The Sixth Japanese Chinese Renal Pathology Conference 2017

Sep. 23, 2017，13:30 – 17:40

Venue: Grand Barony Hotel, Xi'an

Opening address			
13:30-13:40	**Prof. Aiping Yin,** Vice-president of nephropathy hospital of First hospital, Xi'an Jiaotong university **Prof. Michio Nagata,** President of the Japanese Renal Pathology Society, University of Tsukuba, Faculty of Medicine, Ibaraki, Japan		
Mini lecture 1			
13:40-14:00	Evolving concept of membranous nephropathy: stepping out of old school onto new roads	Dr. Ryuji Ohashi Department of Diagnostic Pathology, Nippon Medical School Hospital, Tokyo, Japan	Dr. Kazuho Honda, Department of Anatomy, Showa University School of Medicine, Tokyo, Japan. Dr. Gang Liu, Renal Division, Peking University First Hospital.
14:00-14:10	Summary and discussion	Ping Lan	
Case Session I			
14:10-14:25	Japanese case 1 An autopsy case of HLH-related renal involvement.	Dr. Yayoi Ogawa Hokkaido Renal Pathology Center, Sapporo, Japan.	Dr. Eri Muso, Department of Nephrology and dialysis, Kitano Hospital, Osaka, Japan Dr. Zhigang Zhang，Department of Pathology, Shanghai Medical College, Fudan University.
14:25-14:35	Summary and discussion	Yu Liang	
14:35-14:50	Chinese case 1 An old woman with proteinuria and AKD	Dr. Huijuan Wu Department of Pathology, Shanghai Medical College, Fudan University	
14:50-14:55	Discussion 5 min		
Case Session II			
14:55-15:10	Japanese case 2 Individual Ballooning Foam Cells of Distal Tubules in Female Fabry Disease	Dr. Sae Aratani Division of Nephrology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan.	Dr. Mitsuru Yanai, Department of Pathology, KKR Sapporo Medical Center, Sapporo, Japan. Dr. Yuansheng Xie Department of Nephrology, PLA General Hospital.
15:10-15:20	Summary and discussion	Jia Lv	
15:20-15:35	Chinese case 2 A 14 y boy with mild proteinuria and family history of ESRD	Dr. Zhangxue Hu West China Hospital, Sichuan University	
15:35-15:40	Discussion 5 min		

15:40–16:00	**Coffee Break**		
Mini lecture 2			
16:00–16:20	Advances on pathology of ANCA associated vasculitis (AAV)	Dr. Suxia Wang Laboratory of Electron Microscopy, Pathological Center, Peking University First Hospital	Dr. Kensuke Joh, Department of Pathology, Tohoku University School of Medicine, Sendai, Japan Dr. Wanhong Lu, Nephropathy hospital of First Hospital, Xi'an Jiaotong University
16:20–16:30	Discussion 5 min		
Case Session III			
16:30–16:45	Japanese case 3 Renal pathology of a premature case of POEMS syndrome preceded by renal and neurological dysfunction with diabetes mellitus.	Dr. Hiroko Kakita Department of Nephrology and dialysis, Kitano Hospital, Osaka, Japan.	Dr. Akira Shimizu, Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan Dr. Guming Zou, Renal Division, China-Japan Friendship Hospital
16:45–16:55	Summary and discussion	Xinfang Xie	
16:55–17:10	Chinese case 3 A middle-aged woman with proteinuria and paraproteinemia	Dr. Xiaoxia Pan Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University	
17:10–17:15	Discussion 5 min		
Closing address			
17:15–17:30	Japanese speaker: Dr. Nobuaki Yamanaka, Tokyo Kidney Research Institute, Tokyo, Japan. Chinese speaker: Dr. Wanzhong Zou, Department of Pathology, Peking University First Hospital, Beijing, China.		
17:30–17:40	**Picture time**		

Abstracts:

13:40-14:00 Mini lecture 1

Evolving concept of membranous nephropathy: stepping out of old school onto new roads

Ryuji Ohashi, Department of Diagnostic Pathology, Nippon Medical School Hospital, Tokyo, Japan

