Japan-Korea
The 10th Pediatric Nephrology Seminar 2012

May 12 (Sat) -13 (Sun), 2012
Lecture Hall, Surugadai Nihon University Hospital, Tokyo, Japan

Sponsored by
The Korean Society of Pediatric Nephrology
The Japanese Society of Pediatric Nephrology
International Pediatric Nephrology Association
Invitation to the 10th Japan-Korea Pediatric Nephrology Seminar, 2012

Dear Colleagues and Friends,

We are pleased to have 10th Japan-Korea Pediatric Nephrology Seminar in Tokyo. This seminar was started in 2002 and has been fostered scientific and cultural exchange in two countries. We are very proud of the achievements of this seminar, particularly cultivation of young doctors and many scientific publications.

This year is the 10th celebration and we welcome the Chinese pediatric nephrologists and wish the joint continuously to grow this Seminar more interacting.

In addition, the present seminar includes educational program by the sponsorship of International Pediatric Nephrology Association (IPNA).

Now we are at the re-start point toward another 10 years of this Seminar.

We welcome many participants for discussion and international scientific/cultural exchange in Tokyo.

Come and join us!

Prof. Michio Nagata, M.D.
President of 10th Japan-Korea Pediatric Nephrology Seminar

Department of kidney and Vascular Pathology
Faculty of Medicine
University of Tsukuba
Tsukuba-City, Japan
Organizing Committees
The 10th Japan-Korea Pediatric Nephrology Seminar, 2012

JAPAN

Organizing Committee

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Yuhei Ito  Kurume University
Michio Nagata  University of Tsukuba
Takashi Sekine  Toho University
Ryugo Hiramoto  Matsudo City Hospital
Shori Takahashi  Nihon University (Liaison officer)

Pathologists

Michio Nagata  University of Tsukuba
Satoshi Hisano  Fukuoka University

Advisors

Iekuni Ichikawa  Tokai University
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The 10th Japan-Korea Pediatric Nephrology Seminar, 2012

KOREA

Organizing Committee

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Kee Hyuck Kim  NHIC Ilsan Hospital
Il Soo Ha  Seoul National University Children’s Hospital
Hae Il Cheong  Seoul National University Children’s Hospital (Liaison officer)

Pathologists

Yong-Jin Kim  Yeungnam University
Kyoung Bun Lee  Seoul National University Hospital
Jeong Hae Kie  National Health Insurance Corporation Ilsan Hospital

Advisors

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Chong Guk Lee  Ilsan Paik Hospital
Seung Joo Lee  Ewha Womans University
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General Information

1. Congress Information

Dates: May 12, Saturday – 13th, Sunday
Venue: Surugadai Nihon University Hospital, Lecture Hall (3F of the Hospital).
Kanda Surugadai 1-8-3 Chiyoda-ku, Tokyo, 101-8309, Japan

2. Registration

Registration for Korean members staying Shoryu-kan Hotel will be processed at check in on 11 (Friday).
During the seminar, in 12 and 13, registration desk is located in front of the Venue.

3. IPNA desk

IPNA desk is set next to the registration desk. Please find the information of IPNA on it.

4. Access for Venue and Hotel from the Airport

Pre-registered Korean and Chinese participants will stay in Shoryukan-Hotel with some Japanese members.
Please come directly to the Hotel and Check in on 11 May!

http://www.familyhotel.jp/english/

- Toei-Shinjuku line Ogawa-machi Station 4 min. walk
- Jinbocho Station 5 min.
- Marunouchi Line Ochanomizu Station 6 min.
- Awajicho Station 6 min.
- Toei-Mita Line Jinbocho Station 5 min.
- Hanzomon Line Jinboccho Station 5 min.
- Chiyoda Line Shin-Ochanomizu Station 3 min.

〒101-0052 3chome 24banchi 9 Kanda Ogawamachi Chiyodaku Tokyo
TEL:03-3293-3001
Instruction for presenters

1. Oral presentation

Please submit your presentation data 30 min. prior to your session, and next seated at the next speaker’s seat 15 min before your presentation starts.

Length of the presentation

Case presentation: 30 min in total, including pathological comment and discussion (ca. 8 min).
Please discuss with pathologist how to share.
Please make sure to finish your presentation on time.

For PC Presenters:

PC presentation is possible either by your own PC (Windows or Macintosh) or by submitting your presentation data (Windows only) at the PC Registration Desk. PC and laser pointer are on the flat home desk and please manage your presentation with them. To avoid computer viruses, please scan all your presentation files beforehand with updated anti-virus software. Those who bring their own PC for presentation are also asked to check the data at the PC registration desk.

Using your own PC

* If you are using your own PC, please make sure that your PC is equipped with OS of Windows (Windows 2000, 2002, 2003, or 2007 version) or Macintosh (MacOS 0.9 or later version). The application used for the presentation is PowerPoint only.
* Those whose presentation contains any movie files are advised to bring your own PC for presentation.
* Even if you are using your own PC for presentation, please bring your presentation data on media (either on CD-ROM or USB memory stick) for backup. All links should also be restored in the same backup file.
* Please bring your AC adaptor with you. (Note: Voltage in Japan is 100V)
* The secretariat prepares PC cable connector of miniD-sub 15 pin. If your PC is not compatible with this cable connector, please bring an adjustor to connect your PC and the PC cable connector of MiniD-sub 15 pin.
* Please make sure to cancel the Screen Saver and Power Saving function before you bring your PC to the PC registration room.
* If you bring your own PC, please bring your PC to the Operation desk in the session room after checking your data. You can retain your PC from the Operation desk after you finish your presentation.

Using the Secretariat’s PC

Please bring your presentation data on CD-ROM, or USB Memory Stick. No floppy disk or MO are acceptable.
* Presentation data accepted at the PC registration desk is copied to the secretariat’s PC and made ready for presentation. All the copied data are deleted on the secretariat’s responsibility after the meeting.
* Those who prepared the presentation data on Macintosh are advised to bring your own PC for
presentation. *The secretariat only prepared Windows PC (OS is limited to Windows XP).

*All the presentation data must be backed up in media and brought to the session room to avoid any malfunction or damage of the submitted data.

Please save your presentation data under the following rules;
2. Font types are limited to: Century, Century Gothic, Times New Roman, Arial, Arial Black, Arial Narrow, Courier, Courier New, and Georgia.
3. Movie data is limited to the format operable with the application of Windows Media Player, or Quick Time.
4. If your presentation data is linked to other files (i.e. still and moving images, graphs, etc.), those linked files should also be saved in the same folder, and checked the operation beforehand.
5. Those who bring your presentation in CD-ROM or USB Memory Stick, it is advised to check your presentation with PC other than the one you made your presentation slides in order to make sure that your presentation is operable on the PC that the Secretariat prepares for the Session.

To Chairs:
Please stop by at the registration desk for chairs’ check-in 15 min. prior to your session. Then please be seated at the next chair’s seat located at the top right hand corner of the session hall.

2. Poster Presentation

1. Poster presenters are asked to mount poster at Poster Session Halls (A and B). The secretariat prepares poster board, pins, and presenter’s ribbons, and you are asked to place your poster by yourself. Please remove your poster yourself.
2. Presentation should be made in 4 min, orally followed by 3 min of discussion. Each poster room (A and B) proceeds simultaneously by individual chairpersons.

<table>
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<th>Event</th>
<th>Time</th>
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<tr>
<td>Poster Mounting</td>
<td>7:30AM-11:30AM</td>
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<td><strong>Poster Session</strong></td>
<td><strong>12:30PM-14:00PM</strong></td>
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<td>Poster Removal</td>
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Please prepare your poster to fit into the specification.

* Posters left after the removal time shall be removed and destroyed by the Secretariat.
PRE-PROGRAM

May 11 (Fri), 2012

Business Meeting  17:30 – 19:00
Jazz Olympus! Next door to Shoryu-kan Hotel
Attendant: Core members of JK PN seminar with Chinese professors.

Registration for Korean and Chinese participants
Automatically with hotel check in and please take your name holder.
Shoryu-kan Hotel
May 12 (Sat), 2012

Registration 7:45 – 08:25
Opening Remark 8:25 – 08:30  Dr. Michio Nagata (University of Tsukuba)

Case conference I  8:30 – 12:30

Case 1: A familial case of glomerulopathy associated with IPEX syndrome
Hye Jin Chang, Hee Gyoung Kang, Il Soo Ha, Yong, Choi, Hae Il Cheong, Kyoung Bun Lee* (PC)
Department of Pediatrics and Pathology, Seoul National University Children’s Hospital, Seoul, Korea
Chairperson: Shuich Ito (National Center for Child Health and Development)
*PC: Pathological commentator

Case 2: Pathological aggravation despite complete remission: a case of 6-year-old boy with focal segmental glomerulosclerosis.
Wataru Shimabukuro, Yoshitsugu Kaku, Satoshi Hisano* (PC),
Department of Nephrology, Fukuoka City Children’s Hospital
Department of Pathology, Faculty of Medicine, Fukuoka University*
Chairperson: Prof. Jae Il Shin (Yonsei University Children’s Hospital)

Case 3: Crescentic glomerulonephritis showing membranoproliferative glomerulonephritis (MPGN) like pattern and prominent C3 deposition
Young Ju Hwang, Sang In Lee, Jae Young Choi, Min Hyun Cho, Yong Jin Kim* (PC)
Department of Pediatrics, Kyungpook National University, School of Medicine, Daegu, Korea
Department of Pathology, Yeungnam University, School of Medicine, Daegu, Korea*
Chairperson: Ryuji Ohashi (Nippon Medical University)

Coffee Break

Case 4: A case of atypical thrombotic microangiopathy in a child
Fang Wang¹, Jie Ding¹, Na Guan¹, Yong Yao¹, and Suxia Wang²
Department of Pediatrics¹ and Electron Microscopy² Peking University First Hospital, Beijing, P. R. China
Chairperson: Prof. Hye Won Park (Seoul National University Bundang Hospital)
Case 5: Atypical postinfectious acute glomerulonephritis superimposed on IgA nephropathy
Seiji Tanaka1), Ryota Shindo1), Takuya Esaki1), Kosuke Ushijima, Yuhei Ito1) Satoshi Hisano2) (PC)
Department of Pediatrics, Kurume University Medical Center1), Department of Pathology,
Fukuoka University School of Medicine2*)
Chairperson: Prof. Yong Hoon Park (Yeungnam University)

Lunch, Poster viewing  12:30 – 14:00

Case Conference II  14:00 – 15:30

Case 6: Fever of unknown origin, thrombocytopenia, pleural effusion, and acute renal failure in a 14-year-old girl
Ji Young Oh1), Jeong Hae Kie2)(PC), Beom Jin Lim3), Hyeon Joo Jeong3), Ki Hwan Kim3),
Ji Hong Kim1), Se Jin Park1), Jae Il Shin1)
Department of Pediatrics1) and Pathology3), Yonsei University College of Medicine, Seoul,
Department of Pediatrics, Ajou University School of Medicine3), Suwon, Departments of
Pathology, National Health Insurance Corporation Ilsan Hospital2), Koyang, Korea
Chairperson: Hirotsugu Kitayama (Shizuoka Children’s Hospital)

Case 7: Hyponatremic Hypertensive Syndrome in an Infant Child Presenting as Nephrotic Syndrome: a Case Report
Takeshi Ninchoji1), Hiroshi Kaito1), Hiromi Otsubo1), Fusako Hashimoto1), Shingo Ishimori1),
Yuya Hashimura1), Naoya Morisada1), Ayako Kawasaki2), Masato Yamaguchi3), Kazumoto Iijima1)
Department of Pediatrics1), and Radiology3), Kobe University Graduate School of Medicine,
Department of Pediatrics, Sanda Municipal Hospital2). (No pathological comment)
Chairperson: Prof. Min Hyun Cho (Kyungpook National University)

Case 8: How shall we treat the Henoch-Schönlein purpura nephritis with crescents in children?
Jing Chen1), Hong Xu1), Qian Shen1), Yangyang Ma2)
Department of Nephrology1) and Rheumatology2), Children’s Hospital of Fudan University,
Shanghai, China
Chairperson: Dr. Hiroshi Tanaka (Hirosaki University)

