7. Dekio I, Rajendram D, Morita E, Gharbia S, Shah HN. Genetic diversity of Propionibacterium acnes strains isolated from human skin in Japan and comparison with their distribution in Europe. J Med Microbiol. 2012; Jan 13 [Epub ahead of print]

書籍

1. 森田栄伸：重症薬疹における遺伝的背景（2）DIHS/DRESS の研究動向．薬疹診療のフロントライン　古江増隆総編集、相原道子専門編集　中山書店 pp157-158

浅田　秀夫

1. ○Morito H, Ogawa K, Fukumoto T, Kobayashi N, Asada H: Drug-induced Hypersensitivity Syndrome Followed by Persistent Arthritis. J Dermatol, in press
2. ○Morito H, Kitamura K, Fukumoto T, Kobayashi N, Kuwahara M, Asada H: Drug eruption with eosinophilia and systemic syndrome associated with reactivation of human herpesvirus 7, not human herpesvirus 6. J Dermatol, in press
3. ○Kohei Ogawa, Hironori Morito, Nobuhiko Kobayashi, Takaya Fukumoto, Hideo Asada: A case of drug-induced hypersensitivity syndrome involving multiple-drug hypersensitivity. J Dermatol, in press
4. ○Takao Y, Miyazaki Y, Onishi F, Kumihashi H, Gomi Y, Ishikawa T, Okuno Y, Mori Y, Asada H, Yamanishi K, Iso H, for the SHEZ Study group: Prospective cohort study of herpes zoster in Shozu County: The Shozu Herpes Zoster (SHEZ) Study. J of Epidemiology, in press
5. ○Hasegawa A, Kobayashi N, Fukumoto T, Asada H: A case of eosinophilic pustular folliculitis responded to infliximab. J Am Acad Dermatol, in press
6. ○Hirobe S, Matsuo K, Quan YS, Kamiyama F, Morito H, Asada H, Takaya Y, Mukai Y, Okada N, Nakagawa S: Clinical study of transcutaneous vaccination using a hydrogel patch for tetanus and diphtheria. Vaccine, in press
7. ○Matsuo K, Ishii Y, Quan YS, Kamiyama F, Asada H, Mukai Y, Okada N, Nakagawa S: Compositional optimization and safety assessment of a hydrogel patch as a transcutaneous immunization device. Biol Pharm Bull 34: 1835- 40: 2011.
8. 小川浩平、長島千佳、北村華奈、福本隆也、浅田秀夫、中川智代、笠原敬、古西満、三笠桂一:AIDS に合併した中毒性表皮壊死症に血漿交換療法が奏効した 1 例．皮膚科の臨床 53(4): 609-614,2011
9. 小川浩平、長島千佳、北村華奈、横井祥子、野口隆一、増谷剛、浅井英樹、川井廉之、小林信彦、浅田秀夫:潰瘍性大腸炎に合併した致死的水痘の 1 例.

皮膚の科学 10(1): 71-75, 2011

10. 北見　周、渡辺秀晃、末木博彦、飯島正文、相原道子、池澤善郎、狩野葉子、塩原哲夫、森田栄伸、木下　茂、相原雄幸、白方裕司、藤山幹子、外園千恵、椛島健二、小豆澤宏明、浅田秀夫、橋本公二: Stevens-Johnson 症候群ならびに中毒性表皮壊死症（TEN）の全国疫学調査 -平成 20 年度厚生労働科学研究費補助金（難治性疾患克服研究事業）重症多形滲出性紅斑に関する調査研究-. 日皮会誌 121(12): 2467-2482, 2011.

谷崎　英昭

1. Ono S, Tanizaki H, Miyachi Y, Kabashima K. Late onset of livedo reticularis induced by amantadine treatment concomitant with erythrocytosis. Eur J Dermatol. 2012 in press.
2. Sugita K, Kabashima K, Sawada Y, Haruyama S, Yoshioka M, Mori T, Kobayashi M, Ogasawara K, Tokura Y.　Blocking of CTLA-4 on lymphocytes improves the sensitivity of lymphocyte transformation tests in a patient with nickel allergy. Eur J Dermatol. 2012 in press
3. Murata T, Endo Y, Katoh M, Miyachi Y, Kabashima K. Case of drug rash with eosinophilia and systemic symptoms induced by zonisamide and reactivation of human herpes virus 7. J Dermatol. 201;　38:　918-20
4. ○Otsuka A, Kubo M, Honda T, Egawa G, Nakajima S, Tanizaki H, Kim B, Matsuoka S, Watanabe T, Nakae S, Miyachi Y, Kabashima K. Requirement of interaction between mast cells and skin dendritic cells to establish contact hypersensitivity.PLoS One. 2011; 6: e25538.
5. Nakajima S, Watanabe H, Tohyama M, Sugita K, Iijima M, Hashimoto K, Tokura Y, Nishimura Y, Doi H, Tanioka M, Miyachi Y, Kabashima K. High-mobility group box 1 protein (HMGB1) as a novel diagnostic tool for toxic epidermal necrolysis and Stevens-Johnson syndrome. Arch Dermatol. 2011; 147: 1110-2
6. ○Ueharaguchi Y, Kabashima K, Shimizuhira C, Nakajo W, Kondo T, Kamiya T, Matsubara K, Kondo S. Multiple follicular pustules as an atypical cutaneous manifestation of drug-induced hypersensitivity syndrome. Acta Derm Venereol. 2011; 91: 728-9.
7. ソラフェニブによる多形紅斑型薬疹の 1 例　松本玲子, 松村由美, 宮地良樹 臨床皮膚科 65 巻 2 号 p127-130, 2011.
8. 尋常性乾癬に対する TNF-α阻害薬により生じた膿疱性皮疹および円形脱毛症の 1 例　加来信子、谷崎英昭, 大塚篤司, 荒川明子, 椛島健治, 谷岡未樹, 宮地良樹 Journal of Environmental Dermatology and Cutaneous Allergology, 5 巻

1 号 p39-45, 2011.

