Programme

10:00 I. Opening

1. Kazuo Suzuki (National Inst. of Infect. Dis., Tokyo)
   Needs of Synthetic IVig in the World
2. N. Uemura (Planning Director, Blood and Blood Product Division, Ministry of Health, Labour and Welfare, Tokyo)
   Japan's Blood Product Supply and Regulations

10: 20 II. Epidemiology

Chairs: Y. Inaba (Juntendo Univ. School of Med., Tokyo) and T. Yamazaki (Univ. of Tokyo, Tokyo)

1. S. Fujimoto and H. Nunoi (Miyazaki Univ. School of Med., Miyazaki)
   Incidence of ANCA-associated Primary Renal Vasculitis in Miyazaki Prefecture: The first population-based, retrospective Epidemiological survey in Japan
2. K. Iseki (Dialysis Unit, University Hospital of The Ryukyus)
   Incidence and prevalence of PVS in Okinawa, Japan
3. R. Watts (Norfolk & Norwich Univ. Ipswich, UK)
   Epidemiology of Vasculitis – European studies
4. D. Scott (Norfolk & Norwich Univ. Norwich, UK)
   Epidemiology Studies in Systemic Vasculitis in Norfolk, UK

11: 40 III. Vasculitis in Lung

Chairs: Y. Aizawa (Niigata Univ. Gr. School of Med., Niigata) and
A. Fukatsu (Kyoto Univ. Gr. School of Med., Kyoto)

1. T. Nozu (NIID, Tokyo Women's Medical University Univ.) and M. Kondo (Tokyo Women's Univ., Tokyo)
   Prevalence and clinical manifestation of pulmonary fibrosis in antineutrophil cytoplasmic antibody-associated vasculitis
2. D. Jayne (Addenbrooke's Hospital, Cambridge Univ., UK)
   Association of ANCA vasculitis with pulmonary fibrosis and dementia

12: 20 Lunch

13: 00 IV. Therapy (Clinical Trial of IVIg for RPGN etc.)

Chairs: E. Muso (Kitano Hospital Medical Res. Inst., Osaka) and
T. Okazaki (Hiroshima City Hospital, Hiroshima)

1. E. Muso (Kitano Hospital Medical Res. Inst., Osaka) and Members of the Clinical Trial
   Clinical Trial of IVig therapy in MPO-ANCA related microscopic polyanglitis (MPA) with rapidly progressive glomerulonephritis (RPGN)
2. T. Saji (Toho Univ. School of Med., Tokyo)
   Reduction of Oxydant Stress by High-Dose Intravenous Immunoglobulin in Acute Stage Kawasaki Disease- Evaluation of Serum Reactive Oxygen Species(ROS)
3. E. Imai (Osaka Univ. Gr. School of Med., Osaka)
   An ANCA associated nephritis induced by propylthiouracil
4. K. Yamagata (Tsukuba Univ. Gr. School of Med., Tsukuba)
   Infectious complications in ANCA associated vesculitis; benefits of high-dose intravenous immunoglobulin treatment
5. N. Tamura (Juntendo Univ. School of Med., Tokyo)
   Successful treatment of Wegener's granulomatosis with rituximab in two refractory cases
6. Y. Arimura (Kyorin Univ. School of Med., Tokyo)
   Relationship between pulmonary fibrosis and alveolar hemorrhage in MPO-ANCA associated vasculitis

14:35 Break

14: 50 V. Pathology, Clinical Research and Model Mice-1

Chairs: S. Naoe (Toho Univ., Tokyo) and M. Nose (Ehime Univ. Med School, Ehime)

1. **F. Ferrario (Milano Univ. School of Med., Milano)**
   Morphological features in ANCA-Associated vasculitis
2. **K. Takahashi (Toho Univ. School of Med., Ohashi Hospital, Tokyo)**
   The Effect of Synthetic Immunoglobulin (SyIG) in Mice Vasculitis Model caused by CAWS
3. **N. Ohno (Tokyo Univ. Pharm., Tokyo)**
   Culture condition modulates active moiety of CAWS, vasculitis inducer from *C. albicans*
4. **A-I. Okawara (National Inst. of Infect. Dis., Tokyo)**
   Activation of neutrophils in the initial step of arteritis induction by CAWS
5. **T. Ito-Ihara (Kyoto Univ. Gr. School of Med., Kyoto) and K. Uno (Kyoto Lous-Pateur Medical Institute, Kyoto)**
   Circulating Levels of IL-12, 23 and IL-18 in Patients with MPO-ANCA-associated Vasculitis

16: 20 VI. Pathology, Clinical Research and Model Mice-2

Chairs: N. Ohno (Tokyo Univ. Pharm., Tokyo) and K. Uno (Kyoto Lous-Pateur Medical Institute, Kyoto)

6. **T. Ono (University of Shizuoka., Shizuoka)**
   The relationship between renal lesions and lung vascular lesions in SCG/Kj mice as a model of ANCA-associated crescentic glomerulonephritis
7. **W. Yumura (Tokyo Women's Medical University, Tokyo)**
   A Novel Mouse Model for MPO-ANCA-Associated Glomerulonephritis – Analysis of Pathogenesis
8. **S. Kobayashi (Juntendo Koshigaya Hospital, Saitama)**
   Effect of immune complexes in serum from patients with rheumatoid vasculitis on the expression of cell adhesion molecules on polymorphonuclear cells.
9. **K. Yamamoto and A. Hoshino (IMCJ, Research Institute, Tokyo)**
   Usage of Quantum dots for the evaluation of vasculitis
10. **Y. Yamanishi (Hiroshima City Hospital, Hiroshima)**
    Usefulness of nMPO-ANCA in diagnosing and treating vasculitis - discrepancy between MPO-ANCA and nMPO-ANCA-
11. **Y. Aratani (Yokohama City Univ. Kihara Biol. Inst., Yokohama)**
    Role of Neutrophil-derived ROS for the Ultraviolet-induced Skin Inflammation

17: 50 VII. Synthetic IVIg and Pharmacogenetics-Specific Genes

Chairs: Y. Kameoka (NIID, Tokyo) and Y. Aratani (Yokohama City Univ. Kihara Biol. Inst., Yokohama)

1. **M. Furutani (Sekisui Chemicals, Kyoto)**
   Synthetic polyclonal immunoglobulin
2. **H. Nojima (Osaka Univ., Osaka)**
   Comprehensive isolation of the genes that are specifically expressed in the blood cells of angiitis patients