Membranous nephropathy (MN) is one of the most common glomerular diseases causing nephrotic syndrome usually affecting adult patients. MN is characterized by deposition of IgG in subepithelial regions and unique alterations of basement membranes (GBM) of glomeruli. MN is categorized as primary MN (pMN) and secondary MN (sMN). The majority of pMN cases are caused by binding of IgG to M-type phospholipase A2 receptor whereas in some cases thrombospondin type 1 domain containing 7A plays a role as a target antigen, shown by recent studies. sMN occurs in association with infection, malignant tumors, autoimmune diseases, and drugs. Immunostaining using paraffin sections and/or frozen sections is mandatory to render a diagnosis of MN, and particularly, identification of IgG heavy subclass is helpful in differentiating iMN from sMN. In pMN, IgG4 is predominantly positive along GBM while IgG1 is positive in many of sMN associated with malignancy and hepatitis viral infection. MN can occur as a phenotypic form of proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID), which is characterized by deposition of monoclonal IgG light chain. In MN of PGNMID, IgG3κ type is the most common, followed by IgG1κ and occasionally by IgG2κ.Owing to aforementioned discoveries, the entity of MN, which was once regarded as a single disease, is evolving into a new group of disease with diverse etiologies. Clinicians and pathologists need to be aware of this new concept and update their knowledge to provide patients with appropriate treatment. In this lecture, I will review recent advances of MN with a particular emphasis on immunological aspects from a standpoint of a pathologist.

Case Session I

14:10-14:25 Japanese case 1

An autopsy case of HLH-related renal involvement

Yayoi Ogawa[1)], Sari Iwasaki[2)], Akira Shimizu[3)], Shou Katoh[4)], Yukayo Terashita[4)], Masanori Nakanishi[4)], Masatoshi Tateno[5)]

[1)] Hokkaido Renal Pathology Center, [2)] Department of Pathology, Sapporo City General Hospital, [3)]Department of Analytic Human Pathology, Nippon Medical School, [4)] Department of Pediatrics, and [5)]Department of Pathology, Kushiro Red Cross Hospital.

[Introduction]

Hemophagocytic lymphohitiocytosis (HLH) is characterized by an uncontrolled hyperinflammatory response leading to cytokine release. Although glomerular involvement of HLH is uncommon, a few cases with thrombotic microangiopathy, collapsing glomerulopathy, or intraglomerular hemophagocytosis have been reported. Here we represent the renal histopathology of an autopsied HLH case with the glomerular change.

[Case]

A 2-year-old Japanese girl was attending the hospital for the growth and developmental retardation. She had presented to pediatrics with a high fever and persistent cough 2 days before. Laboratory investigation at admission revealed a positive result on the rapid strept test. After the admission, antibiotics was started for pharyngitis, but serum AST, ALT, LDH, and ferritin began to rise day by day and bone marrow findings showed hemophagocytosis on the 3rd hospital day. Then the patient was started on prednisolone 2mg/kg/day on the diagnosis of HLH. However, her respiratory condition deteriorated rapidly and she died on the 35rd hospital day and the autopsy was performed.

[Autopsy]

Pulmonary volume was elevated and the air space was reduced. Microscopic appearance showed interstitial pneumonia. There was no evidence of cytomegalovirus infection disease or EB viral related lesions. Mediastinal and hilar lymph nodes showed histiocytic infiltration and the erythrophagocytosis in the sinuses. These findings confirm HLH and suggest respiratory failure as the main cause of death.

Renal histology showed glomerular mesangiolysis and focal double contours, and intra-glomerular histiocytes. Several erythrophagocytes were detected. Electron microscopy (EM) showed dilated subendothelial space, which suggested endothelial injury. There was no electron dense deposition.

[Discussion]

In HLH, the cytokine storm has been reported to relate to TMA. According to the serum analysis after autopsy, her serum IL-6 was 24.7pg/ml (ref. <4.0) on the 3rd hospital day and then it had reached to 145pg/ml by the 34th hospital day.

We represent here a case of HLH mainly with the renal histology.

14:35-14:50 Chinese case 1

An old woman with proteinuria and AKD

Liu Xueguang, Cai Xiaofan, Wu Huijuan, Zhang Zhigang
Department of Pathology, Shanghai Medical College, Fudan University.

[Clinical manifestation]

Patient, Female, 60y

Chief Complain: foamy urine for 8month, with SCr elevated for 1 month.

