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GUIDELINE

Clinical practice guide for the treatment of perforating dermatosis

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ABSTRACT

Perforating dermatoses are a heterogeneous skin disease group defined by transepidermal elimination of various skin materials. Four classical forms of primary perforating dermatosis have been described, where the transepidermal elimination mechanism represents the hallmark of the disease: acquired reactive perforating collagenosis, elastosis perforans serpiginosa, Kyrle's disease and perforating folliculitis. Acquired reactive perforating collagenosis presents with transepidermal elimination of collagen fibers. Elastosis perforans serpiginosum presents with the elimination of elastic fibers. Kyrle's disease presents with transepidermal elimination of abnormal keratin. In perforating folliculitis, it is the content of the follicle. We established diagnostic criteria and severity classification. In addition, the Japanese guideline for treatment of perforating dermatoses was updated using the Medical Information Network Distribution Service (MINDS) methodology. The guideline is based on a systematic published work review completed from 1989 to 2019, and on a formal consensus and approval process. Most medical published work on the treatment is limited to individual case reports and small series of patients. The guideline covers treatment options considered relevant by the expert panel and approved in Japan at the time of the consensus conference.

Key words: acquired reactive perforating collagenosis, elastosis perforans serpiginosa, Kyrle's disease, perforating dermatosis, perforating folliculitis.

PREPARATION OF CLINICAL PRACTICE GUIDE

Features of clinical practice guide

Guidelines are "systematic documents designed to assist clinicians and patients in making appropriate decisions in specific clinical situations". The clinical practice guide is based on the Medical Information Network Distribution Service (MINDS) clinical practice guideline. Its purpose is to present recommendations of evidence-based medicine on medical actions of high clinical importance, that we consider to be optimal for supporting decisions of the patient and the medical staff, while considering the balance between benefits and harms. Each item was created in the clinical question (CQ) format, with the aim of creating highly practical guidelines that general clinicians immediately understand and practice in the field, and disseminate thereafter.

Perforating dermatosis has been reported in a small number of patients and has no globally uniform diagnostic criteria; therefore, clinical trials with a high level of evidence such as randomized controlled trials (RCT) and prospective cohort studies are difficult to perform. Sufficient clinical data cannot be accumulated and scientific evidence (clinical studies and articles) with a high level of evidence cannot be obtained. We did not perform a systematic review in this clinical practice guide. Instead, we decided to collect and evaluate the degree of consent to the recommendation by dermatologists to provide the scientific basis with a low evidence level.

When we see an actual patient, there are various individual background factors such as differences in underlying diseases and degrees of symptoms and complications. Although this clinical practice guide shows the present standard medical care in Japan, in the general medical care, the physician should decide the treatment policy based on the consultation with the patient.

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Evidence level and article extraction

The evaluation and classification of the evidence level was based on the guideline for the MINDS clinical practice guidelines 2007[1] and 2014 (Table 1)[2]. In the extraction of articles, we searched for published documents from January 1989 to October 2019. In addition, the latest important articles were added as appropriate. The databases used were Medline, PubMed and the Japan Medical Abstracts Society Web, each of which had their own hand search. In the selection criteria, RCT papers were given priority. When not available, papers from cohort studies, case–control studies, non-control studies, case reports and case series were included. Published work of basic experiments was excluded.

Adaptation of consent level

After extracting articles, due to the lack of RCT papers, the low level of evidence became a problem. On the other hand, even if there is no scientific basis with a high level of evidence, there are many items that are generally recognized in dermatological practice. Based on the Behçet's disease clinical practice guideline 2020,[3] we decided to create a five-tier consent level classification to supplement the recommendation level (Table 2). That is, if the recommendation is followed nine times or more in 10 clinical opportunities, the level of consent is 5 (strongly agree), the level of consent is 4 or more if the recommendation is followed seven times or more (agree), and the level of consent is 3 or more if the recommendation is followed five times or more (agree with conditions). This scoring task was performed by 19 dermatologists with mutual consultation prohibited. The aggregated results are shown as average values. CQ and recommendations that did not obtain consent levels of 4 or higher were considered as not generally used in actual clinical settings, even if there was a certain level of evidence. The CQ itself was deleted and it was decided to not be included in this clinical practice guide.

