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Predictors of renal histopathology in antineutrophil cytoplasmic antibody associated glomerulonephritis

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ABSTRACT

Objectives: Prompt, aggressive therapy is vital for anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. In this regard, we aimed to identify predictors of distinct renal histopathological classes at the time of clinical diagnosis.

Patients & methods: An inception cohort of patients with biopsy proven ANCA-associated glomerulonephritis was studied retrospectively. Demographics, clinical, laboratory, serological and radiological parameters were analyzed. Patients were classified on the basis of renal histopathology. A risk score was developed for each histopathological class using univariate and stepwise logistic regression analyses.

Results: Variables independently associated with focal class included disease duration up to diagnosis <8 weeks, absence of erythrocyte casts by urine microscopy and eGFR >49 ml/min/1.73 m^2; with crescentic class >40 erythrocytes/hpf, identification of erythrocyte casts in urine, upper respiratory tract involvement and eGFR <49 ml/min/1.73 m^2; with mixed class age >54 years, male gender, and absence of upper respiratory tract involvement. In the presence of these risk factors a predictive risk score for each histopathological classes was calculated: odds ratio, 95% confidence intervals (CI), for focal class ($\geq$2 risk factors, 20.8 (95% CI: 5.1–84.2), $p < 0.0001$, and 441.0 (95% CI: 16.8–11,590), $p = 0.0003$ for crescentic class ($\geq$3 risk factors) while the small number of patients in the mixed and sclerotic class precluded any estimates.

Conclusion: We propose a predictive algorithm of specific histolopathological classes of ANCA-associated glomerulonephritis, which might provide a crude estimation of the disease activity in the glomeruli at presentation. This tool might assist the clinician in making decisions regarding the level of intensity of inductive immunosuppressive therapy at clinical diagnosis.

1. Introduction

Kidney involvement is a common manifestation of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. Cardinal histopathological lesions include the presence of crescents and fibrinoid necrosis in conjunction with a paucity of immune deposits by immune fluorescence [1]. According to the severity and extent of glomerular lesions, ANCA-associated glomerulonephritides have been classified into focal, crescentic, mixed and sclerotic [2–10]. Crescentic glomerulonephritis is frequently associated with a rapidly declining glomerular filtration rate over days or weeks. In a minority of patients, a more indolent and progressive course over months can also occur, mainly manifested by asymptomatic

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microscopic hematuria and minimal proteinuria [1].

Kidney biopsy is the gold standard for establishing a diagnosis, assessing prognosis and planning of therapy in long term. For instance, a patient with crescentic glomerulonephritis, who typically presents with severe renal failure, as a result of rapid deterioration of renal function, might need more aggressive management, i.e. addition of plasmapheresis to the standard regimen of cyclophosphamide and corticosteroids; a patient with focal glomerulonephritis, only cyclophosphamide and corticosteroids is usually considered. Lastly, for patients with severe renal scarring, an extended therapeutic trial beyond four months, is unlikely to be beneficial for patients who remain dialysis dependent [11,12]. In clinical practice, there are circumstances in which treatment of ANCA-associated glomerulonephritis should be immediately instituted, even if histopathological findings are not available yet. The aggressive nature of the disease and the frequent occurrence of rapidly progressive glomerulonephritis demands prompt initiation of immunosuppressive treatment to prevent irreversible kidney damage [9,10].

There are not published data to date, relating clinical or laboratory features at the time of renal biopsy with specific classes of histopathological classes of ANCA-associated glomerulonephritis, according to the classification schema proposed by Berden et al. In this regard, in the current study, we aimed to identify a predictive tool of specific histopathological classes of ANCA-associated glomerulonephritis based on routine clinical and laboratory parameters [13].

2. Patients & methods

2.1. Study population-entry criteria

An inception cohort, i.e a cohort of patients identified at or near the time of diagnosis, recruited exclusively by rheumatologists, was studied retrospectively. This cohort consisted of ANCA positive patients, with biopsy proven small vessel vasculitis at any anatomic site, diagnosed between 01.06.1985 and 30.06.2014. To be included in this database, patients should have a positive ANCA test by indirect immuno fluorenscence microscopy, or antigen-specific enzyme-linked immunosorbent assay [6]. Patients might have positive cytoplasmic ANCA, anti proteinase-3 (PR3) ANCA, or both, or perinuclear ANCA, anti myeloperoxidase (MPO) ANCA, or both. Patients having only perinuclear ANCA were required to have a negative antinuclear antibody test [6]. Histological confirmation was based on a kidney, or lung, or upper respiratory tract biopsy, showing pauci-immune small vessel vasculitis, with or without granulomatous inflammation. Patients persistently ANCA negative, or with overlap of any other autoimmune disorder were excluded. All patients were followed at the outpatient Rheumatology Clinic, Department of Pathophysiology, School of Medicine, University of Athens and Rheumatology Clinic, Department of Internal Medicine, School of Medicine, University of Ioannina. All patients gave informed consent through their treating rheumatologist. Due to the retrospective nature of the study, ethical approval was not considered necessary. Medical records were reviewed dating back to the initial diagnosis.

