Clinical Pharmacogenetics Implementation Consortium Guideline for *HLA* Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update

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The variant allele *HLA-B*15:02* is strongly associated with greater risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine or oxcarbazepine. The variant allele *HLA-A*31:01* is associated with greater risk of maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, and SJS/TEN in patients treated with carbamazepine. We summarize evidence from the published literature supporting these associations and provide recommendations for carbamazepine and oxcarbazepine use based on *HLA* genotypes.

Human leukocyte antigen (*HLA*) genetic variation is implicated in the development of specific cutaneous adverse reactions to aromatic anticonvulsants. The purpose of this guideline is to interpret *HLA-B*15:02* and *HLA-A*31:01* genotyping results to guide the use of carbamazepine and oxcarbazepine. Detailed guidelines regarding the selection of alternative therapies, when to conduct genotype testing, and cost-effectiveness analyses are beyond the scope of this document. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at https://cpicpgx.org/guidelines and http://www.pharmgkb.org.

FOCUSED LITERATURE REVIEW AND UPDATE

A systematic literature review focused on *HLA-B*15:02* and *HLA-A*31:01* genotypes and carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions was conducted (details in **Supplemental Material**).

This guideline is an update to the 2013 CPIC guideline for *HLA-B*15:02* and carbamazepine use.[1] The recommendations provided in the original guideline have not changed and are included here. However, the scope of the existing recommendations has now expanded to include the use of carbamazepine and oxcarbazepine based on *HLA-A*31:01* and *HLA-B*15:02* genotypes, respectively. Furthermore, the accompanying **Supplemental Material** now includes resources to facilitate the incorporation of *HLA* genotype results into electronic health records with clinical decision support (https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/).

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Table 1 Assignment of *HLA-B* and *HLA-A* genotypes

Genotype	Definition	Examples of diplotypes
*HLA-B*15:02* negative	Homozygous for an allele other than *HLA-B*15:02*	**X*[a]/**X*[a]
*HLA-B*15:02* positive	Heterozygous or homozygous variant	**15:02/*X*[a], **15:02/*15:02*
*HLA-A*31:01* negative	Homozygous for an allele other than *HLA-A*31:01*	**Y*[b]/**Y*[b]
*HLA-A*31:01* positive	Heterozygous or homozygous variant	**31:01/*Y*[b], **31:01/*31:01*

[a]Where *X = any *HLA-B* allele other than *HLA-B*15:02*. [b]Where *Y = any *HLA-A* allele other than *HLA-A*31:01*.

GENES: *HLA-B* AND *HLA-A*

Background

HLA-B and *HLA-A* are part of a large cluster of genes known as the human major histocompatibility complex (MHC). The cluster contains three subgroups: class I, II, and III. The *HLA-B* and *HLA-A* genes are part of the class I complex, along with *HLA-C*. These genes encode cell surface proteins that present intracellular antigens to the immune system. Intracellular antigens are usually the normal breakdown products of intracellular proteins and are recognized as "self." However, if the antigen presented derives from a pathogen or, in some cases, a transplanted tissue, it may be recognized as "nonself" and trigger an immune response. HLA is inherited in a codominant fashion with one set of class I and II alleles being inherited from each parent where both have full phenotypic expression.

Because HLA proteins present a wide variety of peptides for immune recognition, the *HLA* genes are among the most highly polymorphic genes in the human genome. *HLA* polymorphisms were previously ascertained serologically, but standard molecular approaches that now use DNA sequence-based typing methods either by standard Sanger or next-generation sequencing have revealed much greater complexity of genetic variation within this locus. For example, according to the World Health Organization (WHO) Nomenclature Committee for Factors of the *HLA* System (http://hla.alleles.org), there are more than 4,000 identified *HLA-B* alleles and more than 3,000 identified *HLA-A* alleles, many of which differ by more than one nucleotide from one another. Each allele is designated by the gene name followed by an asterisk and a four- or six-digit identifier giving information about the allele type (designated by the first two digits) and specific protein subtype (second set of digits). The details of HLA nomenclature have been described in a previous CPIC guideline.[2]

The guideline presented here specifically discusses the class I HLA alleles *HLA-B*15:02* and *HLA-A*31:01* as they relate to carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and maculopapular exanthema (MPE).

Genetic test interpretation

Clinical genotyping tests exist for identifying *HLA-B* and *HLA-A* alleles, including *HLA-B*15:02* and *HLA-A*31:01*. Genotyping results are presented as "positive" if one or two copies of the variant allele are present or "negative" if no copies of the variant allele are present. There is no intermediate genotype. Genotype definitions for *HLA-B*15:02* and *HLA-A*31:01* are summarized in **Table 1**. Nucleotide and amino acid sequence alignments for *HLA-B*15:02* and *HLA-A*31:01* and the corresponding reference sequences are available in **Supplemental Figures S1–S4**.

Available genetic test options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry website (http://www.ncbi.nlm.nih.gov/gtr/).

Incidental findings

Although *HLA* alleles have been studied in the context of specific responses to HIV and other pathogens, there are currently no specific diseases or conditions that have been strongly linked to *HLA-B*15:02* or *HLA-A*31:01* independent of drug use.[3–5] However, *HLA-B*15:02* has also been associated with SJS/TEN from phenytoin use, and other *HLA-B* alleles have been strongly associated with adverse drug reactions. For example, *HLA-B*57:01* is associated with abacavir-induced hypersensitivity reaction, and *HLA-B*58:01* is associated with allopurinol-induced severe cutaneous adverse reactions (including SJS/TEN and DRESS). CPIC guidelines are available to guide prescribing of phenytoin,[6] abacavir,[7] and allopurinol,[8] based on *HLA-B* genotype.

Other considerations

*HLA-B*15:02* and *HLA-A*31:01* have distinct ethnic and geographical distributions that are important for evaluating population risk (see ***HLA-A* and *HLA-B* Allele Frequency Table**). The frequency of *HLA-B*15:02* is highest in East Asian (6.9%), Oceanian (5.4%), and South/Central Asian (4.6%) populations. However, not all East Asian subpopulations carry this allele in such high frequencies. *HLA-B*15:02* frequency is much lower in Japanese (<1%) and Korean (<2.5%) populations. The allele is also quite rare in African populations (not observed), African Americans, Middle Easterners, Caucasians, and Hispanics/South Americans (<1%). In contrast, the frequency of the *HLA-A*31:01* allele is higher than the *HLA-B*15:02* allele in Caucasians (3%) and Hispanic/South Americans (6%). However, it is

also found in high frequencies in some East Asians, specifically Japanese (8%) and South Koreans (5%), and South/Central Asians (2%). While these frequencies are helpful in determining broad population risks, they cannot replace genotypes on an individual basis.

DRUGS: CARBAMAZEPINE AND OXCARBAZEPINE

Background

Carbamazepine. Carbamazepine, an aromatic anticonvulsant related to the tricyclic antidepressants, is US Food and Drug Administration (FDA)-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. Carbamazepine reduces the propagation of abnormal impulses in the brain by producing a frequency- and voltage-dependent block of sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus.[8,9] Carbamazepine-induced adverse effects that may have known dose- or concentration-dependency include dizziness, ataxia, and nystagmus. Other adverse effects such as aplastic anemia, hyponatremia, leukopenia, osteoporosis, liver injury, and hypersensitivity reactions such as MPE, DRESS, and SJS/TEN have a complex dose–response relationship such that it is difficult to delineate a clear linear dose–response relationship. For additional information regarding the pharmacokinetics and pharmacogenomics of carbamazepine, please refer to the PharmGKB website: http://www.pharmgkb.org/pathway/PA165817070.[10]

Oxcarbazepine. Oxcarbazepine is the keto-analog of carbamazepine. With its similar structure, oxcarbazepine shares many therapeutic indications and adverse effects with carbamazepine. Furthermore, patients who have had hypersensitivity reactions to carbamazepine may also be predisposed to hypersensitivity reactions with oxcarbazepine; these patients should only be treated with oxcarbazepine if the potential benefit justifies the potential risk.

Linking genetic variability to variability in drug-related phenotypes

There is evidence linking the *HLA-B*15:02* genotype with the risk of carbamazepine- and oxcarbazepine-induced SJS/TEN (**Supplemental Table S1**) and linking *HLA-A*31:01* genotype with the risk of carbamazepine-induced SJS/TEN, DRESS, and MPE (**Supplemental Table S2**). Application of a grading system to evidence linking *HLA* genotypic variations to phenotypic variability with respect to cutaneous adverse reactions indicates a high quality of evidence in the majority of cases. This body of evidence provides the basis for the recommendations in **Table 2** and **Table 3**.

HLA-B*15:02. *HLA-B*15:02* is specific for carbamazepine- and oxcarbazepine-induced SJS and TEN, although the data are strongest for carbamazepine. SJS is characterized by epidermal detachment affecting up to 10% of the body surface area (BSA), while TEN usually involves more than 30% of the BSA. Patients with between 10–30% of the BSA blistered are defined as having an SJS/TEN overlap syndrome. Mortality rates are typically below 5% for SJS and can be above 30% for TEN, with sepsis being the most frequent cause of death.[11] Mortality from SJS/TEN is also related to age, the drug half-life, and how early the drug is discontinued.[12,13] An immune-mediated etiology has been shown for these reactions, which is consistent with the anamnestic response often seen clinically on drug rechallenge.[14] In terms of the immunopathology, cytotoxic T cells, or CD8 + T cells (lymphocytes matured in the thymus that express the CD8 protein on their surface), are involved in SJS and TEN.[15,16] Further discussion on the mechanism of carbamazepine-induced SJS/TEN is presented in the **Supplemental Material**.

Consistent with the regional and ethnic distribution of the *HLA-B*15:02* allele, studies have shown the genetic risk of carbamazepine-associated SJS/TEN to be higher in several Asian countries with increased frequency of the *HLA-B*15:02* allele, including Vietnam,[17] Cambodia,[17] Reunion Islands,[17] Thailand,[18,19] some parts of India,[20] Malaysia,[21] and Hong Kong.[22] The *HLA-B*15:02* allele has not been observed in cases of SJS/TEN in some ancestral groups, such as Japanese and Korean populations or non-Asian descendants in Europe or North America,[17,23–26] where the frequency of the allele is very low. In the Han Chinese population, the sensitivity of *HLA-B*15:02* as a predictive test for SJS/TEN has been estimated at 98% and specificity at 97%[23]; the positive predictive value is estimated at 7.7% and negative predictive value at 100%.[27] However, it is important to note that in one study, in a group of individuals thought to be of European origin, four of 12 individuals with SJS/TEN carried the *HLA-B*15:02* allele.[24] Subsequently, they were found to have some Southeast Asian ancestry. This example underscores the importance of considering the *HLA-B*15:02* allele carrier status in therapeutic decision-making regardless of self-reported ethnicity.

Based on the strong evidence linking *HLA-B*15:02* to carbamazepine-induced SJS/TEN, the FDA issued a Health Alert in 2007 about changes to package labeling and recommendations for genetic testing in patients treated with carbamazepine.[28] The FDA label for carbamazepine carries a boxed warning about the risk of SJS/TEN with the presence of the *HLA-B*15:02* allele and states that patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk. The FDA label for oxcarbazepine does not carry this boxed warning, but there is mention of the association between *HLA-B*15:02* and the risk of SJS/TEN in the warnings and precautions section that advises avoiding oxcarbazepine in *HLA-B*15:02* positive patients unless the benefit clearly outweighs the risk. The positive predictive value of *HLA-B*15:02* for oxcarbazepine-induced SJS/TEN is estimated to be 0.73%, which is much lower than that of carbamazepine-induced SJS/TEN (7.7%); however, the negative predictive value for both nears 100% in Southeast Asian populations.[29]

HLA-A*31:01. Unlike *HLA-B*15:02*, the *HLA-A*31:01* allele is associated with a wider range of carbamazepine hypersensitivity reactions, including MPE, DRESS, and SJS/TEN, in many different populations.[30] DRESS is a severe hypersensitivity reaction characterized by generalized cutaneous eruptions with systemic

Table 2 Recommendations for carbamazepine therapy based on *HLA-B* and *HLA-A* genotypes

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative and *HLA-A*31:01* positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.
		If patient is carbamazepine-naïve and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction.	Optional	N/A
		The latency period for cutaneous adverse drug reactions is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]
*HLA-B*15:02* positive[c] and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	Greater risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naïve, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

DRESS, drug reaction with eosinophilia and systemic symptoms; MPE, maculopapular exanthema; N/A, not applicable; SJS = Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]If only *HLA-B*15:02* was tested, assume *HLA-A*31:01* is negative and vice versa. [b]*HLA-B*15:02* has a 100% negative predictive value for carbamazepine-induced SJS/TEN, and its use is currently recommended to guide use of carbamazepine and oxcarbazepine only. Because there is a much weaker association and less than 100% negative predictive value of *HLA-B*15:02* for SJS/TEN associated with other aromatic anticonvulsants, using these drugs instead of carbamazepine or oxcarbazepine in the setting of a negative *HLA-B*15:02* test in Southeast Asians will not result in prevention of anticonvulsant-associated SJS/TEN.[40] [c]In addition to *HLA-B*15:02*, risk for carbamazepine-induced SJS/TEN has been reported in association with the most common B75 serotype alleles in Southeast Asia, *HLA-B*15:08, HLA-B*15:11*, and *HLA-B*15:21*. Although not described, the possibility of carbamazepine-induced SJS/TEN in association with less frequently carried B75 serotype alleles, such as *HLA-B*15:30* and *HLA-B*15:31*, should also be considered. [d]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.

