Human Pathology (2016) **52**, 119–127

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

The predictive value of kidney biopsy in renal vasculitis: a multicenter cohort study☆

Francisco Diaz-Crespo MD[a,*,1], Javier Villacorta MD[b,1], Mercedes Acevedo MD[c], Teresa Cavero MD[d], Carmen Guerrero MD[e], Eugenio García Díaz PhD[c], Juan Luis Orradre MD[a], Miguel Angel Martinez PhD[f], Manuel Praga PhD[d], Gema Fernandez-Juarez PhD[b]

[a]*Department of Pathology, Hospital Virgen de la Salud, Toledo, 45004, Spain*
[b]*Department of Nephrology, Hospital Universitario Fundacion Alcorcon, 28922, Spain*
[c]*Department of Nephrology, Hospital Virgen de la Salud, Toledo, 45004, Spain*
[d]*Department of Nephrology, Hospital Universitario Doce de Octubre, Madrid, 28041, Spain*
[e]*Department of Pathology, Hospital Universitario Fundacion Alcorcon, 28922, Spain*
[f]*Department of Pathology, Hospital Universitario Doce de Octubre, Madrid, 28041, Spain*

Received 10 November 2015; revised 16 January 2016; accepted 24 January 2016

Keywords:
Kidney;
Vasculitis;
Antineutrophil cytoplasmic antibody;
Glomerulonephritis;
Crescent

Summary The histopathologic classification of antineutrophil cytoplasmic antibody–associated vasculitis has been demonstrated to have prognostic value in small cohorts of patients with pauci-immune extracapillary glomerulonephritis. We aimed to validate this histologic subgrouping system in a large cohort of patients with renal vasculitis from 3 Spanish centers. The additional value of several histologic parameters for predicting renal outcome was investigated. A total of 151 biopsies of patients with renal vasculitis were reviewed and classified as follows: 41% crescentic, 24% mixed, 21% focal, and 14% sclerotic. The cumulative proportions of renal survival at 5 years were 83.2%, 81.2%, 60.5%, and 50.7% for the focal, mixed, crescentic, and sclerotic categories, respectively ($P < .05$). In the crescentic category, patients with less than 75% of glomeruli showing crescents had better survival at 1 and 5 years compared with those having greater than or equal to 75% of crescents (77.9% and 70.6% versus 51.3% and 45.6%; $P = .02$). When adjusted by renal function and other histologic parameters, the percentage of extracapillary proliferation and glomerulosclerosis remained as significant predictors for renal survival (hazard ratio, 1.03; 95% confidence interval, 1.01-1.05; $P = .001$, and hazard ratio, 1.03; 95% confidence interval, 1.01-1.05; $P = .002$, respectively). In conclusion, patients with pauci-immune crescentic glomerulonephritis experienced different outcomes depending on the percentage of crescents observed, so that extensive extracapillary proliferation was associated with the poorest renal survival. These findings validate the prognostic utility of the histologic classification scheme in antineutrophil cytoplasmic antibody positive and negative patients and suggest a subdivision of crescentic category (<75% and ≥75% of crescents) based on the different survival rates observed among these subgroups.

☆ Disclosures: None declared.

* Corresponding author. Hospital Virgen de la Salud, Avda Barber 30, 45005 Toledo, Spain.
E-mail address: franciscod65@yahoo.com (F. Diaz-Crespo).

[1] Both authors equally contributed to the study.

http://dx.doi.org/10.1016/j.humpath.2016.01.015
0046-8177/

1. Introduction

Pauci-immune extracapillary glomerulonephritis (PEGN) is defined histologically by the presence of focal glomerular necrosis and extracapillary proliferation in the absence of significant glomerular immune deposits [1,2]. This glomerulonephritis (GN) is the histologic substrate of renal vasculitis and may occur during systemic diseases such as microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) or just as a renal-limited vasculitis (RLV) [3,4]. Most patients with kidney-limited disease have myeloperoxidase (MPO)–antineutrophil cytoplasmic antibody (ANCA) positivity (81%), and those with destructive lesions of the upper airways have proteinase 3 (PR3)–ANCA positivity (94%) [5]. PR3-ANCA positivity is predominant in northern Europe [6-8], whereas MPO-ANCA positivity is predominant in southern Europe, Japan, and China [8-10].