Coffee Break 15:30 – 15:50
Educational Topics  15:50 – 16:50

1) Genetic approaches in Pediatric Nephrology
   Kazumoto Iijima,
   Department of Pediatrics, Kobe University, Kobe, Japan
   **Chairperson:** Yong Yao (Peking University, First Hospital)

2) School urinalysis program in Korea
   Byoung-Soo Cho,
   Department of Pediatrics, Kyung Hee University, Seoul, Korea
   **Chairperson:** Kenichi Satomura
   (Osaka Medical Center & Research Institute for Maternal and Child Health)

Invited lecture  17:00 – 17:50

Developing the Program for Children with CKD and ESRD in Shanghai, China
   Hong Xu
   Children’s Hospital of Fudan University, China
   **Chairperson:** Prof. Il Soo Ha (Seoul National University Children’s Hospital)

Closing address
   **Dr. Yuhei Ito** (Kurume University)

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Banquet  18:30 –

Welcoming address  Dr. Masataka Honda
Congratulatory address  Dr. Hae II Cheong
‘Hiroto Prize’
Message from Hiroto’s Parents: Koji Yanagisawa and Midori Yanagisawa
Awarding: Dr. Shori Takahashi and Dr. Kee Hwan Yoo
Proposal of a toast  Dr. Yong Choi

Ensemble Beans

- **Divertiment K 136**  Wolfgang Amadeus Mozart
- **Clarinet Quintet in B minor, Op115, 4th movement**  Johannes Brahms

1st Violin: Mai Sato
2nd Violin: Shori Takahashi, Hiroshi Hataya
Viola: Mariko Shimizu, Rieko Harada
Violincello: Takuya Fujimaru, Michio Nagata
Contrabass: Tamaki Karasawa
Clarinet: Kenji Ishikura
Poster presentation

Poster Room A

ChairPerson

P-1〜P-4　Hee Yeon Cho (Samsung Medical Center)
P-5〜P-8　Koichi Kamei (National Center for Child Health and Development)

P-1: A case of pseudohypoaldosteronism type I with SCNNIA mutation manifested as persistent hyperkalemia.
Su-Yon Kim, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

P-2: Superimposition of post-streptococcal acute glomerulonephritis on the course of IgA nephropathy
Rika Fujimaru, Department of Pediatrics, Osaka City General Hospital, Osaka, Japan.

P-3: Spontaneous perinephric urinoma after removal of foley catheter in a patient with acute kidney injury.
Tae Hwan Yang, Department of Pediatrics, College of Medicine, Korea University, Seoul, Korea.

P-4: Intractable hypertension in a patient on peritoneal dialysis was relieved after bilateral nephrectomy.
Eun Gu Kang, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

P-5: Progression of proteinuria after seven years’ treatment with angiotensin converting enzyme inhibitor in a patient with cyanotic nephropathy.
Natsumi Yamamura, Department of Pediatric Nephrology and Metabolism, Osaka Medical Center and Research Institute for Maternal and Child Health, Tokyo, Japan.

P-6: Renovascular hypertension in a child with Klippel-Trenaunay Syndrome.
Kyoung Hee Han, Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea.

P-7: Two cases of Sjögren syndrome primarily presenting as hypokalemic paralysis.
Seong Heon Kim, Department of Pediatrics, Pusan National University Childrens’ Hospital, Yangsan, Korea.

P-8: A case of distal renal tubular acidosis with bilateral renal calcification in a 1-month-old infant
Masayuki Ishihara, Department of Pediatrics, Kochi Medical School, Kochi University, Kochi, Japan.
Poster Room B

ChairPerson
P-9～P-12  Se Jin Park (Ajou University Hospital)
P-13～P-17  Kenichiro Miura (Tokyo University)

P-9:  Renal Manifestations in 4 Patients with Tuberous Sclerosis Complex.
      Ja Hyeon Lim, Department of Pediatrics, Ajou University School of Medicine, Suwon, Korea.

P-10:  A fulminant juvenile SLE with diffuse alveolar hemorrhage, multifocal leukencephalopathy and diffuse proliferative nephritis.
      Jihei Cha, Department of Pediatrics, School of Medicine, Ewha Womans University, Seoul, Korea.

      Mariko Hida, Department of Pediatrics, School of Medicine, Keio University, Tokyo, Japan.

P-12:  Is this a patient with C3 glomerulopathy?
      Saerom Choi, Dept of Pediatrics, National Health Insurance Corporation Ilsan Hospital, Koyang, Korea.

P-13:  Three cases of primary hyperoxaluria type 1 in Korea.
      Hye Jin Chang, Department of Pediatrics, Seoul National University Children’s Hospital, Seoul, Korea.

P-14:  Paradoxical hypoalbuminemia in children with active nephrotic syndrome presenting with no or subtle proteinuria.
      Masao Ogura, Department of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan.

P-15:  Successful renal transplantation in Fechtner syndrome.
      Jin-Soon Suh, Department of Pediatrics, School of Medicine, Catholic University, Seoul, Korea.

P-16:  Wegener’s granulomatosis associated with IgA nephropathy.
      Daisuke Fukuhara, Department of Pediatrics, Kyorin University of Medicine, Tokyo, Japan.

P-17:  D-penicillamine -induced pauci-immune crescentic glomerulonephritis with Wilson’s disease
      Yoshinobu Nagaoka, Department of Nephrology, Tokyo Metropolitan Children’s Medical Center, Tokyo, Japan
May 13 (Sun), 2012

Continuous Professional Development  8:30 – 12:00

Theme: Hemolytic Uremic Syndrome and Thrombotic Microangiopathy

Chairperson
Motoshi Hattori (Tokyo Women’s Medical University)
Hee Gyung Kang (Seoul National University Children’s Hospital)

1. D+ and D- HUS, a comprehensive view.
   Hiroshi Hataya
   Tokyo Metropolitan Children’s Medical Center, Tokyo Japan.

2. Histopathologic Variations of Thrombotic Microangiopathy.
   Yong-Jin Kim
   Department of Pathology, Yeungnam University College of Medicine, Daegu, Korea.

   Heeyeon Cho1), Hye Won Park2)
   1)Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul,
   2)Department of Pediatrics, Health Promotion Center, Seoul National University Bundang Hospital, Gyeonggi-do, Korea.

   Akira Ashida1), Yoko Yoshida2), Xinping Fan3), Masanori Matsumoto2), Toshiyuki Miyata3), and Yoshihiro Fujimura3)
   1)Department of Pediatrics, Osaka Medical College, Osaka, 2)Department of Blood Transfusion Medicine, Nara Medical University, Nara, 3)Department of Molecular Pathogenesis, Research Institute National Cerebral and Cardiovascular Center, Osaka

5. A case of atypical hemolytic uremic syndrome successfully treated with anti-C5 antibody.
   Yaeko Motoyoshi1), Tomohiro Udagawa9), Motoko Chiga9), Yoko Yoshida9), Yoshihiro Fujimura9), Masayuki Nagasawa9), Tomohiro Morio9), Shuki Mizutani1b), Michio Nagata(PC) 9)
   1)Department of Pediatrics, and 2)Nephrology, Tokyo Medical and Dental University, 3)Department of Blood Transfusion Medicine, Nara Medical University, 4)Department of Pathology, University of Tsukuba

6. Novel therapeutic strategy for HUS.
   Anne-Laure Lapeyraque  (IPNA speaker)
   Pediatric Nephrology, CHU Sainte Justine, Université de Montréal Montréal, Canada.
[Case 1]

A familial case of glomerulopathy associated with IPEX syndrome

Hye Jin Chang, Hee Gyoung Kang, Il Soo Ha, Yong, Choi, Hae Il Cheong, Kyoung Bun Lee*

Department of Pediatrics and Pathology*, Seoul National University Children's Hospital, Seoul, Korea

**Introduction:** IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome is a rare disorder resulting in aggressive autoimmunity and early death. This syndrome is caused by mutations in the *FOXP3* gene, a key regulatory gene for the development and function of regulatory T cells. Renal involvement has also been reported in patients with IPEX syndrome. However, most cases revealed tubulointerstitial damages, while only few cases of glomerulopathy (minimal change nephrotic syndrome and membranous nephropathy) have been reported.

**Case:** A male neonate was diagnosed with hypothyroidism on neonatal screening test and started to take synthroid. At the age of 6 months, he developed intractable diarrhea. He visited a hospital at age 4 due to facial swelling with proteinuria, and a renal biopsy revealed membranous nephropathy (MNP) stage I. Laboratory tests showed positive anti-nuclear antibody, anti-dsDNA, anti-SSA/Ro, and anti-cardiolipin IgG. At age 8, he was referred to our hospital due to intractable diarrhea (600–1000cc/day). Chronic active inflammation, possible autoimmune enteritis, was noted on duodenal endoscopic examination. Tacrolimus treatment resulted in improvement of diarrhea and duodenal pathologic lesions. At age 10, he newly developed petechiae. Laboratory tests revealed autoimmune hemolytic anemia, thrombocytopenia, albuminuria and hematuria. A renal biopsy showed MNP. He was treated with oral steroid and methotrexate. At age 11, he developed skin lesions with pruritis, desquamation and pigmentation, which were treated with steroid, hydroxychloroquine and intravenous immunoglobulin. At age 17, he was finally diagnosed as IPEX syndrome with a hemizygous c.736-2A>G in IVS7 mutation in the *FOXP3* gene. He had two elder brothers. The first elder brother had a history of intractable atopic dermatitis, enteropathy, recurrent infections and nephrotic syndrome. The renal pathology was minimal change lesion with tubulointerstitial changes. He expired at age 10 due to fulminant EBV hepatitis and atopic dermatitis. He was expired due to septic shock. The second elder brother also expired at the neonatal period due to intractable diarrhea.

**Discussion:**
1) Delayed diagnosis despite of typical clinical features and family history
2) Different renal pathology in siblings despite of same genetic mutation
3) Treatment plan; Is bone marrow transplantation required?
[Case 2]

Pathological exacerbation despite complete remission: a case of 6-year-old boy with focal segmental glomerulosclerosis.

Wataru Shimabukuro¹, Yoshitsugu Kaku¹, Satoshi Hisano²

Department of Nephrology, Fukuoka City Children’s Hospital¹
Department of Pathology, Faculty of Medicine, Fukuoka University²

Background: Complete remission (CR) is generally thought to be associated with an improvement of prognosis in refractory nephrotic syndrome. However, we recently experienced a pathological exacerbation despite maintained complete remission for 2 years in a boy with focal segmental glomerulosclerosis (FSGS).

Case: Nephrotic syndrome (NS) was developed in a patient at the age of 2 years old and his NS was steroid-resistant. He had no specific family history. Renal biopsy revealed that segmental or global sclerosis was evident in 7 (15%) of 48 glomeruli. The histological diagnosis was FSGS cellular variant. We treated him with the combination of methyl-prednisolone pulse therapy and oral cyclosporine (CYA). Subsequent therapy was combined with intermittent methyl-prednisolone pulse therapy, oral prednisolone and CYA. This combined therapy could lead to CR. At about one year after CR, however, his NS was relapsed when intermittent methyl-prednisolone pulse therapy discontinued.

We treated this combined therapy again, and his proteinuria immediately disappeared. The second biopsy was performed after CR to evaluate CYA nephrotoxicity. Segmental glomerulosclerosis in 2 and global glomerulosclerosis in 5 of 31 glomeruli were found. The rate of sclerosing glomeruli was 23%. There was no evidence of CYA nephrotoxicity. After the second CR, his NS did not relapse in the following 2 years and steroid was tapered off. During his disease course, renal function was not impaired.

The third biopsy was performed at the age of six years old without relapse of NS. Segmental glomerulosclerosis in 2 and global glomerulosclerosis in 31 of 76 glomeruli were recognized. The rate of glomerulosclerosis was exacerbated to 43%. Diffuse interstitial lymphocytic infiltration and mild fibrosis were found.

