 0.8	1.9 ± 0.7	1.2 ± 0.7[b]	0.006	1.6 ± 0.7
κ (0–3)[c]	1.5 ± 0.7	1.0 ± 0.8[a]	0.7 ± 0.6[a]	<0.001	1.1 ± 0.7
λ (0–3)[c]	2.1 ± 0.7	1.2 ± 0.7[a]	0.8 ± 0.5[a]	<0.001	1.4 ± 0.8
C3 dominance present	10, 10%	20, 47%[a]	10, 38%[a]	<0.001	34, 34%
λ dominance present	60, 57%	18, 42%	10, 38%	0.11	39, 39%
Electron microscopy					
Only mesangial EDDs present	58, 56% (n = 104)	8, 19%[a] (n = 43)	11, 46% (n = 24)	0.001	32, 33% (n = 98)
Mesangial and capillary wall EDDs present	45, 42% (n = 104)	34, 79%[a] (n = 43)	4, 17%[a.b] (n = 24)	<0.001	55, 56% (n = 98)
Subepithelial hump present	6, 6% (n = 104)	9, 21%[a] (n = 43)	0, 0%[b] (n = 24)	0.009	14, 14% (n = 98)
Absence of EDDs	1, 1% (n = 104)	1, 2% (n = 43)	9, 38%[a,b] (n = 24)	<0.001	11, 11% (n = 98)

ANCA-GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; ATN, acute tubular necrosis; C-Crescent, cellular crescent; E-hypercellularity, endocapillary hypercellularity; EDDs, electron-dense deposits; FC + F-Crescent, fibrocellular + fibrous crescent; IF/TA, interstitial fibrosis and tubular atrophy; IgAN, immunoglobulin A nephropathy; M-hypercellularity, mesangial hypercellularity; RBC, red blood cell; SAGN/IRGN, *Staphylococcus* infection–associated glomerulonephritis/infection-related glomerulonephritis.
[a]$P < 0.017$ vs. IgAN.
[b]$P < 0.017$ vs. SAGN/IRGN.
[c]Numerical variable. Continuous values are shown with mean ± standard deviation or median (interquartile range). Continuous values were analyzed using Kruskal-Wallis test. Categorical values were analyzed using χ^2 test with *post hoc* Bonferroni correction ($P < 0.017$ would be significant).
This is a 3-group analysis (group X is not included in the statistical analysis).
The term "exudative glomerular lesions" connotes numerous neutrophils marginated in the lumens of the glomerular capillary loops, away from necrotizing glomerular lesions.[20] These were evaluated based on more than or equal to 5 endocapillary neutrophils per glomerulus away from necrotizing lesions or crescents.[21]

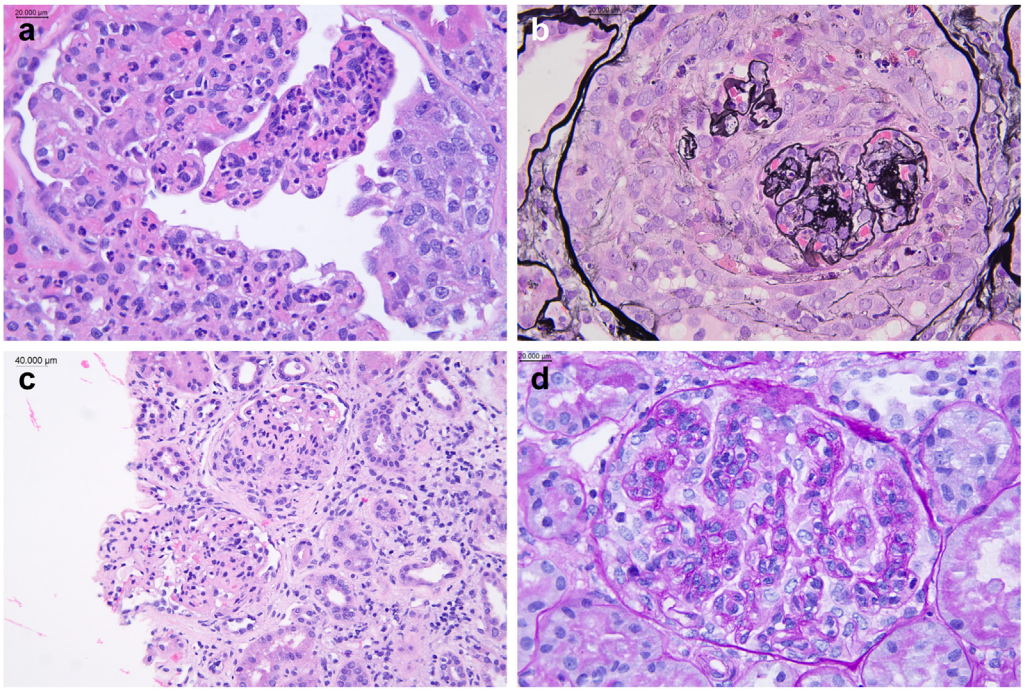

Figure 1. Few characteristic histopathologic features. (a) Exudative endocapillary hypercellularity in SAGN/IRGN H&E stain 400×. (b) Cellular crescent in SAGN/IRGN Jones Methenamine silver stain 400×. (c) Segmental sclerosis in IgAN H&E stain 200×. (d) Endocapillary hypercellularity in IgAN, periodic acid–Schiff 400×.

data.[27] To assess the model's performance, 1000 bootstraps of the data were sampled, the model was refit to each bootstrap, and the mean area under the receiver operating characteristic (AUROC) was calculated.[28]

Ethics

This study was approved by the Ohio State University Internal Review Board (IRB 2011H0364, 2022H0005) and was conducted under the Declaration of Helsinki.

