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GUIDELINE

Diagnostic criteria, severity classification and guidelines of localized scleroderma

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ABSTRACT

We established diagnostic criteria and severity classification of localized scleroderma because there is no established diagnostic criteria or widely accepted severity classification of the disease. Also, there has been no clinical guideline for localized scleroderma, so we established its clinical guideline ahead of all over the world. In particular, the clinical guideline was established by clinical questions based on evidence-based medicine according to the New Minds Clinical Practice Guideline Creation Manual (version 1.0). We aimed to make the guideline easy to use and reliable based on the newest evidence, and to present guidance as specific as possible for various clinical problems in treatment of localized scleroderma.

Key words: **diagnostic criteria, guideline, localized scleroderma, severity classification, treatment.**

DIAGNOSTIC CRITERIA

Cases must satisfy all three of the following items:

- Presence of sclerodermatous skin changes with circumscribed borders
- Histopathological examination shows thickened and increased collagen fibers in the dermis
- The following diseases can be excluded (however, this excludes cases in which the following diseases occur concurrently): systemic sclerosis, eosinophilic fasciitis, lichen sclerosus et atrophicus, keloid, (hypertrophic) scars and sclerosing panniculitis.

SEVERITY CLASSIFICATION

Severity criteria for localized scleroderma

Any condition with a total of 2 points or more is classified as severe:

- Muscle lesions (based on imaging diagnostics or serum muscle enzymes): 2 points
- Functional disorder due to joint contracture: 2 points
- Growth disorder of the affected limb: 2 points
- Central nervous system disorder: 2 points
- Cerebrovascular disorder: 2 points
- Conditions with multiple skin eruptions*: 1 point
- Linear lesion on the face or head (en coup de sabre): 1 point
- New or expanding skin lesion: 1 point.

*Multiple skin lesions are defined as follows:

- Four or more skin eruptions measuring 3 cm or more
- When the rash is distributed in two or more sites when the body is divided into seven different areas: head and neck, left and right upper limbs, trunk front and back, and left and right lower limbs.

GUIDELINES FOR THE TREATMENT

CQ1 How can localized scleroderma be classified?

Recommendation: Classifying localized scleroderma into the five disease types set out in the Padua Consensus classification that is advocated by the Paediatric Rheumatology

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Table 1. New Minds recommendation grades

Presentation of the strength of recommendation	
Recommendation grade	
1	Strongly recommended
2	Advocated
None	When undecided
Evidence level classification	
A	Strong conviction about the estimated effect
B	Moderate conviction about the estimated effect
C	Limited conviction about the estimated effect
D	Almost no conviction about the estimated effect

European Society is recommended, based on clinical and histopathological characteristics: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea and mixed morphea.

Recommendation level: 1D.

Explanation: Localized scleroderma can be classified into a number of disease types depending upon its clinical and histopathological characteristics. To date, a number of disease types have been proposed.[1–4] The pioneering classification was proposed in 1961 by Tuffanelli and Winkelmann (Table 4),[1] and in this classification localized scleroderma was classified into three disease types based on the form and distribution of the skin eruptions: morphea, linear scleroderma and generalized morphea. The characteristics of each disease type are as follows.

Morphea

Normally, there are one to a few patches of well-circumscribed, circular to oblong skin lesions scattered on the trunk or limbs. The individual skin lesions present with various forms that range from erythematous to sclerotic presentations. However, the initial presentation is particularly characteristic, with the central part having an ivory luster surrounded by reddening at the margins, indicating the inflammatory response known as a violaceous halo. This disease type is most commonly seen in adults,[5–7] and fibrosis and inflammation mainly infiltrate the reticular dermis.

Linear scleroderma

This disease type most commonly occurs in children and young people, and accounts for 40–70% cases of localized scleroderma in children.[4,7,8] Generally, sclerotic areas with linear or bands of color changes are distributed unilaterally on the limbs, face and head, and present as depressed areas with comparatively unclear borders. The skin lesions are normally distributed along Blaschko's lines; therefore, somatic mosaicism is thought to possibly be involved in this condition.[9] The lesions often affect deeper areas, causing atrophy of adipose tissue, muscles, tendons and bones. When there is involvement of the skin on the limbs, the disease can induce deformity and joint contracture, and prevent growth of the affected limb in children. Lesions on the head present as linear atrophic areas with mild induration and alopecia. The skin surface appears smooth with a luster, turning an ivory white (some cases also develop pigmentation). It commonly affects the skin from the crown of the head to the forehead, and is referred to as morphea en coup de sabre. The lesions can sometimes infiltrate the cheeks, nose or upper lip; and if the lesions involve deep tissue, they can cause deformity, facial asymmetry and dentition deformity. When the lesions extend to the entire one side of the face, the condition is known as Parry–Romberg syndrome (progressive facial hemiatrophy) (see CQ10).

Generalized morphea

This is a more severe form of localized scleroderma, in which the skin presents with multiple patchy or linear lesions that are spread extensively over the trunk and limbs (the classification criteria are described below). The Tuffanelli and Winkelmann classification is extremely easy to understand, but the boundaries between each different type are not always clear. For generalized morphea in particular, a number of authors have advocated different classification criteria. In 1994, Sato *et al.*[10] addressed this issue by advocating classification criteria that

Table 2. Evidence level correspondence

Old evidence level classification		Evidence level classification used in this guideline	
I	Evidence from systematic review/meta-analysis of randomized controlled trial	A	I, II
II	Evidence from at least one randomized controlled trial	B	III
III	Evidence from at least one controlled study without randomization	C	IV
IV[a]	Evidence from analytical epidemiological studies (cohort study)	D	V, VI
IV[b]	Evidence from analytical epidemiological studies (case control study, cross-sectional study)		
V	Evidence from descriptive studies (case reports, case series)		
VI	Evidence from expert committee reports or opinions or clinical experience of respected authorities, not based on patient data		

In addition, state the strength of evidence in the strength of endorsements or recommendations (A, B, C, D).
(Example) (1) Recommend implementing therapy I for patient P (1A) = (strong recommendation, based on strong evidence).
(2) Propose implementing therapy I compared with therapy C for patient P (2C) = (weak recommendation, based on weak evidence).
(3) Propose not implementing therapy I or therapy C for patient P (2D) = (weak recommendation, based on very weak evidence).
(4) Strongly recommend not implementing therapy I for patient P (1B) = (strong recommendation, based on moderate evidence).

Table 3. Summary of clinical questions

Clinical question	Recommendation level	Endorsement
CQ1 How can localized scleroderma be classified?	1D	Classifying localized scleroderma into the five disease types set out in the Padua Consensus classification that is advocated by the Paediatric Rheumatology European Society is recommended, based on clinical and histopathological characteristics: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and mixed morphea
CQ2 Are skin biopsies useful for diagnosis?	1D	Skin biopsies are recommended for the diagnosis of localized scleroderma
CQ3 Are blood tests useful for the diagnosis and evaluation of disease activity?	2D	No blood test findings are highly disease-specific and useful for diagnosis of this condition. Anti-ssDNA antibodies are positive in approximately 50% of cases, and there is often a correlation between disease activity and antibody titer; therefore, referencing these antibodies as disease activity markers is advocated
CQ4 What imaging tests are useful for evaluating the spread of lesions?	1C	Contrast magnetic resonance imaging (MRI) and Doppler ultrasound are useful for evaluating the extent of the spread of localized scleroderma in the skin and into the underlying tissue (adipose tissue, muscle, tendons and bone). Contrast MRI is particularly recommended to enable accurate evaluation of the spread of lesions into the bone. Computed tomography (CT), MRI, electroencephalogram (EEG) and single-photon emission computed tomography (SPECT) are recommended to evaluate brain lesions in patients with morphea en coup de sabre
CQ5 Does disease activity ever spontaneously resolve?	2C	The disease activity in localized scleroderma generally disappears in approximately 50% of cases within 3–5 years, but relapses can occur. The relapse rate is particularly high in patients with juvenile linear scleroderma, and carefully monitoring the patient's condition over the long term is advocated
CQ6 What complications should be noted with localized scleroderma?	2C	In disease types in which the lesions extend into the tissue underlying the skin, there may be joint and muscle symptoms that are caused by damage and fibrosis of adipose tissue, muscle, tendons and bone. In patients with morphea en coup de sabre, there may be symptoms caused by brain lesions, as well as ocular symptoms. This disease is often complicated by other autoimmune diseases, and when a patient is positive for rheumatoid factor or has generalized morphea, these are often associated with arthritis and/or arthralgia. Therefore, looking for these complications when localized scleroderma has been diagnosed is advocated
CQ7 Are localized scleroderma and limited cutaneous systemic sclerosis the same disease?	None	Localized scleroderma and limited cutaneous systemic sclerosis are different diseases
CQ8 What findings are useful for differentiating localized scleroderma from systemic sclerosis?	1D	Differentiating localized scleroderma from systemic sclerosis is recommended, based on findings including sclerodactylia, Raynaud's phenomenon, abnormalities in the nailfold capillaries, visceral lesions and absence of autoantibodies that are specific to systemic sclerosis
CQ9 Can localized scleroderma transform into systemic sclerosis?	None	Localized scleroderma and systemic sclerosis are different diseases. Localized scleroderma does not transform into systemic sclerosis

Table 3. (continued)

