Clinical features and outcome of infection-related glomerulonephritis with IgA deposits

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Research

Keywords: Infection, Kidney, Staphylococcus, IgA, diabetes

Posted Date: February 4th, 2020

DOI: https://doi.org/10.21203/rs.2.22607/v1

Version of Record: A version of this preprint was published at Diagnostic Pathology on May 27th, 2020. See the published version at https://doi.org/10.1186/s13000-020-00980-6.

Abstract

Background

Infection-related glomerulonephritis with IgA deposits (IRGN-IgA) is being more widely recognized but the precise epidemiology and outcome is lacking, particularly in Europe. We aimed to assess clinical, pathologic and outcome data of IRGN-IgA.

Methods

Clinical and outcome data from patients from 11 French centers over the 2007-2017 period were retrospectively collected. We reviewed pathologic patterns and immunofluorescence of renal biopsies and evaluated C4d expression in IRGN-IgA. We analyzed correlation between histological presentation and outcome using the Chi square test (qualitative data) and Kruskal-Wallis test (quantitative data).

Results

Twenty-seven patients (23 men, mean age: 62 ± 15 years) were included. Most of them had a *Staphylococcus aureus* infection (77.8%) and 44.4% were diabetic. At the time of biopsy, 95.2% had haematuria, 48.1% had a serum creatinine >4 mg/dL, and 16% had a hypocomplementemia. The most common pathologic presentation included mesangial (88.9%) and endocapillary proliferative glomerulonephritis (88.9%) with interstitial fibrosis with tubular atrophy (IF/TA) (85.1%). Diffuse and global glomerular C4d expression, found in 17.8% of the cases, was most frequently observed in biopsies with acute or subacute pattern and associated with a shorter delay between infection and renal biopsy compared to segmental and focal staining. After a median follow-up of 13.2 months, 23.1% died, 46.2% had persistent renal dysfunction and 15.4% reached end-stage renal disease. Renal outcome was correlated to IF/TA severity.

Conclusions

Infection-related glomerulonephritis with IgA deposits is usually associated with *Staphyloccus* infections and mainly affects adult men. This entity has a poor prognosis which is correlated to interstitial fibrosis and tubular atrophy severity.

Background

The epidemiology of infection-related glomerulonephritis (IRGN) has changed over the last two decades. Until recently, IRGN was mainly constituted by poststreptococcal acute post-infectious glomerulonephritis (APIGN) in children.[1,2] Recent reports indicate that poststreptococcal APIGN still exists in developing countries and in Northern Australia.[3,4] However, in other countries, IRGN due to Staphylococcus is increasingly observed in adults and in the elderly.[5–8] Post-staphylococcal glomerulonephritis (GN) can histologically appear with two patterns: one resembling acute poststreptococcal glomerulonephritis, mostly observed in patients with diabetes mellitus, neoplasia or those with chronic alcoholic

consumption, infected with Staphylococcus aureus infection; the other corresponding to a membranoproliferative glomerulonephritis pattern in Staphylococcus epidermidis infection of atrio-ventricular shunt.[8,9] A third form was reported in 1980 by Spector et al., and described in 2003 by Nasr et al. with 5 cases of type 2 diabetes patients with a Staphylococcus aureus infection, presenting with acute renal failure and histologic exudative endocapillary proliferation with predominant mesangial IgA deposits.[10,11] Since then, American or Asian teams reported cases and cohorts of infection-related glomerulonephritis with dominant IgA deposits (IRGN-IgA) or codominant with C3 deposits. However, the precise epidemiology, pathologic findings and outcome of IRGN-IgA have not been described in a large European cohort. The aim of this French nationwide study was to assess clinical, pathologic and outcome of patients with IRGN-IgA.

Methods

Inclusion criteria

Data from 27 patients with IRGN-IgA were retrospectively collected from 11 French hospitals from 2007 to 2017. The diagnostic of IRGN-IgA required following criteria: 1/ proliferative glomerulonephritis (endocapillary and/or mesangial proliferation); 2/ IgA deposits in immunofluorescence (IF); 3/ clinical diagnosis or laboratory evidence of infection preceding the renal biopsy, with a variable delay between infection and renal biopsy.

The study was approved by the Institutional Ethics Committee in Human Research (No. 2018 008).

Biopsy specimens

Since there is no consensus on indication of renal biopsy in such clinical circumstances, biopsy was performed when diagnosis was clinically unsure and when result of biopsy can modify the treatment. All renal biopsy samples were processed by standard techniques of light microscopy and immunofluorescence. They were centrally reviewed by a renal pathologist (E.M.S.) who was blinded from the clinical data. Slides obtained from fixed and paraffin-embedded samples were stained with hematoxylin eosin and saffron, periodic acid-Schiff, trichrome, and Jones or Marinozzi silver. Immunofluorescence was performed in frozen sections using fluorescein isothiocyanate-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, albumin following manufacturer's instructions. Immunohistochemistry was performed in fixed and paraffin-embedded samples using C4d antibody (clone A24T, prediluted, DB Biotech, Kosice, Slovakia) in a BenchMark XT Platform (Ventana Medical Systems, Oro Valley, Arizona, USA) following manufacturer's instructions.