RESULTS

We had a total of 14,500 kidney biopsies at our facility from January 2010 to December 2021, and 1064 had crescents. Of these, we identified kidney biopsies showing glomerular crescents and IgA deposition ($n = 285$). The number of patients in group 1 (IgAN), group 2 (SAGN/IRGN), group 3 (ANCA-GN), and group X (unclassified) were 108, 43, 26, and 101, respectively (Table 1, Supplementary Table S2). There were 7 cases with a diagnosis of IgA vasculitis, but these were not included in our statistical analysis because of the small number.

The IgA staining in the ANCA-GN cases was mild, and many did not show EDDs on ultrastructural examination, as highlighted in Table 2, probably representing incidental IgA staining.[26,29,30] Therefore, these were diagnosed as ANCA-GN with mild IgA deposits rather than "crescentic IgA nephropathy." Group 2 (SAGN/IRGN) had culture-proven infection at the time of GN.

Clinicopathologic Features in Groups 1 to 3

The statistical comparisons are shown in Tables 1 and 2. Group X is shown in the tables but was not included in statistical comparisons with groups 1 to 3. Overall, the patients showed a wide age spectrum (7 to 91 years), but mean patient age in SAGN/IRGN and ANCA-GN was significantly higher than in primary IgAN ($P < 0.001$). Significantly higher serum creatinine levels at the time of biopsy were present in SAGN/IRGN and ANCA groups, compared with crescentic IgAN. The SAGN/IRGN group showed the highest percentage of cases with nephrotic range of proteinuria (60%), significantly higher than ANCA-GN (17%) but not compared with IgAN (48%). SAGN did show a significantly higher proportion of patients with low serum C3 compared with those with IgAN ($P < 0.001$). Of 285 cases, 187 underwent ANCA testing, and 55 cases (26 in ANCA-GN, 4 in SAGN/IRGN, 1 in IgAN, and 24 in group X) were ANCA positive. Twenty were proteinase 3 (PR3) positive, 29 were myeloperoxidase positive, 1 was dual positive, and 5 had undefined specificity. The details of infections in cases with SAGN/IRGN are shown in Supplementary Table S3.

Overall, SAGN/IRGN demonstrated features of active glomerular injury (endocapillary hypercellularity, exudative glomerular lesions, higher percent cellular crescents in the biopsy, necrotizing glomerular lesions, acute tubular necrosis, and tubular red blood cell casts) (Figure 1a and b). In contrast, IgAN showed significantly higher percent fibrocellular