18: 30 Closing Remarks Yoshiyuki Niho (Chihaya Hospital, Fukuoka)

18:45 Reception at Cafeteria

1-1

安全なガンマグロブリン製剤開発—人工ガンマグロブリン グローバル使用の要望に応える

鈴木和男

国立感染症研究所生物活性物質部

血管炎である川崎病の治療をステロイドパルスからガンマグロブリン製剤(IVIg)に変えてから、重篤な病態は激減した。一方、わが国に多く、高齢者に発症する難治性のMPO-ANCA関連血管炎は近年増加しており、急性進行性糸球体腎炎へのIVIg治療が補助療養として有効であるとの成績が報告され(Ito-Ihara et al., Nephron Clin Pract. 102:c35-c42, 2005)、臨床探索試験も開始された。また、他の難治性疾患へのIVIg治療も好成績を示すなど、ガンマグロブリン製剤の使用量の増加が見込まれている。しかし、感染リスクの軽減から人工化製剤が求められている。また、海外とくに東南アジアでの同様な疾患へのIVIg治療が必至であるにもかかわらず、製剤化がままならず、また、日本からの輸出も禁止されている状況にある。本シンポジウムでは、血管炎の「治療」、「臨床」、「モデル動物」、「遺伝子、分子解析・合成」、「疫学」についてグローバルな観点からから討論し、「人工ガンマグロブリン製剤」の開発の要望の現状と展望について討論したい。

Immunomodulatory therapy for vasculitis with synthetic IVIG based on global request

Kazuo Suzuki, National Inst. of Infectious Diseases, Tokyo

High dose intravenous immunoglobulin (IVIg) treatemnthas been ferformed as a standard therapy for Kawasaki disease. On the other hand, for other vasculitis rapid progressive glomerulonephritis (RPGN) classified to MPO-ANCA associated vasculitis, IVIg treatment improves the outcome of this highly life-threatening disease in Europe and Japan. in addition to any therapeutic trials for have been performed. One of potential mechanisms may be the suppression of the presentation of MPO to stimulated neutrophils, although there are many potential mechanisms underlying the beneficial effect of IVIg, The favorable outcome of the IVIg for MPO-ANCA related RPGN in Japan and the partial elucidation of the mechanism of action has been reported (Ito-Ihara et al., Nephron Clin Pract. 102:c35-c42, 2005), and randomized clinical trial for the disease is in progress. For safety, we have to develop a synthetic IgG for the therapy using a novel techniques.

In this symposium, we will discuss about Clinical treatment, Model animals, Gene technology for evaluation and synthesis of IgG, Clinical trials and Epidemiology in the global communications.

1-2

我が国の血液製剤の供給と法規制

植村　展生
厚生労働省血液対策課企画官

○ 血液事業の歴史
　1964 年 ：閣議決定 「献血の推進について」
　2002 年 ：安全な血液製剤の安定供給の確保等に関する法律（血液法）
　　及び 薬事法 (改正)
○ 品質、安全性に係る法的枠組み
　1) 血液法
　　基本方針、計画（献血推進、需給）等
　2) 薬事法
　　許可、承認、GMP 、表示、記録、副作用報告 等
○ 基本理念
　1) 安全性　2) 安定供給　3) 適正使用　4) 透明性
○ 血液事業の概要
　日本赤十字社、 民間事業者（製造、輸入）
○ 血液製剤の国内自給
　1974 ～ ：輸血用血液製剤のすべて
　1994 ～ ：血液凝固第Ⅷ因子製剤 (血漿由来)
　2004　：免疫グロブリン製剤: 88%　アルブミン製剤: 50%
○ 若年層献血者の減少傾向

Japan's Blood Product Supply and Regulations

Nobuo Uemura
Blood and Blood Product Division, Ministry of Health, Labour and Welfare, Tokyo

○ History of Blood Program
　1964 : Cabinet decision on promotion of voluntary, unpaid donation
　2002 : The Law on Securing Stable Supply of Safe Blood Products　&　Pharmaceutical Affairs Law (Revised)
○ Legal Framework on Quality and Safety
　1) The Law on Securing Stable Supply of Safe Blood Products
　　Policy , Plan (Donation Promotion , Demand and Supply) etc.
　2) Pharmaceutical Affairs Law
　　License , Approval , GMP , Labeling , Record , Monitoring etc.
○ Basic Principles
　1) Safety　2) Stable Supply　3) Appropriate Use　4) Transparency
○ Blood Service System in Japan
　Japan Red Cross , Private Manufacturers and Importers
○ Local Production of Blood Products
　1974 ～ : All Blood Transfusion Products
　1994 ～ : Coagulation Factor Ⅷ products (Plasma Derived)
　2004　: Immuno-globulin : 88%　Albumin : 50%
○ Decrease of Donors among Young Generations

2-1

Incidence of ANCA-associated primary renal vasculitis in Miyazaki Prefecture: The first population-based, retrospective epidemiological survey in Japan

Fujimoto S, Uezono S, Hisanaga S, Fukudome K, Kobayashi S, Suzuki K, Hashimoto H, Nunoi H.

Miyazaki Univ. School of Med., Miyazaki

Background: Clinicoepidemiological manifestations of the vasculitides geographically differ. According to a hospital-based nationwide survey, the prevalence of microscopic angiitis (MPA) and/or renal limited vasculitis (RLV) in Japan is much higher than that of Wegener's granulomatosis (WG). However, little is known about the incidence of ANCA-associated primary renal vasculitis (PRV) in Japan. Methods: The incidence of PRV was retrospectively determined by a population-based method in Miyazaki Prefecture, Japan between 2000 and 2004. We defined PRV according to the following criteria by the European Systemic Vasculitis Study Group: 1) new patients with WG, MPA, Churg-Strauss syndrome (CSS) or RLV, 2) renal involvement attributable to active vasculitis and 3) ANCA considered positive if the disease was not histologically confirmed. Results: The numbers of patients with PRV in the years 2000, 2001, 2002, 2003 and 2004 were 9, 9, 9, 16, and 13, respectively. The male to female ratio was 24:32 and the average age was 70.4±10.9 (mean±SD) years. The estimated annual incidence of PRV was 14.8 (95% C.I. 10.8 ▪8.9) and 44.8 (95% C.I. 33.2 ▪56.3) per million adults (≧ 15 years old) and seniors (≧ 65 years old), respectively. Ninety-one percent of the patients were MPO-ANCA positive, but none were positive for PR3-ANCA. There were no WG/CSS patients. Conclusion: The incidence of PRV did not differ between Japan and European countries, but WG was not widespread in Japan. Furthermore, the ratio of serum MPO/PR-3 ANCA among Japanese patients with PRV was much higher than that found among European and American patients.