Criteria for the degree of recommendation and recommendation sentence

The degree of recommendation is determined based on the level of evidence. CQ based on clinical trials and academic articles with a high level of evidence has a high degree of recommendation. However, the strength of the evidence does not directly indicate the strength of the recommendation. There is also a CQ that can be performed in the actual clinical setting even if the evidence level is not high. Because perforating dermatosis has a small number of patients reported and no globally uniform diagnostic criteria, sufficient evidence cannot be proved in RCT articles. Based on the Behçet's disease clinical practice guideline 2020,[3] the criteria for recommendation levels and recommendation sentences were determined (Table 3). Furthermore, a consensus building meeting was held, and the level of recommendation was determined by an unbiased method.

Table 1. Evidence level classification

Evidence level		
1	1a	Meta-analysis of randomized controlled trials
	1b	At least one randomized controlled trial
2	2a	Cohort study with concurrent controls without random assignment
	2b	Cohort study with past controls without random assignment
3		Case–control study (retrospective study)
4		Studies without pre- and post-treatment comparisons or control groups
5		Case reports, case series
6		Expert opinion, expert committee report

Table 2. Degree of consent

Consent level		Frequency to follow recommendations in 10 clinical settings
5	Strongly agree	≥9 times
4	Agree	≥7 times
3	Agree with conditions	≥5 times
2	Moderately disagree	≥4 times
1	Disagree	≤1 time

Source of funding and conflict of interest

Regarding perforating dermatosis, the editorial board is not supported by any specific organization/company or pharmaceutical company. In addition, the members involved in the clinical practice guide and the members involved in the verification have no relationship with any organization that may cause conflicts of interest. In other words, there is no conflict of interest to clarify.

DIAGNOSTIC CRITERIA AND SEVERITY CLASSIFICATION OF PERFORATING DERMATOSIS

Diagnostic criteria for perforating dermatosis

Each disease was reported for the first time by the following: Kyrle's disease in 1916 by Kyrle,[4] elastosis perforans serpiginosa in 1953 by Lutz,[5] and perforating folliculitis and acquired reactive perforating collagenosis in 1968 by Mehregan and Coskey (Table 4).[6] These diseases are characterized by the phenomenon of transepidermal elimination of denatured dermis as a histopathological finding. Rapini *et al*.[7] collectively referred

Table 3. Determination of recommendation sentences

Recommendation sentence	Evidence level	Consent level	Recommendation level
Highly recommend	Mainly 1	≥4.8	A
Recommend	Mainly 2 or 3	≥4.5	B
Suggest	Mainly 4–6	≥4.0	C1
Do not recommend due to no basis	No evidence		C2
Recommend not to do	Invalid or harmful evidence		D

Table 4. Diagnostic criteria for perforating dermatosis

A	Basic findings
	Histopathological findings show transepidermal elimination of degenerated cutaneous components (transepidermal elimination)
B	Substances that are mainly transepidermally eliminated
	1 Collagen tissue from epidermis
	2 Elastic fibers
	3 Keratins
	4 Collagen tissue from hair follicles
C	Clinical cutaneous findings
	1 Umbilicated papules or nodules with a central adherent keratotic plug
	2 Onset at age 18 years and older
D	Reference findings
	Koebner's phenomenon
	Pruritus
Diagnostic category	
A definite diagnosis is made in the following cases:	
A + B1 + C1 + C2 = acquired reactive perforating collagenosis	
A + B2 = elastosis perforans serpiginosa	
A + B3 = Kyrle's disease	
A + B4 = perforating folliculitis	

to them as acquired perforating dermatosis in 1989. At present, given that there are cases of early-onset disease that are not necessarily acquired, they are often collectively referred to as perforating dermatosis. A pathological tissue finding of transepidermal elimination image in which denatured skin components are excreted outside the skin is essential as the diagnostic criteria for perforating dermatosis.