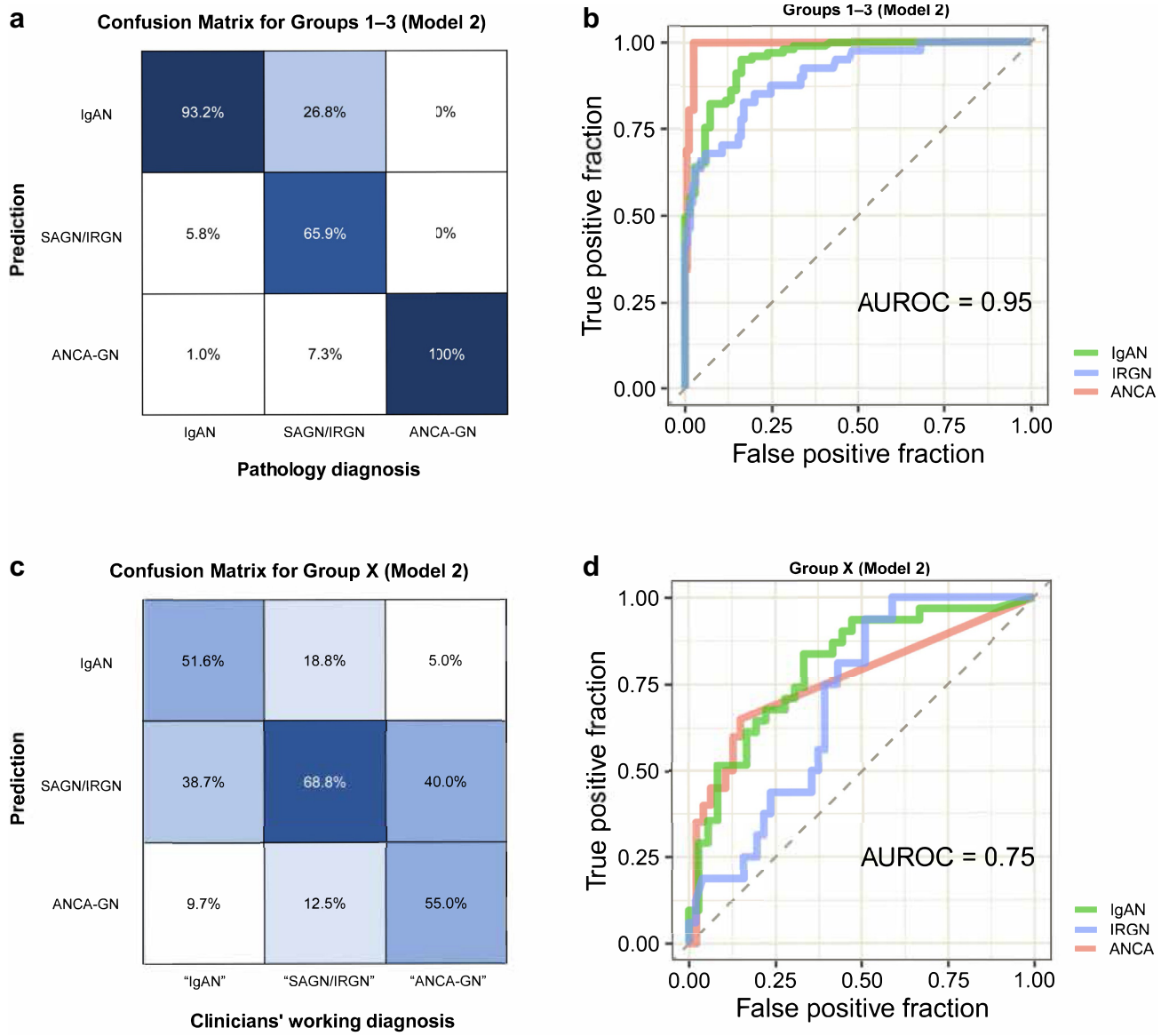

Figure 2. Confusion matrix and ROC curve for model 2 (using parameters ANCA serology, intensity of IgA staining, percent cellular crescents, and percent fibrocellular/fibrous crescents. (a,b) Groups 1–3. (c,d) Group X. For groups 1–3 the pathology diagnosis was compared with the diagnosis predicted by the model. For group X, the working diagnosis of the clinician was compared with the diagnosis predicted by the model (since etiology was undetermined on histological examination). ANCA-GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; SAGN/IRGN, *Staphylococcus* infection–associated glomerulonephritis/infection-related glomerulonephritis.

or fibrous crescents and the presence of segmental glomerular sclerosis (Figure 1c and d).[5,6,10] Oxford scores are provided in Supplementary Table S2. ANCA-GN shows a mix of cellular and fibrocellular or fibrous crescents, necrotizing lesions, acute tubular necrosis, and red blood cell casts as previously described.[11] Although less frequent, mesangial and endocapillary hypercellularity was noted in 12% and 8%, respectively, of ANCA-GN. On IF, C3 dominance is prevalent in SAGN/IRGN and the reverse in IgAN, as previously reported.[6,10,20] ANCA-GN showed EDDs only in 63% of the biopsies (mainly mesangial) despite presence of mild IgA staining on IF.

Statistical Prediction Models (Groups 1–3)

Three different combinations of parameters (models 1, 2, and 3) gave the best results with the highest AUROC of 0.95 for groups 1 to 3 (the accuracy and AUROC values along with the results on bootstraps are shown in Supplementary Tables S4–S6, Supplementary Figures S1–S3). The confusion matrix and ROC curve for model 2 are shown in Figure 2a and b. Model 1 used parameters, ANCA result, IgA intensity, percentage cellular crescents, and segmental sclerosis (present or absent); model 2 used the same but replaced segmental sclerosis with percentage of fibrocellular crescents; and model 3 removed ANCA result and replaced it with

Table 3. Follow-up and statistical prediction model data on group X ($n = 72$)

	Treated as	"IgAN"	"SAGN/IRGN"	"ANCA-GN"	"Others"	Total
	Number (% of total)	31 (43%)	16 (22%)	20 (28%)	5 (7%)	72
	Age (yr)	59 ± 16	60 ± 11	60 ± 14	62 ± 12	60 ± 14
	Male:female	23:8	14:2	8:12	4:1	49:23
Patient survival	Living	23, 74%	10, 63%	17, 85%	4, 80%	54, 75%
	Deceased	6, 19%	5, 31%	2, 10%	0, 0%	13, 18%
	Unknown	2, 6%	1, 6%	1, 5%	1, 20%	5, 7%
Renal function	Improved or unchanged	16, 52%	7, 44%	12, 60%	2, 40%	38, 53%
Renal loss or worsen	13, 42%	7, 44%	7, 35%	2, 40%	28, 39%	
	Unknown	2, 6%	2, 13%	1, 5%	1, 20%	6, 8%
Treatment	Dialysis (including temporary cases)	15, 48%	9, 56%	11, 55%	2, 40%	37, 51%
	Antibiotics only	1, 3%	10, 63%	0, 0%	1, 20%	12, 17%
	Immunosuppressive therapy	17, 55%	0, 0%	17, 85%	3, 60%	37, 51%
	Antibiotics and immunosuppressive therapy	1, 3%	4, 25%	1, 5%	1, 20%	6, 8%
	Supportive only	10, 32%	2, 13%	2, 10%	0, 0%	14, 19%
	Unknown	2, 6%	0, 0%	0, 0%	1, 11%	3, 4%
Accuracy of prediction models for group X		"IgAN"	"SAGN/IRGN"	"ANCA-GN"	"Others"	AUROC
Correctly predicted patients using models	(Model 1): cellular crescent %, IgA intensity, ANCA serology,[a] and segmental sclerosis	12, 39%	9, 56%	13, 65%	N/A	0.73
	(Model 2): cellular crescent %, IgA intensity, ANCA serology,[a] and fibrous and fibrocellular crescent %	16, 52%	11, 69%	11, 55%	N/A	0.75
	(Model 3): cellular crescent %, IgA intensity, fibrous and fibrocellular crescent %, and endocapillary hypercellularity	15, 48%	5, 31%	14, 70%	N/A	0.69