Clinical question	Recommendation level	Endorsement
CQ10 Are localized scleroderma and Parry–Romberg syndrome the same disease?	None	Some cases of Parry–Romberg syndrome are considered to be a subtype of linear scleroderma
CQ11 What findings are useful for differentiating localized scleroderma from lupus erythematosus profundus?	2D	Differentiating localized scleroderma from lupus erythematosus profundus (LEP) is recommended, based on the following points: (i) LEP is associated with painful subcutaneous induration during the inflammatory period; (ii) LEP is an inflammatory condition localized to adipose tissue, and the lesions do not extend into muscle or bone; (iii) LEP does not follow Blaschko's lines; (iv) LEP is characterized histopathologically by lobular panniculitis with neutrophil infiltration, nuclear fragmentation, and denaturing and hyalinization of adipose tissue; and (v) 60–70% of LEP cases test positive in the lupus band test
CQ12 What kind of skin lesions should be targeted for treatment?	Active skin lesions, 1D; non-active skin lesions, 2D	Treating active skin lesions with both topical and systemic therapy is recommended. Physiotherapy and surgical treatment are proposed as options for inactive skin lesions that have caused functional disorders and/or cosmetic problems
CQ13 Are topical corticosteroids effective for treating skin lesions?	1D	Topical corticosteroids are recommended for active lesions
CQ14 Is tacrolimus effective for treating skin lesions?	1B	Topical tacrolimus is recommended for active lesions
CQ15 Is systemic administration of corticosteroids effective for treating skin lesions?	1C	Systemic corticosteroids are recommended for skin lesions that are indicated for systemic treatment
CQ16 Are immunosuppressants effective for treating skin lesions?	Methotrexate combined with systemic steroid therapy, 2B; methotrexate monotherapy, 2C; cyclosporin, 2D; and mycophenolate mofetil, 2C	Methotrexate combined with systemic steroid therapy has demonstrated efficacy in the treatment of skin lesions in which systemic treatment is indicated, and it is proposed as a treatment option. Methotrexate monotherapy, cyclosporin, and mycophenolate mofetil are also proposed as treatment options
CQ17 Is phototherapy effective for treating skin lesions?	Ultraviolet (UV)-A1, 2B; broadband UV-A, 2B; psoralen plus ultraviolet A therapy (PUVA), 2C; and narrowband UV-B, 2C	UV-A1, broadband UV-A, PUVA and narrowband UV-B are effective for treating localized scleroderma lesions of the skin, and are particularly effective for treating circumscribed morphea; therefore, these are proposed as treatment options
CQ18 Are there any therapies other than corticosteroids, immunosuppresants and phototherapy that are effective for treating skin lesions?	Imiquimod topical drugs, 2C; topical calcipotriol hydrate/betamethasone dipropionate combination, 2C; topical calcipotriene, 2C; infliximab, none; imatinib, none; photopheresis, none; D-penicillamine, 2C; topical photodynamic therapy, 1B; oral calcitriol, 1A; interferon (IFN)-γ, 1A	Topical imiquimod drugs, combined topical calcipotriol hydrate/betamethasone dipropionate, topical calcipotriene, infliximab, imatinib and photopheresis are proposed as treatment options. The efficacy of D-penicillamine has been demonstrated, but it is not recommended for treatment of skin lesions due to adverse drug reactions. Topical photodynamic therapy, oral calcitriol and IFN-γ have been shown to be relatively ineffective in controlled trials; therefore, these are not recommended for treatment
CQ19 Is there any effective treatment for muscle spasm?	2D	Anticonvulsants are proposed as an option for muscle spasms with linear scleroderma skin involvement. Local injection of botulinum toxin is proposed as an option for muscle spasms in the head and neck

Table 3. (continued)

Clinical question	Recommendation level	Endorsement
CQ20 What is the treatment for joint flexion contracture and limited range of motion?	Systemic therapy, 1D; physiotherapy, 2D; surgical treatment, 2D	Systemic therapy is recommended for active lesions. Physiotherapy is proposed as an option for inactive lesions. Surgical treatment is not recommended for active lesions
CQ21 Is surgical treatment effective for improving the cosmetic aspect of skin lesions on the face and head?	Lesions with settled disease activity, 2D; active lesions, 2D	Surgical treatment is proposed as an option to improve the cosmetic appearance of lesions with less disease activity. Surgical treatment is not recommended for active lesions
CQ22 Is there any effective treatment for brain lesions?	Antiepileptic drugs, 1D; combined systemic steroid therapy and immunosuppressants, 2D	Antiepileptic drugs are recommended for mild epileptic seizures that are caused by brain lesions. Combined systemic steroid therapy and immunosuppressants are proposed as options for active brain lesions in patients with moderate or severe seizures, including those with generalized tonic clonic seizures or treatment-resistant epileptic seizures

are considered to be valid from a serological perspective (Table 5). Sato *et al.* set out the generalized morphea classification criteria as "four or more skin lesions measuring ≥3 cm in diameter, irrespective of whether the skin lesions are patchy or linear, and the affected skin is distributed in two or more regions of the body". Histone is the main target protein for the autoantibodies that manifest with localized scleroderma. The presence of anti-histone antibodies correlates most strongly

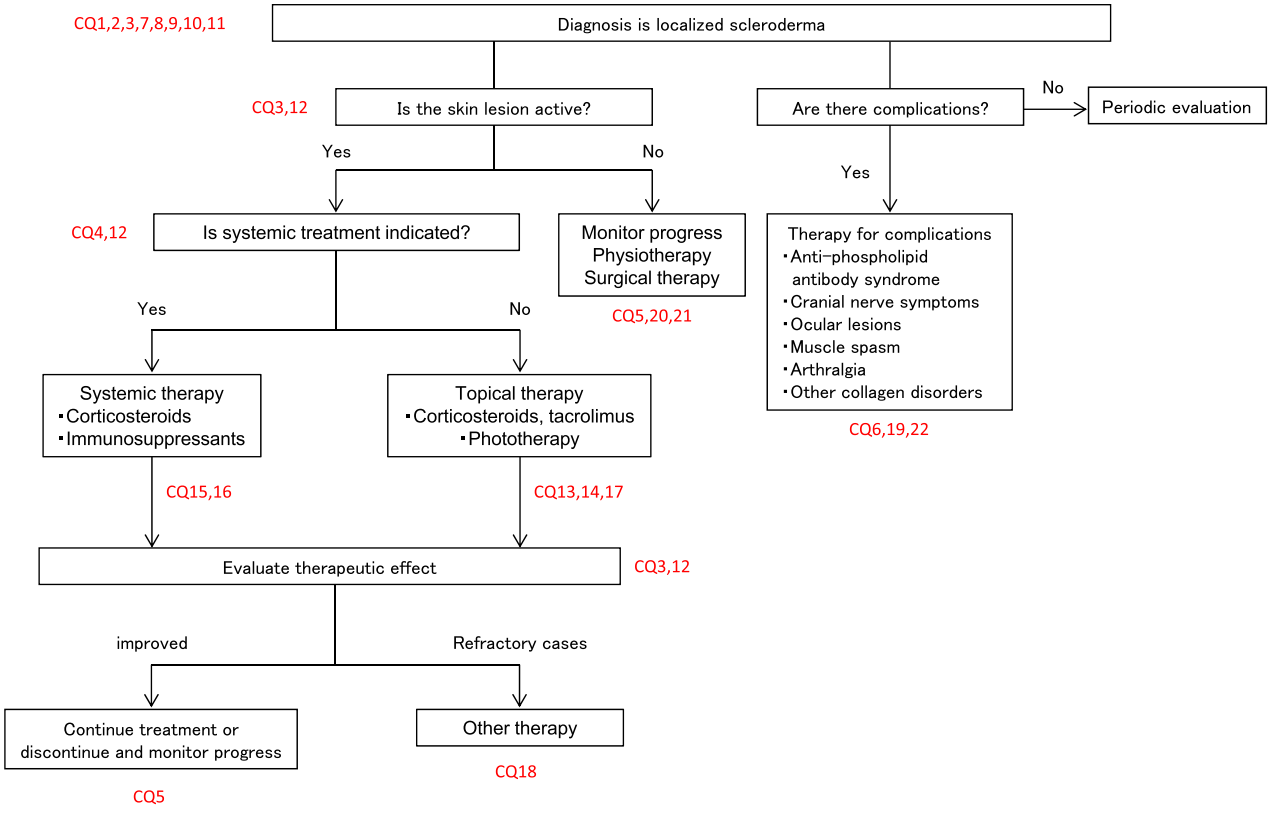

Figure 1. Treatment algorithm for localized scleroderma.

Table 4. Tuffanelli and Winkelmann classification

1. Morphea is usually characterized by circumscribed, sclerotic plaques with an ivory-colored center and surrounding violaceous halo. Punctate morphea is considered to be a variant of morphea, in which there appear small plaque complexes
2. Linear scleroderma appears in a linear, band-like distribution, and scleroderma en bondes is a synonym of linear scleroderma. Frontal or frontoparietal linear scleroderma (en coup de sabre) is characterized by atrophy and a furrow or depression that extends below the level of the surrounding skin
3. Generalized morphea, the most severe form of localized scleroderma, is characterized by widespread skin involvement with multiple indurated plaques, hyperpigmentation and frequent muscle atrophy

with the total number of the affected skin and the extent of distribution, and does not correlate with the type of skin lesion.[10,11] If the above classification criteria are used, patients with generalized morphea have a significantly higher rate of detection of anti-histone antibodies than patients with morphea and those with linear scleroderma.[10] In other words, the same classification criteria are able to appropriately extract patients with generalized morphea, the severe form of localized scleroderma, that is associated with a high incidence of immunological abnormalities (sensitivity, 87%; specificity, 74%). Therefore, it is also considered a valid classification system from a pathological perspective.