We first set up histopathological findings of transepidermal elimination of degenerated cutaneous components as basic findings and set it as item A. Item B was set to include the transepidermally eliminated substances: acquired reactive perforated collagenosis that eliminates collagen tissue from the epidermis, elastosis perforans serpiginosa that eliminates elastic fibers, Kyrle's disease that eliminates keratins and perforating folliculitis that eliminates collagen tissue from hair follicles. Because the substances that are transepidermally eliminated are not clearly classified according to each disease, the term "mainly" was added. In addition, regarding acquired reactive perforating collagenosis, for histopathology, Faver *et al*.[8] published the diagnostic criteria as meeting all of the following three criteria: (i) histopathological findings of elimination of necrotic basophilic collagen tissue into a cup-shaped epidermal depression; (ii) clinical presentation of umbilicated papules or nodules with a central adherent keratotic plug; and (iii) onset of skin lesions after the age of 18 years. The diagnostic criteria have been cited in many articles related to acquired reactive perforating collagenosis, and some consent has been obtained. Item C was set, and umbilicated papules or nodules with a central adherent keratotic plug, and the onset at 18 years or older were listed as clinical findings that lead to the diagnosis of acquired reactive perforating collagenosis.

Kim *et al*.[9] verified 30 cases of acquired perforating dermatosis and observed pruritus in 83.3% and Koebner's phenomenon in 31.8%. In some articles regarding acquired reactive perforating collagenosis that are most commonly encountered in clinical practice, confirmation of pruritus and Koebner's phenomenon is helpful for diagnosis. It was determined that the diagnostic value was also high, and reference diseases include prurigo nodularis, prurigo simplex, folliculitis, insect hypersensitivity and multiple keratoacanthoma.

Perforating dermatosis severity classification

We adopted the infiltration/papulation and excoriations based on the Eczema Area and Severity Index (EASI) score for atopic dermatitis published in 2001 by Hanifin *et al*.[10] Infiltration/papulation and excoriations were scored and summed as item 1 (Table 5). The evaluation was based on EASI: 0–0.5, near remission; 0.6–3.5, mild; 3.6–10.5, moderate; 10.6–25.0, severe; and 25.1–36.0, most severe.

The Eczema Area and Severity Index is an objective index and there is no index of pruritus, which is a characteristic clinical finding of perforating dermatosis. Therefore, the pruritus numerical rating scale was added. That is, pruritus was divided into 11 stages from 0 to 10, and item 2 was set as 0 (no pruritus at all) to 10 (worst pruritus) among possible items. Evaluation was: 0, none; 1–3, mild; 4–7, moderate; and 8–10, severe. The sum of item 1 and item 2 is the severity classification of the total score value (decimal points rounded up): 0–1, near remission; 2–6, mild; 7–15, moderate; 16–33, severe; and 34–46, most severe.

CQ OF PERFORATING DERMATOSIS

Acquired reactive perforating collagenosis

In 1968, Mehregan and Coskey[6] described it as multiple keratotic papules with a central adherent keratinous plug, with histopathology showing transepidermal excretion of collagen fibers. In 1994, Faver *et al*.[8] published the diagnostic criteria as meeting all of the following: (i) histopathological findings of elimination of necrotic basophilic collagen tissue into a cup-shaped epidermal depression; (ii) clinical presentation of umbilicated papules or nodules with a central adherent keratotic plug; and (iii) onset of skin lesions after the age of 18 years (Fig. 1). The diagnostic criteria have been cited in many articles. An adherent keratotic plug is often also described as plaster-like. Moreover, pruritus is present and can be severe, and Koebner's phenomenon is present as well.

CQ1: What are the characteristic comorbidities of acquired reactive perforating collagenosis?

Recommendation: Diabetes and chronic kidney disease recommended to be regarded as comorbidities of acquired reactive perforating collagenosis.

Evidence level: 5
Level of consent: 4.72
Recommendation level: B

Table 5. Severity classification of perforating dermatosis

1	infiltration/papulation and excoriations as a score each (0–18)										
		infiltration/papulation (none, 0; mild, 1; moderate, 2; severe, 3)				Body surface area (0, 0%; 1, 1–9%; 2, 10–29%; 3, 30–49%; 4, 50–69%; 5, 70–89%; 6, 90–100%)					
	Head	0–3	×			0–6					×0.1 =
	Trunk	0–3	×			0–6					×0.3 =
	Upper extremities	0–3	×			0–6					×0.2 =
	Lower extremities	0–3	×			0–6					×0.4 =
		Excoriations (none, 0; mild, 1; moderate, 2; severe, 3)				Body surface area (0, 0%; 1, 1–9%; 2, 10–29%; 3, 30–49%; 4, 50–69%; 5, 70–89%; 6, 90–100%)					
	Head	0–3	×			0–6					×0.1 =
	Trunk	0–3	×			0–6					×0.3 =
	Upper extremities	0–3	×			0–6					×0.2 =
	Lower extremities	0–3	×			0–6					×0.4 =
2	Numerical rating scale of pruritus (0–10)										
	0	1	2	3	4	5	6	7	8	9	10
	None	Mild	Mild	Mild	Moderate	Moderate	Moderate	Moderate	Severe	Severe	Severe
1 + 2 = total score value (decimal points rounded up)											
Near remission, 0–1; mild, 2–6; moderate, 7–15; severe, 16–33; most severe, 34–46											