ANCA, antineutrophil cytoplasmic antibody–associated glomerulonephritis; AUROC, area under the curve of the receiver operating characteristic; IgAN, immunoglobulin A nephropathy; N/A, not available; SAGN/IRGN, *Staphylococcus* infection–associated glomerulonephritis/infection-related glomerulonephritis.
[a]ANCA serology was used at the time of biopsy.
Others include cryoglobulinemic glomerulonephritis ($n = 1$), C3 glomerulonephritis ($n = 1$), drug-induced glomerulopathy ($n = 1$), and unknown cases ($n = 2$).
Continuous values are shown with mean ± SD.

endocapillary hypercellularity (present or absent). Regarding ANCA results, ANCA positive or negative or "not available" were used because ANCA titers were not consistently available.

Prediction Model on Group X Patients

Group X constituted 35% of our entire cohort (101/285). Follow-up information was available for 72 of 101 patients (Table 3). The working diagnosis and management strategy of the treating physician was "IgAN" in 31 (43%), "SAGN/IRGN" in 16 (22%), and "ANCA-GN" in 20 (28%) patients. The remaining 5 (7%) included C3GN ($n = 1$), drug-induced glomerulopathy ($n = 1$), cryoglobulinemic GN ($n = 1$) and remained unknown ($n = 2$) (Table 3).

The multinomial prediction models were applied to these group X cases ($n = 67$, after excluding the 5 other diagnoses or unknown cases stated above). Correlation accuracies of the predicted diagnosis and the working diagnosis of the clinician for all 3 models are shown in Table 3. The results for model 2 are shown in Figure 2c and d. The AUROC was much lower than that seen with groups 1 to 3 (and also compared with the bootstrap validation cohorts), emphasizing the difficulty in the biopsy diagnosis of these group X patients. A summary of the diagnostic pitfalls for group X is provided in Table 4, based on a re-review of all the pathology reports and the discrepancies in predicted versus clinician's diagnosis.

Being a retrospective study, treatment approaches in the 3 main subgroups within group X varied and also showed overlap. Therefore, we condensed these group X cases only into 2 subgroups: "those who received immunosuppressive therapy" and "those who received antibiotics/ supportive treatment only" (Table 5). Cases diagnosed as C3GN, cryoglobulinemic GN, and 3 cases with unclear follow-up were excluded, leaving 67 total patients. On statistical comparison, only C3-dominant IF staining and history of infection (with or without cultures) showed significant difference ($P < 0.05$) and were higher in non-immunosuppression subgroup. Overall outcomes at 1-year postbiopsy are shown in Tables 3 and 4. Renal loss was higher among patients treated without immunosuppression but not statistically significant ($P = 0.11$). Comparing cases with renal failure and those without renal failure, only interstitial fibrosis and tubular atrophy showed statistically significant difference (data not shown).

Trends of Infection in Group X Patients

As illustrated in the flowchart in Figure 3, group X comprised patients with absent clinical and microbiological evidence of infection; patients who had clinical evidence of infection in the recent past (such as

Table 4. Scenarios precluding definitive biopsy diagnosis and differentiation between ANCA-GN, IgAN, and IRGN

Difficulties in diagnosis of ANCA-GN in group X
• Crescentic GN with mild IgA staining, ANCA serology pending at the time of biopsy, or negative ANCA serology.
• ANCA-GN just preceded by history of disseminated staphylococcal infection (MRSA or MSSA). Difficult to exclude possibility of remnant foci of infection causing IRGN vs. infection-induced ANCA.
• Crescentic GN with ANCA positivity, negative culture studies due to difficult-to-grow bacteria (such as *Bartonella*). Serology results usually lacking at the time of biopsy.
• Presence of mesangial and endocapillary hypercellularity, positive ANCA serology but negative or absent culture results.
• Biopsy features resembling ANCA-GN but accompanied by low serum C3 level.
• Positive ANCA serology, but strong IgA staining, no evidence of ongoing infection. May be accompanied by leukocytoclastic vasculitic rash. ANCA-GN, crescentic IgAN, IgA vasculitis, or occult infection are possibilities.
• History of autoimmune disease with positive ANA serology or patients on targeted therapies such as tumor necrosis factor blockers and then presents with positive ANCA serology and crescents.
• Anticoagulant-related nephropathy (e.g., warfarin-related nephropathy) can mimic ANCA-GN with small percentage of crescents in the biopsy and mild IgA deposits.
Difficulties in diagnosis of IgAN in group X
• History of recently treated cellulitis or other infection, negative cultures (but infection reportedly treated before presentation of GN). No history of kidney disease, but biopsy shows strong IgA staining with C3.
• History of intravenous drug use, but cultures negative, mild proliferative lesions and IgA deposits.
• Patients of Asian descent, mild IgA staining with numerous cellular crescents, ANCA serology unavailable at the time of biopsy.
• Elderly patients with crescents and endocapillary proliferative lesions, nephrotic-range proteinuria, strong C3 staining, but lacking evidence of ongoing infection.
Difficulties in diagnosis of SAGN/IRGN in group X
• Clinical evidence of recent infection (identifiable source) but lack of culture positivity, despite biopsy features suggestive of IRGN.
• Recent infection, but history of kidney biopsy with IgA deposits.
• Difficult-to-grow bacteria such as *Bartonella*, oral flora, cultures negative, serology results lacking.
• Cases with weak to absent IgA and C3 staining (pauci-immune pattern), with concomitant crescents and positive ANCA serology.
• Mild focal mesangial hypercellularity with crescents and absent endocapillary hypercellularity can mimic ANCA-GN.
• Repeated episodes of infection superimposed on underlying comorbidity such as repeated episodes of pneumonia in patients with chronic obstructive pulmonary disease, or skin infection in patients with bed sores accompanied by persistent proteinuria and hematuria despite antibiotic courses.
• Underlying liver cirrhosis, spontaneous bacterial peritonitis, persistent GN with IgA deposits but no positive cultures or definitive clinical site of infection.