Definition of histologic parameters from renal biopsies

The following parameters were scored: total glomeruli, globally sclerotic glomeruli, mesangial hypercellularity (defined as 4 or more cells per mesangial area), segmental or global endocapillary proliferation, exudative endocapillary proliferation (defined as endocapillary proliferation made of

neutrophils) with number of neutrophils per glomerulus (< or ≥ 5), membranoproliferative pattern, crescentic proliferation, fibrinoid necrosis, subepithelial (humps) or intramembranous deposits, interstitial fibrosis with tubular atrophy (IF/TA), interstitial inflammation, acute tubular injury, red blood cells casts, chronic arterial lesions. Glomerular lesions were segmental when less than 50% of the flocculus was involved, global when more than 50% of the flocculus involved. Interstitial fibrosis with tubular atrophy, interstitial inflammation (in both fibrotic and non-fibrotic cortex) and acute tubular injury were defined as absent, mild (< 25% of cortical surface area), moderate (26–50%) or severe (> 50%). Chronic arterial lesions were defined as absent, mild (vascular narrowing of up to 25% luminal area by fibrointimal thickening), moderate (26–50%), severe (> 50%). To evaluate potential prognostic involvement, intensity of these four histologic features (IF/TA, interstitial inflammation, acute tubular injury, chronic arterial lesions) was converted into a score: 0 (absent), 1 (mild), 2 (moderate) and 3 (severe).

Renal biopsies were classified into three different histologic patterns, based on Haas et al.'s description: acute (diffuse mesangial and endocapillary proliferation, with 5 or more neutrophils per glomerulus), subacute (diffuse proliferation with mesangial and at least segmental endocapillary hypercellularity but less than 5 neutrophils per glomerulus), resolving (predominantly mesangial hypercellularity). Crescents and fibrinoid necrosis could be observed in both acute and subacute pattern but not in resolving pattern.[12,13]

The intensity of IF staining was scored from 0 to 3 and localization (mesangium and/or peripheral capillary loops) of deposits was assessed. The C4d immunohistochemistry staining was graded as follows: 0 (absent), 1 (segmental and focal), 2 (global and diffuse). C4d staining was defined as segmental when less than 50% of the flocculus was involved, global when more than 50% of the flocculus was involved; focal when less than 50% of the glomeruli were stained and diffuse when more than 50% of the glomeruli were stained.

Baseline clinical and biological data

Clinical data included age, sex, previous medical history, cause of infection, type of pathogen, clinical presentation. Renal parameters included serum creatinine, proteinuria, serum albumin levels and haematuria. Severe acute renal injury was defined as a stage 3 of Kidney Disease Improving Global Outcomes (KDIGO) classification, corresponding to a serum creatinine > 4 mg/dL or need for dialysis.

Other parameters were recorded including serum IgA level, C3 and C4 levels, presence of antineutrophil cytoplasmic antibodies (ANCA) and specific treatments (including specific antibiotics, steroids and immunosuppressive drugs).

Follow-up data

Follow-up parameters were recorded from biopsy date to last visit, dialysis or death. Persistent renal dysfunction was defined as an estimated glomerular filtration rate (eGFR using CKD-Epi) of < 60 mL/min/1.73m². End-stage renal disease (ESRD) was defined as a duration of dialysis > 90 days. Delays were expressed in months or days, interquartile range (IQR).

Statistical analysis

Quantitative data are presented as mean and standard deviation or median and interquartile range. Qualitative data are presented using percentages. Comparisons were made using the Chi square test for qualitative data (or Fisher exact test) and Kruskal-Wallis test for quantitative data. Statistical analysis was performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, California, USA). A P value < 0.05 was considered as significant.

Results

Clinical and demographic features

Twenty-seven patients (23 men, 4 women) with mean age of 62 ± 15 years (range: 5–83) were included (Table 1). Forty-four percent (44.4%) of patients had type 2 diabetes, 69.2% had hypertension, 52% had cardiovascular history (including ischemic heart disease or heart failure). Forty-four percent (44%) were persistent or former smokers, 37.5% had active chronic alcohol consumption and 9.1% had liver cirrhosis. Three patients had an immunocompromised background including treated pulmonary squamous cell carcinoma for one patient, myelodysplasia for one patient, and immunosuppressive drug for Crohn disease for one patient.

Type of infection and pathogens involved

The infectious agent was identified in 88.9% of patients (Table 1).

Table 1

Demographics, predisposing factors to infection and infectious history.