Commentary: There are three case series[8,11–13] that report association with diabetes, and one case report[14] and two case series[8,13] that report complications with chronic kidney disease. There are no studies with a high level of evidence, only case series and case reports, and no evidence can be established. However, acquired reactive perforating collagenosis-related reviews noted the relationship between diabetes and chronic kidney disease, and the degree of consent was high. Therefore, the recommendation level B was set.

CQ2: Is treatment of diabetes and chronic renal disease effective for acquired reactive perforating collagenosis?

Recommendation: We suggest considering the treatment of coexisting diabetes and chronic kidney disease as a treatment for acquired reactive perforating collagenosis.

Evidence level: 5
Consensus level: 4.0
Recommendation level: C1

Commentary: There are three case series[9,13,15] that report treatments of diabetes being effective for acquired reactive perforating collagenosis, and the same three reports of case series[9,13,15] that report treatments of chronic kidney disease being effective for acquired reactive perforating collagenosis. Based on the evidence and consent levels, the recommendation level was set as C1. Acquired reactive perforating collagenosis is often associated with diabetes and chronic kidney disease, and Koebner's phenomenon because pruritus is observed. Therefore, we suggest that the treatment of diabetes and/or chronic kidney disease should be considered for the treatment of acquired reactive perforating collagenosis associated with the above diseases. Controlling pruritus is an important treatment point; however, there are only few reviews that describe the success of conventional antiallergic drugs. In the future, we anticipate that the effect of nalfurafine, a selective opioid κ receptor agonist with an assured indication for pruritus during renal dialysis, for this disease will be verified.

CQ3: Is topical steroid effective for acquired reactive perforating collagenosis?

Recommendation: We suggest considering topical steroid therapy as a treatment for acquired reactive perforating collagenosis.

Evidence level: 5
Consensus level: 4.17
Recommendation level: C1

Commentary: Regarding acquired reactive perforating collagenosis, there are three case series[8,13,16] that noted the effectiveness of topical steroids. The recommendation level C1 was set based on the evidence and consensus levels. In other words, in actual clinical practice, we propose to consider topical steroids as one of the treatments.

CQ4: Is ultraviolet (UV) therapy effective for acquired reactive perforating collagenosis?

Recommendation: We suggest that UV therapy be considered as a treatment for acquired reactive perforating collagenosis.

Evidence level: 5
Consensus level: 4.22
Recommendation level: C1

Commentary: Three case reports noted that UV therapy was effective for acquired reactive perforating collagenosis,[17–19] and one case series reported the same as well.[20] The recommendation level C1 was set based on the evidence level and consensus level. In other words, we propose to consider UV therapy as one of the treatments in clinical practice.

Elastosis perforans serpiginosa

Elastosis perforans serpiginosa was first described by Lutz[5] in 1953 (Fig. 2). The rash has a serpentine appearance with