Physical Examination: non-sepecific

[Lab tests]

SCr88.2 μmol/L, BUN 7.06 mmol/L, cystain C 1.21 mg/L ,
Uric acid 119 μmol/L , Ferritin 204.9 ng/mL,
WBC 3.71×109/L, Neutrophil 1.68×109/L , RBC 3.63×1012/L, Hb109g/L ,
Hematocrit 33.3%, Alb 41.9 g/L, A/G 1.2, Glu5.17 mmol/L, TC 5.44 mmol/L,
HDL 1.02 mmol/L, LDL 3.79 mmol/L, VLDL 0.63 mmol/L, ApoE 51.5 mg/L,
albumin 53.8% , α1 3.0%, α2 6.2%, β1 6.8, β2 22.9%↑(abnormal bands),
γ7.3% , Serum κ 7.3 mg/L, λ 1.0 mg/L, κ:λ= 7.3 :1
Serum IgA 19.7 g/L↑, other Ig & completments in normal range
HBsAg (-), HBsAb (+), HBCAb (+), HBeAb (+), HCV Ab (-),
Tumor markers (-), ANA series (-), ANCA series (-), Anti-GBM (-),
Urinalysis：Protein (2+), RBC (23 /HP), WBC (33/HP),
Urine protein: 969 mg/24h, mAlb/Ucr90.3 mg/g,

Urine ferritin 2.31 mg/L, Ig 9.2 mg/L ,
Urine κ 177 mg/L, urine λ 3.97 mg/L , urine κ/λ 44.58 ,
urine α1 73.95 mg/24h, urine IgG 23.46 mg/24h,
urine ferritin 5.89 mg/24h, urine β2 37230 μg/24h
Renal biopsy was performed.

Case Session II
14:55-15:10 Japanese case 2
Individual Ballooning Foam Cells of Distal Tubulars in Female Fabry Disease

Sae Aratani[1)2)], Dedong Kang[2)], Akira Shimizu[2)]
[1)] Division of Nephrology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan
[2)] Department of Analytic Human Pathology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

[Introduction]

Fabry disease is a progressive, X-linked inherited disorder of glycoshingolipid metabolism due to deficient or absent lysosomal α-galactosidase A (alpha-Gal A) activity. Detecting female Fabry disease from clinical symptoms is challenging, and diagnostic delays is still considerable. Here, we present a female patient with Fabry disease confirmed by renal biopsy, in which characteristic findings in distal tubules had provided morphologically diagnostic information of Fabry disease.

[Case]

A 69-year-old Japanese female was introduced to the nephrologist for the evaluation of proteinuria. Proteinuria had been evident for 2 years without hematuria. Past medical history included hypertrophic cardiomyopathy for more than 30 years. Family history revealed the patient's mother had died of cardiac disease. On admission, the physical examination was unremarkable. Laboratory data showed serum Cr level of 0.7 mg/dL. Auto immune antibodies were negative. Urinalysis revealed proteinuria of 1.0 g/gCr without hematuria. Renal biopsy was performed to investigate the cause of proteinuria.

[Pathological findings]

The biopsy specimen contained 22 glomeruli for light microscopic evaluation, 1 of which was globally sclerosed. One glomerulus revealed focal segmental sclerosis. The other glomeruli showed mild hypertrophy. Vacuolization of podocytes was not observed apparently. On the contrary, vacuolization of distal tubular epithelial cells was evident. In arteries, mild to moderate arterio- arteriolosclerosis was noted. Firstly, we diagnosed hypertensive nephropathy. However, myeline-like structure (zebra body) was detected in some podocytes by electron microscopy. We re-examined the toluidine blue-stained semi-thin sections of electron microscopy, and could detect dark blue osmiophilic cells in some epithelial cells in podocytes, Bowman's capsular epithelial cells, and in distal tubular epithelial cells. In addition, immunofluorescence staining for Gb3 (GL-3) was also detected in these epithelial cells. Pathological findings were most consistent with Fabry disease.

[Summary]

We presented a female patient with Fabry disease revealed by pathological findings of kidneys, in which individual ballooning foam cells of distal tubular epithelial cells were useful morphological finding to consider the presence of Fabry disease. The accumulation of Gb3 is responsible for these

pathological findings.

15:20-15:35 Chinese case 2

A 14 y boy with mild proteinuria and family history of ESRD

Zhangxue Hu, West China Hospital, Sichuan University

[Clinical manifestation]

A 14-year-old male was admitted to our hospital in April 2017. Four years prior to this admission, routine physical exams showed proteinuria 1+. No edema of the lower extremities, hematuria and fever were noticed. Two years before, he came to hospital because of proteinuria 2+. Renal biopsy showed minimal changes of glomeruli. Oral prednisone 45mg per day was initiated for 2 months, then tapered. The patient did not improve with this regimen.

[Family history]

On admission, the patient confessed that his sister died of uremia 4 years before. Her renal biopsy showed chronic sclerosing glomerulonephritis.

[PE]

This patient's blood pressure was 106/72 mmHg. Physical exams did not show any abnormality. Hearing loss and ocular defects were not detected.