小豆澤　宏明

1. ○Hanafusa T, Azukizawa H, Matsumura S, Katayama I. The predominant drug-specific T-cell population may switch from cytotoxic T cells to regulatory T cells during the course of anticonvulsant-induced Hanafusa T, Azukizawa H, Matsumura S, Katayama I. hypersensitivity. J. Dermatol. Sci., in press.
2. ○Hanafusa T, Azukizawa H, Nishioka M, Tanemura A, Murota H, Yoshida H, Sato E, Hashii Y, Ozono K, Koga H, Hashimoto T, Katayama I. Lichen planus-type chronic graft-versus-host disease complicated by mucous membrane pemphigoid with positive anti-BP180/230 and scleroderma-related autoantibodies followed by reduced regulatory T cell frequency. Eur J Dermatol. 2012.
3. Kitaba S, Murota H, Terao M, Azukizawa H, Terabe F, Shima Y, Fujimoto M, Tanaka T, Naka T, Kishimoto T, Katayama I. Blockade of interleukin-6 receptor alleviates disease in mouse model of scleroderma. Am J Pathol. 2012 Jan;180(1):165-76.
4. Crozat K, Tamoutounour S, Manh TP, Fossum E, Luche H, Ardouin L, Guilliams M, Azukizawa H, Bogen B, Malissen B, Henri S, Dalod M. Cutting edge: Expression of XCR1 defines mouse lymphoid-tissue resident and migratory dendritic cells of the CD8α+ type. J Immunol. 2011 Nov 1;187(9):4411-5.
5. ○ Hanafusa T, Igawa K, Azukizawa H, Katayama I. Acute generalized exanthematous pustulosis induced by topical diphenhydramine. Eur J Dermatol. 2011 Nov-Dec;21(6):994-5.
6. Murakami Y, Wataya-Kaneda M, Terao M, Azukizawa H, Murota H, Nakata Y, Katayama I. Peculiar distribution of tumorous xanthomas in an adult case of erdheim-chester disease complicated by atopic dermatitis. Case Rep Dermatol. 2011 May;3(2):107-12.
7. Azukizawa H, Döhler A, Kanazawa N, Nayak A, Lipp M, Malissen B, Autenrieth I, Katayama I, Riemann M, Weih F, Berberich-Siebelt F, Lutz MB. Steady state migratory RelB+ langerin+ dermal dendritic cells mediate peripheral induction of antigen-specific CD4+ CD25+ Foxp3+ regulatory T cells. Eur J Immunol. 2011 May;41(5):1420-34.
8. Hanafusa T, Azukizawa H, Umegaki N, Tani M, Yamaguchi Y, Katayama I. Clinical implications of leukocytapheresis using a centrifugal cell separator for steroid-resistant pyoderma gangrenosum associated with inflammatory bowel disease. J Dermatol. 2011 May;38(5):507-10.
9. ○Azukizawa H. Animal models of toxic epidermal necrolysis. J Dermatol. 2011

Mar;38(3):255-60.

橋爪　秀夫

1. ○橋爪秀夫. 重症薬疹の発症機序update. 医学のあゆみ 238:769-73, 2011.
2. ○矢田貝剛, 三澤淳子, 橋爪秀夫, 新村祐一郎. 臨床例　小児の皮下型環状肉芽腫症 皮膚病診療 33:387-90, 2011.
3. ○馬場まゆみ, 小野孝彦, 服部隆一, 橋爪秀夫. 後天性特発性全身性無汗症の１例. 臨床皮膚科 65:611-4, 2011.
4. ○船井尚子, 小粥雅明, 杉山崇史, 柳生友浩, 橋爪秀夫. 皮膚生検にて診断しえた血管内B細胞リンパ腫の1例. 臨床皮膚科 65:887-90, 2011.
5. ○橋爪秀夫. NK/Tリンパ腫. 日本皮膚科学会誌 121:2455-60, 2011.
6. ○Kito Y, Ito T, Tokura Y, Hashizume H. High-dose Intravenous Immunoglobulin Monotherapy for Drug-induced Hypersensitivity Syndrome. *Acta Derm Venereol* 92:100-1, 2012.
7. ○Kito Y, Hashizume H, Tokura Y. Rosacea-like Demodicosis Mimicking Cutaneous Lymphoma. *Acta Derm Venereol* 2011(Epub ahead of print)
8. ○Hashizume H, Uchiyama I, Kawamura T, Suda T, Takigawa M, Tokura Y. Epstein-Barr virus-positive mucocutaneous ulcers as a manifestation of methotrexate-associated B-cell lymphoproliferative disorders. *Acta Derm Venereol* 2012 (in press).

永尾　圭介

1. ○Takashi T*, Kouno M*, Nagao K, Naoko Wada, Tsuyoshi Hata, Shuhei Nishimoto, Yoichiro Iwakura, Akihiko Yoshimura, Taketo Yamada, Masataka Kuwana, Hideki Fujii, Shigeo Koyasu, and Masayuki Amagai. Desmoglein 3-specific CD4+ T cells induce pemphigus vulgaris and interface dermatitis in mice. Journal of Clinical Investigation, 1;121(9):3677-88, 2011. (*equal contribution)

外園　千恵

1. ○Ueta M, Sotozono C, Kinoshita S: Expression of interleukin-4 receptor α in human corneal epithelial cells. Jpn J Ophthalmol. 55(4): 405-410, 2011.
2. ○Ueta M, Sotozono C, Yokoi N, Inatomi T, Kinoshita S: Prostaglandin E Receptor Subtype EP3 Expression in Human Conjunctival Epithelium and Its Changes in Various Ocular Surface Disorders. PLoS One. 6(9): e25209, 2011.
3. ○Yagi T, Sotozono C, Tanaka M, Fuwa M, Sekiyama E, Ueta M, Tashiro K, Kinoshita S. Cytokine storm arising on the ocular surface in a patient with Stevens-Johnson syndrome. Br J Ophthalmol. 95(7): 1030-1031, 2011.
4. ○Nakamura T, Takeda K, Inatomi T, Sotozono C, Kinoshita S. Long-term results

of autologous cultivated oral mucosal epithelial transplantation in the scar phase of severe ocular surface disorders. Br J Ophthalmol. 95(7): 942-6, 2011.

5. ○Nakatsukasa M, Sotozono C, Shimbo K, Ono N, Miyano H, Okano A, Hamuro J, Kinoshita S. Amino Acid profiles in human tear fluids analyzed by high-performance liquid chromatography and electrospray ionization tandem mass spectrometry. Am J Ophthalmol. May;151(5):799-808.e1., 2011.
6. ○Takeda K, Nakamura T, Inatomi T, Sotozono C, Watanabe A, Kinoshita S. Ocular Surface Reconstruction Using the Combination of Autologous Cultivated Oral Mucosal Epithelial Transplantation and Eyelid Surgery for Severe Ocular Surface Disease. Am J Ophthalmol. 152(2):195-201, 2011.

[V]

班会議プログラム

厚生労働省科学研究費補助金
「難治性疾患克服研究事業：重症多形滲出性紅斑に関する調査研究
（**H22 - 難治 - 一般 - 003**）」

平成 23 年度班会議プログラム

研究代表者：杏林大学医学部皮膚科、塩原哲夫

日時： 平成 23 年 7 月 30 日（土）９：３０から１７：００まで
場所： 東京駅前：マルビルコンファレンススクエア ルーム 5
住所：〒100-6307 東京都千代田区丸の内 2-4-1 丸ビル 8 階
TEL 03-3217-7111 （平日 10：00～19：00） FAX 03-3217-7501）
●JR ご利用の場合／東京駅丸の内南口より徒歩 1 分
●地下鉄をご利用の場合／丸ノ内線東京駅より直結
千代田線二重橋前駅 7 番出口より徒歩 2 分

Asian SCAR Meeting

9:30

開会の挨拶 研究代表者 塩原哲夫 先生 (5 min)
・班員自己紹介：京都大学 皮膚科 谷崎英昭 先生
・Drs. from Taiwan：Drs. Chia-Ying Chang, Cheng-Han Lee,
Chin-Fang Lu, Ting-Jui Chen, and Jen-Yu Wang.