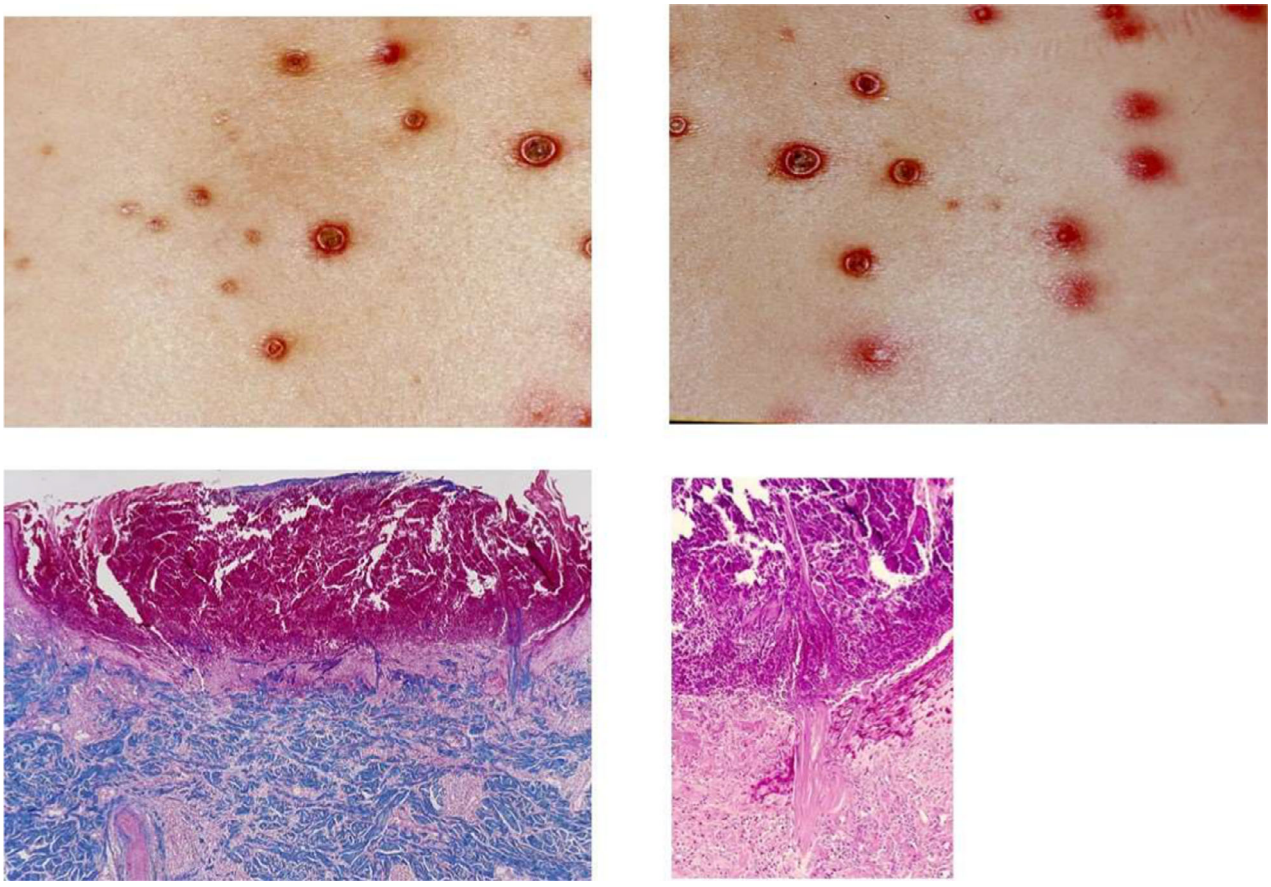

Figure 1. Acquired reactive perforating collagenosis Azan-Mallory staining (lower left; original magnification ×40) HE staining (lower right; original magnification ×100).

keratinized papules arranged arcuately or annularly to form plaques. It frequently occurs in the neck, trunk and extremities. Histopathologically, transepidermal elimination of degenerated elastic fibers can be seen. Generally, it is classified into three types: (i) reactivity type associated with diseases with abnormal connective tissue; (ii) drug-induced type induced by D-penicillamine; and (iii) idiopathic type with presumed genetic background. Treatments include active vitamin D_3 external use, cryotherapy and laser irradiation, but they are intractable.

CQ5: What are the characteristic comorbidities of elastosis perforans serpiginosa?

Recommendation: We suggest considering Down syndrome as a comorbid disease of elastosis perforans serpiginosa.

Evidence level: 5
Consensus level: 4.28
Recommendation level: C1

Commentary: There are five case reports[21–25] and two case series[26,27] that report association with Down syndrome. There are no research articles with a high level of evidence, and there are many papers; however, they are only case reports and case series. The recommendation level C1 was set based on the evidence and consensus level. It is also known to occur in conjunction with genetic connective tissue diseases such as Marfan syndrome, Ehlers–Danlos syndrome and osteogenesis imperfecta.

CQ6: Should D-penicillamine be discontinued if elastosis perforans serpiginosa develops during oral D-penicillamine treatment?