Table 3 Recommendations for oxcarbazepine therapy based on *HLA-B* genotype

Genotype	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative	Normal risk of oxcarbazepine-induced SJS/TEN	Use oxcarbazepine per standard dosing guidelines.	Strong	N/A
*HLA-B*15:02* positive	Greater risk of oxcarbazepine-induced SJS/TEN	If patient is oxcarbazepine-naïve, do not use oxcarbazepine.	Strong	Other aromatic anticonvulsants[a] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used oxcarbazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of oxcarbazepine in the future.	Optional	Previous tolerance of oxcarbazepine is not indicative of tolerance to other aromatic anticonvulsants.[a]

N/A, not applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
[a]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.

manifestations that can be life-threatening, whereas MPE is a milder reaction with only the presence of rash without mucosal or organ involvement, or systemic features. Available evidence suggests an association between the presence of *HLA-A*31:01* and carbamazepine-induced MPE, DRESS, and SJS/TEN, with the data strongest for DRESS and SJS/TEN in European and Japanese populations, where the allele frequency is higher; however, no such evidence exists for oxcarbazepine.

In Southeast Asian populations, the strong association between *HLA-B*15:02* and carbamazepine-induced SJS/TEN would overwhelm any potential association between *HLA-A*31:01* and carbamazepine-induced SJS/TEN. In European, African, and Japanese populations where the carriage rate of *HLA-B*15:02* is less than 1%, *HLA-A*31:01* appears to be the primary driver of carbamazepine-induced SJS/TEN and other hypersensitivity reactions. *HLA-A*31:01* is also a risk factor for MPE and DRESS in Han Chinese populations. The positive predictive value and number needed to test to prevent one case of all carbamazepine-induced hypersensitivity reactions (most influenced by MPE >>> DRESS) combined are most favorable for European populations, and they are estimated at 43% and 47, respectively.[31] Limited, if any, evidence exists to support an association between *HLA-A*31:01* and hypersensitivity associated with other aromatic anticonvulsants, including lamotrigine,[32] oxcarbazepine, eslicarbazepine, phenytoin, fosphenytoin, and phenobarbital, and thus no recommendations can be given regarding the safety of these agents in *HLA-A*31:01* positive patients. In light of evidence supporting clinical crossreactivity among aromatic anticonvulsants, however, in the instance where a severe hypersensitivity reaction has occurred with one agent, avoidance of the others is recommended.[33]

Therapeutic recommendations

The therapeutic recommendations for *HLA-B*15:02* and carbamazepine remain unchanged from the original guideline,[1] but in this update they are now also applicable to oxcarbazepine (**Tables 2**, **3**). These recommendations hold irrespective of the patient's region of origin or ethnic group. For patients who are *HLA-B*15:02* negative, carbamazepine or oxcarbazepine may be prescribed per standard guidelines. If a patient is carbamazepine-naïve or oxcarbazepine-naïve and *HLA-B*15:02* positive, carbamazepine and oxcarbazepine should be avoided, respectively, due to the greater risk of SJS/TEN. Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital, have very limited evidence, if any, linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used when choosing an alternative agent. With regular dosing, carbamazepine- or oxcarbazepine-induced SJS/TEN usually develops within the first 4–28 days of therapy; therefore, patients who have been continuously taking carbamazepine or oxcarbazepine for longer than 3 months without developing cutaneous reactions are at extremely low risk (but not zero) of carbamazepine- or oxcarbazepine-induced adverse events in the future, regardless of *HLA-B*15:02* status.[34,35]

For patients who are *HLA-A*31:01* negative, carbamazepine may be prescribed per standard guidelines (**Table 2**). If a carbamazepine-naïve patient also received testing for *HLA-B*15:02* and is positive for this allele, carbamazepine should be avoided regardless of the *HLA-A*31:01* genotype result. If a patient is carbamazepine-naïve and *HLA-A*31:01* positive, and if alternative agents are available, carbamazepine should be avoided

due to the greater risk of SJS/TEN, DRESS, and MPE. Other aromatic anticonvulsants, including oxcarbazepine, have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent. If alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at the first evidence of a cutaneous adverse reaction. As previously mentioned, since the latency period for cutaneous adverse drug reactions is known, if the patient is *HLA-A*31:01* positive and has previously used carbamazepine for longer than 3 months without incidence of a cutaneous adverse reaction, cautiously consider use of carbamazepine.

Pediatrics. Data describing the relationship between *HLA-B*15:02* and *HLA-A*31:01* genotype and carbamazepine- or oxcarbazepine-induced cutaneous adverse reactions in pediatric patients are scarce (**Supplemental Tables S1, S2**). In the absence of data suggesting a different relationship between these *HLA* alleles and drug-induced hypersensitivity in pediatric patients, the recommendations may be used to guide use of carbamazepine and oxcarbazepine in both adult and pediatric patients.

Recommendations for incidental findings

Aromatic anticonvulsants that are structurally similar to carbamazepine have also been associated with SJS/TEN and *HLA-B*15:02*. The drug-specific evidence linking *HLA-B*15:02* and SJS/TEN is discussed in the **Supplemental Material** and may have implications for choosing alternatives to carbamazepine in those who carry the *HLA-B*15:02* allele.

Other considerations

***HLA-B75* serotypes.** *HLA-B*15:02* is the most common *HLA-B75* serotype allele in Southeast Asia. Other less frequently carried members of the *HLA-B75* serotype include *HLA-B*15:08, HLA-B*15:11*, and *HLA-B*15:21*. The HLA proteins coded by these alleles share structural similarity and peptide binding grooves, and hence peptide binding specificities, with *HLA-B*15:02* and have also been reported in association with carbamazepine-induced SJS/TEN.[26,36–38] Currently, the majority of available data focuses on the risk of carbamazepine-induced SJS/TEN conferred by the presence of *HLA-B*15:02* and is the basis for the design of efficient single allele molecular typing assays. However, some labs may provide high-resolution *HLA-B* typing and the possibility of carbamazepine-induced SJS/TEN with *HLA-B*15:08, HLA-B*15:11, HLA-B*15:21*, and even less common *HLA-B75* serotype alleles such as *HLA-B*15:30* and *HLA-B*15:31* where carbamazepine-induced SJS/TEN has yet to be described, needs to be considered a potential risk if this information is available.

Implementation of this guideline. The guideline supplement and CPIC website (https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/) contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* in the **Supplemental Material**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

A potential benefit of *HLA-B*15:02* and *HLA-A*31:01* testing is a reduction in the incidence of serious, and sometimes fatal, cutaneous adverse reactions to carbamazepine and oxcarbazepine by identifying those who are at significant risk and using alternative therapy. The success of *HLA-B*15:02* prospective screening in reducing the rate of SJS/TEN has been demonstrated clinically in a Chinese population.[39]

A potential risk of *HLA-B*15:02* or *HLA-A*31:01* testing is ruling out the use of carbamazepine or oxcarbazepine in patients who may not ever develop a hypersensitivity reaction to the drug. This risk is mitigated by the fact that there are often alternatives to carbamazepine or oxcarbazepine with comparable effectiveness; however, consideration must be given to the risk of cutaneous adverse reactions with other anticonvulsants. For example, it has been demonstrated in an Asian population that an *HLA-B*15:02* screening policy for carbamazepine will not decrease the overall rate of SJS/TEN if other anticonvulsants associated with SJS/TEN (e.g., phenytoin) are used instead of carbamazepine.[40] The risk of phenytoin-associated SJS/TEN is described in more detail in the CPIC guideline for *CYP2C9* and *HLA-B* genotypes and phenytoin dosing.[6] Furthermore, other anticonvulsants may be associated with more unfavorable adverse effect profiles compared to carbamazepine or oxcarbazepine.

Although genotyping is considered reliable when performed in qualified clinical laboratories, laboratory error and sample mix-up is always a distinct possibility. If an *HLA-B*15:02*-negative, Southeast Asian individual who does not carry another B75 serotype of *HLA* develops carbamazepine-induced SJS/TEN, for instance, the *HLA* typing should be repeated to rule out sample or typing error. Genotype results are associated with a patient for a lifetime; as such, a genotyping error could have a broader impact on healthcare should other *HLA-B*15:02* or *HLA-A*31:01* associations be identified in the future.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

If a patient has taken carbamazepine or oxcarbazepine consistently for more than 3 months, it is highly unlikely that a severe cutaneous adverse reaction will occur after that time. As a result, known *HLA-B*15:02* or *HLA-A*31:01* genotypes will be less helpful for treatment-experienced patients compared to treatment-naïve patients. Furthermore, because extensive ethnic admixture has occurred globally and not all carbamazepine- and oxcarbazepine-induced cutaneous adverse reactions can be attributed to *HLA-B*15:02* or *HLA-A*31:01*, clinicians should carefully monitor all patients as standard practice.

SUPPLEMENTARY MATERIAL is linked to the online version of the article at http://www.cpt-journal.com

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CONFLICT OF INTEREST

The authors declare no competing interests for this work.

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REVIEW

Antigen presentation and adaptive immune responses in skin

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Abstract

For the induction of adequate cutaneous immune responses, the antigen presentation and recognition that occur in both the skin and skin-draining lymph nodes are essential. In each process of cutaneous immune responses, several distinct subsets of immune cells, including dendritic cells and T cells, are involved, and they elicit their respective functions in a harmonious manner. For example, in the elicitation phase of cutaneous acquired immunity, immune cells form a specific lymphoid structure named inducible skin-associated lymphoid tissue (iSALT) to facilitate efficient antigen presentation *in situ*. In this short review, we will overview the mechanisms of how antigens are presented and how cutaneous adaptive immune responses are conducted in the skin, especially focusing on contact hypersensitivity, a prototypic adaptive immune response in the skin.

Keywords: contact hypersensitivity, dendritic cells, Langerhans cells, Tc1, Th1

Introduction

Skin is the forefront organ that separates our body from the outer environment and is constantly exposed to various stimuli and antigens (1, 2). To protect the host against the invasion of such foreign antigens, the skin possesses not only a physical barrier (the corneal layer and tight junctions) but also an immunological barrier that is composed of various immune cells residing in the skin. Among the immune cells, antigen-presenting cells (APCs), such as dendritic cells (DCs), play central roles in the induction of adaptive immunity.

When foreign antigens invade the skin they are captured by skin DCs, which subsequently migrate to skin-draining lymph nodes and undergo maturation. Therein, the migrated DCs present the antigens to naive T cells in an antigen-specific manner and promote their differentiation into effector T cells (this process is referred to as 'sensitization'), such as Th1/Tc1, Th2 and Th17 cells. Several kinds of DCs exist in the steady-state skin, and each DC subset has its own characteristics to provoke appropriate immune responses depending on the types of antigens or their routes of entry into the skin. The skin DCs also present the antigens to skin-infiltrated effector T cells *in situ* and activate effector T cells to produce cytokines/chemokines, which lead to antigen-specific immune responses (this process is referred to as 'elicitation').

In this short review, we will first discuss how various immune responses are induced by each skin DC subset in the draining lymph nodes (dLNs) during sensitization. Then, we will introduce recent findings on the mechanisms of antigen presentation by DCs in the skin, i.e. elicitation, mainly focusing on contact hypersensitivity (CHS), a prototypic adaptive immune response in the skin.

Skin DC subsets in mice and humans

In both mice and humans, cutaneous DCs are categorized into two major subtypes in the steady state: Langerhans cells (LCs) in the epidermis, and dermal DCs (dDCs). Although recent ontogenic analyses have revealed that LCs are a subset of tissue-resident macrophages (3, 4), they can be functionally classified as DCs because of their migratory capacity to dLNs and advanced antigen-presentation ability. The dDCs are further divided into at least two subsets in both mice and humans: conventional DC1 (cDC1) and cDC2. In mice, cDC1 cells are also called XCR1$^+$ dDCs or CD103$^+$ dDCs and cDC2 cells are also called CD11b$^+$ dDCs or CD301b$^+$ dDCs. In humans, cDC1 cells are also called CD141$^+$ or BDCA3$^+$ dDCs and cDC2 are also called CD1c$^+$ dDCs. For the detailed ontogeny and surface markers in each dDC subset, see recent reviews by others (3–6).

Each DC subset has its own functional characteristics and induces appropriate immune responses depending on the types and distribution of external antigens intruding into the skin. For example, cDC1 has a superior ability to cross-present viral and self-antigens in the skin (7, 8), whereas cDC2 induces Th2-type immune responses during sensitization with either haptens (9) or protein antigens (10). Although each DC subset has a significant functional diversity, they may play some redundant roles in a context-dependent manner.