9:35

1. DIHS の治療指針の検討 Guideline of treatment for DIHS
・サラゾスルファピリジンによる DIHS の２例 (10 min)
DIHS due to salazosulfapyridine
奈良県立医大 森戸 啓統 ・小川浩平 先生
・DIHS 経過中に TEN を発症し救命し得なかった症例(10 min)
DIHS followed by clinical manifestations of TEN
昭和大 渡辺秀晃 先生
・DIHS３例の免疫学的なフォローアップのまとめ(10 min)
Immunological aspects of DIHS
慶應大 足立剛也 先生

・愛媛大皮膚科における DIHS 治療経験 (15 min)

Treatment for DIHS in Ehime University

愛媛大　藤山幹子　先生

10:40

・DIHS 治療指針案の検討

Discussion: Guideline of treatment for DIHS

杏林大　狩野葉子

12:00　昼食　（お弁当）

12:40-12:45　事務局連絡、次回班会議日程 (Official announcement of the next meeting) など

12:45

2. 症例呈示・研究報告

・Case report: DIHS with severe CNS involvement (15 min)

Dr. Chia-Ying Chang

・Generalized bullous fixed drug eruption mimicking TEN: A clinical and pathological study of 10 cases (15 min)

Dr. Cheng-Han Lee

・Enterovirus induced SJS-like reaction (15 min)

Mackay Memorial Hospital, Taipei, Taiwan

Drs. Chin-Fang Lu, MD, Wen-Hung Chung

・Serine protease inhibitors as early prognostic markers and implication of treatment in Stevens-Johnson syndrome and toxic epidermal necrolysis (15 min)

Wan-Fang hospital-Taipei Medical University, Taiwan

Drs. Ting-Jui Chen, Wen-Hung Chung

13:50

・2008-2010 SJS/TEN 眼障害患者の国内実態調査 進行状況

高度の眼障害を伴った急性期 SJS および亜急性期 SJS (15 min)

Ocular complications of SJS/TEN: Survey of SJS/TEN in Japan 2008-2010

Severe ocular complications in acute and subacute stages of SJS

京都府立大　外園千恵　先生

・DIHS における HMGB-1 の関与　(15 min)

Involvement of HMGB-1 in DIHS

島田市民病院　橋爪秀夫　先生

14:20　Coffee Break

14:30

3. HLA 解析の報告とカルバマゼピン介入臨床研究について（30 min）

Analyses of HLA in patients with carbamazepine-induced drug eruptions

理化学研究所　莚田泰誠　先生

15:00

4. 講演「カルバマゼピンのてんかん治療における位置づけ

―当院の治療状況―」

Carbamazepine for treatment of epilepsy

愛知医科大学精神科教授

兼本浩祐　先生

質疑応答 Q and A

16:00

5. その他

共同研究について(5 min)

事務局より

16:30 終了予定

厚生労働省科学研究費補助金
「難治性疾患克服研究事業：重症多形滲出性紅斑に関する調査研究
（**H22 - 難治 - 一般 - 003**）」

平成 23 年度 第 2 回 班会議プログラム

研究代表者：杏林大学医学部皮膚科、塩原哲夫

日時： 平成 23 年 12 月 24 日（土） ９：３０から１７：００まで
場所： 東京駅前：マルビルコンファレンススクエア ルーム 5
住所：〒100-6307 東京都千代田区丸の内 2-4-1 丸ビル 8 階
TEL 03-3217-7111 （平日 10：00～19：00） FAX 03-3217-7501）
●JR ご利用の場合／東京駅丸の内南口より徒歩 1 分
●地下鉄をご利用の場合／丸ノ内線東京駅より直結
千代田線二重橋前駅 7 番出口より徒歩 2 分

Asian SCAR Meeting

9:30
開会の挨拶 研究代表者 塩原哲夫

9:35
1. DIHS 全国疫学調査について：DIHS 臨床像調査の担当研究者の決定
Epidemiological survey for DIHS
黒沢美智子（順天大 衛生学）

9:50
2. DIHS 関連薬内服中の患者における唾液中 HHV-6 HHV-7DNA 量の検討
HHV-6 and HHV-7 DNA loads in saliva in patients with drug administration
森戸啓統、小川浩平、浅田秀夫（奈良医大）

10:10
3. 薬疹の原因薬同定における DLST と BAT 法（basophil activation test）の比較
Comparison between DLST and BAT in the evaluation of culprit drug
足立剛也（慶應大）

10:30

4. Clinical characteristics and risk factors of lamotrigine induced hypersensitivity reactions
   Chung Wen-Hung

11:00

5. Long-term sequelae of DIHS--A retrospective cohort study from a medical center in northern Taiwan
   Chia-Yu Chu

11:30

6. 重症薬疹の長期予後調査について
   Prognosis of severe drug eruptions
   平原和久（杏林大）

11:50　昼食（お弁当）Lunch

12:45　事務局連絡 Official announcement
次回班会議日程 next meeting 、契約書、IVIG treatment

12:50

2008-2010 年発症 SJS/TEN の調査状況
木下茂　（京都府立大・眼科）

13:00

7. アロプリノールによる重症薬疹国内例の HLA 解析
   HLA analysis of severe drug eruptions due to allopurinol
   新原寛之、金子　栄、森田栄伸（島根大）

13:20

8. 「遺伝子型に基づくカルバマゼピンのオーダーメイド投薬の検証に関する前向き臨床研究 」の進行状況
   Genotype-based carbamazepine therapy (GENCAT) study
   莚田泰誠、久保充明（理化学研究所　ゲノム医科学研究センター）

13:40

9. 薬疹データベースについて
   Data base of drug eruptions
   永尾圭介（慶應大）

14:00

10. ラミクタールによる SJS の 2 例

Lamotrigine induced Stevens-Johnson syndrome

松倉節子 （横浜市立大　市民総合医療センター）

14:10

11. 放射線照射が誘因となったと考えられた Stevens-Johnson 症候群の 1 例

Stevens-Johnson syndrome triggered by radiation therapy

谷崎英昭　野々村優美　中島沙恵子　椛島健治 (京都大)

14:20

12. DIHS 治療指針案の検討 資料配付

Discussion: Guideline of treatment for DIHS

狩野葉子、平原和久（杏林大）

14:30　Coffee break

15:00

13. その他

16:30　終了

[VI]

研究成果の刊行物・印刷

to the Wickham striae) surrounded by dotted or linear vessels *(figure 1D)*. In contrast, the atrophic plaque on the sacrum showed structureless white areas and chrysalis structures [5] and diffusely arranged elongated, partially looped telangiectasias of different lengths and calibers *(figure 1E)*. Finally, dermoscopy of the hyperpigmented plaque allowed the observation of fine lilac vessels arranged in a ring-like distribution *(figure 1F)*. Due to the dermoscopic polymorphims, biopsies were taken from one papule on the leg, the sacral plaque and from the peripheral border of the hyperpigmented plaque on the abdomen; subsequent histopathologic examination revealed LP, extragenital LS and morphea, respectively.

The diagnosis of LP was based on the presence of compact orthokeratosis, wedge-shaped hypergranulosis, irregular acanthosis, a dense band-like infiltrate, predominantly of lymphocytes, in the papillary dermis, accumulation of melanophages and vacuolar alteration of the basal layer.

Histopathologically, LS revealed a compact hyper- and orthokeratotic scale with follicular plugging and an atrophic epidermis with vacuolar alteration of the basal layer; a zone of pallor (lymphedema) in the papillary dermis and an interstitial lymphocytic inflammatory infiltrate in the medial dermis were present.

The diagnosis of morphea was based on the presence of dermal sclerosis with swollen collagen fibers and decreased spaces between collagen bundles of the reticular dermis; in addition, a moderately perivascular inflammatory infiltrate of lymphocytes and loss of adnexal structures were noted.

Standard laboratory tests, antibodies against thyroid and antinuclear antibodies, antinuclear antibodies (ANA), IgG and IgM Borrelia serology, as well as hepatitis A, B and C virus serology were within normal ranges or negative.

To our knowledge, our patient represents the third documented case of co-existing LP, LS and morphea. Despite the rare co-occurrence of all three entities, our case suggests that dermoscopy not only aids clinical recognition, by revealing different patterns in each corresponding entity, but may also guide selection of the most representative lesion for biopsy. ■

Disclosure. *Financial support: none. Conflicts of interest: none.*

[1] Clinic of Dermatology and Venerology,
University of Nis, Nis,
Serbia
[2] Dermatology Unit,
Arcispedale Santa Maria Nuova,
Reggio Emilia,
Italy
[3] Department of Dermatology,
Medical University of Graz,
Auenbruggerplatz 8,
8036 Graz,
Austria
<iris.zalaudek@gmail.com>

Danica TIODOROVIC-ZIVKOVIC[1]
Giuseppe ARGENZIANO[2]
Danijela POPOVIC[1]
Iris ZALAUDEK[3]

1. Yashar S, Han KF, Haley JC. Lichen sclerosus-lichen planus overlap in a patient with hepatitis C virus infection. *Br J Dermatol* 2004; 150: 168-9.
2. Connelly MG, Winkelmann RK. Coexistence of lichen sclerosus, morphea and lichen planus. *J Am Acad Dermatol* 1985; 12: 844-51.
3. Zalaudek I, Argenziano G, Di Stefani A, *et al.* Dermoscopy in general dermatology. *Dermatology* 2006; 212: 7-18.
4. Micali G, Lacarrubba F, Massimino D, Schwartz RA. Dermatoscopy: Alternative uses in daily clinical practice. *J Am Acad Dermatol* 2011; 64: 1135-46.
5. Marghoob AA, Cowell L, Kopf AW, Scope A. Observation of chrysalis structures with polarized dermoscopy. *Arch Dermatol* 2009; 145: 618.

doi:10.1684/ejd.2011.1585

Diffuse large B-cell lymphoma as a sequela of Stevens-Johnson syndrome associated with an increased Epstein-Barr virus load

Little attention has been paid to long-term sequelae developing years after complete recovery of Stevens-Johnson syndrome (SJS) [1]. We present a SJS patient who developed diffuse large B-cell lymphoma (DLBCL) two years after complete resolution of SJS.

A 48-year-old woman was treated with minocycline, and then cefcapene pivoxil (CFPN PI) for pneumonia. On days 7 and 14 of the treatment with CFPN PI and minocycline, respectively, an eruption appeared on the trunk and face. Examination revealed high-grade fever (38.5°C), widespread erythematous macules with erosions *(figures 1A, B)*, and severe erosive lesions on the lips; conjunctivas were hyperemic. No cervical lymphadenopathy was detected. Histology of a biopsy from the flat

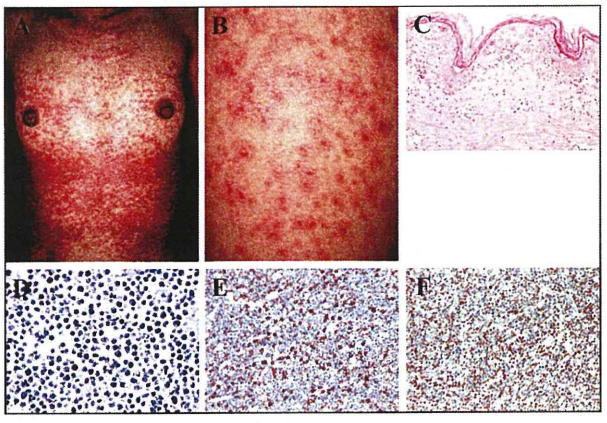

Figure 1. A) Erythematous macules with erosions on the trunk.
B) Atypical target lesions on the thigh.
C) Epidermal necrosis with a mild lymphocytic infiltration in the upper dermis (hematoxylin and eosin stain; original magnification X 100).
D) Atypical lymphoid cells in the cervical lymph node (hematoxylin and eosin stain; original magnification X 400).
E) Positive CD20 expression on atypical lymphoid cells in the lymph node (original magnification X 200).
F) Positive Bcl-2 expression on lymphoid cells in the lymph node (original magnification X 200).

erythematous abdominal macule showed epidermal necrosis and a mild lymphocytic infiltration in the upper dermis *(figure 1C)*. Direct immunofluorescence demonstrated no depositions. Laboratory findings on admission: white blood cell count 3.7×10^9/L with no atypical lymphocytosis or eosinophilia, with mild liver dysfunction. Anti-Epstein-Barr virus (EBV) virus capsid antigen (VCA) IgG titer, anti-EBV VCA IgM titer and EBNA were 640-fold, 10-fold>, and 20-fold, respectively. EBV DNA loads were 440 copies/10^6 leukocytes. Chest X-ray was normal.

After the SJS diagnosis, treatment with systemic corticosteroids 50 mg daily was initiated. Her eruptions steadily improved, corticosteroids were tapered to 60% over 4 weeks and zero over 8 weeks. To determine the causative agents of SJS, lymphocyte transformation test (LTT) was performed on the second day of admission. Positive LTT reactions for CFPN-PI and minocycline were obtained. No significant increases in anti-human herpesvirus 6 (HHV-6) IgG titers or HHV-6 DNA loads were detected during the course of the disease. This patient had persistently detectable levels of EBV DNA (150-280 copies/10^6 leukocytes) for 5 months after complete resolution. 9 months after resolution, the viral load declined.

Two years later, when the EBV load was undetectable, she noticed swelling of cervical lymph nodes and a high-grade fever. Examination revealed a large subcutaneous mass in the neck and multiple palpable axillary and inguinal lymph nodes. Anti-EBV VCA IgG titer, anti-EBV VCA IgM titer and EBNA were 640-fold, 10-fold>, and 40-fold, respectively. Computed tomography scan showed multiple lymph nodules around the aorta and splenomegaly. A cervical lymph node biopsy revealed marked proliferation of atypical lymphoid cells *(figure 1D)* and immunohistochemical stainings for CD 20 *(figure 1E)*, CD 79, CD 10, and Bcl-2 *(figure 1F)* showed strong immunopositivity. Positive EBV-encoded small RNA (EBER) staining cells were not detected. DLBCL was diagnosed. Despite a good response to combination therapy with rituximab and CHOP, she died of pneumonia from opportunistic infections.