2-2

沖縄県におけるPVCの頻度および発症率調査

井関邦敏

琉球大学院学部附属病院血液浄化療法部

沖縄県中南部地域、成人人口約78万人（16病院、9クリニック）を対象に原発性血管炎（primary vasculitis syndrome, PVS）の頻度、発症率を2005年度より調査している。また2000年度から2004年度にかけて当該施設より提出されたPR3 ANCAおよびMPO ANCAの検体数を調査している。2005年度上半期のMPO ANCAおよびウゲナー症候群の頻度、発症数はそれぞれ24 (7)、5 (0)であった。主要3施設の検体数は2002年度より増加傾向にある。PR3 ANCAおよびMPO ANCAの検体数の増加に伴い、血清診断は陽性であるが、臨床症状が軽度ないし伴わない例も知られている。

Incidence and Prevalence of PVS in Okinawa, Japan

Kunitoshi Iseki

Dialysis Unit, University Hospital of The Ryukyus

We are investigating the prevalence and incidence of primary vasculitis syndrome (PVS) in Okinawa, Japan. The target area is the central-southern part of the main island of Okinawa, where the adult population is about 780,000. There are 16 hospitals and 9 clinics, where they might treat such patients. All of them have dialysis facilities. We are also asking to report the total number of samples sent to the laboratory such as PR3 ANCA and MPO ANCA.

In 2005, January to June, the prevalent (incident) number of patient with MPO ANCA was 24 (7), and that of PR3 ANCA was 5 (0). According to the three main hospitals, the number of samples sent to the laboratory has increase from 2000 to 2004. The total number of sample was 522 for MPO ANCA and 264 for PR3 ANCA in 2004. There are cases in which the test are positive, but have slight or no clinical symptoms.

2-3&2-4

Epidemiology of Vasculitis – European and UK Studies

David G I Scott and Richard Watts
Norfolk and Norwich University Hospital, Ipswich Hospital,
Department of Medicine, University of East Anglia

Data, particularly from Europe, suggests that differences reported on the frequency of the primary systemic vasculitides (PSV) – Wegener's Granulomatosis (WG) and microscopic polyangiitis (MPA) may be linked to latitude with WG more common in Northern Europe and MPA more common in Southern Europe but similar overall incidences of the combined diseases (including Churg-Strauss syndrome as well as WG and MPA) of 15 to 20 new cases per million population per year. In Japan MPA appears to be much more common than WG although any relationship to latitude is unknown. Differences appear to exist between the associations of the PSV with ANCA where renal vasculitis is almost exclusively associated with MPO ANCA in Japan whereas in Europe there is a slightly stronger association with PR3 ANCA than with MPO ANCA.

One explanation for some of these geographical findings may be the different use of classification systems to define the different diseases (PSV). We therefore as part of a European initiative and in conjunction with the European Medicines Evaluation Agency (EMEA) and with colleagues from 6 different European countries have developed an algorithm, designed purely for epidemiological purposes, to address this issue using the ACR classification criteria and the Chapel Hill Consensus definitions, together with some surrogate markers. Our preliminary results suggest that this system is useful, reproducible and relatively easy to use for clinical and paper cases of PSV and is being evaluated for future European epidemiological studies.

In Norfolk, UK we have used this system to review our own cases of PSV over the past 15 years and compared changes in PSV epidemiology with that of systemic rheumatoid vasculitis over the same time period. In contrast to SRV which has declined in incidence quite significantly over the last 15 years (falling from 10/million/year to 3/million/year), the incidence of the PSV has remained relatively stable with an overall incidence of 20/million/year (?similar to some data from Japan) with WG still more common (10/million/year) than MPA (6/million/year).

3-1

間質性肺炎におけるANCA陽性例のPrevalenceと病態

野津朋子[1,2]、近藤光子[1]、鈴木和男[2]、永井厚志[1]
[1]東京女子医大、[2]国立感染症研究所

ANCA関連血管炎で共通に侵される臓器は肺と腎で、肺血管炎は通常、全身の血管炎症候群の一症状として発症する。MPO-ANCA陽性症例の肺病変の内訳は間質性肺炎と肺出血が主体である。本調査では間質性肺炎におけるANCA陽性例の頻度と病態について検討した。
2000年から2005年までに東京女子医科大学呼吸器内科に間質性肺炎として入院し、ANCAを測定できた42症例を対象とした。初発症状、血液検査(MPO-ANCA、PR3-ANCA、CRP、KL-6、SP-D、SP-A、BUN、Cr)AaDO2、肺機能検査、胸部レントゲンを施行した。
MPO-ANCA陽性症例は42症例中7症例(16.7%)で、PR3-ANCA陽性症例は42症例中4症例(9.5%)であった。MPO-ANCA陽性症例ではAaDO2、CRPが高値で%DLCOが低値の傾向にあった。PR3 -ANCA陽性症例では%DLCOが低値の傾向にあった。ANCA陽性の間質性肺炎症例において、診断時に肺病変が腎病変に先行していたのは10症例中7症例であった。間質性肺炎と診断された段階で治療を行い、腎病変の発症を予防できる可能性がある。それには早期発見が重要である。また、ANCA陽性の間質性肺炎症例では陰性症例に比べ、癌化率が有意に高いといわれており、今後の検討が更に期待される。また、症例数を増やし、更なる検討を行う。

Prevalence and clinical manufestation of pulmonary fibrosis in antineutrophil cytoplasmic antibody-associated vasculitis

Tomoko Nozu[1,2], Mitsuko Kondo[1], Kazuo Suzuki[2], and Atushi Nagai[1]
[1]Tokyo Women's Medical University, [2]National Institute of Infectious Diseases

[Objective] Some cases of patients with alveolar haemorrhage, bronchiolitis obliterans organizing pneumonia, diffuse panbronchiolitis, bronchiolitis, diffuse alveolar damage and pleuritis have been reported to show anti-neutrophil cytoplasmic antibody (ANCA) in the sera, indicating ANCA-associated pulmonary diseases. However, the association of these diseases with pulmonary fibrosis (PF) has not been well documented. The aim of this study is to present the clinical manifestations of PF associated with ANCA in serum. [Methods] ANCA titer of sera of 42 patients with PF, who admitted to our respiratory division during the period 2000 through to 2005, was examined. The clinical features, blood test, chest CT scan images, pulmonary function test, pathological findings were evaluated. [Results and Discussion] Among the 42 patients, sera of 7 patients (16.7%) showed MPO-ANCA positive, and 4 patients (9.5%) PR3-ANCA positive. Patients with MPO-ANCA positive were shown tendency to high level in AaDO2 and CRP, and low level in %DLCO, indicating association with respiratory dysfunction. In addition, pulmonary dysfunction in patients with ANCA-positive PF (73%).was observed prior to renal dysfunction, suggesting that pulmonary vasculitis may occur prior to renal vasculitis.