Migration of cutaneous DCs to skin-draining lymph nodes

After acquiring antigens in the skin, cutaneous DCs migrate to skin dLNs through dermal lymphatics to present the antigens to naive T cells. The essential chemokine that mediates the migration of LCs from epidermis to dermis is CXCL12 (stromal cell-derived factor; SDF-1) (11). In the dermis, CCL19 and CCL20 mediate the movement of LCs and dDCs to lymphatics and to the paracortex of the skin dLNs (12).

After hapten application, dDCs reach dLNs within 24 h and peak at day 2, whereas LCs reach dLNs much more slowly than dDCs do, peaking at day 4 (13). A recent study using a novel monitoring system for cell migration, in which a photoconvertible protein KiKGR was used for cell labeling, further revealed the detailed kinetics of migration of each cutaneous DC subset (14). This study demonstrated that the migrated LCs in dLNs reached a plateau 4 days after photoconversion in the skin, which was consistent with the previous report. However, migration of cDC2 from skin to dLNs reached a plateau within 1 day after photoconversion, whereas migration of cDC1 reached a plateau 3 days after photoconversion, indicating that cDC2s move faster than cDC1s to dLNs. Such different migration kinetics would probably influence the role of each DC subset during sensitization.

The role of cutaneous DC subsets in the sensitization phase of CHS

CHS is a mouse model of human contact dermatitis, such as that induced in allergies to metals or plants and is regarded as a prototype of Th1/Tc1-type immune responses in the skin (15). Small chemicals called haptens bind to self-proteins and become antigens in CHS. Since haptens are usually small molecules (<500 Daltons), they easily pass through the corneal layer and tight junctions and can theoretically be captured by all subsets of DCs in the skin (Fig. 1). Langerin is expressed on LCs and cDC1s in mice. Extensive studies have been performed to identify the skin DC subset that establishes sensitization in CHS using various DC-depletion systems, such as mice expressing murine Langerin linked to diphtheria toxin receptor (murine Langerin–DTR mice) (16, 17), mice expressing human Langerin linked to diphtheria toxin subunit A (human Langerin–DTA mice) (18) and bone marrow chimera mice expressing murine Langerin–DTR (19). The results show that all subsets of DCs can mediate sensitization in CHS depending on the experimental conditions (15).

Among cutaneous DCs, cDC1 are considered to be the central APCs for the induction of Th1/Tc1 in CHS (17) despite their relatively small number in the skin. LCs also seem to have an ability to induce Tc1/Th1 in CHS, since depletion of LCs leads to impaired Th1/Tc1 responses (16, 20), especially during sensitization with low-dose haptens (21). In addition, human LCs recognize urushiol, an antigen in poison ivy, through CD1a and induce Th17-mediated skin inflammation (22).

However, LCs may also play regulatory roles in the sensitization phase of CHS depending on the context. Using human Langerin–DTA mice (18) or human Langerin–DTR mice (23), depletion of LCs leads to exacerbated CHS responses, indicating that LCs play regulatory roles in certain situations. As a regulatory mechanism, IL-10-mediated inhibition of $CD4^+$ T-cell proliferation has been proposed (24). It has also been reported that LCs play a regulatory role in sensitization with innocuous haptens by tolerizing $CD8^+$ T cells and activating regulatory T cells (Tregs) (25).

Thus, LCs seem to be endowed with functional plasticity according to their surrounding immunological environments. The cDC2 subset can induce Th1/Tc1 responses in CHS, since simultaneous depletion of both LCs and cDC1 abrogates, but does not completely diminish, CHS responses (17, 19). The cDC2 subset is also reported to mediate sensitization in CHS induced by fluorescein isothiocyanate (FITC) plus dibutyl phthalate in a thymic stromal lymphopoietin (TSLP)-dependent manner (10, 26). The current main findings about the role of each DC subset in the sensitization phase of CHS are summarized in Table 1.

The role of cutaneous DC subsets in epicutaneous sensitization with protein antigens

In a physiological situation, the penetration of protein antigens into the skin is blocked by the tight-junction barrier (Fig. 1). In the steady state, LCs position their dendrites upwards, but the dendrites never cross the tight-junction barrier. However, LCs activated by various cytokines or external stimuli elongate their dendrites across this tight-junction barrier and capture protein antigens (27). Therefore, LCs are assumed to be the key APCs for epicutaneous sensitization with protein antigens. In repetitive epicutaneous sensitization with a protein antigen, ovalbumin (OVA), LCs mediate the production of OVA-specific IgE in a TSLP-dependent manner (28). Similarly, LCs induce IgG1 production in a mouse model of staphylococcal scalded skin syndrome (29), suggesting that LCs are important for antigen-specific antibody responses to epicutaneously applied protein antigens.

However, similar to the studies in CHS, regulatory functions of LCs, such as induction of Tregs (30) and $CD4^+$ T-cell anergy (31), have been reported in epicutaneous sensitization with protein antigens. The ability of LCs to induce Tregs has been reported in various conditions, such as ultraviolet irradiation (32), exposure to ionizing irradiation (33) and self-antigen expression on LCs (34) or keratinocytes (35), suggesting that LCs have an ability to induce peripheral tolerance to both endogenous and exogenous protein antigens.

On the other hand, LCs are important to defend against cutaneous microbes, such as *Candida albicans* and *Staphylococcus aureus.* In a mouse model of epicutaneous *C. albicans* infection, Dectin-1 on LCs recognizes the budding yeast form of *C. albicans* and induces Th17 responses

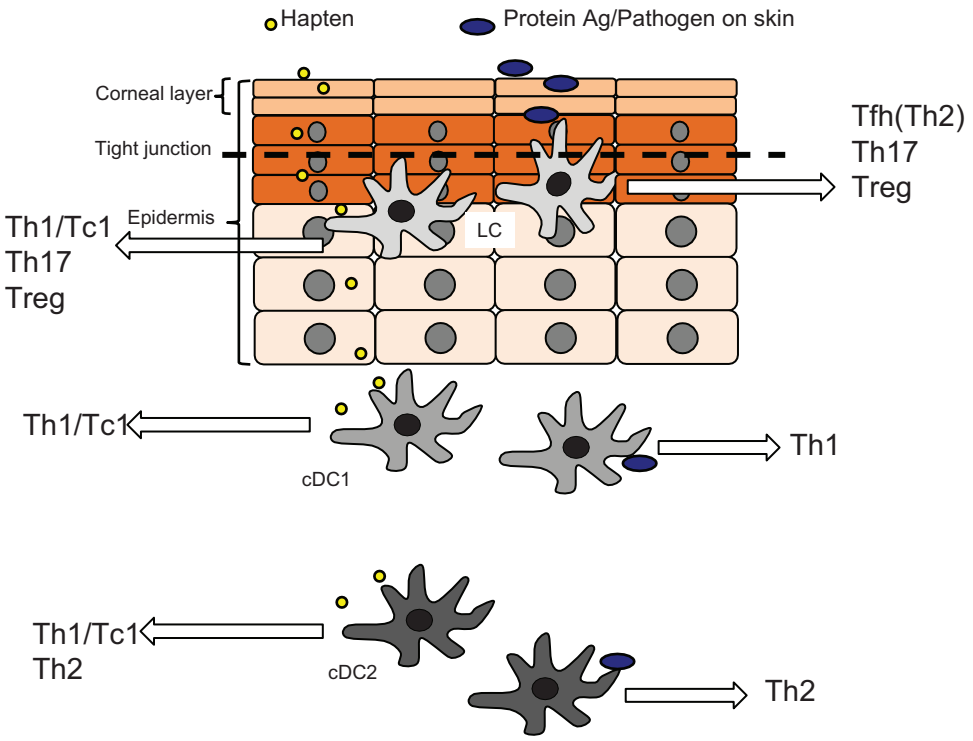

Fig. 1. Possible roles of each cutaneous DC subset in the sensitization with haptens or protein antigens. Each DC subset exerts characteristic but sometimes redundant roles in sensitization with haptens and/or protein antigens. See also Table 1.

Table 1. Possible functions of skin DC subsets during epicutaneous sensitization with haptens and protein antigens

Antigens	APCs	Functions
Haptens (DNFB, oxazolone, FITC, urushiol)	LC	Th1/Tc1 differentiation in CHS (16, 19–21) Tolerization of $CD8^+$ T cells (25), induction of Tregs (25), inhibition of $CD4^+$ T-cell proliferation through IL-10 production (18, 24) Th17 differentiation (22)
	cDC1	Th1/Tc1 differentiation (17, 65)
	cDC2	Th1/Tc1 differentiation (26) Th2 differentiation in CHS induced by FITC plus dibutyl phthalate (10)
Protein antigens (OVA, *C. albicans*, *S. aureus*)	LC	Tc1 anergy (cross-tolerance) in OVA sensitization (66) Th1 tolerance (31) Induction of IgE production in epicutaneous OVA sensitization (28, 29) Induction of IgG1 in a mouse model of Staphylococcal scalded skin syndrome 29 Th17 differentiation in epicutaneous *C. albicans* yeast infection (36, 37), *S. aureus* dysbiosis (39) Induction of Tregs in epicutaneous immunotherapy in OVA-sensitized mice (30) Induction of proliferation of T_{RM} in response to *C. albicans* (67)
	cDC1	Th1 differentiation in epicutaneous infection with *C. albicans* pseudohyphae (37) Tc1 differentiation in OVA sensitization (66) Tc17 response to *S. epidermidis* (38)
	cDC2	Th2 differentiation in subcutaneous OVA/papain immunization (9), Tc17 response to *S. epidermidis* (38)

DNFB, dinitrofluorobenzene.

(36, 37). On the other hand, cDC1 induces Th1 responses to the filamentous form of *C. albicans* in a Dectin-1-independent manner (37). Although cDC1 and cDC2 subsets are not involved in the Th17 differentiation in the *C. albicans* infection model, they mediate Tc17 responses to the skin commensal *S. epidermidis* (38). In mice that lack the protease ADAM17 in keratinocytes, in which the overgrowth of cutaneous *S. aureus* occurs spontaneously, LCs induce the proliferation of Th17 and IL-17-producing γδ T cells in the skin (39).

Thus, each DC subset can exert roles according to the type of infecting pathogen in mice, whereas in epicutaneous OVA sensitization, LCs are mainly involved in the sensitization by exerting both pro-inflammatory and regulatory functions in a context-dependent manner (Table 1).

Elicitation of adaptive immune response in the skin

The antigen presentation and T-cell activation by cutaneous APCs in the elicitation phase of CHS take place in the skin (15), which is in sharp contrast to the situation in the sensitization phase, in which the antigen presentation occurs in the dLNs. The APC subsets involved in the elicitation phase are considered to be different from those in the sensitization phase. In addition, the T-cell subsets that recognize cutaneous antigens are different between these two phases: naive T cells and activated/memory T cells, respectively. It is therefore necessary to discuss the immune mechanisms in the elicitation phase from a different perspective compared with the sensitization phase.

The role of APC subsets in the elicitation phase

The process of antigen presentation in the skin during the elicitation phase is less clear compared with that in the dLNs during the sensitization phase. It remains unclear which APC subsets in the skin play essential roles in this process, but a bone marrow chimeric technique with Langerin–DTR mice has demonstrated that both epidermal LCs and dermal Langerin$^+$ cDC1 are dispensable for the elicitation of CHS in mice (40). On the other hand, the depletion of CD11c$^+$ cutaneous APCs abrogates the elicitation of CHS. CD11c is expressed on all subsets of cutaneous DCs. These results suggest that antigen presentation in the skin is indispensable to elicit cutaneous adaptive immunity and that cutaneous APCs have redundant roles, which indicates the existence of strong compensatory mechanisms.

A recent study shed light on the role of monocyte-derived cells as APCs in the skin (41). Upon inflammation, many monocytes extravasate and are recruited into the skin. These cells express CD11b, Ly6c, CX3CR1 and some of them are CD11c$^+$. We should note that these monocyte-derived cells have several confusing synonyms, including inflammatory monocytes, inflammatory macrophages, inflammatory DCs and, when they enter the epidermis, they are called inflammatory dendritic epidermal cells (IDECs). Intriguingly, monocyte-derived cells cluster around hair follicles during inflammation. An *in vivo* imaging study demonstrated that CX3CR1$^+$ monocyte-derived cells formed clusters around hair follicles within a day in a CCR2-dependent manner in the elicitation phase (41). Although the immunological function of these clusters remains elusive, the activation of T cells and their production of interferon-γ (IFN-γ) were facilitated by the cluster formation (41), suggesting that the antigen presentation in the skin under inflammatory conditions depends, at least in part, on activated monocyte-derived cells.

T-cell recruitment during cutaneous inflammation

Upon cutaneous inflammation, numerous T cells as well as neutrophils and monocytes are recruited to the skin. Most of these T cells are effector T cells and they require presentation of cognate antigen–MHC complexes on the surface of the APCs or target cells before effector functions are initiated. During the interstitial migration, effector T cells exhibit a 'stop and go' behavior that is reminiscent of naive T cells in the LNs (42, 43). This behavior might provide an effective strategy for screening large regions of the tissue, because the effector T cells can reorient their axis before they recommence scanning after a short migratory run.