Variables	n = 27
Male (n (%))	23 (85.2)
Age, year (mean ± SD)	62 ± 15
Comorbid conditions	
Diabetes mellitus (n (%))	12/27 (44.4)
Hypertension (n (%))	18/26 (69.2)
Cardiovascular disease (n (%))	13/25 (52.0)
Active or former smokers (n (%))	11/25 (44.0)
Alcoholism (n (%))	9/24 (37.5)
Liver cirrhosis (n (%))	2/22 (9.1)
Immunosuppressive drug (n (%))	1/27 (3.7)
Infectious agent	
Staphylococcus (n (%))	21 (77.8)
MRSA (n (%))	4 (14.8)
MSSA (n (%))	16 (59.3)
Staphylococcus haemolyticus (n (%))	1 (3.7)
Morganella morganii (n (%))	2 (7.4)
Streptococcus oralis (n (%))	1 (3.7)
ESBL-producing Escherichia coli (n (%))	1 (3.7)
Enterococcus faecalis (n (%))	1 (3.7)
Enterobacteraerogenes (n (%))	1 (3.7)
Chlamydia pneumoniae (n (%))	1 (3.7)
Corynebacterium amycolatum (n (%))	1 (3.7)
Dermabacter hominis (n (%))	1 (3.7)
More than one pathogen (n (%))	7 (25.9)
Unknown (n (%))	3 (11.1)

Abbreviations: ESBL: extended-spectrum beta-lactamases, MRSA: methicillin-resistant Staphylococcus aureus, MSSA: methicillin-sensitive Staphylococcus aureus, SD: standard deviation.

Variables	n = 27
Sites of infection	
Bone and joint infection (n (%))	12 (44.4)
Skin infection (n (%))	11 (40.7)
Bacteremia (n (%))	11 (40.7)
Other sites	
Prosthesis, plate osteosynthesis or implantable venous access port (n (%))	5 (18.5)
Endocarditis (n (%))	4 (14.8)
Pneumonia (n (%))	4 (14.8)
Urinary tract infection (n (%))	3 (11.1)
Abbreviations: ESBL: extended-spectrum beta-lactamases, MRSA: methicillin-resistant Staphylococcus aureus, MSSA: methicillin-sensitive Staphylococcus aureus, SD: standard deviation.	

Staphylococcus was the most frequent causative agent (77.8%) (methicillin-sensitive Staphylococcus aureus (MSSA) in 59.3% and methicillin-resistant Staphylococcus aureus (MRSA) in 14.8%). In 25.9% of the cases, two or more pathogens were identified. A variety of other pathogens were identified including Streptococcus oralis, Chlamydia pneumoniae or Escherichia coli.

Sites of infection were identified in all patients: bone and joint (44.4%) and skin (40.7%) were the most frequent sites. Other infections included prosthesis, plate osteosynthesis, or implantable venous access port infections, endocarditis, pneumonia and urinary tract infection. Bacteremia was present in 40.7% of cases.

Clinical presentation

Clinical renal presentation included nephrotic syndrome for 66.7% of patients, with acute nephritic syndrome in 55.6% and rapidly progressing glomerulonephritis in 55.6% of cases (Table 2).

Table 2

Clinical presentation and laboratory findings.

Renal parameters	
Nephrotic syndrome (n (%))	18/27 (66.7)
Acute nephritic syndrome (n (%))	15/27 (55.6)
Rapidly progressive glomerulonephritis (n (%))	15/27 (55.6)
Haematuria (n (%)) (microscopic/macroscopic)	20/21 (95.2) (11/8)
Serum creatinine, mg/dL (mean ± SD (range))	4.24 ± 2.93 (0.99–13.64)
Creatinine > 4 mg/dL (n (%))	13/27 (48.1)
eGFR, mL/min/1.73m² (mean ± SD (range))	23.7 ± 19.9 (3–82)
Albumin, g/L (mean ± SD (range))	24.7 ± 7.4 (15–42)
Proteinuria, g/day (mean ± SD)	5 ± 3.4 (0.4–16.4)
Baseline serum creatinine, mg/dL (mean ± SD (range))	1.06 ± 0.3 (0.61–1.75)
Other biological parameters	
Low C4 levels (n (%))	2/26 (7.7)
Low C3 levels (n (%))	4/25 (16.0)
Both C3 and C4 low levels (n (%))	2/25 (8.0)
High serum IgA levels (n (%))	11/13 (84.6)
ANCA (n (%))	4/15 (26.7)
Abbreviations: ANCA: antineutrophil cytoplasmic antibodies, eGFR: estimated glomerular filtration rate, SD: standard deviation.	

All patients had proteinuria (mean proteinuria: 5 ± 3.4 g/day), 95.2% had haematuria, with macroscopic haematuria in 8 cases. The serum creatinine ranged from 0.99 mg/dL to 13.63 mg/dL (mean: 4.24 ± 2.93) and estimated glomerular filtration rate (eGFR) varied from 3 to 82 mL/min/1.73m² (mean: 23.7 ± 19.9). Severe acute renal injury was present in 48.1% of patients and 33% required hemodialysis. Hypocomplementemia was detected in only 16% of patients (both low C3 and C4 levels in 8%). Serum IgA level was increased in 84.6% of the 13 patients tested. Antineutrophil cytoplasmic antibodies (ANCA) were detected in 26.7% of 15 patients.

