

Program

The 7th Japanese-Chinese Renal Pathology Conference

January 13th, 2019. 8:50AM-16:00PM

Dokkyo Medical University Saitama Medical Center

8:30- Registration

8:50-9:00 Opening remarks

Japanese speaker: Michio Nagata MD, President of the Japanese Renal Pathology Society, Japan

Chinese speaker: Gang Liu MD, Institute of Nephrology, Peking University, Beijing, China

Session 1 Case conference & Mini Lecture (Chairpersons: Akira Shimizu MD & Guolan Xing MD)

9:00-9:30 Case 1

THSD7A associated membranous glomerulonephritis due to antibody produced by lymph node metastasis around the thymoma

Wei Han MD, Division of Nephrology and Hypertension, St Marianna University School of Medicine, Kawasaki, Japan

9:30-10:00 Case 2

A case of CFHR5 nephropathy caused by a novel mutation of CFHR5 gene

Shaomin Gong MD Department of Nephrology, Zhongshan Hospital, Fudan University, Shanghai Institute of Kidney and Dialysis, Shanghai Key Laboratory of Kidney and Blood Purification, Shanghai, China

10:00-10:30 Mini Lecture 1

Pathological implication of iIFTA in chronic active T cell mediated rejection; having worth or not?

Sekiko Taneda MD, Department of Pathology, Tokyo Women's Medical University, Tokyo, Japan

10:30-10:45 Coffee Break

Session 2 Case conference & Mini Lecture (Chairpersons: Gang Xu MD and Joh Kensuke MD)

10:45-11:15 Mini Lecture 2

The advances of renal amyloidosis with pathologic features and subtyping

Zhigang Zhang PhD, Department of Pathology, Shanghai Medical College, School of Basic Medical Science, Fudan University, Shanghai, China

11:15-11:45 Case 3

A case of fibrillary glomerulonephritis associated with fibrinogen

Nobuhiro Kanazawa MD, Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

11:45-12:15 Case 4

Hereditary fibrinogen A α -chain renal amyloidosis caused by the p.Lys558Argfs mutation

Min Han MD, Department of Nephrology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China

Session 3 Luncheon Seminar (Chairperson: Yoshihiko Ueda MD)

12:25-13:15

Renal tubular transporters: relation to renal drug disposition and drug-induced nephropathy

Naohiko Anzai, M.D, Department of Pharmacology, Chiba University Graduate School of Medicine, Chiba, Japan

13:15-13:45 Coffee break & business meeting

Session 4 Case conference (Chairpersons: Kazuho Honda MD and Chun Zhang MD)

13:45-14:15 Case 5

Comparison among dominant C1q positive cases including C1q nephropathy classified by immunofluorescence

Shuichiro Endo MD, Department of Nephrology, Kyoto University Hospital, Kyoto, Japan

14:15-14:45 Case 6

A case of Granulomatous Interstitial Nephritis

Ruimin Hu MD, Department of Nephrology, The First Affiliated Hospital of Zhengzhou University

Session 5 Sweets Seminar (Chairperson: Gang Liu MD)

14:45-15:20

Mesangiolysis: histopathological features and clinical implications

Ryuji Ohashi MD, Department of Diagnostic Pathology, Nippon Medical School Musashikosugi Hospital, Kanagawa, Japan

Session 6 Mini Lecture3 (Chairperson: Kentaro Matsuoka MD)

15:20-15:50

Pathology of lupus nephritis: recent debate and update

Beom Jin Lim MD, Department of Pathology, GangNam Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea

15:50-16:00 Closing remarks:

Japanese speaker: Nobuaki Yamanaka MD, Tokyo Kidney Institute, Tokyo, Japan

Chinese speaker: Chun Zhang MD, Department of Nephrology, Wuhan Union University, Wuhan, China

16:05- Photo-taking

17:30 Welcome Banquet (TOBU HOTEL LEVANT TOKYO)

Abstract

Case 1:

THSD7A associated membranous glomerulonephritis due to antibody produced by lymph node metastasis around the thymoma

Wei Han¹, Tomo Suzuki¹, Shiika Watanabe¹, Mayumi Nakata¹, Daisuke Ichikawa¹, Atsuko Ikemori^{1,2}, Junki Koike³, Yugo Shibagaki¹

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Introduction: Membranous glomerulonephritis (MGN) are known to be associated with malignant tumor and tumor resection can lead to remission of MGN. We present a first case of THSD7A-associated MGN with thymoma that was later diagnosed with lymphatic metastasis.