Engagement of the T-cell antigen-receptor (TCR) with the cognate antigen–MHC complex on the APCs or target cells represents a stop-signal for migrating T cells. An *in vivo* imaging study on the elicitation phase of CHS demonstrated that effector T cells stopped migration only in the presence of a cognate antigen–MHC complex (44, 45). Similar findings were also reported in a delayed-type hypersensitivity model, in which T cells stop migration only in the presence of cognate peptide antigen (42). The stable interaction between CD4$^+$ T cell and APCs results in T-cell-mediated production and release of inflammatory cytokines such as IFN-γ, and IFN-γ gradients may reach up to 80 μm away from the interaction site between the T cells and the APCs (46). On the other hand, cytotoxic effector CD8$^+$ T cells induce target cell apoptosis by various means, including the release of cytokines and cytotoxic mediators such as perforins and granzymes.

Involvement of resident memory T cells during cutaneous inflammation

Recent studies have demonstrated that some effector T cells are recruited to the skin during cutaneous inflammation but never return to the circulation (47). This non-circulating memory T-cell subset comprises tissue-resident memory T cells (T_{RM}). The T_{RM} have been identified not only in the skin but also in the gut, lung, brain and female reproductive tract (48–50), although the longevity of T_{RM} greatly differs between tissues. For example, skin T_{RM} in mice persist for over a year (51), whereas lung T_{RM} are maintained for only a few months (52).

Of note, the distribution and migration patterns of CD4$^+$ and CD8$^+$ T_{RM} are different. In a herpes simplex virus (HSV) infection model, antigen-specific CD4$^+$ T_{RM} re-distribute within the dermis, whereas CD8$^+$ T_{RM} localize to the epidermis after pathogen clearance (48). In addition, CD4$^+$ T_{RM} have amoeboid morphology and actively migrate throughout the dermis, whereas CD8$^+$ T_{RM} show a dendritic morphology and are almost sessile in the epidermis. Until recently, it remained unclear whether CD4$^+$ T_{RM} are actually distinguishable from circulating effector memory T cells since a proportion of the memory CD4$^+$ T cells found within the dermis appear to be capable of entering the circulation.

A recent study has demonstrated that CD4$^+$ T cells form clusters in the dermis, which are referred to as memory lymphocyte clusters (MLCs), during vaginal HSV2 infection (53). Using parabiotic mice, it has been demonstrated that CD4$^+$ T_{RM} in MLCs are sequestered from circulating memory T-cell subsets and that MLCs are maintained for at least 3 months in the absence of any local inflammation or antigens.

Accumulated evidence suggests that the rapid control of antigen invasion at peripheral sites requires the presence of T_{RM}. In a viral infection model, T_{RM} respond to antigens and produce pro-inflammatory cytokines such as IFN-γ within hours, whereas circulating memory T cells re-enter the infected site after 2 days and do not produce IFN-γ until 5 days after the challenge (53). T_{RM}-derived cytokines activate local innate

immunity by driving antiviral/antibacterial genes, DC maturation, NK cell activation and vascular cell adhesion molecule 1 (VCAM-1) expression on blood endothelium (54, 55).

The involvement of T_{RM} has also been reported in the context of mouse CHS and human contact dermatitis. Application of a hapten to mouse skin induces T_{RM}, which determines the rapid-onset and high magnitude of CHS responses after repeated challenges with the hapten, whereas circulating memory T cells induce slower and weaker responses (56). In humans, the number of some particular T-cell clones increased in hapten-challenged skin after sensitization and elicitation with the hapten (56), suggesting that T_{RM} are also involved in the development of human contact dermatitis. Therefore, T_{RM} seem to function as antigen-specific effectors and provide robust site-specific immunity.

Formation of iSALT during cutaneous inflammation

We previously reported that a leukocyte-clustering structure, named inducible skin-associated lymphoid tissue (iSALT), is formed in the dermis during cutaneous acquired immune responses (Fig. 2) (1). The iSALT does not exist in the steady state, but upon various inflammatory stimuli including haptens and infection, they transiently appear at the perivascular area, especially around post-capillary venules. The iSALT is composed of various immune cells, including perivascular macrophages, dDCs and T cells. After hapten application, dDCs exhibit cluster formation around post-capillary venules within 6 h. IL-1α produced by keratinocytes upon external insults stimulates perivascular macrophages, which in turn produce CXCL2 and recruit dDCs to form the clusters.

The iSALT is considered to be an essential structure for efficient antigen presentation in the skin, because the blockade of CXCL2 or IL-1 receptor signaling impairs leukocyte-cluster formation and subsequent effector T-cell activation. Similar lymphoid structures in the peripheral tissues, which are called tertiary lymphoid structures, are also found in other non-lymphoid tissues such as the lung and gut under some pathological conditions such as infection, chronic inflammation or cancer formation (57). In the lung, for example, leukocyte clusters called inducible bronchus-associated lymphoid tissue (iBALT) are formed after pulmonary inflammation or infection (58). Unlike iSALT, iBALT is composed of T cells, DCs and B cells, and can prime B-cell activation. Therefore, iBALT should mediate both T-cell-mediated and antibody-mediated immune responses.

It still remains unclear whether iSALT is formed in human skin. However, the potential function of perivascular macrophages to present antigens to T cells *in situ* in human dermis has been proposed, the structure of which was referred to as a dermal microvascular unit (59). In allergic contact dermatitis, histological analysis demonstrated that clusters of DCs with T cells are found in the perivascular area and that epidermal edema and clinical vesicle formation are often found in the epidermis above the clusters, which suggests that the activation of T cells occurs in the clusters (40). Clusters of DCs with T cells in the dermis have also been reported in the lesions in the skin of patients with psoriasis (60), secondary syphilis infection (61), cutaneous lupus erythematosus (62), Kimura's disease (63) and melanoma (64). Although the functional significance of the leukocyte clusters in the skin remains unclear in humans, these structures may play important roles in the promotion or regulation of disease development.

Conclusion

The skin is the first line of defense against external stimuli and threats or dangers and harbors sophisticated immune mechanisms to eliminate antigens that have invaded the skin.

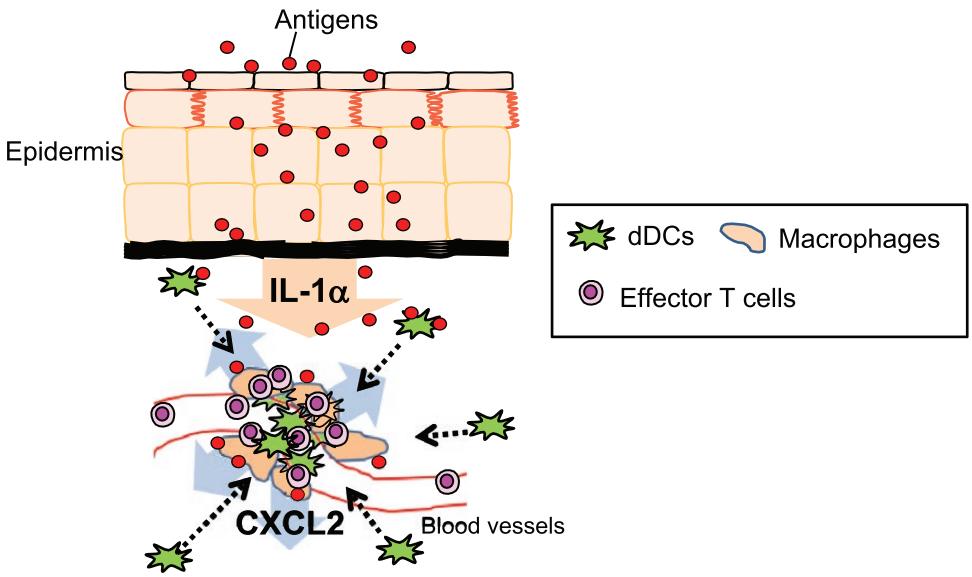

Fig. 2. Schema of iSALT formation during the elicitation phase of CHS. Perivascular macrophages produce CXCL2 to form clusters of dDCs and effector T cells. This type of cluster, which is called an iSALT, may function as an efficient antigen-presentation site in the skin to facilitate the induction of adaptive immune reactions.

Various immune responses are elicited in response to different types of antigens such as haptens, proteins, bacteria and viruses. Recent novel experimental techniques such as intravital imaging microscopy, multiparametric flow cytometry and new murine reporter strains have allowed researchers to dig deeper into the functions of cutaneous immune cells. The continued efforts to unravel the complexity of cutaneous adaptive immune responses will certainly provide novel insights and therapeutic targets for inflammatory skin diseases.

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Differential expression of alarmins: IL-33 as a candidate marker for early diagnosis of toxic epidermal necrolysis

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Clinical Implications

- Serum level of IL-33, which might be released from epidermal keratinocytes, was elevated in patients with toxic epidermal necrolysis (TEN) in the early stage. Serum level of IL-33 might be useful for the early diagnosis of TEN.

TO THE EDITOR:

IL-33 and high mobility group box-1 protein (HMGB1) are known as alarmins and initiate rapid innate immune responses when released from necrotic cells.[1,2] Soluble ST2 (sST2) acts as a decoy receptor for IL-33 and reduces the effect of T_H2-mediated responses.[3] Several biomarkers, such as granulysin,[4] FasL,[5] and HMGB1,[6] have been reported to be useful in diagnosing Stevens Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in the early stage but IL-33/sST2 have not been reported. We compared their serum levels with those of HMGB1 and examined the histopathological localization of IL-33 and HMGB1.

Nineteen adult patients (9 men, 10 women; 61.8 ± 17.4 years old) and 14 healthy controls (HCs; 6 men, 8 women; 56.4 ± 16.1 years old) were enrolled in the study. Of the patients, 4 had TEN, 4 had SJS, 3 had drug-induced hypersensitivity syndrome/drug reaction with eosinophilia systemic symptoms, and 8 had other types of drug eruptions. Day 0 in patients with SJS/TEN was defined as the day when mucocutaneous involvements occurred. The early and late stages were defined as days 0 to 3 and days 4 to 14, respectively. All subjects provided written consent, and the protocols of this study were approved by the Ethical Committee of Jichi Medical University Graduate School of Medicine and Kyoto University Graduate School of Medicine. The serum levels of IL-33, sST2, and HMGB1 were evaluated using an IL-33 ELISA kit (R&D Systems, Minneapolis, Minn), sST2 ELISA kit (MBL, Woburn, Mass), and HMGB1 ELISA

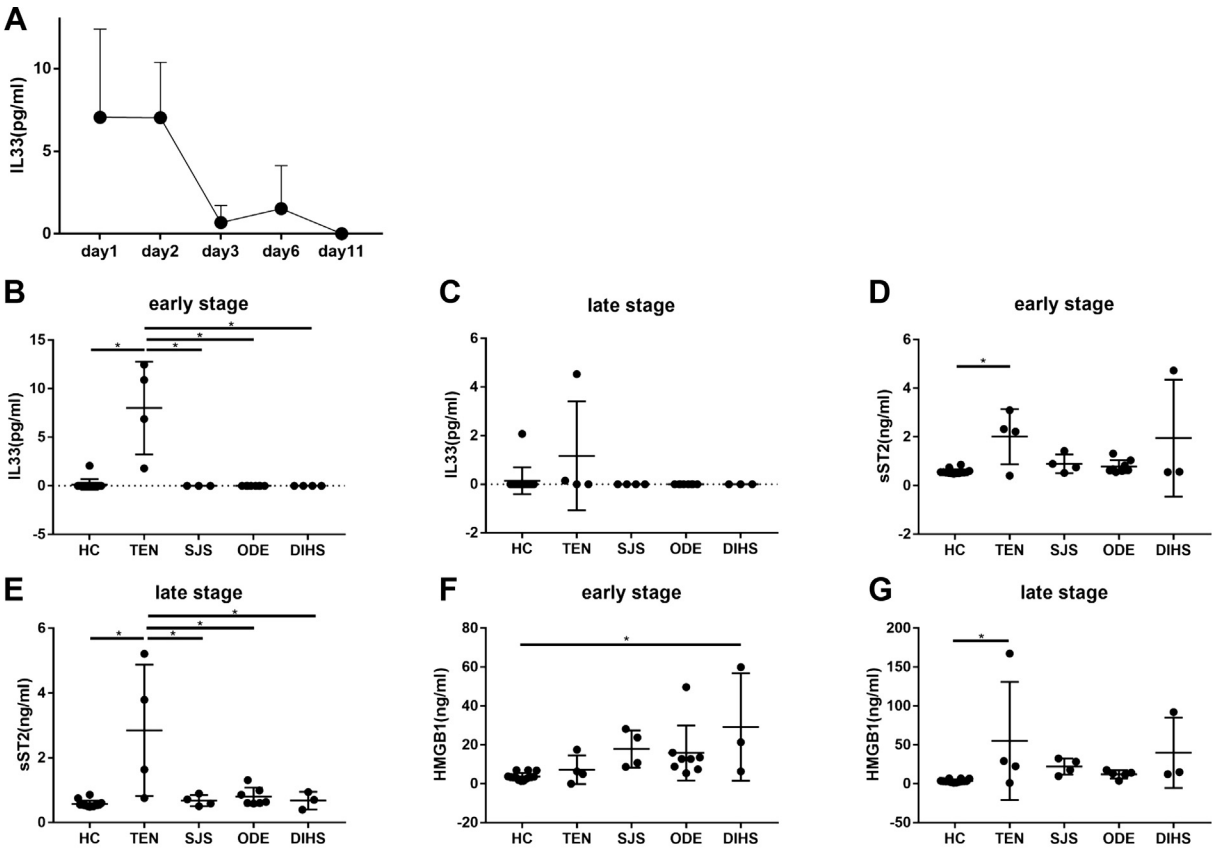

FIGURE 1. A, Average serum IL-33 level over time in patients with TEN. Serum levels of (**B**) IL-33, (**D**) sST2, and (**F**) HMGB1, in the early stage, and (**C**) IL-33, (**E**) sST2, and (**G**) HMGB1, in the late stage. One-way ANOVA with Tukey multiple comparison test was used to compare serum levels. *DIHS*, drug-induced hypersensitivity syndrome; *ODE*, other types of drug eruptions.

