International Symposium of Systemic Sclerosis and Connective Tissue Diseases 2020

Saturday, 14 March 2020

8:30 – 8:35 Opening remark
Kazuhiko Takehara (Kanazawa University)

8:35 – 9:25 Scleroderma I
Chairperson: Yoshiki Miyachi (Kyoto University)
Shinji Shimada (University of Yamanashi)
8:35 – 9:00 ST-1: History of scleroderma research
Kazuhiko Takehara (Kanazawa University)
9:00 – 9:25 ST-2: Future of scleroderma research
Masataka Kuwana (Nippon Medical School)

9:25 – 10:45 Scleroderma II
Cosponsored by Taiho Pharmaceutical Co., Ltd.
Chairperson: Osamu Ishikawa (Gunma University)
Daisuke Goto (University of Tsukuba)
9:25 – 10:05 SL-1: Vascular disease in scleroderma
Maria Trojanowska (Boston University)
10:05 – 10:25 SY-1: New animals model of scleroderma
Yoshihide Asano (University of Tokyo)
Takuya Miyagawa (University of Tokyo)
O-2: PI3K-Akt pathway plays a crucial role in production of collagen in Fli1 deficient condition and its inhibitor has the therapeutic potential in treating fibrosis
Yuko Ota (Nippon Medical School)

10:45 – 12:05 Scleroderma III
Cosponsored by Actelion Pharmaceuticals Japan Ltd.
Chairperson: Sumiaki Tanaka (Kitasato University)
Koichi Yanaba (Jikei University School of Medicine)
10:45 – 11:25 SL-2: Vasculopathy in systemic sclerosis, focus on the early phase
Marco Matucci-Cerinic (University of Florence)
11:25 – 11:45 SY-2: Treatment of Raynaud’s phenomenon in systemic sclerosis: Evaluation of the efficacy and safety of botulinum toxin injection
Seiichiro Motegi (Gunma University)

11:45 – 12:05 O-3: Anti-fractalkine monoclonal antibody therapy inhibits the progress of skin inflammation, fibrosis, and vascular injury in systemic sclerosis mouse models
Akira Utsunomiya (University of Fukui)

O-4: Monocytes/macrophages may contribute to the pathogenic process of systemic sclerosis via downregulation of interferon regulatory factor 8.
Yasushi Ototake (Yokohama City University)

12:05 – 12:15 Coffee Break and Poster viewing

12:15 – 13:05 Luncheon seminar Myositis I
Cosponsored by Japan Blood Products Organization.

Chairperson: Naoyuki Tsuchiya (University of Tsukuba)
Masanari Kodera (Chukyo Hospital)

12:15 – 12:40 LS-1: Clinical features of anti-ARS Ab-positive dermatomyositis
Takashi Matsushita (Kanazawa University)

12:40 – 13:05 LS-2: Cutaneous manifestations of dermatomyositis characterized by myositis specific autoantibodies
Naoko Okiyama (University of Tsukuba)

13:05 – 13:15 Coffee Break and Poster viewing

13:15 – 14:30 Scleroderma IV
Cosponsored by Mitsubishi Tanabe Pharma Corporation

Chairperson: Tsuneyo Mimori (Kyoto University)
Atsuyuki Igarashi (NTT Medical center Tokyo)

13:15 – 13:40 SY-3: Autoreactive B Lymphocytes in Scleroderma
Shinichi Sato (University of Tokyo)

13:40 – 14:05 SY-4: New Treatment approach for scleroderma
Hironobu Ihn (Kumamoto University)
### 14:05 – 14:30
**SY-5: Clinical course and biomarkers in Japanese patients with systemic sclerosis**
Minoru Hasegawa (University of Fukui)

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### 14:30 – 15:45 Myositis II and other diseases

**Cosponsored by Eisai Co., Ltd.**

**Chairperson:** Hirahito Endo (Kitasato University)
Takamitsu Makino (Kumamoto University)

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<td>14:30 – 14:55</td>
<td><strong>SY-6: Autoantibodies in dermatomyositis</strong></td>
<td>Manabu Fujimoto</td>
<td>Osaka University</td>
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<td>14:55 – 15:20</td>
<td><strong>SY-7: Biomarker and treatment of anti-MDA5 Ab-positive dermatomyositis</strong></td>
<td>Yasushi Kawaguchi</td>
<td>Tokyo Women's Medical University</td>
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<td>15:20 – 15:45</td>
<td><strong>SY-8: IgG4-related disease</strong></td>
<td>Hiroki Takahashi</td>
<td>Sapporo Medical University</td>
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### 15:45 – 16:10 Coffee Break and Poster viewing

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### 16:10 – 17:30 Scleroderma V

**Cosponsored by Maruho Co., Ltd.**

**Chairperson:** Toshiyuki Yamamoto (Fukushima Medical University)
Yoshihito Shima (Osaka University)

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<td>16:10 – 16:50</td>
<td><strong>SL-3: Development of targeted therapies for SSc - from bench to bedside</strong></td>
<td>Oliver Distler</td>
<td>University Hospital Zurich</td>
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<td>16:50 – 17:10</td>
<td><strong>SY-9: microRNA abnormalities in scleroderma</strong></td>
<td>Masatoshi Jinnin</td>
<td>Wakayama Medical University</td>
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<td>17:10 – 17:30</td>
<td><strong>O-5: Inhibitory effect of bleomycin-induced skin fibrosis by regulating the balance of regulatory T cells and Th17 cells</strong></td>
<td>Akiko Sekiguchi</td>
<td>Gunma University</td>
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**O-6: Apremilast inhibits the progression of bleomycin-induced skin fibrosis in mice**
Tomoaki Higuchi (Tokyo Women's Medical University)
17:30 – 18:50  Scleroderma VI

Cosponsored by Torii Pharmaceutical Co., Ltd.

Chairperson: Hidekata Yasuoka (Fujita Health University)
Yukie Yamaguchi (Yokohama City University)

17:30 – 18:10  SL-4: Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD).
Richard M. Silver (Medical University of South Carolina)

18:10 – 18:30  SY-10: Treatment of skin ulcers in scleroderma
Yasuhito Hamaguchi (Kanazawa University)

18:30 – 18:50  O-7: Roles of platelet-derived growth factor receptor (PDGFR) inhibitor for the fibrosis of systemic sclerosis
Katsunari Makino (Kumamoto University)

O-8: Selective S1P$_1$ receptor modulator attenuates murine sclerodermatous models
Miyu Kano (Kanazawa University)

18:50 – 18:55  Closing remark

19:20 – 21:00  Reception Party
ST- 1  History of scleroderma research

Kazuhiko Takehara
Kanazawa University, Department of Dermatology

Scleroderma is a generalized connective tissue disorder characterized by sclerotic changes in the skin and many other organ systems. In addition, nowadays scleroderma is known to be associated with autoimmunity and vascular abnormality. Here, I introduce history of scleroderma research from basic research aspect and clinical research aspect.

Landmark study of basic research of scleroderma is skin fibroblast culture by LeRoy (1972). Since then, many studies have been conducted using cultured skin fibroblasts derived from scleroderma patients. Afterward cytokine abnormalities as TGF-β, CTGF, and other cytokines were revealed. Recently various animal models have been established and used for the establishment of new treatment.

A lot of scleroderma specific autoantibodies have been identified and now commonly used for early diagnosis. In 2013, ACR and EULAR proposed new classification criteria including autoantibody detection. For the evaluation of skin sclerosis, mRSS has been world widely used and this was primary endpoint in many clinical trials. For interstitial lung disease, cyclophosphamide, MMF, and nintedanib have been proved to be effective. For pulmonary arterial hypertension, over ten drugs were proved in this two decades. Among them, bosentan is also used for skin ulcer prevention in various countries including Japan.

Finally I wish whole pathology of scleroderma will be elucidated and new treatments which totally cure the patients will be established in the near future.

Academic background:

1979-1980  Residency, Department of Dermatology, University of Tokyo
1980-1987  Assistant Professor, Department of Dermatology, University of Tokyo
1984-1987  Research Associate, Division of Rheumatology, Department of Medicine, Medical University of S.C.
1987-1994  Lecturer, Department of Dermatology, University of Tokyo
1994-2001  Professor, Department of Dermatology, Kanazawa University, School of Medicine
2001-present  Professor, Department of Molecular Pathology of Skin, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University
ST- 2 Future of scleroderma research
Masataka Kuwana
Department of Allergy and Rheumatology, Nippon Medical School

Systemic sclerosis (SSc) is a complex disease characterized by early microvascular abnormalities, immune dysregulation and chronic inflammation, and subsequent fibrosis of the skin and internal organs. In recent years, sophisticated research techniques have greatly improved our understanding of the pathogenic process of SSc: excessive fibrosis mediated through a complex series of interlinked vascular injury, immune activation, and maladaptive repair process. These tremendous efforts in our community have provided novel avenues for developing molecular targeted therapies with potential disease-modifying effects, resulting in implementation of a number of clinical trials. We will soon have many options for the SSc treatment targeting a variety of molecules, cell types, and signal pathways. In this age, researches using human samples should be increasingly appreciated. Since clinical course of SSc patients are highly variable, precise clustering and risk stratification is critical before treatment introduction. For this purpose, biobank repository using registries and prospective intervention studies is becoming more important. Artificial intelligence should play an active part in optimizing management in patients with SSc.

Dr. Masataka Kuwana is currently a Professor of Allergy and Rheumatology at Nippon Medical School Graduate School of Medicine in Tokyo, Japan, since July 2014. He is also a director of the Section of Rheumatology and Connective Tissue Diseases at Nippon Medical School Hospital.

In March 1988, he graduated from Keio University and obtained his M.D. He completed residency at the Department of Internal Medicine of Keio University Hospital, and received his Ph.D. in Medicine and Immunology with distinction at Keio University Graduate School of Medicine in 1992.

In May 1993, he joined the Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, the United States, as a postdoctoral fellow under supervision of Professor Thomas A. Medsger, Jr.

After completion of the fellowship program in May 1996, Dr. Kuwana spent most of his professional career at the Division of Rheumatology, Department of Internal Medicine, Keio University in Tokyo, Japan, where he held several leadership positions, including a chief investigator of the Autoimmunity and Regeneration research group and a chief of the Rheumatology section at the University Hospital.

He has published more than 370 peer-reviewed scientific articles and written more than 10 book chapters. He has also edited three books on systemic sclerosis and serves as an editorial board in 6 peer-reviewed journals on rheumatology, especially as an editor-in-chief of Journal of Scleroderma and Related Disorders and Modern Rheumatology. He is considered an internationally recognized leading expert in systemic sclerosis, pulmonary complications of connective tissue diseases, and autoimmunity.
SL- 1 Vascular disease in scleroderma

Maria Trojanowska, PhD
Arthritis Center, Boston University, Boston, MA

Systemic sclerosis (SSc, scleroderma) is a complex autoimmune disease characterized by early microvascular abnormalities, inflammation and subsequent fibrosis of the skin and internal organs. Several mechanisms have been proposed to trigger vascular injury in SSc, but so far, these early events remain poorly understood. Our current studies are aimed at characterizing these early pathogenic microvascular changes in the setting of tissue fibrosis. Because clinical data have demonstrated reduced protein levels of several transcription factors, including Fil1 (Friend leukemia integration-1), ERG (ETS-related gene), and GATA6 (GATA binding factor 6) in SSc vascular lesions, we wished to determine how the deficiency of these factors affects the pathogenic processes in dermal and pulmonary vasculature. We showed that all three factors play a key role in maintaining vascular homeostasis. Specifically, depletion of Erg or Fil1 led to increased production of inflammatory cytokines, while decreasing expression of the genes involved in vascular integrity. On the other hand, Gata6 protected endothelial cells from oxidative stress. Deficiency of Gata6 led to reduced levels and activity of antioxidant enzymes, elevated oxidative stress, and activation of ER stress, as well as increased inflammation. These studies support an important role of Erg, Fil1, and Gata6 in regulating vascular homeostasis and suggest that restoring their expression levels in diseased tissues may represent a valid therapeutic strategy to treat early SSc.

