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Use of C4d as a diagnostic tool to classify membranoproliferative glomerulonephritis

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ABSTRACT

Background: Membranoproliferative glomerulonephritis (MPGN type I, II and III) was reclassified in 2013 as MPGN and C3 glomerulopathy (C3G) based on the complement system activation mechanism.
Objectives: To evaluate whether C4d, a component of the classical pathway, could be a diagnostic tool in differentiating between MPGN and C3G.
Methods: We conducted a retrospective study of 15 MPGN type I, II and III and 13 minimal change disease (MCD) patients diagnosed between 2000 and 2012. C4d staining using the peroxidase method was employed.
Results: Using the 2013 C3G consensus classification, the 15 MPGN types I, II and III biopsies were re-classified as MPGN (8) and C3G (7). Following C4d staining, of the 8 biopsies diagnosed as MPGN, 4 had classical pathway involvement [C1q (+), C3 (+), C4d (+)]; two had lectin pathway involvement [C1q (−), C3 (+), C4d (+)]; and, two were reclassified as C3G because the absence of C4d and C1q suggested the presence of the alternative pathway [C1q (−), C3 (+), C4d (−)]. Three of the seven C3G biopsies presented classical pathway involvement and were reclassified as MPGN. The alternative pathway was present in one of the other 4 biopsies considered to be C3G. Two C3G biopsies involved the lectin pathway and the one case of dense deposit disease had lectin pathway involvement.
Conclusions: C4d staining may help to differentiate between MPGN and C3G. In addition, the lectin pathway could play a role in the pathogenesis of these glomerulopathies.

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Uso de C4d como herramienta diagnóstica para clasificar la glomerulonefritis membranoproliferativa

Palabras clave:
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Patología

RESUMEN

Antecedentes: La glomerulonefritis membranoproliferativa (GnMP, tipo I, II y III) fue reclasificada en 2013 como GnMP y glomerulopatía C3 (GC3) en base al mecanismo que activa el sistema del complemento.

Objetivos: Evaluar si C4d, componente de la vía clásica, puede diferenciar GnMP y GC3.

Métodos: Estudio retrospectivo incluyendo 15 pacientes con GnMP (tipo I, II y III) y 13 con enfermedad de cambios mínimos (CM) diagnosticados entre 2000 y 2012. Realizamos tinción renal con C4d mediante el método de la peroxidasa.

Resultados: En base a la definición de GC3 consensuada en 2013, las 15 biopsias diagnosticadas como GnMP se reclasificaron como GnMP y GC3 en 8 y 7 casos respectivamente. Tras la tinción de C4d; de las 8 biopsias diagnosticadas como GnMP, 4 mostraron activación de la vía clásica [C1q (+), C3 (+), C4d (+)], 2 activación de la vía de las lectinas (VL) [C1q (-), C3 (+), C4d (+)]; y 2 fueron reclasificadas como GC3 dada la ausencia de C4d y C1q sugiriendo participación de la vía alternativa [C1q (-), C3 (+), C4d (-)]. Tres de 7 biopsias diagnosticadas de GC3fueron reclasificadas como GnMP debido a las presencia de activación de la vía clásica. La vía alternativa estuvo presente in 1 de las otras 4 biopsias consideradas GC3. VL estuvo activada en 2 de biopsias diagnosticadas de GC3 y en el único caso de enfermedad de depósitos densos.

Conclusiones: C4d puede ayudar a diferenciar GnMP y GC3. La VL podría jugar un papel en la patogenia de estas glomerulopatías.

Introduction

Membranoproliferative glomerulonephritis is a pattern of glomerular injury that results from several distinct etiologies of glomerular disease. Since the 1970s, the initial classification for MPGN has included MPGN type I, II (dense deposit disease or DDD), and III based on light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM).[1–5]

Membranoproliferative glomerulonephritis is characterized on LM by mesangial and endothelial hypercellularity, increased mesangial matrix, and thickening of the glomerular capillary wall, often giving it an accentuated lobular appearance. By IF, there is granular capillary wall deposition of (IgG and/or IgM) with complement C3 in MPGN type I. Immunoglobulins are usually absent in the glomeruli of DDD and MPGN type III. On EM, electron dense deposits are usually located in the subendothelial region in MPGN type I, intramembranous location in DDD, and subendothelial, intramembranous and subepithelial areas in MPGN type III. DDD is defined by its characteristic osmiophilic intramembranous deposits on EM and predominance of complement C3 on IF.

The first C3 Glomerulopathy[6] consensus introduced a classification for membranoproliferative glomerulonephritis based on the pathogenesis involving the complement cascade. MPGN associated with deposition of immunoglobulins and complement (previously called MPGN type I or III) is believed to be immune complex mediated and; therefore, activates the classical complement pathway. Cases with predominant C3 deposition with little or no immunoglobulin staining implies complement activation via the alternative pathway and are designated C3 glomerulopathy (C3G).[7–18] Using a strict approach, C3G has been defined as "dominant C3 of ≥2 orders of magnitude of intensity by IF greater than any other immune reactant".[14] C3G is subdivided into DDD and C3 glomerulonephritis (C3GN). DDD continues to be characterized by dark, osmophilic intramembranous deposits on EM and predominance of complement C3.[19] C3GN now incorporates some of those that were previously designated as MPGN types I and III.

As previously mentioned, the pathogenesis of MPGN and C3G involves the activation of the classical and alternative pathways, respectively. The complement system consists of three pathways: classical, lectin, and alternative. All three pathways end up activating C3, which then progresses to form the membrane attack complex (C5-C9) to induce localized cellular injury and inflammation.[20,21] The classical pathway is initiated by immunoglobulins and involves the early complement components of C1q, C2 and C4. The lectin pathway is initiated by mannose-binding lectin or ficolins which activate C2 and C4. No C1q is involved in the lectin pathway. The classical and lectin pathways end result is the formation of C3 convertase (C4b2b). The alternative pathway has a spontaneous activation of C3 by hydrolysis of its thioester bond that initiates the complement cascade and does not involve the early components of the cascade (C1q, C2 and C4). As the result of the cleavage of C4 in the lectin and classical pathways, C4d is formed. Since C4d has an internal thioester bond, it has the ability to form a covalent bond to cell surfaces. With C4d being tightly anchored to the tissue site, it is an ideal marker of inflammation or injury.[22]