Conversely, in 1995, Peterson *et al.*[2] published a more detailed classification system than that of Tuffanelli and Winkelmann (Table 6). In this classification, the five major disease types are listed as plaque morphea, generalized morphea, bullous morphea, linear morphea and deep morphea. A number of subtypes are also listed for each disease type. This classification also includes rare conditions as well as all the disease types for localized scleroderma. However, this classification is problematic because it includes diseases for which a consensus had not been reached in terms of the spectrum of this condition (atrophoderma of Pasini and Pierini, lichen sclerosus et atrophicus and eosinophilic fasciitis), and this classification also does not have a proposal for which disease type a case should be classified if it satisfies more than one characteristic. Therefore, proposals that were published after this classification often use a slightly amended version of the classification.[12–18] Under that situation, in 2004 the Paediatric Rheumatology European Society published a new classification (Padua Consensus classification).[3] This new classification excluded atrophoderma of Pasini and Pierini, lichen sclerosus et atrophicus and eosinophilic fasciitis, and added minor modifications to the subclassifications, while adding the concept of mixed morphea (the coexistence of two or more disease types), and advocated classifying the condition into five disease types: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea and mixed morphea (Table 7). In 2006, the Paediatric Rheumatology European Society investigated 750 cases of localized scleroderma in juvenile patients, and reported that 15% of patients matched the concept of mixed morphea.[4] Currently, much of the work published in Europe or the USA uses this classification without alteration, or the classification is partially changed by individual authors.

The characteristics of the disease types and subtypes described in the Peterson *et al.* classification and Padua Consensus classification (not included in the Tuffanelli and Winkelmann classification) are described below.

Plaque morphea/circumscribed morphea

Plaque morphea in the Peterson *et al*. classification and circumscribed morphea in the Padua Consensus classification are synonymous with morphea in the Tuffanelli and Winkelmann classification.

Guttate morphea

This condition presents as comparatively small, multiple circular or oblong plaques on the skin, and it corresponds with the subtype classification of plaque morphea in the Peterson *et al.* classification.

Atrophoderma of Pasini and Pierini

This name is used for a condition that presents as slightly indurated lesions that appear slate-gray to brown in color. These lesions commonly occur on the trunk and proximal parts of the limbs.[13,17] Generally, these are considered to be an incomplete form or a superficial variant,[3,19,20] and this condition corresponds with a subtype classification of plaque morphea in the Peterson *et al.* classification. It is not described in the Padua Consensus classification, but it is thought to be a superficial variant of circumscribed morphea. Supporting data for the relationship between morphea and atrophoderma of Pasini and Pierini include the following: 20% of circumscribed morphea is complicated by atrophoderma of Pasini and Pierini;[19] and in almost all cases of circumscribed morphea in which fibrosis is limited to the shallow layer of the reticular layer, pigmentation is the main clinical profile and there is virtually no induration.[21]

Keloid morphea/nodular morphea

These conditions form protruding lesions similar to keloid and hypertrophic scars; therefore, these are classified as a subtype of plaque morphea in the Peterson *et al.* classification.

Table 5. Generalized morphea classification criteria proposed by Sato *et al*.

A case is classified as having generalized morphea if both the following criteria are satisfied:

1. Four or more skin lesions that measure 3 cm or more in diameter (irrespective of whether the skin lesions are patchy or linear)
2. The skin lesions are distributed in two or more sites of the seven regions of the body (head and neck, left and right upper limbs, trunk front and back, and left and right lower limbs). If the above criteria are not satisfied simultaneously, the condition is classified as morphea or linear scleroderma based on the morphological characteristics of the skin lesions

Table 6. Peterson *et al.* classification

Plaque morphea
Plaque morphea
Guttate morphea
Atrophoderma of Pasini and Pierini
Keloid morphea (nodular morphea)
(Lichen sclerosus et atrophicus)
Generalized morphea
Bullous morphea
Linear morphea
Linear morphea (linear scleroderma)
Morphea en coup de sabre
Progressive facial hemiatrophy
Deep morphea
Morphea profunda
Subcutaneous morphea
Eosinophilic fasciitis
Pansclerotic morphea of childhood

Table 7. Padua Consensus classification

Circumscribed morphea
(i) Superficial
(ii) Deep
Linear scleroderma
(i) Trunk/limbs
(ii) Head
Generalized morphea
Pansclerotic morphea
Mixed morphea

Lichen sclerosus et atrophicus

This is considered an independent disease, but given that the pathohistological image resembles that of localized scleroderma, and there are reports of cases with both localized scleroderma and this condition, the differences of both diseases are under discussion.[22–25] In the Peterson *et al.* classification, this condition is classified as a subtype of plaque morphea. Attempts have been made to differentiate the two diseases based on immunohistological findings and electron microscope findings;[24,26,27] but at the present time, no consensus has been reached on the difference between the two diseases.

Bullous morphea

A rare form of circumscribed morphea is known as bullous morphea, in which the condition presents as blisters and erosion. The pathohistological image is similar to that of lichen sclerosus et atrophicus.[28]

Linear morphea/morphea en coup de sabre/ progressive facial hemiatrophy

In the Peterson *et al.* classification, linear morphea is synonymous with linear scleroderma, as described in the Tuffanelli and Winkelmann and Padua Consensus classification systems. In the Peterson *et al.* classification, morphea en coup de sabre and progressive facial hemiatrophy are described as subtypes of linear morphea, but these disease names are not stated in the Padua Consensus classification, and linear scleroderma is classified as two subtypes: trunk/limbs and head.

Deep morphea/morphea profunda/subcutaneous morphea

Generally, fibrosis is localized to the dermis in patients with circumscribed morphea, but in patients with linear scleroderma, the lesions are present not only in the dermis but may also extend into the underlying tissue. In deep morphea in the Peterson *et al.* classification, the lesions invade the tissue underlying the skin, but the lesions are broader than those seen in linear scleroderma and do not form linear shapes. Based on these characteristics, deep morphea in the Peterson *et al*. classification corresponds to the circumscribed morphea deep variant in the Padua Consensus classification. In the Peterson *et al.* classification, deep morphea is classified into two subtypes: subcutaneous morphea, in which the lesions are localized to the subcutaneous tissue; and morphea profunda, in which the lesions are present both in the skin and the subcutaneous tissue. Furthermore, since the lesion extends into the subcutaneous tissue, eosinophilic fasciitis and pansclerotic morphea of childhood is also classified as a subtype of deep morphea.

Eosinophilic fasciitis

This is considered an independent disease, but in the Peterson *et al.* classification it is classified as a variant of deep morphea. Eosinophilic fasciitis and localized scleroderma often occur together; therefore, the difference between the two diseases is under discussion.

Pansclerotic morphea/pansclerotic morphea of childhood

These are the names used to describe a type of generalized morphea that is severe and progressive, with the lesions extending deep into the underlying tissue, invading muscle, tendons and bone.[29] This condition mainly affects children; therefore, in the Peterson *et al.* classification, it is referred to as pansclerotic morphea of childhood. However, subsequent reports described the disease as occurring in adults; therefore, in the Padua Consensus classification, it is described as pansclerotic morphea.[30] Skin lesions typically appear on the extensor side of the four limbs and trunk, and progressively infiltrate the skin of the whole body, including the head and neck, causing joint contracture, deformity, ulceration and calcification.[29–31] Squamous cell carcinomas have also been reported to form on skin lesions.[32,33]

Mixed morphea

In the Padua Consensus classification, mixed morphea is defined as the coexistence of two of more disease types, including circumscribed morphea, linear scleroderma, generalized morphea and pansclerotic morphea.

As indicated above, the Tuffanelli and Winkelmann classification was created using unitary evaluation criteria that are

based on the standard lesion morphology and distribution, while the Peterson *et al.* and Padua Consensus classifications focus not only on the lesion morphology and distribution, but also on histological characteristics, and they are therefore dual classification systems that are based on two evaluation criteria. The Tuffanelli and Winkelmann classification is unitary, which makes it very easy to understand, but its disadvantage is that it does not classify severe cases, in which the most important lesions in clinical terms extend deep into the underlying tissue, into a single disease type. The Padua Consensus classification is dual, which means that the boundaries between individual disease types are somewhat blurred, but it is considered to be useful in clinical practice because by adding the histological criteria, it clearly categorizes the clinically important disease types, such as circumscribed morphea/deep variant and pansclerotic morphea. If we consider that the Padua Consensus classification is used as the global standard for classification of localized scleroderma disease types, we recommend classifying localized scleroderma into five different disease types: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea and mixed morphea. The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ2 Are skin biopsies useful for diagnosis?

Recommendation: Skin biopsies are recommended for the diagnosis of localized scleroderma.

Recommendation level: 1D.

Explanation: The main pathology of localized scleroderma is damage to a local area of the skin and the underlying tissue, as well as secondary fibrosis, and it is thought that the autoimmune system is involved in this process. The main histological characteristics that reflect the pathology are inflammation and fibrosis, but neither of these histological findings is specific to localized scleroderma. The histological profile also changes depending upon the stage of the disease. Namely, in the early stages, inflammation is predominant and there is little fibrosis, but once the disease activity declines, either through the natural course of the disease or through treatment, fibrosis forms the main part of the lesion and there is little inflammation. Thus, the histological profile of localized scleroderma is varied, therefore it is essential to evaluate the histology comprehensively considering the clinical activity of the lesion.

Typically, the inflammatory stage is characterized by dense infiltration of monocytes into the perivascular region. Taniguchi *et al.*[34] evaluated the histology of 16 cases of morphea en coup de sabre, and in addition to dense perivascular infiltration of monocytes, they frequently found liquefaction degeneration and incontinentia pigmenti histologica over the entire epidermis including the perifollicular region, as well as dense perineural infiltration of cells. These changes are reported to be particularly profound in lesions with high disease activity. Fibrosis (deposition of dense collagen fibers) is normally limited to the dermis in cases of circumscribed morphea, but in circumscribed morphea/deep variant and pansclerotic morphea, the fibrosis and inflammation extend into the underlying tissue of the skin, and even in linear scleroderma and generalized morphea, lesions sometimes extend to a deep level.