ANA, antinuclear antibody; ANCA-GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; GN, glomerulonephritis; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

cellulitis, deep-seated abscess, or pneumonia) already treated, but negative or absent culture results; and few cases that did have culture-proven infection, but it was already treated with prolonged antibiotic courses, just before presentation of the acute GN. Infection had reportedly resolved before the onset of acute GN. Subsequent blood cultures were negative and three-fourths of them showed positive ANCA serology.

Clinical Management of Group X Patients

Among the 16 patients managed as IRGN in group X (Supplementary Table S7), 4 did develop positive cultures after the biopsy (3 showed MRSA, 1 showed *Bartonella henselae*). Among the 16 patients with presumed SAGN/IRGN, most received mainly antibiotics and 4 received antibiotics and steroids (when definite source of infection was not identified). Management for patients with presumed IgAN mainly included corticosteroids (up to 6 cases did get cyclophosphamide as well),[24,25] but up to 10 patients were managed only with supportive measures. Management for ANCA-GN included treatment with corticosteroids and cyclophosphamide (or rituximab) with or without plasmapheresis.[22,23]

DISCUSSION

This is a retrospective single-center cohort study on patients with biopsies showing GN with crescents and IgA deposits. Differential diagnosis included crescentic IgAN, SAGN/IRGN, and ANCA-GN with incidental IgA deposits. Differentiation between them is critically important. A large number of clinicopathologic features need to be taken into consideration when evaluating such biopsies to arrive at the correct etiologic diagnosis (Tables 1 and 2).[6,10,20] Using these features, majority of the biopsies (184/285 cases, 65%) were accurately differentiated. Each group showed a characteristic constellation of features with good discrimination on the statistical prediction models (AUROC up to 0.95 and 0.93 on bootstrap validation cohorts). However, there was a large subset of biopsies that we called "group X" (101/285, 35%) in which this differentiation was not possible with certainty because the constellation of clinicopathologic features was not concordant with either of the 3 groups (IgAN, SAGN/IRGN, or ANCA-GN). The same statistical prediction models when applied and correlated with the clinician's working diagnosis showed lower accuracy for group X. In addition, a major

Table 5. Clinicopathologic data of followed-up patients in group X ($n = 72$) with or without immunosuppression therapy