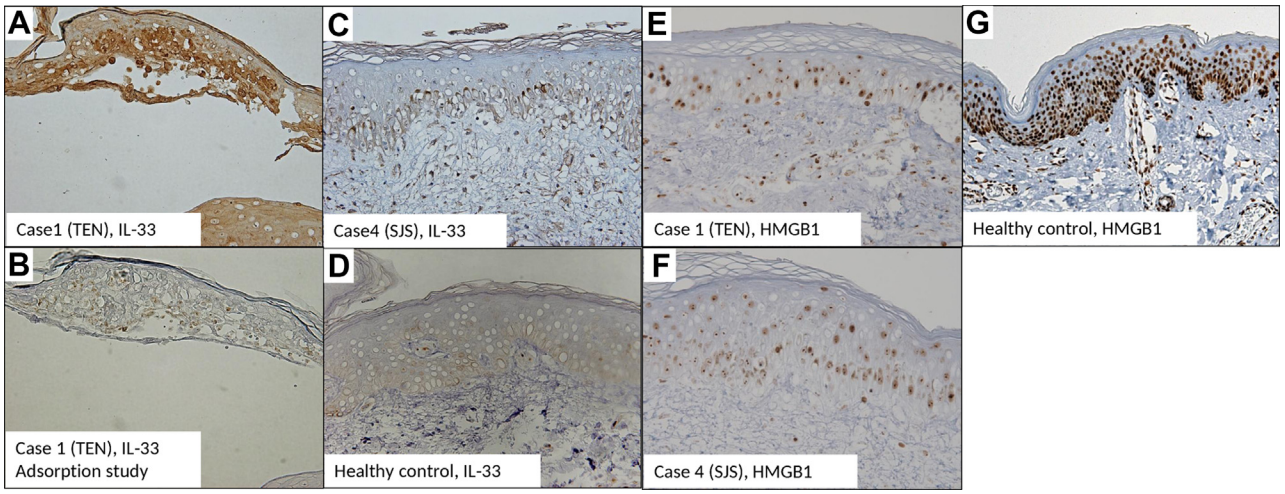

FIGURE 2. Immunohistochemical analysis of (**A**) IL-33 in case 1 (patient with TEN) (400×), (**B**) absorption study of IL-33 in case 1 (400×), (**C**) IL-33 in case 4 (patient with SJS) (400×), (**D**) IL-33 in the healthy control (400×), (**E**) HMGB1 in case 1 (400×), (**F**) HMGB1 in case 4 (400×), and (**G**) HMGB1 in the healthy control (400×).

kit (Shino-Test Co., Tokyo, Japan), according to the manufacturers' protocols.

We performed immunohistochemical staining using the avidin-biotin-horseradish peroxidase method with mAbs to human IL-33 (mouse IgG1κ, Nessy-1; Enzo Life Sciences, Farmingdale, NY) and human HMGB1 (rabbit IgG, EPR3507; Abcam, Cambridge, Mass). To confirm the specificity of staining with anti–IL-33 antibody, we performed an adsorption study using a recombinant human IL-33 N-terminal peptide (*Escherichia coli*–derived, Ser112-Thr270; R&D Systems). The IL-33 mAb was adsorbed with recombinant human IL-33 peptide for 1 hour at 37°C.

The serum level of IL-33 in the early stage in patients with TEN was 8.00 ± 4.76 pg/mL, which gradually decreased during their clinical course (Figure 1, *A* and *C*), whereas that in other patients as well as 13 HCs was not detected except in 1 HC (Figure 1, *B*). The serum level of sST2 in patients with TEN was significantly elevated compared with that in HCs but was not elevated compared with that in other patients in the early stage (Figure 1, *D*). In contrast, the serum level of sST2 was significantly elevated in the late stage compared with that in other patients and HCs (Figure 1, *E*). The serum level of HMGB1 in patients with TEN was not significantly elevated in the early or late stage, compared with that in other patients (Figure 1, *F* and *G*). IL-33 staining was positive in the nucleus and cytoplasm of keratinocytes in patients with TEN, which was abolished in the absorption study (Figure 2, *A* and *B*). However, in other types of drug eruption and HCs, IL-33 staining was positive in only a small number of nucleus of keratinocytes (Figure 2, *C* and *D*). HMGB1 staining was positive in the nucleus of keratinocytes in all patients (Figure 2, *E* and *F*), whereas a greater number of positive cells were observed in HCs (Figure 2, *G*).

We demonstrated that, in patients with TEN, the serum level of IL-33 was elevated in the early stage and IL-33 staining was positive in the nucleus and cytoplasm of keratinocytes, whereas IL-33 is typically localized in the nuclei of keratinocytes in the steady states and IL-33 signal is generally low with immunohistochemical analysis.[7] In the late stage, the serum level of sST2 was elevated only in patients with TEN, and this result corresponds to the action of sST2 as a decoy receptor for IL-33. TEN and SJS are thought to be due to the same pathogenesis; however, serum level of IL-33 was not detected in patients with SJS in our system. We assume that the elevation of serum level of IL-33 depends on the area of epidermal necrosis. In contrast, serum level of HMGB1 was not elevated in the early stage in patients with TEN, and HMGB1 was stained with fewer keratinocytes than in HCs. These results suggest that HMGB1 expression might vary on a case-to-case basis, according to the previous report.[6] Collectively, the serum level of IL-33 may be a good marker of the early stage of TEN; however, this study included only a small number of patients and a larger sample size would be needed in future studies.

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CORRESPONDENCE

Improvement of erosive pustular dermatosis of the scalp following discontinuation of chemotherapy with afatinib

Erosive pustular dermatosis of the scalp (EPDS) is an idiopathic pustulosis that affects the scalp of the elderly. The onset of EPDS is often preceded by chemical or mechanical trauma such as sun damage, surgery, radiation, herpes zoster, and topical agents including tretinoin, imiquimod, latanoprost, ingenol mebutate, and minoxidil [1].

Here, we present a case of EPDS preceded by herpes zoster, which promptly resolved after the discontinuation of afatinib, an epidermal growth factor receptor (EGFR) inhibitor (EGFR-I) that the patient had been receiving for the treatment of lung cancer.

A 73-year-old Japanese woman with non-small-cell lung carcinoma and multiple metastases was initially treated with whole-brain radiotherapy without notable adverse effects. Six months later, she received four courses of a combination therapy consisting of carboplatin, pemetrexed, and bevacizumab, followed by four additional courses of pemetrexed, with no effect. She was switched to oral afatinib at 20 mg/day on Day 0. On Day 47, she developed herpes zoster involving the right ophthalmic nerve dermatome, and was referred to our department (*figure 1A*). Acyclovir for seven days was effective and she was discharged on Day 59. On Day 119, she revisited us complaining of a folliculitis-like eruption without comedos and thick crusts on the area previously afflicted by zoster (*figure 1B*). The lesions were refractory to topical steroids. Neither bacterial nor fungal infection was detected in the lesions, except for methicillin-sensitive *Staphylococcus aureus* which we regarded as colonization since topical and oral antibiotics exerted no effect. A punch skin biopsy specimen on Day 263 showed a dense infiltration of neutrophils, lymphocytes, and plasma cells (*figure 1E, F*). The hair follicles were destroyed. Immunohistochemistry ruled out continuous herpes zoster infection (data not shown). Neurological examination did not reveal perception defects, excluding herpes zoster-induced trigeminal trophic syndrome. Considering the course of the disease, we diagnosed the patient with EPDS. On Day 363, afatinib was discontinued due to its inefficacy. Within a few months, the pustules and erythema of the scalp improved and crusts disappeared, leaving scarring alopecia (*figure 1D*).

EPDS is diagnosed by excluding other pustular conditions. It is difficult to rule out EGFR-I-induced eruption, which resembles EPDS [2-4]. However, in our patient, the lesions were limited to the right ophthalmic nerve dermatome,

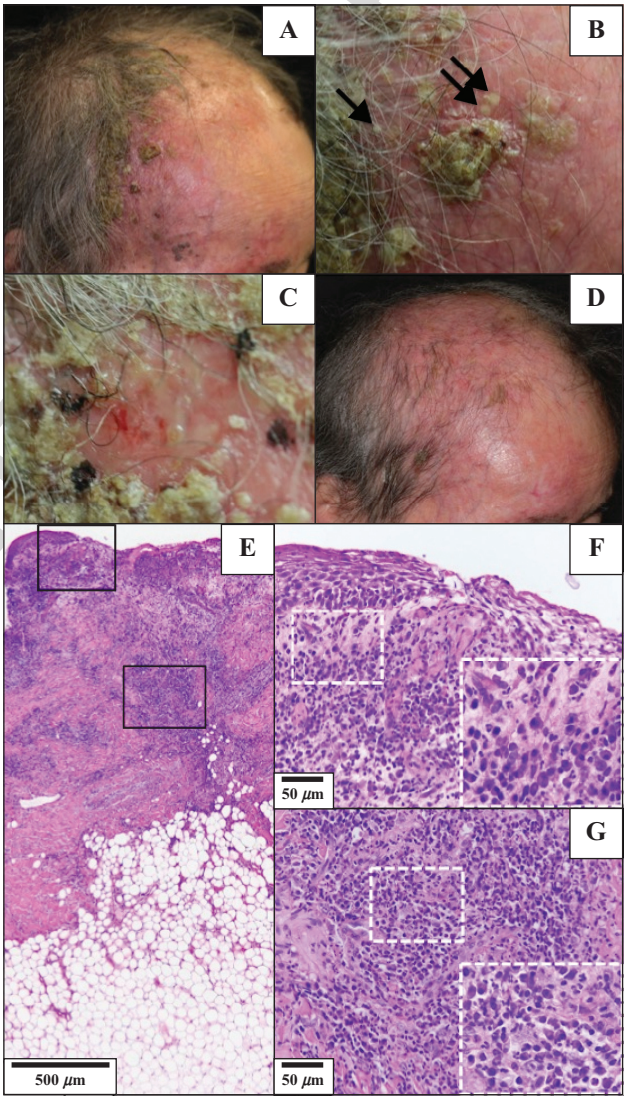

Figure 1. A) Erythema and thick crusts on the area once affected by herpes zoster. **B**) The thick crust is fringed by pustules (arrows) and erythema. **C**) Erosion under the crust where the biopsy was performed. **D**) Three months after the withdrawal of afatinib. **E**) Histopathology of the lesion shows an epidermal erosion and dense infiltration in the whole dermis, sparing the subcutaneous fat (hematoxylin-eosin; ×5). **F**) Infiltration with numerous plasma and lymphoid cells, intermingled with neutrophils (hematoxylin-eosin; ×40). **G**) Varicella-zoster virus antigen was not detected by immunohistochemistry (×40).

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where herpes zoster had developed two months previously. Furthermore, neither very thick crusts nor scarring alopecia are common in eruptions due to EGFR-I. Based on these clinical, histological, and microbial findings, we diagnosed the case as EPDS.

The aetiology and molecular pathogenesis of EPDS are unknown. Trauma may induce autoimmunity towards hair follicles, as supported by the efficacy of topical immunosuppressants [5]. However, no abnormal immune function has ever been demonstrated in EPDS [1]. Delayed wound healing has also been suggested to cause EPDS because actinic damage and atrophy of the scalp, both risk factors for EPDS, can impair healing of the skin [6].

In our case, the discontinuation of afatinib improved the scalp lesions. We therefore speculate that EGFR-I may impair skin wound healing, resulting in the persistence of EPDS. The fact that EGFR stimulates epidermal/dermal regeneration and that amphiregulin (a ligand for EGFR) mediates cutaneous healing by regulatory T cells supports this idea [7, 8]. Reports on EPDS-like eruptions under treatment with EGFR-I (such as gefitinib or cetuximab) further corroborate the role of EGFR in the onset of EPDS [9, 10]. Two types of eruptions associated with EGFR-I exist; acneiform eruptions (or erythematous papulopustular eruptions) and scarring folliculitis [2-4]. In our patient, we found scarring folliculitis but no comedo formation in the affected area. However, the distinction between EPDS and EGFR-I-associated eruptions remains subtle.

In summary, we describe a patient with EPDS succeeding herpes zoster infection, which was dramatically improved by the discontinuation of concurrent afatinib. Our observation suggests an involvement of the EGFR pathway in the onset and development of EPDS. However, the improvement of the eruption after discontinuation of EGFR-I afatinib and the histopathological similarity between EPDS and EGFRI-associated eruption argue in favour of the diagnosis of EPDS in our case. Observation of additional cases and histological studies will help to better distinguish EPDS from acneiform eruptions due to EGFR-I. ■

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CORRESPONDENCE

Contact leukoderma induced by rotigotine transdermal patch (Neupro®)

Contact chemical leukoderma is an acquired depigmentation or hypopigmentation caused by repeated exposure to a specific agent which is toxic to epidermal melanocytes in genetically-susceptible persons. Three of the following four criteria should be present for diagnosis: (1) acquired vitiligo-like depigmented lesion(s); (2) a history of repeated exposure to a specific chemical compound; (3) patterned

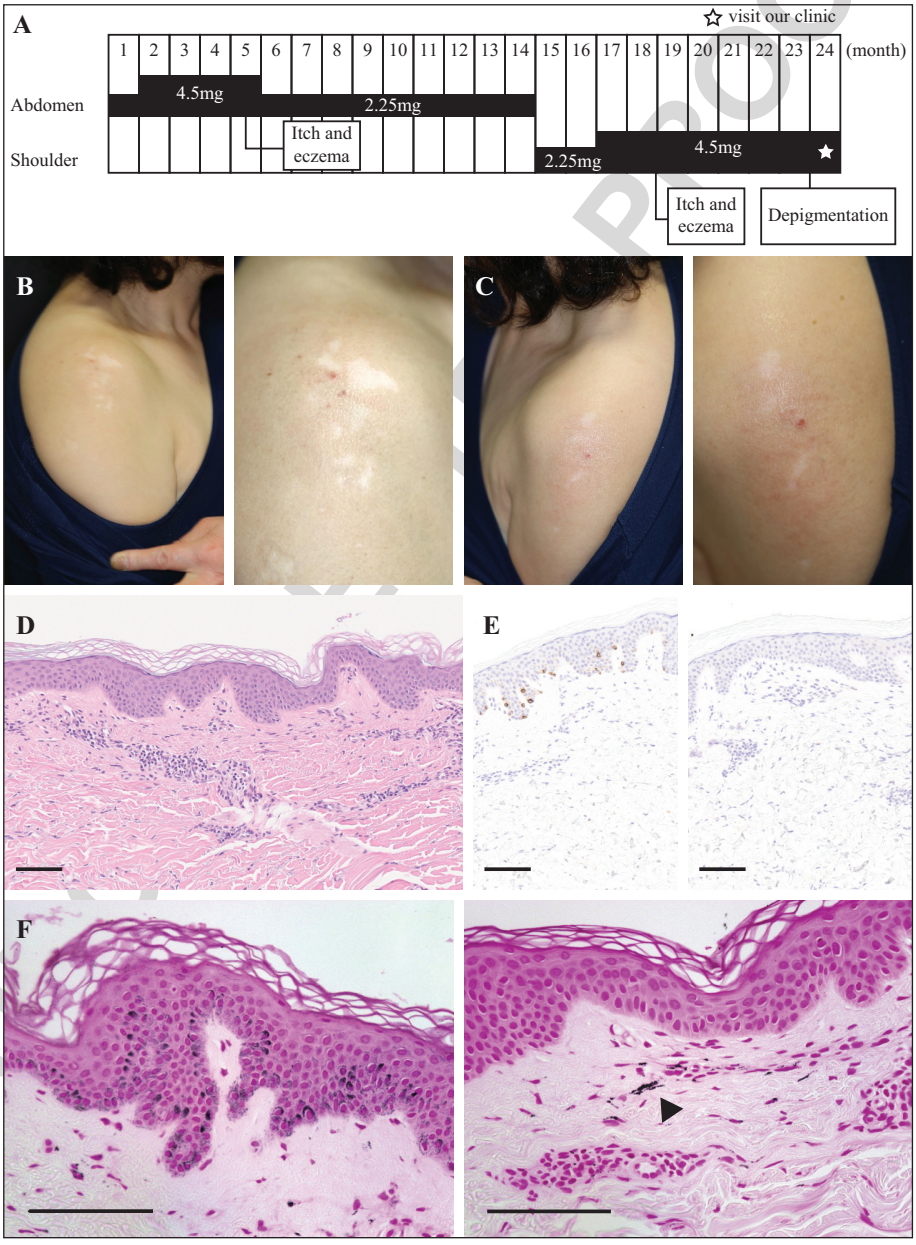

Figure 1. **A**) The timeline of drug dosage and clinical manifestations. **B**, **C**) Depigmented lesions on the shoulders. **D**) Histological aspect of haematoxylin-eosin stained sections of a depigmented lesion. **E**) Immunohistochemical staining with Melan-A antibody of normal-coloured skin (left panel) and the depigmented lesion (right panel). **F**) Fontana-Masson staining of normal-coloured skin (left panel) and the depigmented lesion (right panel); the arrowhead denotes melanin granules in the dermis (scale bar=100 μm).

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vitiligo-like macules conforming to site of exposure; and (4) confetti macules [1]. Here, we report a rare case of contact leukoderma associated with treatment with the dopamine receptor agonist, rotigotine.

A 56-year-old Japanese woman suffering from restless legs syndrome was treated with rotigotine transdermal patch (Neupro®). The treatment was commenced with 2.25 mg/patch applied on the abdomen; the dosage was rapidly increased to 4.5 mg/patch (*figure 1A*). Five months later, she experienced mild pruritus and the drug dosage was decreased to 2.25 mg/patch. During the fourteenth month of treatment, the application site was changed to the shoulders. Although she experienced an uncomfortable sensation on her shoulders, she continued to apply the patches and increased the dosage to 4.5 mg/patch because of the exacerbation of the primary disease. Ten months after having started to apply the patch on her shoulders, she noticed white macules at the same location (*figures 1B, C*). She had no other pre-existing diseases and was not taking other medications.

Well-circumscribed depigmented areas (1-2 cm in diameter) were clustered within the patch application areas, and some eczematous papules and scratch scars were present on a background of slight erythema. Histological examination of haematoxylin-eosin stained sections revealed a perivascular lymphocyte infiltration with mild vacuolar degeneration in the epidermis, suggesting an eczematous reaction (*figure 1D*). Melan-A+ epidermal melanocytes were abundant in normal-coloured skin (*figure 1E; left panel*), but completely absent from the depigmented lesions (*figure 1E; right panel*). Upon Fontana-Masson staining, a few melanin granules were observed in the dermis of the depigmented lesion, suggesting the presence of melanophages (*figure 1F*).

We speculated that the depigmentation was associated with the rotigotine patches because the depigmented lesions did not spread beyond the areas of patch application. Since the patient desired to continue using the patches, we instructed her to change application sites frequently and prescribed topical steroid ointments. Although the irritation and the eczematous papules decreased, no re-pigmentation has been observed so far, consistent with the histological observation that epidermal melanocytes were completely destroyed in the patch application area.

Rotigotine is a D1/D2/D3 dopamine agonist, and the patch is approved for the treatment of Parkinson's disease and restless legs syndrome [2]. Our literature search revealed only one case report of rotigotine patch-induced leukoderma as an application site reaction [3]. Therefore, leukoderma appears to be a very rare side effect of rotigotine patch, which occurs in some patients.

The mechanism responsible for rotigotine inducing leukoderma is unknown. Since melanocytes and neurons share an embryological origin from the neural crest and also share melanin and melanin-synthesizing enzymes, it is possible that drugs which modulate neural functions can cause melanocytic disorders. Indeed, chemical leukoderma is also reported in patients with attention-deficit hyperactivity disorder treated with methylphenidate transdermal patch [4]. Wick *et al.* showed that L-dopa exerts direct cytotoxicity on melanoma cells *in vitro* [5]. Based on these reports, one possibility for the pathomechanism of the rotigotine-induced leukoderma is direct cytotoxicity to the melanocytes. Another possibility is the involvement of inflammation, since irritation and pruritus preceded the development of leukoderma in both our patient and the previously reported patient [3]. Histological findings, such as vacuolar changes in the epidermis and melanophages in the dermis, also support this hypothesis. Compared with the previous case [3], in our patient, the skin inflammation was less severe and the leukoderma appeared late, although the dosage was comparable in these cases. The reason for this is unknown, but could reflect genetic susceptibility to this drug. We could not clarify which of these two events, melanocyte apoptosis or inflammation, is the initial cause in our patient.

In summary, we report a case of contact leukoderma associated with rotigotine patch. Further cases and basic research are necessary to elucidate the mechanism of this unusual local side effect. ■

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LETTER TO THE EDITOR

Nail pitting and splinter hemorrhage possibly induced by zolpidem

Dear Editor,

Nail abnormalities can arise in conjunction with or as a result of systemic pathologies.[1] Among these abnormalities, nail pitting has been associated with cutaneous or other systemic diseases and drug intake.[1] Because nail symptoms tend to be overlooked, or because pre-existing systemic diseases often mask their clinical signs such as nail pitting, nail symptoms associated with the intake of specific drugs have not attracted the attention of many clinicians. Here, we report a case of nail pitting and splinter hemorrhage suspected to be associated with zolpidem intake.

A 20-year-old woman noticed pitting, splinter hemorrhage and yellowish changes on all of the nails on her hands and feet (Fig. 1a). She did not have any past medical history including eczema, lichen planus, alopecia areata or psoriasis. She did not have a history of nail biting. She did not claim any skin rash or inflammation around the nails during the observation period. Microscopic observation with 10% potassium hydroxide revealed no fungal infections in the nails. She had no other systemic symptoms besides occasional headaches and insomnia, for which she had been taking loxoprofen (60 mg) and zolpidem (5 mg) chronically. She had changed her medication from zopiclone to zolpidem 10 months before she attended our clinic. She noticed nail abnormalities 4 months after starting zolpidem (Fig. 1a,d). However, zolpidem was changed to rilmazafone by her psychiatrist after 10 months because it was not effective (Fig. 1d). Her nail changes gradually ameliorated without treatment, and her nail symptoms had almost cleared 9 months after discontinuing zolpidem (Fig. 1b,c).

Nail pitting is reported to develop in cases of cutaneous, endocrine, hematological, infectious and rheumatological diseases; renal failures; and drug intake.[1] Our patient had no history of these systemic diseases. Because she was taking loxoprofen and zolpidem when she developed the nail

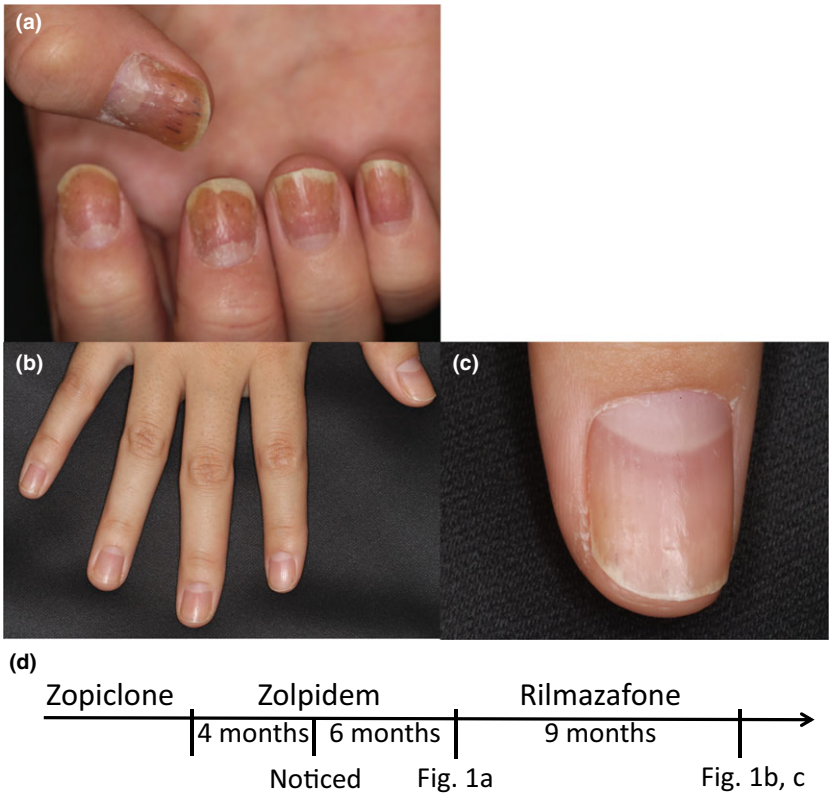

Figure 1. (a) Clinical picture at her first visit. Nail pitting was observed across all fingernails. Splinter hemorrhages were observed on the thumbnail. (b, c) Clinical picture taken 9 months after the first visit. Nail pitting and splinter hemorrhages were ameliorated. (d) A scheme of the clinical course of the case.

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abnormalities and her nail pitting improved after discontinuing zolpidem, we suspected that zolpidem was the culprit drug.

Past reports have shown that the concentration of zolpidem at the distal edge of the fingernail reaches its peak 3 months after starting zolpidem, which is compatible with the average speed of human nail growth.[2,3] This indicates that it takes approximately 3 months for oral zolpidem to affect the nail plate. These observations are consistent with the timing when our patient first noticed her nail abnormalities after starting oral zolpidem (Fig. 1d).