Skin biopsies are useful for differentiating localized scleroderma from other diseases that have a similar clinical profile. A single lesion of connective tissue nevus has a similar clinical profile as circumscribed morphea, while zosteriform connective tissue nevus, characterized by multiple lesions with a dermatomal distribution, resembles linear scleroderma. Keloid morphea is similar to keloid and hypertrophic scars. When skin lesions in circumscribed morphea are marginally fibrotic in the early stages of the disease, they can sometimes resemble mycosis fungoides or parapsoriasis en plaque. Differentiating lupus erythematosus profundus from the circumscribed morphea/deep variant and facial linear scleroderma (Parry–Romberg syndrome) is sometimes essential. All of these diseases present with a characteristic histopathological profile, and it is possible to differentiate them histologically.

However, some diseases are histologically similar to localized scleroderma, and the differences between localized scleroderma and these diseases are still under discussion. Typical cases of eosinophilic fasciitis are characterized by eosinophilic infiltration and fibrosis that mainly appear in the fascia, but eosinophilic infiltration is also often absent, and fibrosis often extends into the adipose tissue and the lower dermis. Therefore, it can be difficult to histologically differentiate eosinophilic fasciitis from the type of localized scleroderma in which fibrosis extends to the tissue underlying the skin.

Lichen sclerosus et atrophicus is characterized by dermal fibrosis as well as liquefaction degeneration and edema from the papillary dermis to the upper reticular dermis, but the histological profile is similar to that of bullous morphea, and it can sometimes be difficult to differentiate these two diseases. Atrophoderma of Pasini and Pierini is characterized by fibrosis that is localized in the area from the papillary dermis to the upper reticular dermis, but this condition can present with a similar histological profile when the lesions in circumscribed morphea have only mild hardening and pigmentation as the main component, and the same disease can be considered an incomplete form of circumscribed morphea or a superficial variant. A part of Parry–Romberg syndrome is considered a subtype of linear scleroderma (see CQ10), but many cases have no abnormalities in the dermis and only have atrophy of the tissue underlying the skin. Therefore, differentiating this condition from histologically active localized scleroderma is possible.

Localized scleroderma and systemic sclerosis can be differentiated based on their clinical characteristics (see CQ8), but there are also histological differences. In systemic sclerosis, the fibrosis starts at the deep dermal layer and spreads towards the upper reticular dermis. Conversely, in localized scleroderma, the distribution and extent of dermal fibrosis varies depending upon the subtype, and the fibrosis may extend to the tissue underlying the skin. In systemic sclerosis, mild to moderate inflammatory cell infiltration is found in the perivascular region, consisting mainly of monocytes; but in localized scleroderma, dense inflammatory cell infiltration, comprised

mainly of monocytes, is frequently seen in the perivascular area. In linear scleroderma, there is liquefaction degeneration and incontinentia pigmenti histologica over the entire epidermis, including the perifollicular area, and perineural infiltration of cells.[34] Thus, localized scleroderma exhibits a characteristic inflammatory infiltration. However, in case of inactive skin lesions, inflammation is scarce, therefore it is it difficult to histologically differentiate localized scleroderma from systemic sclerosis.

Based on the above information, a skin biopsy is useful to diagnose localized scleroderma, but this condition presents with a varied histological profile depending upon the stage of the disease, and it is vital to evaluate the histological profile with due consideration of the clinical profile. It can be difficult to histologically differentiate this condition from diseases in which the differences are still under debate, including eosinophilic fasciitis, lichen sclerosus et atrophicus, and atrophoderma of Pasini and Pierini.

Accordingly, the evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ3 Are blood tests useful for the diagnosis and evaluation of disease activity?

Recommendation: No blood test findings are highly disease-specific and useful for the diagnosis of this condition. Anti-ssDNA antibodies are positive in approximately 50% of cases, and there is often a correlation between disease activity and antibody titer; therefore, referencing these antibodies as disease activity markers is advocated.

Recommendation level: 2D.

Explanation: The main pathology of localized scleroderma is damage to the local area of the skin and underlying tissue, as well as secondary fibrosis, and it is thought that the autoimmune system is involved in this process. Various abnormal blood test findings reflect the pathology of this condition, and it has been reported that some test values correlate with the severity and activity of the disease.

In localized scleroderma, 46–80% of cases test positive for antinuclear antibodies that reflect various immune dysfunction,[35] anti-ssDNA antibodies are detected in approximately 39–59% of cases,[35] anti-histone antibodies in 36–87%[10,36] and rheumatoid factor in 60%.[11] The titers and positivity rate of these antibodies often correlate with the range of distribution of skin lesions. Rheumatoid factor is positive in 82% of cases with generalized morphea,[37] and this is a predictive factor for the development of arthritis and arthralgia.[4] The most important autoantibody that serves as an indicator for disease activity is the anti-ssDNA antibody; and in many cases, a high antibody titer correlates with disease activity, joint contracture and severity of muscular lesions. It is also a clinically useful marker because the antibody titer decreases in response to the therapeutic effect.[37,38] Anti-histone antibodies often reflect the severity of the condition, strongly correlating with the number of skin lesions and range of distribution.[10]

The serum markers that reflect the pathology of fibrosis include procollagen I carboxy-terminal propeptide and type III procollagen-N-propeptide. These markers are at a high level in patients with generalized morphea and serve as indicators for severity.[39,40]

Other abnormal blood tests that are frequently seen in patients with localized scleroderma include peripheral blood eosinophilia, elevated gammaglobulin, elevated soluble interleukin-2 receptors, elevated erythrocyte sedimentation rate, hypocomplementemia and positivity for antiphospholipid antibodies.[35,41–45]

Based on the above information, no disease-specific blood test findings are useful for the diagnosis of localized scleroderma, but anti-ssDNA antibodies are useful for evaluating disease activity. In some cases, the anti-ssDNA antibody titer does not correlate with disease activity. The anti-ssDNA antibody titer may serve as reference to evaluate disease activity, but evaluation of clinical symptoms is the most important when evaluating disease activity in clinical practice.

CQ4 What imaging tests are useful for evaluating the spread of lesions?

Recommendation: Contrast magnetic resonance imaging (MRI) and Doppler ultrasound are useful for evaluating the extent of the spread of localized scleroderma lesions in the skin and into the underlying tissue (adipose tissue, muscle, tendons and bone). Contrast MRI is particularly recommended to enable accurate evaluation of the spread of lesions into the bone. Computed tomography (CT), MRI, electroencephalogram (EEG) and single-photon emission CT (SPECT) are recommended to evaluate brain lesions in patients with morphea en coup de sabre.

Recommendation level: 1C.

Explanation: Localized scleroderma is a disease that is characterized by localized damage to the skin and underlying tissue, as well as secondary fibrosis. Circumscribed morphea forms clearly circumscribed circular or oblong plaques, while linear scleroderma forms lesions with somewhat unclear borders in linear or band-like lesions following Blaschko's lines. The spread of lesions in the skin can be evaluated comparatively easily with macroscopic findings and palpation, but imaging tests are indispensable for evaluating the spread of the lesions to the tissue underlying the skin (adipose tissue, muscle, tendons and bone).

Contrast MRI is the most useful imaging test for evaluating the spread of lesions in patients with localized scleroderma. It is possible to accurately evaluate lesions that extend into the skin, adipose tissue, muscle, tendons and bone with contrast MRI, including subclinical, early stage lesions. Schanz *et al.*[46] performed MRI scans on 43 patients with localized scleroderma (circumscribed morphea or deep variant, $n = 9$; linear scleroderma, $n = 19$; generalized morphea, $n = 12$; and pansclerotic morphea, $n = 3$; mean age 42 years) and found that musculoskeletal lesions were present in 74% of all patients, 96% of patients with joint or muscular symptoms and 38% of patients without joint or muscular symptoms (thickening of the subcutaneous partition, 65%; fascial thickening, 60%; fascia enhancing effect, 53%; synovitis, 40%; tenosynovitis, 21%; perifascial enhancing effect, 16%; myositis, 14%; enthesitis,

7%; and bone marrow lesions, 5%). With respect to disease type, they reported abnormal findings in all patients with pansclerotic morphea, 68% of patients with linear scleroderma, 50% with generalized morphea and 44% with circumscribed morphea/deep variant. Musculoskeletal lesions were found in 38% of patients without joint or muscular symptoms. It is unknown whether these early subclinical lesions are associated with clinical symptoms through the course of the disease, but treatment is extremely difficult once deformity or functional disorders develop. Therefore, it is vital to carefully monitor the skin lesions with these imaging findings and evaluate whether systemic therapy is required for them.

Ultrasound scans enable measurement of the thickness of the dermis and adipose tissue, and it is also possible to check for increased blood flow using enhanced echogenicity or Doppler ultrasound, which enables evaluation of the spread of lesions in the skin and into the underlying tissue (adipose tissue, muscle and ligaments). Enhanced echogenicity and increased blood flow are not seen in inactive lesions; therefore, ultrasound scans are useful for evaluating disease activity.[47–52] Ultrasound scanning is also comparatively easy to perform in clinical practice; considering that there is no need, even with children, to sedate the patient, unlike with MRI imaging, it is an extremely useful form of imaging. It is also the first-line test for evaluating the spread of lesions when contrast MRI cannot be used due to contrast allergy or kidney dysfunction.

It is essential to scan for the presence of brain lesions in patients with morphea en coup de sabre, and head CT and MRI scans are useful for detecting calcification, enlarged ventricles, hemorrhage and inflammation. EEG frequently detects functional abnormalities, and abnormal findings are often seen with SPECT, even when no organic abnormalities are found on CT or MRI.[53]

No investigation has compared contrast CT and contrast MRI in terms of their utility in evaluating the spread of lesions in patients with localized scleroderma, but these techniques were compared in a case report on scleroderma-like skin lesions in a patient with chronic graft-versus-host disease. According to this report, in contrast CT, changes that suggested edema/inflammation or fibrosis were found in the subcutaneous adipose tissue, but there was no enhancing effect, and skin lesions could not be detected. On the other hand, with contrast MRI, there was a definite enhancing effect that corresponded to edema or inflammation in the skin and subcutaneous tissue. In particular, it is possible to differentiate edema or inflammation from fibrosis using contrast MRI, and this technique was reported to be useful for evaluating lesion activity.[54]

Based on the above information, contrast MRI and ultrasound scans are useful for evaluating the spread of localized scleroderma lesions in the skin and into the underlying tissue, and contrast MRI in particular is extremely useful because it can detect bone lesions. CT, MRI, EEG and SPECT are useful for evaluating lesions in patients with morphea en coup de sabre. Accordingly, the evidence level is low, but the recommendation level is set as 1C, based on the consensus of the committee that created this guideline.