3-2

Association of ANCA Vasculitis with pulmonary fibrosis and dementia

David Jayne
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Abstract

The lung is involved in over 60% of patients with ANCA associated systemic vasculitis and several patterns of lung Vasculitis are recognised. The presence of chronic lung diseases, such as cystic fibrosis and bronchiectasis, and occupational exposure to silica is associated with an increased risk of ANCA Vasculitis. It has recently been observed that there is an association between pulmonary fibrosing syndromes, such as usual interstitial pneumonitis, and ANCA Vasculitis. These patients are typically MPO-ANCA positive but it is unclear to what extent MPO-ANCA contributes to the pathogenesis of the pulmonary fibrosis. Clinical involvement of the central nervous system is rare in ANCA associated Vasculitis but radiological abnormalities are frequently found of uncertain significance. The recent observation of the co-occurrence of ANCA Vasculitis and dementia raises the possibility that clinically significant central nervous system involvement is more frequent than previously recognised and this merits further study. The different patterns of Vasculitis between individuals and ethnic groups remain a challenge for investigators to explain and awaits improved understanding of the genetic susceptibility to Vasculitis.

4-1

Clinical Traial for IVIg therapy in MPO-ANCA related microscopic polyangiitis (MPA) with rapidly progressive glomerulonephritis(RPGN).

われわれは MPO-ANCA 陽性の顕微鏡的多発血管炎(MPA)に伴う急速進行型糸球体腎炎の免疫抑制治療まえに IVIg療法単独使用し、その免疫修飾作用した。全国症例の報告のまとめでは、良好な腎予後に加え、治療後の6ヶ月時点で、感染による生命死は報告されていないことも明らかとなった。

本治療法の MPO-ANCA 関連急速進行型糸球体腎炎に対する良好な効果を裏づけるべく、わが国において多施設共同での RCT が計画され、2005 年8月から厚生労働省の認可をえて開始された。本試験では、対象をわが国の ANCA 関連急速進行性糸球体腎炎の分類での I, II 群に絞って、IVIg 療法とわが国の進行性腎障害に関する調査研究班の急速進行性糸球体症候群分科会の制定したガイドラインに沿った治療を平行して行い、IVIg使用、非使用群間で、腎機能の改善度、ステロイド、免疫抑制剤の使用量、感染症の発症頻度などをエンドポイントとして比較検討を行う。現在4症例がエントリーされており、最初の2症例の経過では、その盲検性の確保などいくつかのポイントが重要であることが明らかとなり、今後の本試験の進行に役立つ経験がなされている。

Clinical Traial for IVIg therapy in MPO-ANCA related microscopic polyangiitis (MPA) with rapidly progressive glomerulonephritis(RPGN).

Eri Muso[1], Toshiko Ito-Ihara[1,2] Kazuko Uno[3], Tsunataro Kishida[3],Kazuo Suzuki[4], Hiroshi Hashimoto[5] and the Study Group for the Prospective Randomized Control Trial of IVIg in MPO-ANCA related RPGN

[1]Division of Nephrology , Kitano Hospital The Tazuke Kofukai Medical Research Institute, Osaka, [2]Department of Nephrology, Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, [3]Luis Pasteur Center for Medical Research [4]Department of Bioactive Molecules, National Institute of Infectious Diseases, [5]Department of Clinical Immunology, Medical School of Juntendo University, Tokyo

Recently we experienced the favorable results of IVIg monotherapy for 15 MPO-ANCA positive RPGN patients in MPA showing rapid decrease of CRP, WBC, Cr, and BVAS in association with down regulation of the serum inflammatory cytokines especially of TNF α. In addition, the survey of IVIg therapy has proved its efficacy for 30 MPO-ANCA related RPGN patients (male 17, female 13 average age with 68±11.8) revealed high renal survival rate and no fatal infection at 6 months after IVIg treatment.

To establish the evidence of the effectiveness of this therapy for RPGN due to MPO-ANCA positive MPA, a double-blind, multi-center, randomaized controlled trials (RCTs) was planned. Enrollement was started in August 2005. Considering the severity of the disease, the grade of the diasese severity of the enrolled patients was restricted to relatively low. In addition, to avoid the progression of renal dysfunction during the infusion of IVIg or placebo, concomitant start of steroid therapy was obligated. The study course of starting two cases showed the promissing process of this nationwide trial..

4-2

急性期川崎病に対する免疫グロブリンの酸化ストレス抑制効果

佐地 勉、高月晋一、岡松千都子、嶋田博文、中山智孝、松裏裕行
東邦大学医療センター大森病院小児科

我々は急性期川崎病 aKD において酸化ストレス(OS)の代謝産物である尿中 8-イソプロスタンが上昇していること,さらに IVIG により正常化する事を報告した。近年、OS の原因物質として reactive oxygen species (ROS) が報告されている。ROS には super anion radical,hydrogen peroxide,hydroxyl radical が含まれ、再灌流傷害、糖尿病、低酸素血症で上昇する。
方法:血清 ROS 測定:再現性・安定性に優れている Total ROS assay system。
対象・方法:aKD10 名、年齢:3m-3y、男 6 女 4.、 対象 19 名、 男 8 女 11。
使用 IVIG 1g/kg・日:2 例、2g/kg・日:8 例
結果:aKD—IVIG 前値 284±57(unit):健常対照:190±53 で有意に ROS 値は上昇していた。IVIG 投与前と投与 3 日後(240±49、)、投与 7 日後(226±66)では有意に低下していた。ROS は心筋傷害のパラメータである BNP と有意に相関していた。

Reduction of Oxydant Stress by High-Dose Intravenous Immunoglobulin in Acute Stage Kawasaki Disease - Evaluation of Serum Reactive Oxygen Species(ROS)

Saji T, Takatsuki S, Okamatsu C, Shimada H, Nakayama T, Matsuura H.
Department of Pediatrics, Toho University, Medical Center, Omori Hospital, Tokyo, Japan.