Variable	Non-immunosuppression ($n = 26$)	Immunosuppression ($n = 41$)	*P* value
Age (yr)[a]	61 ± 18	59 ± 13	0.57
Age range	(31–84)	(29–91)	
Male:female	20:6	23:18	0.08
Caucasian	19, 90% ($n = 21$)	31, 89% ($n = 35$)	0.82
History of diabetes	7, 27%	6, 15%	0.22
History of infection (excluding UTI and URTI)	12, 46%	7, 17%	**0.01**
ANCA+	5, 31% ($n = 16$)	17, 47% ($n = 36$)	0.31
sCr (mg/dl)[a]	5.2 ± 4.1	4.6 ± 2.1	0.95
Low C3 (yes)	5, 23% ($n = 22$)	3, 9% ($n = 35$)	0.13
Low C4 (yes)	1, 5% ($n = 22$)	2, 6% ($n = 35$)	0.88
Proteinuria (yes)	21, 100% ($n = 21$)	32, 100% ($n = 32$)	1.00
Nephrotic proteinuria or ≥3+ (dipstick)	15, 71% ($n = 21$)	16, 50% ($n = 32$)	0.11
Hematuria (yes)	21, 95% ($n = 22$)	35, 100% ($n = 35$)	0.16
Light microscopy			
M-hypercellularity present	15, 58%	20, 49%	0.48
E-hypercellularity present	9, 35%	15, 37%	0.87
Segmental sclerosis present	4, 15%	5, 12%	0.71
Sclerotic glomeruli (%)	20 (7–45)	17 (5–32)	0.41
C-crescents (%)	8 (4–23)	19 (5–36)	0.18
FC + C-crescents (%)	0 (0–11)	0 (0–17)	0.49
Total crescents (%)	18 (5–32)	29 (16–50)	0.05
≥5 neutrophils per glomerulus present	3, 12%	3, 7%	0.56
Necrotizing lesions present	12, 46%	26, 63%	0.16
IF/TA grade (0–3)[a]	1.7 ± 0.7	1.5 ± 0.7	0.34
ATN present	17, 65%	32, 78%	0.26
RBC casts present	14, 54%	27, 66%	0.33
Immunofluorescence			
IgG (0–3)[a]	0.6 ± 0.7	0.9 ± 0.8	0.11
IgA (0–3)[a]	1.5 ± 0.6	1.7 ± 0.7	0.41
C1q (0–3)[a]	0.3 ± 0.4	0.1 ± 0.3	0.22
C3 (0–3)[a]	1.7 ± 0.6	1.4 ± 0.8	0.02
κ (0–3)[a]	1.2 ± 0.7	1.3 ± 0.8	0.56
λ (0–3)[a]	1.2 ± 0.7	1.4 ± 0.8	0.17
C3 dominance present	11, 42%	8, 20%	**0.045**
λ dominance present	6, 23%	15, 37%	0.24
Electron microscopy			
Only mesangial EDDs present	7, 30% ($n = 23$)	17, 41% ($n = 41$)	0.38
Mesangial and capillary wall EDDs present	14, 61% ($n = 23$)	20, 49% ($n = 41$)	0.35
Subepithelial humps present	3, 13% ($n = 23$)	5, 12% ($n = 41$)	0.92
Absence of EDDs	2, 9% ($n = 23$)	4, 10% ($n = 41$)	0.89
Renal outcomes (improved:worsened)	11:14 ($n = 25$)	25:14 ($n = 39$)	0.11

ATN, acute tubular necrosis; ANCA, antineutrophil cytoplasmic antibodies; C-Crescent, cellular crescent; E-hypercellularity, endothelial hypercellularity; EDDs, electron-dense deposits; FC + F-Crescent, fibrocellular + fibrous crescent; IF/TA, interstitial fibrosis and tubular atrophy; M-hypercellularity, mesangial hypercellularity; RBC, red blood cell; sCr, serum creatinine level; UTI, urinary tract infection; URTI, upper respiratory tract infection.

[a]Numerical variable. Continuous values are shown with mean ± SD or median (interquartile range). Continuous values were analyzed using Wilcoxon sum test. Categorical values were analyzed using χ^2 test ($P < 0.05$ would be significant). C3 glomerulonephritis case ($n = 1$), cryoglobulinemic glomerulonephritis case ($n = 1$), and 3 cases with unclear follow-up were excluded from this analysis.

Renal outcomes were not available in 3 cases: non-immunosuppression ($n = 1$) and immunosuppression ($n = 2$).

limitation of these models is that a combination of only a few selected parameters can be used at a time.

Upon dividing the group X cases based on whether they received immunosuppressive treatment or antibiotics or supportive treatment only (Table 5), none of the clinicopathologic features showed statistically significant differences between them except for history of recent infection (4 had previous culture positivity, the rest had clinical evidence but no microbiological culture results) and C3-dominant IF staining (ratio of C3 to IgA intensity >1), highlighting the ambiguity in histologic diagnosis and variability in the management approach among these group X cases.

Therefore, looking for clinical evidence of infection seems to be most critical for decision-making in these difficult cases. Some cases had identifiable source of infection, usually treated or still undergoing treatment, but lacking positive cultures (Figure 3). Some pathologists may diagnose these as "postinfectious GN in adults" according to criteria described by Nasr *et al.*[7] However, a large percentage of patients in group X had neither clinical evidence nor laboratory evidence of