[Labs]

Laboratory data showed a serum creatinine 0.68 mg/dL, serum albumin 4.48 g/dL, eGFR 138.86ml/min/1.73 m^2, urinary protein/creatinine ratio 1.54 g/g; urinary sediments were normal. Serum lipid profiles were normal. Serum ANA, ds-DNA, ANCA, anti-GBM antibody and rheumatoid factor were all negative. Serum C3 and C4 were normal. HBV and HCV tests were all negative. Renal ultrasonography showed increased medullary echogenicity.

16:00-16:20 Mini lecture 2

Advances on pathology of ANCA associated vasculitis (AAV)

Suxia Wang, MD, PhD
Laboratory of Electron Microscopy, Pathological Center, Peking University First Hospital;
Institute of Nephrology, Peking University, Beijing 100034, PR China

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is characterized by the necrotizing vasculitis with few or no immune deposits, affecting mainly small vessels (including small arteries, arterioles, capillaries, and venules), in association with autoantibodies against the cytoplasmic region of neutrophils, including proteinase 3 (PR3) and myeloperoxidase (MPO). According to the clinicopathological features, AAV included three major types: microscopic polyangiitis(MPA), granulomatosis with polyangiitis(GPA, formerly as Wegner's granulomatosis) and eosinophilc granulomatosis with polyangiitis(EGPA, formerly as Churg-Strauss syndrome). Single-organ AAV (for ex. renal-limited AAV) and drug-induced AAV were also reported. GPA is characterized by necrotizing granulomata of upper and lower respiratory tract, necrotizing vasculitis and glomerulonephritis. The periglomerular and perivascular granulomatus inflammation was the pathological features of GPA the pulmonary nodules and hemorrhage was frequent occurred.

PR3-ANCA was the predominant target antigen in GPA. MPA is characterized by a multiple-system necrotizing small vessel vasculitis without the evidence of granulomatous lesions of respiratory tract. The necrotizing and crescentic GN was the predominant feature of MPA, pulmonary capillaritis with hemorrhage occurs often. EGPA is extremely uncommon in children, and is characterized by eosinophil-rich necrotizing granulomatous inflammation of small to medium-sized vessels involving respiratory tract and neurological, gastrointestinal systems, the kidney was involved in about 40%, far less than GPA and MPA. Both of MPA and EGPA expressed more MPO-ANCA than PR3-ANCA.

The pathological spectrum of AAV varied with the indolent and relapsed course, there was acute lesions (fibrinoid necrosis, cellular and fibrocelluar crescents, necrotizing vasculitis), chronic lesions (glomerular sclerosis, fibrous crescents, arteriosclerosis) and mixed lesions existed simultaneously, it is necessary to make a classification based on the pathological lesions, so as to guide the therapy and prognostigation. Berdon et al have founded a histologic classification of ANCA-associated glomerulonpohritis, which included four classes (i.e. focal, crescentic, mixed, and sclerosed classes). This classification have been evaluated to be valuable for evaluation of prognosis.

Reference

1. Plumb LA, Oni L, Marks SD, et al. Paediatric anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: an update on renal management. Pediatric Nephrol, 2017(DOI 10.1007/s00467-016-3559-2.)
2. Pagnoux,C. Updates in ANCA-associated vasculitis. Eur J Rheumatol 2016; 3: 122-33.

Case Session III

16:30-16:45 Japanese case 3

Renal pathology of a premature case of POEMS syndrome preceded by renal and neurological dysfunction with diabetes mellitus.

Hiroko Kakita[1], Takaya Handa[1], Tomomi Endo[1], Hiroyuki Suzuki[1], Tatsuo Tsukamoto[1] Eri Muso[1+2]

1) Department of Nephrology and dialysis, Tazuke Kofukai, Medical Research Institute, Kitano Hospital, Osaka, Japan

2) Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan

A 65 years old female was admitted to our hospital for leg edema and numbness of limbs. Renal dysfunction with Cr 1.0 mg/dl, proteinuria with 2 g/g Cr and occult blood were detected. She had been diagnosed with SLE 32 years ago and 5 mg prednisolone was maintained. In addition, diabetes mellitus had been also diagnosed five years ago, however, diabetic retinopathy was not accompanied. To detect the origin of renal dysfunction, abnormal urinalysis and edema, renal biopsy was performed.

Renal pathology showed enlarged glomeruli with mild mesangial cell proliferation and matrix expansion accompanied focal but apparent nodule formation and double contour of glomerular basement membrane. No immunological deposition was detected in immunofluorescence staining. Although typical exudative lesion and hyalinosis were rarely seen, diabetic nephropathy nodular type was temporary diagnosed and control of diabetes was performed. Edema was improved by salt restriction and diuretics and proteinuria also improved to 0.8 g/gCr without progression of renal dysfunction. Numbness of limbs was diagnosed with polyneuropathy due to diabetic neuropathy. Before electron microscopic findings was obtained, she was discharged.