Discussion:
1) Pathological exacerbation of FSGS despite long term CR
2) Treatment indicators of FSGS: Is long term CR not though indicator of FSGS ?
3) Future treatment plan: Immunosuppression or R-A-A system suppression?
Crescentic glomerulonephritis showing membranoproliferative glomerulonephritis (MPGN) like pattern and prominent C3 deposition

Young Ju Hwang, Sang In Lee, Jae Young Choi, Min Hyun Cho, Yong Jin Kim*

Department of Pediatrics, Kyungpook National University, School of Medicine, Daegu, Korea
Department of Pathology, Yeungnam University, School of Medicine, Daegu, Korea*

Background: Primary MPGN is one of the least common types of glomerulonephritis, accounting for approximately 4% and 7% of nephrotic syndrome developed in children and adults. Secondary MPGN is usually associated with infectious diseases including viral hepatitis (HBV, HCV), malaria and mycoplasma or systemic diseases including cryoglobulinemia, systemic lupus erythematosus and hereditary deficiency of complement components. Here we report a case of rapidly progressive glomerulonephritis (RPGN) due to MPGN with uncertainty of classification and underlying cause.

Case: A 6-year-old boy was admitted to our hospital due to gross hematuria and generalized edema. Initial laboratory tests on admission were as follows. His BUN 43.3 mg/dL, serum creatinine 1.43 mg/dL, total protein 3.6 g/dL, albumin 2.0 g/dL, ASO 2.4 IU/mL, C3 44.3 mg/dL and C4 29.3 mg/dL. Renal biopsy was performed because of the rapid elevation of serum creatinine level. On light microscopic findings, total 24 glomeruli were observed and 15 glomeruli of them showed crescent formation. All glomeruli exhibited typical lobular pattern compatible with MPGN. IF study showed marked deposition of C3 in basement membrane and mesangium. EM findings showed huge amount of electron dense deposit in subendothelial area, but these findings were not compatible with typical pattern of idiopathic MPGN type I, or type II (dense deposit disease) either. The tests for HBV, HCV, ANA, ANCA and cryoglobulin were all negative and we performed genetic study of factor H deficiency. Although he was treated with methylprednisolone pulse, plasmapheresis and cyclophosphamide therapy under the diagnosis for RPGN, he did not response to those treatments and finally progressed to end stage renal disease. During follow-up, the normal C4 and decrease of C3 level continues.

Point of discussion:
1) What is the diagnosis of this patient?
2) What is the cause of glomerulonephritis showing MPGN like pattern with C3 deposits?
A case of atypical thrombotic microangiopathy in a child

Fang Wang¹, Jie Ding¹, Na Guan¹, Yong Yao¹, Suxia Wang²

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An 8-year-old boy with 6 years' history of intermittent proteinuria was referred to our hospital at 23rd February 2012. At age 2.3, the patient presented with remarkable edema in face and both legs 6 days after a preceding upper respiratory tract infection. Laboratory findings revealed hypoalbuminaemia (26.8 g/l), significant proteinuria (1.5 g/24h), microscopic hematuria (20-40 RBC/HPF) and normal renal function. A diagnosis of nephrotic syndrome was made, and the child was then treated with prednisolone at 7.5 mg thrice daily. Proteinuria did not improve after 3 weeks of the therapy, so a renal biopsy was performed that showed glomerular endothelial cells significant proliferation and foam degeneration, with swelling of the endothelial cells in the stromal artery. Immunofluorescence studies revealed granular deposits of IgG, IgA, IgM, C3, C4 and C1q within the glomerular capillary walls, with 1+ ~2+ fluorescence intensity. Eight weeks after steroid therapy, the patient did not go into remission, therefore, prednisolone was reduced to alternate day treatment, and cyclosporin therapy was started in a dose of 75 mg/day. After 1.5 months of administration of prednisolone and cyclosporin, proteinuria disappeared without further relapse, prednisolone and cyclosporin were then gradually weaned. However, proteinuria relapsed at age 3.8 and 4.2, respectively. At that time, laboratory findings indicated thrombocytopenia (40×10⁹/L, 29×10⁹/L), anemia (72 g/L), proteinuria (3+, 3+), and elevated level of serum creatinine (83 μmol/L, 120 μmol/L). Bone marrow analysis showed a normocellular bone marrow. He was treated with oral administration of methylprednisolone (3 mg/day) on alternative days along with tacrolimus at 1.5 mg/day. The response to the therapy was satisfactory. Platelet counts, haematoglobin, and renal function improved completely, and proteinuria decreased to 1+. At age 6, the patient manifested with gross hematuria. His physical exam was remarkable for a blood pressure of 170/110 mmHg. Laboratory findings included thrombocytopenia (44×10⁹/L), proteinuria (4+), and elevated level of blood creatinine (171 μmol/L) and blood urea nitrogen (59 mmol/L). Antibiotics, diuretics, and antihypertensive were used with the combination of oral administration of methylprednisolone and tacrolimus. Gross hematuria disappeared, blood pressure was normal (105/62 mmHg), platelet counts increased to 258×10⁹/L, and renal function improved to the normal range (57 μmol/L). On follow-up six months later, the child was normotensive, and presented with proteinuria (trace~1+) and normal renal function. At age 6.6, the patient presented with persistent headache without any causes, MRI revealed chronic right subdural hematoma. After surgical intervention, the symptom disappeared. His past medical history was negative for systemic illness, rash or joint pain. Family history was not remarkable for renal disease. On admission, there were no abnormal signs. Laboratory data indicated the blood cell count, bilirubin, liver enzymes and coagulation data were normal. The serum creatinine level was 105 μmol/L, urea nitrogen level was 21.4 mmol/L, and cholesterol 7.39 mmol/L. The glomerular filtration rate was 39.8 ml/min/1.73 m². Urinalysis showed hematuria and proteinuria (2+), and the 24 hour urinary protein excretion was 910 mg. The serum level of C3 and C4 was normal. The anti-nuclear antibody, anti-DNA antibody, anti-neutrophil cytoplasm antibodies, and anti-hepatitis B virus were all negative. There were normal plasma levels of complement factor H and ADAMTS-13 activity. Anti-complement factor H antibodies were negative. The patient underwent a renal biopsy on the fourth hospital day. On light microscopy, the biopsy showed 35 glomeruli. Eight glomeruli demonstrated global sclerosis, and the remainder glomeruli had mild mesangial hypercellularity. The glomerular capillary walls were irregularly thickened with segmental ischemic changes have occurred. Immunofluorescence examination was positive for immunoglobulin IgG, IgA, IgM, C3 and C1q deposition. The ultrastructural examination of glomerular basement membrane showed widening of the subendothelial space, without electron-dense deposit. The pathology was consistent with thrombotic microangiopathy. Thereafter, methylprednisolone and tacrolimus were stopped, and the child was treated with an angiotensin converting enzyme inhibitor and an angiotensin receptor blockade. On the 23rd hospital day, the serum creatinine level was 38 μmol/L, urea nitrogen level was 7.4 mmol/L, and cholesterol 5.21 mmol/L. The glomerular filtration rate was 122.6 ml/min/1.73 m². Urinalysis showed hematuria and proteinuria (1+), and the 24 hour urinary protein excretion was 610 mg. He was discharged without any symptoms.
[Case 5]

Atypical postinfectious acute glomerulonephritis
superimposed on IgA nephropathy

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Background: Postinfectious acute glomerulonephritis (PIAGN) superimposed on IgA nephropathy is rarely seen. Unclear-onset IgA nephropathy complicated by atypical PIAGN is difficult to diagnose and treat. We report a case with no clinical hypertension and hypocomplementemia diagnosed as having PIAGN superimposed on IgA nephropathy from histological findings.

Patient: A 5-year-old boy with no past history of abnormal urinalysis underwent medical examination at his local clinic because of palpebral edema. Laboratory results at the time of the visit included blood pressure 98/56 mmHg, hematuria 3+, proteinuria 3+, urinary protein 2.3 g/day, serum Alb. 1.7 g/dl, serum Cr 0.4 mg/dl, anti-streptolysin O (ASO) 488 IU/ml and normal complement concentrations. Although steroid therapy started, he was referred to our hospital because of no response to four-week steroid therapy. The urinary protein excretion at the initial visit was 0.6 g/day. Light microscopy revealed diffuse mesangial proliferative glomerulonephritis with segmental endocapillary proliferation. Immunofluorescence showed moderate IgG and mild IgA and C3 deposition in the mesangial region. Electron microscopy (EM) revealed hump and intramembranous electron dense deposit(EDD), accompanied by membranolysis and severe injury of glomerular basement membrane (GBM). The urinary protein value improved to 0.2 g/day within several months after the methylprednisolone pulse therapy was additionally 1 time(3 days) and oral prednisolone 1mg/kg/48h, and the course was uneventful.

Discussion:
1. Diagnosis of PIAGN: i) Based on the results of histological findings and the clinical courses, PIAGN was suspected, but why were characteristic hypertension and reduced GFR not observed. ii) Based on the EM findings, PIAGN was suspected, but why was hypocomplementemia as an indicator of immune-complex disease not observed despite the presence of humps and EDD.
2. Diagnosis of IgA nephropathy: Immunofluorescence showed moderate IgG and C3 deposition in the mesangial region, but showed reduced IgA deposition. When PIAGN is superimposed on IgA nephropathy, the reduction of IgA deposits is evident. Can the patient be considered to have this disease condition.
3. Treatment: It has often been reported that patients with IgA nephropathy complicated by PIAGN have spontaneous remission of urinary protein. As with the present patient, possible acute onset of chronic nephritis is difficult to select treatment methods. How should it be treated.
Case: A 14-year-old girl was referred to our hospital for three weeks of ongoing fever, abdominal pain, diarrhea, and edema that gradually worsened. She had no specific family and medical history.

Initial laboratory studies showed a hemoglobin level of 12.4 g/dL, reticulocyte count 1.24 %, a white blood cell count of 9,420/mm³, platelet count of 93,000/mm³, serum BUN/creatinine level was 12.8/1.16 mg/dL, total protein level of 4.5 g/dL, serum albumin of 2.1 g/dL and peripheral blood smear showed no burr cells or schistocytes. Liver function test, lactate dehydrogenase level and serum complement levels were within normal range. Anti-platelet antibody was positive. Urinalysis showed normal at presentation but showed proteinuria and hematuria 3 days after hospitalization. Twenty-four hour urinary protein excretion was 1622 mg/day. Serum creatinine was increased to 2.02 at 3rd hospitalization day. All culture studies from blood, urine and stool showed no growth and serologic tests for brucella and legionella were negative. Chest x-ray showed bilateral pleural effusion. Abdominal ultra-sonogram presented increased cortical echogenicity of both kidneys with mild obliteration of corticomedullary junction. Diffuse gall bladder wall thickening and splenomegaly were also observed.

Suspecting idiopathic thrombocytopenic purpura (ITP) and an unknown cause of acute renal failure as our initial diagnoses, intravenous immunoglobulin (500mg/kg) and dexamethasone (0.3 mg/kg/day) was initiated. High blood pressure (170/100 mmHg) and seizure was suddenly developed at 43th hospitalization day and posterior reversible encephalopathy syndrome was diagnosed by brain magnetic resonance imaging.

Fever and thrombocytopenia was gradually resolved. We performed a renal biopsy due to an unknown cause of acute renal failure and persistent proteinuria and hematuria and serum creatinine and proteinuria was normalized gradually.

Discussion points:
1) What is the most probable cause of acute renal failure in this patient?
2) What is the possible precipitating factor for the development of renal pathologic findings?
Hyponatremic Hypertensive Syndrome in an Infant Child Presenting as Nephrotic Syndrome: a Case Report

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Background: The most common cause of nephrotic syndrome (NS) in children is idiopathic NS and acute or chronic glomerulonephritis. Hyponatremic hypertensive syndrome (HHS), which is characterized by hypertension and hyponatremia secondary to unilateral renal artery stenosis or occlusion, has been reported to cause secondary NS, but little is known about the presence and pathophysiology of the rare syndrome, especially for pediatricians.