Recommendation: In cases in which elastosis perforans serpiginosa develops during the use of D-penicillamine and a causal relationship is strongly suspected, we suggest discontinuing D-penicillamine and consider changing to another drug.

Evidence level: 5
Consensus level: 4.28
Recommendation level: C1

Commentary: There are four case reports[26–31] in which elastosis perforans serpiginosa is thought to have occurred during the use of D-penicillamine, a therapeutic agent for rheumatoid arthritis. Based on the evidence and consent levels, the recommendation level was set as C1. We suggest discontinuing D-penicillamine and consider changing to another drug in cases where a causal relationship is strongly suspected.

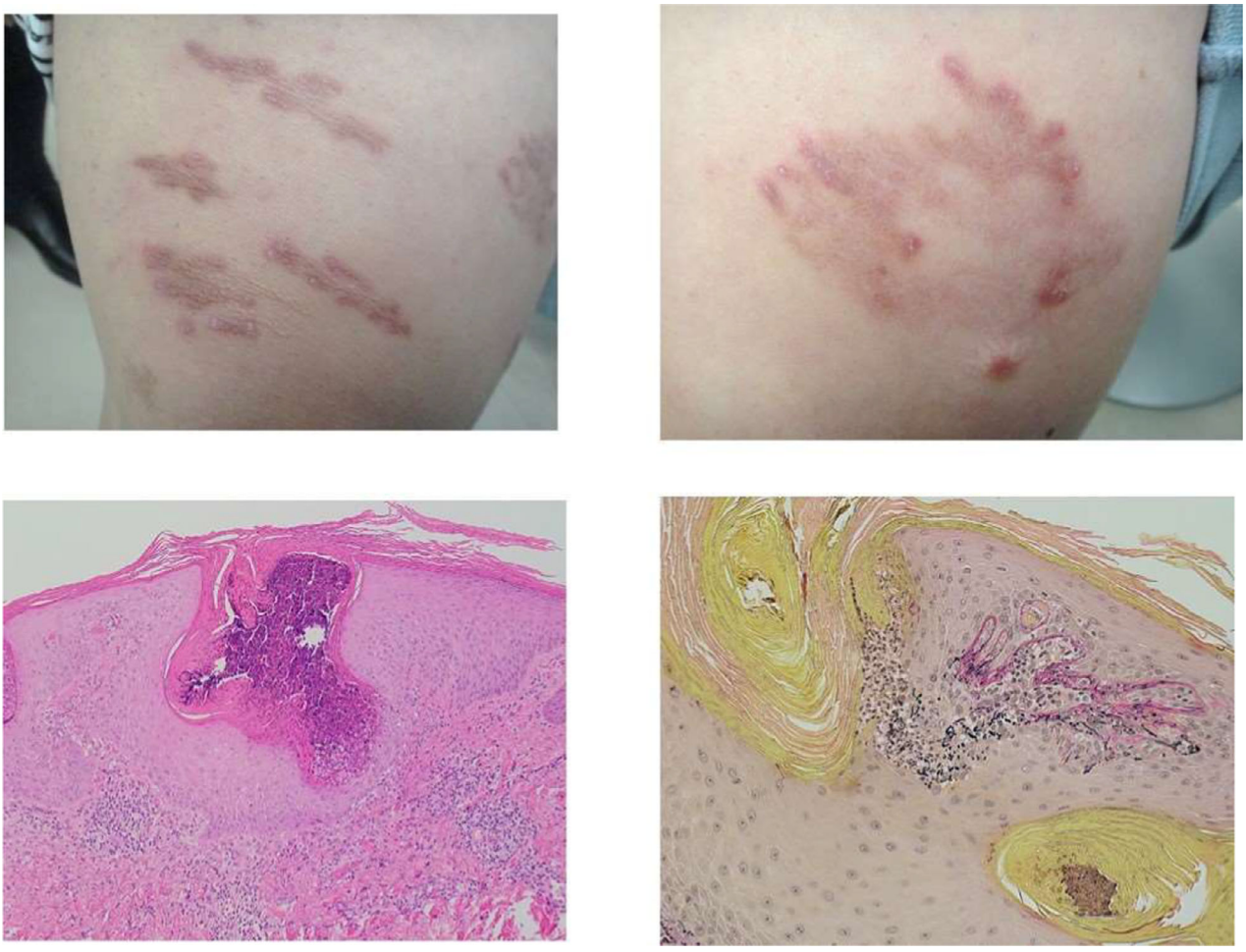

Figure 2. Elastosis perforans serpiginosa Provided by Dr. Jun Asai, Department of Dermatology, Kyoto Prefectural University of Medicine HE stain (bottom left; original magnification ×100) Elastica van Gieson stain (bottom right; original magnification ×200).