Nail pitting and splinter hemorrhage develop in response to inflammation of the nail matrix.[1,4] A previous report showed that physical contact with zolpidem over a long period of time can induce local hyperemia and cell destruction.[5] This may indicate that accumulation of zolpidem in the nail plate and chronic exposure to the medication can possibly induce local toxicity and affect the nail bed capillaries, inducing nail pitting and splinter hemorrhage. This accumulation might have prolonged our patient's symptoms even after discontinuing zolpidem. Although we cannot exclude other possibilities such as contact dermatitis or drug interactions, oral zolpidem may carry a potential risk of developing nail abnormalities.

CONFLICT OF INTEREST: None declared.

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LETTERS TO THE EDITOR

Three cases of facial erythema with dryness and pruritus in psoriasis patients during treatment with IL-17 inhibitors

Editor

The development of psoriasis, a common, chronic inflammatory skin disease, significantly depends on interleukin (IL)-17.[1] Anti-IL-17 inhibitors, such as ixekizumab (anti-IL-17A antibody), secukinumab (anti-IL-17A antibody) and brodalumab (anti-IL-17 receptor A (IL-17RA) antibody), exert excellent therapeutic effects on psoriasis.[2] On the other hand, as IL-17 is an important cytokine for preventing fungal infections, skin side-effects such as cutaneous candidiasis are occasionally seen during the administration of IL-17 inhibitors.[3] Little is known, however, about the other skin side-effects of IL-17 inhibitors. Here, we report three cases of facial erythema with dryness and pruritus in patients with psoriasis during treatment with IL-17 inhibitors.

Case 1. A 70-year-old man with psoriatic arthritis over 20 years ago was started on ixekizumab. After the start of ixekizumab, psoriatic lesions such as erythema and desquamation of the soles significantly improved. Six weeks after the ixekizumab was started, however, pruritic erythema with dryness appeared on his face (Fig. 1a). The facial lesions improved with a heparinoid ointment.

Case 2. A 58-year-old woman who had been diagnosed with psoriatic arthritis seven years ago was started on brodalumab. Two months after the brodalumab treatment, her psoriatic lesions had drastically improved, but facial erythema with dryness and pruritus appeared eight weeks after the brodalumab was started (Fig. 1b). The facial lesions were treated with petrolatum and hydrocortisone butyrate and have been well controlled.

Case 3. A 49-year-old man who had been diagnosed with psoriasis vulgaris four years ago was started on secukinumab. After the secukinumab treatment, the psoriatic lesions gradually improved; however, three weeks after the start of secukinumab, facial erythema with dryness and pruritus appeared (Fig. 1c). The facial lesions improved with petrolatum.

We have experienced three cases of facial erythema with dryness and pruritus during psoriasis treatment with IL-17 inhibitors. As different kinds of IL-17 inhibitors provoked similar symptoms, it is likely that regulation of IL-17 signalling itself is involved in the development of the facial erythema.

Although the means by which inhibition of IL-17 signalling caused such symptoms remains unknown, IL-17 may have protective roles in skin barrier functions as reported in a recent study using a mouse model of atopic dermatitis,[4] and its inhibition may therefore cause dysfunction of skin barriers, leading to the development of facial erythema with dryness and pruritus. Inhibition of IL-17 may also shift the systemic immune response to T-helper (Th)2 type immune responses, which may cause skin barrier dysfunction and pruritus.[5,6] Indeed, elevated expressions of Th2-cell-associated proteins such as IgE and eotaxin in the skin have been reported in a clinical study of patients with psoriasis treated with secukinumab.[7]

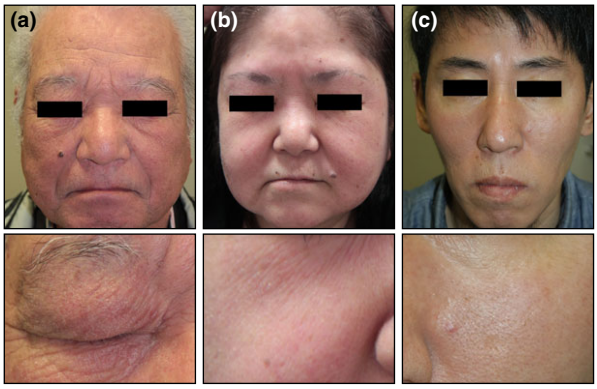

Figure 1 Clinical pictures of facial erythema (a, b, c) Facial erythema with dryness and pruritus six weeks after the start of ixekizumab (a), eight weeks after the start of brodalumab (b), three weeks after the start of secukinumab (c). Lower panels show close-up views of the erythema.

Although our observations are only from limited cases, these cases may shed new lights on the roles of IL-17 in the maintenance of skin homeostasis. In addition, clinicians should be aware of the possible occurrence of facial erythema with dryness and pruritus during the treatment with IL-17 inhibitors.

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Time required for a standard sunscreen to become effective following application: a UV photography study

Editor

Sunscreens are recommended that it should be applied generously (2 mg/cm^2) half an hour before exposure and reapplied every 2 h.[1,2] It is not, however, always easy to apply in normal life (e.g. children doing outdoor activities at school or beachgoers who have to travel some distance to get to the sea), and in addition, sunscreen can be rubbed off or displaced by friction from clothing during the wait time and lose efficacy.

The aim of this study was to determine the time needed for a sunscreen to offer optimal protection from the moment of application. To do this, we performed an *in vitro* analysis of spectral transmittance and an *in vivo* analysis using UV photography.

To avoid any trade-oriented path, we prepared a standard formulation (sun protection factor of 16 and a UVA protection factor of 12.7) described in ISO-24443.[3] The ISO standard is a fully composed photoprotective galenic formulation with the finality of comparison with each commercial one.

In vitro transmittance spectra (290–700 nm) of the sunscreen were determined by evenly spreading 2 mg/cm^2 of the product over a 5 × 5 cm^2 PMMA plates and followed spectrophotometrically at 0, 0.5, 1.5, 5, 10, 15 and 30 min. Percentage changes in transmittance were calculated for the sunscreen with respect to the blank (glycerol).

In vivo UV radiation absorption performance of the sunscreen was followed in five healthy phototype III adult volunteers. Four replicates of 5 × 5 cm^2 squares clean dry skin were followed sequentially at 5-min intervals by means of UV photography in each volunteer after application of 50 mg of sunscreen formulation using a Canon camera fitted with two flashes provided with UV band-pass filters. The images were then uploaded into an image processing software, and percentage changes of colour reflectance were calculated at each measurement time with respect to initial. The degree of UV absorption by a sunscreen is observed by the darker tones in the UV photographs (Fig. 1a,b). For each image, the mean (blue-black) colour value was calculated using the colour histogram representing all the pixels in the image (Fig. 1c).

Results showed that although the sunscreen offered immediate protection when applied, it took 5 min to achieve photostability by sample transmittance (Fig. 2). In the visible region, initial mean transmittance of 49.9% increased progressively to reach 100% at minute 5, while UV transmittance rates decreased progressively to reach 53.3% of the initial value at minute 5. After that, values remained constant up to minute 30.

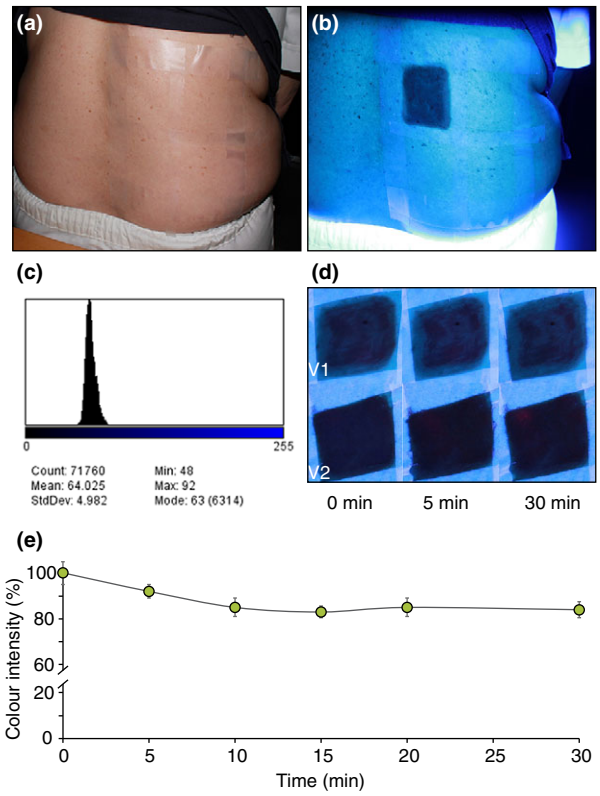

Figure 1 *In vivo* analysis using UV photography. (a) Normal photograph in a volunteer after the application of sunscreen to the upper inner square showing the four 5 × 5 cm squares, with sunscreen applied to the first one. (b) UV photographs after sunscreen applied to the first square in the same volunteer. (c) UV reflectance colour histogram from the image (ImageJ image processing software). (d) Example of UV photographs from two volunteers showing the results at minutes 0, 5 and 30. (e) Mean values from histograms corresponding to the first square according to the time the sunscreen have been on the skin.

MB Derma, 268：29-34, 2018.

◆特集／これが皮膚科診療スペシャリストの目線！ 診断・検査マニュアル―不変の知識と最新の情報―

紅斑とは―多彩な臨床症状から―

水川良子*

Key words：紅斑(erythema)，多形紅斑(erythema multiforme；EM)，スウィート病(Sweet disease)，環状紅斑(annular erythema)，結節性紅斑(erythema nodosum；EN)，サルコイドーシス(sarcoidosis)，移植片対宿主病(graft-versus-host disease；GVHD)

Abstract 真皮毛細血管の拡張や充血を反映する紅色の斑状皮疹の総称である紅斑にはさまざまな臨床型が含まれ，疾患には多様性がある．滲出性～浮腫性紅斑では多形紅斑，蕁麻疹様紅斑やSweet病などの好中球性皮膚症でみられる炎症性疾患が，浸潤性紅斑では結節性紅斑，硬結性紅斑に代表される皮下組織の炎症を伴う疾患が含まれる．サルコイドーシスや日光角化症やBowen病も紅斑を呈する．さまざまな顔をもつ紅斑は，病理所見でも表皮の変化を伴うものから，真皮の浮腫を主体とするもの，真皮深層から皮下組織の炎症を伴うものまでさまざまである．本稿では，臨床型から紅斑を呈する疾患を概説する．

紅斑は，真皮の毛細血管の拡張や充血を反映する紅色の斑状皮疹の総称である．色調のみでは赤血球の血管外漏出による紫斑と鑑別が難しい場合もあるが，硝子圧を加えることで紅斑は消退するので，これで鑑別する．紅斑にはさまざまな臨床型があり，滲出性～浮腫性紅斑，鱗屑性紅斑，環状紅斑，浸潤性紅斑，萎縮性紅斑，有痛性紅斑などと形容される(表1)．滲出性～浮腫性紅斑では多形紅斑や蕁麻疹様紅斑，Sweet病などの好中球性皮膚症でみられる炎症性疾患が，浸潤性紅斑では結節性紅斑，硬結性紅斑に代表される皮下組織の炎症を伴う疾患が含まれる．萎縮性紅斑としてサルコイドーシスや日光角化症も鑑別に挙げられる．病理所見でも，表皮の変化を伴うものから，真皮の浮腫を主体とするもの，真皮深層から皮下組織の炎症を伴うものまで，さまざまな臨床型に一致して多様性に富んでいる．臨床型から主な紅斑を呈する疾患の概略を述べる．

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滲出性～浮腫性紅斑

1．多形紅斑(erythema multiforme；EM)(図1)

典型疹では虹彩状を呈し(iris formation，target lesion)，急性の経過をとる．原因はさまざまで，症状の軽重によりステロイド外用のみで軽快する症例からステロイド内服を用いて加療する症例までvarietyがある．

EMは若年の成人に発症することが多く，小型の紅色丘疹で初発し遠心性に拡大する．四肢伸側に好発し，躯幹や顔面にも拡大する．左右対称性に生じることが多い．個疹はやや浮腫性で，典型疹では中央が隆起し虹彩状となる．EMは皮疹の範囲，水疱・壊死・粘膜症状の有無，発熱などの全身症状の有無により，EM minor，EM major，Stevens-Johnson症候群(SJS)，中毒性表皮壊死症(toxic epidermal necrolysis；TEN)へと進展する可能性があり，初期の軽症の段階でも慎重に経過をみる必要がある．早期の段階では，類円形，境界比較的明瞭で，経過とともに2～3層の同心円状を呈する(虹彩状)．SJSやTENではflat