Dr. Maria Trojanowska earned her M.S. from Warsaw University and Ph.D. from the Polish Academy of Sciences, Institute of Biochemistry and Biophysics in Warsaw. She began to study scleroderma in 1986, when she joined an internationally renowned Scleroderma Program directed by Professor Carwile Leroy at the Medical University of South Carolina. In 2009 her laboratory has relocated to Boston, where she was appointed a Professor of Medicine and Director of the Arthritis Center at the Boston University School of Medicine. Her team investigates the molecular and cellular mechanisms regulating extracellular matrix (ECM) synthesis in healthy tissues and in pathological conditions such as scleroderma. Another area of active investigation focuses on scleroderma vascular disease. Vascular disease contributes significantly to the morbidity and mortality of patients with scleroderma, however the mechanisms contributing to scleroderma vasculopathy and the relationship between inflammation, vasculopathy and fibrosis remain poorly understood. Her laboratory has generated novel genetic mouse models that recapitulate many of the vascular and fibrotic features of SSc. Such models are instrumental in elucidating the mechanisms of vascular disease and for the discovery and validation of potential therapeutic targets to treat vasculopathy and fibrosis in patients with scleroderma.
Vasculopathy in systemic sclerosis, focus on the early phase

Marco Matucci-Cerinic, MD, PhD
University of Florence, Italy

Microcirculation represents the primary target in both the initiation and spreading of SSc. In fact, Raynaud’s phenomenon and the presence of swollen and edematous fingers (commonly referred to as puffy fingers) are the most frequent early clinical manifestations being even considered as “red flags” to suspect the presence of the disease. In the early phases of the disease, recurrent hypoxia-reperfusion injury determines the generation of reactive oxygen species, which trigger the degradation of the endothelial glycocalix and the opening of the endothelial cell junctions. This causes an increase in vascular permeability and extravasation. The following vascular leak, cellular homing and concomitant lymphatic vessel insufficiency lead to persistent tissue edema and significant perivascular accumulation of inflammatory cells. Consequently, this triggers the activation of tissue resident fibroblasts and the transdifferentiation of endothelial cells into myofibroblasts (i.e. endothelial-to-mesenchymal transition) through the release of TGFβ and other profibrotic cytokines and growth factors. In this microenvironment, endothelial-to-mesenchymal transition may contribute substantially to different features of SSc-related vasculopathy. These are the remodeling of the arteriolar and small vessel wall, with an accumulation of profibrotic myofibroblasts in their intima and media and the loss of endothelial cells of capillary vessels and generation of perivascular myofibroblasts with a “destructive vasculopathy” characterized by microvessel rarefaction and parallel tissue fibrosis. This bulk of events leads inesorably to a “fibroproliferative vasculopathy” characterized by fibrosis and thickening of the vessel wall with occlusive vascular disease. At this point the vascular fibrosis is definitively structured and it will be very difficult in practice to deremodel the vessel wall with a targeted therapy. Today a preventive therapeutic approach in the very early and edematous disease is highly warranted.

Marco Matucci-Cerinic is Professor of Rheumatology and Medicine at the Department of Experimental and Clinical Medicine, Director of the Division of Rheumatology at the Azienda Ospedaliera Universitaria Careggi and Director of the PhD programme in Clinical Science of the University of Florence, Italy.

- Dr. Matucci has published more than 600 peer review manuscripts widely in the field of rheumatology, particularly on the pathogenesis, clinical features and treatment of scleroderma, on spondyloarthritis and on osteoarthritis;

- Has served as EULAR General Secretary and as Chairman of the EULAR Scleroderma Trial and Research Group (EUSTAR).

- Is currently chairman of the World Scleroderma Foundation.

- Is Co-Editor in Chief of the Journal of Scleroderma & Related Diseases;

- Is Associate Editor of Arthritis Research & Therapy and Clinical & Experimental Rheumatology, past Associate Editor and Co-Editor of Rheumatology;


- At present he is leading 88 clinical trials;

- Has published more than 600 scientific papers.
SL- 3 Development of targeted therapies for SSc - from bench to bedside

Oliver Distler, MD, PhD
Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland

Anti-fibrotic targeted therapies have reached clinical practice in systemic sclerosis. In this talk, drug development für anti-fibrotic drugs will be reviewed. Specifically, their preclinical portfolio and lessons learned from preclinical characterization of both positive and negative clinical trials in systemic sclerosis will be addressed. Different clinical trial designs to address different stages of the disease will be discussed. Finally, an overview of current treatment possibilities for fibrosis will be given.

Education
1989-1996 Medical student at the University of Erlangen, Germany and Duke University, North Carolina, USA
1997 Doctor of Medicine (Dr. med.)
2004/2005 Specialization in Internal Medicine
2006 Specialization in Rheumatology, Privatdozent at the University of Zurich, Switzerland
2012 Certificate of Advanced Studies in Healthcare Management, University of St. Gallen, Switzerland
2013 Professor ad personam at the University of Zürich, Switzerland
2016 Full Professor of Rheumatology, University of Zürich, Switzerland

Employment history
1996-1998 Intern/Resident at the Department of Internal Medicine II, Bamberg and the Department of Internal Medicine I, University of Regensburg, Germany
1998-2004 Postdoc at the Center of Experimental Rheumatology, Department of Rheumatology, and Department of Clinical Immunology, University of Zurich, Switzerland
2004-2006 Resident at the Departments of Clinical Immunology and Rheumatology, University Hospital Zurich, Switzerland
2006-2009 Attending Physician (Oberarzt), Department of Rheumatology, University of Zurich, Switzerland
2009-2016 Senior Attending Physician (Leitender Arzt) and Director Scleroderma Program, Department of Rheumatology, University of Zurich, Switzerland
2012 Visiting Professor, University of Gothenburg, Sweden
2015-2017 Adjunct Professor, University of Florence, Italy
2015 Visiting Professor, Stanford University, USA

Current ongoing institutional responsibilities
2016- Professor, University of Zurich, Switzerland; Chairman Department of Rheumatology, University Hospital Zurich and Balgrist University Hospital, Switzerland
2016- Chairman Center of Experimental Rheumatology, University of Zurich, Switzerland
2018- Head of Business Division, Traumatology-Dermatology-Rheumatology-Plastic Surgery and Emergency Medicine (TDR), University Hospital Zurich, Switzerland
2018- Board Member, Faculty of Medicine, University of Zurich

Research projects (currently running, O. Distler as PI or Co-PI)
2017-2020: Foundation for Research in Science and the Humanities at the University of Zurich (STwF). Topic: The role of the bromodomain proteins in arthritis susceptibility and synovial biology.
2019-2021: Clinical Research Priority Program (CRPP) at the University of Zurich. Topic: Pain - from phenotypes to mechanisms.
Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD).

Richard M. Silver, MD, MACR,  
Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, USA.

Systemic sclerosis (SSc, scleroderma) is a rare autoimmune connective tissue disease characterized by immune dysregulation and progressive fibrosis typically affecting the skin with variable degrees of internal organ involvement. Lung involvement in the form of interstitial lung disease (SSc-ILD) is the most common disease-related cause of death. Prognosis is variable but appears to be worse for males, those of African American race, and those having the diffuse cutaneous subset of SSc with antitopoisozerase I auto-antibodies. Although long thought to be the result of a bland fibrotic process, research over the past four decades has demonstrated multiple different immunologic and inflammatory pathways that contribute to pulmonary fibrosis. Knowledge of such pathways has led to important therapeutic advances, initially with immunosuppressants and more recently with anti-fibrotic drugs. Many challenges remain including the refinement of non-invasive means of detection and staging of lung involvement, choice and timing of treatment(s), and the development of more targeted immunosuppressants and improved anti-fibrotics. Immunoablation followed by autologous hematopoietic stem cell transplantation may be beneficial in selected patients, and lung transplantation for end-stage disease may be considered at selected centers.

Dr. Silver is a graduate of the University of Tennessee (BS) and Vanderbilt University School of Medicine (MD). He completed training in Internal Medicine at the University of North Carolina - Chapel Hill, followed by a fellowship in Pediatric Rheumatology with Dr. Barbara Ansell at London’s Northwick Park Hospital and Taplow. He completed a fellowship in Adult Rheumatology with Dr. Nathan Zvaifler at the University of California - San Diego. Dr. Silver was recruited by Dr. Carville LeRoy to join the MUSC faculty in 1981, where currently he is Professor of Medicine and Pediatrics. Dr. Richard M. Silver served as Director of the Division of Rheumatology & Immunology at the Medical University of South Carolina in Charleston, SC from 1995-2018. MUSC’s Board of Trustees named him a “Master Teacher” and bestowed the University’s highest academic recognition, “Distinguished University Professor”. He was named the 2007 “Doctor of the Year” by the Scleroderma Foundation and in 2014 Dr. Silver was named a Master in the American College of Rheumatology. Dr. Silver’s research interests include the pathogenesis and treatment of scleroderma interstitial lung disease, as well as environmental exposures and the risk of systemic sclerosis.
SY-1  New animal models of scleroderma

Yoshihide Asano
Department of Dermatology, University of Tokyo Graduate School of Medicine

The pathogenesis of systemic sclerosis (SSc) remains enigmatic, but animal models recapitulating disease-related manifestations provide us with a useful clue to further understand its disease pathology. We recently established a unique research system of animal models which allows us to dissect the role of each cell type in SSc-like disease conditions. In this system, we focused on Friend leukemia virus integration 1 (Fli1), a member of Ets transcription factor family that is constitutively downregulated in various cell types in SSc lesional skin. Fli1 haploinsufficiency augments bleomycin-induced SSc-like phenotypes in fibroblasts, endothelial cells, keratinocytes, macrophages, B cells and T cells, suggesting that Fli1 deficiency serves as a critical predisposing factor of SSc. Based on this idea, we generated various kinds of conditional Fli1 knockout mice by using LoxP-Cre system and examined their phenotypical features. Of note, B cell-specific Fli1 knockout mice and myeloid cell-specific Fli1 knockout mice recapitulated the three cardinal pathological features of SSc (fibrosis, vasculopathy and autoimmune inflammation), and epithelial cell-specific Fli1 knockout mice developed dermal, esophageal and pulmonary fibrosis (organ selectivity characteristic of SSc). Thus, this research system is useful to determine the hierarchy of disease-associated cell types in SSc pathogenesis.

Education
1998  M.D. Faculty of Medicine, The University of Tokyo, Tokyo, Japan
2004  Ph.D. Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Professional experience
1998-2000  Resident, Department of Dermatology, The Tokyo University Hospital, Tokyo, Japan
2004-2005  Dermatologist, Kanto Medical Center, NTT EC, Tokyo, Japan
2005-2006  Assistant Professor, Department of Dermatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
2006-2008  Postdoctoral fellow, Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, USA
2009-2015  Assistant Professor, Department of Dermatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
2015-  Associate Professor, Department of Dermatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Honors and awards
2009  Rohto Dermatology Prize
2010  JSID’s Fellowship SHISEIDO Award
2011  Actelion Academia Prize
2016  JSID award
2017  Maruho Takagi Dermatology Foundation Award
2018  Edith-Busch Prize for Young Investigators 2018 (Systemic Sclerosis World Congress)
2018  Rising Star (International Investigative Dermatology 2018)
2019  Pola Pharma Rising Star Award 2019
Treatment of Raynaud’s phenomenon in systemic sclerosis: Evaluation of the efficacy and safety of botulinum toxin injection

Sei-ichiro Motegi
Department of Dermatology, Gunma University Graduate School of Medicine

Patients with systemic sclerosis (SSc) typically develop Raynaud’s phenomenon (RP) and persistent digital ischemia and often develop digital ulcers (DUs). The pathogenesis of RP in SSc is complex and still undetermined. It has been suggested that episodic vasospasm may be caused by dysregulation of the balance between vasoconstriction and vasodilation, and that dysregulation of the autonomic nervous response may be involved in the pathogenesis of RP. Pharmacological treatments of RP have targeted the regulation of vasodilation and/or vasoconstriction, and calcium channel blockers, antiplatelet agents, sarpogrelate hydrochloride, cilostazol, and oral and intravenous prostanoids have been challenged. The endothelin receptor antagonist bosentan and phosphodiesterase-5 inhibitors may be beneficial for SSc-related RP. However, a satisfactory outcome for RP in SSc remains elusive.

We have examined the therapeutic efficacy and safety of the local injection of botulinum toxin (BTX) for RP and DU in SSc patients, and several our clinical studies showed that BTX injection might have promising therapeutic potential for RP and DU in SSC patients. We recently examined the efficacy of BTX-B injection for RP and RP-related DU in patients with SSc by a double-blind, randomized, placebo-controlled, investigator-initiated, clinical trial. In this lecture, I present the results of this RCT.

Education and professional experience
1999 M.D., Gunma University School of Medicine
1999-2000 Residency - Department of Dermatology, Gunma University Hospital
2001-2004 Graduate Student, Gunma University Graduate School of Medicine
2004 Ph.D. Gunma University Graduate School of Medicine
2004-2005 Clinical and Research Staff Member, Department of Plastic and Reconstructive Surgery, Tokyo University
2007-2011 Visiting fellow, Dermatology Branch, National Cancer Institute (NCI), National Institutes of Health (NIH) Dr. Mark C. Udey Lab.
2009-2010 JSPS Research Fellow in Biomedical and Behavioral Research at NIH
2011-2012 Assistant Professor, Department of Dermatology, Gunma University
2013-2017 Senior Lecturer, Department of Dermatology, Gunma University
2017- Associate Professor, Department of Dermatology, Gunma University
2017- Junior Board of Director, Japanese Society for Investigative Dermatology
2018- Section Editor, Journal of Dermatological Science

Awards and grants
2010 The Fellows Award for Research Excellence (FARE) 2011 in NIH
2012 Japanese Dermatological Association basic medical research grant (Shiseido donation)
2014 The Society of Geriatric Dermatology, Research Grant (ROHTO Award)
2014 Best Teacher Award in Gunma University Graduate School of Medicine (Ishii Award)
2016 JSID’ s Fellowship Shiseido Research Grant (Shiseido Award)
2017 The 9th Rhoto Dermatology Prize
2017 The Japanese Society for Investigative Dermatology Award (JSID Award)
2018 Maruho Takagi Dermatology Foundation, The 2nd Takagi Award
2018 The Japanese Society of Pressure Ulcers Ohura Award
2018 Journal of Dermatology (JD) Award (Most cited paper 2017 impact factor period)
2019 The 49th Annual Meeting of Japanese Society for Wound Healing, Research Award
SY- 3  Autoreactive B Lymphocytes in Scleroderma

Shinichi Sato
Department of Dermatology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

Systemic sclerosis (SSc) is a connective tissue disease characterized by excessive extracellular matrix deposition in the skin and visceral organs. The presence of autoantibodies, especially anti-topoisomerase I (topo I) Ab, is a central feature of immune activation in SSc. B cells have various and critical functions in immune responses and subtle changes in B cell signaling lead to generation of not only autoreactive B cells, but also autoreactive T cells through autoantigen presentation to T cells, indicating that B cells are a primary driver for autoimmunity. Since anti-topo I Ab is not considered to be pathogenic in SSc, mechanisms other than autoantibodies are involved in the disease manifestations. Our hypothesis is that strong production of cytokines, especially IL-6, by SSc autoreactive B cells leads to the disease manifestations. Microfluidic ELISA system that enables us to measure very small amounts of cytokines at single cell level revealed that topo I-specific autoreactive B cells produced higher IL-6 and less IL-10 production. Moreover, topo I-specific autoreactive B cells induced fibrosis in topo I-immunized SSc model mice probably through IL-6 production. Collectively, these results indicate that abnormal cytokine production by autoreactive B cells in SSc contributes to the disease manifestations.