Kyrle's disease

Kyrle's disease was described by Kyrle[4] in 1916 (Fig. 3). Skin eruptions mainly consist of papules, accompanied by erythema or pigmentation. Kyrle's disease also shows verrucous plaques. It frequently occurs in the extremities and buttocks. Histopathologically, transepidermal elimination of degenerated keratins (mainly keratin proteins) is seen.

CQ7: What are the characteristic comorbidities of Kyrle's disease?

Recommendation: We suggest that diabetes and chronic kidney disease be considered as comorbidities for Kyrle's disease.

Evidence level: 5
Consensus level: 4.22
Recommendation level: C1

Commentary: There are six case reports[32–36] describing cases of complications with diabetes, and five case reports[32,36–38] describing cases of complications with chronic kidney disease. Based on the evidence and consent levels, the recommendation level was set as C1.

Perforating folliculitis

Perforating folliculitis is a disease first reported by Mehregan and Coskey[6] in 1968 (Fig. 4). The eruption is frequently seen as follicular papules with keratotic plug. It frequently occurs in the extremities and buttocks. Histopathologically, the enlarged follicular infundibulum is filled with necrotic material, keratinized substances and degenerated inflammatory cells. The follicular infundibulum is perforated, and an image of transepidermal elimination with invasion of collagen and elastic fibers is seen.

CQ8: What are the characteristic comorbidities of perforated folliculitis?

Recommendation: We suggest considering diabetes and chronic renal disease as comorbidities of perforated folliculitis.