Introduction: Kawasaki Disease is characterized as a mid-sized systemic arteritis complicating well-known coronary arterial aneurysms. High-dose(1~2g/kg/day) intravenous immunoglobulin(IVIG) has been used since 1990's to suppress the polyclonally activated immune responces in aKD. We've reported that the increased urinary 8-isoprostane, which is a stable oxidant stress product in urine, is significantly reduced by IVIG. This time, we examined the serum reactive oxygen species (ROS) , including super anion radicas, hydrogen peroxide, hydroadical, materials for OS, @ before, 3days and 7days after IVIG in patients with aKD.
Patients: aKD: n=10,M6:F4, age:3m-3y, **Control**: n=19, M8:F11, age 6m-4y
Method: Total ROS assay System
Rseults: aKD—before IVIG: 284±57(unit) vs Controls : 190±53 ($p<0.05$)
before IVIG vs 3 days after IVIG: 240±49($p<0.0004$)、7 days after IVIG :226±66($p<0.05$). Significanty correlation between ROS and brain natriuretic peptide (BNP) which is a sensitive serum myocardial biomarker was demonstrated($k=0.74, p<0.02$)。
Conclusion: IVIG can reduce oxygen stress and reactive oxygen species.

4-3

An ANCA associated nephritis induced by propylthiouracil

症例 47歳女性 39歳時より気管支拡張症とPs.aeruginosaの持続感染にて当院に通院。43歳時より甲状腺機能亢進症を来たし thiamazole 30 mg/day を開始したが、薬疹のためpropylthiouracil(PTU) 300 mg/dayに変更した。47歳時、発熱があり抗生剤治療をするも改善せず呼吸器内科にて肺胞出血が診断された。血液検査にて MPO-ANCA1820EU、PR-3ANCA106EUと高値であり、PTUによる薬剤誘発性ANCA関連腎炎と診断された。

なお保存血清による確認では約1年前からMPO-ANCAは400EUと高値でありその後も高値が持続していたが、PR-3ANCAは陰性であり、発症直前でも15EU、発症後は106EUと上 昇していた。本症例に対して大量IVIG(400mg/Kg/day*5day)療法に引き続き、プレ ドニンパルス療法を施行し、直ちにCRPは陰性化し、基礎疾患にあるPs.aeruginosaも プレドニン投与量の多い1ヶ月間は悪化することなく経過した。IVIG の感染予防効果 の薄れる1ヵ月後からは抗生剤の投与が必要となった。大量IVIG療法はANCA関連血管 炎の治療に有効であると同時に感染症の予防として有効であると考えられた

An ANCA associated nephritis induced by propylthiouracil

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Case 47 years female. She had been suffering from bronchiectasis and continuous infection of Ps.aeruginosa from her age of 39 and she came to our hospital. From 43 years old, she was suffered from hyperthyroidism and thiamazole 30 mg/day was administrated, but drug rush made the drug changed to propylthiouracil (PTU) 300 mg/day. At the age of 47, she had fever and administration of antibiotics had no effect, and she was hospitalized to our hospital. Bronchfiberscope revealed alveolar hemorrhage. In blood analysis, MPO-ANCA was 1820EU, PR3-ANCA was 106EU, so the patient was diagnosed as ANCA associated nephritis induced by propylthiouracil. Our hospital has her frozen serum because of her hyperthyroidism. We checked previous ANCA activity, and 1 year before her fever and alveolar hemorrhage, MPO-ANCA was already 400EU, but PR-3ANCA was negative, and just before her hospitalization, PR-3ANCA was 15EU and after her fever PR-3ANCA was 106EU. We administrated intravenous immunoglobulin administration (IVIG) (400mg/Kg/day*5day) and steroid pulse therapy. Her CRP became negative immediately, and during first one month when she took large amount of steroid Ps.aeruginosa did not go worse. After one month when the anti-biotic effect of IVIG became weak, we had to administrate antibiotics drug to her Ps.aeruginosa. IVIG might be effective both for treatment of ANCA nephritis and for prevention of infection.

4-4

Infectious complications in ANCA associated vesculitis; benefits of high-dose intravenous immunoglobulin treatment.

わが国のANCA関連血管炎の特徴として、中高齢者のMPO-ANCA関連血管炎の比率が極めて高いことがあげられる。MPO-ANCA関連血管炎の特徴としては、欧米に多いPR3-ANCA関連血管炎に比べ、慢性、硬化性病変が主体であり、従来の血管炎症候群の治療に比べ、マイルドな免疫抑制療法を行うことで予後がより改善することを示してきた。その結果、6ヶ月生存率は1998年以前77.5%であったものが1999-2001年80.4%、2002年以降86.0%と、近年生命予後の著しい改善が認められた。しかしながら、この間の死亡原因における感染症の割合は、1998年以前50.0%、1999-2001年34.7%、2002年以降63.6%であり、未だ高率に死亡原因としての感染症があることが明らかとなった。本症による感染症の併発は、高齢患者の免疫能の低下による易感染性やMPO-ANCAの産生刺激、病態との関与が指摘されているものの、本症の治療法としてのステロイドならびに免疫抑制薬による免疫抑制療法が、日和見感染の罹患という最大の弱点を有しているのも事実である。一方、アフェレーシス治療やγグロブリン治療は少なくとも宿主の免疫抑制を来さずに血管炎治療が可能となる方法とも考えられている。本シンポジウムにおいては、更なるMPO-ANCA関連血管炎の予後改善のために、本症の治療法の工夫やその可能性について自験例を中心に検討する。

Infectious complications in ANCA associated vesculitis; benefits of high-dose intravenous immunoglobulin treatment.

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Patients with MPO-ANCA associated vasculits are older, and have more chronic and sclerotic lesions than patients with PR3-ANCA associated vasculitis. Recent advances of therapeutic methods for MPO-ANCA associated vasculits resulted in a significant improvement of prognosis of these patients in Japan. From a nation-wide survey for RPGN in Japan, six months survival rate of MPO-ANCA associated vasculits before 1998, 1999 to 2001, and after 2002 were 77.5%, 80.4% and 86.0% respectively. Fifty percent of the patients died due to infectious complications before 1998, however, 63.6% of the patients still died due to infectious complications even after 2002. Although principal treatment methods for ANCA associated vasculits are immunosuppressive drugs such as steroid or cyclophosphamide, high-dose intravenous immunoglobulin or apheresis are considered treatment options for avoiding opportunistic infections. We will show our experiences for high-dose intravenous immunoglobulin or apheresis in relapsing cases of MPO-ANCA associated vasculits, and discuss indications and effects of these treatment methods.