Case: A previously healthy 19-month-old boy was referred to our hospital because of NS (serum albumin: 2.0 g/dL and urinary protein/creatinine ratio: 41.8 g/gCre) accompanied by loss of appetite, polyposia and polyuria. Blood examination revealed severe hyponatremia (120 mEq/L) and metabolic alkalosis, and his blood pressure was 160/100 mmHg. Serum creatinine and complement titer were normal, and fractional excretion of sodium (FENa) was less than 0.5%. Contrast enhanced computed tomography revealed severe stenosis of his left renal artery, and he was diagnosed as HHS. Following percutaneous angioplasty and the administration of angiotensin II receptor blocker, most parameters including blood pressure normalized. However, his urinalysis still revealed massive proteinuria of around 2.0 g/gCre until now.

Point of Discussion:
1) What is the pathophysiology mechanism of HHS? How do we evaluate the relationship among sodium balance, polyuria and polyposia especially at the initial visit?
2) What is the cause of persistent proteinuria until now?
3) All the patients with unilateral renal artery stenosis do not experience episodes of HHS. What was the possible factor in this case contributing to the development of HHS?
How shall we treat the Henoch-Schönlein purpura nephritis with crescents in children?

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Henoch-Schönlein purpura (HSP) is the most common vasculitic disease of childhood. Renal involvement is reported to occur in 15% - 62% of affected patients. Previous studies show that 1% - 21% of patients with renal involvement progress to ESRD and all renal deaths occurred in patients with clinical and histological findings of crescentic glomerulonephritis.

We retrospectively analyzed the data of biopsy-proven Henoch-Schönlein purpura nephritis (HSPN) in our center. Renal biopsy was performed in children with acute nephritic syndrome and/or nephrotic range proteinuria, and in children with persistent proteinuria >0.5-1g/m²/d for more than 2-3 months. The analyzed data showed 119 children with biopsy-proven HSPN received follow-up. Among these children, 44 cases had crescents in the renal biopsy (ISKDC class III or class IV). The initial clinical manifestation of these 44 cases showed 24 cases (54.5%) only with mild proteinuria, 3 cases with acute nephritic syndrome and the other 17 cases with nephrotic range proteinuria or nephrotic syndrome. After renal biopsy, all these 44 cases with crescents received intensive treatment including prednisolone, ACEI, antiplatelet agent and most of them received methylprednisolone pulse and/or other immunosuppressants (cyclophosphamide or mycophenolate mofetil) at the same time. At the last observation (the mean duration of follow-up was 31 months and 12 cases were followed more than 5 years), only 1 case progressed to ESRD due to non-compliance (clinical manifestation with nephrotic syndrome, renal biopsy with class III, methylprednisolone and cyclophosphamide pulse initially with good response, tapered the prednisolone quickly by the parents and stopped the immunosuppressants later by themselves, ESRD at 5 years after onset and automated peritoneal dialysis at present), 1 case had active renal disease with nephrotic range proteinuria, and the other 42 cases had good outcome (26 cases with normal urinalysis and 16 cases with minor urinary abnormality).

Our data indicated that patients with mild proteinuria as the initial clinical manifestation might have severe biopsy findings in HSPN and children with HSPN even with severe pathological manifestations would have good outcome if they received intensive immunosuppressive treatment and regular follow-up. Compared with other reports (AJKD 2006; Pediatr Nephrol 2010; Pediatr Nephrol 2011…), HSPN with crescents in our center had a satisfactory prognosis. Is it due to the aggressive treatment or the timing of renal biopsy?
It is well known that many pediatric kidney diseases are caused by genetic abnormalities. Genetic approach is important for confirmation of diagnosis, precise genetic counseling, better understanding of pathophysiology and supporting clinical management. As diagnostic technologies for genetic approach, we can utilize chromosomal karyotyping, Sanger DNA sequencing, microarray-based comparative genomic hybridization (array CGH), multiplex ligation-dependent probe amplification (MLPA). The latter 2 techniques were recently developed, and are useful for detecting copy-number variation such as deletions and duplications.

The basic principle of array CGH relies on the mixture of reference DNA with test (patient) DNA, each labeled with a different fluorofore, and hybridization to an array containing a panel of immobilized oligonucleotide probes to identify net loss (deletion) or gain (duplication) of DNA sequences. MLPA is a variation on the PCR, which relies on probes to hybridize to the gene region of interest before amplification. The probes are designed to lie immediately adjacent to each other, so that they can be ligated together in the subsequent step before amplification by PCR. The primer is fluorescently labeled, thereby enabling the PCR product to be quantified. If parts of the gene are deleted and a probe could not hybridize, no amplification can occur. Conversely, if there is a duplication, more probes will hybridize and there will be increased amplification.

In this brief lecture, a few cases of childhood genetic renal diseases, whose genetic abnormalities were detected by relatively new techniques including array CGH and MLPA, will be presented.
2) School urinalysis program in Korea

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In Korea, since the school-screening program was established by law in 1998, mass urine screening tests have been performed on all school children annually. Elementary, junior high and senior high school children are instructed to completely empty the bladder at night, and the early morning urine is sampled by a simple dipstick method for the detection of proteinuria, hematuria and glucose. To date, about five million students participated in this yearly screening program. Among them, isolated proteinuria was about 0.18%, occult blood was about 0.7%, and glucosuria was about 0.06% from January 1998 to December 2008. After identifying with abnormal urine results, a total of 5,134 children were referred to pediatric nephrologists at 7 nationwide hospitals for further evaluation. Among referred patients, renal biopsy was taken in 26.77% of isolated hematuria, 9.09% of isolated proteinuria and 51.19% of combined hematuria and proteinuria. Histopathological findings are IgA nephropathy in 38.23%, mesangial proliferative glomerulonephritis in 23.99%, thin basement membrane nephropathy 13.02%, Henoch-Schonlein purpura nephritis in 2.5%, membranoproliferative glomerulonephritis 1.6%, and lupus nephritis 0.83%. Alport syndrome showed 0.45% as a hereditary disease. In conclusion, the school urinalysis program in Korea is useful to detect incipient chronic renal disease at its early stage.
Developing the Program for Children with CKD and ESRD in Shanghai, China

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Chronic kidney disease is prevalent in China. Analysis showed that the percentage of patients with Chronic renal failure increased by 1.31% annually by a survey of 0-14 Years old hospitalised patients from 1990–2002. Nevertheless, many ESRD patients remained in untreated. Financial problems, scarcity of dialysis facilities, and insufficient numbers of skilled health care providers were among reasons why renal replacement treatment is not so well developed in children in China. In Shanghai, regular chronic peritoneal dialysis (CAPD and APD) program begun in 2001, hemodialysis in 2005, and renal transplantation begun in 2004. The structural organization of ESRD program in children may need focusing on the following domains: (1) adequate chronic kidney disease education for patients and their parents, (2) provision and support of physician training in the principles and practice of RRT, (3) adequate size and organization of RRT centers of multidisciplinary Team (including pediatric nephrologist, urologist, dialysis nurse, PICU professional, pediatric dietitian, social worker…), (4) development of appropriate support systems from society, etc. In Shanghai, Charity foundations played an important role to improve the development of a successful ESRD Program for Children.
**Continuous Professional Development**

1. D+ and D- HUS, a comprehensive view

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HUS is defined by the triad of clinical features; microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. HUS is divided by whether or not it associates with shiga-like toxin. Shiga-like toxin associated HUS is the most common form of HUS accounting for 90 percent in children. It usually occurs after a prodrome of bloody diarrhea. Non-shiga toxin associated HUS is a heterogeneous disorders distinguished by the absence of diarrhea. It associates with *Streptococcus pneumonia* infection and Complement disorders. It is also referred to as D+HUS or typical HUS in former cases, D-HUS or atypical HUS in the latter cases. Recently the terms typical/atypical HUS becomes widely used due to acute colitis may trigger the HUS with complement disorders in some atypical HUS.

The diagnosis of HUS is made on triad from laboratory findings. The prognosis and treatment differ substantially according to typical/atypical HUS, especially the cause of HUS. Therefore it is very important to make a different diagnosis to make decision. Prognosis of typical HUS is relatively favorable compared to atypical HUS with complement disorders. In a patient of HUS without prodromal episode of bloody diarrhea, we consider atypical HUS, clinically. Although negative results of stool culture do not always suggest atypical HUS, due to limitations of culture.

Recent topics in typical HUS are microbiology and new drug.

1) Microbiology: Shiga toxin producing enterohemorrahgic *E. coli* (EHEC) is the most common cause of typical HUS. Main strain of EHEC is different depending on the country, for example, O157:H7 in Japan and USA, O111 in Australia and O26 in Italy. Two outbreaks occurred last year, O111 in Japan and O104 in Germany. New or rare strain in the area tends to become outbreak.

2) Treatment: The main approach to typical HUS is supportive therapy, such as tight control of fluid and electrolyte disturbances, anemia, hypertension, convulsion, and introduce dialysis like any AKI. There are no evidence of specific therapy include plasma exchange, plasma infusion, and oral Shiga toxin binding agents. A monoclonal antibody to complement factor C5 (eculizumab) has been used in the treatment of atypical HUS, and a case report showed rapid clinical improvement of 3 typical HUS children with severe central nervous system.
2. Histopathologic Variations of Thrombotic Microangiopathy

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The morphological characters of HUS and TTP are similar and did not help to distinguish between the diseases. Thrombotic microangiopathy (TMA) has been used for them because their common pathogenesis is endothelial cell injury.

By definition, TMA is characterized by micro vascular thrombosis with thrombocytopenia, hemolytic anemia and RBC fragmentation. TMA also occurs in a wide range of diseases other than HUS/TTP, such as autoimmune diseases, malignant hypertension, vascular rejection, endothelial damage due to drug toxicity. Typical histologic features of TMA are vessel wall thickening with endothelial swelling and detachment of endothelial cells from the basement membrane and formation of hyaline micro thrombi that occlude arterioles and capillaries. Glomerular lesion is sometimes leading to MPGN-like changes with double contour of basement membrane and later endothelial cell proliferation. There are no or only minor glomerular deposition of IgG and C3. Electron dense deposits are not noted.

In some instances, atypical HUS may be associated with an unusual glomerulonephritis with isolated C3 deposits (GN C3). Servais A et al. divided them in two groups based on renal pathology findings. Group I disclosed typical features of type I MPGN with isolated C3 deposits at subendothelial and mesangial sites without evidence of immunoglobulins deposits. It showed mesangial proliferation, double contours of glomerular basement membrane. Group II showed mesangial and epimembranous C3 deposits without MPGN pattern. Both have uncontrolled activation of the complement alternative pathway, which is a well established risk factor for the occurrence of HUS. The detection rate of factor H, factor I or membrane cofactor protein (MCP) mutation was higher in group II. With these evidences, GN C3 should be added to the spectrum of TMA.

3. Complement Regulatory Proteins: the Physiology and Disease Relevance

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The complement system is a complex protein network that mediates innate and adaptive immune functions and is activated in a sequential manner which can be divided into four main steps: initiation of complement activation, C3 convertase activation and amplification, C5 convertase activation, and the assembly of the terminal complement complex. Complement is initiated by three major pathways: alternative pathway, classical pathway, and lectin pathway. The classical pathway is triggered by an antibody bound to the target antigen. The lectin pathway is initiated by carbohydrates on microbial surfaces. The alternative pathway is in a continuous state of activation due to spontaneous hydrolysis of plasma C3. The activation of these pathways results in assembly of the first enzyme of the cascade known as C3 convertase. Once activated, the reactions are amplified and can result in potent immune reactions.

The Complement system maintains a delicate regulation between activation and inhibition to allow activation on foreign surfaces and protection of self. Complement regulation is achieved by proteins present in plasma and on cell surfaces that inhibit activation at different steps in the pathways. These regulator can be divided into fluid phase complement regulators, membrane-bound complement regulators (CR1, CD55, CD46, CD59, and CR1g), and cell surface receptors for complement effector molecules (CR1, CR2, CR3, CR4, CR1g, C3aR, C5aR, C5L2, and C1qR). Fluid phase complement regulators are distributed in human plasma and in body fluids and grouped according to their activity: alternative pathway regulators (factor H, FHL1, and properdin), all three major pathway regulator (carboxypeptidase N), classical and lectin pathway regulators (C1q, C1 inhibitor, and C4BP), and terminal pathway inhibitors (clusterin, vitronectin, and CFHR1). Several fluid phase complement regulators such as factor H also attach to cell surfaces and to biomembrane such as the glomerular basement membrane of the kidney and the Bruch's membrane of the retina.

