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Renal Pathology Associated with Monoclonal Gammopathy

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Monoclonal gammopathy (MG) refers to the existence of monoclonal immunoglobulin or its fragments (light or heavy chain) in serum, also known as M protein (MIg) or paraprotein, which are produced by clonal hyperplasia of B cells or plasma cells secondary to either hematological tumors or low-grade lymphoproliferative disorders. Besides the overt hematological malignancies including multiple myeloma(MM), Waldenström macroglobulinaemia(WM) and lymphoma, quite a lot of MG derived from asymptomatic or low-grade hematological tumors or monoclonal B cell lymphocytosis, which secreted low level, but high toxic MIg leading to various end-organ damage. Kidney is one of the most common and early involved organ, and manifested with a wide spectrum of renal lesions caused by MG. The new term of monoclonal gammopathy of renal significance (MGRS) was proposed firstly by IKMG in 2012, and renewed the diagnostic criteria for MGRS-related diseases in 2018.

MGRS related renal lesions can affect each compartment of the kidney and present with various pathological patterns, which are determined by the physicochemical properties of MIg, including the molecular weight, charge, and stability of molecular conformation. During the processes of differentiation and maturation of lymphocyte, the clonal rearrangements of germline genes and somatic hypermutations by antigen stimuli lead to variations in the molecular structure of immunoglobulins secreted by lymphocytes, particularly in the variable regions of light chains and heavy chains. These variations determine their pathogenic characteristics and resulting different pathological types. Among them, light chain-related renal injury is most common, such as light chain amyloidosis, light chain deposition disease (LCDD), light chain proximal tubulopathy(LCPT), and light chain cast nephropathy. The entire immunoglobulin containing heavy and light chains usually cannot be filtered through the glomerular filtration barrier of kidneys due to its large molecule, and form deposits

within glomeruli or thrombi/crystals within capillary lumens. This leads to kidney diseases characterized by glomerulonephritis such as cryoglobulinemic glomerulonephritis(GN), proliferative GN with monoclonal immunoglobulin deposition (PGNMID), fibrillary glomerulonephritis, and immunotactoid glomerulopathy, etc. In rare conditions, there is no direct deposition of MIg in renal tissue, while MIg acted as auto-antibodies or caused the secretion of cytokines by indirect mechanisms, which leading to abnormal activation of the alternative complement pathway resulting in C3 glomerulopathy including C3 glomerulonephritis and dense deposit disease (DDD); or endothelial injury manifesting as thrombotic microangiopathy(TMA). The major pathological patterns of MGRS-related renal lesions are summarized in table 1.

The pathological diagnosis of MGRS-related lesions demands an integration on the findings of light microscopy, immunofluorescence(IF) and electron microscopy(EM), especially a complete panel of IF including Igs, complements, light chain subtypes, IgG subclasses is essential for its diagnosis. EM and immuno-EM are critical for differential diagnosis among different types. Further more, mass spectrometry combined with laser microdissection technology to identify the compositions of deposits as amyloid typing is highlighted for the diagnosis of challenging case.

Keywords: