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Podocyte Antigen Staining to Identify Distinct Phenotypes and Outcomes in Membranous Nephropathy: A Retrospective Multicenter Cohort Study

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Abstract

Rationale & objective: Membranous nephropathy (MN) is characterized by deposition of immune complexes along glomerular basement membranes. M-type phospholipase A_2 receptor (PLA_2R), thrombospondin type-1 domain-containing 7A (THSD7A), exostosin (EXT), and neural epidermal growth factor-like 1 protein (NELL-1) have been identified as established or potential podocyte antigens in MN. We investigated the association of podocyte antigen staining with MN clinical phenotype and outcomes.

Study design: Multicenter retrospective cohort study.

Setting & participants: 177 consecutive patients with MN unrelated to lupus erythematosus, identified from a cohort of 3875 native kidney biopsies performed in the Belgian UCLouvain Kidney Disease Network from 2000 through 2018.

Predictor: Positive immunostaining for podocyte antigens on archived kidney biopsy samples.

Outcomes: Association with different phenotypes (baseline characteristics of patients and pathologic findings on kidney biopsy), time to cancer and to kidney failure.

Analytical approach: Kaplan-Meier estimates and Cox regression analyses to assess time to cancer and kidney failure.

Results: 177 patients were followed for a median of 4.0 years (IQR, 1.3-8.0). Diagnosis of PLA2R$^+$, THSD7A$^+$, and double-negative MN was made in 117 (66.1%), 6 (3.4%), and 54 (30.5%) patients, respectively. Progression to kidney failure was similar in all groups. Although the number of patients with THSD7A$^+$ MN was small, they showed a higher incidence (50%) and an increased risk of developing cancer during follow-up (adjusted HR 5.0, 95% CI 1.4-17.9, P=0.01). Eight percent and 5% of the patients with PLA2R$^-$/THSD7A$^-$ MN stained positively for EXT and NELL-1, respectively. Most patients with EXT$^+$ MN were women, had features of systemic autoimmunity, and showed glomerular C1q deposits.

Limitations: Retrospective design; small number of patients in the THSD7A group; lack of evaluation of IgG subclasses deposition.

Conclusions: Our real-world data describe the relative prevalence of subgroups of MN, and support the hypothesis that a novel classification of MN based on podocyte antigen staining might be clinically relevant.