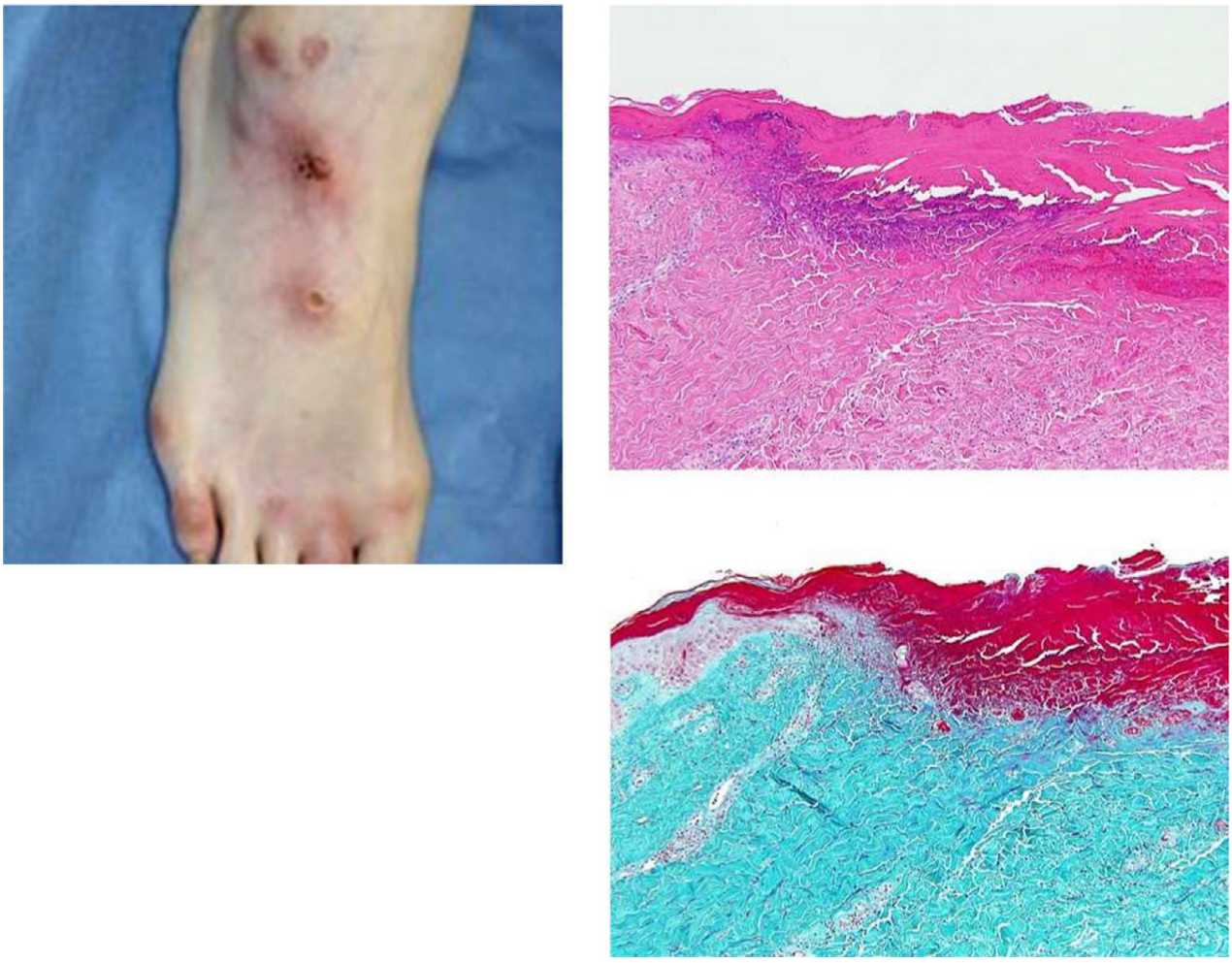

Figure 3. Kyrle's disease Provided by Dr. Shoko Nakano, Dr. Masahiro Hayashi, and Dr. Kei Nagatani, Yamagata University Department of Dermatology HE stain (upper right; original magnification ×100) Elastica Masson stain (lower right; original magnification ×100).

Evidence level: 5
Consensus level: 4.11
Recommendation level: C1

Commentary: There are three case series in reports of complications with diabetes.[39–41] There is one case series reporting the complications with chronic kidney disease.[42] In which, perforating folliculitis was reported in three of 122 patients (2.5%) with chronic renal disease over the age of 18 years. Hemodialysis was performed in all three cases. Based on the evidence and consent levels, the recommendation level was set as C1.

CQ9: If perforating folliculitis develop during molecular-targeted drug (kinase inhibitor) treatment, should the molecular-targeted drug (kinase inhibitor) be discontinued?

Recommendation: There are many articles indicating that perforating folliculitis might have occurred during the use of molecular-targeted drugs (kinase inhibitors). In cases where a causal relationship is strongly suspected, we suggest discontinuing the molecular-targeted drug (kinase inhibitor) and consider changing to another drug.

Evidence level: 5
Consensus level: 4.17
Recommendation level: C1

Commentary: There is an increasing number of case reports of perforating folliculitis caused by the administration of molecular-targeted drugs (kinase inhibitors). There are four case reports on sorafenib, a multikinase inhibitor,[43–46] and two reports on nilotinib, a tyrosine kinase inhibitor.[47,48] There is also one report each for infliximab,[49] a tumor necrosis factor inhibitor, and vemurafenib, a BRAF kinase inhibitor.[50] Based on the evidence and consent levels, the recommendation level was set as C1. Because a molecular-targeted drug (kinase inhibitor) is considered as an inducer, it is suggested that if

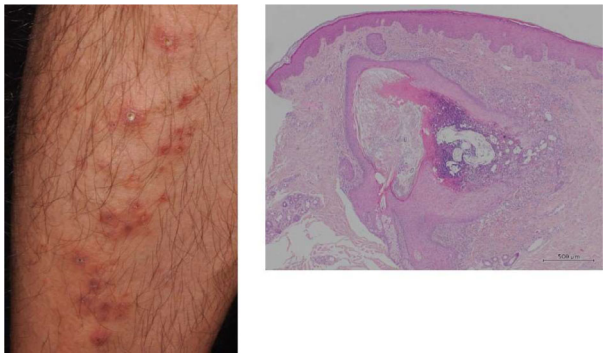

Figure 4. Perforating folliculitis HE staining (right; original magnification ×40).

perforating folliculitis develops, the drug should be stopped and a change to another drug should be considered.

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CONFLICT OF INTEREST: None declared.

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