Education:
1989  M.D. The University of Tokyo
1994  Ph.D. The University of Tokyo

University appointments:
1989-1994  Assistant, Department of Dermatology, The University of Tokyo
1994-1997  Research Associate, Department of Immunology, Duke University Medical Center, Durham, NC, USA
1997-2002  Assistant Professor, Department of Dermatology, Kanazawa University School of Medicine
2002-2004  Associate Professor, Department of Dermatology, Kanazawa University, Graduate School of Medical Science
2004-2009  Professor and Chairman, Department of Dermatology, Nagasaki University Graduate School of Biomedical Sciences
2009-      Professor and Chairman, Department of Dermatology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo
SY- 4  New Treatment approaches for scleroderma

Hironobu Ihn, MD, PhD
Department of Dermatology and Plastic Surgery, Faculty of Life Sciences,
Kumamoto University

Scleroderma, or systemic sclerosis (SSc) is a generalized connective tissue disease that involves sclerotic changes in the skin and sometimes various other organ systems. Clinical outcomes have improved probably due to better management of the complications, but SSc is still considered to be incurable and diffuse cutaneous SSc carries high risk of fatality. I would like to talk about new treatment approaches for this disease.

1990  Graduated from University of Tokyo
1990  Assistant, Department of Dermatology, Faculty of Medicine, University of Tokyo
1994-1997  Research Fellow, Division of Rheumatology & Immunology, Medical University of South Carolina, SC, USA
2001  Lecturer, Department of Dermatology, Faculty of Medicine, University of Tokyo
2005  Associate Professor, Department of Dermatology, Faculty of Medicine, University of Tokyo
2005  Professor & Chairman, Department of Dermatology & Plastic Surgery, Faculty of Life Sciences, Kumamoto University
2013  Vice President, Kumamoto University Hospital
Clinical course and biomarkers in Japanese patients with systemic sclerosis

Minoru Hasegawa
Department of Dermatology, University of Fukui

Since the symptoms of systemic sclerosis (SSc) is heterogeneous, it is important to estimate the disease progression and undergo proper medical intervention in the early stage. At present, SSc-specific autoantibodies are the most useful markers for serodiagnosis and predicting the ongoing and/or subsequently developed clinical features. However, other helpful biomarkers for SSc have not been standardized yet. Additionally, previous studies have shown that race affects the clinical features and outcome of individual SSc subjects, but precise clinical course of Japanese SSc remains unclear. Therefore, we designed a multicenter prospective study to investigate the time-course of clinical symptoms and laboratory findings in Japanese early diffuse cutaneous SSc and early SSc with interstitial lung disorders (ILD) during 7-years of follow up. We also examined whether serum levels of chemokines and adhesion molecules can be useful in predicting the severity of skin sclerosis and ILD. Most patients had been treated with systemic steroids, immunosuppressants, and vasodilators. Although skin sclerosis was attenuated during their clinical course, other parameters including ILD, clinically suspected pulmonary arterial hypertension, digital ulcers, and physical dysfunction were gradually exacerbated during the period. Serum levels of ICAM-1 and IL-8/P-selectin were predictive for subsequent respiratory dysfunction and physical disability, respectively.

Experience
1991-1998 Medical Doctor, Department of Dermatology, Kanazawa University
1998-2001 Research associate, Department of Immunology, Duke University Medical Center
2001-2003 Assistant professor, Department of Dermatology, Kanazawa University,
2003-2013 Lecturer, Department of Dermatology, Kanazawa University
2013- Professor and Chairman, Department of Dermatology, School of Medicine, Faculty of Medical Sciences, University of Fukui
Autoantibodies in dermatomyositis

Manabu Fujimoto
Department of Dermatology, Osaka University Graduate School of Medicine

Dermatomyositis (DM) is an autoimmune connective tissue disease which mainly affect the muscle and skin. Whereas autoantibody production is a hallmark of rheumatic diseases, the significance of autoantibodies in polymyositis and DM had been regarded to be limited, especially in DM. However, in addition to already established myositis-specific autoantibodies (MSAs) such as anti-aminocyl tRNA synthetase antibodies and anti-Mi-2 antibodies, several novel DM-specific autoantibodies were identified during the last two decades. These autoantibodies include anti-melanoma differentiation antigen 5 (MDA5), anti-transcriptional intermediary factor 1 (TIF1), anti-nuclear matrix protein (NXP-2), and anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies. Consequently, disease-specific autoantibodies now cover more than 80% of DM patients, and thus the detection of MSAs is useful for the diagnosis. Moreover, these MSAs have been clarified to have strong associations with distinct clinical phenotypes, such as age of onset, muscle manifestations, cutaneous manifestations, and complications including interstitial lung disease and internal malignancy, and disease course. Therefore, identification of MSAs enables further classification of subsets within the disease. Furthermore, antibody titer of some MSAs correlates with disease activity. Importantly, these serologically determined subsets are also related with characteristic skin manifestations.

Education
1992 M.D. University of Tokyo, Japan

Professional experience
1992-1993 Resident, The University of Tokyo Hospital and Tokyo Metropolitan Police Hospital
1994-1997 Fellow in Dermatology, University of Tokyo Hospital and Kosei General Hospital
1997-2000 Research Associate, Department of Immunology, Duke University Medical Center, NC, USA
2000-2003 Division Chief, Research Institute, International Medical Center of Japan
2004-2005 Assistant Professor, Department of Dermatology, University of Tokyo Hospital
2005-2013 Associate Professor, Department of Dermatology, Kanazawa University School of Medicine
2013-2019 Professor and Chair, Department of Dermatology, Faculty of Medicine, University of Tsukuba
2019-present Professor and Chair, Department of Dermatology, Graduate School of Medicine, Osaka University; Laboratory of Cutaneous Immunology, Osaka University Immunology Frontier Research Center
SY-7 Biomarker and treatment of anti-MDA5 Ab-positive dermatomyositis

Yasushi Kawaguchi
Department of Rheumatology Tokyo Women’s Medical University

Dermatomyositis (DM) is an autoimmune disease characterized by specific dermatitis (Heliotrope and Gottron) and myositis. Interstitial lung disease (ILD) are often complicated with DM and are treated with corticosteroids and immunosuppressants including tacrolimus, cyclosporin, azathiopurin, and so on. The progression of ILD is usually slow and well responds to the treatment. However, rapid progressive ILD (rILD) is associated with DM with anti-MDA5 antibody and may be resistant to the conventional treatment.

Our investigation revealed the levels of serum ferritin correlated to the severity of ILD with anti-MDA5 ab positive DM. Moreover, rILD was involved in amyopathic DM who showed a clinical feature lack of myositis.

The regimen of the treatment for DM patients who were fulfilled with amyopathy, positivity of anti-MDA5 antibody, and more than 500 ng/ml of serum ferritin should be the combination therapy of corticosteroid, tacrolimus, and intravenous cyclophosphamide.

Research and professional experience:

1988-1990 Resident, National Defense Medical College Hospital, Tokorozawa, Japan
1990-1994 Rheumatology Fellow, Internal Medicine I, National Defense Medical College, Tokorozawa, Japan
1992-1997 Research Fellow, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
1994-1996 Postdoctoral Research Fellow, Department of Medicine, Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
1997-2003 Instructor, Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan
2003-2007 Assistant Professor, Institute of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan
2008 Nov Associate Professor, Aoyama Hospital, Tokyo Women’s Medical University, Tokyo, Japan
2010 April Associate Professor, Department of Rheumatology, Tokyo Women’s Medical University, Tokyo, Japan
2011 August Clinical Professor, Department of Rheumatology Tokyo Women’s Medical University, Tokyo, Japan

Awards and honors:

1994 Research Fellowship Award in the Uehara Memorial Foundation
1994 Ootaka Award in Japanese Society for Connective Tissue Research
1996 Research Award of the Arthritis Foundation, Western Pennsylvania Chapter, USA
1999 Research Award of the Kanae Foundation
2000 Research Award of the Uehara Memorial Foundation
2001 Research Award of the Naito Foundation
2004 Young Investigator Award of APLAR 2004
2006 Research Award of the Japan Research Foundation for Clinical Pharmacology
2019 Award of Japan College of Rheumatology
SY- 8 IgG4-related disease

Hiroki Takahashi
Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by elevated serum IgG4 concentrations, tissue infiltration by IgG4-positive plasma cells and storiform fibrosis in various organs, including the pancreas (autoimmune pancreatitis: AIP), salivary and lacrimal glands (so-called Mikulicz’s disease: MD), lungs, kidneys, aorta, and retroperitoneum et al. The elevated levels of serum IgG4 concentrations and diffuse infiltration of IgG4-positive plasma cells in lesions in AIP patients reported in the early 21st century is the trigger of establishing the disease concept of IgG4-RD as multi-organ systemic disease. This discovery enabled separation of MD, which had been considered a subtype of Sjögren’s syndrome. Immune abnormality has been assumed to exist on the basis of IgG4-RD because IgG4-RD patients present with hyper-gamma globulinemia, diffuse infiltration of mononuclear cells and prompt responsiveness to glucocorticoids. Actually, T-cell subset bias leading to increased production of IgG4 and autoantibodies causing IgG4-related lesions have been reported. In particular, attention has been focused on new T cell subsets (Tph and CD4+CTL) and M2 macrophages as abnormalities associated with fibrosis. I would like to introduce unique clinical characteristics of IgG4-RD and mention problems that should be solved.

1989-1991 Visiting Researcher in City of Hope Research Institute, California, USA
1999-2007 Assistant Professor of the First Department of Internal Medicine, Sapporo Medical University School of Medicine
2007-2013/3 Associate Professor of the First Department of Internal Medicine, Sapporo Medical University School of Medicine
2013/4-2017/4 Associate Professor of the Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine
2017/5-present Professor of the Department of Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine
SY- 9  

**microRNA abnormalities in scleroderma**

Masatoshi Jinnin
Department of Dermatology, Wakayama Medical University Graduate School of Medicine

Inherited genetic factors cannot fully explain the pathogenesis of systemic sclerosis. Environmental factors may also play a role in the pathogenesis, and recent researches have suggested that they are mediated by epigenetics, at least partly. The abnormalities in epigenetics include methylation, histon modification, and non-coding RNAs. microRNAs are very small non-coding RNAs, which consist of 19-25 nucleotides. They bind to complementary sequences of 3’-untranslated regions of target mRNAs, resulting in the modulation of gene translation. microRNAs can affect various cellular behaviors including proliferation, migration and development, and a lot of researches have shown that microRNAs are involved in the pathogenesis of various human diseases including fibrotic disorders.

Furthermore, recent studies indicate that microRNAs can stably exist in the extracellular space including sera or saliva, and their expression levels may be useful for the diagnosis and/or the evaluation of disease activity of human disorders. Tissues of hairs or nails also contain microRNAs, and their clinical significance is currently under examination. Based on the recent advances of microRNA researches, this talk will discuss the possible applications of microRNAs in the diagnosis or treatments of systemic sclerosis.

**Educational background & professional experience**

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<td>1993-1999</td>
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<tr>
<td>1999-2000</td>
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<td>2001-2005</td>
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<tr>
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**Honors and awards**

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SY-10  Treatment of digital ulcers in systemic sclerosis

Yasuhiro Hamaguchi
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Digital ulcers are one of the major complications of systemic sclerosis (SSc), developing in both diffuse and limited forms. Digital ulcers are a relatively frequent complication, affecting approximately 30% of patients. Digital ulcers often cause severe pain and subsequent functional disturbance, which may impair the quality of life. Although the pathogenesis for digital ulcers in SSc remains unclear, peripheral circulatory disturbance, tissue remodeling and fibrosis caused by local inflammation may play a role in the development of digital ulcers. Growth factors, cytokines, matrix metalloproteinases and endothelin (ET)-1 produced by vascular endothelial cells are considered to disturb blood flow and lead to the inflammatory response in SSc patients. Initial treatment of digital ulcers secondary to SSc is conservative. Vasodilators are administrated in addition to local treatment with topical agents, including antibiotics and prostaglandin (PG) E1 preparations. Conventional oral medications include calcium channel antagonists, antiplatelet agents, PGE1/prostacyclin, ET receptor antagonists, phosphodiesterase type 5 inhibitors and antithrombin agents. Keeping the fingers warm is also important for preventing and treating digital ulcers. Clinically, establishment of an effective treatment strategy is highly anticipated for SSc patients.