Mutations in the genes encoding complement regulators can result in host cell damage and accumulation of immunological debris to lead to autoimmune disease. For example, different abnormalities in the gene encoding factor H are associated with renal disorders (atypical haemolytic uremic syndrome and dense-deposit disease), and retina disorder (age-related macular degeneration). This finding that the different abnormalities including heterozygous, homozygous, or polymorphism in the same gene can cause distinct diseases in different organs suggests that the quantity of protein at local sites is relevant and that mutated proteins attach to different surfaces in distinct organs.
4. Strategy and algorithm for diagnosis of typical/atypical hemolytic uremic syndrome

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Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Over 90% of such cases are due to Shiga-like toxin-producing *Escherichia coli* (STEC) infection ‘typically’ presenting with a diarrheal prodrome. The remaining 10% of childhood HUS comprises so-called, atypical HUS (aHUS) which is a heterogeneous disease associated with defective regulation of the alternative complement pathway in over 50% of cases. Mutations have been identified in genes encoding both complement regulators and complement activators. An additional 6-10% of aHUS cases are associated with inhibitory complement factor H (CFH) autoantibodies that block the C-terminal recognition domain of CFH and reduce CFH binding to C3b.

In contrast to typical HUS, aHUS is associated with a poor long-term prognosis, and is characterized by frequent relapses and progression to end-stage renal disease. Furthermore, the incidence of aHUS recurrence after renal transplantation is high, and has been reported to depend on the underlying complement defect. Therefore, it is necessary to diagnose aHUS as accurately and quickly as possible. If HUS is suspected, the first step is to measure ADAMTS13 activity and perform stool culture to identify STEC in order to exclude TTP caused by ADAMTS13 deficiency, and STEC-associated HUS. The latter can also be diagnosed if abdominal ultrasonography demonstrates thickening of the colonic mucosa, and if serum examination reveals antibodies against lipopolysaccharide in patients with hematochezia and severe abdominal pain, since STEC is detectable in only 60-70% of patients harboring it. After exclusion of TTP and STEC-associated HUS, further investigation for possible aHUS should be done through measurement of C3, C4, CFH, and CFH autoantibodies, hemolysis assay, and genetic mutation analysis for the susceptibility genes, CFH, CFI, C3, THBD, CFB, and MCP CFHR1 and CFHR3 deletions.

For the diagnosis of HUS/TTP, the clinical data of patients after exclusion of STEC-associated HUS have been collected at institutes including Osaka Medical College, analysis of the gene mutation site through measurement of ADAMTS13 activity and protein assay including hemolytic assay have been performed at Nara Medical University, and the final diagnosis based on gene mutation analysis has been done at the National Cerebral and Cardiovascular Center. A diagnostic network for HUS/TTP centered on these three institutions has thus been established. Through this diagnostic network, the analytical procedures from measurement of ADAMTS13 activity to genetic mutation analysis can be completed within 2 to 3 weeks. Here we describe our strategy for diagnosis of HUS/TTP.
5. A case of atypical hemolytic uremic syndrome successfully treated with anti-C5 antibody (eculizumab).

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Seven year old female patient visited a clinic because of abdominal pain and nausea, and was diagnosed as gastroenteritis. But her symptoms got worsened and visited a general hospital two days later. Blood examination revealed Hb 7.6 g/dL, Plt 7.4 X 10^4 /μL, BUN 160 mg/dL, Cre 4.7 mg/dL, LDH 2400 IU/L, then she was diagnosed to have hemolytic anemia, thrombocytopenia and acute renal failure, and transferred to intensive care unit of our hospital. By detection of proteinuria, macrohematuria and fragmented erythrocyte, we diagnosed the patient as hemolytic uremic syndrome (HUS). She had no particular past history, but her great-grandmother of father’s side suffered from end stage renal disease on her forties.

We started with fluid therapy and observed closely. On seventh day of admission, she presented symptoms of disseminated intravascular coagulation, and we started intravenous injection of recombinant thrombomodulin (130 U/kg/day). Because stool culture did not show any pathogen as HUS, and that the level of complement 3 was apparently lower than normal range, we diagnosed as atypical HUS. Although we performed plasma exchange three times, renal function did not improve and pulmonary edema had appeared. We started treatment with eculizumab (monoclonal antibody directed against the complement protein C5) 600mg per single dose once a week. She recovered immediately and platelet level became normal within eight days after first infusion. Hemolysis disappeared and the kidney function recovered gradually.

We performed kidney biopsy one month after admission. Light microscopic findings revealed mesangial expansion and narrowing of capillary lumina in ca. 70% of glomeruli without morphological features of typical TMA. Tubulointerstitium showed diffuse edema with focal fibrosis up to 30% of area. In addition, acute tubular necrosis with vacuolated tubule was observed in the limited area. Immunostaining revealed predominant C3 deposition by granular pattern.

Eculizumab therapy in every two weeks normalized hemoglobin level and kidney function gradually, and she backed in the normal daily life without renal replacement therapy. The patient’s level of complement factor H activity was low and now undergoing genetic analysis.

This is the first report of atypical HUS case treated with eculizumab in Japan. Although a single case experience is insufficient to conclude the efficacy of eculizumab, it suggests that C5 blocking at an early stage of atypical HUS with low complement might improve vital prognosis and kidney prognosis.
6. Novel therapeutic strategy for HUS.

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Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, acute renal failure, and thrombocytopenia. Shigatoxin-associated HUS (STEC-HUS) accounts for the majority of cases. Atypical HUS (aHUS) represents 5-10% of HUS in children but the majority of HUS in adults. aHUS is marked by frequent relapses (half of patients) and poor prognosis: 2 to 10% of patients die and one third progress to end-stage renal failure at first episode. In addition, post-transplant recurrence can occur in 80-100% of patients which, for the majority of them, results in graft loss. The past decade has revealed aHUS to be a disease characterized by over-activation of the alternative complement pathway in at least 50% of cases. Mutations have been identified in genes encoding both complement regulators (complement factor H (CFH), complement factor I, complement factor H-related protein, thrombomodulin, and membrane cofactor protein) as well as complement activators (complement factor B and C3). Inhibitory auto-antibodies to CFH account for an additional 5-10% of cases. In addition, complement hyperactivation in STEC-HUS and novel regulatory effects of STEC as a complement modulator were recently reported. Alternative pathway complement hyperactivation results in endothelial damages leading to platelet aggregation and thrombotic microangiopathy.

Plasmatherapy (plasma infusions and plasma exchange) has been first line treatment in aHUS but there is variable success and little consensus regarding long-term tolerance and effectiveness. In addition, plasmatherapy has no proven role in STEC-HUS.

Unrestricted and uncontrolled complement activation leads to generation of the inflammatory anaphylatoxin C5a and formation of the terminal complement complex. Therefore, targeting and inhibiting complement at the level of the C5 convertase seems a very promising approach for HUS therapy. Eculizumab is a C5 targeting humanized monoclonal antibody and has been approved for treating paroxysmal nocturnal hemoglobinuria and more recently atypical HUS. It has been recently reported as effective for STEC-HUS patients with neurological involvement.

In this review, we discuss the emerging evidence for the role of complement inhibitor therapy in the management of HUS cases associated with over-activation of the alternative complement pathway.
A case of pseudohypoaldosteronism type I with SCNN1A mutation manifested as persistent hyperkalemia

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Introduction: Hyperkalemia is one of the most alarming electrolyte abnormalities because of the potential for lethal arrhythmias. Plasma renin and aldosterone level must be checked to differentiate the cause of hyperkalemia in patients with normal renal function. Pseudohypoaldosteronism (PHA) is a condition characterized by renal salt wasting, hyperkalemia and metabolic acidosis because of renal tubular resistance to the action of aldosterone with the findings of elevated plasma renin and aldosterone levels. We report a patient who had a persistent hyperkalemia with high renin and aldosterone level.

Case: A 7 day-old male infant was admitted to local hospital due to poor oral intake, dehydration and jaundice. He was born at term gestation with the birth weight of 4.1 kg without perinatal problem. His one older sibling was healthy and the family history was unremarkable. His external genitalia were normal. The initial laboratory findings were as follows: serum sodium, 124 mmol/L; serum potassium, 10 mmol/L; blood urea nitrogen, 43 mg/dL; serum creatinine, 1 mg/dL; Plasma renin activity, above 30 ng/mL/hr (normal range, below 1.16); aldosterone, above 1660 pg/mL (normal range 50-900). The venous blood gas analysis revealed metabolic acidosis with pH 7.276. Renal ultrasonography showed no abnormal findings. He was treated with hydrocortisone, fludrocortisones, regular insulin, sodium bicarbonate, calcium gluconate, and furosemide. Hyperkalemia persisted without effect of fludrocortisones treatment. Ventricular tachycardia occurred during admission due to hyperkalemia which needed cardioversion. He was transferred to our hospital due to persistent hyperkalemia when he was 52 days old. Transtubular potassium gradient was 0.15 ~ 0.5, and fractional excretion of sodium 1.3 ~ 6.1%. As he had persistent high plasma renin (above 40 ng/ml/hr) and aldosterone (607 ng/dL, normal range 5-90 ng/dL) levels, had normal renal function and had no obstructive uropathy, the diagnosis of PHA was suspected. Genetic analysis showed a heterozygous c.913T>C mutation in the SCNN1A gene encoding Amiloride-sensitive sodium channel subunit alpha. Mineralocorticoid receptor gene was normal. We maintained kallimate, sodium chloride, and sodium bicarbonate for the treatment of hyperkalemia, hyponatremia and metabolic acidosis. We discontinued fludrocortisones because it had no effect on hyperkalemia.

Conclusion: We report a patient who had a persistent hyperkalemia due to pseudohypoaldosteronism type I. It is caused by defective transepithelial sodium transport due to mutations in the genes encoding α (SCNN1A), β (SCNN1B) or γ (SCNN1G) subunit of the epithelial sodium channel at collecting duct. Even though it is a rare disease, genetic studies can be performed in patients with normal renal function, high plasma renin and aldosterone levels without history of potassium sparing diuretics or obstructive uropathy.
Superimposition of post-streptococcal acute glomerulonephritis on the course of IgA nephropathy

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Objective: We here report an evaluation of the clinicopathological findings in our patient with severe acute kidney injury (AKI) that developed in the course of mild IgA nephropathy (IgA-N).

Case: A 10-year old boy admitted to our hospital because of general fatigue and oliguria. He complained of two-day fever 2 weeks before admission. He had a past medical history of macrohematuria and mild proteinuria at the age of 7 and a renal biopsy revealed mild mesangial proliferative glomerulonephritis with mesangial IgA deposition. He had been treated with angiotensin-converting enzyme inhibitor. His clinical course had remained stable, with less than 0.5 g/day proteinuria, microscopic hematuria, normal renal function and normal blood pressure. Physical examinations on admission revealed blood pressure of 116/69 mmHg and no edema. Laboratory examinations were as follows: serum blood urea nitrogen 117.7 mg/dl, serum creatinine (sCr) 5.61 mg/dl, serum albumin 3.1 g/dl, CRP 0.97 mg/dl, C3 16.2 mg/dl, C4 19.7 mg/dl, CH50 20.1 mg/dl, anti-streptolysin O 450 IU/ml and anti-streptokinase titer 5210. Urinalysis revealed severe proteinuria (673 mg/dl) with sediment containing more than 100 erythrocytes and leukocytes. Kidney dysfunction and streptococcal infection were obvious. The second renal biopsy revealed diffuse endocapillary proliferative glomerulonephritis with crescents. Immunofluorescence showed stronger deposition of C3 than IgA in the mesangium. Decrement in intensity of IgA deposition was apparent when compared with the first biopsy. Electron microscopy revealed no typical “hump” deposit, but dome-shaped electron-dense deposits were observed in the sub-epithelial space. These features were consistent with post-streptococcal acute glomerulonephritis (PSAGN) superimposed on IgA-N. Spontaneous recovery was expected. But after 3 weeks, persisting renal impairment and proteinuria necessitated steroid therapy. Eight weeks later his renal function had improved with sCr 0.51 mg/dl and C3 61.4 mg/dl, except for mild proteinuria and microhematuria.

