It has been reported that basophils induce T_H2 through TSLPR and that LCs are essential in the vitamin D_3-induced skin lesions through TSLP signaling.[13,15] In this study, we have demonstrated the significance of TSLP-TSLPR signaling on LCs under epicutaneous sensitization with protein antigens, which is clinically relevant to AD. Our findings will lead to the understanding of the underlying mechanism and developing new therapeutic targets for inflammatory skin diseases.

Clinical implications: TSLPRs on LCs can be a therapeutic target of skin inflammatory reactions induced by epicutaneous sensitization with protein antigens, such as in the development of AD.

REFERENCES

1. Egawa G, Kabashima K. Skin as a peripheral lymphoid organ: revisiting the concept of skin-associated lymphoid tissues. J Invest Dermatol 2011;131:2178-85.
2. Moniaga CS, Kabashima K. Filaggrin in atopic dermatitis: flaky tail mice as a novel model for developing drug targets in atopic dermatitis. Inflamm Allergy Drug Targets 2011;10:477-85.
3. Werfel T. The role of leukocytes, keratinocytes, and allergen-specific IgE in the development of atopic dermatitis. J Invest Dermatol 2009;129:1878-91.
4. Nickel R, Beck LA, Stellato C, Schleimer RP. Chemokines and allergic disease. J Allergy Clin Immunol 1999;104:723-42.
5. Shimada Y, Takehara K, Sato S. Both Th2 and Th1 chemokines (TARC/CCL17, MDC/CCL22, and Mig/CXCL9) are elevated in sera from patients with atopic dermatitis. J Dermatol Sci 2004;34:201-8.
6. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al. Immunobiology of dendritic cells. Annu Rev Immunol 2000;18:767-811.
7. Novak N, Peng W, Yu C. Network of myeloid and plasmacytoid dendritic cells in atopic dermatitis. Adv Exp Med Biol 2007;601:97-104.
8. Poulin LF, Henri S, de Bovis B, Devilard E, Kissenpfennig A, Malissen B. The dermis contains Langerin$^+$ dendritic cells that develop and function independently of epidermal Langerhans cells. J Exp Med 2007;204:3119-31.
9. Ginhoux F, Collin MP, Bogunovic M, Abel M, Leboeuf M, Helft J, et al. Blood-derived dermal Langerin$^+$ dendritic cells survey the skin in the steady state. J Exp Med 2007;204:3133-46.
10. Bursch LS, Wang L, Igyarto B, Kissenpfennig A, Malissen B, Kaplan DH, et al. Identification of a novel population of Langerin$^+$ dendritic cells. J Exp Med 2007;204:3147-56.
11. Kubo A, Nagao K, Yokouchi M, Sasaki H, Amagai M. External antigen uptake by Langerhans cells with reorganization of epidermal tight junction barriers. J Exp Med 2009;206:2937-46.
12. Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. Nat Immunol 2010;11:289-93.
13. Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. Nature 2011;477:229-33.
14. Oyoshi MK, Larson RP, Ziegler SF, Geha RS. Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. J Allergy Clin Immunol 2010;126:976-84, 984.e1-5.
15. Elentner A, Finke D, Schmuth M, Chappaz S, Ebner S, Malissen B, et al. Langerhans cells are critical in the development of atopic dermatitis-like inflammation and symptoms in mice. J Cell Mol Med 2009;13:2658-72.
16. Ebner S, Nguyen VA, Forstner M, Wang YH, Wolfram D, Liu YJ, et al. Thymic stromal lymphopoietin converts human epidermal Langerhans cells into antigen-presenting cells that induce proallergic T cells. J Allergy Clin Immunol 2007; 119:982-90.
17. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol 2002;3:673-80.
18. Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. J Exp Med 2006;203:269-73.
19. Kaplan DH, Jenison MC, Saeland S, Shlomchik WD, Shlomchik MJ. Epidermal Langerhans cell-deficient mice develop enhanced contact hypersensitivity. Immunity 2005;23:611-20.
20. Carpino N, Thierfelder WE, Chang MS, Saris C, Turner SJ, Ziegler SF, et al. Absence of an essential role for thymic stromal lymphopoietin receptor in murine B-cell development. Mol Cell Biol 2004;24:2584-92.
21. Honda T, Nakajima S, Egawa G, Ogasawara K, Malissen B, Miyachi Y, et al. Compensatory role of Langerhans cells and Langerin-positive dermal dendritic cells in the sensitization phase of murine contact hypersensitivity. J Allergy Clin Immunol 2010;125:1154-6.e2.
22. Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. J Clin Invest 1998;101:1614-22.
23. Kissenpfennig A, Henri S, Dubois B, Laplace-Builhe C, Perrin P, Romani N, et al. Dynamics and function of Langerhans cells in vivo: dermal dendritic cells colonize lymph node areas distinct from slower migrating Langerhans cells. Immunity 2005; 22:643-54.
24. Kaplan DH. In vivo function of Langerhans cells and dermal dendritic cells. Trends Immunol 2010;31:446-51.
25. Kitajima M, Lee HC, Nakayama T, Ziegler SF. TSLP enhances the function of helper type 2 cells. Eur J Immunol 2011;41:1862-71.
26. Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. J Exp Med 2005;202:1213-23.
27. He R, Oyoshi MK, Garibyan L, Kumar L, Ziegler SF, Geha RS. TSLP acts on infiltrating effector T cells to drive allergic skin inflammation. Proc Natl Acad Sci U S A 2008;105:11875-80.
28. Merad M, Manz MG, Karsunky H, Wagers A, Peters W, Charo I, et al. Langerhans cells renew in the skin throughout life under steady-state conditions. Nat Immunol 2002;3:1135-41.
29. Seshasayee D, Lee WP, Zhou M, Shu J, Suto E, Zhang J, et al. In vivo blockade of OX40 ligand inhibits thymic stromal lymphopoietin driven atopic inflammation. J Clin Invest 2007;117:3868-78.
30. Klechevsky E, Morita R, Liu M, Cao Y, Coquery S, Thompson-Snipes L, et al. Functional specializations of human epidermal Langerhans cells and CD14$^+$ dermal dendritic cells. Immunity 2008;29:497-510.
31. Kaplan DH, Kissenpfennig A, Clausen BE. Insights into Langerhans cell function from Langerhans cell ablation models. Eur J Immunol 2008;38:2369-76.
32. Mori T, Kabashima K, Yoshiki R, Sugita K, Shiraishi N, Onoue A, et al. Cutaneous hypersensitivities to hapten are controlled by IFN-gamma-upregulated keratinocyte Th1 chemokines and IFN-gamma-downregulated Langerhans cell Th2 chemokines. J Invest Dermatol 2008;128:1719-27.

METHODS

Cell culture, reagents, antibodies, and flow cytometry

The complete RPMI (cRPMI) culture medium consisting of RPMI 1640 (Invitrogen, Carlsbad, Calif) containing 10% heat-inactivated fetal calf serum, 5×10^{-5} mol/L 2-mercaptoethanol, 2 mM L-glutamine, 25 mM *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, 1 mmol/L nonessential amino acids, 1 mmol/L sodium pyruvate, 100 units/mL penicillin, and 100 μg/mL streptomycin was used unless otherwise indicated.

For BM-derived DC culture, 5×10^6 BM cells generated from WT and $TSLPR^{-/-}$ mice were cultured in 10 mL of cRPMI supplemented with 3 ng/mL of recombinant murine granulocyte-macrophage colony-stimulating factor (PeproTech, Rocky Hill, NJ) for 5 to 7 days. Then, 5×10^5 cells were seeded in a 24-well culture dish (Nunc, Rochester, NY) in 500 μL of cRPMI and stimulated with 100 ng/mL of recombinant mouse TSLP (R&D Systems, Minneapolis, Minn) for 6 hours.

For epidermal cell suspensions, dorsal skin sheets were floated on dispase II (Godo Shusei Co, Ltd, Aomori, Japan) diluted to 5 mg/mL in cRPMI for 1 hour at 37°C and 5% CO_2. The epidermis was separated from the dermis with forceps in RPMI medium supplemented with 2% fetal calf serum. The isolated epidermis was cut finely with scissors and floated in 0.25% trypsin-EDTA for 10 minutes at 37°C and 5% CO_2, and filtered through a 40-μm cell strainer (BD Bioscience, San Diego, Calif).

We purchased OVA from Sigma-Aldrich, and CFSE was acquired from Invitrogen. Fluorochrome-conjugated antibodies to CD4, CD11c, CD90.1, MHC class II, OX40L, CD40, and CD80 were purchased from eBioscience Inc (San Diego, Calif). Anti-mouse TSLPR and isotype control were purchased from R&D systems. Cells were analyzed by using the FACS LSR Fortessa flow cytometric system (BD Bioscience) and FlowJo software (Tree Star, Ashland, Ore).