Pathology findings

The median delay between clinically apparent onset of infection and biopsy was 42 days (IQR: 26–69). Pathology findings are summarized in Table 3.

Table 3

Light microscopy findings.

Variables	n = 27
Light microscopy	
No. of glomeruli (mean ± SD (range))	15 ± 9 (3–46)
Globally sclerotic glomeruli (mean ± SD (range))	2 ± 2 (0–8)
Mesangial hypercellularity (n (%))	24 (88.9)
Endocapillary proliferation (n (%))	24 (88.9)
Segmental (n (%)) / Global (n (%))	9 (33.3) / 15 (55.6)
Exudative endocapillary proliferation (n (%))	22 (81.4)
<5 neutrophils per glomerulus (n (%)) / ≥5 neutrophils per glomerulus (n (%))	15 (55.5) / 7 (25.9)
Membranoproliferative pattern (n (%))	9 (33.3)
Crescentic proliferation (n (%))	10 (37.0)
Cellular (n(%)) / Fibrocellular (n(%)) / Fibrous (n(%))	7 (25.9%) / 5 (18.5%) / 0
Fibrinoid necrosis (n (%))	3 (11.1)
Deposits (n (%))	16 (59.2)
Subepithelial humps (n (%)) / Intramembranous (n (%))	13 (48.1) / 3 (11.1)
Interstitial fibrosis and tubular atrophy (n (%))	23 (85.1)
Mild (n (%)) / Moderate (n (%)) / Severe (n (%))	12 (44.4) / 5 (18.5) / 6 (22.2)
Interstitial inflammation (n (%))	21 (77.8)
Mild (n (%)) / Moderate (n (%)) / Severe (n (%))	16 (59.3) / 5 (18.5) / 0
Acute tubular injury (n (%))	23 (85.1)
Mild (n (%)) / Moderate (n (%)) / Severe (n (%))	8 (29.6) / 8 (29.6) / 7 (25.9)
Red blood cells casts (n (%))	18 (66.7)
Chronic arterial lesions (n (%))	24 (88.9)
Mild (n (%)) / Moderate (n (%)) / Severe (n (%))	4 (14.8) / 16 (59.3) / 4 (14.8)

Abbreviations: SD: standard deviation.

Variables	n = 27
Histologic pattern	
Acute (n (%))	7 (25.9)
Subacute (n (%))	17 (63.0)
Resolving (n (%))	3 (11.1)
Abbreviations: SD: standard deviation.	

Endocapillary proliferation associated with mesangial proliferation was the most frequent pattern (81.5%) (Fig. 1A). Mesangial proliferation was pure in 7% of cases. Endocapillary proliferation was most frequently made of neutrophils (81.4%) (Fig. 1B). In one patient we observed only globally sclerotic glomeruli without proliferation. Membranoproliferative pattern and crescentic proliferation were also observed (33.3% and 37% respectively) (Figs. 1C and 1D). Patients with crescentic proliferation had cellular (7 out of 10) or fibro-cellular crescents (5 out of 10). All biopsies with crescent formation had endocapillary proliferation and almost all (9 out of 10) had mesangial proliferation. In almost all biopsies we observed de novo proliferation, except in one case (4%) in which proliferation was superimposed on diabetic nephropathy. We identified subepithelial humps deposits in 48.1% of biopsies and prominent deposits in glomerular capillary wall of 11.1% of biopsies, with hyaline thrombi resembling cryoglobulin in one (Figs. 1E and 1F). Interstitial fibrosis and tubular atrophy (IF/TA) were observed in 85.1% of cases (44.4% mild, 18.5% moderate, 22.2% severe). Classification according to pattern presentation revealed 25.9% of acute, 63% of subacute and 11.1% of resolving GN (Table 3).

Immunofluorescence and immunohistochemistry

Immunofluorescence features are summarized in Table 4.

Table 4
Immunofluorescence and immunohistochemistry findings.

Immunofluorescence	
IgA	27/27 (100)
+/ ++ / +++ (n (%))	8 (29.6) / 9 (33.3) / 10 (37.1)
Mesangial / Capillary loop / Both (n (%))	9 (34.6) / 5 (19.2) / 12 (46.2)
C3	27/27 (100)
+/ ++ / +++ (n, %)	5 (19.2) / 6 (23.1) / 15 (57.7)
Mesangial / Capillary loop / Both (n (%))	9 (36.0) / 2 (8.0) / 14 (56.0)
IgA and C3 codominant (n (%))	15 (55.5)
IgA dominant (n (%))	3 (11.1)
IgG staining (n (%))	4/27 (14.8)
IgM (n (%))	6/27 (22.2)
C1q (n (%))	0
Kappa (n (%))	9/24 (37.5)
Lambda (n (%))	14/24 (58.3)
C4d Immunohistochemistry	23/27 (85.2)
0/+ / ++ (n (%))	8 (34.8) / 11 (47.8) / 4 (17.4)

IgA granular deposits were observed in all biopsies with various locations: mesangium (34.6%), both mesangium and peripheral capillary loops (46.2%), capillary loops (19.2%). A “starry sky” pattern was noticed in 4 cases (15%). C3 deposits were observed in 96.3% of biopsies. Dominant IgA deposits were observed in 3 cases (11.1%) or most frequently codominant with C3 (55.5%). C1q deposits were not identified.