4-5

Rituximab が有効であった難治性 Wegener 肉芽腫症の 2 症例

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Rituximab による B 細胞除去療法が有効であった難治性 Wegener 肉芽腫症の 2 症例を報告する。症例1は 10 歳時発症の 14 歳女性、眼窩内病変による失明、および気道病変による呼吸器症状の増悪を認めたが、副腎皮質ステロイドおよび cyclophosphamide などによる治療に反応せず、rituximab 375 mg/mm2/week を 4 回投与した。MRI にて眼窩内病変の縮小、気管支鏡にて気管粘膜のびらん改善が認められ、BVAS は 13 から 5 点に低下した。症例2は右眼痛と眼球突出、および肥厚性硬膜炎を認めた 35 歳女性。難治性の眼窩内肉芽腫と肥厚性硬膜炎に対し、rituximab 投与を行ったところ、眼窩内病変の縮小と疼痛の改善、肥厚性硬膜炎の改善を認めた。また、2症例ともに direct ELISA 法で測定した PR3-ANCA は今回の増悪時も陰性であったが、capture ELISA 法では高値であり、臨床症状の改善に伴い低下を認めた。Rituximab による B 細胞除去療法は難治性の Wegener 肉芽腫症に対して有効な治療法と考えられた。

Successful treatment of Wegener's granulomatosis with rituximab in two refractory cases

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The first patient was a 14 year old girl with Wegener's granulomatosis began at the age of 10. She had headache, visual loss, cough, hemoptysis and short bless due to orbital and bronchial involvement, and her disease had not been responded to immunosuppressive therapy, including steroid and cyclophosphamide. We started rituximab, 375 mg/mm2/week, and treated totally 4 times. After the treatment, MRI showed diminishment of orbital granuloma, and bronchoscopy showed improvement of bronchial erosions. BVAS was decreased from 13 to 5. The second case was a 35 year old woman who had ophthalmalgia and exophthalmos of right eye due to orbital granuloma accompanied with refractory hypertrophic pachymeningitis. We treated her with rituximab. The ophthalmalgia disappeared with diminishment of orbital granuloma, and pachymeningitis also improved. In both cases, PR3-ANCA, which was negative measured by direct ELISA method, raised when measured with capture ELISA method, and decreased concomitantly with clinical improvement. B cell depletion therapy by rituximab is effective even in refractory Wegener's granulomatosis.

4-6

MPO-ANCA 関連血管炎に於ける 肺線維症と肺胞出血の関連についての検討

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[目的] MPO-ANCA 関連血管炎の間質性肺炎および間質性肺炎と肺胞出血の関連について検討した。[対象] MPO-ANCA関連血管炎91例(顕微鏡的多発血管炎78例、Churg-Strauss症候群10例、Wegener肉芽腫症3例)、男39例、女52例、平均年齢64.6歳、方法:対象を間質性肺炎単独群(A 群),肺出血単独群(B 群)、間質性肺炎と肺胞出血合併群(C 群)に分け、各群の臨床像を比較検討した。[結果]1)各群の頻度は、A群27例(48%)、B群10例(17%)、C群16例(28%)であった。2) 各群で年齢、MPO-ANCA 値、CRP 値に有意差はなかった。血清クレアチニン値はA群で最も低かった(A群 3.3mg/dl, B 群 5.6 mg/dl, C 群 4.5 mg/dl)　3)C群では、間質性肺炎先行例が 8 例(50%)、肺出血先行例が5例(31%)、同時発症例が3例(19%)であった。4) 死亡率はA群 26%, B 群 20%,C 群 50%であった。5)臨床的に間質性肺炎のみであったが、組織学的検討で肺胞出血を同時に認めた症例を1例認めた。[結論] MPO-ANCA 陽性間質性肺炎は肺胞出血の危険因子であり、間質性肺炎の成因に肺毛細血管炎の関与が示唆された。

Relationship between pulmonary fibrosis and alveolar hemorrhage in MPO-ANCA associated vasculitis

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OBJECTIVE: We investigate the clinical characteristics of PF and relationship between PF and alveolar hemorrhage (AH) in MPO-ANCA associated vasculitis (MPO-ANCA AV). *METHODS:* 91 patients with MPO-ANCA AV (39 patients Male, 52 Female , Average age 64.6). 78 had MPA, 10 had CSS, 3 had WG. These patients were classified into 3 groups, FP without AH (A Group), AH without PF (B Group), PH with AH (C Group) and clinical characteritics in each group were investigated. *RESULTS:* 1) The prevalence of each group was 48% in Group A, 17% in Group B and 28% in Group C. 2) Serum creatinine level in Group A was the lowest among these groups (Group A; 3.3mg/dl, Group B; 5.6 mg/dl, Group C; 4.5 mg/dl). No significant difference was detected in ages, MPO-ANCA titer and CRP level. 3) In Group C, PF was detected firstly in 8 cases (50%) , AH was detected firstly in 5 cases (31%), PF and AH were detected simultaneously in 3 cases (19%). 4) Mortality was 26% in Group A, 20% in Group B, 50% in Group C. 5) Histological examination showed not only PH but also AH in one patient with PH without AH by clinical examination. *CONCLUSION:* It is suggested that MPO-ANCA positive patients with PF is the high risk group for AH and alveolar capillaritis might have an important role in the pathogenesis of PF.

5-1

Morphological Features in ANCA-Associated Vasculitis

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The current classifications of renal vasculitis is based on a mixture of histological, clinical, and, more recently, immunological features.

Since the first description and also in more recent attempts at classification, the morphological approach to differentiating different forms of vasculitis is mainly based on the type and size of the vessels involved. In fact, the frequency of histologically identifiable arteritis in renal specimens is relatively low, ranging from about 10% to 30%.

The presence of necrotizing glomerulonephritis in the majority of patients influenced many authors to consider the involvement of vessels smaller than arteries, especially glomerular capillaries (capillaritis), as an expression of renal vasculitis. A recent Chapel Hill consensus conference on nomenclature of systemic vasculitides concluded that the presence or absence of necrosis in glomerular capillaries, or involvement of capillaries at other sites, should be the differentiating characteristic for polyarteritis nodosa and microscopic polyarteritis.