Histology and allergen penetration in the skin

The clinical severity of skin lesions was scored according to the macroscopic diagnostic criteria that were used for the NC/Nga mouse.[E1] In brief, the total clinical score for skin lesions was designated as the sum of individual scores, graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe), for the symptoms of pruritus, erythema, edema, erosion, and scaling. Pruritus was observed clinically for more than 2 minutes.

For histologic examination, tissues were fixed with 10% formalin in PBS, and then embedded in paraffin. Sections with a thickness of 5 μm were prepared and subjected to staining with hematoxylin and eosin. The histologic findings were evaluated as reported previously.[E2]

For immunohistochemical analysis, OVA-sensitized skin samples were directly frozen at −80°C in Tissue-Tek O.C.T. (Sakura Finetek, Tokyo, Japan). Skin cryosections were fixed with 4% paraformaldehyde (Nacalai Tesque) and permeabilized with 0.1% Triton-X (Sigma-Aldrich) in PBS for 10 minutes at room temperature. Next, slides were incubated with anti–claudin-1 polyclonal antibody (Abcam, Cambridge, United Kingdom). Immunodetection was performed by using Alexa Fluor 594–coupled secondary antibody (Invitrogen). The slides were mounted in ProLong Gold Antifade reagent (Invitrogen), and fluorescence images were obtained by using a BIOREVO BZ-9000 system (Keyence, Osaka, Japan).

For assessing the penetration of allergen, mice were percutaneously sensitized with 100 μg of FITC-conjugated OVA (Molecular Probes, Inc, Eugene, Ore) diluted in 100 μL of normal saline onto the shaved and tape-stripped back skin. Seventy-two hours later, immunohistochemical analysis of the skin to assess allergen penetration was performed. Similarly, 100 μL of 1% FITC (Sigma-Aldrich) in acetone/dibutyl phthalate (1/1) was applied to shaved dorsal skin of B6 mice; 72 hours later, immunohistochemical analysis was performed to assess hapten penetration into the skin.

ELISA for OVA-specific serum IgE

Total serum IgE levels were measured by using a Bio-Rad (Hercules, Calif) Luminex kit according to the manufacturer's instructions. To measure OVA-specific IgE/IgG1/IgG2a levels, the appropriate mouse IgE/IgG1/IgG2a ELISA kit (Bethyl Laboratories, Montgomery, Tex) was used with slight modifications. Specifically, plates were coated and incubated with 10 μg/mL of OVA diluted with coating buffer for 2 hours. After a blocking period of 30 minutes, 100 μL of 5× diluted serum was added to each well and incubated for 2 hours. Anti-mouse IgE/IgG1/IgG2a-horseradish peroxidase conjugate (1:15,000; 100 μL) was used to conjugate the antigen-antibody complex for 60 minutes at room temperature; from this point on, the ELISA kit was used according to the manufacturer's instructions. Absorbance was measured at 450 nm. The difference between the sample absorbance and the mean of negative control absorbance was taken as the result.

To measure IgE levels on peritoneal mast cells, the peritoneal cavity was rinsed with 10 mL of ice cold, sterile PBS. The collected cell suspension was incubated with Fc-block antibody (BD Biosciences; 2-4G2), washed, and split in half. Half of the cells were kept untreated while the other half were incubated with 10 μg/mL of anti-DNP-IgE (mouse monoclonal IgE, Sigma-Aldrich) for 40 minutes on ice. After being washed with staining media, the cells were further incubated with an anti–c-kit and anti-mouse IgE and analyzed by using a flow cytometer.

Quantitative RT-PCR analysis

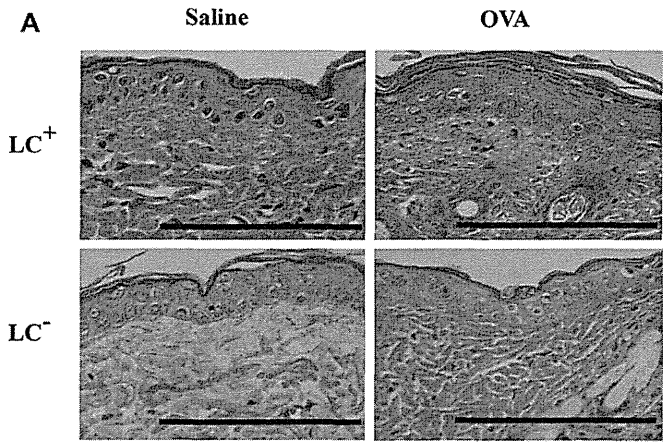
Total RNAs were isolated with RNeasy kits and digested with DNase I (Qiagen, Hilden, Germany). cDNA was reverse transcribed from total RNA samples by using the Prime Script RT reagent kit (Takara Bio, Otsu, Japan). Quantitative RT-PCR was performed by monitoring the synthesis of double-stranded DNA during the various PCR cycles, using SYBR Green I (Roche, Basel, Switzerland) and the Light Cycler real-time PCR apparatus (Roche) according to the manufacturer's instructions. All primers were obtained from Greiner Japan (Tokyo, Japan). The primer sequences were IFN-γ, 5′-GAA CTG GCA AAA GGA TGG TGA-3′ (forward), 5′-TGT GGG TTG TTG ACC TCA AAC-3′ (reverse); IL-4, 5′-GGT CTC AAC CCC CAG CTA GT-3′ (forward), 5′-GCC GAT GAT CTC TCT CAA GTG AT-3′ (reverse); CCL17, 5′-CAG GGA TGC CAT CGT GTT TCT-3′ (forward), 5′-GGT CAC AGG CCG TTT TAT GTT-3′ (reverse); CCL22, 5′-TCT TGC TGT GGC AAT TCA GA-3′ (forward), 5′-GAG GGT GAC GGA TGT AGT CC-3′ (reverse); CXCL10, 5′-CCA AGT GCT GCC GTC ATT TTC-3′ (forward), 5′-GGC TCG CAG GGA TGA TTT CAA-3′ (reverse). The cycling conditions were as follows: initial enzyme activation at 95°C for 10 minutes, followed by 40 cycles at 95°C for 10 seconds and at 60°C for 20 seconds. All cycling reactions were performed in the presence of 3.5 mM of $MgCl_2$. Gene-specific fluorescence was measured at 60°C. For each sample, triplicate test reactions and a control reaction lacking reverse transcriptase were analyzed for the expression of the genes, and results were normalized to those of the "housekeeping" glyceraldehyde-3-phosphate dehydrogenase mRNA.

REFERENCES

E1. Leung DY, Hirsch RL, Schneider L, Moody C, Takaoka R, Li SH, et al. Thymopentin therapy reduces the clinical severity of atopic dermatitis. J Allergy Clin Immunol 1990;85:927-33.

E2. Nakajima S, Honda T, Sakata D, Egawa G, Tanizaki H, Otsuka A, et al. Prostaglandin I2-IP signaling promotes Th1 differentiation in a mouse model of contact hypersensitivity. J Immunol 2010;184:5595-603.

A



B

	LC^+		LC^-		
	saline	OVA	saline	OVA	
Inflammation	0±0	3.2±0.20	0.17±0.20	1.2±0.2	*
Neutorophils	0.7±0.51	1.3±0.25	0.33±0.25	1.3±0.26	
Mononuclear cells	1.5±0.54	3.3±0.41	1.33±0.25	1.5±0.27	*
Edema	0±0	2.3±0.25	0±0	1.2±0.2	*
Epithelial hyperplasia	0.7±0.51	3.5±0.23	0.33±0.26	1.5±0.27	*

FIG E1. A, Hematoxylin and eosin staining of the back skin of LC–non-depleted or LC-depleted mice after OVA application 3 times (hematoxylin and eosin, original magnification ×400). Scale bar = 100 μm. **B,** The histologic findings were scored by inflammation, neutrophil infiltration, mononuclear cell infiltration, edema, and epithelial hyperplasia. Data are presented as means ± SDs (n = 5).

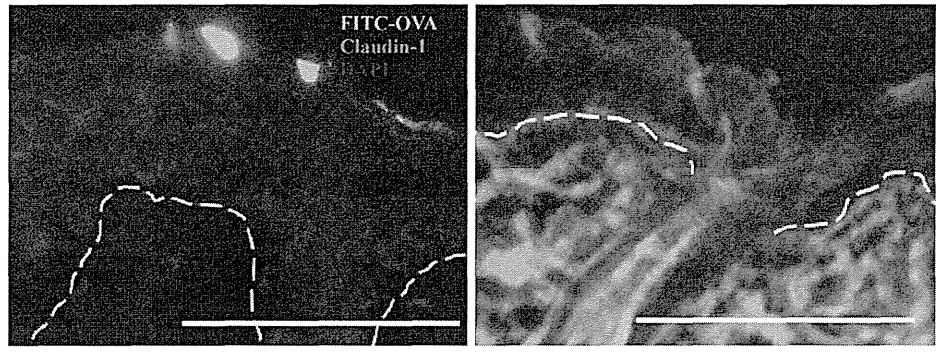


FIG E2. Impaired penetration of protein antigen into the dermis. B6 mice were patched with FITC-conjugated OVA on the back skin; 72 hours later, patched skin area was analyzed by immunohistochemistry. FITC-conjugated OVA *(green)* retained above the TJ was indicated by staining with anti–claudin-1 antibody *(red) (left panel).* FITC *(green)* readily penetrated into the dermis *(right panel). Blue* staining (4′-6-diamidino-2-phenylindole, dihydrochloride) indicates nuclei. *Dashed white lines* represent the border between the dermis and the epidermis. Scale bars = 100 μm.

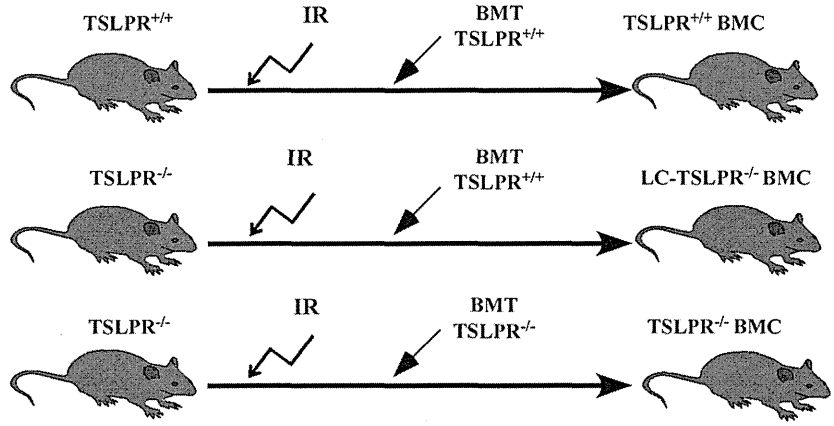
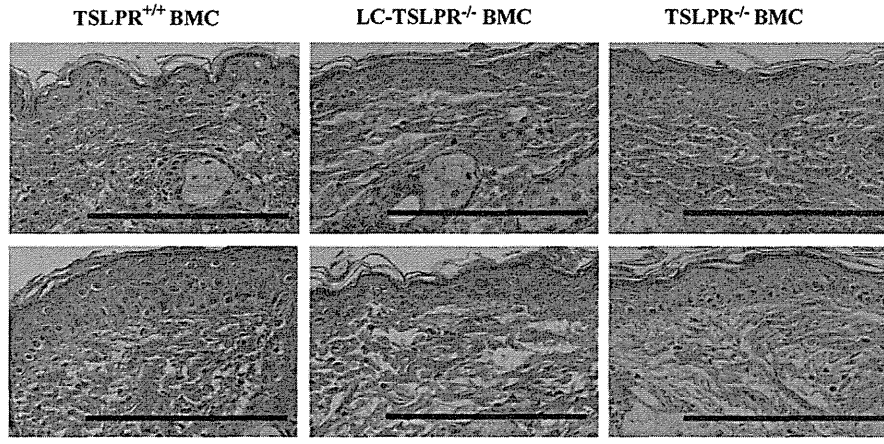


FIG E3. Establishment of BMC mice deficient in TSLPR on LCs (LC-TSLPR$^{-/-}$ BMC). B6 mice and B6-background TSLPR$^{-/-}$ mice were irradiated *(IR)* and transplanted with BM cells (BMT) from B6 mice or TSLPR$^{-/-}$ mice. Because LCs were radioresistant, when TSLPR$^{-/-}$ mice were reconstituted with BM cells from B6 mice, they were deficient in TSLPR on LCs (LC-TSLPR$^{-/-}$ BMC mice).

A



B

	TSLPR$^{+/+}$ BMC		LC-TSLPR$^{-/-}$ BMC			TSLPR$^{-/-}$ BMC	
	saline	OVA	saline	OVA		saline	OVA
Inflammation	0±0	3.2±0.2	0.4±0.24	1.2±0.2	*	0.4±0.24	1.4±0.24
Neutorophils	0.8±0.2	1.8±0.37	0.4±0.24	1.2±0.2	*	0.6±0.24	1.4±0.24
Mononuclear cells	1.6±0.24	3.2±0.37	1.2±0.2	1.6±0.24	*	1.0±0.32	1.2±0.2
Edema	0.2±0.2	2.4±0.24	0±0	1.4±0.24	*	0.2±0.2	1.4±0.24
Epithelial hyperplasia	0.8±0.2	3.6±0.24	0.4±0.24	1.2±0.2	*	0.6±0.24	1.2±0.24

FIG E4. **A,** Hematoxylin and eosin staining of the back skin of TSLPR$^{+/+}$, LC-TSLPR$^{-/-}$, and TSLPR$^{-/-}$ mice after OVA application 3 times (hematoxylin and eosin, original magnification ×400). Scale bar = 100 μm. **B,** The histologic findings were scored by inflammation, neutrophil infiltration, mononuclear cell infiltration, edema, and epithelial hyperplasia. Data are presented as means ± SDs (n = 5).

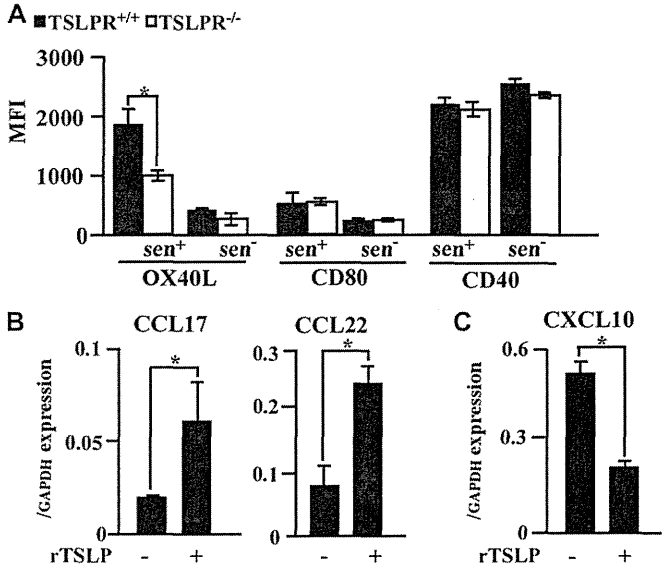


FIG E5. TSLP promotes the expression of OX40L and the production of T_H2 chemokines by DCs. **A,** The expression levels of OX40L, CD80, and CD40 of LCs with *(sen$^+$)* or without *(sen$^-$)* OVA sensitization in TSLPR$^{+/+}$ and TSLPR$^{-/-}$ mice (n = 5 mice per group). Cells were pregated on MHC class II$^+$ CD11c$^+$ LC cells. **B** and **C,** BM-derived DCs were incubated with or without recombinant TSLP *(rTSLP)*, and mRNA levels of chemokines—CCL17, CCL22, and CXCL10—were measured by real-time quantitative PCR. *P < .05. *GAPDH*, Glyceraldehyde-3-phosphate dehydrogenase; *MFI*, mean fluorescence intensity.

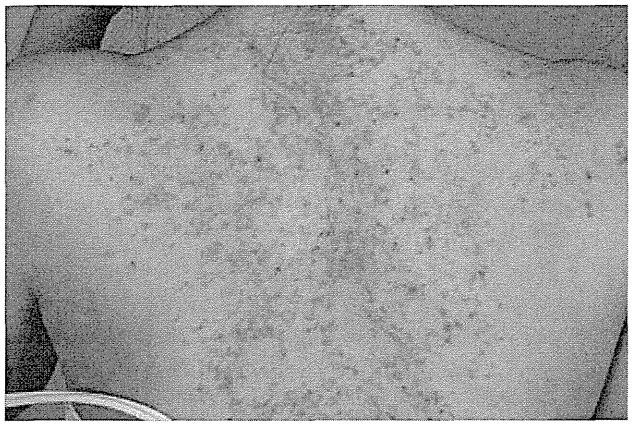


Figure 1 Scattered erythematous papules seen on the upper back with a reticulate pattern of hyperpigmentation.

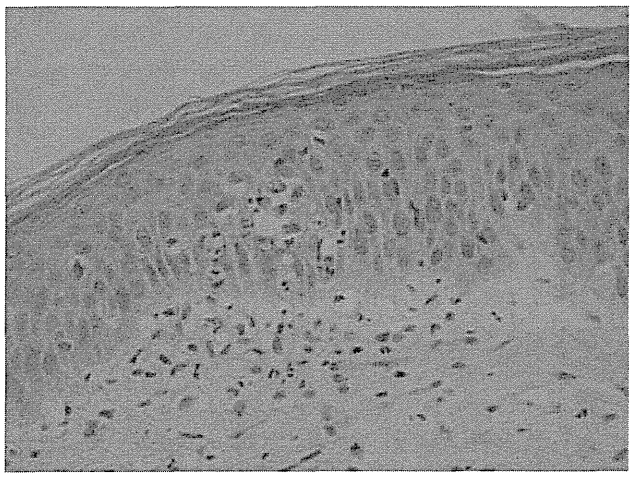


Figure 2 Mild epidermal acanthosis with neutrophilic and eosinophilic exocytosis, and occasional apoptotic keratinocytes. Mild upper dermal oedema and a superficial perivascular infiltrate that was mainly lymphocytic, with occasional neutrophils and eosinophils (haematoxylin and eosin, ×40).

rashes improved gradually over few months. She had no further new eruptions and at a 5-month review, only a fading patch of hyperpigmentation was noticeable.

In our patient, it is interesting to note that her disease was triggered only by excessive sweating during sporting activity, and this bears similarity to aggravation of atopic dermatitis and itch after exercise and sweating. Proteinase-activated receptor-2 (PAR-2) has been found to be increased in the epidermis in atopic dermatitis lesions, and PAR-2 has been found to play an essential role in the transmission of itch.[8] In a recent study in keratinocyte cultures, Ishikawa *et al.* examined the effect of tetracyclines on the production of interleukin 8 (IL-8), the latter being an important chemoattractant for neutrophils. It was shown that levels of IL-8 were decreased by minocycline, doxycycline and tetracycline through PAR-2 mediation.[9] In our patient, there was a rapid resolution in itch symptoms and subsequent progressive resolution of rashes upon initiation of doxycycline; antagonism of PAR-2 may possibly have a role.

In a recent case series in Taiwan, Lu *et al.* reported that doxycycline at 200 mg/day for 1–5 weeks provided good response in all their 16 patients.[10] Our patient further demonstrated a similar positive response. Although minocycline and dapsone have been the mainstays of treatment in prurigo pigmentosa, doxycycline offers an appealing and effective alternative with its more favourable side effect profile.

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References

1 Nagashima M. Prurigo pigmentosa – clinical observations of our 14 cases. *J Dermatol* 1978; **5**: 61–67.
2 Boer A, Asgari M. Prurigo pigmentosa: an underdiagnosed disease? *Indian J Dermatol Venereol Leprol* 2006; **72**: 405–409.
3 Chiam LY, Goh BK, Lim KS, Ng SK. Prurigo pigmentosa: a report of two cases that responded to minocycline. *Clin Exp Dermatol* 2009; **34**: e584–e586.
4 Matsumoto C, Kinoshita M, Baba S, Suzuki H, Kanematsu S, Kanematsu N. Vesicular prurigo pigmentosa cured by minocycline. *J Eur Acad Dermatol Venereol* 2001; **15**: 354–356.
5 Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am J Clin Dermatol* 2001; **2**: 253–262.
6 Baykal C, Buyukbabani N, Akinturk S, Saglik E. Prurigo pigmentosa: not an uncommon disease in the Turkish population. *Int J Dermatol* 2006; **45**: 1164–1168.
7 Ekmekci TR, Altunay IK, Koslu A. Prurigo pigmentosa treated with doxycycline. *Dermatol Online J* 2006; **12**: 9.
8 Steinhoff M, Neisius U, Ikoma A *et al.* Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003; **23**: 6176–6180.
9 Ishikawa C, Tsuda T, Konishi H, Nakagawa N, Yamanishi K. Tetracyclines modulate protease-activated receptor 2-mediated proinflammatory reactions in epidermal keratinocytes. *Antimicrob Agents Chemother* 2009; **53**: 1760–1765.
10 Lu PH, Hui RC, Yang LC, Yang CH, Chung WH. Prurigo pigmentosa: a clinicopathological study and analysis of associated factors. *Int J Dermatol* 2011; **50**: 36–43.

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Comparison of basophil infiltration into the skin between eosinophilic pustular folliculitis and neutrophilic folliculitis

Editor

Eosinophilic pustular folliculitis (EPF), first described by Ofuji *et al.*,[1] is characterized by recurrent clusters of pruritic, follicular,

sterile papules and pustules, and is often accompanied by peripheral blood eosinophilia. EPF is a rare dermatosis of unknown aetiology, but a Th2 cytokine-dominant condition has been postulated as an underlying mechanism.[2]

It is well established that basophils exert effector functions during allergic responses through the cross linking of FcεRI during immediate- or late-phase reactions following allergen exposure. In addition, recent studies have shown that basophils promote Th2 skewing by antigen presentation in helminth infection and in response to protease allergens and that dendritic cells are not necessary in this process.[3–5]

A recent study has reported three cases of EPF in which basophils infiltrate the follicular region using the monoclonal antibody BB1, which recognizes a unique granule constituent of basophils.[6,7] Before this finding can be considered a hallmark of EPF, however, we must assess more cases and evaluate whether such basophil infiltration is unique to EPF, that is, whether it is not seen in conventional infectious neutrophilic folliculitis. In the present study, we demonstrate that a significant number of basophils can infiltrate into the follicular and sebaceous gland regions in EPF but not in neutrophilic folliculitis.

Skin biopsies from folliculitis lesions of 13 patients with EPF (eight men, five women, mean age: 48.7 years) and nine patients with infectious neutrophilic folliculitis (four men, five women, mean age: 53.6 years) were examined by means of immunostaining. Deparaffinized sections were immersed in 0.3% H_2O_2 to abolish endogenous peroxidase activity and incubated with BB1 mouse mAb overnight. Slides were incubated with biotinylated horse anti-mouse serum, and then incubated with avidin-biotin-peroxidase complex (ABC-Elite; Vector Laboratories, Burlingame, CA, USA). Colouring reaction was performed with 3,3′-diaminobenzidine (DAB) and nuclei were counterstained with haematoxylin.

In EPF patients, basophils were observed to infiltrate not only into the perifollicular regions but also into the perisebaceous glands (Fig. 1a,b); in neutrophilic folliculitis patients, on the other hand, almost no basophils were detected in these regions (Fig. 1c). The number of basophils infiltrating into the skin in EPF ranged from 1 to 31 (average, 10.5; SEM, 2.6). In neutrophilic folliculitis, the number ranged from 0 to 3 (average, 0.4; SEM, 0.3) (Fig. 1d).

Consistent with previous findings, we have demonstrated that basophils infiltrate into the follicular and sebaceous gland regions at a very high density in EPF patients, and that this infiltration constitutes a clear distinction between EPF and neutrophilic folliculitis. Intriguingly, however, our study has shown that some EPF cases presented low basophil densities, and that one EPF case exhibited no infiltration of basophils. Several treatments for EPF have been proposed, but responses to these treatments vary, suggesting that subtypes of EPF exist and that the variation in the extent of basophil infiltration in EPF might reflect this sub typing. To determine whether this is the case, we must look for a correlation between each patient's responsiveness to each treatment and the magnitude of that patient's basophil infiltration.

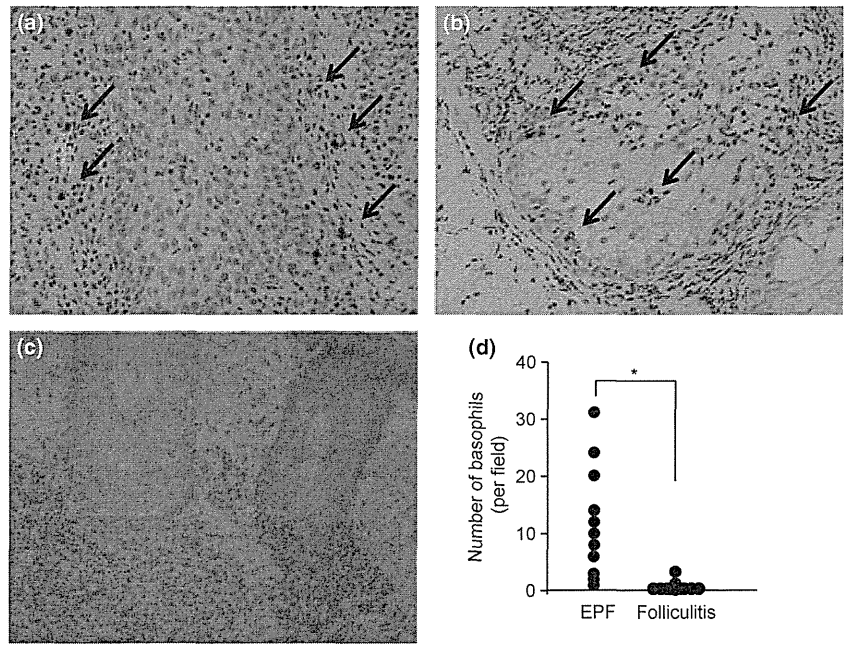

Figure 1 Immunohistochemistry of basophils. BB1-immunoreactive cells infiltrated the follicular region (a) and the sebaceous gland region (b) in eosinophilic pustular folliculitis patients, but not in folliculitis patients (c). (d) The number of BB1-positive basophils was calculated in 5 high-power fields (×40 objective). Data were analysed with the paired *t*-test. *A *P*-value of <0.05 was considered statistically significant.

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References

1 Ofuji S, Ogino A, Horio T, Oseko T, Uehara M. Eosinophilic pustular folliculitis. *Acta Derm Venereol* 1970; **50**: 195–203.

2 Otsuka A, Doi H, Miyachi Y, Kabashima K. Treatment of eosinophilic pustular folliculitis with ciclosporin: suppression of mRNA expression of IL-4 and IL-13. *J Eur Acad Dermatol Venereol* 2010; **24**: 1489–1491.

3 Sokol CL, Chu NQ, Yu S, Nish SA, Laufer TM, Medzhitov R. Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response. *Nat Immunol* 2009; **10**: 713–720.

4 Yoshimoto T, Yasuda K, Tanaka H *et al.* Basophils contribute to T(H)2-IgE responses *in vivo* via IL-4 production and presentation of peptide-MHC class II complexes to CD4+ T cells. *Nat Immunol* 2009; **10**: 706–712.

5 Perrigoue JG, Saenz SA, Siracusa MC *et al.* MHC class II-dependent basophil-CD4+ T cell interactions promote T(H)2 cytokine-dependent immunity. *Nat Immunol* 2009; **10**: 697–705.

6 Satoh T, Ito Y, Miyagishi C, Yokozeki H. Basophils infiltrate skin lesions of eosinophilic pustular folliculitis (Ofuji's disease). *Acta Derm Venereol* 2011; doi: 10.2340/00015555-1052. Epub ahead of print.

7 Ito Y, Satoh T, Takayama K, Miyagishi C, Walls AF, Yokozeki H. Basophil recruitment and activation in inflammatory skin diseases. *Allergy* 2011; doi: 10.1111/j.1398-9995.2011.02570.x. Epub ahead of print.

DOI: 10.1111/j.1468-3083.2011.04091.x

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展望

太藤病の病型

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Key words
太藤病，好酸球性膿疱性毛包炎，EPF (eosinophilic pustular folliculitis)，新病型分類，診断・治療アルゴリズム

はじめに

太藤病，別名好酸球性膿疱性毛包炎(eosinophilic pustular folliculitis，以下，EPF)は，瘙痒を伴う毛包一致性の好酸球性膿疱が，主に顔面に出現する原因不明の疾患である．ステロイド外用に抵抗することが多く，また，インドメタシン内服が奏効するなどの特徴を呈する．

EPFは，太藤が報告した古典型(classic)に加え，human immunodeficiency virus(HIV)感染に続発するHIV関連型(HIV-associated)，乳幼児に発症する小児型(infancy-associated)の三型に分類されてきた．しかし近年，HIV以外の免疫不全症に続発する例や，非典型例の報告がされている．また小児型EPFの疾患独立性の是非も問題提起されている．

EPFは，難治性痤瘡やアトピー性皮膚炎などと誤診されることも多い．正しく診断できればHIV感染者や免疫抑制状態を早期に発見できる可能性もある．また，インドメタシン内服が著効することは特筆に値する．本稿では，現在のEPF病型分類とその問題点を考察し，これからのEPFの診断と治療について展望したい．

Ⅰ．太藤病とは

1965年IseとOfujiは，痒みを伴う顔面の無菌性の膿疱性毛包炎に好酸球増多症を随伴した42歳の女性を"subcorneal pustular dermatosis：a follicular variant？"として報告した[1]．これが太藤病の最初の症例である．さらに1970年，太藤らは類似の3症例を追加報告し，好酸球性膿疱性毛包炎(EPF)として新しい疾患単位を提唱した[2]．その概念は，臨床的に顔面を中心に出現する，毛包一致性の瘙痒性丘疹・無菌性膿疱が環状ないし局面状に遠心性に拡大し，病理組織学的に毛包脂腺系に好酸球浸潤を伴う滲出性炎症を認めるもの，である[3]．東アジア人を中心に多くの症例が報告され，EPFまたはOfuji's disease(太藤病)として認知されている．

1986年にヒト免疫不全ウイルス(HIV)感染に関係したHIV-associated eosinophilic folliculitisが米国で報告されると[4]，欧米を中心に同様の症例報告が相次ぎ，現在はHIV関連型(HIV-associated) EPFとして認識されている．一方，1984年に毛包一致性の好酸球性膿疱を呈した乳幼児の症例が"EPF in infancy"として報告されると[5]，同様の報告が続き，現在は小児型(infancy-associated) EPFとして認識されている．

以上の経緯からEPFは，古典型EPF(太藤病)，HIV関連型EPF，小児型EPFの三型に分類されている(表1)．しかし小児型EPFは，頭皮に好発し，臨床像や病理組織像が異なることから，成人で認められるEPFと同一とは考えにくい[6]．また後述

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表1　EPFの病型とその特徴

	古典型	HIV関連型	小児型
病変の特徴	・辺縁に膿疱を環状に配列 ・膿疱は融合傾向	・紅斑が主体 ・膿疱は孤立性	・孤立性丘疹
病変の分布	顔面，体幹，四肢，掌蹠	顔面，頸部，体幹（掌蹠の報告なし）	頭皮
症状	瘙痒	瘙痒	瘙痒
経過	・遠心性に拡大 ・中心治癒傾向を示しながら色素沈着 ・数カ月から数年にわたる寛解増悪	・HIV感染に合併 ・HAART療法に続発	・数日から数週間にわたる間歇性の再燃
病理組織	・好酸球浸潤による外毛根鞘の細胞間浮腫，海綿状態，水疱形成（早期） ・毛包全体と脂腺を巻き込む好酸球浸潤（進行期） ・毛包周囲表皮の海綿状態，好酸球を容れた表皮内膿疱 ・真皮への好酸球を混じる単核球の稠密な細胞浸潤	・古典型に同じ	・毛包・脂腺周囲の真皮への好酸球浸潤
治療反応性	・インドメタシン内服が奏効	・インドメタシン内服が奏効	・ミノマイシン内服 ・ステロイド外用
補足		・ときにニキビダニや真菌を認める	

HAART：highly active anti-retroviral therapy

するように，病理組織像や臨床経過がEPFに類似するが，非典型的な発疹形態を示す例も存在する．そのような症例をEPFの特殊な表現型としてとらえるべきか，EPFではない別の疾患とするべきかについては，まだ結論は出ていない．症例の蓄積とEPFの病態解明を通して解決すべき今後の課題である．

Ⅱ．EPFの病型とその特徴

EPFは，現在，古典型（classic），HIV関連型（HIV-associated），小児型（infancy-associated）の三型に分類されている（表1）．

1．古典型EPF

太藤らが提唱したEPFの基本型である．原著によると（1）顔面に好発し，（2）紅斑が遠心性に拡大し，（3）膿疱が辺縁に環状に配列した局面を形成し，（4）中心治癒傾向を示しつつ色素沈着を残す．病理組織学的に（5）毛包上部（毛包表皮開口部から脂腺開口部）および脂腺と，それら周辺に好中球を混じる好酸球主体の細胞浸潤を認めるが，（6）無菌性である，などの特徴を示す[1,2]．

Katohらによれば[7]日本人の古典型EPFの発疹は，顔面（全古典型の88％），体幹（40％），四肢（26％），掌蹠（17％）に出現する．75％の患者が瘙痒を訴える．古典型EPFの17％において，毛包のない掌蹠に好酸球性膿疱が認められたことは，毛包に依存しない病態がEPFに存在する可能性を示唆するが，この点については明確な解答はまだ得られていない．

EPFはインドメタシンの内服が奏効する．Katohによると日本人症例報告では古典型EPFの75％に奏効している[7]．残る25％はインドメタシンに抵抗性を示しており，何がインドメタシンの奏効性に影響するのかは明らかでない．