CQ5 Does disease activity ever spontaneously resolve?

Recommendation: The disease activity in localized scleroderma generally disappears in approximately 50% of cases within 3–5 years, but relapses can occur. The relapse rate is particularly high in patients with juvenile linear scleroderma, and carefully monitoring the patient's progression over the long term is advocated.

Recommendation level: 2C.

Explanation: The results of multiple retrospective studies on the long-term prognosis of mainly localized scleroderma in juvenile patients have been reported.

Peterson *et al.*[5] conducted a follow-up study on 82 cases of localized scleroderma (the median age at diagnosis was 30 years), using the medical database of Olmsted County, MN, USA (the mean length of follow up was 9.2 years and the longest period was 33 years). They reported that in 50% of patients, the overall duration of disease until improvement of skin lesions was 3.8 years; in those with circumscribed morphea, it was 2.7 years; and in those with deep morphea, it was 5.5 years.

On the other hand, four large-scale studies have been conducted on the long-term prognosis of juvenile patients with localized scleroderma. Christen-Zaech *et al.*[8] investigated 136 children in a study at Northwestern University, and reported that 3.7% of patients experienced relapse after symptoms were stabilized for 6 months or more after completing treatment, and this was particularly common in patients with linear scleroderma. Saxton-Daniels *et al.*[55] conducted a study on 27 patients who were registered in the localized scleroderma registry of the University of Texas Southwestern Medical Center (linear scleroderma, $n = 20$; generalized morphea, $n = 5$; and circumscribed morphea, $n = 2$) and reported that new lesions appeared in 24 cases (89%), lesions were continuously present in eight (29%) and the condition relapsed after going into remission in 16 (59%) (the time until relapse ranged 6–18 years). This also included a patient who developed the condition at 9 years of age and had three relapses over a period of 50 years. Mirsky *et al.*[56] investigated 90 children who were treated with methotrexate for 3 months or longer in Canada (linear scleroderma/limbs, $n = 48$; circumscribed morphea, $n = 26$; and linear scleroderma/head, $n = 23$; including duplicate cases), and reported that 28% of cases experienced relapse within a mean of 1.7 years after the end of treatment, and the predictive factors of relapse included linear scleroderma/limbs and older age at onset (relapsed cases, 9.25 years at onset; non-relapsed cases, 7.08 years at onset). Furthermore, they also reported that linear scleroderma/head tended to have a high relapse rate, the relapsed cases tended to have shorter periods of treatment with methotrexate than the non-relapsed cases, and systemic steroid therapy had no effect on relapse. Piram *et al.*[57] investigated 52 cases of juvenile patients with linear scleroderma in Canada, and reported that disease activity disappeared after a mean period of 5.4 years, including in patients who underwent systemic therapy; but there were also patients who experienced relapse after long-term remission, and 31% of cases had disease activity even after 10 years.

Based on the above information, disease activity in patients with localized scleroderma generally disappears in approximately 50% of cases within 3–5 years, but the disease can relapse after maintaining long-term remission. The relapse rate is particularly high in juvenile patients with linear scleroderma, necessitating careful long-term follow up of these patients. In retrospective studies on the long-term prognosis of localized scleroderma, there was a tendency to select cases with data obtained during adulthood, and cases with long-term disease activity and those with repeated relapse might have been collected selectively. Therefore, the relapse rate might have been estimated as higher than that seen in actual clinical practice.

CQ6 What complications should be noted with localized scleroderma?

Recommendation: In disease types in which the lesions extend into the tissue underlying the skin, there may be joint and muscle symptoms that are caused by damage and fibrosis of adipose tissue, muscle, tendons and bone. In patients with morphea en coup de sabre, there may be symptoms caused by brain lesions, as well as ocular symptoms. This disease is often complicated by other autoimmune diseases, and when a patient is positive for rheumatoid factor or has generalized morphea, these are often associated with arthritis and/or arthralgia. Therefore, looking for these complications when localized scleroderma has been diagnosed is advocated.

Recommendation level: 2C.

Explanation: Localized scleroderma is characterized by localized damage to the skin and underlying tissue, as well as secondary fibrosis, and it is thought that the autoimmune system is involved in this process. Localized scleroderma presents with various symptoms and opinions are divided on what symptoms are defined as complications, but we have defined complications as any symptoms that are caused by damage or fibrosis in tissues other than the skin.

Various complications can occur in disease types in which the lesions extend into the tissue underlying the skin, namely circumscribed morphea/deep variant, linear scleroderma, generalized morphea and pansclerotic morphea. These complications are broadly separated into symptoms that are caused by damage and/or fibrosis of the adipose tissue, muscle, tendons and bone; symptoms caused by brain lesions; and ocular symptoms. Furthermore, localized scleroderma is often complicated by other autoimmune diseases, and there is a high frequency of arthritis and arthralgia in patients who are positive for rheumatoid factor and those with generalized morphea.

Symptoms caused by damage to adipose tissue, muscle, tendons and bone

If the lesions are on the head or neck, they can cause deformity due to atrophy of the underlying adipose tissue, muscle and/or bone (the lesions may also extend into the gums and tongue), and muscle contraction abnormalities may also be caused by damage to the muscles or nerves. If the lesions extend into the periocular tissue, they can cause symptoms such as enophthalmos, paralysis of the orbicularis oculi muscle and ptosis. If the lesions extend into the jawbone, they can cause jaw deformity, occlusal abnormalities, dentition deformities, tooth root atrophy and delayed tooth eruption.[58] If the lesions develop in the limbs, there may be similar atrophy of the underlying adipose tissue, muscle, tendons and/or bone. Synovitis, tenosynovitis and joint contracture may occur, particularly if the lesions develop close to the joints. If the lesions extend deep into the bone, they may cause osteomyelitis. Lesions on the limbs of children can cause a growth disorder of the affected limb.

Symptoms caused by brain lesions

Approximately 20% of patients with morphea en coup de sabre or Parry–Romberg syndrome experience neurological symptoms.[4,53,58] The most serious neurological symptoms are epilepsy, migraine and cranial neuropathy (such as neuralgia, paralysis or convulsions) (see CQ22). Organic and functional abnormalities are frequently detected with CT, MRI, EEG and SPECT, including in patients who do not have neurological symptoms (see CQ4).

Ocular symptoms

Approximately 15% of patients with morphea en coup de sabre or Parry–Romberg syndrome have ocular symptoms.[59] Common abnormalities include sclerosis of adnexa and secondary inflammation of the anterior chamber of the eye and uveitis. Secondary inflammation of the anterior chamber of the eye and uveitis are often asymptomatic and unilateral.[59] A report indicates that there is an increased risk of brain lesions with ocular symptoms.[59]

Other autoimmune disease complications

Two studies have reported that the incidence of autoimmune diseases is high in adults with localized scleroderma.[4,7] Conversely, another report indicates that the incidence of complications due to autoimmune diseases in children with localized scleroderma is no different than that of normal healthy individuals, while other reports indicate that the incidence is higher.[7] It has also been reported that there is often a family history of autoimmune disease in juvenile localized scleroderma; adult localized scleroderma cases complicated by autoimmune diseases are often juvenile-onset cases.[4,7]

Antiphospholipid antibodies are detected with high frequency in patients with localized scleroderma. Sato *et al.*[60] reported that 46% of patients with localized scleroderma tested positive for immunoglobulin (Ig)M and/or IgG anticardiolipin antibodies, and 24% tested positive for the lupus anticoagulant. In a disease type-based investigation, anticardiolipin antibodies were detected in 30% of circumscribed morphea cases, 35% of linear scleroderma and 67% of generalized morphea. The lupus anticoagulant was detected only in generalized morphea cases, but it was positive in 71% of those. Furthermore, Hasegawa *et al.*[43] reported that 17% of patients with localized scleroderma tested positive for one of the antiphospholipid antibodies or antiphosphatidylserine/prothrombin antibodies, which are the main autoantibodies that induce the anticoagulant activity of lupus, and these antibodies were

detected in 27% of patients with generalized morphea. Therefore, testing for the presence of antiphospholipid antibodies when diagnosing patients with localized scleroderma is preferred, and if a patient tests positive, he or she should be screened for thromboembolism.

Arthritis and arthralgia

In an investigation of 750 patients with juvenile localized scleroderma, the incidence of arthralgia and/or arthritis was significantly high in patients who were positive for rheumatoid factor,[4] and 40% of patients with generalized morphea are reported to also have arthralgia.[3,17]

CQ7 Are localized scleroderma and limited cutaneous systemic sclerosis the same disease?

Recommendation: Localized scleroderma and limited cutaneous systemic sclerosis are different diseases.

Recommendation level: None.

Explanation: Localized scleroderma is characterized by localized damage to the skin and underlying tissue, as well as secondary fibrosis. On the other hand, systemic sclerosis is characterized by vasculopathy and fibrosis of the skin and various internal organs. Immune disorders are also thought to be intimately involved in the pathology of systemic sclerosis. Both diseases are characterized by hardening of the skin, and the diseases have been compiled into the single disease concept of scleroderma. However, as can be seen from the completely different distribution of the skin lesions and the lack of vascular disorders and visceral lesions in patients with localized scleroderma, these diseases have different pathologies.