The discovery of antineutrophil cytoplasmic antibody (ANCA) and their prevalent association with necrotizing glomerulonephritis allowed a more precise classification of these disorders, and the term "ANCA-associated renal vasculitis" is now widely accepted. Wegener's granulomatosis, microscopic polyarteritis, and glomerulonephritis should be considered as a single pathological condition with different organ involvement. Two major glomerular lesions are characteristic of ANCA-associated renal vasculitis: necrosis of the tufts and extracapillary proliferation, with wide variability in intensity and degree. Necrosis can be the only lesion present, and is probably an expression of an early phase of the disease. In about one-third of cases, the picture is characterized by typical focal and segmental necrotizing extracapillary glomerulonephritis. Massive tuft necrosis with diffuse, non-homogeneous circumferential crescents can also be observed. Mesangial proliferation, mesangial matrix expansion, and endocapillary infiltration are usually mild, and undamaged glomeruli and non-necrotic parts of the glomerular tuft often appear to be normal.

Interstitial leucocyte infiltrates are another important feature of renal vasculitis, and their intensity and extent usually correlate with the severity of the glomerular lesions. The infiltrates are mainly composed of T lymphocytes and monocytes. The leucocyte infiltration is sometimes intense, with periglomerular accentuation and concomitant rupture of Bowman's capsule, making it difficult to distinguish between glomerular and interstitial lesions.

In some cases, there is a granuloma-like reaction around recognizable glomeruli, characterized by total destruction of glomeruli with circumferential accumulation of epitheloid cells and sometime giant cells.

The granulomatous reaction around glomeruli is not specific for Wegener's granulomatosis and was also seen in 17% of cases of microscopic polyarteritis and 7% of the renal-limited variant in our experience of 231 cases.

Tubular alterations and interstitial fibro-oedema are frequent features in all renal vasculitides and usually correlate with the intensity of glomerular alterations.

The absence or the presence of only a few scattered glomerular immune depositions is described by the majority of authors as typical of ANCA-associated renal vasculitis, and the term "pauci-immune" necrotizing glomerulonephritis is now widely accepted. Nevertheless, other authors have described an immunohistological picture characterized by the presence of mesangial or parietal deposits and, in our experience, about two-thirds of patients with renal vasculitis have variable degrees of mesangial/parietal deposits of immunoglobulin and complement. By contrast, fibrin is always present in active renal vasculitis, with variable deposition in glomerular tufts and crescents.

Most authors agree that the prognosis of renal vasculitis has improved during the past decade, probably due to earlier diagnosis and therapeutic intervention, and the use of more aggressive treatment.

Resolution of active lesions after early treatment is widely recognized and in our experience of repeat biopsies, the total disappearance of necrotizing lesions and interstitial infiltrates is impressive. Therefore, we agree with many authors that renal biopsy provides important information about the activity of renal vasculitis and is crucial for the therapeutic management of patients with these diseases.

5-2

CAWS 誘発マウス血管炎モデルにおける合成免疫グロブリン(SyIG)の血管炎抑制効果

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Candida albicans Water Soluble fractions(CAWS)誘発マウス動脈炎モデルにおける経静脈的SyIG 投与の有効性について検討した。

C57BL/6N マウス(4 週齢、雄)の腹腔に CAWS 4mg を連続 5 日間接種した。CAWS 接種 3 日目から 5 日間 SyIG を投与し、実験 28 日目に安楽死させた。大動脈起始部のステップ標本を作製。大動脈や冠状動脈における炎症の有無・その性状について病理組織学的に比較検討した。

未治療群における動脈炎発生率は 80%であった。一方、様々な容量で SyIG を静脈投与したが、多くの場合汎動脈炎発生率の低下をみた。この抑制効果はヒト IG を投与した場合と同程度であった。

The effect of synthetic immunoglobulin (SyIG) in mice vasculitis model caused by CAWS

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The effect of SyIG administration in the development of mice vasculitis caused by CAWS was examined. CAWS were injected into peritoneal cavity of the C57BL/6N mice for 5 consecutive days in the 1st week. Mice were killed under anesthesia on 28th experimental day. Tissue specimens were fixed, embedded in paraffin and H&E-stained sections were prepared using routine histological techniques. The incidence of panarteritis in control group was approx. 80%. Incidence of panarteritis was reduced by SyIG administration for 5 consecutive days from 3rd experimental day. The degree of inhibitory effect by SyIG administration was similar to when human IG was administered in this vasculitis mice model.

5-3

Candida albicans 培養条件とCAWSの血管炎，急性致死活性の関連性について

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CAWSは *Candida albicans* の産生する強力な血管炎惹起物質であり，主構成成分は mannan である．CAWS惹起血管炎の強度は著しい系統差を示し，DBA/2では致死的であり，CBA/jでは殆ど発症しない．本血管炎について詳細に解析するためには，活性中心と受容体の解析が必須である．そこで，本研究ではCAWSの活性中心について，mannan構造の観点から解析した．Candidaの mannan構造はpHや培養温度の影響をうけるので，pHを2,5,7ならびに培養温度を27,37として *C. albicans* IFO1385菌株を完全合成培地で培養し，得られた菌体外多糖画分を得た．各々の成分を DBA/2 マウスに接種し生存率を比較した．また血管炎惹起活性は冠状動脈起始部を組織化学的に比較した．致死活性ならびに血管炎惹起活性は 37 度培養(CAWS-37)や pH2(CAWS-27-2)での培養で認められた．一方，27 度，pH5(CAWS-27-5)，や 27 度-pH7(CAWS-27-7)に制御したときには著しく減弱した．これらの画分の mannan構造の特徴を NMR 分析ならびに抗体との反応性をもとに比較したところ活性の減弱した画分では□1,2-結合含量が増加していることがわかった．以上のことから，CAWS の血管炎惹起活性の強度は Candida mannanの構造によって厳密に制御されており，□結合は血管炎惹起に対して抑制的に作用することが強く示唆された．

Culture condition modulates active moiety of CAWS, vasculitis inducer from *C. albicans*

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CAWS is a water-soluble extracellular mannoprotein-beta-glucan complex obtained from the culture supernatant of *Candida albicans*, which grows in a chemically defined medium. CAWS induced toxic reactions, such as acute anaphylactoid reaction, by intravenous administration and coronary arteritis by intraperitoneal administration. To clarify the structure responsible for these toxic reactions, *C. albicans* was cultured in pH- and temperature-controlled conditions and prepared with CAWS with or without the β1,2-linked mannosyl segment (BM). The structure of CAWS was assessed by immunochemical and spectroscopic methodologies, and we found that CAWS prepared under the natural culture conditions contained only small amounts of BM and CAWS prepared at neutral conditions at 27 ℃ contained a significantly higher percentage of BM. Both the acute lethal toxicity and coronary arteritis induction was significantly more severe in the absence of BM. Activation of a complement pathway, the lectin pathway, by CAWS was significantly stronger in the absence of BM. These facts strongly suggest that BM linkages in CAWS negatively modulate acute and chronic toxicity of CAWS, and may be strongly related to the lectin pathway of the complement activation.