Case description: A 61-year-old woman with past medical history of asthma was referred to our clinic for bilateral edema in lower extremities and proteinuria. Her labs showed nephrotic syndrome and kidney biopsy was done. Although there was no proliferative nor spike lesions in glomeruli on light microscopy, IgG and THSD7A were stained strongly positive along glomerular capillary on immunofluorescence and subepithelial deposits on electron microscopy. Thus, she was diagnosed as THSD7A-associated MGN and subsequently found to have thymoma. She underwent extended thymectomy and postoperative radiation since thymoma type B3 was confirmed pathologically. However, proteinuria persisted in spite of steroid administration for asthma. Three years later, positron emission tomography (PET) revealed a tumor of right subclavian space. A biopsy was done, in which the specimen showed histology similar to that of thymoma, a diagnosis of metastatic recurrence was made. The following PET taken after the biopsy confirmed complete disappearance of the metastasis, and she underwent a radiation therapy for recurrence prevention. The proteinuria decreased to less than 1 g/gCr in a year after the biopsy, and the serum THSD7A antibody level which was 32 at diagnosis in February 2013 was decreased to 10 in September 2018. According to additional examination, anti-THSD7A antibody thymoma itself and its' metastatic lesion was negative staining. On the other hand, the lymphatic node around metastatic lesion had much more THSD7A positive cell, and similar distribution of IgG4, CD138.

Discussion: This is a first case showing the relationship between THSD7A associated MGN and thymoma using renal histology, clinical course and radiology. In addition, we suggest that MGN of this case was caused by THSD7A antibody produced not from tumor directly, but from the lymph node around the metastasis.

Case 2

A case of CFHR5 nephropathy caused by a novel mutation of CFHR5 gene

SHAOMIN GONG, ZIYAN SHEN, SHI JIN, WEILI LUO, XIAOQIANG DING, HONG LIU

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C3 nephropathy is a form of rare glomerulonephritis resulting from the dysregulation of alternative complement pathway which includes C3 glomerulonephritis, dense deposit disease(DDD) and complement factor H related protein 5(CFHR5)nephropathy. CFHR5 nephropathy which was related with mutation of complement factor H related protein were mostly reported in Cypriot ancestry. We reported a case of CRHR5 nephropathy caused by a novel mutation of CRHR5 gene in an Asian woman. The patient was a 58-years-old Asian women manifested with nephrotic proteinuria, microscopic hematuria, hypertension, declined renal function and hypocomplementemia. Renal biopsy revealed mesangial proliferative glomerulonephritis, immunofluorescence examination showed prominent C3 deposits. Electron dense deposited were observed in GBM and mesangium in electron microscope. Tumor, autoimmune disease, hepatitis were excluded after serum markers test, bone marrow biopsy and radiographic exams. In exome sequencing, a heterozygous c. 1674T>A (p.C558X) substitution in exon 10 of the complement factor H-related protein 5 (CFHR5) gene was detected, which had not been reported previously. After steroids combined with mycophenolate mofetil therapy for 8 weeks, the patients only achieved partial remission in proteinuria without significant improvements in renal function and hypocomplementemia. Then plasm exchange at every two weeks interval was employed. The patients had complete remission in proteinuria, the level of serum creatine and complements were in normal range after 6 treatments. We gradually tapered the steroids and mycophenolate mofetil to low dose, as the proteinuria remained less than 0.2g/d and serum creatine, complements were in normal range in follow-up up till now.

Mini Lecture 1

Pathological implication of iFTA in chronic active T cell mediated rejection; having worth or not?