As the EBV DNA load was more than 8 times that in asymptomatic EBV carriers in our study, elevated EBV DNA loads may predispose the development of lymphoma. DLBCL is thought to arise from EBV-immortalized B cells which escaped T-cell surveillance, suggesting that the impairment of anti-EBV immunity during SJS results in uncontrolled, EBV-driven B cell proliferation in the absence of adequate T-cell surveillance [2, 3]. EBV-specific immunity in this patient may have exhibited a reduced ability to control the outgrowth of EBV-infected B cells during SJS. The EBV load during the acute stage of SJS was higher than after resolution and persistence was observed even during resolution, this patient may have had defects in long-term anti-EBV immunity. Interestingly, the persistently elevated EBV load declined just prior to the development of DLBCL.

Other factors, particularly those associated with drug therapy, may also be important. Systemic corticosteroid use has been associated with an increased risk of non-Hodgkin lymphoma [4, 5]. However, systemic corticosteroids were only given for 8 weeks in this patient; it is implausible that the DLBCL would be caused by such a short exposure. The causative drug of SJS may also have influenced the risk of lymphoma development because minocycline is well known to have the potential to cause lymphoproliferative disorders [6]. This is also unlikely, however, in view of the duration of exposure.

Our case emphasizes the importance of long-term follow-up in patients with SJS. ■

Disclosure. *Financial support: This work was partly supported by grants from the Ministry of Education, Culture, Sports, Science and Technology (to T.S. and to Y.K.) and the Ministry of Health, Labour and Welfare of Japan (to T.S.) and the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR). Conflicts of interest: none.*

Department of Dermatology,
Kyorin University School of Medicine,
6-20-2 Shinkawa Mitaka,
Tokyo 181-8611,
Japan
<kano@ks.kyorin-u.ac.jp>

Kazuhisa HIRAHARA
Yoko KANO
Tadashi ISHIDA
Tetsuo SHIOHARA

1. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR study. *J Am Acad Dermatol* 2007; 58: 33-40.

2. Yajima M, Imadome K, Nakagawa A, *et al.* T cell-mediated control of Epstein-Barr virus infection in humanized mice. *J Infect Dis* 2009; 15: 1611-5.

3. Morales D, Beltran B, De Mendoza FH, *et al.* Epstein-Barr virus as a prognostic factor in de novo nodal diffuse large B-cell lymphoma. *Leuk Lymphoma* 2010; 51: 66-72.

4. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. *Cancer Res* 1992; 52: 5510s-5s.

5. Sørensen HT, Mellemkjœr L, Nielsen GL, Baron JA, Olsen JH, Karagas MR. Skin cancers and non-Hodgkin lymphoma among users of systemic glucocorticoids: a population-based cohort study. *J Natl Cancer Inst* 2004; 96: 709-11.

6. Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline Report of 13 patients and review of the literature. *Arch Dermatol* 1996; 132: 934-9.

doi:10.1684/ejd.2011.1584

Basal cell carcinoma which developed on the surface of recurrent parotid pleomorphic adenoma: coincidence or causality?

Pleomorphic adenoma is the most common benign tumor of salivary gland and basal cell carcinoma (BCC) is the most common cutaneous malignant tumor. Coexisting pleomorphic adenoma and BCC has rarely been reported.

A 66-year-old female complained of a painless enlarging mass on her left post-auricular and mandibular area. She had received tumor excision on the same area ten years ago. The pathology report was a benign pleomorphic adenoma at that time. Several years later, the patient found recurrence of the subcutaneous tumor and a gradually enlarging red plaque above the tumor. The patient denied any systemic

Included in the theme issue:
ADVERSE DRUG REACTIONS
Acta Derm Venereol 2012; 92: 193–220

Herpes Zoster in Patients with Drug-induced Hypersensitivity Syndrome/DRESS

Yoko Kano, Chiho Horie, Miyuki Inaoka, Ishida Tadashi, Yoshiko Mizukawa and Tetsuo Shiohara
Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa Mitaka, Tokyo, 181-8611, Japan. E-mail: kano@ks.kyorin-u.ac.jp
Accepted December 6, 2011.

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a severe systemic hypersensitivity reaction caused by specific drugs and involves the reactivation of human herpesvirus 6 (HHV-6) (1, 2). Accumulating evidence suggests that other herpesviruses, such as Epstein-Barr virus (EBV) (3, 4), HHV-7 (5) and cytomegalovirus (CMV) (6) reactivate during the course of DIHS/DRESS, similar to the herpesvirus reactivation observed in recipients who have undergone bone marrow transplantation (BMT) (7). Although varicella-zoster virus (VZV) reactivations are frequently observed in recipients with BMT (8), VZV reactivations have rarely been reported in the setting of DIHS/DRESS (9). In view of the similarity between BMT and DIHS/DRESS (10), it is likely that VZV reactivation might also be present in patients with DIHS/DRESS. Because herpes zoster (HZ) is often observed without any relationship to the underlying disease, it is difficult to determine whether there is any relationship between HZ and DIHS/DRESS. We have therefore retrospectively analysed patients with DIHS/DRESS who developed HZ.

METHODS

Between 1998 and 2010, 28 patients who developed DIHS/DRESS and were treated in our hospital were enrolled in this study. The criteria used for DIHS/DRESS were the presence of a high fever, a widespread maculopapular and/or diffuse erythematous eruption, lymphadenopathy, leukocytosis with atypical lymphocytosis and/or eosinophilia, liver dysfunction and HHV-6 reactivation (11). To detect HHV-6 reactivation, patients with suspected DIHS/DRESS were tested for anti-HHV-6 IgG antibody titres and/or real-time PCR assays for HHV-6 DNA loads in peripheral leukocytes. HHV-6 reactivation was defined by a >4-fold increase in anti-HHV-6 IgG antibody titres or detection of HHV-6 DNA in the leukocytes. The 6-month observation period after the onset of drug reactions was defined. Patients who were followed up for less than the 6-month observation period or those who did not satisfy the criteria for DIHS completely were excluded in this study. The DIHS/DRESS patients were classified into two groups: 12 patients who received systemic corticosteroid therapy, and 16 patients who received supportive care for dehydration alone. As a drug eruption control group, patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) were selected. SJS/TEN was diagnosed according to the criteria described by Bastuji-Garin et al. (12). There were 8 cases of SJS and 3 of TEN who satisfied the criteria for SJS/TEN and were treated with systemic corticosteroids. The clinical features of each group are summarized in Table I. The clinical diagnosis of HZ was made based on the assessment by the dermatologists at our hospital in the follow-up period. A questionnaire was sent to the control patients who were not regularly followed up.

RESULTS

Three out of the 28 patients with DIHS/DRESS developed HZ within 6 months after the onset of DIHS/DRESS; all 3 patients had been given systemic corticosteroids. No patient with SJS/TEN developed HZ in the same period (Table II). The 3 patients had had childhood varicella, but not HZ before the onset of DIHS/DRESS. One patient had a renal cell cancer. The causative drug of DIHS/DRESS was anticonvulsants in all 3 patients. HZ developed approximately 60 days after the onset of DIHS/DRESS during the tapering period of administration of systemic corticosteroids in cases 1 and 2; HZ developed 30 days after the cessation of systemic corticosteroids in case 3. There was no identical dermatomal involvement with HZ, and the cutaneous manifestations were mild with no complications. A significant increase in the anti-VZV IgG antibody titre at >2 weeks after the onset of the HZ was seen in all cases. Two patients (cases 2 and 3) were treated with systemic acyclovir and one patient was treated with topical acyclovir alone. Analysis of CMV DNA was

Table I. *Characteristics of 28 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) and 11 patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). DIHS/DRESS patients are divided into two groups depending on whether or not they received corticosteroids*

Diagnosis *n* (M:F)	Corticosteroid treatment[a] (*n*)	Age, years Mean ± SD	Underlying disease (*n*)	Causative drug (*n*)
DIHS/DRESS				
16 (7:9)	None	56.7 ± 14.8	Cerebral infarction (2), convulsion (5), epilepsy (1), hyperuricaemia (3), neuralgia (2), psychiatric disease (3)	Allopurinol (3), carbamazepine (10), phenobarbital (1), phenytoin (2)
12 (8:4)	0.6–1.0 mg/kg/day (12)	55.2 ± 18.6	Arrhythmia (1), cerebral infarction (2), convulsion (1), epilepsy (3), hyperuricaemia (1), psychiatric disease (3), rheumatoid arthritis (1)	Allopurinol (1), carbamazepine (6), mexiletine (1), phenobarbital (2), phenytoin (1), salazosulphapyridine (1)
SJS/TEN				
11 (5:6)	0.8–1.0 mg/kg/day (8) 1000 mg/day[b] (3)	51.5 ± 21.5	Asthma (1), convulsion (1), cardiovascular disease (2), LE (1), multiple sclerosis (1), pneumonia (2), psychiatric disease (2), ulcerative colitis (1)	Lamotrigine (1), loxoprofen (1), phenytoin (1), salazosulphapyridine (1), sulphamethoxazole trimethoprim (1), unknown (6)

[a]Initial dose. [b]Steroid pulse therapy. SD: standard deviation; M:F: male:female; LE: lupus erythematosus.

Table II. *Characteristics of patients with herpes zoster (HZ) in DIHS/DRESS*

Case no./ Age, years/sex	Underlying illness	Causative drug Duration[a], day	Detection of HZ Duration[b], day	Corticosteroid treatment dose[c]	Dermatome involved	Alteration of anti-VZV IgG antibody titre[d]
1/39/M	Psychiatric disease	Carbamazepine 44	60	+ 40 → 10	Lt. L5	30 → 277
2/63/M	Convulsion due to metastatic tumour	Carbamazepine 27	63	+ 40 → 20	Lt. V2	87 → 514
3/70/F	Cerebral infarction	Phenytoin 43	147	+ 40 → 0	Rt. C5 & C6	36 → 653

[a]Between the initial drug intake and the onset of DIHS/DRESS. [b]Between the onset of drug reaction and that of HZ. [c]At the initial dose and the dose at the onset of HZ (mg/daily). [d]Anti-varicella-zoster virus (VZV) IgG antibody titres were examined at the onset of HZ and more than 2 weeks after that of HZ using an enzyme immunoassay method. Lt: left side; Rt: right side.

carried out in cases 1 and 2. After HHV-6 reactivation, CMV DNA was detected in the blood and then HZ lesions appeared in one patient (case 2).

DISCUSSION

Our results demonstrated that HZ was present in only 11% of patients who developed DIHS/DRESS in the 6-month observation period after the onset of drug reaction. As VZV reactivation is thought to occur in the absence of skin lesions following renal transplantation (13), it is likely the case also in DIHS/DRESS. Thus significant increases in anti-VZV IgG antibody titre were detected in 2 out of the 11 patients with DIHS/DRESS without any clinical symptom in this observation period (unpublished observation).

The chronological timing of VZV reactivation after BMT is highly variable, ranging from days to several years after BMT (13). In our study, HZ appeared during corticosteroid treatment of DIHS/DRESS in 2 patients and one month after complete recovery in one patient. Alas, our study was not large enough to demonstrate the exact timing of HZ onset.

The administration of systemic corticosteroid for treatment of DIHS/DRESS may have contributed to the increased risk of HZ. Indeed, HZ was not detected in patients with DIHS/DRESS who were treated with only supportive care. On the other hand, HZ was also not observed in patients with SJS/TEN who were given systemic corticosteroids. Presumably, the altered underlying immunological pathomechanism of DIHS/DRESS due to the systemic corticosteroid might have played an important role in the onset of HZ. It has been shown that DIHS/DRESS is a manifestation of newly observed immune reconstitution syndrome (IRS) (14), and HZ is observed as the most common manifestation of IRS after highly active antiretroviral therapy in AIDS (15). Therefore, it is possible that the reduction or withdrawal of corticosteroid in the setting of DIHS/DRESS could contribute to the development of HZ.

ACKNOWLEDGEMENT

This work was partly supported by grants from the Ministry of Education, Culture, Sports, Science and Technology (T.S. and Y.K.) and the Ministry of Health, Labour and Welfare of Japan (T.S.).

The authors declare no conflicts of interest.

REFERENCES

1. Descamps V, Bouscarat F, Laglenne S, Aslangul E, Veber B, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. Br J Dermatol 1997; 137: 605–608.
2. Suzuki Y, Inagi R, Aono T, Yamashita K, Shiohara T. Human herpesvirus 6 infection as a risk factor of the development of severe drug-induced hypersensitivity. Arch Dermatol 1998; 134: 1108–1112.
3. Descamps V, Mahe E, Houhou N, Abramowitz L, et al. Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. Br J Dermatol 2003; 148: 1032–1034.
4. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transpl Med 2010; 25: 45ra62.
5. Mitani N, Aihara M, Yamakawa Y, Yamada M, Itoh N, Mizuki N, et al. Drug-induced hypersensitivity syndrome due to cyanamide associated with multiple reactivation of human herpesviruses. J Med Virol 2005; 75: 430–434.
6. Seishima M, Yamanaka T, Fujisawa M, Tohyama M, Hashimoto K. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. Br J Dermatol 2006; 155: 344–349.
7. Zaia JA. Viral infection associated with bone marrow transplantation. Hematol/Oncol Clin N Amer 1990; 4: 603–623.
8. Steer CB, Szer J, Sasadeusz J, Matthews JP, Beresford JA, Grigg A. Varicella-zoster infection after allogeneic bone marrow transplantation: incidence, risk factors and prevention with low-dose acyclovir and ganciclovir. Bone Marrow Transpl 2000; 25: 657–664.
9. Kano Y, Hirahara K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. Br J Dermatol 2006; 155: 301–306.
10. Kano Y, Sakuma K, Shiohara T. Sclerodermoid graft-versus-host disease-like lesions occurring after drug-induced hypersensitivity syndrome. Br J Dermatol 2007; 156: 1061–1063.
11. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol 2007; 156: 1083–1084.
12. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993; 129: 92–96.
13. Jantsch J, Schmidt B, Bardutzky J, Bogdan C, Eckardt KU, Raff U. Lethal varicella-zoster virus reactivation without skin lesions following renal transplantation. Nephrol Dial Transplant 2011; 26: 365–368.
14. Shiohara T, Kurata M, Mizukawa Y, Kano Y. Recognition of immune reconstitution syndrome necessary for better management of patients with severe drug eruption and those under immunosuppressive therapy. Allegol Int 2010; 59: 333–343.
15. Jevtovic DJ, Salemovic D, Ranin J, Pesic I, Zerjav S, Djurkovic-Djakovic O. The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. HIV Med 2005; 6: 140–143.

制御性T細胞と重症薬疹

石田　正[1]　高橋　良[2]　塩原　哲夫[1]

1. はじめに

1995年にSakaguchiらにより，制御性T細胞（Regulatory T cell：Treg）の存在と機能が明らかになった[1]．Tregは基本的には自己抗原に対する免疫寛容．すなわち自己反応性リンパ球の活性化および増殖を抑制する特殊なCD4⁺T細胞の一ポピュレーションであるが，それ以外にも後述する様々な免疫反応に関与する．実際の疾患では，主に自己免疫疾患や悪性腫瘍との関連が報告されてきたが，薬疹では今まで殆ど注目されてこなかった．

2. Tregとは

TregはCD4⁺T細胞のサブセットの一つであり，過剰な免疫反応や自己免疫などを抑制し，生体の恒常性を維持している．その作用機序は未だ不明なところも多いが，細胞同士の直接接触やIL-10等の抑制性サイトカインの放出を介し，標的細胞のapoptosisや増殖抑制などを起こすこと等が知られている[2]．様々な疾患でTregの関与が指摘されており，例えば関節リウマチ[3]やSLE患者[4]においてTregの機能異常が報告されている．これはTregによる自己抗原への免疫寛容が破綻することが，自己免疫疾患の発症に関与する可能性を示す有力な根拠である．逆に悪性腫瘍では，腫瘍細胞がTregを誘導して腫瘍免疫から逃れている機序が推測されている[5]．薬疹においては，Tregが中毒性表皮壊死症（toxic epidermal necrolysis：TEN）の発症を抑制する可能性が，2005年のAzukizawaらの動物モデルでの報告によって初めて示された[6]．しかし，実際の患者における報告はこれまで殆どなかった．

1）杏林大学医学部皮膚科学教室
〒181-8611 東京都三鷹市新川6-20-2
2）杏林大学大学院医学研究科共同研究施設フローサイトメトリー部門皮膚科
〒181-8611 東京都三鷹市新川6-20-2
【別刷請求先】石田　正
杏林大学医学部皮膚科学教室
〒181-8611 東京都三鷹市新川6-20-2
電話：0422-47-5511　FAX：0422-47-9632
e-mail：tadashi-i1584@ks.kyorin-u.ac.jp

3. 重症薬疹患者におけるTregの動態

我々はTregが薬疹の発症に関与している可能性を考え，薬疹患者におけるTregの動態を検討してきた．そして重症薬疹であるTENと薬剤性過敏症症候群（drug-induced hypersensitivity syndrome：DIHS）患者の病態の違いが，Tregによって見事に説明できることを見出した[7]．

TENは原因薬剤の投与後，急激に発症し高度の表皮壊死を起こす．致死率も高く，日常診療で最も気をつけるべき疾患の一つである．一方，DIHSは遅発性で，TEN程の皮膚障害はないが，ヘルペスウイルスの再活性化や臓器障害を伴い症状が遷延し，時に致死的となる．このようにTENとDIHSは相反する臨床症状を呈するが，それを反映するかのように，我々は各患者におけるTregの動態も全く逆の傾向を示すことを明らかにした．

a. Tregの機能異常がTENをおこす

TENとDIHS患者の末梢血単核球（peripheral blood mononuclear cell：PBMC）におけるTregの解析を行ったところ，急性期TEN患者のTregの数は健常人と同程度であったが，その機能は著しく低下していた．TENではTregの機能異常からエフェクターT細胞（Teff）の過剰な活性化が引き起こされ，それにより急激な経過で高度の表皮障害がおこると考えられた（図1a）．

b. 増加したTregがDIHS特有の臨床像を形成する

TENとは対照的に，急性期のDIHS患者では機能が正常なTregが著明に増加していた．このTregはcutaneous lymphocyte-associated antigen（CLA）やE-セレクチンリガンドなどの皮膚指向性マーカーを発現しており，実際に皮疹部の病理組織でも浸潤していることが確認された．つまり，皮膚の場において，TregはTeffの遊走や活性化を抑制していると考えられた．このようなTregの増大が，DIHSではTENと比し遅発性で，皮膚障害も軽度となる理由と思われた．またDIHS最大の特徴として，経過中のhuman herpesvirus 6（HHV-6）再活性化があげられるが，これも増加したTregによる免疫抑制が原因である可能性があ

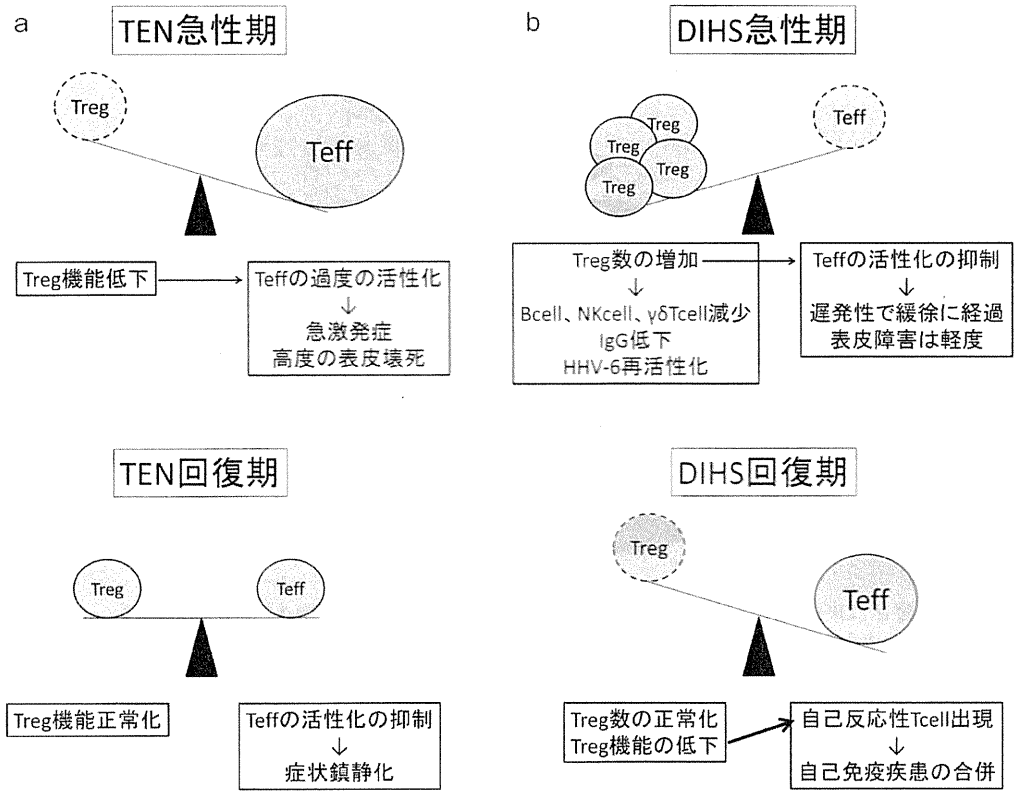

図 1　Treg と Teff のバランスが重症薬疹の臨床症状を決定する

a. TEN 急性期では Treg の機能が低下しているため，薬剤刺激による Teff 活性化を抑制することができない．このため Teff が過度に活性化してしまい，急激な経過で高度の表皮障害を起こす．しかし Treg の機能の回復とともに，炎症症状は鎮静化し回復に向かう．