Systemic sclerosis is classified into two disease types based on the scope of the skin lesions. In systemic sclerosis, the skin lesions start at the fingers and spread continuously; but one type, in which the skin lesions extend proximally past the elbow, is known as diffuse cutaneous systemic sclerosis; and another type, in which the skin lesions stop distal to the elbow, is known as limited cutaneous systemic sclerosis.[61] Namely, limited cutaneous systemic sclerosis is a mild form of systemic sclerosis, and is a completely different disease than localized scleroderma. In English, terminology is used to appropriately express the differences in the distribution of skin lesions in each of the diseases (localized and limited); but in Japanese, there are no appropriate terms to express those differences and they are both written as "*genkyoku*". Given the similarity of this term, even doctors often mistakenly believe that both diseases are the same, but the treatment strategy and prognosis are completely different, so doctors should strictly refrain from mistakenly identifying these diseases.

CQ8 What findings are useful for differentiating localized scleroderma from systemic sclerosis?

Recommendation: Differentiating localized scleroderma from systemic sclerosis is recommended, based on findings including sclerodactylia, Raynaud's phenomenon, abnormalities in the nailfold capillaries, visceral lesions and lack of autoantibodies that are specific to systemic sclerosis.

Recommendation level: 1D.

Explanation: Localized scleroderma is characterized by localized damage to the skin and underlying tissue, as well as secondary fibrosis. On the other hand, systemic sclerosis is characterized by vascular disorders, left–right symmetrical continuous spread of skin lesions proximally from the fingers, and fibrosis of various internal organs, including the lungs. Immune abnormalities are thought to be involved in the onset of these diseases, and systemic sclerosis is particularly associated with disease-specific serological abnormalities. Therefore, these diseases can be differentiated based on differences in the distribution of lesions in the skin, the presence or absence of vascular disorders, presence or absence of visceral lesions and differences in serological abnormalities. Namely, localized scleroderma can be clearly differentiated from systemic sclerosis due to the lack of sclerodactylia, Raynaud's phenomenon, abnormalities in the capillaries of the nailfolds and visceral lesions.[62] Antinuclear antibodies are positive in 90% or more of systemic sclerosis cases and autoantibodies that are highly disease-specific; and testing, including anti-topoisomerase I (Scl-70) antibody (positive in 30–40% of Japanese patients with systemic sclerosis) and anti-RNA polymerase III antibody (positive in ~5% of Japanese patients with systemic sclerosis) is covered by insurance. Antinucleolar antibodies (such as anti-U3RNP antibodies and anti-Th/To antibodies, which are positive in ~5% of Japanese patients with systemic sclerosis) are also highly disease-specific to systemic sclerosis. On the other hand, anticentromere antibodies are often positive in patients with other diseases and healthy individuals. Therefore, even if a person tests positive for these antibodies, a diagnosis of localized scleroderma cannot be ruled out immediately. Approximately 50% of patients with localized scleroderma test positive for antinuclear antibodies, but the main corresponding antigen is histone.[11] Moreover, although the disease specificity is low, 39–59% of cases test positive for anti-ssDNA antibodies, and in many cases, this antibody titer reflects disease activity.[35]

The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ9 Can localized scleroderma transform into systemic sclerosis?

Recommendation: Localized scleroderma and systemic sclerosis are different diseases. Localized scleroderma does not transform into systemic sclerosis.

Recommendation level: None.

Explanation: Localized scleroderma is a completely different disease than systemic sclerosis (see CQ7). The name of mild systemic sclerosis, limited cutaneous systemic sclerosis, resembles the name of the disease localized scleroderma; therefore, localized scleroderma is often mistaken for mild systemic sclerosis. Localized scleroderma is often mistakenly thought to transform into the severe diffuse skin lesion type called diffuse cutaneous systemic sclerosis during the disease process. These mistakes are made not just by patients, but they are also frequently made by doctors. However, both diseases have very different prognoses, and it is very important to

refrain from misidentifying these diseases, as it may cause unnecessary distress to patients.

On the other hand, both diseases can occur concurrently. It is known that juvenile localized scleroderma is frequently complicated by autoimmune diseases in adulthood;[4,7] and very rarely, localized scleroderma can be complicated by systemic sclerosis. However, this is simply a complication, and it does not mean that localized scleroderma has transformed into systemic sclerosis. In fact, three independent retrospective studies have reported that 2–3% of patients with juvenile localized scleroderma test positive for anti-topoisomerase I (Scl-70) antibodies, and one of these patients developed typical systemic sclerosis 17 years after developing linear scleroderma.[4,6,57]

The skin symptoms in systemic sclerosis can sometimes develop patchy scleroderma-like skin eruptions during the disease process. Soma *et al.*[63] investigated 135 patients with systemic sclerosis in Japan and found that nine (circumscribed skin lesions, $n = 4$; diffuse skin lesions, $n = 5$) had well-circumscribed sclerotic plaques. The authors reported that these skin eruptions could not be differentiated from localized scleroderma either clinically or histologically. These sclerotic plaques are seen in 6.7% of patients with systemic sclerosis, which is markedly higher than the incidence of localized scleroderma in the general public (in the investigation using the medical database of Olmsted County, MN, USA, the incidence of localized scleroderma was 2.7/100 000 people per year, and the prevalence at 80 years of age was 0.2%).[5] Therefore, the authors decided that the appearance of patchy scleroderma-like skin eruptions should be considered one of the symptoms of systemic sclerosis.

Generalized morphea-like systemic sclerosis is a subtype of systemic sclerosis, but not overlap of systemic sclerosis and localized scleroderma.[64]

CQ10 Are localized scleroderma and Parry–Romberg syndrome the same disease?

Recommendation: Some cases of Parry–Romberg syndrome are considered to be a subtype of linear scleroderma.

Recommendation level: None.

Explanation: In Parry–Romberg syndrome, there is progressive atrophy of half of the face, as illustrated by its other name, progressive facial hemiatrophy. Normally, skin lesions are not seen in this disease; instead, it is characterized by marked atrophy of the adipose and muscle tissue underlying the skin, as well as facial deformity when the lesions extend into the bone. Other than the lack of skin lesions, this disease is similar to localized scleroderma, including development of brain lesions and the distribution of lesions along Blaschko's lines. Reports have indicated that 42% of patients with Parry–Romberg syndrome have morphea en coup de sabre and 25% develop trunk and/or limb linear scleroderma; and it can also coexist with circumscribed morphea.[53,58,65] Furthermore, similar to localized scleroderma, 57% of Parry–Romberg syndrome cases test positive for antinuclear antibodies, which suggests that the autoimmune system may be involved. Patients with Parry–Romberg syndrome often test positive for anti-ssDNA antibodies, anticardiolipin antibodies and rheumatoid factor; therefore, Parry–Romberg syndrome and localized scleroderma have common characteristics. Therefore, some Parry–Romberg syndrome cases are perceived as subtypes of localized scleroderma.

Parry–Romberg syndrome has a similar clinical profile to lupus erythematosus profundus on the cheeks, but it is possible to differentiate these two diseases based on the clinical findings during the inflammatory stage, spread of the lesions, distribution of the lesions and pathohistological imaging (see CQ11).

CQ11 What findings are useful for differentiating localized scleroderma from lupus erythematosus profundus?

Recommendation: Differentiating localized scleroderma from (LEP) is recommended, based on the following points: (i) lupus erythematosus profundus is associated with painful subcutaneous induration during the inflammatory period; (ii) lupus erythematosus profundus is an inflammatory condition localized to adipose tissue, and the lesions do not extend into the muscle or bone; (iii) lupus erythematosus profundus does not follow Blaschko's lines; (iv) lupus erythematosus profundus is characterized histopathologically by lobular panniculitis with neutrophil infiltration, nuclear fragmentation and denaturing and hyalinization of adipose tissue; and (v) 60–70% of lupus erythematosus profundus cases test positive in the lupus band test.

Recommendation level: 2D.

Explanation: Lupus erythematosus profundus is characterized by panniculitis and is associated with atrophy of adipose tissue and skin induration. The rash commonly occurs on the face, extensor side of the upper arms and buttocks, and it often appears as painful subcutaneous induration that gradually progresses. Lupus erythematosus profundus can sometimes accompany with discoid lupus erythematosus on the surface of the skin (this condition can be classified as lupus erythematosus profundus when discoid lupus erythematosus appears and as lupus panniculitis when there is no such lesion). When this rash occurs, differentiating lupus erythematosus profundus from localized scleroderma is not difficult. However, when there is only panniculitis and skin induration, differentiating lupus erythematosus profundus from localized scleroderma is often difficult. It has a striking similarity to Parry–Romberg syndrome when the rash appears on the cheeks. However, both conditions can be differentiated based on: (i) clinical findings of the skin during the inflammatory stage; (ii) the spread of lesions; (iii) the distribution of lesions; and (iv) differences in pathohistological imaging.

In terms of the clinical findings during the inflammatory stage, lupus erythematosus profundus should be suspected when there is painful subcutaneous induration. Even in localized scleroderma, the skin lesions can be painful or uncomfortable while the lesions are progressing, but it is not possible to palpate a painful subcutaneous induration. In terms of the depth of the lesions, in localized scleroderma, the lesions can extend into adipose tissue and the muscle, tendon and bone; but in lupus erythematosus profundus, the inflammation is limited to adipose tissue. Therefore, when there is confirmation that the lesions extend into the muscle, tendons and bone

using contrast MRI or other imaging, there are grounds for suspecting localized scleroderma. In terms of skin lesion distribution, when the lesions follow Blaschko's lines, this would lead to a suspicion of localized scleroderma.

Skin biopsy findings are useful when it is difficult to differentiate different diseases, and it is also preferable to make a histological diagnosis. In the acute stage, lupus erythematosus profundus has the characteristic findings of lobular panniculitis with neutrophil infiltration and nuclear fragmentation, as well as denaturing and hyalinization of adipose tissue, and 60–70% of cases test positive in the lupus band test. However, when only adipose tissue atrophy and fibrosis are seen in inactive lesions, it can be difficult to histologically differentiate lupus erythematosus profundus from localized scleroderma.