Sekiko Taneda¹, Kazuho Honda²

¹Department of Pathology, Tokyo Women's Medical University, Tokyo, Japan

²Department of Anatomy, Showa University School of Medicine, Tokyo, Japan

The 2015 Banff criteria for chronic active T cell-mediated rejection (CATCMR) listed only chronic vascular lesion (arterial intimal fibrosis with mononuclear cell infiltration within the sclerotic intima; cv), and did not provide specific criteria regarding tubulointerstitial changes considerable for diagnosing CATCMR. The 2017 Banff conference focused on clinical implications of inflammation in areas of interstitial fibrosis and tubular atrophy (iFTA). iFTA is associated with reduced graft survival (1), and iFTA involving more than 25% of sclerotic cortex in association with tubulitis is often a sequela of acute TCMR (ATCMR) under insufficient immunosuppression (2). Based on these studies, iFTA was thought to be a feature of ongoing T cell-mediated alloimmunity, and was incorporated into the 2017 Banff Classification for diagnosing CATCMR (3).

The pathological features of ATCMR are determined by severity of tubulitis (t), inflammation of non-sclerotic cortex (i), and arteritis (v), which seems to be appropriate, because ATCMR is an acute cytotoxic T cell reaction to HLA antigens, and T cells can affect the tubules, interstitium and arteries on the donor kidney. In contrast, the pathogenesis of CATCMR is still not completely understood. It is conceivable that CATCMR occurs consequence of persistent/recurrent ATCMR. However, scoring iFTA still has potential problems, because scattered inflammatory cells are often seen in some disease processes at some points. Furthermore, unlike early transplant damage, subsequent chronic damage becomes more complex because of accumulated previous non-immune and immune injury including chronic interstitial fibrosis, vascular impairment, subclinical rejection, and injury from late rejection. In this mini-lecture, pathological characteristics and clinical features of CATCMR will be discussed, through a typical and some complex cases of CATCMR experienced in our hospital.

Early diagnosis and treatment for CATCMR are necessary to achieve more long-term allograft survival. However, multiple damages obtained in early/late post-Tx phases and non-immune factors are also considered to be major contributors to injury process of CATCMR, which leads to diagnostic difficulties. Moreover, TCMR has no objective verification method such as C4d or DSA utilized in diagnosis for ABMR. Molecular transcript analysis was recently introduced (4), but the diagnostic value of it is very limited owing to methodological difficulty. Detailed insights in the pathogenesis of CRTCMR are indispensable for appropriate diagnosis and further treatment.

References

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- (2) Nankivell B, Shingde M, Keung K, et al. The causes, significance, and consequences of inflammatory fibrosis in kidney transplantation: the Banff i-IFTA lesion. *Am J Transplant.* 2018 18(2):364-376
- (3) Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant.* 2018 18(2):293-307
- (4) Reeve J, Sellarés J, Mengel M, et al. Molecular diagnosis of T cell-mediated rejection in human kidney transplant biopsies. *Am J Transplant.* 2013 13(3):645-55.

Mini Lecture 2

The advances of renal amyloidosis with pathologic features and subtyping

Zhigang Zhang Ph.D

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Amyloidosis is a heterogeneous group of disorders associated with deposits of amyloid fibrils. Kidney is a major target organ for systemic amyloidosis. Apart from traditional diagnostic methods such as immunohistochemistry and immunofluorescence, Congo red and electronic microscopy, genetic testing as well as laser microdissection followed by mass spectrometry (LMD /MS) are used recently to confirm the diagnosis of hereditary amyloidosis. There have been some advances in the research concerning amyloid fibril formation , organ tropism of amyloid, the mechanisms of kidney injury and the pathologic features of renal amyloidosis. The amyloid nephropathy is classified as: ① Monoclonal immunoglobulin amyloid nephropathy (primary type) ; ② Serum amyloid A protein amyloid nephropathy (secondary type) ; ③ Hereditary amyloid nephropathy; ④unclassified. Here the new advances of studies on subtyping of renal amyloidosis are reviewed.