Conclusions: The present paper described a boy with IgA-N complicated by AKI and nephrotic syndrome. The histological findings indicated that the AKI was not due to exacerbated extant IgA-N, but rather to PSAGN superimposed on IgA-N. As previously reported by others, the most interesting pathological finding was the decrease of mesangial IgA deposition, which also was true for the present case. Corticosteroid therapy, in our patient, significantly reduced urinary protein excretion and helped to recover renal function. These results suggest that superimposition of PSAGN on IgA-N cause severe damage to renal parenchyma interfering with spontaneous remission of AKI, requiring active anti-proliferative treatment with steroid hormone. These results suggest that superimposition of PSAGN on IgA-N further damages renal parenchyma interfering with spontaneous recovery of AKI and gives rationale for active anti-proliferative treatment with steroid hormone.
Spontaneous perinephric urinoma after removal of foley catheter in a patient with acute kidney injury

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Introduction: Urinoma is an encapsulated collection of extravasated urine from genitourinary system in the perinephric space. It is common after renal trauma or perforation of the collecting system during an endosurgical procedure. However, spontaneous urinomas are rare and mainly secondary to obstructive uropathies, such as posterior urethral valves, uretero-pelvic junction obstruction, ureterocele, urethral atresia, and bladder neck obstruction in conjunction with reflux.

Case: An 18-year-old girl was referred to our hospital because of high fever, oliguria and dyspnea for seven days. She has been followed up for Down syndrome after birth and had cardiac operation for ventricular septal defect when she was 5 years old. Upon admission, vital sign was as follows; blood pressure 140/90 mm Hg, pulse rate 108/min respiration rate 40/min, and body temperature 39.7°C. Mental status was in a stupor and generalized edema on whole body was observed. Breathing sound with crackle was auscultated on both lung fields. The arterial blood gas analysis showed severe metabolic acidosis and the peripheral blood investigation indicated as follows: hemoglobin 11.0 g/dL, white blood cell counts 33,200 /mm³, platelet 310,000 /mm³, blood urea nitrogen 196 mg/dL, creatinine 15.4 mg/dL, sodium 126 mmol/L, potassium 8.2 mmol/L, chloride 84 mmol/L, protein 7.0 g/dL, albumin 3.3 g/dL, total calcium 7.4 mg/dL, phosphorus 11.1 mg/dL, uric acid 20.8 mg/dL, total cholesterol 182 mg/dL, AST 26 IU/L, ALT 20 IU/L, and c-reactive protein 20 mg/dL. The urine analysis showed hematuria and pyuria (> 60 red blood cells/HPF and 10~29 white blood cells/HPF). The chest x-ray and abdomen ultrasonogram revealed pulmonary edema and mild bilateral hydronephrosis. She was diagnosed as septic shock, acute kidney injury, and acute respiratory distress syndrome and treated with intravenous antibiotics and steroid pulse therapy. After two weeks, her clinical course including acute kidney injury and pulmonary edema was improved. Peripheral blood investigation showed as follows: white blood cell counts 11,220 /mm³, C-reactive protein 3.52 mg/dL, blood urea nitrogen 18.0 mg/dL, creatinine 1.0 mg/dL and creatinine clearance 98 mL/min/1.73m2. However, after the removal of foley catheter placed during seven days, she complained of voiding difficulty persistently despite anticholinergic medication. Clean intermittent urethral catheterization was performed and abdomen computed tomography scan revealed the large amount of fluid collection in left retroperitoneal and perirenal space suggesting a huge urinoma (size 9.1 cm x 12 cm x 21 cm). Then, double-J catheter was placed, confirming leakage of contrast agent on rupture site of left renal pelvis. The size of urinoma was markedly decreased and voiding cystourethrography showed grade III/V of left vesicoureteral reflux in 2 weeks. Double-J catheter was removed after 6 weeks and reflux in left kidney disappeared. In our patient, perinephric urinoma might be secondary to an abnormally elevated intra-bladder pressure conjunction with reflux. Children who are symptomatic with urinary obstruction require prompt diagnosis with explanation of the cause.
Intractable hypertension in a patient on peritoneal dialysis was relieved after bilateral nephrectomy

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Introduction: Hypertension is a common finding in dialysis patients. The etiology of hypertension in end-stage renal disease is multifactorial: sodium and volume excess, activation of the rennin-angiotensin-aldosterone system, increased sympathetic activity, altered endothelial cell function, erythropoietin, etc. Some dialysis patients are resistant to both volume control and antihypertensive medications. We report a patient on peritoneal dialysis whose hypertension persisted after administration of multiple antihypertensive drugs and who was treated successfully after bilateral nephrectomy.

Case: A 13-year-old girl on peritoneal dialysis was admitted due to headache and hypertension. She was diagnosed as steroid resistant hypertension 5 years ago. She received cyclosporine but had to stop the medication due to cyclosporine induced posterior reversible encephalopathy syndrome. Proteinuria persisted in spite of the treatment with intravenous methylprednisolone. Her renal function deteriorated slowly and she began peritoneal dialysis 2 years ago. Blood pressure was 142/94 mmHg on admission. She had one younger brother and had no other specific past medical history or family history of disease. She was treated with calcium-channel blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker and minoxidil, but her blood pressure was persistently elevated. Echocardiographic findings showed left ventricular hypertrophy. BNP level increased up to 388 pg/mL. Bilateral nephrectomy was performed 2 months later due to persistent hypertension. Her blood pressure slowly decreased and normalized without medication about 10 months after surgery. She received a renal transplantation from deceased donor without problem.

Conclusion: We report a patient on peritoneal dialysis whose intractable hypertension was relieved after bilateral nephrectomy. Bilateral nephrectomy may be considered in the rare conditions when life-threatening hypertension is unresponsive to multiple antihypertensive drugs, and is unable to be controlled with any dialysis modality.
Progression of proteinuria after seven years’ treatment with angiotensin converting enzyme inhibitor in a patient with cyanotic nephropathy

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Recently, the development of cyanotic nephropathy has been recognized as a potential complication of cyanotic congenital heart disease (CCHD). The mechanisms involved in the development of cyanotic nephropathy are not entirely clear. One possibility is that glomerular hyperfiltration may occur due to increased efferent arteriolar resistance and glomerular capillary hydraulic pressure induced by elevated right atrial pressure. Hyperviscosity may also contribute to glomerular hypertension. Other possibility is that marked increase in the glomerular capillary surface area may impair podocyte function. Angiotensin converting enzyme inhibitor (ACEI) has been expected to exert its effect on cyanotic nephropathy through a direct influence on glomerular hypertension and hyperfiltration by dilating glomerular efferent arterioles. Although several studies have demonstrated that urinary protein excretion decreased in patients with cyanotic nephropathy treated with ACEI, long-term outcomes are unknown. We report a case of cyanotic nephropathy that urinary protein excretion increased after seven years’ treatment with ACEI. A twelve-year-old boy with tetralogy of Fallot and pulmonary atresia was referred to our department for proteinuria which was pointed out by routine school urinalysis. 24-hour urine protein was 0.3 g. Simultaneously, ACEI (Enalapril) was started for the treatment of pulmonary hypertension. After seven years’ treatment with ACEI, 24-hour urine protein increased to 0.8 g. Hematuria was negative and creatinine clearance, oxygen saturation and hematocrit were 98 ml/min/1.73m², 80%, and 67%, respectively. He was overweight and his body mass index was 27.6. Renal biopsy was performed at 19 years of age. The biopsy specimen showed mesangial hypercellularity without glomerular sclerosis, and partial interstitial fibrosis with tubular atrophy. The glomeruli were enlarged; the maximum glomerular size was 51,096 μm² and that was two times larger than the normal glomerular size in adult male. Immunofluorescence study revealed no significant deposit of immunoglobulin or complements. The diagnosis of cyanotic nephropathy was made and angiotensin receptor blocker was added to ACEI. In our case, progression of polycythemia and obesity were considered to be responsible for the progression of proteinuria. Glomerulomegaly due to hyperfiltration has been reported to be frequently observed in patients with obesity-related nephropathy. In this regard, weight control will be necessary in patients with cyanotic nephropathy. We speculate that the number of patients with cyanotic nephropathy will increase, because increasing number of patients with CCHD are now surviving longer into adulthood by the recent advances in cardiovascular surgery. Further study is needed to establish the treatment strategy for cyanotic nephropathy.
Renovascular hypertension in a child with Klippel-Trenaunay Syndrome

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**Background:** Klippel-Trenaunay syndrome (KTS) is a congenital vascular anomaly characterized by a triad of cutaneous capillary malformation, bone or soft-tissue hypertrophy and varicose veins or venous malformations. Vasculatlr malformation of KTS sometimes involves visceral organs and involvement of renal vessels may cause microscopic or gross hematuria, or renal failure. Renovascular hypertension was once reported to be associated with KTS in an adult case. Here we report a boy with KTS associated with renovascular hypertension.

**Case:** A 26 months old boy presented with hypertension despite mediation with angiotensin converting enzyme (ACE) inhibitor. Previously he had asymptomatic proteinuria, which was misdiagnosed as nephrotic syndrome, but later managed conservatively with ACE inhibitor. Search for the underlying cause of his hypertension revealed atrophy and dysfunction of the left kidney, hemangiomatous mass adjacent to the left kidney. The patient had a cutaneous hemangioma and bony hypertrophy of left femur from the time of presentation, but diagnosis of KTS was possible only after intensive work-up for secondary hypertension, which revealed intra-abdominal hemangiomatous lesions. During work up, and high renin activity from the left renal vein were observed, suggesting the possibility of localized internal occlusion of the left renal artery or hemodynamic disturbance by the hemangiomatous mass adjacent to the left kidney. Under the impression of renovascular hypertension associated with KTS, the patient has been managed with ACE inhibitor and angiotensin receptor blocker, with excellent clinical course for more than one and half years.

**Conclusion:** The findings of cutaneous hemangioma and hemihypertrophy with hypertension should raise clinical suspicion for renovascular hypertension associated with KTS. Appropriate BP control can effectively prevent the progression of damage in peripheral organs and early treatment is able to restore the existing damage even in secondary hypertension of childhood.
Two cases of Sjögren syndrome primarily presenting as hypokalemic paralysis

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Introduction: Sjögren (SS) syndrome is autoimmune is disease that involve both glandular and extraglandular organ. Typical glandular symptoms are xerophthalmia and xerostomia. However approximately 40 % of patients have extraglandular manifestations. The kidney is one of the common extraglandular involvements. Renal tubular acidosis (RTA) is a well-recongized extraglandular complication of adult Sjögren syndrome but has been reported only rarely in pediatric patients. Here we report two cases of renal involvement of Sjögren syndrome which presented hypokalemic paralysis caused by RTA.

Case 1 A 14 y old girl was admitted with complaint of walking inability and dry mouth. Her lab findings showed severe hypokalemia, metabolic acidosis, strong positivity of ANA, and anti Ro/La. Her TTKG showed renal loss of potassium. Her urine ph and FEHCO3- was compatible with distal RTA. Her renal us showed diffusely increased echogenesity and renal stones. Latent hypothyroidism with Hashimoto’s thyroiditis was suspected by labs. Her renal biopsy specimen showed tubulointerstitial inflammation.

Case 2 A 17 y old girl had paralysis episodes of extremities due to hypokalemia and was referred. Her lab findings revealed severe hypokalemia, metabolic acidosis, hypophosphatemia, hypouricemia, strong positivity of ANA, anti-Ro/La, and RF. Her urine ph and FEHCO3- was compatible with distal RTA. TRP showed tubular defect of P reabsorption. Her urine glucose was negative. Urine amino acid analysis showed no prominent abnormality. She was treated with potassium citrate, calcitriol, and Joulie soln, with improvement.