CQ12 What kind of skin lesions should be targeted for treatment?

Recommendation: Treating active skin lesions with both topical and systemic therapy is recommended. Physiotherapy and surgical treatment are proposed as options for inactive skin lesions that have caused functional disorders and/or cosmetic problems.

Recommendation level: Active skin lesions, 1D; inactive skin lesions, 2D.

Explanation: Localized scleroderma treatment can be classified into two categories: (i) treatment to inhibit disease activity; and (ii) treatment for functional disorders and cosmetic issues caused by the complete lesions. Therefore, it is important to select the appropriate treatment after accurate evaluation of disease activity.

Currently, there are no evidence-based evaluation criteria for disease activity, but in 2012, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) juvenile localized scleroderma CORE workgroup published disease activity evaluation criteria based on past published work (Table 8).[66] These criteria were created for juvenile patients with localized scleroderma, but they are also applicable to adult cases, and it is good to reference these criteria when evaluating disease activity in clinical practice. Specifically, a case is defined as having disease activity if it satisfies one of the following criteria: (i) appearance of a new lesion or extension of an existing lesion within the prior 3 months (confirmed by a physician); (ii) marked or moderate erythema (including violaceous border) or violaceous color change; or (iii) the existence of progressive deep lesions (confirmed with clinical findings, clinical photographs, MRI or ultrasound). Or, alternatively, if the lesion satisfies two of the following criteria: (i) appearance of a new lesion or extension of an existing lesion within the prior 3 months (reported by the patient at the first visit to the clinician's office); (ii) lesion warmth; (iii) mild erythema of the lesion; (iv) marked or moderate induration of the lesion's border; (v) worsening hair loss in the scalp, eyebrow or eyelashes (confirmed by the physician); (vi) elevated creatine kinase (CK; excluding elevated CK attributable to pathology other than localized scleroderma); or (vii) lesion pathohistological findings that suggest disease activity.

Important imaging tests for evaluating disease activity include thermography, ultrasound and contrast MRI. In the CARRA criteria, elevated skin temperature is an element to evaluate inflammation, and a previous report has shown that thermography is a useful indicator for evaluation of disease activity.[67] Similarly, ultrasound scans have also been shown to be useful for the evaluation of disease activity.[47–52] The evaluation of blood flow using Doppler ultrasound is particularly effective at reflecting the extent of lesion inflammation, and it is a predictive factor for progression of the

Table 8. Juvenile localized scleroderma disease activity evaluation criteria published by the Childhood Arthritis and Rheumatology Research Alliance (CARRA)

Active disease definition for comparative effectiveness studies*
Group 1
New lesion(s) within the prior 3 months, documented by a clinician
Extension of an existing lesion within the prior 3 months, documented by a clinician†
Erythema of moderate or marked level in lesion or an erythematous lesion border
Violaceous lesion or border color
Documentation of active or progressive deep tissue involvement; documentation can be by clinical examination, photographs, magnetic resonance imaging or ultrasound
Group 2
Patient or parent report a new lesion OR extension of an existing lesion occurring within the prior 3 months. Note: this ONLY applies for new patients (i.e. first visit to clinician's office)
Lesion warmth
Mild erythema of lesion
Marked or moderate induration of lesion border
Worsening hair loss in scalp, eyebrow, or eyelashes, documented by a clinician
Elevated creatine kinase level in the absence of another source
Lesion biopsy sample showing active disease (i.e. inflammation and progressive tissue fibrosis, microvasculature occlusion and increased connective tissue macromolecules [e.g. collagen, glycosaminoglycans, tenascin and fibronectin])

*Patients can have either one item from group 1 or two items from group 2 to qualify as having active disease. †Lesion extension observed in serial photographs or tracings, or documentation of 30% or more difference in lesion size (maximum length × width).

condition.[50] Contrast MRI can be used to evaluate the spread of the lesions into the skin and underlying tissue (adipose tissue, muscle, tendons and bone) and for evaluating disease activity. Disease activity is deemed to be present if there is an enhancing effect, and it is also possible to evaluate bone lesions, which cannot be evaluated with ultrasound, with contrast MRI.[46] In the CARRA criteria, elevated CK was the only blood test finding, but elevated myogenic enzymes in blood tests should be considered a possible sign of active lesions that extend into the fascia or muscle when there is no pathology other than localized scleroderma to explain this abnormality.

Active lesions should be treated after determining whether topical therapy (topical corticosteroids, topical tacrolimus or phototherapy) and/or systemic therapy (oral corticosteroids and immunosuppressants) are indicated. Topical therapy and phototherapy act on the outermost layer of the skin, and it is thought that the therapeutic effect of these therapies is low for some types of circumscribed morphea/deep variant, in which the lesions are localized to the underlying tissue. However, apart from these special disease types, topical therapy is generally applicable to all cases. On the other hand, because localized scleroderma is extremely varied clinically, application of topical therapy must be determined flexibly based on individual cases, with consideration given to the site of the lesion, the patient's lifestyle habits, social situation, extent of adverse drug reactions and therapeutic effect of systemic therapy (when systemic therapy is indicated). There is no clear evidence-based standard for the indication for systemic therapy, but various researchers have proposed reference criteria. Takehara *et al.*[38] recommend that systemic steroid therapy should be considered if the condition meets one of the following criteria: (i) there are strong clinical inflammation findings and rapid spread of lesions; (ii) functional disorder is apparent or there is concern that functional disorder may develop in the future; (iii) there is concern of future growth disorder; and (iv) there are muscle lesions and/or high levels of anti-ssDNA antibodies. Additionally, Zwisch-Enberger and Jacobe[68] recommended methotrexate monotherapy or steroid pulse therapy combined with methotrexate for cases that satisfy one of the following: (i) lesions extending into subcutaneous adipose tissue, fascia or muscle; (ii) lesions that cause functional disorders; (iii) rapidly progressing active lesions or active lesions that extend over a wide area; and (iv) disease activity that is not inhibited by phototherapy (appearance of new lesions or expansion of existing lesions during phototherapy or within 6 months of completing irradiation). In the future, it is hoped that evidence-based systemic therapy adaptive criteria will be established, but at present, determining whether systemic therapy is indicated is preferable, with reference to the above-mentioned criteria.

Physiotherapy and surgical treatment are options to treat functional disorders and cosmetic issues that are caused by complete, inactive skin lesions, but the use of these should be determined based on the necessity for each individual case.

The evidence level for descriptions relating to active skin lesions is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ13 Are topical corticosteroids effective for treating skin lesions?

Recommendation: Topical corticosteroids are recommended for active lesions.

Recommendation level: 1D.

Explanation: No clinical study reports have investigated the efficacy of topical corticosteroids to treat localized scleroderma lesions of the skin, but one report on a prospective open-label study investigated the efficacy of topical betamethasone dipropionate ester and calcipotriol hydrate combination therapy.[69] This therapy was applied to six patients with circumscribed morphea with active lesions (aged 15–59 years old) once or twice a day, and the patients were evaluated after 3 months. Five of the six patients experienced clinical improvement of their skin lesions, and two of these patients also experienced improvement in dermal thickening, seen on ultrasound scans. No reports have investigated the efficacy of topical steroid monotherapy, but topical steroids inhibit inflammation and are known to have an antifibrotic effect by inhibiting the proliferation of fibroblasts.[70] Therefore, the use of comparatively potent topical steroids (very strong or strongest class for lesions on the trunk and mild class for lesions on the face) is considered suitable for the treatment of active circumscribed morphea.[71] On the other hand, no studies have investigated the efficacy of topical therapy for lesions in which systemic therapy is generally indicated, including linear scleroderma, but topical therapy is a suitable option for treatment. The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ14 Is tacrolimus effective for treating skin lesions?

Recommendation: Topical tacrolimus is recommended for active lesions.

Recommendation level: 1B.

Explanation: One placebo-controlled double-blind study and two open-label studies have reported on the efficacy of topical tacrolimus for the treatment of circumscribed morphea.

Kroft *et al.*[72] reported the results of a placebo-controlled double-blind study investigating the efficacy of topical 0.1% tacrolimus in 10 patients with circumscribed morphea with multiple active lesions (mean age, 44 years; duration of disease, 1–9 years). All the subjects who were selected had two active lesions to which topical 0.1% tacrolimus or a placebo was applied under double-blinded conditions to each of the lesions twice a day for 12 weeks. Kroft *et al.* reported that there was no change in the lesions in the placebo group before and after the study, but there was a clinically significant improvement in the lesions in the treatment group.

Stefanaki *et al.*[73] conducted an open-label study investigating the efficacy of topical 0.1% tacrolimus in 13 patients with circumscribed morphea (age, 41–74 years; duration of disease, 2 months to 3 years). The drug was applied twice a day for

4 months, and the authors reported that while improvement was seen in lesions with erythema and comparatively weak skin hardening, the response was poor in lesions with strong skin hardening. They reported that in the histological examinations there tended to be improvements in fibrosis after treatment of lesions with mild to moderate fibrosis, and lymphocyte infiltration was reduced, irrespective of the pretreatment status.

Conversely, Mancuso *et al.*[74,75] conducted an open-label placebo-controlled study on topical 0.1% tacrolimus that was applied twice a day, with the night-time portion applied as an occlusive dressing technique (ODT), in seven patients with circumscribed morphea (age, 22–72 years; duration of disease, 3 months to 7 years). In the placebo group, there was no difference in the lesions before and after the study, but in the treatment group, erythema markedly improved within 1 month after starting treatment; and at the 3-month mark, early stage lesions had completely disappeared. Histologically, the skin had almost returned to normal. However, while significant improvement was seen in lesions with strong skin hardening, the authors of the study reported that there was residual atrophy and scarring.