Professional experience
1998-2003  Medical Doctor, Department of Dermatology, Kanazawa University
2003-2005  Research associate, Department of Immunology, Duke University Medical Center
2005-2008  Assistant professor, Department of Dermatology, Kanazawa University,
2008-2013  Lecturer, Department of Dermatology, Kanazawa University
2013-present  Associate Professor, Department of Dermatology, Kanazawa University
LS- 1  Clinical features of anti-ARS Ab-positive dermatomyositis

Takashi Matsushita
Department of Dermatology, Kanazawa University

Patients with polymyositis and dermatomyositis (DM) frequently have myositis-specific autoantibodies, which are closely associated with different clinical features. Patients with anti-Mi-2 Ab typically present with conventional DM without cancer or ILD. Detectable anti-TIF1-γ Abs are closely associated with cancer in patients with DM, while patients with anti-aminoacyl tRNA synthetase (ARS) and anti-MDA5 Abs frequently have interstitial lung disease (ILD). Furthermore, anti-MDA5 Ab positive ILD is rapidly progressive and a life-threatening disease, while ILD with anti-ARS Ab positive patients can be characterized by the chronic course of ILD. In addition, anti-ARS Ab positive patients present common symptoms such as myositis, ILD, polyarthritis, Raynaud’s phenomenon, fever, and mechanic’s hand (anti-synthetase syndrome), although there are 8 anti-ARS abs, including anti-Jo-1, anti-EJ, anti-PL-7, anti-PL-12, anti-KS, anti-OJ, anti-Zo, and anti-Ha. Among these anti-ARS Abs, DM-specific skin manifestations were more frequently observed in patients with anti-Jo-1, anti-EJ, anti-PL-7, and anti-PL-12 compared with anti-KS and anti-OJ. For the treatment, some immunosuppressive agents, in addition to oral corticosteroids, are required in anti-ARS Ab positive patients. In this session, I would like to talk about clinical features and treatment of anti-ARS Ab-positive DM.

Education:
1999  M.D. Kanazawa University School of Medicine, Ishikawa, JAPAN
2006  Ph.D. Kanazawa University School of Medical Science, Ishikawa, JAPAN

Academic appointments:
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2000-2001  Residency, Department of Dermatology, International Medical Center of Japan, Tokyo, JAPAN
2001-2002  Clinical fellow, Department of Dermatology, Kurobe City Hospital, Toyama, JAPAN
2002-2003  Clinical fellow, Department of Dermatology, Ishikawa Prefectural Central Hospital, Ishikawa, JAPAN
2003-2006  Clinical fellow and Graduate Student, Department of Dermatology, Kanazawa University School of Medical Science, Ishikawa, JAPAN
2006-2007  Clinical fellow, Department of Dermatology, Kanazawa University School of Medical Science, Ishikawa, JAPAN
2007-2010  Research associate, Department of Immunology, Duke University, NC, USA
2010-2013  Assistant professor, Department of Dermatology, Kanazawa University School of Medical Sciences, Ishikawa, JAPAN
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Major research interests:
1. Clinical and basic research of Scleroderma and Dermatomyositis
2. The role of regulatory and effector B cells in autoimmunity
LS-2  Cutaneous manifestations of dermatomyositis characterized by myositis specific autoantibodies

Naoko Okiyama
Department of Dermatology, Faculty of Medicine, University of Tsukuba

Cutaneous manifestations are characterized according to myositis-specific autoantibodies for dermatomyositis (DM). Cutaneous ulceration and palmar violaceous macules/papules are related to anti-MDA5 antibody. Severe cutaneous manifestations are often observed in patients with anti-TIF1γ antibody-associated DM. Mechanic’s hands is generally specific to patients with antisynthetase syndrome including those with anti-ARS antibody-associated DM. Anti-NXP2 antibody-positive patients have a high risk of calcinosis. In contrast, anti-SAE antibody-positive patients demonstrated extensive rash, including erythroderma with ‘angel wings’ sign’.

We previously analyzed of the histological findings of finger lesions characterized according to anti-ARS, anti-MDA5, and anti-TIF1γ antibodies, which were classified according to the followings: (i) interface dermatitis; (ii) psoriasiform dermatitis; (iii) eczematous reaction; (iv) vascular injury, and also analyzed by immunohistochemistry to detect myxovirus resistance A (MxA) expression associated with type I interferon activity. Finger eruptions of anti-ARS antibody-positive DM were characterized by not only interface dermatitis but also psoriasiform dermatitis and eczematous reaction, which were rarely observed in the others. Dyskeratotic cells were frequently observed in anti-ARS antibody-positive DM, while vascular injury was found in anti-MDA5 antibody-positive DM. Epidermal MxA expression was high in anti-MDA5 antibody-positive DM and rarely observed in anti-ARS antibody-positive DM. These cutaneous histological characteristics are shared with those of the muscle.

2014  Assistant Professor, Department of Dermatology, Faculty of Medicine, University of Tsukuba
2011  Visiting Fellow, Dermatology Branch, CCR, NCI, NIH
2010  Assistant Professor, Department of Dermatology, Hospital Faculty of Medicine, Tokyo Medical and Dental University (TMDU), Japan
2008  Research Fellow, JSPS, MEXT
2007  Junior Research Associate, Laboratory for Clinical Immunology, RCAI, RIKEN
2005  Graduate Student, Department of Dermatology, Graduate School of Medical and Dental Sciences, TMDU
2004  Staff Clinician, Tokyo Metropolitan Bokutoh Hospital, Japan
1999  Resident, Hospital Faculty of Medicine, TMDU, Japan
O-1  Fli1-deficient adipocytes promote spontaneous skin fibrosis and vasculopathy: Potential roles of adipocytes in systemic sclerosis

Takuya Miyagawa
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Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by autoimmunity, vasculopathy and extensive organ fibrosis. Although its pathogenesis still remains to be seen, adipokines have recently caught much attention as a family of cytokines regulating the three cardinal pathological features of this disease. On the other hand, our studies have demonstrated that the deficiency of transcription factor Fli1 induces SSc-like phenotypes in various cells, such as dermal fibroblasts, endothelial cells, macrophages and epithelial cells. Furthermore, our preliminary study showed that Fli1 expression is decreased in adipocytes of SSc patients. Based on these back grounds, we generated adipocyte-specific Fli1 knockout (Fli1 AdipoKO) mice (Fli1^floxed;Adipo-Cre) and investigated whether these mice recapitulate the cardinal features of SSc. Of note, Fli1 AdipoKO mice spontaneously developed dermal fibrosis at the age of 3 months. The skin of these mice demonstrated higher levels of total collagen content and myofibroblast counts. In double immunofluorescence for a-smooth muscle actin and perilipin, double positive fusiform cells were evident throughout the deep dermis in Fli1 AdipoKO mice, suggesting the promotion of adipocyte-to-myofibroblast transdifferentiation. In addition, vascular structural and functional abnormalities, such as arteriolar stenosis and increased permeability, were remarkable in Fli1 AdipoKO mice. Importantly, bone marrow-derived mesenchymal stem cells (BM-MSCs), a precursor of pro-angiogenic hematopoietic cells, of Fli1 AdipoKO mice exhibited de-differentiated phenotype characterized by a-smooth muscle actin downregulation and Rgs5 upregulation, suggesting the contribution of defective vasculogenesis to the development of vascular abnormalities. This phenotype was induced by co-culture of Fli1-deficient adipocytes and BM-MSCs of wild type mice. Furthermore, upregulated IL-6 induced by Fli1-deficient adipocytes changed BM-MSCs of wild type mice into de-differentiated phenotype. In addition, vascular structural and functional abnormalities were restored after the treatment by an IL-6 receptor inhibitor. Taken together, these results indicate that Fli1-deficient adipocytes can be involved in the development of dermal fibrosis and vasculopathy recapitulating SSc, suggesting a potential contribution of phenotypically altered adipocytes to the development of SSc.
PI3K-Akt pathway plays a crucial role in production of collagen in Fli1 deficient condition and its inhibitor has the therapeutic potential in treating fibrosis.

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²Mucosal Immunity Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

[Background/Purpose] Systemic sclerosis (SSc) is a connective tissue disease characterized by fibrosis of the skin and internal organs. Previous studies have shown that dermal fibroblast in patients with SSc frequently shows decreased levels of Fli1 due to hypermethylation. We aimed to clarify the mechanisms underlying the regulation of Fli1 gene of fibrosis using Fli1 deficient cells and mice generated by the CRISPR/Cas9-mediated gene edition.

[Methods] Fli1-deficient fibroblast cell line (Fli1 ΔNIH3T3 cells) and mice (Fli1−/− mice) were generated by CRISPR/Cas9 system using paired guide RNAs specific for mouse Fli1 and a nickase Cas9 that reduces off-target problem. NIH3T3 cells were transfected with a lentivirus vector v2 vector and then selected by puromycin. We evaluated collagen and profibrotic cytokine production in the absence of Fli1 by mRNA level. To reveal the mechanism for induction of collagen in Fli1 ΔNIH3T3 cells, we treated the cells with various antibodies and inhibitors and performed RNA-sequencing. In order to estimate in vivo efficacy of LY294002 derivative on fibrotic disease, we utilized bleomycin-induced lung fibrosis with Fli1−/− mice and treated with LY294002 derivative by intra-peritoneal injection 3 times and evaluated lung fibrosis by histology, collagen content, and Ashcraft scores. We also evaluated the ex vivo effect of candidate drug using skin fibroblasts from patients with SSc.

[Results] Fli1 ΔNIH3T3 cells were found to have pro-fibrotic characteristics such as increased expression of COL1A1, COL1A2 as well as increased expression of TGF-β1, CTGF, IL-6, FN, and ACTA2. Antibody neutralization of TGF-β1 and IL-6 didn’t inhibit collagen synthesis in Fli1 ΔNIH3T3 cells. In addition, whereas MAPK inhibitors of Erk U0126, JNK SP600125, p38 SB20358 failed to suppress the increased collagen production, Nintedanib, a triple kinase inhibitor of VEGFR, FGFR, and PDGFR partially inhibited collagen synthesis. Surprisingly, a phosphoinositide 3-kinases (PI3K) inhibitor, LY29402, which also has inhibitory activity against bromodomain-containing protein (BRD) 2, 3 and 4, had a major inhibitory effect on COL1A2 mRNA expression, suggesting the PI3K-Akt and bromodomain pathways have a major pro-fibrotic role in Fli1NIH3T3 cells. This correlated with the fact that, p-Akt expression was increased in Fli1 ΔNIH3T3 cells. In addition, a low toxicity LY294002 derivative also inhibited collagen synthesis in Fli1 ΔNIH3T3, confirming PI3K and BRD4 dual inhibition was most effective to reduce COL1A2 production. Furthermore, analyses of RNA-seq revealed several molecules to induce collagen via PI3K-Akt pathway. Finally, LY294002 derivative treatment significantly ameliorated lung fibrosis in Fli1−/− mice as evaluated by Masson Trichrome staining, decreased collagen accumulation in the lung and Ashcraft clinical scores. In both normal and SSc fibroblasts, COL1A2 mRNA were significantly inhibited by LY294002 derivative.

[Conclusion] Lack of Fli1 expression activates the molecule that induces collagen accumulation through PI3K-Akt pathway. PI3K inhibitor showed therapeutic potential in treating fibrosis.
Anti-fractalkine monoclonal antibody therapy inhibits the progress of skin inflammation, fibrosis, and vascular injury in systemic sclerosis mouse models

Akira Utsunomiya¹, Vu Huy Luong¹, Takenao Chino¹, Noritaka Oyama¹, Takashi Matsushita², Takashi Obara³, Yoshikazu Kuboi⁴, Naoto Ishii⁴, Akihito Machinaga⁴, Hideaki Ogasawara⁴, Wataru Ikeda¹, Toshio Imai¹, Minoru Hasegawa¹
¹Dermatology, University of Fukui, ²Dermatology, Kanazawa University, ³Eisai Co., Ltd., ⁴KAN Research Institute, Inc.