Conclusion: Sjögren syndrome is rare in children, but should be involved in the differential diagnosis in hypokalemia and RTA, especially in case of preceding typical sicca syndrome. Renal involvement of Sögren syndrome may cause RTA and various tubular dysfunction including Fanconi syndrome.
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A case of distal renal tubular acidosis with bilateral renal calcification in a 1-month-old infant

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Introduction: Distal renal tubular acidosis (dRTA) is a well known disease for renal calcification formation. In the textbook, it is described that renal calcification is preventable by appropriate treatment. We report a case of dRTA infant with bilateral renal calcification.

Case: A patient is 2-year-old boy. Chief complaint was failure to thrive. He was referred to our hospital at 32-day-old because of severe metabolic acidosis after administration of sodium bicarbonate injection at previous hospital. When he arrived at our hospital, venous blood gas analysis revealed still severe metabolic acidosis, pH 7.167, pCO₂ 33.8 mmHg, HCO₃ 12.3 mmol/l, B.E. -15.6 mmol/l. He was also pointed out bilateral renal calcification on ultrasonography and CT scan. After blood, urine and genetic examination, he was diagnosed dRTA. Genetic mutation was ATP6V0A4. ATP6V1B1 and ATP6V0A4 gene mutations are the causes of dRTA. Past report revealed that ATP6V0A4 has a relation to neurosensory hearing loss. Renal calcification is one of a common complication of dRTA, but is rare in infant. In the present case, severe metabolic acidosis and hypercalciuria may be the causes of rapid calcification formation.

Conclusion: We experienced a dRTA infant with bilateral renal calcification. Abnormality was not pointed out during the pregnancy. Renal calcification formation progressed rapidly after the birth. Renal calcification is irreversible, and increasing the risk of renal insufficiency. This case suggests that more closely and longer observation is necessary regarding dRTA.
Renal Manifestations in 4 Patients with Tuberous Sclerosis Complex

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Introduction: Tuberous sclerosis complex (TSC), or tuberous sclerosis, is a genetic disorder that can affect multiple organ systems and can cause tumors in the skin, brain, heart, eyes, lungs, teeth or oral cavity, and kidney. Population-based studies suggest a prevalence of 1 in 9,000 individuals in the general population, but its incidence has been estimated to be 1 in 6,000 live births. The diagnosis of TSC and further evaluation of people at risk for TSC involve careful examination of the skin, heart, eyes, brain, lungs and kidneys, as well as genetic testing. It is important to know the disorder’s manifestations and to follow the recommendations for screening and evaluation TSC.

Several types of renal abnormalities may be seen in individuals with TSC, including angiomyolipoma, renal cyst, and polycystic kidney disease. Once kidney involvement is suspected, magnetic resonance imaging which is the best imaging technique should be performed immediately. Care for an individual with TSC may require ongoing and different treatment for each renal disease depending on the manifestations they have.

Cases: We report 4 patients with TSC who presented with 4 different types of renal manifestations such as angiomyolipoma, renal cell carcinoma, renal infarction, multiple angiofibromatous nodules and nephrolithiasis.

Points of discussion:
1) What kind of renal disease can occur in patients with TSC?
2) What are the best treatment and prognosis for each renal disease?
3) What is the pathomechanism to induce renal infarction in patients with TSC?
A fulminant juvenile SLE with diffuse alveolar hemorrhage, multifocal leukoencephalopathy and diffuse proliferative nephritis

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Introduction: The mortality of lupus has been decreased by early diagnosis and intensive immunosuppression, so early death from active lupus has been rare. We report a fulminant case of juvenile SLE, which was refractory to intensive induction therapy with all reported immunosuppressive agents and plasmapheresis.

Case: A 15-year-old girl visited the emergency room due to abdominal pain and vomiting. Prior to this visit, she had been treated as depressive mood disorder for 2 months at private psychiatric clinic. Despite severe anorexia, her body weight progressively increased. At ER, she looked ill-looking, very pale and edematous. Recent weight gain was almost 8kg. She was slightly tachypneic and lung sound was coarse. Neurologic examination was normal. Laboratory values were as follows: hemoglobin 7.9 g/dl, hematocrit 23.8%, WBC 3200/mm2, Platelet 227k, BUN/Serum creatinine 12/0.5 mg/dL, total protein/albumin 5.0/2.3 g/dL, cholesterol 225 mg/dl. Ca/P 7.7/4.9 mg/dL, Urine protein (3+), occult blood (4+), RBC many/HPF. 24 hour urine protein 7.6 g/m2/day. Ccr 76.6 mL/min/1.73 m2, Antinuclear antibody (4+), P-anti neutrophil cytoplasmic antibody (+), C3 23.3 mg/dL, C4 4.4mg/dL, and CH-50 0 U/mL. Anti-dsDNA 1436 IU. Anti-cardiolipin antibody IgG (+) and IgM (-). Anti-RNP (+), Anti-sm (+), Anti SSA (+), Anti-SSB (+). Chest x-ray was normal. Renal US showed increased echogenecities in both kidneys suggesting renal parenchymal disease.

She was diagnosed as lupus nephritis with nephrotic syndrome and hypovolemic crisis, and was treated with deflazacort (72mg/day) and 20% albumin with lasix. Five days later, hemoptysis developed and follow-up chest x-ray showed bilateral diffuse infiltrates with pleural effusion. High resolution computerized tomography (HRCT) was compatible to diffuse alveolar hemorrhage (DAH). Brain MRI showed multifocal leukoencephalopathy involving periventricular, thalamus and deep white matter. A renal biopsy revealed diffuse proliferative lupus nephritis (ISN/RPS stage IV-GA).

She was diagnosed as severe active lupus simultaneously associated with DAH and multifocal leukoencephalopathy and diffuse proliferative nephritis. She was treated with intensive induction therapy with intravenous pulse methylprednisolone (1 g/day) for 3 days followed by oral mycophenolate mophetil (2 g/day → 4 g/day), rituximab (500 mg), intravenous cyclophosphamide (500 mg) and IVIG (400 mg/kg) in order. Depression improved and proteinuria fluctuated. But renal function and pulmonary hemorrhage aggrevated. Plasmapheresis was started on 21st hospital day. After the second plasmapheresis, massive pulmonary hemorrhage developed and she was transferred to ICU for mechanical ventilation. Her lupus was persistently refractory to above intensive immunosuppression and plasmapheresis and expired on the 24th hospital day.
A case of secondary FSGS in a 19-year old male with Russell-Silver Syndrome.

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**Background:** Russell-Silver syndrome (RSS) is a disorder characterized by intrauterine growth retardation (IUGR) with preservation of head circumference, short stature without catch-up, and triangular face. Renal involvement including hydronephrosis, renal tubular acidosis, posterior urethral valves, and horseshoe kidney have been reported.

**Case:** The patient is a 19-year old male born at 39 weeks’ gestation with birth weight 1485 g, height 37 cm, and head circumference 34 cm. He was diagnosed as RSS by typical features including small triangular face, bilateral incurved fifth fingers, scoliosis, and small asymmetrical rib cage. He had 4 episodes of respiratory failure, and was diagnosed as pulmonary hypertension and cor pulmonale at age 4. He had been treated with home oxygen therapy until age 17 and with beraprost thereafter. He had also received growth hormone until then. At age 16, proteinuria was detected by urine screening at school. At age 19, he visited out hospital. His height was 133.7cm, weight 24.4 kg, blood pressure 128/81 mmHg. Serum creatinine was 0.91 mg/dL, BUN 23.8 mg/dL, total protein 7.1 g/dL, albumin 4.5 g/dL, cholesterol 183 mg/dL, and uric acid 9.0 mg/dL. Urinalysis showed protein 2+, blood -, RBC <2/ HPF, WBC <2/ HPF, and lipid casts. Urine protein/creatinine was 0.3-0.5 g/g. Ccr was 90 mL/min/1.73 m² with urine creatinine 21 mg/kg/day. Urine protein was 0.75 g/day/1.73 m². Urine b2M was 229 µg/L and NAG/Cr 8.3.

Ultrasonography revealed no abnormalities. The right and left kidney length was 8.4 cm (-0.9 SD for height) and 7.8 cm (-1.5 SD), respectively. The diagnosis of RSS was confirmed by hypomethylation of the H19-DMR. Renal biopsy was performed. There were only four glomeruli in biopsy specimens for light and electron microscopy. The glomeruli were hypertrophic and no mesangial alterations were observed. One glomerulus showed a segmental hyaline lesion. Another glomerulus in the electron microscopy specimen showed solidification of the segment at the vascular pole with hyalinosis. The electron microscopy revealed no electron dense deposit in the glomeruli. Immunohistochemical staining of the specimen were negative for IgA. With the diagnosis of FSGS, losartan was started. Blood pressure, serum creatinine, and uric acid gradually decreased, and urine protein/creatinine fell to 0.17 g/g.

**Conclusion:** Low birth weight, especially that with IUGR, is associated with reduced nephron number and glomerular hypertrophy resulting in secondary FSGS. Pulmonary hypertension has also been associated with glomerulomegaly and proteinuria, and may have contributed to the development of FSGS as well as growth hormone.
Is this a patient with C3 glomerulopathy?

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Introduction: C3 glomerulopathy (C3G) is a new uprising classification and it encompasses C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). C3G is a disease group caused by abnormality of alternative complement pathway and it is pathologically characterized by C3 deposition without immunoglobulin or C1q/C4 deposition associated with classic complement pathway. C3GN shows various histologic patterns including MPGN, mesangial proliferation, FSGS, etc. with isolated C3 immunofluorescent activity and Subendothelial/mesangial electron dense deposits. Initially it was reported as a kind of genetic disorder associated with a number of mutations including CFH, CFI, or CD46 etc. but now it is known that sporadic cases are more common. On the other hand, DDD was originally classified as MPGN II because of its histologic similarity with other idiopathic MPGN. However many literatures revealed that it shows various histologic findings and now it is considered as one of C3G because of its immunofluorescent activity for C3 without immunoglobulin. Even though, C3GN and DDD show some differences in histologic and ultrastructural findings to each other, it has not been disclosed until now what mechanical difference is associated. Intriguingly recent data showed that C3GN can be confused with post infectious GN in resolving phase because of hump-like subepithelial electron dense deposits. Here we report a case suggested as C3GN, which was initially diagnosed as postinfectious GN (PIGN).

Case: A 7 year old boy with nonspecific past history and family history was noticed to have microscopic hematuria at school health screening in Jul. ’2010. During 5 months follow up at a local clinic, urynalysis showed persistence of hematuria (RBC 3+, 41-50 HPF) and proteinuria. In Dec. 2010, urynalysis performed at NHIC Ilsan hospital had a result of protein (1+), blood (3+, 11-20 HPF), urine P/C ratio 2500 (mg/g). Lab results revealed BUN 10 mg/dL, creatinine 0.3 mg/dL, serum C3 29 mg/dL (88-201 mg/dL), C4 31mg/dL (16-47 mg/dL), and ANA negative. At the time of presentation, there were no specific signs or symptoms of proteinuria such as edema. In Feb. 2011, follow up of urinalysis showed protein (1+), blood (3+), P/C ratio 1,900 (mg/g), and serum C3 29 mg/dL. A renal biopsy was performed for further evaluation of its etiology. Pathologically mesangial proliferation was observed with immunofluorescent activity for C3 and electron dense deposits were observed mainly in mesangium with occasional subepithelial humps. The possibility of PIGN in resolving phase was suggested. Enalapril was applied from Mar. 2011 until present. We observed the continuance of proteinuria and microscopic hematuria and maintenance of low level of serum C3 with the range of 29 – 38mg/dL from Feb. to Dec. 2011. In Jan. 2012, a renal biopsy follow up was performed. Compared with 1st biopsy, capillary GBM was more thickened and immunofluorescent activity for C3 was more dominant along the capillary loop. Also electron microscopic examination revealed multifocal intramembranous electron dense deposits with constant occasional subepithelial humps. The possibility of C3G was suggested.
Three cases of primary hyperoxaluria type 1 in Korea

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Introduction: Primary hyperoxaluria (PH), a rare cause of chronic renal failure, can be classified into two subtypes according to the underlying genetic defect. PH type 1 (PH1) is more common type and is caused by deficiency of the alanine-glyoxylate aminotransferase (AGXT), which is expressed in the liver peroxisomes. There have been several case reports of PH in Korea, but none of the cases were confirmed genetically. Here, we report three cases of genetically confirmed PH1.