表 1. さまざまな紅斑を呈する疾患

紅斑の性状	疾患名				
滲出性～浮腫性	蕁麻疹様紅斑	多形紅斑	LE(蝶形紅斑など)	好中球性皮膚症(Sweet 病)	水疱性類天疱瘡
環　状	遠心性環状紅斑(Darier)	Sjögren 症候群	亜急性皮膚エリテマトーデス(SCLE)	線状 IgA 水疱性皮膚症(LABD)	Duhring 疱疹状皮膚炎
浸潤性	結節性紅斑	硬結性紅斑	好中球性皮膚症	肉芽腫性疾患	
萎縮性	DLE	サルコイドーシス	日光角化症		
鱗屑性	湿疹・皮膚炎群	乾癬	体部白癬	Bowen 病	
有痛性	結節性紅斑	好中球性皮膚症			

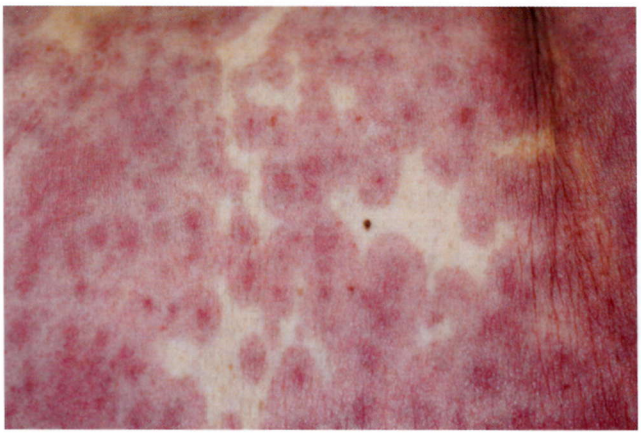

図 1. 多形紅斑

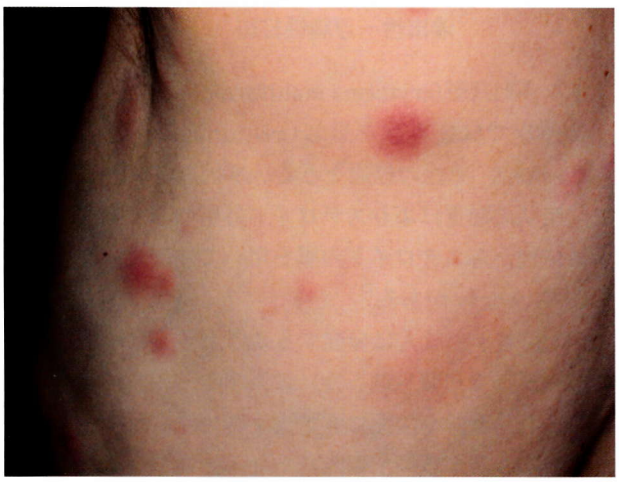

図 2. Sweet 病

(macular) atypical target と表されるように，境界不明瞭な皮疹の所見が鑑別点として挙げられている．

病因として各種感染症(HSV，マイコプラズマ，EBV，コクサッキーウイルスなど)との関連が指摘されている．また，薬剤，エリテマトーデスなどの膠原病，接触皮膚炎症候群でも生じることがあり，さまざまな因子が原因となりえる．

病理組織所見は真皮の浮腫と表皮内へのリンパ球浸潤を認める．EM では表皮細胞の apoptosis を認めるが，2016 年に改訂された「重症多形滲出性紅斑 スティーヴンス・ジョンソン症候群・中毒性表皮壊死症診療ガイドライン」では，「SJS の完成した病変では，表皮全層性の壊死を呈するが，少なくとも 200 倍視野で 10 個以上の表皮細胞(壊)死を確認することが望ましい」と SJS の病理組織所見が厳密に定義されている．

感染が原因の場合には，ステロイド外用や抗ヒスタミン剤・抗アレルギー剤を対症的に用いる．EM major や SJS，TEN への移行が疑われる場合にはステロイド内服を積極的に行う．SJS, TEN の治療に関しては診療ガイドラインを参照されたい[1]．

2．Sweet 病・Sweet 症候群(図 2)

躯幹，上肢に有痛性の紅斑が多発し高熱を伴う．血液系の基礎疾患を有することがあり，注意が必要である．

本症は広義の好中球性皮膚症に含まれる．発熱，関節痛などの全身症状とともに，顔面，躯幹，上肢にくるみ大前後の有痛性の浸潤を伴うやや浮腫性の紅斑が多発する．ときに水疱や膿疱を伴い痂皮化することもある．小水疱や膿疱を伴う場合はしばしば白血病を伴うとする報告もある．下肢に生じると結節性紅斑との鑑別を要する．EM に比較すると浸潤を有し，水疱，膿疱や丘疹といった成分を伴う点が鑑別になる．白血球増加，CRP 上昇を認めることが多い．

原因は不明であるが，IL-1β，IL-6，G-CSF などのサイトカインの変調の関与が指摘されている．上気道感染，白血病を主とする血液系悪性腫

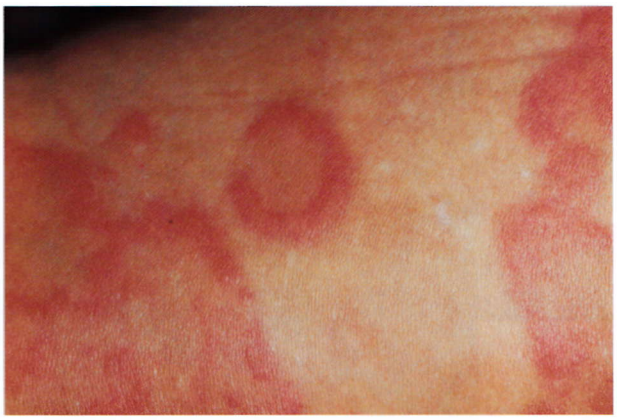

図 3. 遠心性環状紅斑

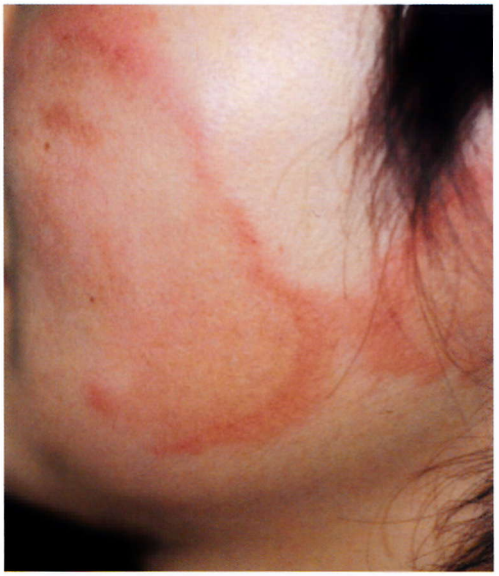

図 4. Sjögren 症候群

瘍，胃癌などの内臓悪性腫瘍，炎症性疾患(炎症性腸疾患)との関連が指摘されている．近年，さまざまな免疫チェックポイント阻害薬による皮膚有害事象が報告されてきているが，ニボルマブなどの免疫チェックポイント阻害薬による Sweet 病様皮疹の報告がなされており，周知しておく必要がある[2]．

特徴的な病理組織所見は，真皮の好中球の稠密な浸潤である．好中球破砕を伴う血管炎の所見は認めない．通常は表皮壊死などの表皮の所見は伴わない．

治療にあたっては基礎疾患の有無を検索する．NSAIDs やヨウ化カリウム，ダプソン，コルヒチンが有効であることが知られている．有効性が高いのはステロイド内服であるが，基礎疾患の検索終了以前の内服開始は慎重に行うべきと考えられる．

環状紅斑

環状を呈する紅斑の総称で，小紅斑が遠心性に拡大して環状を呈し，ときに辺縁が堤防状に隆起し，鱗屑を伴う場合もある．遠心性環状紅斑，遠心性丘疹状紅斑や Sjögren 症候群が代表的な疾患と思われる．線状 IgA 水疱性皮膚症(LABD)や Duhring 疱疹状皮膚炎などの水疱症のなかにも環状を呈する疾患が存在する．Darier が提唱した遠心性環状紅斑は浸潤を強く触れ，病理組織学的に表皮の変化を伴わない．近年，浸潤が軽度で表皮変化を伴う遠心性環状紅斑を表在型，従来の浸潤の強い環状紅斑を深在型として区別する考え方が提唱され，一般的になりつつある．

1．遠心性環状紅斑(表在型)(図 3)

個疹は淡い小紅斑で始まり遠心性に拡大し，数週～数か月の経過で色素沈着を残して消退する．辺縁は軽度隆起し鱗屑を伴い，ときに C 字状などの不定形を呈する．感染症や内臓悪性腫瘍を基礎疾患として有することが指摘されている．

病理組織所見は非特異的な炎症所見である．臨床所見を反映し鱗屑部では軽度の海綿状態を認め，真皮では血管周囲性のリンパ球浸潤をみる．他の環状紅斑を呈する疾患を除外診断する必要がある．ステロイド外用，抗ヒスタミン剤で対症的に加療する．

2．Sjögren 症候群(SjS)(図 4)

環状紅斑を生じる膠原病の代表的な疾患の 1 つ．顔面に好発し，くるみ大～鶏卵大前後の辺縁が堤防状に隆起する環状紅斑から C 字状，馬蹄形の紅斑を生じる．遠心性に拡大しながら中央は淡褐色調を呈する．SjS では，環状紅斑以外にも高ガンマグロブリン血症に伴う点状紫斑や乾皮症な

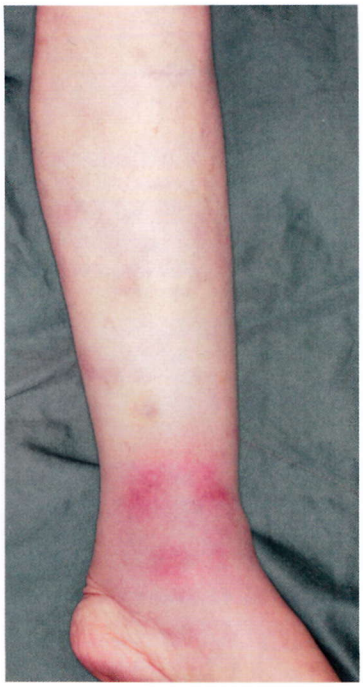

図 5. 結節性紅斑

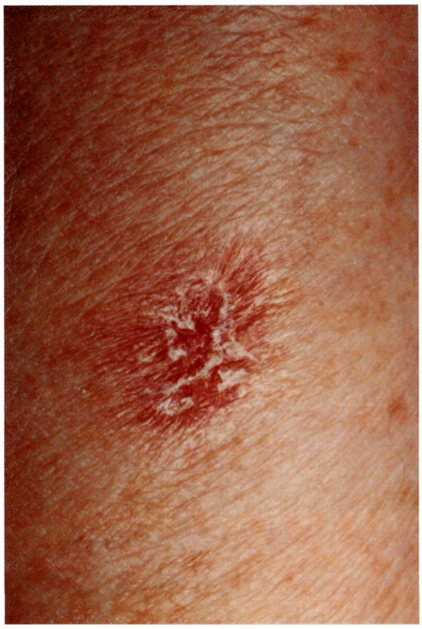

図 6. サルコイドーシス

どの皮膚症状がみられるが，環状紅斑はSjSを疑うきっかけになりえる特徴的な皮疹といえる．液状変性などの表皮変化は軽度で，真皮上層を主体とする血管周囲性のリンパ球浸潤に加え，汗腺周囲の細胞浸潤がみられることもある．ステロイド外用で治療する．膠原病で環状紅斑を認める疾患としては，他に亜急性皮膚エリテマトーデス，新生児エリテマトーデスが挙げられる．

浸潤性紅斑

1．結節性紅斑(図5)

病態の基本は皮下脂肪織炎で，有痛性の強い浸潤を触れ，皮下結節や硬結を伴う紅斑性皮疹である．女性に好発し，上気道感染などが先行することが多く，溶連菌感染，エルシニア，マイコプラズマなどの感染症が契機になることが報告されている．また，サルコイドーシス，Behçet病などの炎症性腸疾患を基礎疾患として有することも知られており，注意が必要である．下腿伸側に指頭大からくるみ大，手拳大まで大小さまざまで，ときに上肢にもみられる．Behçet病に伴う場合には比較的小型，サルモネラでは比較的大型の皮疹を呈するとされる．浮腫性紅斑の項でも記載したが，免疫チェックポイント阻害薬投与時に，結節性紅斑を生じることが近年報告されている．病理組織所見は脂肪隔壁を主体とする細胞浸潤(septal panniculitis)で，初期では好中球を認め，経過とともにリンパ球が主体となり，組織球，巨細胞を混じるようになる．治療の基本は下肢の安静で，対症的にNSAIDsなどを併用する．症状によりヨウ化カリウムやステロイド内服を行う．

2．硬結性紅斑

結節性紅斑と鑑別を要するが暗赤色調を呈し，やや萎縮性，皮下硬結，板状硬結，潰瘍を伴うことがある．女性の下腿に好発し，結核との関連が示唆される症例も存在する．

萎縮性紅斑

1．サルコイドーシス(図6)

サルコイドーシスは，結節型，局面型，びまん浸潤型，皮下型，瘢痕浸潤型，結節性紅斑様皮疹など多彩な皮膚症状を示す．局面型は顔面に好発し，中央がやや萎縮性の鱗屑を伴う小型の紅斑を呈し，DLEなどが鑑別となる．病理組織所見で

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