Systemic sclerosis (SSc) is a collagen disease characterized by inflammation, fibrosis, and vascular injury. We previously reported that the expression of fractalkine and its unique receptor, CX3CR1 was augmented in patients with SSc. In the current study, we investigated the utility of anti-mouse fractalkine monoclonal antibody (mAb) therapy for skin lesion in two mouse models of SSc. In the first model, daily subcutaneous injections of bleomycin increased serum levels of soluble fractalkine and induced skin fibrosis subsequent to inflammation in C57BL/6 mice. However, administration of anti-fractalkine mAb significantly reduced the skin inflammation and fibrosis. The dermal infiltration of CX3CR1⁺ cells, macrophages (inflammatory and alternatively activated [M2-like] subsets), and CD3⁺ cells was reduced by anti-fractalkine mAb. Results of RNA microarray and qRT-PCR demonstrated that mRNA expression of fibrogenic molecules, such as osteopontin (Spp1) and TSLP induced by bleomycin injection was significantly suppressed by anti-fractalkine mAb therapy. Anti-fractalkine mAb administration also protected the microvascular injury in bleomycin-injected skin. In the second model, BALB/c newborn mice received subcutaneous injections of TGF-β followed by that of CTGF. Anti-fractalkine mAb significantly inhibited the progress of skin fibrosis and inflammation. In these models, no obvious side effects were found. Furthermore, anti-CX₃CL1 mAb treatment significantly inhibited Smad3 phosphorylation and expression of type I collagen and fibronectin 1 in human dermal fibroblasts stimulated with TGF-β1. Therefore, anti-fractalkine mAb therapy could be a novel therapeutic approach for inflammatory-driven fibrotic skin disorders such as SSc.
Monocytes/macrophages may contribute to the pathogenic process of systemic sclerosis via downregulation of interferon regulatory factor 8

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¹Department of Environmental Immuno-Dermatology, ²Department of Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Recent observations have suggested that monocytes/macrophages play important roles in the pathogenic process of systemic sclerosis (SSc). Interferon regulatory factor (IRF) 8 is a transcriptional regulator which plays essential roles in the differentiation and function of monocytes/macrophages. We hypothesized that IRF8 may be involved in the fibrotic process of SSc by regulating phenotypes of monocytes/macrophages.

In this study, we first determined IRF8 levels in circulating monocytes from 26 SSc patients (diffuse cutaneous SSc (dcSSc), n=11; limited cutaneous SSc (lcSSc), n=15) and 14 healthy controls by quantitative real time PCR (qRT-PCR). IRF8 was next silenced in monocytes by RNA interference, and these monocytes were differentiated into macrophages (siIRF8-MDMs). Cell surface markers, cytokine/chemokine profiles, and expression levels of extracellular matrix (ECM) were assessed by flow cytometry, qRT-PCR, and bead-based immunoassay. Also, these macrophages were co-cultured with fibroblasts, and mRNA expressions of fibrotic factors in fibroblasts were analyzed by qRT-PCR. Finally, bleomycin-induced skin fibrosis was assessed in myeloid cell-specific IRF8 conditional knockout mice (Cre(LysM)IRF8(flox/flox) mice).

As results, IRF8 levels in circulating monocytes from dcSSc patients were significantly lower than those from healthy controls and lcSSc patients. Its level was negatively correlated with modified Rodnan total skin thickness score. siIRF8-MDMs exhibited M2 phenotype, and mRNA expression levels of pro-fibrotic cytokines and ECMs were significantly upregulated in these macrophages than that from control. The same trend was observed in protein level. The fibroblasts co-cultured with siIRF8-MDMs expressed significantly higher levels of pro-fibrotic transcriptional factor Sp.1. In bleomycin-induced skin fibrosis model, dermal thickness, skin infiltrating macrophages, hydroxyproline contents, and levels of pro-fibrotic factors were aggravated in Cre(LysM)IRF8(flox/flox) mice.

In conclusion, IRF8 was significantly downregulated in circulating monocytes from dcSSc patients, and pro-fibrotic phenotype was induced in vitro and in vivo. Altered regulation of IRF8 in monocytes/macrophages is probably involved in the pathogenic process of SSc.
O- 5   Inhibitory effect of bleomycin-induced skin fibrosis by regulating the balance of regulatory T cells and Th17 cells

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Osamu Ishikawa¹ Sei-ichiro Motegi¹
¹Department of dermatology, Graduate School of Medicine, Gunma University,
²Department of parasitology, National Institute of Infectious Diseases,
³Laboratory for Intestinal Ecosystem, RIKEN Center for Integrative Medical Sciences

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of skin and internal organs, vasculopathy and immune dysregulation. There is growing evidence that dysfunction of regulatory T (Treg) cells and activation of Th17 cells is involved in the pathogenesis of SSc. Helminth infection is known to activate Treg and suppress the symptoms of animal model of various autoimmune diseases. Objective was to elucidate the effects of the activation of Treg cells by helminth infection on bleomycin-induced skin fibrosis in mice and the mechanism of the inhibitory action of fibrosis. We identified that prior infection with helminth significantly inhibited bleomycin-induced skin fibrosis in mice. The number of α-SMA⁺ myofibroblasts and CD68⁺ macrophages in the lesional skin were significantly reduced by helminth infection. Flow cytometric analysis of lymph nodules revealed that the number of CD4⁺Foxp3⁺ Treg cells increased and Th17 cells decreased in helminth infected mice. Furthermore, depletion of Treg reversed the suppression of bleomycin-induced skin fibrosis caused by helminth infection and increased Th17 cells. In addition, intestinal microbiota examination suggested that the inhibitory effect on bleomycin-induced skin fibrosis due to helminth infection might be related to alterations in microbiota involved in the induction of Treg cells. Our results suggest that regulation of the balance between Treg and Th17 cells by helminth infection mediated by microbiota modulation could be applied to the treatment of scleroderma in SSc patients.
O- 6  Apremilast inhibits the progression of bleomycin-induced skin fibrosis in mice

Tomoaki Higuchi, Kae Takagi, Yasushi Kawaguchi
Department of Rheumatology, Institute of Rheumatology, Tokyo Women’s Medical University

Apremirast, a phosphodiesterase (PDE)-4 inhibitor, has been approved for the treatment of psoriasis and other inflammatory diseases. In addition to anti-inflammatory effects of apremilast, recently its anti-fibrotic effects have been reported using such as a mouse model of pulmonary fibrosis. The aim of our present study is to investigate whether apremilast could attenuate the progression of skin fibrosis using human skin fibroblasts and a preclinical systemic sclerosis (SSc) mouse model. A mouse model of bleomycin-induced skin fibrosis was established by administering a subcutaneous injection of 100 \( \mu \)g bleomycin five times a week for four weeks on the back of BALB/c mice. Mice were administered either PBS or apremilast (1 mg/kg or 5 mg/kg) peritoneally five times a week for four weeks. Skin thickness, collagen content, and the number of \( \alpha \)SMA-positive myofibroblasts and immune cells in mice skin were evaluated. Apremilast significantly suppressed the expression of profibrotic markers in skin fibroblasts. Apremilast significantly attenuated skin thickness and decreased the number of \( \alpha \)SMA-positive myofibroblasts and CD3-positive cells in the skin specimen of bleomycin-treated mice. Our present study suggested that apremilast may be a candidate of drug-repositioning for the treatment of tissue fibrosis in SSc.
O- 7 Roles of platelet-derived growth factor receptor (PDGFR) inhibitor for the fibrosis of systemic sclerosis

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²Arthritis Center, Boston University School of Medicine, USA

Systemic sclerosis (SSc) is an acquired autoimmune disorder that typically results in fibrosis of the skin and internal organs. Activated fibroblasts are the key effector cells in SSc responsible for the production of collagen and the development of fibrosis. In this study, we examined the role of crenolanib, an inhibitor of PDGFR signaling, in cultured skin fibroblasts and evaluated its antifibrotic effect in the angiotensin II (Ang II)-induced mice skin and heart fibrosis. Healthy control (HC) and SSc dermal fibroblasts were cultured in the presence of crenolanib, TGF-β₁, PDGF ligands and CTGF. Cell proliferation was measured using the Incucyte® system. Skin biopsy samples collected from 15 healthy controls and 33 dcSSc were included in the microarray analysis. Ang II was administered by subcutaneous osmotic pumps. Crenolanib effectively inhibited proliferation of SSc and HC fibroblasts, and attenuated basal and TGF-β₁-induced expression of CTGF and peristin. In contrast to HC fibroblasts, SSc fibroblasts proliferated in response to PDGF-AA, while a combination of PDGF-AA and CTGF was required to produce a similar response in HC fibroblasts. PDGFRα mRNA correlated with CTGF and other fibrotic markers in the skin of SSc. In mice challenged with Ang II, PDGFRα-positive cells were increased in the skin and heart. These PDGFRα-positive cells co-localized with PDGFRβ₁, procollagen and peristin. Treatment with crenolanib by daily intraperitoneal injections attenuated the skin and heart fibrosis in the Ang II model. Our data suggest that inhibition of PDGF signaling presents a new attractive therapeutic approach in SSc.
Selective S1P\textsubscript{1} receptor modulator attenuates murine sclerodermatous models

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Sphingosine-1-phosphate (S1P), a lipid mediator, regulates lymphocyte migration between lymphoid tissue and blood. S1P participates in several physiological phenomena including angiogenesis, inflammation, immune regulation, and neurotransmitter release. S1P/S1P receptor signaling involves in systemic sclerosis (SSc) pathogenesis. Although FTY720 reportedly ameliorates murine sclerodermatous chronic graft versus host disease (Scl-cGVHD) mice, it has side effects such as bradycardia. Cenerimod is a potent, selective, safe and orally administrable selective S1P\textsubscript{1} receptor modulator, which reportedly attenuated murine experimental autoimmune encephalomyelitis model. This study aimed to investigate whether the selective S1P\textsubscript{1} receptor modulator cenerimod attenuates murine sclerodermatous models. Cenerimod was orally administered to murine Scl-cGVHD mice, either from day 0 to 42 or day 22 to 42 after bone marrow transplantation. Bleomycin-induced scleroderma model mice were administered cenerimod from day 0 to 28. Early cenerimod administration inhibited, and delayed cenerimod administration attenuated skin and lung fibrosis in Scl-cGVHD mice. Furthermore, cenerimod attenuated bleomycin induced scleroderma model in the skin and lung. Cenerimod suppressed the infiltration of CD4’ T cells, CD8’ T cells, and CD11b’ cells into the inflamed skin of Scl-cGVHD mice as opposed to control mice. Additionally, cenerimod attenuated the mRNA expression of extracellular matrix and fibrogenic cytokines such as IL-1\textbeta, IL-6 and IL-13, in the skin of Scl-cGVHD mice. In contrast, cenerimod increased the frequency of regulatory T cells in the spleen and skin of Scl-cGVHD mice. Furthermore, collagen production in fibroblasts was inhibited by cenerimod. Cenerimod apparently exerts an immunosuppressive effect with attenuation of immune cell infiltration into the skin, decreased fibrogenic cytokine environment, accompanied by an increase in splenic and skin regulatory T cells. These results suggest that the selective S1P\textsubscript{1} receptor modulator cenerimod is a promising candidate for treating patients with SSc.
P-01
全身性強皮症におけるカルバイン阻害剤の有用性の検討

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カルバン阻害剤は、マウスにおいて肺線維症、
皮膚の瘢痕形成、血管障害などを軽減するとの報告
があり、強皮症の線維化、血管障害の治療薬として
有用な可能性がある。そこで、まずALLN (calpain
inhibitor) で検討した。正常皮膚培養線維芽細胞を使
用了qRT-PCRでCOL1A2、Fibronectin1、α SMAの発
現を有意に抑制した。また、pSmad2/3の免疫染色では、
核内の染色性が減退していた。現在はブレオマイシ
ン誘発強皮症マウスマウスを用いてALLN投与の有用
性を検討している。

P-02
LG283のブレオマシン誘発強皮症モデルマウスにおける抗線維化作用の検討

宇都宮裕1、知野剛直1、Vu Huy Luong1、尾山徳孝1、
長谷川敏1、丹羽雅一郎2、大塚雅己3、尹 浩信4
(1福井大皮膚科、2リンク・ジェノミクス株式会社、
3熊本大生体機能化学、4熊本大皮膚病態治療再建学)

全身性強皮症の治療では、抗線維化作用をもつ新
規薬剤の開発が望まれている。そこで、多数の薬剤
の中からヒト皮膚線維芽細胞の分化を抑制する薬剤
をスクリーニングし、合物LG283に注目した。ブレ
オマシン誘発強皮症モデルマウスに薬を経口投
与し、生体内での抗線維化作用を検証した結果、用
量依存的に皮膚の線維化が有意に抑制された。機序
の解明のため、上皮細胞や内皮細胞の間葉転換に対
する抑制作用を検討した。

P-03
A novel mouse model of PAH characterized fibrosis and inflammation.

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(1National Cerebral and Cardiovascular Center Research Institute/Department of Vascular Physiology, 2National Cerebral and Cardiovascular Center Research Institute/Department of Advanced Medical Research for Pulmonary Hypertension)

Recently we created a novel mouse model of PAH reflecting hypoxia, fibrosis, and inflammation through combination of pristane with exposure to chronic hypoxia (PriHx). Hemodynamic and histological analysis revealed that the PriHx mice exhibited more severe phenotype of PAH than mice exposed to chronic hypoxia alone.