2 months later, she was emergently hospitalized due to rapid progression of anasarca and pulmonary edema. Because of intravascular dehydration without progression of proteinuria, edema at this time was considered due to vascular hyper permeability. Hypothyroidism and IgA-lambda type M protein became apparent, and high titer of VEGF was detected. With persisting polyneuropathy, splenomegaly, and skin changes, POEMS syndrome was diagnosed. Expanded mesangial matrix with nodular formation was considered to be due to this disease but not diabetic nephropathy. Electron microscopy findings of expanded subendothelial space was consistent with high vascular permeability of POEMS syndrome.

POEMS syndrome is a para neoplastic syndrome due to an underlying plasma cell disorder. Renal optical microscopic finding with expanded glomerular matrix expansion frequently accompanied nodular formation resembles diabetic nephropathy, however, exudative lesion is faint. We should suspect POEMS syndrome with these renal pathological findings even if full syndromes of this disease is not apparent yet.

16:55-17:10 Chinese case 3

A middle-aged woman with proteinuria and paraproteinemia

Xiaoxia Pan

Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University, School of medicine

48 y/o, female.

Chief history of present illness: The patient has experienced recurrent retrosternal pain and tightness for six months, which was exacerbated three weeks ago with dizziness, headache and syncope. Four months ago, the patient's blood pressure elevated and two months ago, foam urine and lower limbs edema occurred accompanied with hearing loss.

Past medical history: No history of diabetes mellitus or hypertesion. She underwent uterectomy because of hysteromyoma. No history of hepatitis, tuberculosis and other infectious diseases.

Family history: Two sisters had coronary heart disease. Family history of renal disease was denied.

Physical examination: Height 160cm，weight 72.5kg，BMI 28.32kg/m^2. T 36.6℃P 78 bpm, R 16/min, BP 146/76 mmHg. No skin rash or bruise and swollen lymph nodes were found. Mild edema was found in the lower extremities. Lung, heart and abdomen examination were normal.

Laboratory examination:

Blood routine: WBC 7.2x10^9/L, N% 57.6%, RBC 2.04×10^{12}/L↓, Hb 86g/L↓, PLT 111×10^9/L

Urianalysis: protein (-), WBC (-), RBC 1-3/HP

Proteinuria: 470-800mg/24h↑

Liver function: ALT 12 IU/L，AST 23 IU/L，TB 4.1 umol/L，DB 1.2 umol/L，total protein 57g/L↓，Alb 27g/L↓

Renal function: BUN 2.9mmol/L, Scr 69 umol/L (CKD-EPI 89.8 ml/min/1.73m^2), UA 338 umol/L

Electrolytes: K^+ 4.4mmol/L，Na^+ 142mmol/L，Ca^{2+} 2.14mmol/L, P 1.47mmol/L，CO2CP 26mmol/L

Fasting blood glucose 7.39mmol/L↑, 2h postpradial blood glucose 11.5mmol/L↑, capillary blood glucose 20mmol/L

Blood viscosity: low shear blood viscosity 16.66 mpa.s↑, middle shear blood viscosity 10.86 mpa.s↑, high shear blood viscosity 8.81 mpa.s↑, low shear blood reduced viscosity 24.43 CP↑, middle shear blood reduced viscosity 14.77 CP↑, high shear blood reduced viscosity 11.35 CP↑, plasma viscosity 2 CP↑, erythrocyte aggregation index 8.33 CP, erythrocyte rigidity index 14.68 CP↑, erythrocyte deformation index 1.49 CP↑, HCT 0.3↓
Plasma immunofixation electrophoresis: IgG(+), λ (+)
Urine immunofixation electrophoresis: λ (+)
Plasma Free light chain: κ 8.95mg/L, λ 57.20↑mg/L, κ/λ 0.16, IgG 1330mg/dl
ANCA, anti-GBM, ANA, ENA all negative.
HBV, HCV, RPR, TPPA, HIV all negative.
Bone marrow: 9% plasma cell, mostly mature.
Bone marrow flow cytometry: 2.6% clonal plasma cell.
EKG: ST-T change.
Cardiac ultrasound: left ventricular hypertrophy, left ventricular ejection fraction 63%.
Brain MR and CT: no obvious abnormalities.
Ambulatory electroencephalogram (EEG): segmental θwave.
PET-CT: paranasal sinusitis, left thyroid gland node, no bone damage and organ enlargement.