Case 3

A case of fibrillary glomerulonephritis associated with fibrinogen

Nobuhiro Kanazawa¹, Dedong Kang², Masayuki Iyoda¹, Daisuke Sanada¹, Tomohiro Saito¹, Motonori Sugiyama¹, Takashi Takaki³, Kazuho Honda², and Takanori Shibata¹

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Background: Fibrillary glomerulonephritis (FGN) is glomerular deposition disease characterized by non-amyloid fibrils in glomeruli on electron microscopy. Fibrils are approximately 18-20 nm in diameter and randomly arranged. Although a novel biomarker for FGN, DNAJB9, is reported recently, the pathogenesis of FGN is unknown.

Herein, we report a case of FGN associated with fibrinogen confirmed by laser microdissection and liquid chromatography tandem mass spectrometry (LC-MS/MS).

Case presentation: A 68-year-old Japanese woman had been treated as hypertension for 6 years but her renal function was normal. Six months prior to admission, edema occurred in her feet and anemia was pointed out. After this, her renal function progressively worsened, then she was referred to our hospital as nephrotic syndrome.

The results of laboratory test on admission were as follows: hemoglobin 8.5 g/dl; white cell count 3,200 / μ l; platelet count 90,000 / μ l; serum creatinine 1.75 mg/dl; albumin 2.5 g/dl. Urinalysis showed proteinuria (4.5 g/gCr) and microscopic hematuria (10-29 /HPF). The levels of serum free light chains were within normal limits, but electrophoresis of urine revealed lambda type Bence-Jones protein. A renal biopsy was performed.

Light microscopy showed glomerulomegaly and mesangial expansion with lobular accentuation. Microaneurysm and intracapillary fibrin formation were also seen. Immunofluorescent study revealed positive kappa and lambda light chains in the cytoplasm of the tubular epithelia, but negative in glomeruli. Congo red staining was negative. Electron microscopy showed massive fibrillary deposits in the mesangial area. The fibrils were randomly arranged, measuring approximately 15-20 nm in diameter. A large microtubular structure suggesting cryofibrinogen was not observed. To evaluate the proteomics of the glomerular fibrillary deposition, we performed a laser microdissection of the glomeruli and LC-MS/MS, using formalin-fixed paraffin-embedded biopsy specimens.

The LC-MS/MS analysis revealed fibrinogen as a component of glomerular deposits, but none of light chains, amyloid-associated proteins (ApoE, ApoA4 and SAP) or DNAJB9, a novel FGN biomarker, was detected. Thus, we speculate that fibrinogen could deposit and form fibrillary structure in the glomeruli of this case.

Conclusion: We report a case of FGN associated with fibrinogen. LC-MS/MS was useful for the detection of precursor fibril protein of FGN.

Case 4

Hereditary fibrinogen A α -chain renal amyloidosis caused by the p.Lys558Argfs mutation

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Mutation of fibrinogen A α -chain (FGA) genes is the most common cause of hereditary renal amyloidosis. Here, we reported a case of renal amyloidosis with a new heterozygous mutation on FGA gene. 31-year-old Chinese woman presented with nephrotic syndrome, normal renal function and familial renal disease history, without cardiac involvement or neuropathy. In renal biopsy sample, Congo red positive amorphous, eosinophilic material was found in glomeruli, barely in interstitium and vascular walls under light microscopy. Electron microscopy showed the presence of disorderly arrangement, branchless amyloid fibrils in the glomeruli. The positive staining was detected in glomeruli by using immunohistochemistry with anti-human fibrinogen antibody. Then the diagnosis was confirmed by gene sequence analysis of the AFib gene, which demonstrated a new heterozygous mutation of FGA-p.Lys558Argfs.

