Cytomegalovirus Antigens in IgA Nephropathy: Fact or Artefacts?

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Departments of aMorbid Anatomy, bMicrobiology and cMedicine, The Chinese University of Hong Kong, Shatin, Hong Kong

Dr. F. Mac-Moune Lai, Department of Morbid Anatomy, Prince of Wales Hospital, Room 34055, Shatin, NT, (Hong Kong)

Dear Sir,

Glomerular deposition of cytomegalovirus (CMV) antigens and a pathogenetic role of CMV in IgA nephropathy remain to be established. While Gregory et al. [1] reported positive mesangial staining using polyclonal anti-CMV antibodies (Polysciences and Lee Biomolecular) in 31 renal biopsies of patients with IgA nephropathy; Waldo et al. [2] demonstrated that the same antibodies failed to stain after absorption with uninfected fibroblasts and the antisera reacted with proteins from fibroblast by western blot analysis. Furthermore, Dueymes et al. [3] showed inconsistent immunofluorescence stainings when 3 different anti-CMV monoclonal antibodies (58/2 and 77/8, Institut Pasteur; E13, Biosoft) and polyclonal antisera were used. These observations question the heterogeneity and specificity of anti-CMV antibodies used and undermine the notion of a putative role of CMV in IgA nephropathy.

We have also attempted to detect glomerular CMV antigens in biopsy of patients with IgA nephropathy and other mesangial proliferative glomerulonephritis (table 1). Two anti-CMV monoclonal antibodies, one directed against nuclear early antigen, at 1:15 dilution (Du Pont Specialty Diagnostics, Wilmington, Del.), and the other directed against a late nuclear antigen, undiluted (Whitaker Bioproducts, Walkersville, Md.), were used for indirect immunofluorescence studies. Positive stains were observed in several tissue sections of a patient who died of disseminated CMV infection. None of the specimen from patients with IgA nephropathy and with other mesangial proliferative nephropathies demonstrated glomerular staining for CMV antigens, with either monoclonal antibody.

Interpretation of immunofluorescence studies are highly dependent on the specificity of the antibody used [4]. The conflicting findings and disparity of results observed in glomerular staining of CMV antigens clearly reflect the lack of specificity of the antibodies used. We encountered similar problems with use of antibodies against hepatitis B virus antigens [5], but were able to clarify the respective role of hepatitis core, e and surface antigens.
Renal pathology

Number tested
Anti-CMV early
Anti-CMV late
Mesani

IgA
IgG
IgM
IgA nephropathy
35
0
14
18
HSP
4
2
2
IgM nephropathy
antigens in hepatitis B virus-associated glomerulopathies by comparative and controlled studies using different antibodies [5, 6]. Perhaps a cross-reactivity of antibodies against various CMV antigenic subtypes is not critical in pathogenetic terms, but a cross-reactivity between CMV antigens and non-viral antigens (i.e. mesangium, or fibroblasts) is obviously unacceptable. The cross-reactivity between CMV antigens and mesangium revealed independently by Waldo et al. [2] and Tomino et al. [7] suggests a possible artefact when a positive mesangial staining was observed. This precludes a true mesangial CMV antigen deposition. Artefactual staining of viral antigens was reported when glomerular IgM deposits were present [8], possibly because a non-specific binding of immunoglobulin Fc-receptor. Whether cases reported by Gregory et al. [1] were subject to artefactual stain by IgM are uncertain as informations regarding IgM deposits were not mentioned; however, our observations indicate that the antibodies with whole molecule we used did not react with IgM deposits (table 1).

From the conflicting results in previous reported studies, an unequivocal identification of glomerular CMV antigens in IgA nephropathy is lacking. Furthermore, although our negative findings do not necessarily exclude a pathogenetic role of CMV in IgA nephropathy, they fail to
support the implication of CMV in IgA nephropathy or in other glomerular disease [9]. While it is critical to establish specificity and reactivity of different antibodies, it is our view that failure to identify glomerular CMV may be due to a low sensitivity rather than specificity of antibodies. In situ hybridization with viral specific DNA sequences, complemented by polymerase chain reactions (DNA amplification) may help to circumvent this problem.

References