2．HIV関連型EPF

HIV関連型EPFは，顔面に好発する以外は古典型EPFの特徴を示さない．発疹は，浮腫性に隆起した紅斑局面と，孤立性丘疹が主体である．大きな膿疱の形成や膿疱の融合傾向がないのが特徴で

ある．古典型と同様に強い瘙痒を訴える．ときに*Demodex folliculorum*（ニキビダニ）や真菌が同定されることがあり[4,8]，病原体の介在による好酸球性毛包炎の発症が示唆されている．感染説はEPFの遠心性拡大や中心治癒傾向を説明するには好都合だが，無菌性であることが実証されているEPFの一般的原因としては採用しがたい．

表2　京都大学医学部附属病院で経験した非典型的EPFの臨床症状と治療

症例	年齢	性別	発疹	部位	痒み	治療	備考
1	39	女	丘疹	額，頬	あり	トラニラスト内服（インドメタシンは腹部症状のため内服を継続できず）	
2	40	男	丘疹・紅斑	額，頬	あり	インドメタシン内服 プロトピック外用	
3	29	男	丘疹・紅斑	眼囲を除く顔面全体	あり	HAART	AIDS
4	56	女	滲出性紅斑	額，眉，鼻唇溝	あり	インドメタシン内服	
5	60	女	滲出性紅斑	側頭部，頬，口囲	あり	インドメタシン内服	

HAART：highly active anti-retroviral therapy　（文献12より引用）
AIDS：acquired immune deficiency syndrome

HIV関連型EPFは，日本でもHIV感染者の増加とともに増えている．古典型と同様にインドメタシンが奏効することが多い．またHAART治療後の免疫再構築症候群（immune reconstitution syndrome）との関連が報告されており[9]，EPFの病態が免疫系と密接な関係にあることがわかる．

興味深いことに，HIV感染に限らず，血液疾患，悪性腫瘍，骨髄移植による免疫抑制患者にEPFが発症する例が報告されている[7]．したがって，HIV関連型EPFは，HIV感染に特異的な病態ではなく，免疫抑制に続発するEPFの一表現型として理解するべきだろう．文献には免疫抑制関連型（immunosuppression-associated）との表記もある[10]．

3. 小児型EPF

小児型EPFはまれである．国内では1980年から2010年に4例の小児型EPFが報告されている[7]．頭皮を中心に皮疹が出現することが特徴である．古典型EPFは，顔面，体幹，四肢，掌蹠に膿疱が出現するが，頭皮部に出現することは通常ない．膿疱は古典型EPFに似るが，環状には配列しない．

海外では小児型EPFとして1984年から2004年に53例が報告されている．しかしながらZiemer & Boerによれば，これらの症例は虫刺症，貨幣状湿疹，膿痂疹，疥癬などとしても矛盾しない所見であり，EPFと診断するに十分な根拠を見出せなかったという[6]．さらに彼らは，小児型EPFとして報告された症例の組織所見を検討し，好酸球が毛包漏斗部に浸潤していないことに注目した．太藤によれば，EPFの病理組織学的特徴は，毛包上部（毛包の表皮開口部から脂腺開口部の間，すなわち毛包漏斗部）への好酸球浸潤と海綿状態である[1,2]．Ziemerらは，小児型EPFとして発表された症例の病理組織学的所見にこの特徴がなく，付属器周囲真皮への好酸球浸潤でしかないと述べている[6]．

また小児型EPFの症例報告によると，エリスロマイシン内服とステロイド外用が奏効したと記載されており，古典型EPFの臨床像と異なる[11]．ただし，インドメタシン内服が試されていないだけで，小児型EPFがインドメタシン内服に抵抗性であるかどうかは不明である．

以上のように，小児型EPFについては疾患独立性が問題視されている．理想的には病理所見を含めた診断基準が用意されるべきであろうが，現状ではそれはむずかしい．小児に発症し，数日から数週間にわたり寛解，増悪を繰り返すEPF様の病態については，虫刺症，疥癬，湿疹，膿痂疹などを可能な限り除外し，好酸球の浸潤部位を吟味し，インドメタシンの有効性を参考にしながら，太藤の原著に立ち返って慎重に診断すべきであろう．

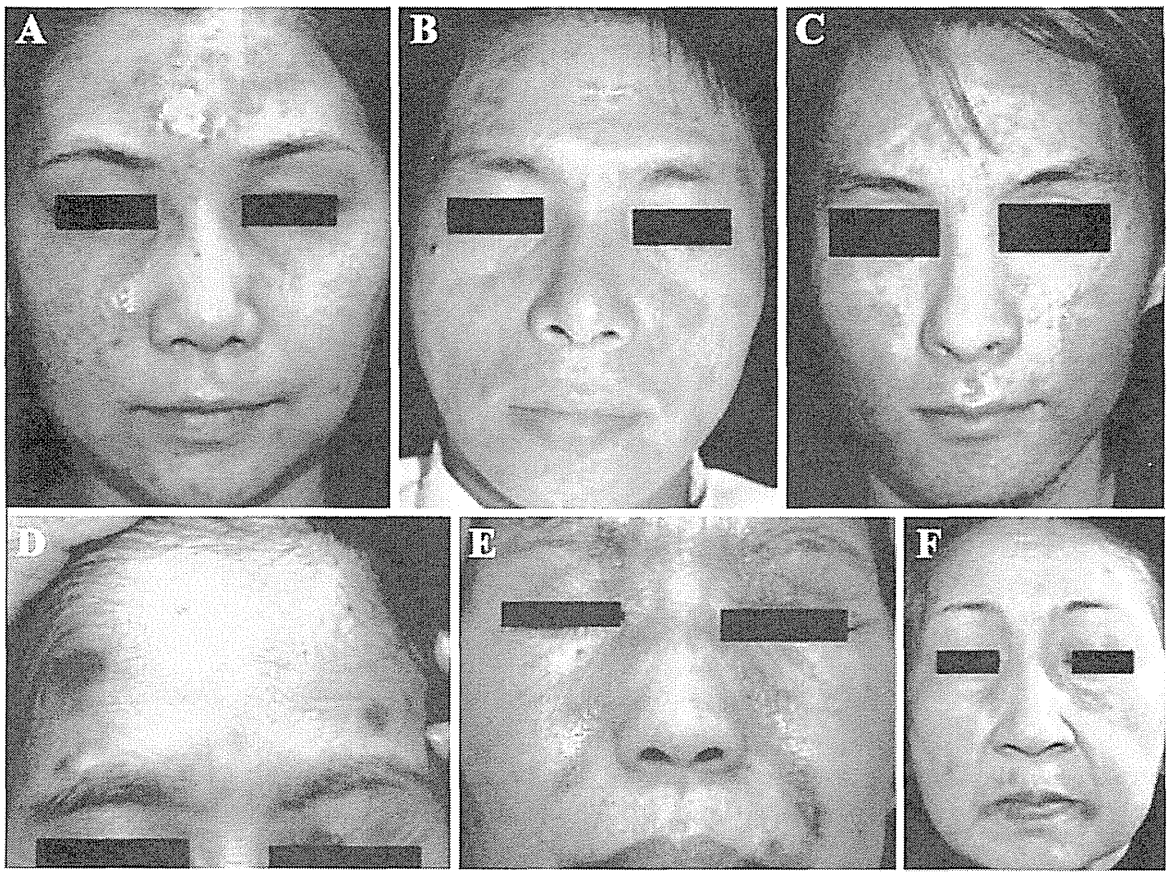

図1　非典型的EPFの臨床像．(A)症例1：額，頬の充実性丘疹．(B)症例2：額，頬の浸潤を触れる紅斑．(C)症例3：眼瞼を除く顔面全体の紅斑と丘疹．(D, E)症例4：額，眉，鼻唇溝の滲出性紅斑．(F)症例5：側頭部，頬，口囲の紅斑〔John Libbey Eurotext社より許可を受け文献12より転載(Reprint with permission of John Libbey Eurotext)〕．

Ⅲ．非典型的なEPF

ここに，非典型的なEPFとして，京大病院皮膚科で2005～2010年に経験した5症例(表2) を紹介する[12]．これらの症例は丘疹，膿疱，紅斑など多彩な皮膚所見を示し(図1)，病理組織学的には毛包およびその周囲への好酸球浸潤を認めた(図2)．5例中3例でインドメタシン内服が奏効した．症例1は，額・頬部の瘙痒を伴う充実性丘疹が主訴の39歳女性で，脂腺周囲，毛包周囲に好酸球の浸潤を認めた．インドメタシンは胃腸症状のため継続できなかったがトラニラスト内服が有効であった．症例2は額・頬部の瘙痒を伴う紅斑と丘疹が主訴の40歳男性で，毛包周囲の好酸球浸潤を認めた．インドメタシン内服，プロトピック外用が有効であった．症例3は眼周囲を除く顔面全体の瘙痒を伴う紅斑と丘疹が主訴の29歳男性で，インドメタシン内服，ミノマイシン内服，トラニラスト内服に抵抗を示した．血液検査でHIV感染が判明しHAART療法を施行したところ発疹は消失した．症例4は額，眉，鼻唇溝に出現した瘙痒を伴う滲出性紅斑が主訴の56歳女性で，毛包周囲の好酸球浸潤を認めた．インドメタシン内服が有効であった．症例5は側頭部，頬部，口囲の瘙痒を伴う滲出性紅斑が主訴の60歳女性で，毛包への好酸球浸潤を認

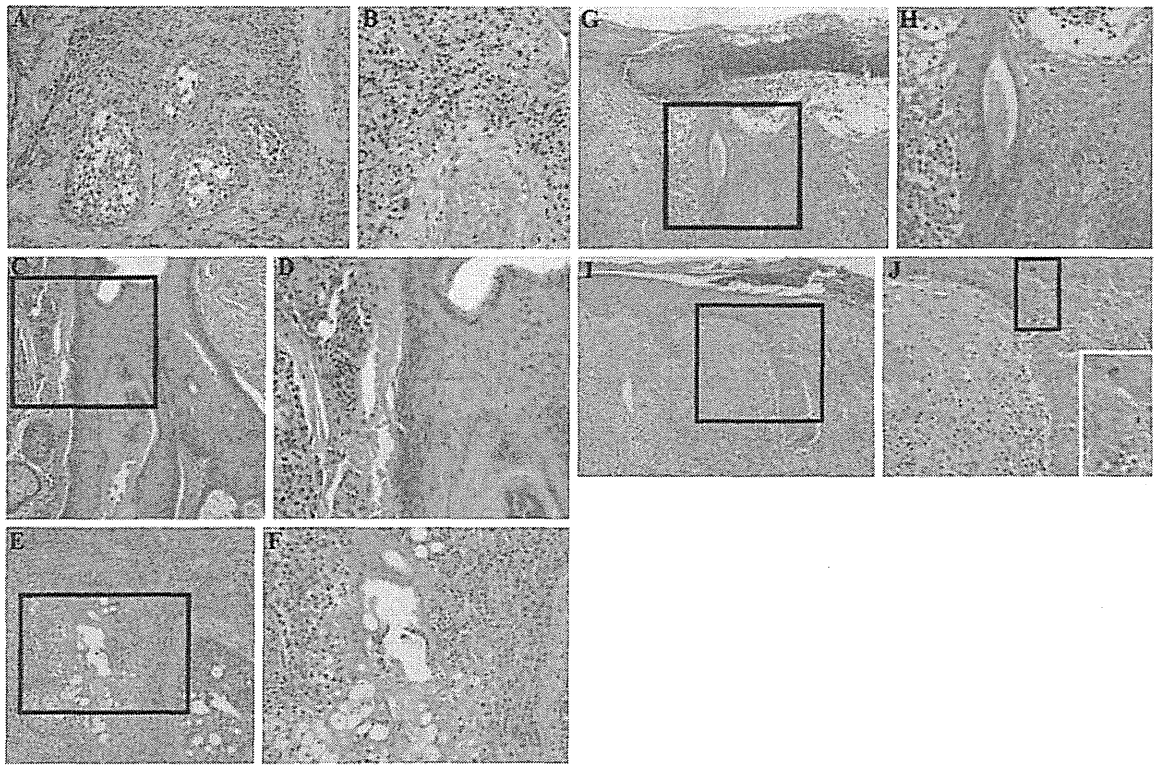

図2 非典型的EPFの病理組織．症例1：(A)脂腺および(B)毛包周囲への好酸球浸潤．症例2：(C)ニキビダニの存在と(D)(C)の拡大．毛包内および周囲への好酸球浸潤．症例3：(E)毛包と脂腺の破壊．(F)(E)の拡大．症例4(紅斑部位)：(G)毛包の角層下膿疱．(H)(G)の拡大．好酸球を認める．症例5：(I)毛包の角層下膿疱と外毛根鞘の海綿状変化．(J)(I)の拡大．毛包周囲にはわずかな好酸球のみ〔John Libbey Eurotext社より許可を受け文献12より転載(Reprint with permission of John Libbey Eurotext)〕．

めた．インドメタシン内服が有効であった．これらの非典型的症例を包括して特徴をまとめると以下になる．

1) 丘疹，膿疱，紅斑のいずれもあり，炎症後色素沈着を残す．
2) 遠心性拡大傾向があってもよい．
3) 眼周囲を避け，脂腺毛包の存在部位に発症する．
4) 痒みを伴う．
5) インドメタシン内服への反応がよい．
6) ステロイド外用に抵抗性である．
7) 再発を繰り返す．
8) 組織学的に毛包，脂腺に好酸球が浸潤する，あるいは角層下に好酸球性膿疱を形成する．

以上の特徴をもつ非典型的なEPFは，いずれも顔面に好発し再発性であり，組織所見が古典型EPFと合致しない例も含むことから，episodic eosinophilic dermatosis of the face(EEDF)として独立可能であるとの提案もある[12]．

Ⅳ．EPFの新病型分類の試み

前項で述べたように，従来のEPF分類に当てはまらない症例が多数存在する．そこでわれわれは古典型EPFの典型的所見を基盤とし，非典型的なEPFも包括する概念が必要ではないかと考えるに至り，新たに病型分類を試みた(表3)．

表3　EPFの新病型分類(案)

	古典型		免疫抑制関連型	特殊型	
	インドメタシン奏効型	その他：抗菌薬反応型・ステロイド反応型など		小児型	好酸球性皮膚炎(episodic eosinophilic dermatosis of the face：EEDF)
基礎疾患	なし		HIV感染，悪性腫瘍，骨髄移植後などの免疫抑制状態	なし	さまざま
瘙痒	あり		あり	あり	あり
部位	顔面，体幹，四肢，掌蹠		顔面，体幹，四肢	頭皮	顔面，体幹，四肢，掌蹠
臨床	・辺縁に環状に配列する膿疱 ・膿疱はしばしば融合する ・炎症後色素沈着あり ・遠心状に拡大 ・中心治癒傾向あり		・紅斑が主体 ・膿疱は孤立傾向	・孤立性丘疹	・丘疹・膿疱・紅斑のいずれもありえる ・炎症後色素沈着あり ・遠心性拡大傾向があってもよい ・眼周囲を避け，脂腺毛包の存在部位に発症 ・インドメタシン内服への反応がよい ・ステロイド外用に抵抗性 ・再発を繰り返す
病理組織	・好酸球浸潤による外毛根鞘の海綿状態，水疱形成(早期) ・毛包全体と脂腺を巻き込む好酸球浸潤(進行期) ・毛包周囲の海綿状態，好酸球を容れた表皮内膿疱 ・真皮への好酸球を混じる単核球の稠密な細胞浸潤		・古典型に同じ	・一定の見解なし	・毛包・脂腺への好酸球浸潤 ・角層下好酸球性膿疱

まず，古典型EPFはインドメタシン奏効型と，その他(抗菌薬・ステロイド反応型)に分類した．HIV関連型EPFは，免疫抑制関連型EPFとして分類した．

小児型EPFは発疹が頭皮に出現することや，組織所見の問題をはじめ，その疾患独立性に疑問が投げかけられている．現時点では，特殊型の1つとして小児型EPFの包括を試みた．

発疹が非典型的であるが，顔面に好発し，インドメタシン内服の反応が良好で，組織学的に毛包・脂腺周囲の好酸球浸潤を認めるタイプを特殊型として包括を試みた．

Ⅴ．EPFの診断と治療(診断・治療アルゴリズム)

特殊型EPFを含め，EPFの診断はむずかしい．標準的な痤瘡治療に抵抗する痤瘡様発疹に遭遇し

た場合は，まずEPFを疑うことが重要である．われわれは「厚生労働科学研究費補助金　難治性疾患克服研究事業　好酸球性膿疱性毛包炎の病態解明と新病型分類の提言研究班」での活動を通して，EPFの診断・治療アルゴリズムを試作した(図3)．