P-04
ブレオマシン誘発強皮症モデルマウスを用いた全身性強皮症におけるB細胞除去の影響に関する研究

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浅野若英1、藤原伸1
(1東京大皮膚科、2日赤医療センター大皮膚科)

ブレオマシン誘発強皮症モデルマウスを対象と
し、抗CD20抗体によるB細胞除去を行い、B細胞の全
身性強皮症に及ぼす影響を検討した。ブレオマシン
誘発強皮症モデルマウスから抽出したB細胞は、IL-6
を放出することで、マクロファージ分化をM2へと傾
移させた。ブレオマシン誘発強皮症モデルではM2
/M1が上昇し、皮膚及び肺の線維化が起きたが、B細
胞除去を行うとM2/M1は低下し線維化は抑制された。
P-05
オーバーラップ症候群モデルマウスを用いた、全身性強皮症および全身性エリテマトーデスの病態干渉に関する検討
遠山聡、三浦俊介、三枝良輔、山下尚志、中村流樹、
平林恵、宮川卓也、福井夕輝、尾松淳、淡路健太郎、
吉崎歩、佐藤伸一、浅野善英
（東京大学皮膚科）

全身性強皮症 (SSc) 様症状を自然発症するKI5 ”Fii” (DH)マウスを用いてイミキモドを用いた全身性エリテマトーデス (SLE) モデルマウスを作成し、SScとSLEの病態干渉を検討した。イミキモドを用いたDHマウスはSLEモデルマウスより腎炎が軽く、DHマウスより線維化や血管障害が悪化しており、SScの病態は線維化や血管障害を悪化させる可能性が示唆された。

P-06
上皮細胞特異的Fii欠失マウスにおける創傷治癒に関する検討
尾松淳、高橋岳浩、三枝良輔、宮川卓也、福井夕輝、
遠山聡、淡路健太郎、吉崎歩、佐藤伸一、浅野善英
（東京大学皮膚科）

全身性強皮症(SSc)では創傷治癒が遅延している。その主要な因は血管障害と考えられるが、表皮細胞の関与については不明である。今回は、SSc表皮細胞の形質を再現する上皮細胞特異的Fii欠失マウスを用いて創傷治癒について検討した。同マウスでは創傷治癒が遅延していたが血管新生の異常はみられず、表皮細胞の遊走能、増殖能が低下していた。以上より、SScの創傷治癒遅延に再上皮化の障害が関与している可能性が示唆された。

P-07
全身性強皮症の皮膚組織と血清におけるIL-16の検討
牧野貴充、牧野雄成、押川由佳、澤村健一郎、島田秀一、
宮村智孝、石松翔子、尹浩信
（熊本大学皮膚科）

全身性強皮症は自己免疫異常を背景に、様々なサイトカインの発現異常が皮膚や組織の病態に関与している。今回我々は、強皮症の発症に関、皮膚組織および血清中のIL-16の発現について検討を行った。皮膚組織の免疫染色では、びまん性皮膚硬塞全身性強皮症において、IL-16の高発現を認めた。さらに強皮症において血清中IL-16濃度は上昇しており、皮膚硬塞や紅斑、色素沈着などの皮膚症状に有意な関連を認めた。

P-08
全身性強皮症における表皮細胞でのIL-36, IL-38の関与
秋田亜妙美、山口由衣、乙竹 泰、池田範子、相原道子
（横浜市立大学皮膚科）

全身性強皮症 (SSc) の病態における表皮細胞の役割に着目し、表皮細胞に多く発現するとされるIL-1ファミリーのIL-36, IL-38の関与について検討した。SSc患者の表皮細胞ではIL-36γの発現が増加しており、血清ではIL-38が低下していた。またIL-36γ刺激により角化細胞の上皮間葉移行が促進される可能性が考えられた。

-36-
P-09
全身性強皮症における血清ガレクチン-9、可溶性LAG-3、可溶性CD155値の臨床的意義
篠場広一、千葉真未、栗田美紀
（東京慈恵会医科大学総合医療センター皮膚科）
全身性強皮症62例、健常人26例において、血清ガレクチン-9、可溶性LAG-3、CD155値をELISA法にて測定し、臨床状態、検査所見との相関を検討した。血清ガレクチン-9値は全身性強皮症において有意に上昇しており、赤血球沈降速度との間に正の相関がみられた。可溶性LAG-3、可溶性CD155値は健常人と差があらわなかった。ガレクチン-9は全身性強皮症の病態形成に関与している可能性が示唆された。

P-10
悪性腫瘍合併皮膚筋炎患者の腫瘍組織におけるTIF1γの発現と病態への関与
山崎直保里、間口明子、茂木精一郎、石川 治
（群馬大学医学系研究科皮膚科学）
抗TIF1γ抗体陽性皮膚筋炎患者は高率に悪性腫瘍を合併し、生命予後を左右する。悪性腫瘍合併皮膚筋炎の発症機序として、腫瘍細胞にTIF1γが高発現し、それに対する自己免疫反応によって抗TIF1γ抗体が産生され、皮膚筋炎の発症に関与すると考えられているが、十分に検討されていない。我々は、悪性腫瘍合併皮膚筋炎におけるTIF1γの発現と病態への関与を明らかにするため、皮膚筋炎患者と非皮膚筋炎患者の腫瘍組織におけるTIF1γの発現を比較検討した。

P-11
膠原病患者における定量的輪流反応性発汗試験(QSART)を用いた発汗機能の検討
芦田真輔1、宮崎マリ子1、江原大輔1、小池雄太1、
室田浩之2、森本心平2
（1長崎大学皮膚科、2長崎大学総合医療センター皮膚科）
長崎大学病院皮膚科アレルギー科外来にて定期受診中の膠原病患者(全身性強皮症、混合性結合織病、SLE、シューグレン症候群、皮膚筋炎)について、暖房期(2019年6月〜9月)と寒冷期(12月〜2020年1月)の2ポイントで定量的輪流反応性発汗試験(QSART)を施行し、主にレイノー症候群の関連について検討した。また全身性強皮症患者については、特異抗体や合併症、喫煙歴など患者背景との関連についても検討を行った結果を発表する。

P-12
本邦における全身性強皮症早期例の臨床経過：多施設前向き研究
宇都宮慧1、長谷川敏1、浅野善英1、石川 治1、
遠藤平仁1、川口文hurst1、川口敏司1、桑名正隆2、
後藤大輔1、佐藤伸一1、高橋裕樹1、竹原和宏1、
田中佳明1、藤本 亮2、伊藤浩信2
（1福井大皮膚科、2東京大皮膚科、3群馬大皮膚科、4寿永総合病院リウマチ膠原病内科、5小川皮膚科・アレルギー科、6東京女子医大膠原病リウマチ内科、7日本医大アレルギー膠原病内科、8筑波大内科、9札幌医大免疫・リウマチ内科、10金沢大皮膚発症態学、11北里大膠原病・感染内科、12大阪大皮膚科、13熊本大皮膚病態治療再建学）
日本人の全身性強皮症早期例における臨床経過を明らかにするため、多施設で登録された207例を対象に7年後までの経過を解析した。大半の症例で免疫抑制剤療法を行われ、スキンスコア(mRSS)は改善した。しかし、指尖潰瘍や関節性肺炎を合併する症例は経時に増加し、%VC%DLcoなどの肺機能、HAQ-DIは悪化した。このように身体の機能障害は徐々に悪化することが示唆され、今後の治療の課題と考えられた。
P-13
強皮症腎クリーレゼにおける前駆症状

木村 弘1,2, 坂本芳伸1,2, 松下貴史1, 濱口健人1,
竹原和彦1
(1) 金沢大皮膚分子病態学、(2) 加賀市医療センター、(3) 福井県立病院

2001年から2014年の間に発症した強皮症腎クリーレゼ（SNC）の12症例を対象に、前駆症状について検討した。病型分類は典型的SRCが8例、血栓性微小血管障害（TMA）様病態が9例、混在が5例。前駆症状は、全身倦怠感が9例（75%）、微熱が3例（25%）、筋肉痛が5例（42%）、頭痛が2例（17%）。前駆症状としての検査所見は血中Hb値低下が2例（17%）、Plt数低下が5例（42%）、血清CR値上昇が6例（50%）。前駆症状はTMA様病態を伴った症例に高頻度にみられた。

P-14
全身性強皮症における爪郭部毛細管撮影所見の10年経過と臨床所見との関連性

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竹原和彦3
(1) 金沢大附属病院リハビリ、(2) 金沢大リハビリテーション科、(3) 金沢大皮膚分子病態学

爪郭部毛細管所見の経時的変化と関連する臨床所見について調査した。
キャピラリースコープにて10年後に再評価した73例を対象として、初診時と10年後のキャピラリースコープパターンを比較した。また初診時の各臨床所見との関連性を検討した。
10年後のパターンに関して、改善する症例も一定数存在した。抗Topo-1抗体陽性のlateパターンを示す症例は皮膚潰瘍や手指拘縮に至りやすることが示された。

P-15
全身性強皮症患者における手指発汗異常の検討

田畑佳世子1、三木田真哉2、安永美砂生1、松沼 邦1、
田中克典1、藤本洋生1、谷 洋香2、糸引宏子2、
神人正寿1、藤井隆夫1
(1) 和歌山県立医大リウマチ膠原病科、(2) 和歌山県立医大皮膚科

【目的】全身性強皮症における発汗量の異常の有無と、発汗量が疾患マーカーとなる可能性を検討した。
【方法】強皮症を疑われた37例を対象として、発汗量はキャピラロスコピーを用いて定量化した。
【結果】強皮症を疑われた患者のうち、診断基準を満たした例で発汗量が有意に多かった。また強皮症患者のうち、トポイソメラーゼI抗体陽性例で有意に多い傾向が見られた。

P-16
自己抗体陰性全身性強皮症の臨床的特徴の解析

保原亜希子、小川陽一、小中真央、松崎公瑠美、
富田英恵、島田貴路、川村龍吉
(山梨大学皮膚科)

当科で診察している臨床的・病理学的に皮膚硬化を認める全身性強皮症患者57名のうち、抗トポイソメラーゼI抗体・抗RNAポリメラーゼIII抗体・抗セントロメリア抗体・抗RNP抗体がすべて陰性の患者9名の臨床的特徴について検討を行なった。
P-17
琉球大皮膚科の全身性強皮症患者の自己抗体について

宮城拓也、山本雄一、高橋健造
（琉球大皮膚科）

2019年11月までに琉球大皮膚科で診察し、特異抗体を同定した全身性強皮症患者は133例で、抗セントロメア抗体陽性が70例と最多で、抗Tpo-1抗体が38例、抗U1-RNP抗体が14例、抗RNAポリメラーゼIII抗体が9例、抗ARS抗体が2例に陽性であった。皮膚潰瘍の発症は、抗ARS抗体陽性例で100%、抗Tpo-1抗体で47.4%、抗U1-RNP抗体で42.9%と高かった。

P-18
当科過去5年にエリテマトーデス（LE）の頭部皮疹より系統的病理診断を施行した16例における臨床・病理組織学的検討

鈴岡夏帆、竹中祐子、澤田佳織、宮田龍治、石黒直子
（東京女子医大皮膚科）

男4例、女14例、年齢21から50歳。皮疹型はDLE型16例、深在性LE型1例、その他紅斑1例。観察、水平断（対照部、顔部、毛球上部、毛球部）で切り出し標本を作製。観察で波状変性の他、DLE型、その他紅斑では毛包周囲性、深在性LE型では脂肪繊維にもリンパ球浸潤あり。水平断で全例100％領域にリンパ球浸潤、一部で線維化する毛包数が減少。毛包の質、量の診断が可能な系統的病理診断はLE頭部皮疹の早期診断と治療決定に有用。

P-19
サイトメガロウイルス感染症を合併した皮膚筋炎患者の臨床的特徴

西尾麻由、関口明子、山崎京保里、茂木裕一郎、
石川 治
（京都大学医学系研究科皮膚科学科）

皮膚筋炎患者52例について検討したところ、21例（40.4%）が治療経過中にサイトメガロウイルス（CMV）感染を合併した。CMV感染群は非感染群と比較して、発症時のリンパ球数が少なく、間質性肺炎及び糖尿病の合併頻度が高かった。また、CMV感染群では免疫抑制剤の併用が多く、経過中のリンパ球数及び総蛋白量は低く、フェリチンは高値であった。これらの特徴を有する患者では、CMV感染に注意を要すると考えた。

P-20
妊娠期間に発症する抗TIF1γ抗体陽性皮膚筋炎

大矢和正1、藤本 学2、沖山奈緒子1
（1筑波大皮膚科、2大阪大皮膚科）

皮膚筋炎（DM）の発症機会には、抗TIF1γ抗体陽性例の悪性腫瘍があるが、妊娠との関連は不明である。2010〜2015年に当科で診断したDM52例中、妊娠年齢13例のうち、3例が妊娠・産褥期に発症し、その3例全てが抗TIF1γ抗体陽性で判明した。一方、抗TIF1γ抗体陽性16例の内、妊娠年齢発症の7例中全て女性で、妊娠・産褥期発症3例、悪性腫瘍合併1例、発症前後不13例であった。
P-21
金沢赤十字病院における乾癬性関節炎の
治療成績

川原 繁、伊川友香
(金沢赤十字病院)

乾癬性関節炎の治療はこの10年間に目覚ましい進
歩をとげている。今回、金沢赤十字病院において過
去5年間に3ヶ月以上経過観察を行った乾癬性関節
炎24例 (男19例、女5例) の治療成績について検討し
たので報告する。初回治療に生物学的製剤を用いた
患者は11例、内服薬が15例 (アプレミラスト7例、メ
トトレキサート6例、消炎鎮痛剤2例) であった。初
回治療の効果が不十分または二次無効が4例あり、
他の治療に変更した。