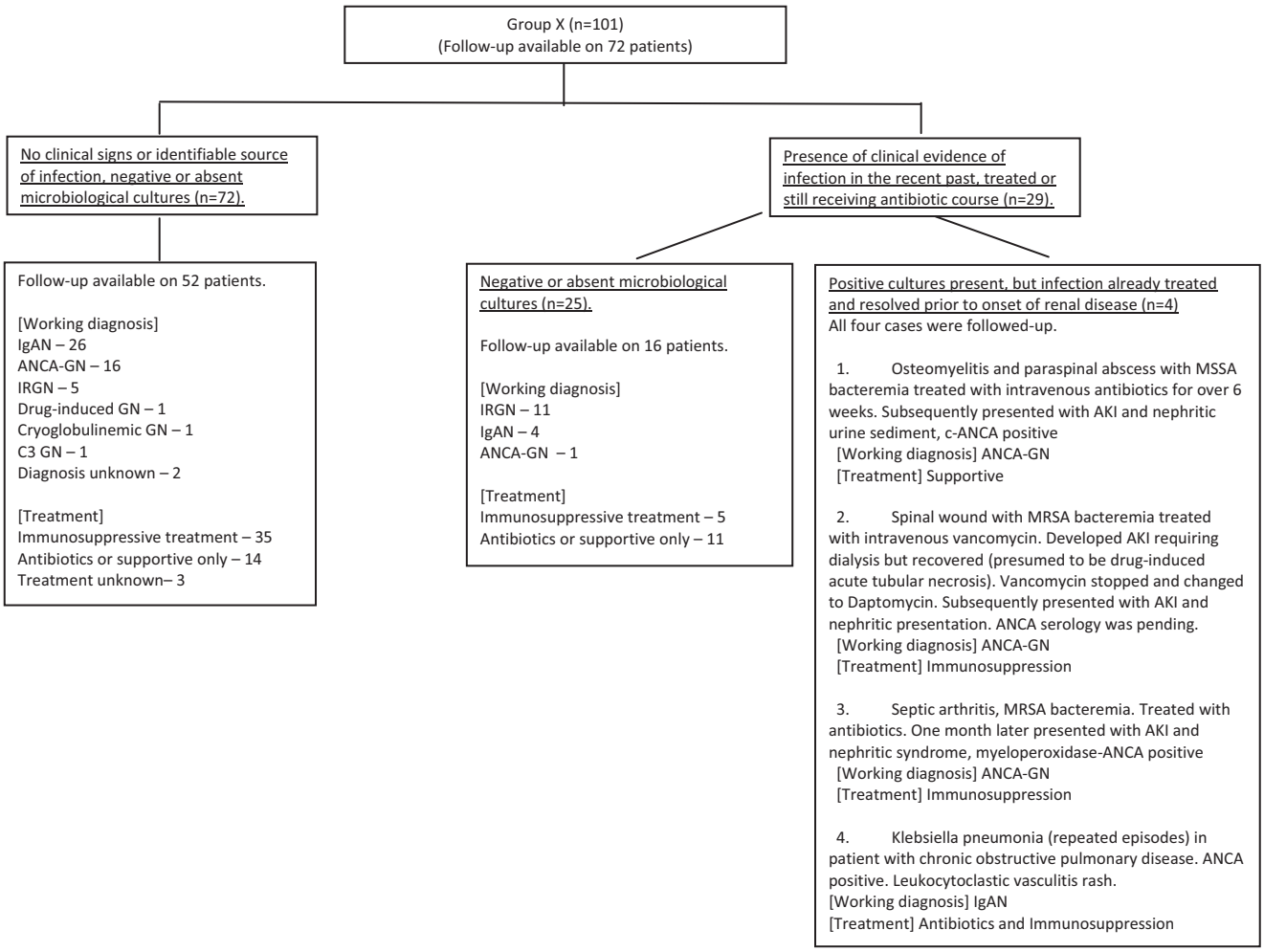

Figure 3. Flowchart showing group X classified based on history of infection ($n = 101$). Follow-up information about working diagnosis of treating physician, management approach (immunosuppression or not), and kidney function was available for 72 of 101 patients. AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; IRGN, infection-related glomerulonephritis; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

infection, despite having biopsy features resembling SAGN/IRGN (high median patient age, high serum creatinine at biopsy, nephrotic-range proteinuria, frequency of active glomerular inflammatory lesions, acute tubular necrosis, and tubular red blood cell casts). It remains unclear what these cases truly are. These were treated as IgAN by the nephrologist if ANCA serology was negative (although treatment ranged from supportive to administration of immunosuppression), and the remaining were treated as ANCA-GN. Some failed and some recovered (no statistical difference). Few were thought to be IRGN/postinfectious and treated with antibiotics and steroid, but most did not recover (Figure 3). The clinicopathologic features in these cases differ significantly from typical IgAN cases in group 1 (Supplementary Table S8). Our study thus draws attention to this high-risk subset of presumable IgAN cases (older age, crescentic with nephrotic-range proteinuria),[31–34] similar to those described by Sevillano *et al.*[35] They come to attention late in life. Majority of these cases did not have a known history of microscopic hematuria or an established diagnosis of IgAN in the past. These are most likely to be confused with SAGN/IRGN on biopsy. The overall renal outcomes with and without immunosuppression in group X were not significantly different on retrospective follow-up (Table 5), similar to the findings in the 2 recent outcomes studies on adult IRGN with and without steroid treatment.[36,37] However, definite conclusions are not possible to draw without large prospective trials, and unfortunately these are difficult to conduct because of the following reasons: comorbidities (most of these patients are older adults with comorbidities such as diabetes mellitus; as well as obesity and such patients have a high threshold for steroid and immunosuppressive therapy); varying degree of chronic renal injury on the biopsy; varying extent of glomerular crescents; patients are at different stages of treatment with antibiotics (some have completed antibiotic courses, whereas some are still receiving antibiotics); renal function (some have

stable renal function, whereas some have worsening function); and some infectious agents (such as *Bartonella*) cannot be detected in culture studies, precluding the diagnosis in the absence of timely serology. Therefore, treatment decisions have to be taken on an individual basis rather than a predesigned protocol.

The other reasons for diagnostic difficulty revolve around ANCA serology results. Five of 72 patients followed up in group X did not have ANCA results at the time of biopsy but were noted to be positive on follow-up. Biopsy sign-out cannot wait until ANCA results are available. In such cases, the decision is up to the nephrologist whether to wait for the ANCA results or start immunosuppressive treatment depending on the extent of activity seen in the biopsy, but occult infection needs to be excluded. Positive ANCA serology in active infection is a known phenomenon. Usually, it is low titer with atypical specificity (lack myeloperoxidase and PR3 specificity) and often accompanied by mixed serologies (antinuclear antibody, rheumatoid factor). This is particularly common in patients with infective endocarditis.[10,15] ANCA positivity in patients with strong IgA staining and EDDs in the absence of clinical and laboratory evidence of infection can pose a diagnostic dilemma ("crescentic IgAN with incidental ANCA positivity" vs. "ANCA-GN with IgA deposits"). In such cases, rather than struggling for the "correct diagnosis," focusing on immunosuppressive treatment is more crucial and appropriate.