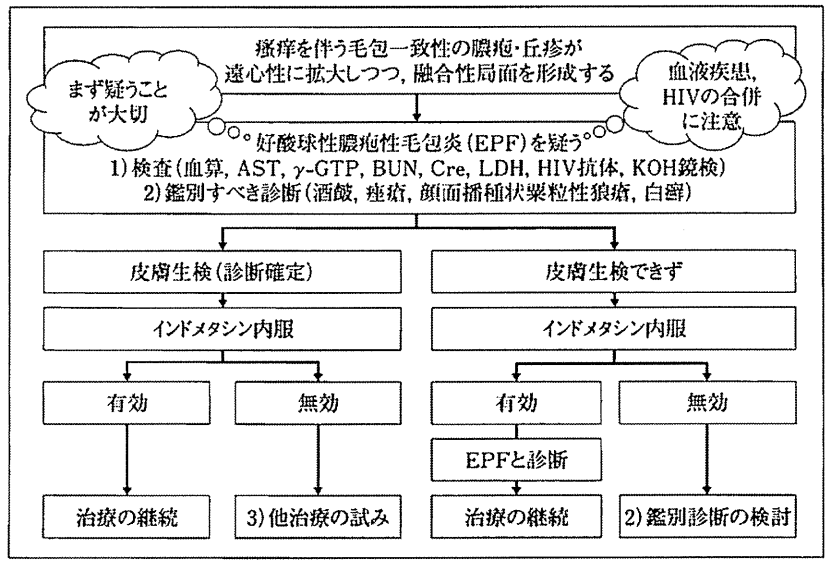

図3　EPFの診断・治療アルゴリズム(案)．1)標準的な検査として：血算，一般生化学(AST，γ-GTP，BUN，Cre，LDH)，抗HIV抗体，KOH鏡検．2)鑑別診断：アトピー性皮膚炎，酒皶，痤瘡，顔面播種状粟粒性狼瘡，細菌性毛包炎，掌蹠膿疱症，白癬，疥癬，虫刺症，脂漏性皮膚炎，菌状息肉症．3)効果不良例では：タクロリムス軟膏やインドメタシンクリームの外用，ジアフェニルスルホンやロキシスロマイシンの内服(保険適応外)

EPFの診断で重要なことは，まずこの疾患を疑うことに始まる．本疾患は難治性痤瘡やアトピー性皮膚炎などの他疾患と誤診されて治療に難渋しているケースが多い．また，ときにEPFはHIV感染や造血系腫瘍，悪性腫瘍に関連するため，血算(好酸球の増加や異型細胞の有無)，一般生化学，HIV抗体は検査したい．皮膚鱗屑を採取しKOH法により白癬を除外しておく．確定診断は皮膚生検であり，連続切片を作製し，毛包全体の所見をとる．生検できない場合は，第一選択薬のインドメタシンを1週間内服させてもよい．インドメタシンが有効ならばEPFの可能性が高い．

EPF治療の第一選択はインドメタシンの内服である．組織学的にEPFであってもインドメタシンに反応しない場合は，タクロリムス軟膏，インドメタシンクリーム，ジアフェニルスルホン内服，ロキシスロマイシン内服などが有効である．ステロイド外用が有効な場合もあるが，EPFは寛解と増悪を繰り返し慢性に経過するので，長期にわたる使用はすべきでない．

Ⅵ. 病態生理

EPFの病態生理を理解することは，正しい診断と治療に大きく貢献する．現在のところ原因は明らかでないがTh2サイトカイン環境やプロスタグランジンの関与が強く示唆されている．

インドメタシン治療前後で血中サイトカインを比較すると，インターフェロンガンマ(IFN-γ)の増加が認められる[13]．INF-γの投与でEPFを制御できた症例では，末梢単核球のIL-5発現(mRNA)が減少していた[14]．IL-5は好酸球の増殖・分化因子である．これらの知見はTh2型サイトカイン環境がEPFに関与することを示唆する．

一方，われわれはインドメタシンの奏効性に着目した研究を行った[15]．インドメタシンはシクロオキシゲナーゼ(COX)阻害薬である．COXはアラキドン酸を代謝しプロスタグランジン(PG)を生成する．EPFはインドメタシンが奏効するため，われわれはPG経路が病態に関与すると考え検討した．その結果，1)EPF病変部でPGD2合成酵素の発現が増加していること，2)PGD2が非酵素的に転換したPGJ2が，ヒト脂腺細胞株の好酸球遊走ケモカインCCL26(別名eotaxin-3)の産生を促すこと，

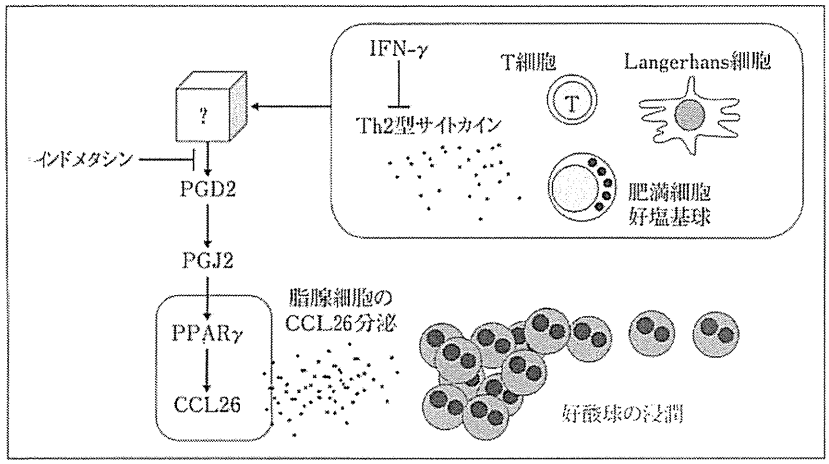

図4　EPFの病態モデル．免疫細胞の活性化や，Th2型サイトカインが，未同定の細胞によるプロスタグランジン(PG) D2の産生を促す．PGD2は非酵素的にPGJ2に変換され，近傍の脂腺細胞に作用する．その結果，PPARγ依存性にCCL26が産生され，好酸球の浸潤を誘導する．IFNγはTh2型サイトカインを抑制し，インドメタシンはPGD2の産生を抑制することでEPFをコントロールすると考えられる．

3) その際に転写因子PPARγが関与すること，を明らかにした．以上から，脂腺細胞におけるPGD2→PGJ2→PPARγ→CCL26産生という経路がEPFにおける好酸球浸潤に関与すると考えられる．また，この経路は新規の治療標的としても期待される．

以上の知見からEPFの病態は次のように考えられる(図4)．なんらかの原因でT細胞，Langerhans細胞，肥満細胞，好塩基球などが活性化し，Th2型サイトカイン環境(IFN-γの減少とIL-4/IL-5の増加)が形成される．このような全身的または局所的免疫変調が，脂腺細胞周囲の未知の細胞に作用してPGD2産生を増加させる．PGD2がPGJ2に変換され脂腺細胞に作用するとPPARγ依存性にCCL26を産生する．その結果，無菌性の好酸球浸潤が誘導されると考えられる．

実際には，EPFでは脂腺周囲のみならず外毛根鞘にも好酸球が浸潤する．この原因を解明することは，今後の課題である．

Ⅶ. 結　語

日本人により見出されたEPFは，その定義，分類の是非，病態解明を巡って現在もなお活発に議論されている．インドメタシンの奏効性，免疫再構築症候群との関連，Th2型サイトカインの関与など，学術的にも興味深く，多々ある好酸球関連疾患の解明にもつながる可能性を秘めている．今後は分子生物学的な観点から研究が進み，好酸球，プロスタグランジン，免疫系の意外なクロストークが見出されるものと期待される．

その一方で，EPFの臨床的な知名度は高くなく，難治性瘙痒として適切な治療を受けていない患者が多数存在する．今回紹介したEPFの診断・治療アルゴリズムがそのような症例の発掘と治療の一助となれば幸いである．

<文　献>

1) Ise, S., Ofuji, S.：Arch Dermatol　92：169, 1965
2) Ofuji, S. et al.：Acta Derm Venereol　50：195, 1970
3) 玉置邦彦(編)：最新皮膚科学大系 6，中山書店，東京，p. 244, 2002
4) Soeprono, F. F., Schinella, R. A.：J Am Acad Dermatol　14：1020, 1986
5) Lucky, A. W. et al.：Pediatr Dermatol　1：202, 1984
6) Ziemer, M., Böer, A.：Am J Dermatopathol　27：443, 2005
7) Katoh, M. et al.：J Dermatol　32：(in press) 2012
8) Ferrándiz, C. et al.：Int J Dermatol　31：193, 1992
9) Rajendran, P. M. et al.：Arch Dermatol　141：1227, 2005
10) Nervi, S. J. et al.：J Am Acad Dermatol　55：285, 2006
11) Duarte, A. M. et al.：Am J Dis Child　147：197, 1993
12) Matsumura, Y., Miyachi, Y.：Eur J Dermatol　22：658, 2012
13) Teraki, Y. et al.：Dermatology　192：16, 1996
14) Fushimi, M. et al.：Br J Dermatol　134：766, 1996
15) Nakahigashi, K. et al.：J Allergy Clin Immunol　129：536, 2012