5-4

Activation of neutrophils in the initial step of arteritis induction by CAWS

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【目的】われわれは、*C. albicans* 培養外液より精製したマンノースを主要成分とする mannoprotein-β-glucan 複合体 (CAWS)をマウスに連続投与することによって動脈炎を発症するモデル系を確立した。本発表では、CAWS 投与直後の、末梢好中球数、好中球活性化およびサイトカインの関与について報告する。【材料と方法】CAWS を PBS に懸濁して C57BL/6N マウス(♂, 6w)腹腔内に投与後、10 分から 16 時間で経時的に屠殺して、末梢好中球数、末梢好中球の機能を解析すると共に、骨髄、末梢血の分画 profile を解析した。一方、血漿中の complement 3、炎症性サイトカイン、ケモカイン、ICAM-1 を定量した。さらに、無処置マウスから単離した末梢好中球に、CAWS を作用させ、好中球活性化の原因について解析した。また、心大動脈局所における ICAM-1 の発現について検討した。【結果と考察】CAWS 投与直後 10 分から、末梢血球数は著しく増加し、特に好中球は、数、割合共に増加が顕著であり、活性酸素産生および myelopeoxidase 放出の亢進を認めた。一方、血漿中の complement 3 は有意に減少し、IL-1β、IL-12、MIP-2、 G-CSF、ICAM-1 の有意な増加を認め、in vitro の解析から、CAWS 刺激で、好中球による IL-6 産生が認められた。心大動脈局所では組織傷害のマーカーである ICAM-1 の mRNA が検出された。【結論】CAWS 誘導の血管炎発症にいたる初期のイベントに、炎症性サイトカイン、ケモカイン、末梢好中球数の増加・活性化が関与すること、その活性化は CAWS による補体活性化を介していることが示唆された。

Activation of neutrophils in the initial step of arteritis induction by CAWS

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【Introduction】 CAWS, *C. albicans* water-soluble mannoprotein-β-glucan complex, which is released into cultured medium, has various biological activities. We have established a mouse model which shows the symptoms of arteritis with MPO-ANCA production by consecutive injections to a mouse. In this study, we examined about neutrophil activation in short time after CAWS injection. 【Materials and Methods】 CAWS solution was intraperitonealy injected into a mouse. Then the mouse was sacrificed, blood profile and neutrophil function were analyzed after 10 min to 16 hours. At the same time, levels of complement 3, inflammatory cytokines, chemokine and ICAM-1 in plasma were measured. Furthermore, message of ICAM-1 as a marker of lesion of endothelial cell of artery was also examined. 【Results】 The number of peripheral leukocytes increased immediately after CAWS injection, especially, neutrophil remarkably increased. In addition, neutrophil sensitivity to stimuli was enhanced. Moreover, complement 3, was significantly decreased and proinflammatory cytokines, IL-1β, IL-6 and IL-10, G-CSF, MIP-2 and soluble ICAM-1 levels were significantly increased. In locally, ICAM-1 message in artery was significantly increased at 16 hr after CAWS injection. 【Conclusion】 In conclusion, neutrophil activation by complement activation could be an initial event, subsequent production of proinflammatory cytokines, chemokines could be involved to heart arteritis development.

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ANCA 関連血管炎症候群における IL-12, IL-23, IL-18 の動態

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目的： Anti-neutrophil cytoplasmic antibody (ANCA) 関連血管炎症候群の病態には多彩な炎症性サイトカインが関わっている。今回 ANCA 関連血管炎症候群患者の血中 IL-12 family と IL-18 を測定し、血中および組織の活動性パラメーターと関係を検討した。**方法：** 治療前の本疾患患者(n=38)と、健常人(n=29) における血中 IL-12p70, IL-12p40, IL-18 を測定し疾患および病期特異性を調べた。さらに治療前期で末梢白血球数、血清 CRP、クレアチニン値、腎生検での活動性半月体形成率との相関を検討した。これらサイトカインと IL-12family との関係を検討するため IL-23 について血管炎患者治療前(n=39), 健常人(n=9)についても検討し、IL-12p40 との関係を検討した。**結果：** 血中 IL-18, IL-12p70, IL-12p40, IL-23 はいずれも健常人に比べ有意に高値を示した。血中 IL-18 は末梢血好中球数, CRP との正の相関を認め、血中 IL-12p40 は、腎糸球体活動性半月体形成率と、血清クレアチニンとの間に正の相関を認めた。IL-12p40 と IL-23, IL-12p70 との間には相関を認めなかった。**結語：** ANCA 関連血管炎症候群患者において IL-18 は向全身性炎症反応を引き起こし、IL-12p40 は糸球体半月体形成に関与する可能性が示唆された。IL-12p40 と IL-23, IL-12p70 が相関しなかったことは、p40 様物質が活性を持つ可能性が示唆された。

Circulating levels of IL-12, 23 and IL-18 in patients with MPO-ANCA-associated vasculitis.

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Objective: To identify circulation levels of IL-12 family and IL-18 in patients with MPO-ANCA-associated vasculitis, plasma levels of IL-12p70, p40, IL-23, IL-18 were measured by ELISA method. **Patients and Methods:** Plasma levels of IL-12p70, IL-12p40 and IL-18 were measured by ELISA method in patients with MPO-ANCA-associated vasculitis before any treatment (n=38) and compared with healthy controls (n=29). Plasma levels of these cytokines were compared with WBC, serum levels of CRP, Creatinine (Cre), and active crescent formation (%) in renal histology of the patients with vasculitis. To clarify the relationship between IL-23 and IL-12 family, IL-23 was measured in patients with MPO-ANCA-associated vasculitis (n=38) and compared with these IL-12p70 and p40. **Results:** Plasma levels of IL-18, IL-12p70, IL-12p40, and IL-23 were significantly higher in patients with vasculitis than those in healthy controls. Plasma levels of IL-18 were positively correlated with WBC and CRP levels. Plasma levels of IL-12p40 were positively correlated with active crescent formation (%) and serum Cre. There are no significant correlation between IL-12p40, IL-23 and IL-12p70. **Conclusion:** IL-18 may have systemic pro-inflammatory roles, whereas IL-12p40 may be involved with crescentic formation in the kidney.