Another important cause for ambiguity in biopsy diagnosis is when there is culture-proven disseminated staphylococcal infection just before the onset of ANCA-positive GN (Figure 3). The infection was reportedly treated with prolonged antibiotic courses before the onset of GN. This raises the vexing question of whether this is truly IRGN/postinfectious GN with positive ANCA serology or whether this is ANCA-GN triggered by staphylococcal antigens released during the infection due to uncontrolled neutrophilic activation, ineffective apoptosis, and neutrophil extracellular traps, as described for idiopathic ANCA-GN.[16,17] At what point can ANCA-positive infection-associated GN be safely excluded and a diagnosis of ANCA-GN be rendered can be a difficult issue.[38] One such patient (patient 1 in Figure 3) refused steroids and cyclophosphamide-based treatment regimen and soon progressed to end-stage renal disease. In contrast, another patient (patient 3) was treated with immunosuppression regimen and did recover renal function. Therefore, carefully considering the temporal relationship between onset of GN in relation to the infection and treating accordingly is very important. Another difficult situation arises in patients with repeated episodes of infection superimposed on underlying comorbidity (such as pneumonia in chronic lung disease in patient 4; Figure 3). Despite repeated courses of antibiotics, there may be persistent nephritic kidney disease. At some point, steroid treatment and even cyclophosphamide may be needed, tailored to the underlying condition of the patient.[39,40] Several other difficult diagnostic scenarios found in group X are summarized in Table 4. In cases with dual myeloperoxidase and PR3-positive serology, the possibility of drug-induced glomerulonephritis is a consideration.[41,42]

Five patients in this entire cohort of 285 patients had advanced liver cirrhosis. Such cases provide another diagnostic challenge. Microbiological cultures may be negative. The cause of GN in such cases often remains unclear. It could be multifactorial with severe disturbance in the gut-liver axis and lack of clearance of immune complex deposits from blood.[3,4,43,44] In addition, these patients tend to be critically ill and tend to have a poor prognosis irrespective of immunosuppressive treatment or antibiotic therapy alone.

This is a retrospective single-center study and has a few pitfalls. Retrieving clinical follow-up for biopsies received from outside hospitals is challenging. Treatment approaches were not uniform particularly for presumed IRGN and IgAN in Group X and varied depending on physician and patient decisions; therefore, correlation of pathologic diagnoses with outcomes was not possible with this study design. In addition, clinical outcomes are influenced by patient age, associated comorbidities, and underlying chronic renal injury. ANCA titers were not consistently available. Therefore, only ANCA-positive/negative results were used. Complement levels were missing in a sizable portion of the patients (particularly in cases with IgAN). For our multinomial regression prediction models, we did perform internal validation using 1000 bootstraps from our data set itself; however, it lacks a separate validation cohort. Patients in this study were mainly Caucasian, but geographic differences in prevalence and severity of IgAN do exist.[1,2,11]

In summary, definitive etiologic diagnosis on biopsies with crescentic GN and concomitant IgA deposits may not be possible in a subset of cases even after evaluating all the histologic features described. The most important thing is to exclude ongoing or occult infection (based on clinical signs, imaging studies, culture studies, and also serologic studies for fastidious bacteria, presence of a niche for infection such as prosthetic devices, artificial heart valves, intravenous drug use). Source of infection and positive culture results may not be identified in every case. If acute ongoing infection (or even chronic infection as in patients with diabetes) can be safely excluded and/or

has been adequately treated and biopsy shows extensive active crescents and worsening renal function, use of immunosuppressive treatment tailored to the underlying condition of the patient may be beneficial because they are at high risk for disease progression. If crescents are few and segmental and renal dysfunction is not progressing (as in "postinfectious" GN), then a brief period of observation to see if it resolves may also be reasonable. Standardized treatment protocols are difficult to design. Decision needs to be made on a case-by-case basis in these older patients with comorbidities. Treatment for IRGN and postinfectious GN in the older patients remains challenging.[36,37] Outcomes are difficult to predict. Targeted therapies against dysregulated neutrophilic activation may be an option to explore.[45]

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Confusion matrix and ROC curve of models 1 and 3 for groups 1–3

Figure S2. Confusion matrix and ROC curve of models 1–3 for all bootstrap models

Figure S3. Confusion matrix and ROC curve of models 1 and 3 for group X

Table S1. Selected candidate parameters for prediction models

Table S2. Oxford classification for IgA nephropathy (group 1)

Table S3. Details of infections in the SAGN/IRGN group (group 2)

Table S4. Coefficients of the variables for the 3 models

Table S5. Summary of area under the ROC in the 3 models

Table S6. Accuracy of the prediction models (groups 1–3)

Table S7. Follow-up summary of cases managed as "infection related glomerulonephritis" in group X

Table S8. Difference between groups 1–3 and followed up cases in group X at 1 year

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