Immunohistochemistry with C4d antibody was performed in 23 biopsies of IRGN-IgA. Most of the biopsies had no glomerular staining (C4d 0, 34.8%) or C4d 1 + staining (47.8%). C4d 2 + glomerular staining was only noticed in 4 biopsies of IRGN-IgA (17.4%). These 4 biopsies presented acute (n = 2) or subacute (n = 2) pattern. In biopsies presenting resolving pattern, only C4d 0 (n = 1) or C4d 1+ (n = 2) staining was observed. We observed that the delay between infection and renal biopsy tended to be shorter in C4d 2 + staining biopsies (median: 24.5 days) compared to C4d 0 and C4d 1 + staining biopsies (median: 43 and 45 days respectively, P value = 0.05).

Clinical and renal characteristics according to histologic pattern

The delay between infection and renal biopsy, available for 88.9% of patients, was significantly increased according to glomerulonephritis pattern from acute GN (median: 21.5 days, IQR: 20.3–27.3) to subacute (median: 43.5 days, IQR: 32.5–72.8) and resolving GN (median: 94.5 days, IQR: 85.3-103.8) (P value = 0.03) (Fig. 2).

Comparing the three histologic patterns (acute, subacute and resolving), we observed that the percentage of skin infections tended to be more frequent in the acute than in the subacute and resolving groups (respectively 46.2% vs 14.8% and 20%, P value = 0.09) whereas bone and joint infections tended to be less frequent in the former group (7.7% vs 33.3% and 40% respectively, P value = 0.1) (data not shown).

Therapeutic management and outcome

All patients received antibiotics according to the infectious agent and antibiotic resistance pattern (Additional Table 1). The most frequent antibiotics used were penicillin (77.8%) and rifampicin (40.7%), and 88.9% of patients received two or more antibiotics. Other antibiotics included cephalosporin, aminoside, macrolide, quinolone, glycopeptides and penem. In addition to antibiotics, corticosteroids were used in 37% of patients.

Clinical follow-up was available in 26 of 27 patients (96.3%) with a median follow-up of 13.2 months (IQR: 4.0-22.2) (Additional Table 2).

At last follow-up, poor outcome was observed in 84.6% of patients: 23.1% died, 46.2% had persistent renal dysfunction, 15.4% had ESRD. One patient died because of the progression of a pulmonary carcinoma, one died of an aspiration pneumonia, another of a septic shock. For the 3 remaining patients, the etiology of death was not available. Twenty-five patients (92.5%) could be classified according to their eGFR at follow-up (Table 5): 28% had eGFR > 60 mL/min/1.73m², 56% had persistent renal disease (PRD) and 16% had end-stage renal disease (ESRD).

Table 5

Outcome and prognostic factors (25 patients).

	eGFR > 60 mL/min/1.73m² ¥	PRD ▯	ESRD †	P values
No. of patients	7	14	4	
% of patients	28	56	16	
Age, year	61	64	68	0.8
Median follow-up, months	8.3	16.5	21.6	0.3
Mean eGFR, ml/min/1.73m²				
At biopsy	28.9	20.9	17.5	0.6
Follow-up	84.6	37.5	-	< 0.001
Mean proteinuria at biopsy, g/day	3.5	5.5	6.5	0.2
Corticosteroids, % of patients	0	64	25	0.01
Median infection-renal injury delay, days (IQR)	13 (8.5–36)	23 (17.8–69)	13 (10-47.3)	0.3
Histologic pattern (acute/subacute/resolving, %)	29/57/14	29/64/7	50/25/25	0.1
Global glomerulosclerosis, % of glomeruli	13	18	44	0.2
Crescentic proliferation, % of glomeruli	4	6	5	0.9
Interstitial inflammation score, mean	0.9	0.9	1.5	0.2
Acute tubular injury score, mean	1.6	1.8	1.75	0.8
IF/TA score, mean	0.9	1.6	2.5	0.02
Chronic arterial lesion score, mean	2	1.8	2	0.6
¥One patient with eGFR > 60 died; ▯One patient with PRD died; †Two patients with ESRD died.				
Abbreviations: eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, IF/TA: interstitial fibrosis with tubular atrophy, IQR: interquartile ranges, PRD: persistent renal disease (eGFR < 60 ml/min/1.73m²)				

In univariate analyses, there was no significant correlation between renal outcome and respectively age, eGFR at biopsy, proteinuria at biopsy, or histologic pattern (acute/subacute/resolving pattern). The only association between histologic findings and renal outcome was related to IF/TA: IF/TA score was

significantly higher in PRD group (IF/TA score = 1.6) and ESRD (IF/TA score = 2.5) groups compared to eGFR > 60 mL/min (IF/TA score = 0.9) group (P value = 0.02).