In recent years, several studies have shown the prognostic relevance of renal biopsy in ANCA-associated vasculitis (AAV). Histologic factors such as the percentage of normal glomeruli, the percentage of sclerosed glomeruli, and interstitial fibrosis in the initial renal biopsy have been proven to be prognostic indicators of renal outcome [11-13]. An international working group of renal pathologists proposed a classification system for ANCA-associated GN based on histologic parameters such as glomerulosclerosis, extracapillary proliferation, and the percentage of normal glomeruli [14]. This classification comprised 4 subgroups: focal, crescentic, mixed, and sclerotic, and the probability of progressing to end-stage renal disease (ESRD) increased with the ascending sequence of focal, mixed, crescentic, and sclerotic GN. This classification takes into account glomerular lesions assessed by light microscopy, but tubulointerstitial features were not found to improve the prognostic value.

Several studies have confirmed the use of the classification system as a predictor of renal outcome and progression to ESRD, but their differences highlight variation in different population groups [15,16]. Most of the studies have been performed in Asiatic and northern European populations, which imply different prevalence of MPA, GPA, and RLV as well as different ANCA-serotype distribution from those observed in a Mediterranean population [17,18]. Therefore, further studies are needed in different population groups to achieve a more accurate validation of the histologic subgrouping system. The aim of this multicenter study was to evaluate the histologic characteristics of PEGN in a large cohort of southern European patients, analyzing the clinical correlation and long-term prognostic implications of the histologic features as well as the histologic classification system.

2. Materials and methods

2.1. Patients

Adult patients diagnosed with PEGN were enrolled in this study between 1995 and 2014 from the nephrology and pathology divisions of the Hospital Fundacion Alcorcon (Alcorcon), Hospital Virgen de la Salud of Toledo (Toledo), and Hospital Doce de Octubre (Madrid). Renal biopsy was performed at the time of diagnosis. The diagnosis of PEGN was based on histologic assessment of renal biopsy tissue with hematoxylin and eosin, Masson's trichrome, periodic acid–Schiff (PAS), and methenamine silver for light microscopy and staining with antibodies against IgG, IgA, IgM, C1q, and C3 for immunofluorescence. PEGN was defined histologically by the presence of extracapillary proliferation associated with focal glomerular necrosis and/or small vessel vasculitis, in the absence of significant glomerular immune deposits. *Pauci-immune* was defined as "the intensity of glomerular c3, IgG, IgM, and IgA staining by direct immunofluorescence assay in renal sections was less than 2+ staining on a scale of 0 to 4" [2]. Patients with secondary vasculitis or with antiglomerular basement membrane antibodies were excluded. Patients with hepatitis C or B infection were also excluded.

The medical records and pathologic data were reviewed, and the following information at the time of renal biopsy as well as during follow-up was recorded: patient age, sex, presence or absence of macroscopic hematuria, hypertension (defined as systolic blood pressure 140 mm Hg and/or diastolic blood pressure 90 mm Hg or the use of antihypertensive agents), 24-hour urine protein excretion, serum creatinine level, and estimated glomerular filtration rate (eGFR) measured by CKD-EPI creatinine formula [19]. MPA, GPA, and RLV were diagnosed according to the American College of Rheumathology and Chapel-Hill Consensus Conference criteria [4,20]. For extrarenal involvement, only manifestations that were both strongly suggestive of vasculitis and included in the Birmingham Vasculitis Activity Score [21] were analyzed. The immunosuppressive treatment agents and response rates and relapses in the follow-up were also recorded. *Treatment response* was defined as the absence of systemic disease activity with improvement or stabilization of renal function in the absence of hematuria. Relapse was defined as the presence of active urine sediment and/or increase in creatinine by greater than 30% attributable to active vasculitis. Major complications during the follow-up as well as causes of death were analyzed. Serious infections were defined as those that led to death or hospitalization. Informed consent was obtained from each patient. The study was approved by the medical ethics committee at the participating centers.

2.2. Immunological data

Testing for ANCA was performed by Indirect immunofluorescence (IIF) in ethanol-fixed neutrophils, according to standardized European guidelines, at initial clinical presentation before immunosuppressive treatment was instituted and during follow-up, particularly during relapses of vasculitis. We used a commercial kit (Euroimmun, Lubeck, Germany, distributed by Bioadvance in France), and standard IIF assays were performed according to the manufacturer's instructions. Tests for anti-MPO and