P-22
強指症・手指屈曲縮縮を呈しうるdiabetic
digital sclerosis本邦報告のまとめと考察

五十嵐健1、中村直男1 • 2
(東京中央病院皮膚科、2芝浦皮膚科)

糖尿病に伴う強皮症様皮膚症状は種々の名称で報
告・記載されていたが、本邦において我々がdiabetic
digital sclerosisの2例 (日本皮膚科学会雑誌112
(8):1111-4,2002) として報告して以来、この疾患名
として計12例の報告数を上げた。本邦報告の概要
と特徴を述べ検討し、報告する。

P-23
多施設共同研究による、好酸球性筋膜炎
の実態調査

伊藤 繁、山本俊幸
(福島県立医大)

国内外において好酸球性筋膜炎患者は少なく、ま
とまった報告は稀少である。本邦の実態を調べる目
的で、厚労省の強皮症・皮膚線維化疾患の研究班で、
過去5年間に好酸球性筋膜炎と診断した症例を有す
る7施設 (熊本大、金沢大、東京大、群馬大、筑波大、
和歌山県立医大、福島県立医大) の協力を得て集計し
た結果を報告する。

P-24
結節状性強皮症の1例

植田信子1、松 浩治1、大島 茂1、山本啓之1
(1関西医大皮膚科、2関西医大リウマチ・膠原病科、
3枚方市)

48歳、男性。4年程前よりレイノー現象、1年程
前より上腕に結節が出現し紹介受診した。両手に爪
上皮出血点があり、手指から前腕にかけて皮膚硬化
があった。前腕部から上腕、肩に淡紅色の結節が多
発していた。抗RNAポリメラーゼIII抗体陽性。上部
内視鏡で逆流性食道炎、CTで肺底部の間質性肺炎あり。
皮膚生検組織像で真皮の膠原線維の膨化増生が
あった。結節状強皮症と診断し血流改善薬を投与し
経過観察中である。
P-25
血清中IL-6値が上昇していた全身性強皮症の2例
小村一浩1、小林元夫2、北島 進3、//==========================================================

症例1. 48歳女性。8年前強皮症と診断され、3年前より皮膚硬化は増悪し、関節可動域制限、嘔下困難、消化管麻痺が出現した。1年前から摂食・消化・吸収困難となった。血清中IL-6値19 pg/mlと上昇していた。症例2. 49歳女性。3年前からレイノー現象皮膚硬化が出現、嘔下困難、心不全、腎不全も伴った。寛大な治療を目的に紹介された。血清中IL-6値58 pg/mlと上昇。

P-26
タキサン製剤による強皮症様皮膚硬化的2例
越後俊士1、佐藤孝津美1、簡井清広1、吉野裕司2、== トンネル型

症例1. 55歳女。乳癌術後療法として、ドセタキセラム療法開始2ヶ月後から両下腿にしびれ感を伴う浮腫性硬化が出現。プレドニゾロン20mg/日内服にて皮膚硬化は徐々に改善。症例2. 60歳男、肝頭部部（Stage IV）に対し、ゲムスタビシラセラマ療法開始4ヶ月後から両下腿に疼痛・しびれを伴う皮膚硬化が出現。病理組織はいずれも真皮乳頭層の膨化増生、脂肪組織の線維化がみられた。強皮症関連抗体は陰性。

P-27
低温サウナ療法を併用し治癒した全身性強皮症の足部潰瘍
西島 千博、穂積 真
（金沢医科大学センター）

76歳、女性。左4趾の角質をハサミで切ったところ、骨膜に至る潰瘍が形成した。難治性で、高度の疼痛があるため受診した。プロスタグランディン拮抗薬、炭酸浴、局所外用療法では全く改善しなかった。患趾のSPP(皮膚組織細胞間圧)は13mmHgであった。低温サウナ療法を開始したところ、疼痛の緩和がみられ、1か月後には疼痛が無くなった。肉芽形成、潰瘍の縮小がみられ、3か月後には潰瘍は治癒した。SPPも改善した。

P-28
右足趾全壊疽に対し10年の経過で上皮化を得た全身性強皮症の1例
石井義之1、荒井美奈子1、平野敬代1、八田尚人1、== トンネル型

48歳、女性。16年前に他社を診断するとともに指先潰瘍にて当科通院。2ヶ月より右足の疼痛と冷感が出現、右足趾を中心に皮膚潰瘍を形成、感染を生じた。抗酸素薬にて感染は軽快し全趾の障害が残存。MRAでは髄液動脈以下のがんまん性狭窄をみとめ術後再建の適応なし。局所処置に加えトラピアおよびシルデナフィルを導入、腐骨除去と骨幹露出療法を繰り返し、外来通院10年で上皮化。
P-29
妊娠の全身性強皮症に合併した間質性肺炎の一例

菅田実重1、小寺雅也1、田辺裕明1、植木高久1、
久田智子1、伊藤有美1、加藤幹人2
(1JCHO中京病院皮膚科、2JCHO中京病院産婦人科)

30歳女性。2年前から手足の浮腫と上肢の皮膚硬
化、半年前からレイノー症状あり。頭部の色素脱
失を主訴に前医を受診、全身性強皮症が疑われ紹
介。初診時妊娠8週、2か月前から軽労作での呼吸
苦を自覚。びまん性の皮膚硬化を認めmRSS20点、抗
Topo-I抗体陽性びまん皮膚硬化型全身性強皮症と診
断、間質性肺炎を合併。妊娠を継続希望あり、妊娠中
期からPSL内服とシクロスポリシンA投与を開始し、
出産後アザチオブリンで維持治療中。

P-30
高齢者の両側下腿に発症し、当初うつ性
脂肪組織炎を考えた限局性強皮症の一例

市村洋平、石井光子、菅谷　誠
(国立医療福祉大)

88歳男性。初診4ヶ月前から両側下腿に色素沈着を
伴う硬皮局面が出現。生検にて血管壁の膨化と脂肪
組織の線維化を認めた。年齢と臨床、病理からうつ
性脂肪組織炎と診断した。下肢に弾性包帯装着を
行うも、皮膚硬化局面が拡大し、両側前腕にも硬化
局面が生じた。アジェパンはなく、全身検査を行
って悪性腫瘍は否定された。限局性強皮症と診断し、
ステロイド内服によって皮膚硬化は改善した。

P-31
難治性逆流性食道炎により浮腫性声帯炎
を認めた限局皮膚硬変型全身性強皮症の
1例

伊藤友彰1、本橋　玲2、坪井良治1
(1東京医大皮膚科外、2東京医大耳鼻咽喉科頭頸部外
科外)

58歳女性。2014年　限局皮膚硬変型全身性強皮症
と診断され当院にて通院中。レイノー症状、爪上皮
内出血点、手指端の間性発疹、逆流性食道炎を
認める。mRSSは左右手指2点、左右手背中2点、左
右前腕1点、その他0点で合計10点。胃内視鏡検査
では、食道胃接合部にびらんを認め、ランザルス
分類ではGradeA。2016年より嘔声を認め耳鼻科受診。
逆流性食道炎により浮腫性声帯炎と診断。現在、逆
流性食道炎の治療にて嘔声は経過観察中。

P-32
足関節の拘縮を伴ったLinear scleroderma
の1例

井波真矢子、五十嵐健之
(NTT東日本関東病院皮膚科)

17歳、女性。初診1年前のめまい後から右大腿部や
鼠径部に皮膚硬化あり。その後、他部位にも出現し、
初診時には、頭部、体幹、下肢に皮膚硬化がみられた。
抗ssDNA抗体陽性で、病理組織観では真皮から皮下組織
に膠原線維の膨化と増生あり。足関節は拘縮があり、
安定立位で踵は接地せず、同部位の造影MRI
で増強効果がみられた。以上より、Linear scleroderma
と診断。プレドニゾロンの内服と関節可動域訓練で、
可動域は改善。
P-33
線状円板状エリテマトーデスの発症4年後に全身性エリテマトーデスに移行した女児の1例

後藤和哉1、鬼頭昭彦1、野々出義子2、加来洋1、
桜島健治1
(1京都大学医学部附属病院 皮膚科、2長浜赤十字病院
皮膚科)

8歳時に右顔部の淡红色紅斑が出現し徐々に拡大。前医で偽リンパ腫として治療をうけるも改善なく、11歳時に当科を紹介受診した。当科初診時、同部位のBlaucke線に沿う、鱗屑を伴い浸潤のある線状の
紅斑を認めた。病理組織所見から、円板状エリテマトーデスと診断した。ステロイド外用で皮疹は改善したが、12歳時に関節痛、レイノー現象、自己抗体の陽性を認め、全身性エリテマトーデスへの移行と
診断した。

P-34
尋常性乾癬に全身性エリテマトーデスを合併した1例

藤本明子1、清水高子1、大石京介1、松下善史1、
濱口健人1、竹原和彦1、川原 紫1、伊川友香2
(1金沢大皮膚科病態学、2金沢赤十字病院皮膚科)

37歳男性。当院初診4年前に尋常性乾癬と診断。3年前より関節痛が出現しタクロリムスの内服を開始。3ヶ月前にタクロリムス中止の上、インセクス
マップを開始。その後、顔面・手指の紅斑、発熱、頭
部の脱毛が出現。抗ss-DNA抗体＞800 AU/mL、抗ds-
DNA抗体：31 IU/mL、抗リポソームP抗体23 index、全
身性エリテマトーデスの合併と診断。ステロイドバ
ルス療法、プレドニゾロン50mg/日、タクロリムス
2mg/日投与にて改善。

P-35
顔面に広範な紫斑と強い色素沈着を伴っ
た慢性円板状エリテマトーデスの1例

古志有紗、竹内文、宮本敬、門野岳史
(聖マリアンナ医大)

75歳女。45年前より両頬部に皮疹を自覚。4年前
より顔面の皮疹の範囲が拡大。また同期間に脳梗塞
罹患し、抗血小板薬内服開始。内服後より皮疹の色
調が濃くなった。当科紹介時、両頬部・眉毛部・上
眼瞼に不整形の角化と浸潤を伴う紫褐色斑を認めた。
皮膚生検では、表皮の萎縮、表皮真皮境界部の空胞
変性、真皮にリンパ球浸潤。ループスバンドテスト
陽性。DLIと診断。ステロイド外用で皮疹は色素沈
着傾向。

P-36
抗ARS抗体と抗U1-RNP抗体の重複陽性を呈した皮膚腫瘍/SLのoverlap症候群の1例

上松 藤、鶴田昌洋、多田弥生
(帝京大)

38歳女。2週間より倦怠感、1週前より上肢、顔
に発疹し発熱を伴う。顔面中央に発赤性の浮腫性紅
斑、前額部、両上腕、手指に胡桃大までの淡紅色
斑が散在。爪上皮の延長と出血あり。指の腫脹・硬変、
レイノーなし。口腔潰瘍、疲れ感覚性白斑あり。近位
筋の筋力低下、CK上昇、筋電図異常、ARS抗体を認
め、自血球減少、抗核抗体・RNP抗体陽性、補体低下。
ds-DNA抗体・Sm抗体は陰性で腫、神経障害なし。組織
編は波状変性、真皮角チン沈着。
P-37
抗TIF1γ抗体陽性皮膚炎に全身性エリテマトーデスを発症した1例

新川宏樹1, 植木小節1, 村上香緒1, 天谷雅行1, 太田裕一郎2, 花岡洋成2, 谷川瑛子1（1慶應義塾大学皮膚科, 2慶應義塾大学リウマチ膠原病内科）

71歳、男性。3ヶ月前より顔面を中心に紅斑が出現した。皮膚生検の上、抗TIF1γ陽性皮膚炎と診断した。約1年後に日光暴露を契機に露光部の皮疹の増悪と近位筋筋力低下が出現した。同時期から抗核抗体の上昇、尿蛋白・顆粒円柱を認め、全身性エリテマトーデス及びループス腎炎V型の併発と診断。ヒドロキシンクロロキンを開始すると皮疹を認めた。プレドニゾロン及びタクロリムス内服により初期治療反応は良好であった。

P-38
サルコイドーシスを合併した抗PM/Scl抗体陽性皮膚炎

牧野輝彦, 清水忠道（富山大学院医学薬学研究部皮膚科学）

76歳男性、近医でレノード症状、下肢筋力低下、CT検査での胸部異常所見を指摘され、当院膠原病内科および当科紹介受診。手指關節背側、両拇指・示指側面に近角化を認めた。胸部CT検査では間質性陰影をBHLあり。血液検査ではCK 1755 U/L, KL-6 655.6 U/mlと上昇。ACEは正常。抗核抗体640倍（Nue）、抗PM/Scl75抗体、抗PM/Scl100抗体陽性。その他の膠原病特異抗体は陰性。筋生検では非乾燥性肉芽腫と筋線維の壊死あり。以上よりサルコイドーシスと抗PM/Scl抗体陽性皮膚炎の合併と診断した。