Luncheon Seminar

Renal tubular transporters: relation to renal drug disposition and drug-induced nephropathy

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Kidney plays important roles for 1) excretion of waste products such as creatinine, uric acid, drugs, etc., 2) controlling water, electrolytes, and acid-base balance as well as blood pressure, 3) endocrine function such as EPO production, etc., and 4) metabolic function for sugar, ammonia, drug metabolism, to maintain homeostasis of the living body. In patients with chronic kidney disease (CKD) who are suffering renal disorder chronically demonstrated the reduction of the above function, so it is necessary to take care about drug administration on such patients because kidney is important excretion route in pharmacokinetics. That is, due to the reduction of excretion as well as metabolic function, the excretion of renal excretory drugs delayed, the increase drug concentration in blood enhances the risk of side effect.

Drug excretion in the kidney involves glomerular filtration, tubular secretion and reabsorption, but in terms of "substance transport" including drugs, transepithelial transport in renal tubules is important for drugs excretion. In such process, membrane transport protein named "transporters" contribute to the membrane permeation of drugs across tubular epithelial cells

Recently, transporters, which are attracting attention as molecular targets of drugs, are also known as contributing factors of pharmacokinetics (absorption, distribution, metabolism, excretion), and are also related to inter-individual differences in drug efficacy and its side effects. In this lecture, I'd like to talk about concerning notice on medication to CKD patients from the viewpoint of drug excretion mechanism, such as drug-induced nephropathy involving transporter and inter-individual differences between gene polymorphisms (SNPs) and in vivo drug reaction.

Case 5

Comparison among dominant C1q positive cases including C1q nephropathy classified by immunofluorescence

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Background: Although the disease entity of C1q nephropathy was first described by Jennette and Hippius in 1985, the characteristics of the heterogeneous phenotypes and the pathogenic role of C1q for the disease progression has not been elucidated yet. We analyzed dominant C1q positive renal biopsy specimens to speculate the significance of C1q localization.

Methods: A total of 1763 consecutive patients performed renal biopsy at Kyoto University Hospital from 1982 through 2001 were investigated. We analyzed 34 cases (1.9%) with dominantly C1q-positive staining excluding lupus nephritis, IgA nephropathy, and membranous nephropathy. Next, we classified these patients into three groups; C1q mono-dominant (mono C1q) group (n=3) with no immunoglobulin deposition and C1q co-dominant group (total n=31) with IgG (co C1q-IgG) (n=19) or IgM (co C1q-IgM) (n=12).

Results: Precise pathological analysis showed in mono C1q group, minor glomerular abnormality in light microscopy (LM), with mesangium localization of C1q with C3d positivity in immunofluorescence microscopy (IF). Apparent electron dense deposit (EDD) and foot process effacement were observed in electron microscopy (EM). Co C1q-IgG group revealed variety of glomerulonephritis pattern frequently showing capillary wall involved glomerular lesion such as double contour, subendothelial deposit and crescent formation with high frequency of global sclerosis. C1q localized in capillary wall and mesangium accompanying IgG, and IgM in all cases and additional IgA in 15 cases with strongly positive C3c and C3d in IF. Co C1q-IgM group exhibited focal segmental sclerosis and double contour in LM. C1q was positive in mesangium colocalized with IgM and C3d in all but C3c in some in IF. EDD was negative in all 6 cases in EM. Laboratory data revealed co C1q-IgG group included relatively severe cases in creatinine level and hematuria compared with the other two groups.

Conclusions: The hypothesis of glomerular injury through activation of complement system might be applicable via immune complex formation in co C1q-IgG group, directly in mono C1q group and not applicable in co C1q-IgM group. The analysis of dominant C1q-positive renal biopsy specimens include several diseases in these case series raises the possibility that current category of C1q nephropathy indicates some specific condition of existing diseases.