Discussion

Infection-related glomerulonephritis with IgA deposits, rarely reported in Europe,[14,15] affects patients who present staphylococcal infection, hematuria, proteinuria and acute kidney injury with a proliferative glomerulonephritis at the biopsy. This presentation is comparable to that observed in American and Asian populations with some particularities in European patients. Moreover, the wide spectrum of both clinical presentation and histologic pattern can make the diagnosis challenging.[16]

Most affected patients are adult males aged 60 years. This finding is comparable to previous results reporting that 75–86% of the patients are male with a mean age of 55 to 65 years.[9,10,13,17–21] It must be noticed that the youngest of our patients is a 5-year-old boy, meaning that IRGN-IgA, even if rarely reported, can be observed in pediatric patients. In our case and in other reported pediatric cases, children with Staphylococcus-related GN have the same presentation than adults, namely proteinuria and renal function impairment.[22]

Poststaphylococcal GN can occur in various immunocompromised background and poor prognosis is mainly linked to age and comorbidities.[5,6] The initial description of Nasr et al. reported diabetic nephropathy in all biopsies. Nevertheless, the association between diabetes and IRGN-IgA is inconstant, reported in 8 to 55% of the patients in previous studies and in 44% of the patients in our study.[10,13,17–19,23–25] As noticed since the first report, Staphylococcus represents the most frequent germ (78% in our study, 60 to 100% in other studies). A higher frequency of MRSA was observed in Asian and American studies (50 to 60%) compared to our cohort (15%). This observation is consistent with the low incidence of MRSA observed in France.[26]

Regarding the histological features of IRGN-IgA, we noticed some differences as compared to Asian and American studies. Most of them, but not all, reported mesangial proliferation, crescentic proliferation or fibrinoid necrosis in the same proportion. In our study, endocapillary proliferation (89% vs 23–63% in previous series) made of neutrophils in most cases (81% vs 15 to 63% of the biopsies) was more frequent whereas pure mesangial proliferation was less frequent compared to other studies.[9,10,13,18,19,21] We also noticed differences when we compared histological patterns as classified in acute, subacute and resolving by Haas et al. in 2008.[13] The authors reported more resolving and less acute or subacute patterns compared to our cohort, with 15% of acute, 23% of subacute and 62% of resolving GN vs 26%, 63% and 11% respectively in our cohort. Since we observed that the mean time from clinical onset of infection to renal biopsy increased with histological pattern from acute to resolving GN, one explanation could be a shorter delay between infection and renal biopsy in French centers (mean of 54 days for our patients, no data for other studies). The relation between the infection-to-biopsy delay and histological pattern supports the concept that these patterns represent different evolving aspects of the same

disease. Never previously analyzed in IRGN-IgA, C4d deposits were observed in 65% of our biopsies. Diffuse and global (C4d 2+) staining was observed in biopsies with proliferative pattern (acute and subacute), and with shorter delay between infection and biopsy assessment, in favor of the activation of the complement pathway during the active phase of infection.

Regarding deposits, in addition to subepithelial “humps” deposits which are commonly described in IRGN-IgA, we also observed large subendothelial deposits with hyaline thrombi in 11% of the biopsies. These deposits are rarely encountered but were previously reported by Satoskar et al. in one biopsy.[19]

IRGN-IgA is a renal disease with poor prognosis. According to the literature data, risk of hemodialysis varies from 8 to 100% of the patients, risk of end-stage renal disease from 20 to 80% of patients, and risk of death reaches 30%.[5,11,13,19,21] In our study, 33% of the patients required hemodialysis during acute phase of GN, 15% of the patients progressed to an end-stage renal disease, and 23% died. Previous studies did not show correlation between histologic pattern and renal prognosis, even though some authors observed that patients with renal recovery had less frequent acute tubular injury, interstitial inflammation or IF/TA.[5,19] Our results confirmed the association between severity of IF/TA and renal prognosis in French patients. We did not find any correlation between other histological features or histologic patterns and renal outcome.

Regarding treatment, 10 patients (37%) in our study received corticosteroids in addition to antibiotics, without significant improvement of renal outcome. The use of corticosteroids remains controversial. For some authors,[27] steroids may have a place in the treatment of patients who fail to respond to antibiotic therapy or patients with crescentic proliferation, whereas for other authors[28] it can be deleterious in this form of GN in which infection is often ongoing.

Conclusions

Immune deposits-associated glomerulonephritis is a rare, particular form of infection-associated GN that mostly occurs in patients who are more than 60 years old, with nephrotic range proteinuria, haematuria and/or rapidly progressive glomerulonephritis. As previously reported, various patterns are observed but acute endocapillary proliferation was more frequent in our French and associated with a global and diffuse C4d staining. This entity, sometimes histologically difficult to distinguish from IgA nephropathy particularly in resolving pattern, has a poor prognosis with a high rate of end-stage renal disease.