P-39
子宮体癌の切除によって劇的な改善をみた抗NXP-2抗体陽性皮膚炎の1例

伏田奈津美1, 小林忠弘1, 大石京介1, 前田達太郎1, 松下貴史1, 濱口慎人1, 竹原和彦1, 水本泰成2（1金沢大学皮膚病学, 2金沢大学薬学部）

51歳。初診1ヶ月前になびきに浸潤性紅斑、2週間より近位筋の筋痛、1週前より爪部紅斑が出現。IPウエスタンプロット法で抗NXP-2抗体陽性。筋力低下と嘔下困難も出現。mPSLバルス、PSL 50 mg/日、アザチオブリンで治療するも改善せずCK 1834 IU/Lまで上昇。精査にて判明した子宮体癌の手術を施行したところ、術翌日よりCKが正常化し筋力、嘔下機能も徐々に回復。PSLを減量するも再燃なし。

P-40
皮膚症状が診断の契機となった抗MDA5抗体陽性のamyopathic dermatomyositisの2例

張田修平1, 井上里佳1, 足立晶子1, 大原輝章1, 林伸和1, 田村麻衣1, 長谷川光子2, 澤直樹2, 星野洋一2（1虎の門病院皮膚科, 2虎の門病院神経センター）

症例1：44歳、女性。上眼瞼の紫红色斑、手指背の角化性紅斑、頸部から前胸部の汎紅色斑があった。症例2：56歳、女性。頸部から上胸部に汎紅色斑、肘甲部に強い腫脹を伴う多数の線状の紅斑、手指屈側の角化性紅斑と掌側紅斑を認めた。いずれの症例も筋力低下なく、当科から内科に精査依頼しCTで間質性肺炎の合併が示された。皮疹から診断、迅速な治療で救命に繋がり、初期の段階での皮膚科医の果たすべき役割が重要と考えられた。
P-41全身に多発皮膚潰瘍を認めた抗MDA 5抗体陽性皮膚筋炎の1例

出野りか子、花岡佑真、清原英司、寿 順久、藤本 学
大阪大皮膚科

40代男性。既往歴なし。2019年4月より両側手の腫痛、上腕痛が出現。その後、ペリオトローピ報告。

10月に当科紹介、四肢近位節の著明な筋力低下を認め、6月に他科で抗MDA5抗体陽性皮膚筋炎と診断された。抗MDA5抗体及び免疫抑制剤にて治療を開始されたが、関節部荷重部に皮膚潰瘍が多発し、10月に当科紹介。多発性皮膚潰瘍は抗MDA5抗体陽性例の特徴的所見として従来米にて報告があるが、本邦では稀であり、文献的考察を加え報告する。

P-42再燃時急性進行性間質性肺炎を発症した抗
PL-7抗体陽性抗ARS抗体陰性群の1例

周 冬ら1、服部有希2、松山かなこ3、加納宏行3、
清島文理子1、大野 康1
1岐阜大、2岐阜県総合医療センター、3岐阜市民病院、
4岐阜大呼吸器内科

57歳、女性。近医で間質性肺炎 (IP) と診断される
も無治療。1年後に発熱、咳と関節痛を自覚し当科
紹介。CK 2857 IU/Lと上昇。多発性筋炎と診断し、プ
レドニゾロン (PSL) 50mg/月より開始、経過中ステロ
イドパルスを追加し、シクロスポリンも併用。その後、
抗PL-7抗体陽性と判明。9年後、PSL 10mg/日投与中、
高熱と咳が出現しCKも上昇。約1週後に両肺野の広範
圍にスリガラス陰影がみられ、IPの急速増悪と考えス
テロイドパルスを施行し軽快。

P-43抗MDA 5抗体陽性皮膚筋炎の改善過程で
尋常性乾癬を発症した1例

岡本芳伸、越後岳士
(福井県立病院皮膚科)

51歳男。1週前から爪甲の紅斑と角化、手指腫脹
が出現し当科紹介。爪下皮出血点、尿細空の手、コッ
トロン微候、Vネックサイン等を認め。皮膚筋炎と診
断。組織は衛星細胞壊死を伴う接合部皮膚炎。CK上
昇なし、抗MDA5抗体価が高価陽性。PSL 1mg/kgと
TAC併用で、間質性肺炎は進行せず皮疹も改善、抗
体価も陰性化した。治療を減減する経過で、角化性
紅斑が出現し、組織は乾癬の典型。両者合併の報告
は稀である。

P-44抗MDA 5抗体陽性急性進行性間質性肺炎
合併皮膚筋炎の経過中に乳癌を併発した
一例

田邇徳明、市来尚久、久田智子、菅田実穂、伊藤有美、
小寺雅也
(JCHO中京病院皮膚科)

33歳女性。日焼けを契機に頭部に皮疹を生じた。血
清フェリチン値やKL-6の上昇を認め、抗MDA5
抗体陽性の無症候皮膚筋炎と診断。間質性肺炎を
併発していた。ステロイドパルス療法後、PSL、タ
クロリムス、シクロスポリン等による多剤
併用療法を開始。抗MDA5抗体価、血清フェリチン、
KL-6のいずれも低下した。PSLは減減し、タクロリ
ムスを終了した。初診から13か月後に初診時に見ら
れなかった乳癌と多発骨転移像を認めた。
P-45
寻常性乾癬患者に生じた皮膚筋炎の1例
遠藤喜夫、葉山雅大、井沢栄、藤田英樹、照井 正
(日本大学医学部皮膚科学分野)

54歳女性。筋力低下と皮疹を主訴に受診。40歳時
に寻常性乾癬(PV)、52歳時に卵巣癌の診断で治療中、
初診時は、ヘリオトロープ疹、ショール徵候、Vネック
徵候、Gottron徵候、肘頭-膝蓋-アキレス腱部に鱗
屑を伴う境界明瞭な紅斑あり。血清筋原性酵素の上
昇、筋電図・筋生検・皮膚生検の所見からPV患者に
生じた皮膚筋炎と診断。抗TIF-1γ抗体陽性。PSLと
CyAで治療。両疾患の皮疹の鑑別が困難であった。

P-46
嚥下障害を伴い肺膿瘍が合併した抗TIF-1γ抗体陽性皮膚筋炎の1例
中尾将治1, 大石直人1, 福井雅人2, 河脇由紀男2, 丸山裕美子1
(1黒部市民病院皮膚科、2黒部市民病院呼吸器内科、
3黒部市民病院耳鼻咽喉科)

81歳男。3ヶ月前から鼻背部、前胸部、四肢伸側、
手指根側に暗紅色斑が出現。抗TIF-1γ抗体陽性、CK
正常。CT、気管支鏡検被検で右下葉肺膿瘍合併あり。
化学療法が開始されたが同時期よりCK上昇、嚥下障
害が出現。PSL 15mg/day服用で改善せず、ステロイ
ドパルス療法 (mPSL 1 g × 3日間) 施行しPSL 50mg/
dayに増量。大量ガングロプラン療法も施行し嚥下障
害は改善、CK正常化。

P-47
皮膚筋炎を合併したstage IV恶性黑色腫
に対して、nivolumab、ipilimumabを投
与できた1例
内山俊彦1, 江峰英子1, 山田麻以1, 小松由美1, 
山崎善里1, 市山 進1, 田中真百合2, 田中俊子1, 
五野貴久2, 森田正雄2, 佐伯季友1
(1日本大学医学部皮膚科、2日本大学医学部皮膚科)

85歳女性。右母趾悪性黑色腫に対して切除、植皮が
行われていた。2年半後に右頸転移を主訴に受診。ARS
陽性、間質性肺炎があることから、皮膚筋炎の合併
が判明した。Nivolumabを投与開始したが、間質性肺
炎の増悪をみたため、休止し、ステロイド内服を開
始した。以後、ステロイドを投与しながらnivolumab
を再開した。肝転移巣が出現したため、ipilimumab
の投与も行い、間質性肺炎は増悪することなく、
薬剤を投与することができた。

P-48
難治性筋炎を伴ったシェーグレン症候群
の1例
藤本俊調1, 田中俊雄1, 潮口優人2
(1滋賀医科大学皮膚科, 2金沢大学皮膚科)

40歳代女性。下肢の片状紫斑を主訴に受診した。
皮膚検査では血管炎を認め、唾液腺検査などの検査
結果よりシェーグレン症候群と診断した。筋力低下、
CK値の上昇、肝生検所見などより筋炎の合併と判断
し、プレドニゾロンで治療を開始した。血液検査所
見は一旦改善したが減量中に再燃し、アザチオブリ
ン、タクロリムス、IVIGで治療しているが治療に難
渉している。自己抗体は免疫プロットで抗SS-A抗体
のみが検出された。
P-49
無汗症を契機に診断されたSjögren症候群

高橋裕里恵、影山玲子、青島正浩、藤山俊晴、戸倉新樹
（浜松医科大学皮膚科）

56歳、女性。13年前より発汗低下、夏季にうつ熱症状が出現した。Minor法により一部を除きほぼ全身、低汗から無汗であった。抗SS-A抗体・抗SS-B抗体陽性、シルマーテスト、ローズペンタルテスト陽性。組織学的にエクリン汗腺周囲にリンパ球はほとんど浸潤せず、汗腺が萎縮・減少していた。アセチルコリンM3受容体発現は低下していない。Sjögren症候群に伴う高度の無汗症は過去18例報告されている。

P-50
関節リウマチに対するセルトリスマプペゴル投与中に生じた薬麻疹様血管炎の1例

冨来吉朗1,2、石川博士3、岩永 希1、和泉泰衛4、
松岡健毅5、三浦史郎6、川上 純6
1国立病院機構長崎医療センターリウマチ科、2国立病院機構長崎医療センター臨床研究センター、3国立病院機構長崎医療センター皮膚科、4国立病院機構長崎医療センター総合診療科、5国立病院機構長崎医療センター病理診断科、6長崎大学大学院薬学総合研究科先端予防医学共同研究（第一内科）

症例は52歳女性。23歳時に関節リウマチ（RA）と診断。2016年2月セルトリスマプペゴル（CZP）投与開始。2019年1月頃から薬麻疹様紅斑が持続、皮膚生検で真皮表層の赤血球血管外浸出、炎症細胞浸潤及び核破砕物を認め薬麻疹様血管炎（UV）と診断、経口プレドニゾロンを增量し軽快した。CZPはその構造上安全性が高いと考えられているが、他のTNF阻害薬と同様にUV等の血管炎の出現に注意が必要と考えた。

P-51
関節リウマチに伴った皮膚深在性真菌症の5例

二ツ谷剛俊、安澤敏史、加藤俊樹、西村明子、望月 陵
（金沢医科大学病院）

2010年から2019年の10年間に金沢医科大学病院で診断し治療を行った深在性真菌症は13例あり、内9例はステロイドなどの免疫抑制薬を内服しており、その内5例は関節リウマチ（RA）であった。RA症例の原因菌は、黒色真菌2例、白癬菌1例、その他の真菌が2例であり、感染部位は上肢3例、下肢2例であった。

P-52
ATP 2 C 1遺伝子エクソン23に変異を認めた家族性良性慢性天疱瘡の1例

足立 真、武井薫子、鳥山風夏、北島麻耶子
（関東労災）

52歳、男性。数年前から夏期に増悪する両側顔のびらんと紅斑を認め近医皮膚科を受診し外用剤で治療。2016年秋に両側顔紅斑の増強・強い疼痛を主訴に当科を受診。病理組織では表皮内の剥離形成と表皮基底層での棘細胞解像を認めたが蛻光抗体直接法では免疫グロブリン及び補体の沈着を認めなかった。末梢血を用いた遺伝子解析でATP2C1遺伝子エクソン23に既知のタンセンス変異c.2236G>A（p.A746T）がヘテロで同定された。以上より家族性良性慢性天疱瘡と診断。
P-53
冒髄治疗後に発症した、palmar fasciitis and polyarthritis syndromeの一例

佐藤篤子、小宮根真弓、村田 哲、大阪ママ太郎
(自治医大皮膚科)

68歳、男性。初診2か月前に体調不良、体重減少あり、その後、両肩関節痛、両手指のむくみ出現。当科初診時、両手背掌側に紅斑を伴う腫脹、手
指関節の屈曲運動障害あり。既往に66歳時に胃癌切除、術後1年9か月のTS-1治療歴あり。抗核抗体80倍
で強皮症特異抗体は陰性。皮膚生検で膠原線維の増
生無く変性あり。PETで臓器への異常集積なく、両
肩、関節に集積亢進。MRIで関節炎所見あり。胃
癌治療後に発症した、palmar fasciitis and polyarthritis syndromeと診断。

P-54
血管炎に伴う難治性皮膚潰瘍に多血小板血漿（PRP）治療が奏功した1例

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(1 国立国際医療研究センター病院皮膚科、2 国立国際医
療研究センター病院研究所)

75歳男性。2006年右外婆の皮膚潰瘍にて当院膠原
病科入院。病理は真皮中層〜皮下の血管にて好中球
浸潤は少ないが血管炎に矛盾せず。アルプロスタジ
ル投与と局所処置で軽快。退院後は主に他院へ通院。2012年末より右外顎に潰瘍が再発、PSL10mg/日開始
するも増悪し、2013/3/14当院膠原病科入院。PSL増
量しスルファジアシン銀・トラフェルミン等にて潰
瘍は縮小せず、6/17〜PRP治療を開始。開始時長径
30mmの潰瘍は、11週後の終了時8 mmまで縮小。