Patients from the above cohort were eligible to be included in this study, if they had kidney involvement at clinical presentation (glomerular hematuria with or without renal impairment), with a native kidney biopsy, performed before initiation of any immunosuppressive treatment, showing pauci-immune glomerulonephritis. Patients were also required to be older than 16 years to be included in this study. A minimum of ten glomeruli was considered adequate tissue for histopathologic techniques and pathologic evaluation.

All patients underwent a complete work up for vasculitis at the time of admission in our hospital, including chest X-Rays, and/or computed tomography, and upper respiratory tract evaluation by a specialist. Of 147 eligible patients (136 from the University of Athens and 11 from the University of Ioannina), 105 had biopsy proven renal involvement. None of these patients had received any kind of immunosuppressive treatment at the time of kidney biopsy. Twenty out of the 105 patients with renal involvement were excluded, as they were younger than 16 years and had inadequate biopsy specimens (<10 glomeruli) [1,9,13] (Supplementary Fig. 1). Thus, the final study population consisted of 85 ANCA positive patients with biopsy proven glomerulonephritis.

Kidney biopsies were classified according to the report by Berden et al. for ANCA-associated glomerulonephritis [1], by a renal pathologist, (G.L) into: focal class (≥50% normal glomeruli that were not affected by the disease process), crescentic class (≥50% of glomeruli with cellular crescents), sclerotic class (≥50% of glomeruli with global sclerosis), while all remaining biopsies were by definition not characterized by any of the predominant glomerular phenotypes and were classified as mixed class [1].

Histopathological confirmation was based on a kidney, lung, or upper respiratory tract biopsy, showing pauci-immune, small vessel vasculitis. Medical records were reviewed dating back to the initial diagnosis. Disease duration up to diagnosis was defined as the time interval from onset of vasculitic symptoms to the date of kidney biopsy. Due to the retrospective nature of the study, ethical approval was not considered necessary.

Clinical phenotypes were assigned according to the second Chapel Hill vasculitides nomenclature Consensus Conference [13,15]. A diagnosis of granulomatosis with polyangiitis was based on the presence of necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium size vessels. A diagnosis of microscopic polyangiitis was undertaken in the presence of systemic necrotizing small vessel vasculitis and no evidence of granulomatous inflammation or asthma [13,14]. Patients with eosinophilic granulomatosis with polyangiitis characterized by the triad of asthma, eosinophilia, and necrotizing granulomatous inflammation were excluded from this study. Vasculitic manifestations were recorded as following: constitutional symptoms (disease-related fever, weight loss), musculoskeletal manifestations (arthralgias/arthritis, myalgias), cutaneous (purpura, subcutaneous nodules, skin ulcers), mucous, (mouth ulcers, apthous stomatitis), eye involvement (iritis, conjunctivitis, episcleritis, eye inflammatory pseudotumor, retinal vasculitis), gastrointestinal, (ischemic colitis, bloody diarrhea), neurological, (headache, stroke, mononeuritis multiplex, sensorial neuropathy, facial nerve paralysis), upper respiratory tract, (nasal crusting, rhinitis, epistaxis, acute sinusitis, chronic sinusitis, mastoiditis, soft tissue formation, subglotic stenosis, hearing loss, otitis media, granuloma identification, saddle nose deformity, invasive bone disease), pulmonary, (infiltrates, nodules, cavities, diffuse alveolar hemorrhage, respiratory failure). Fever was defined as the persistent, documented oral or axillary temperature elevation due to active vasculitis, after excluding other potential causes (i.e. infection, neoplasm). Hematuria was measured in the first-morning urine specimen in all cases. The minimum urine volume for urine microscopy measurements was 12 ml, which was quantified for erythrocytes and erythrocyte casts using both low power field (10×/lpf) and high power field (40×/hpf) after centrifugation for 5 min. Radiological parameters incorporated findings from X-rays and/or computed tomography of the upper respiratory system (mucosal thickening, total or subtotal opacification, mastoiditis, invasive bone disease, soft tissue density and retro-orbital mass) and the lungs (infiltrates, nodules, cavities, diffuse alveolar

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