Case 6

A case of Granulomatous Interstitial Nephritis

Ruimin Hu, Guolan Xing, Songxia Quan, Yingzi Wang

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Granulomatous interstitial nephritis is a rare histological diagnosis found in 0.5~0.95% of native renal biopsies, underlying aetiologies include drug reaction, infections (particularly mycobacterial), sarcoidosis and granulomatosis with polyangiitis. However, the cause cannot be established frequently, and the differentiating between these aetiologies by histological features is very difficult. Here we report a case of 67-years-old woman manifested with renal insufficiency, moderate anemia, mild proteinuria, microscopic hematuria. Laboratory examination: Blood routine examination: WBC $9.36 \times 10^9/L$, RBC $2.48 \times 10^{12}/L$, Hb 60.4g/L, PLT $423 \times 10^9/L$; Urine routine : protein(\pm), RBC 9/ul(0-7), glucose(-) ; 24-hour total urine protein: 0.46g; Inflammatory index: ESR 108.00mm/h, CRP 126.40mg/L; Complement : C3 1.26g/L, C4 0.18g/L, C1q 18.50mg/dL; Autoantibody: ANA (\pm), dsDNA, ENA, ANCA (twice), GBM all (-), atypical ANCA(\pm), anti-PLA2R (-); Tuberculosis T-spot: (-); Thyroid function test : TSH 1.49uIU/mL, FT3 0.45pml/L(1.34-2.73), FT4 16.65 poml/L; Blood sugar, glycosylated hemoglobin, blood lipids, coagulation function results are in normal range; infectious diseases (HBV, HCV, syphilis, HIV) :(-); M proteinemia screening: Blood immunoglobulin: IgA 2.80g/L, IgG 20.57g/L(8-16), IgM 0.91g/L; IgG subtype analysis : IgG1 13.1g/L(4.05-10.01), IgG2, IgG3 and IgG4 are in normal range; Blood free light chain:free Kappa light chain 159.00 mg/L (3.3-19.4), free Lambda light chain 111.00 mg/L (5.71-26.3), free κ/λ 1.43 (0.26-1.65); Urine Bence-Jones protein: (-); Imaging examination: US of kidney: both kidneys are in normal shape; renal artery resistance index is increased; CT: uneven density of both kidneys; pelvic fluid; left hepatic cyst; retroperitoneal small lymph node; inflammation in both lungs; bronchiectasis in the left lower lobe. Head MRI : bilateral lacunar infarction; senile brain atrophy. Renal biopsy revealed granulomatous interstitial nephritis, immunofluorescence examination showed negative, and no electron dense deposited were observed in electron microscope.

Sweets Seminar

Mesangiolytic: histopathological features and clinical implications

Ryuji Ohashi MD, PhD,

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Mesangiolytic is a form of histopathological changes characterized by histolysis of glomerular mesangial cells and surrounding extra-cellular matrix component in various conditions. Although the term “mesangiolytic” is commonly used to describe a process of glomerular injury, its morphological features and mechanical aspects are not well understood. Mesangiolytic occurs through direct and indirect etiologies. The direct mesangiolytic is induced by inflammatory stimuli produced during severe systemic bacterial infection or the acute phase of primary glomerular diseases including immune-complex mediated glomerulonephritis. Morphological analysis of animal experiments using anti-Thy1 nephritis and Habu venom nephritis models facilitates tracking of the initiation, progression, and resolution of mesangiolytic. In clinical settings, mesangiolytic is more likely to occur secondarily following glomerular endothelial injury represented by thrombotic microangiopathy associated with hemolytic uremic syndrome, bone marrow transplantation, irradiation, and drug toxicity, as a cause of renal dysfunction. In renal histology of POEMS syndrome, a rare multisystem disorder, mesangiolytic is one of the most characteristic features representing glomerular lesions, leading to renal failure. In diabetic nephropathy, subendothelial edema of the glomerulus extends to mesangial region, developing as widespread dissolution of mesangial matrix and formation of nodular sclerotic lesion over time. Similar phenomenon is reported in monoclonal immunoglobulin deposition disease. Whatever the circumstance, mesangiolytic often causes aneurysmal dilatation of glomerular capillary regarded as “ballooning”, resulting in an irreversible sclerotic lesion when the initial insult is substantial. In this lecture, the histopathological features of mesangiolytic will be overviewed in a variety of experimental and clinical situations, and its clinical implications are also discussed with reference to recent literature.