Abbreviations

ANCA: antineutrophil cytoplasmic antibodies

APIGN: Acute post-infectious glomerulonephritis

eGFR: estimated glomerular filtration rate

ESRD: end-stage renal disease

GN: glomerulonephritis

IF: Immunofluorescence

IF/TA: Interstitial fibrosis with tubular atrophy

IQR: interquartile range

IRGN: Infection-related glomerulonephritis

IRGN-IgA: Infection-related glomerulonephritis with IgA deposits

KDIGO: Kidney Disease Improving Global Outcomes

MRSA: methicillin-resistant *Staphylococcus aureus*

MSSA: methicillin-sensitive *Staphylococcus aureus*

Declarations

Ethical approval and consent to participate

The study was approved by the Institutional Ethics Committee in Human Research (No. 2018 008).

Consent for publication

Not available.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

Funding

Authors declare no funding.

Authors' contribution

EMS, JMH provided the idea and the design of the study; EMS, CJ, MR, MCM, NR, CB, AH, AK, CG, TC, DD, JFS, CA, JR, ECL, FP, CD, DN, NS, SF, AC, DB, NRL, LD, JMG, KR, JMH acquired and provided the data; EMS,

CJ analyzed and interpreted the histological and clinical data respectively; EMS and JMH performed statistical analysis. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

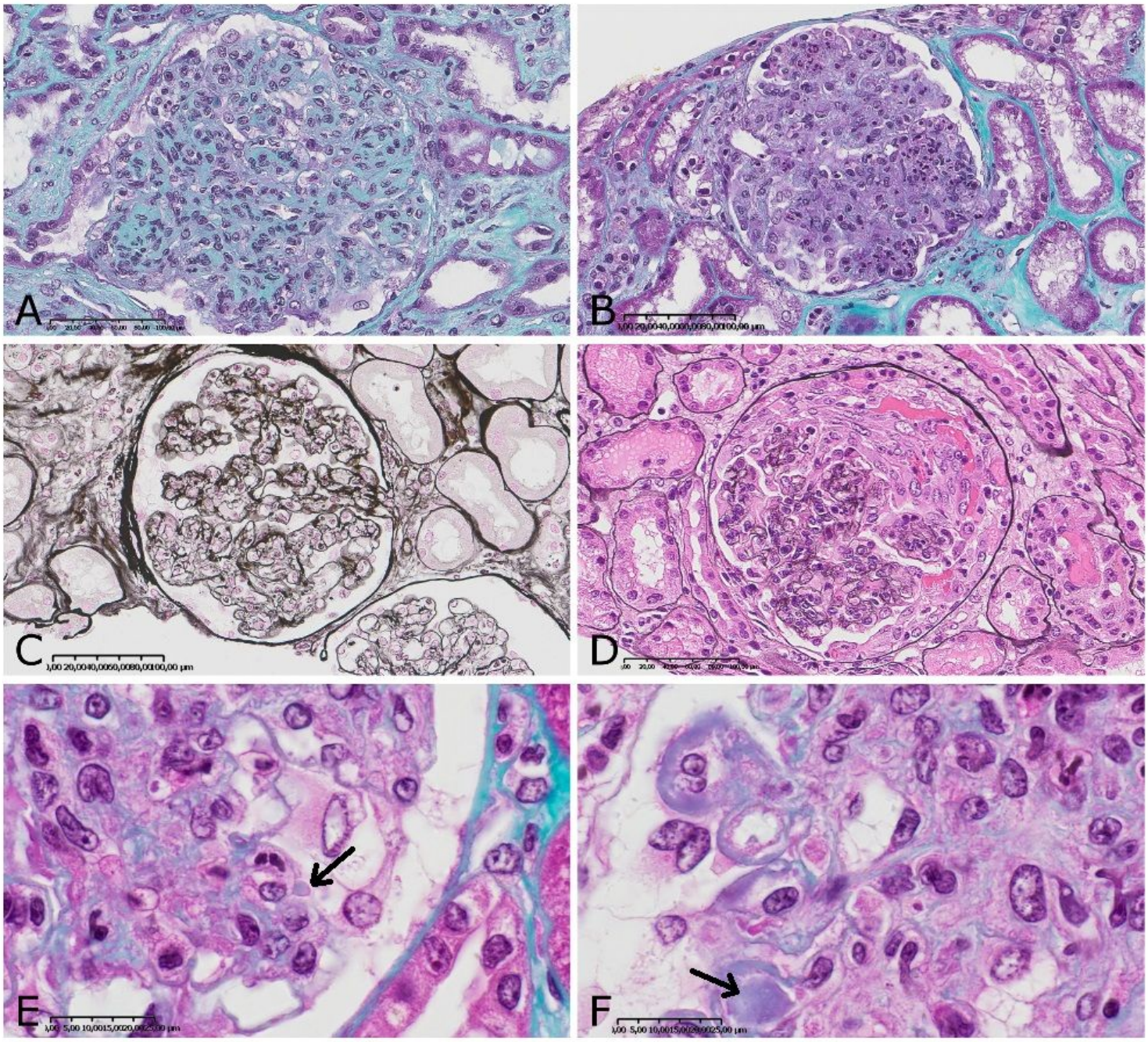

Figure 1

Light microscopy. A: mesangial with endocapillary proliferation was the most frequent pattern (Masson's trichrome stain x300); B: exudative endocapillary proliferation (Masson's trichrome stain x200); C: membranoproliferative glomerulonephritis (Jones silver stain x200); D: crescentic proliferation with fibrinoid necrosis (Jones silver stain x300); E: subepithelial humps deposit (arrow) (Masson's trichrome stain x1000); F: subendothelial deposits with hyaline thrombus resembling cryoglobulin (arrow) (Masson's trichrome stain x1000).

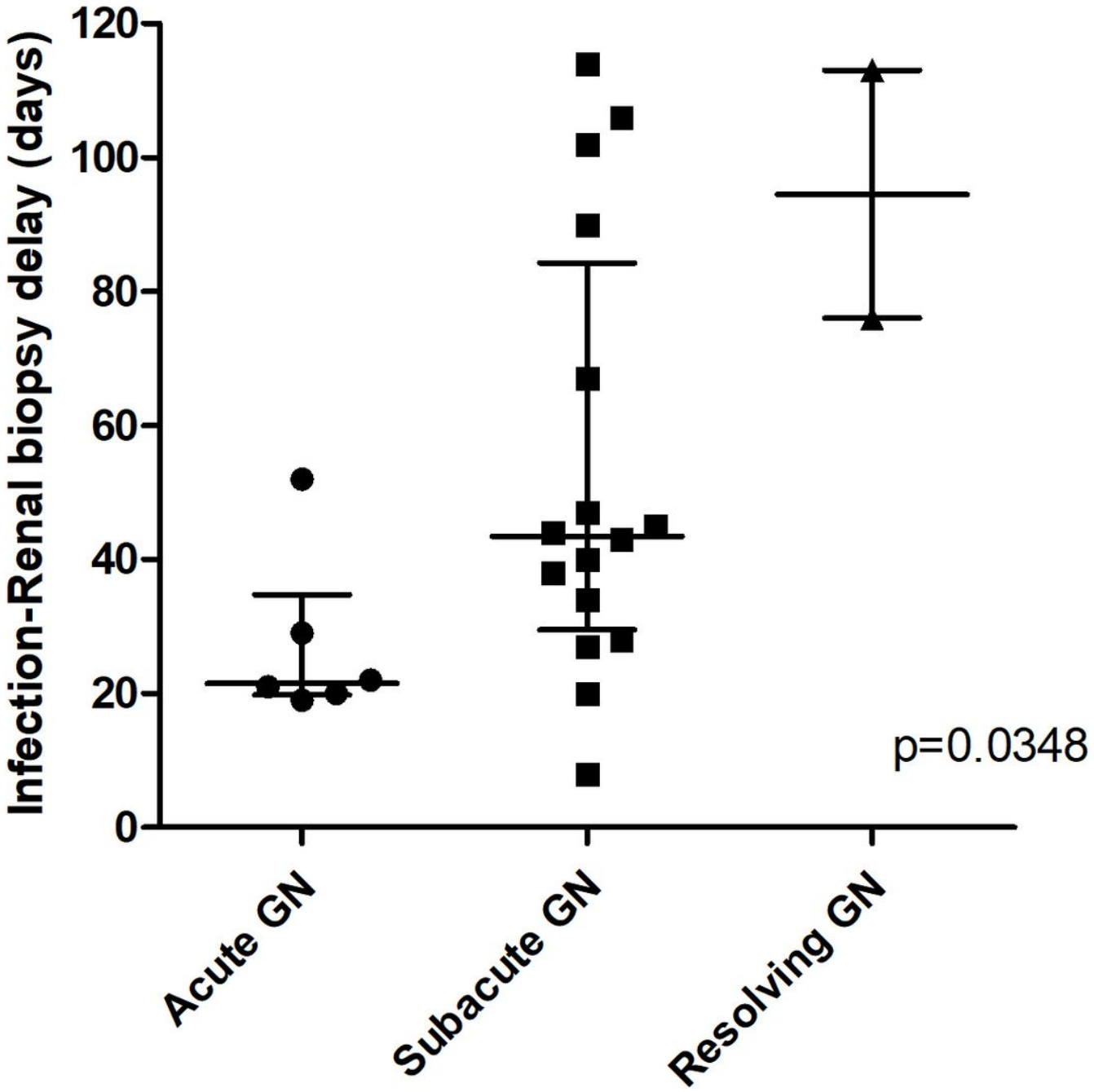

Figure 2

Glomerulonephritis pattern according to delay in days between documentation of infection and renal biopsy. Abbreviations: GN: glomerulonephritis

Supplementary Files

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- AdditionalTable2.docx
- AdditionalTable1.docx