b. DIHS では急性期に機能が正常な Treg が増加しており，Teff が抑制されている．そのため通常の薬疹よりも遅発性で，皮膚障害も軽度となる．しかし Treg による免疫抑制は，B 細胞や NK 細胞，γδT 細胞などの免疫担当細胞の減少や低 γ グロブリン血症をもたらし，HHV-6 を始めとしたヘルペスウイルス再活性化の連鎖につながり，症状の遷延化を引き起こす．急性期を過ぎた後の回復期では，増加していた Treg の数は正常化するが，その機能は低下する．そのため自己反応性 T 細胞の制御が出来ず，自己免疫疾患を合併する．

る．実際に DIHS 急性期では $CD19^+$ B 細胞，γδT 細胞や $CD56^+$ NK 細胞などの免疫担当細胞の数が減少し[8]，免疫グロブリン IgG も低値を示す[9]ことが分かっている．

Treg は一方で薬剤リンパ球刺激試験（drug lymphocyte stimulation test：DLST）の結果にも影響を及ぼす．DIHS は通常の薬疹と異なり，急性期に DLST が陰性となるが，1 カ月ほど経過した後に初めて DLST は陽転化する[10]．これも急性期に増加した Treg が，*in vitro* で薬剤に反応する Teff を抑制するためにおこる現象と考えられ，注意する必要がある（図 1b）．

c. DIHS の経過中に新たに生ずる免疫再構築症候群

DIHS では，HHV-6 以外にも EBV や CMV 等の様々なヘルペスウイルスが経時的に再活性化し，様々な症状を繰り返しながら遷延化する．この現象は HIV 患者における HAART 後に生じる免疫再構築症候群（immune reconstitution syndrome：IRS）と類似している．IRS とは，減少した $CD4^+$ T 細胞が HAART（highly active antiretroviral therapy）後に回復するに伴って，それまで潜伏感染していたウイルスや真菌などに対する免疫応答も回復する結果，感染症状が顕在化することをいう．これに対し，DIHS では発症前にも機能的な Treg のある程度の増大があるが，原因薬剤の中止とともに急速な免疫応答の回復（それに伴う Treg の二次的増大）があり，それは IRS と類似の病態をもたらす．それは潜伏感染していたヘルペスウイルスの再活性化と，それに伴う Teff の活性化による感染

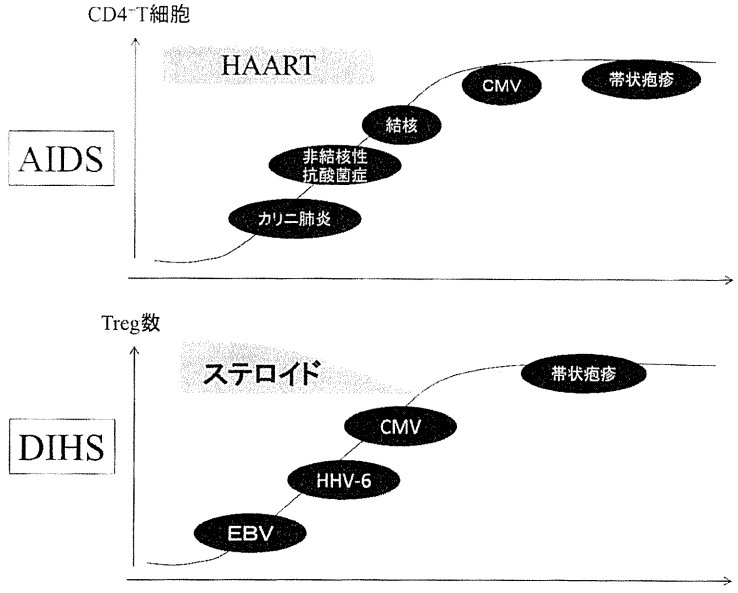

図2　DIHS自体がIRSであり，その免疫抑制から回復する過程で様々な感染症が起こる．
AIDS患者ではHIV感染によりCD4⁺T細胞が減少しているが，HAART施行後にHIVウイルス量が減少すると共にCD4⁺T細胞数も回復する．この過程において，それまで潜伏感染していた病原微生物に対する免疫応答も回復する．その結果，IRSとしての様々な感染症状が引き起こされる．DIHS患者においても類似した現象がおこる．発症前から急性期のDIHS患者では機能的なTregが増加しており，個体は免疫抑制状態となっている．しかし原因薬剤の中止に伴いTregの数も正常化し，それに応じて次第に免疫抑制状態から回復していくこととなる．この過程で潜伏感染していたヘルペスウイルスの認識が次々と起こり，症状が遷延化していく．

症状の増悪として認められる(図2)．このようにDIHSそのものもIRSとみなせる上に，DIHSの治療としてステロイド内服を行うと，その減量のたびに新たなIRSが生じることになる．実際，DIHSにおけるCMV感染症はステロイドの減量のたびに起こる．そのため，DIHSの経過中にIRSと考えられる感染症状が出現した際には，ステロイドの減量は，一時中止するか，減量を行ったにしても緩徐に行うことが重要となる[11]．

d. Tregの機能低下が後遺症に関与する

前述のようにDIHSでは急性期にTregの数が増加するが，それは回復期には健常人と変わらないレベルまで戻る．しかしヘルペスウイルス再活性化の連鎖とそれに伴うTeffの過度の活性化は，Tregに疲弊をもたらす．回復期のTregの機能を調べてみると，有意に低下していることが分かった．DIHSの経過中，あるいは軽快した後に甲状腺疾患や1型糖尿病などの自己免疫疾患を合併する[12]ことがあるが，これはこのようなTregの機能低下によるものと考えると理解しやすい(図1b)．

4. おわりに

薬疹では，皮膚障害を起こすTeffのみが注目されがちだが，それらの活性化を抑制するTregも重症薬疹の表現形の決定に重要な因子である．さらに急性期のみならず，回復期の状態も含め検討することによって，初めて予後を含めた病態の全体像を把握することが可能になる．薬疹だけではなく，様々な病態は急性期の一面のみから判断されることが多いが，幅広い観点から経時的に解析を加えることこそが真の病態の解明に重要であるといえよう．

文献

1) Sakaguchi S, et al: Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol*, 1995; 155: 1151-1164.
2) Shevach EM: Mechanisms of Foxp3+ T regulatory cell-mediated suppression. *Immunity*, 2009; 30: 636-645.
3) Oh S, Rankin AL, Caton AJ: CD4+CD25+ regulatory T cells in autoimmune arthritis, *Immunol Rev*, 2010; 233: 97-111.
4) Bonelli M, Smolen JS, Scheinecker C: Treg and lupus.