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Pathological Diagnosis of Diabetic Nephropathy

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Diabetic nephropathy (DN) is a very common renal disease, but in clinical practice, renal biopsy is rarely performed because it can be usually diagnosed by history and typical clinical findings of patients. There are two types of diabetes, but both types of DN look identical, pathologically. Diabetes is the most common cause of chronic kidney disease in Korea, and other causes include glomerulosclerosis, hypertension, and adult-type polycystic kidney disease. In Type I diabetes, it is known that DN occurs about 15 years after onset of diabetes, but it is not well known for type 2 to date. Diagnosis of DN can be done with typical histories of diabetes, if there are no symptoms or signs of other renal diseases. The most common indication of renal biopsy in patients with diabetes is for the diagnosis of non-diabetic kidney disease (NDKD), for predicting the renal prognosis, and for the research on the pathogenesis of DN. Several papers have shown that type 2 diabetic patients need no renal biopsy, unless they have nonspecific symptoms of DN after at least 10 years of diabetic history. It is known that glucotoxicity, which is a persistent hyperglycemia in the pathogenesis of DN. DN is the most important for long-term complications. The most well-known mechanism is advanced glycation end-product (AGE). Pathologic findings of DN were first described by Kimmelstiel-Wilson in 1936 on special glomerular lesions observed in the kidneys of diabetic patients and similar changes were described in Japan at similar times. Kidneys can be slightly larger initially by hyperinfiltration and is usually larger than other nephritis at late stage. DN affects all four major structures of the kidney - glomeruli, tubules, blood vessels and interstitium. DN could be divided into early and late stages. Initially, functional GFR increases, urine albumin excretion increases, and structurally, glomeruli show hypertrophy, GBM thickening, and mesangial matrix expansion. In later stages, the mesangial matrix is further increased, resulting in typical diffuse & nodular mesangial sclerosis. Eventually, glomerulosclerosis will occur. Light microscopic findings show that the glomerular capillary wall is thickened, diffusely, but it may be difficult to be observed with a light microscope. If the damage continues persistently, glomeruli result in microaneurysm, exudative and hyalinosis lesions. As DN progresses, the number of podocytes is reduced. Those were proved clinically and experimentally. Other glomerular changes include glomeruli hypertrophy and atubular glomeruli. Tubular changes included atrophy of the tubules around the glomeruli, resulting in smaller epithelial cells and narrowed diameter of the tubular lumens. Rarely, Armani-Epstein changes showing the lipid vacuole in the cytoplasm of proximal tubules may be observed. Interstitial fibrosis and infiltration of acute and chronic inflammatory cells are observed and these interstitial changes have a big influence on the prognosis of the patient rather than the change of the glomeruli. Finally, changes in blood vessels, arteriosclerosis and arteriolosclerosis are typical histologic features of DN, and these vascular changes are associated with the degree of glomerular injury. Immunofluorescent findings are nonspecific and IgG can be stained with linear pattern along the glomerular capillary walls and similar findings can be seen on the tubular basement membrane. Electron microscopic findings show diffuse thickening of glomerular basement membrane, no abnormal electron-dense deposits and severe loss of the foot process. The tubular basement membranes are also thickened. In 2010, the DN classification system by Tervaert et al., which is very easy to apply clinically, has been introduced and widely used. This classification system has been studied by several papers and most of them have been shown to correlate with the prognosis of the patient. If classification of tubular and interstitial blood vessels as well as glomerular changes is appropriately used, it is considered as a good classification system to predict the prognosis of DN. Differential diagnosis should include several kidney diseases. First, differentiation from amyloidosis is necessary. The nodule seen in amyloidosis is a virtually acellular nodule and can be differentiated as

positive for Congo red stain. It can also be distinguished by observing a very thin 8-10 nm thick non-branching fibril on an electron microscope. Ig deposition disease is characterized by mesangial expansion, negative for Congo red and Silver stain, and it shows monoclonal light chain, especially kappa chain positivity, which is positive along GBM with linear staining pattern. Immunotactoid and fibrillary glomerulonephritis also need to be differentiated. Immunofluorescent stain is nonspecific, but electron microscopy is capable of distinguishing between them. Microtubule structure with thickness of 30nm or fibril of 12~22nm is observed in these conditions. Membranoproliferative glomerulonephritis also needs to be differentiated. It has a higher cellular density than DN and can show definite nodular accentuation pattern. Finally, idiopathic nodular glomerulosclerosis needs to be differentiated. There is no history of diabetes. It is associated with hypertension, hyperlipemia and smoking. Histologic findings are difficult to distinguish from DN. DN can be accompanied with several different kidney diseases. All primary and secondary glomerular diseases can be occurred with DN simultaneously. Therefore, a kidney biopsy must be performed to identify these superimposed kidney diseases. In summary, DN is a renal disease involving all renal compartment, glomeruli, tubule, interstitium and blood vessels. DN is a dynamic process that can be accompanied by various NDKDs. For diagnosis, predicting prognosis, research for pathogenesis of DN, a kidney biopsy must be performed.