Case 1 was a 2-month-old male who presented with oliguria and azotemia. The urine oxalate level, fundoscopic examination, renal ultrasonography and renal biopsy suggested systemic oxalosis. Compound heterozygous mutations (c.33_34insC [p.K12Qfs] and c.577_578insC [p.L193Pfs]) were detected in the AGXT gene. He underwent deceased donor liver transplantation at the age of 4 month, but expired due to the graft failure at the 50th postop day.

Case 2 a 4-month-old male, manifested with azotemia. The urinary laboratory tests were consistent with hyperoxaluria. The patient had compound heterozygous mutations in AGXT (c.33delC [p.K12RfsX34] and c. C335A [p.A112D]). The patient is waiting for liver or combined liver and kidney transplantation.

Case 3 was a 43-year-old male patient. The patient developed sudden oliguric renal failure at the age of 33 year. The kidney ultrasonography revealed cortical nephrocarcinosis, but the diagnosis of underlying renal disease was not confirmed at that time. After three months of hemodialysis, the patient underwent renal transplantation. However, the graft kidney was surgically removed at the 23th postop day due to acute allograft rejection, and hemodialysis was started again. Seven years later, he developed severe anemia, splenomegaly and multiple bony deformities. Multiple oxalate crystals were detected by a bone marrow examination. The AGXT gene analysis revealed a homozygous mutation (c.G568A [p.G190R]). He is waiting for combined liver and kidney transplantation.

Conclusion:
This is the first genetic study of PH1 in Korea. The diagnosis of PH must be considered in the differential diagnosis of patients presenting with chronic renal failure with a history of recurrent nephrolithiasis or nephrocalcinosis. Delayed diagnosis results in significant morbidity and mortality.
Paradoxical hypoalbuminemia in children with active nephrotic syndrome presenting with no or subtle proteinuria

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Background: We experienced three children with nephrotic syndrome who paradoxically showed hypoalbuminemia despite no or subtle proteinuria in the acute period. One of these patients showed no proteinuria, although his serum albumin was 1.2 g/dL before treatment. Interestingly, massive proteinuria immediately developed after loading of intravenous albumin. We hypothesized that the proximal tubules remarkably increase their protein resorption from primitive urine in these patients. However, intravenous albumin loading may induce more proteinuria beyond the threshold of resorption. Based on this experience, we performed a nuclear medicine study and histological evaluation to verify our hypothesis in these patients.

Patients and Methods: All three patients underwent ⁹⁹mTc-human serum albumin (HSA) scintigraphy to evaluate stagnation of albumin in the kidneys during the acute period. We also performed immunohistochemical staining for megalin, cubilin and neonatal Fc receptor in kidney biopsy samples that were physically associated with resorption of urinary albumin at proximal tubules in the patients with paradoxical hypoalbuminemia (n=3). As positive and negative controls, kidney biopsy samples from children with nephrotic syndrome presenting with severe proteinuria (n=3) and in remission (n=3) were examined, respectively.

Results: ⁹⁹mTc-HSA scintigraphy revealed that labeled albumin was strongly accumulated in the kidneys of all three patients, even after 48 hours. The prolonged stagnation of labeled albumin suggested that albumin may be remarkably reabsorbed in the kidneys. In the patients with nephrotic syndrome presenting with severe proteinuria (n=3) and in remission (n=3), megalin was immunostained along the brush border of the proximal tubules. However, in the three patients with paradoxical hypoalbuminemia despite no or subtle proteinuria, megalin was more strongly stained not only along the brush border but also within the cytoplasm of epithelial cells of the proximal tubules. In contrast, cubilin and neonatal Fc receptor showed no significant differences in their staining patterns and intensities among the three groups. Clinically, all patients with paradoxical proteinuria responded well to prednisolone, and their serum albumin returned to the normal range, although the urinary protein levels were absent or subtle.

Discussion: Megalin expressed on proximal tubules plays an essential role in albumin resorption from primitive urine. The resorbed albumin is degraded into amino acids and recycled. In our patients, increased expression and upregulation of megalin could have led to the transport of huge amounts of urinary albumin from the tubules to the cytoplasm, which might have resulted in the paradoxical hypoalbuminemia despite no or subtle proteinuria in active nephrotic syndrome.
Successful renal transplantation in Fechtner syndrome

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Background: Fechtner syndrome is one of the MYH9-related disorders (MYH9-RD), a group of autosomal dominantly inherited disorders caused by mutations of the MYH9 gene, which encodes the non-muscle myosin heavy chain IIA (NMMHC-IIA). The cardinal feature of MYH9-RD is macrothrombocytopenia. Fechtner syndrome has the additional clinical features of glomerulopathy, sensorineural hearing loss and cataracts. Successful renal transplantation has been rarely reported in patients with MYH9-RD. This report covers our experience performing renal transplantation in a patient with Fechtner syndrome.

Case: A 17-year-old girl was admitted to Kyung Hee University medical center for living-related renal transplantation. She was diagnosed at two years old as having idiopathic thrombocytopenic purpura which proved refractory to intravenous immunoglobulin (IVIG), steroid and anti-D IG. At age 9 years, she developed hematuria and proteinuria and two years later, she performed renal biopsy. Based on the diagnosis of diffuse mesangial proliferative glomerulonephritis with interstitial tubulitis, she had taken immunosuppressants including steroid and cyclosporine. Despite of these managements, her renal function worsened gradually and subsequently progressed to end-stage renal disease at her age of 17 years. Because of uremic symptoms, she underwent hemodialysis for 2 weeks before receiving a renal transplant. On admission for transplantation, her platelet count was 44,000/mm³, BUN 47 mg/dL and creatinine 7.9 mg/dL. To prevent and control bleeding, she received IVIG (1g/kg) at D-1 and 10 packs of platelets perioperatively. The operation was performed without excessive bleeding and postoperatively, the platelet count was 126,000/mm³. However, since 1 hour after surgery, her blood pressure dropped, urine output decreased and excessive oozing developed at the surgical site. After removing large hematoma around transplanted kidney, her graft function was improved. At D4, seizure activity and left hemiparesis developed abruptly. Her blood pressure was 180/97 mmHg and serum calcium was 6.2 mg/dL. Bain CT showed infarctions at both parietal lobes and the diagnosis of posterior reversible leukoencephalopathy was made. She performed genetic study and a mutation was detected in MYH9 exon 16 (p.Arg702Cys), compatible with Fechtner syndrome. This mutation was not found in her parents and younger sister, which was a de novo mutation. An audiogram revealed bilateral high-frequency hearing deficit and she needs a hearing aid. The peripheral blood smear showed giant platelets, but no apparent inclusion bodies. On ophthalmic examination, cataracts were found in both eyes. All of these finding were compatible with Fechtner syndrome. She discharged with good graft function and improved neurologic symptoms. An eight month follow-up of the patient showed a favorable clinical course. His platelet count was stable and the graft function was well maintained.
[Poster presentation]

Wegener’s granulomatosis associated with IgA nephropathy

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Background: Wegener’s granulomatosis (WG) is a rare necrotizing granulomatous vasculitis that affects small to medium sized vessels. Glomerular lesion of WG is demonstrated typically as crescentic glomerulonephritis with or without necrotizing lesion, where little or no staining for immunoglobulins and complements is observed. We present a rare child case of WG associated with IgA nephropathy that is a representative immune-mediated glomerular disease.

Case: A 13-year-old girl had been admitted to a previous hospital because of the ankle joint pain and the purpura on the upper and lower extremities. Although her symptoms had been temporarily cured by the high dose of oral prednisolone treatment, its dose tapering led to the recurrence of joint pain and purpura. She had also had microscopic hematuria and proteinuria and high titer of serum PR-3 ANCA, and thus she had been transferred to our hospital. The first kidney biopsy was performed.

Light microscopic examination contained 8 glomeruli, which revealed necrotizing sclerosis in 1 glomerulus and mild mesangial proliferation in the other 7 glomeruli. Immunofluorescence microscopy and electron microscopy demonstrated no immune deposits and electron dense deposits, respectively. Based on the diagnosis of WG, she first underwent the intravenous methylprednisolone pulse therapy that was followed by oral prednisolone (1mg/kg/day) and oral cyclophosphamide (2mg/kg/day) for 12 weeks. This combined immunosuppressive therapy led to the drastic reduction of serum PR-3 ANCA associated with the absence of any WG-like symptoms including urinalysis. However, despite the PR-3 ANCA level was stable within nearly normal range, urinalysis revealed the reappearance of proteinuria (protein/creatinine, 1.1) and microscopic hematuria, thus the second renal biopsy was performed. Light microscopic examination containing 18 glomeruli revealed segmental sclerosis in 1 and fibrous crescent in 1. Other glomeruli showed mild ~ moderate mesangial matrix expansion and cell proliferation. Immunofluorescence microscopy demonstrated predominant IgA and C3 deposition in the mesangium as a granular pattern. Electron-dense deposits were apparently recognized in the paramesangial region.

Conclusion: Thus, we concluded that IgA nephropathy was associated with WG. Oral prednisolone was again increased, which led to rapid improvement of urinary findings. We will also discuss the relevance of this case based on the literature.
**Background:** The most common kidney complication induced by D-penicillamine in Wilson’s disease is membranous nephropathy. Minimal change and antineutrophilic cytoplasmic antibody (ANCA)-associated crescentic glomerulonephritis are also reported. However, the present case interestingly showed ANCA-negative pauci-immune crescentic glomerulonephritis.

**Case:** A 21-year-old woman was referred to our division for proteinuria, hematuria, and kidney dysfunction. She was diagnosed as Wilson’s disease at age 5. D-penicillamine therapy was initiated, and microhematuria first appeared at age 18. At the initial visit, urine protein/creatinine (Cr) was 4.9 g/gCr; urinary RBC count, 30-49/high-power field; blood urea nitrogen, 39.5 mg/dL; serum Cr, 1.89 mg/dL; albumin, 3.8 g/dL; and cystatin C, 1.53 mg/dL. D-penicillamine was discontinued immediately, but her renal function was not improved. Kidney biopsy revealed that 90% of glomeruli showed diffuse scleroses and fibrous crescents, and 70% of tubulointerstitial area were atrophied. Immunofluorescence revealed nonspecific entrapment of IgG, IgM, and C3 in sclerotic area. Electron microscopy demonstrated tiny amount of dense deposit in mesangium or subendothelium area. Both serum myeloperoxidase (MPO) ANCA and proteinase 3 (PR3) ANCA were negative. For these reasons, this patient was diagnosed as pauci-immune crescentic glomerulonephritis. Methylprednisolone pulse therapy followed by oral prednisolone was performed; however, hypoalbuminemia and edema progressed gradually. From 12 weeks after initiation of treatment, oral cyclophosphamide therapy (50 mg/day) was added for 12 weeks. Thereafter, serum albumin level was normalized, and kidney dysfunction has not progressed for two years.

**Discussion:** This patient showed characteristic findings as follows: First, ANCA-negative pauci-immune crescentic glomerulonephritis was observed. Glomerular injury has not been reported in Wilson’s disease itself: most cases were D-penicillamine-induced membranous glomerulopathy. To our knowledge, this is the first report of ANCA-negative pauci-immune type gloemrulonephritis. Second, kidney dysfunction progressed after more than a decade. Proteinuria typically develops within the first 6 to 12 months of chelating therapy. Even in other drug-induced crescentic glomerulonephritis, administration duration is less than several years at the longest. Finally, immunosuppressive therapy was required for our patient. Usually, discontinuation of medication leads to resolution of the proteinuria within two years. In contrast, ANCA-negative pauci-immune glomerulonephritis is known to have unfavorable prognosis. Therefore, she was treated with strong immunosuppressant, which resulted in successful outcome.

**Conclusions:** We reported a unique case in which D-penicillamine therapy for Wilson’s disease induced pauci-immune crescentic glomerulonephritis after more than ten years of therapy. Attention needs to be paid to occurrence of rapidly progressive glomerulonephritis during D-penicillamine therapy, even after long-term administration without complications.