Cantisani *et al.*[76] treated one case with generalized morphea with circumscribed morphea lesions only, with topical 0.1% tacrolimus with an ODT that were administrated twice a day. After 8 weeks, the erythema had disappeared and the skin lesions had improved. After 5 months the skin was clinically almost normal, but there was no change in the untreated lesions.

Based on the above information, topical 0.1% tacrolimus is effective for treating circumscribed morphea; it is particularly effective for active lesions, and it is thought that administrating an ODT may achieve an even higher degree of efficacy. While there are no reports on the efficacy of topical 0.1% tacrolimus in disease types in which systemic therapy is indicated, such as linear scleroderma, topical 0.1% tacrolimus could be considered a treatment option.

CQ15 Is systemic administration of corticosteroids effective for treating skin lesions?

Recommendation: Systemic corticosteroids are recommended for skin lesions that are indicated for systemic therapy.

Recommendation level: 1C.

Explanation: Both a prospective open-label study and a retrospective study have been conducted on the efficacy of systemic steroid therapy to treat localized scleroderma disease types in which the lesions extend into the underlying tissue.

Joly *et al.*[77] conducted a prospective open-label study on the efficacy of systemic steroid monotherapy (not combined with another systemic therapy or topical therapy) for 17 patients with severe localized scleroderma (morphea en coup de sabre, $n = 7$; linear scleroderma, $n = 5$; and generalized morphea, $n = 5$; age range, 14–63 years; duration of disease, 6–96 months). Seven patients were treated with 0.5 mg/kg per day (depending on the severity of the disease), and 10 patients were treated with 1 mg/kg per day for 6 weeks, after which the dose was tapered and treatment was continued for 5–70 months (mean, 18.3 months). In responsive cases ($n = 4$), the skin lesions started to improve within 1–3 months and all the lesions had disappeared by 6–12 months. In the remaining 13 patients, the skin lesions improved; none of these patients developed new lesions during treatment, but six (35%) experienced relapsed at a mean period of 36.8 months (range: 6–114 months) after completing treatment, and the reported adverse drug reactions included hypertension ($n = 2$) and diabetes ($n = 1$).

Piram *et al.*[57] conducted a retrospective study on the efficacy of methotrexate and/or systemic steroid therapy in 52 patients with juvenile linear scleroderma (methotrexate monotherapy, $n = 4$; systemic steroid monotherapy, $n = 4$; methotrexate and systemic steroid combination therapy, $n = 20$; and other therapy, $n = 24$), and they reported that more patients experienced improvement in the steroid treatment group ($n = 24$) than in the non-steroid treatment group ($n = 28$). One patient developed Cushing's syndrome during the course of treatment, and the skin lesions improved after onset of this condition.

Zulian *et al.*[78] conducted a randomized double-blind study on 70 patients with juvenile localized scleroderma (linear scleroderma, generalized morphea or mixed morphea) using methotrexate and systemic steroid combination therapy, but in this study the patients who were allocated to the placebo group ($n = 24$) were treated with systemic steroid therapy (1 mg/kg per day prednisolone, 50 mg maximum) for only 3 months, and their progress was then monitored for 9 months without treatment. The therapeutic effect was evaluated with thermography and skin scores, and in this patient group, all subjects significantly improved for all indicators at 3 months after the start of treatment. The authors of this study also reported that the therapeutic effect weakened as time passed, and in the evaluation at the 12-month interval after starting treatment, the therapeutic effect was no longer maintained (see CQ16).

Based on the above results, systemic steroid therapy is thought to be effective at 0.5–1 mg/kg per day, but in Japan, 0.5 mg/kg per day is the standard. The evidence level is low, but the recommendation level is set as 1C, based on the consensus of the committee that created this guideline.

CQ16 Are immunosuppressants effective for treating skin lesions?

Recommendation: Methotrexate combined with systemic steroid therapy has demonstrated efficacy in the treatment of skin lesions in which systemic treatment is indicated, and it is proposed as a treatment option. Methotrexate monotherapy, cyclosporin and mycophenolate mofetil are also proposed as treatment options.

Recommendation level: Combined methotrexate and systemic steroid therapy, 2B; methotrexate monotherapy, 2C; cyclosporin, 2D; and mycophenolate mofetil, 2C.

Explanation: One randomized double-blind study on combined methotrexate and systemic steroid therapy has evaluated the efficacy of immunosuppressants on localized scleroderma lesions of the skin, mainly targeting disease types in which the lesions extend into the underlying tissue. Four prospective open-label studies and seven retrospective studies

on combined methotrexate and systemic steroid therapy or methotrexate monotherapy have been reported. There has also been one retrospective study on mycophenolate mofetil and two case reports on cyclosporin.

Zulian *et al.*[78] conducted a randomized, double-blind study on 70 patients with juvenile localized scleroderma (linear scleroderma, generalized morphea or mixed morphea; age range, 6–17 years; mean duration of disease, 2.3 years), administrating methotrexate 15 mg/m^2 (20 mg maximum) or placebo once a week for 12 months. All participants concurrently took prednisolone 1 mg/kg per day (50 mg maximum) for the first 3 months, and the therapeutic effect in both groups was evaluated with thermography and skin scores. The participants in both groups had significant improvement in both evaluation methods at 3 months after the start of treatment. In the methotrexate group, the therapeutic effect persisted up to 12 months, while in the placebo group, the therapeutic effect gradually disappeared, and the authors reported that 12 months after starting treatment, there was not a significant improvement compared with before starting treatment. There was no difference between the two groups in terms of the number of new lesions.

Four prospective open-label studies investigated the efficacy of methotrexate monotherapy or combined methotrexate and systemic steroid therapy in 70 patients (adults, $n = 24$; children, $n = 46$) with active localized scleroderma.

Seyger *et al.*[79] conducted a study on nine adults (generalized morphea, $n = 7$; circumscribed morphea, $n = 2$; mean age, 48 years; duration of disease, <6 months or with active lesions) with methotrexate 15 mg/week that was administrated p.o. for 24 weeks (if the therapeutic effect was insufficient at 12 weeks, the dose was increased to 25 mg/week). They reported that skin lesions significantly improved after treatment based on skin scores and Visual Analog Scale scores.

Uziel *et al.*[80] conducted a study on 10 pediatric patients (generalized morphea, $n = 6$; linear scleroderma, $n = 3$; and Parry–Romberg syndrome, $n = 1$; mean age, 6.8 years; mean duration of disease, 4 years), with oral methotrexate 0.3–0.6 mg/kg per week and steroid pulse therapy (30 mg/kg for 3 days) concurrently administrated to nine patients for 3 months. They reported that improvement in skin lesions was seen at a median of 3 months in all nine participants (excluding one, who stopped using methotrexate after 1 month). One patient who stopped using methotrexate after 1 year due to leukopenia experienced relapse 2 months later, and one patient whose condition worsened 10 months after starting treatment subsequently improved with an increased dose of methotrexate and steroid pulse therapy.

Kreuter *et al.*[81] conducted a study on 15 adults (generalized morphea, $n = 10$; linear scleroderma, $n = 4$; and morphea en coup de sabre, $n = 1$; age range, 18–73 years; mean duration of disease, 8.7 years) who were administrated oral methotrexate 15 mg/week and steroid pulse therapy (1000 mg for 3 days) concurrently for 6 months, and they reported that almost all 14 patients who completed the protocol had marked improvement in inflammation and skin lesions, and these findings were confirmed with histological and ultrasound evaluations.

Torok *et al.*[82] conducted a study on 36 pediatric subjects (linear scleroderma/limbs, $n = 12$; linear scleroderma/head, $n = 6$; generalized morphea, $n = 12$; subcutaneous morphea, $n = 3$; and circumscribed morphea, $n = 3$; median age at onset, 7.86 years; median duration of disease, 19.15 months), with treatment that began with methotrexate 1 mg/kg/week s.c. injection (maximum 25 mg/week) and prednisolone 2 mg/kg per day (60 mg/day maximum), followed by an s.c. injection of methotrexate for 24 months, after which the administration route was changed to p.o. and then continued for 12 months. The prednisolone dose was tapered to 0.25 mg/kg per day and continued for 12 months. The authors reported that the skin lesions in all patients significantly improved (median time until improvement, 1.77 months).

Seven retrospective studies[8,56,57,83–86] investigated 397 pediatric patients with active localized scleroderma, who were treated with methotrexate monotherapy or combined methotrexate and systemic steroid therapy. The doses were all different and it is therefore difficult to compare them, but the methotrexate monotherapy group tended to have less consistent results than the methotrexate combined with prednisolone group.

The above results demonstrate the efficacy and safety of combined methotrexate and systemic steroid therapy, which is considered to be effective. A certain proportion of patients relapsed after completing treatment, but the occurrence of relapse tended to decrease with longer methotrexate treatment periods; therefore, long-term administration of methotrexate is recommended. In Japan, methotrexate for treatment of localized scleroderma is not covered by insurance, and it is generally not used as a therapeutic agent for localized scleroderma due to adverse drug reactions. Therefore, the recommendation level is set as 2B, based on the consensus of the committee that created this guideline.

Two case reports have evaluated the effectiveness of cyclosporin to treat juvenile patients with linear scleroderma. Both patients were unresponsive to topical therapy and were treated with oral cyclosporin 3 mg/kg per day. A 12-year-old girl with linear scleroderma on her thigh experienced improvement 3 weeks after starting treatment, and the skin lesions completely disappeared after 4 months. The patient did not experience relapse within 1 year after stopping treatment.[87] The other case report was on a 7-year-old girl with morphea en coup de sabre, whose skin lesions improved 3 months after starting treatment. The erythema disappeared, but the lesions relapsed 18 months after she completed treatment.[88] Adverse drug reactions were not reported in either case report.

Martini *et al.*[89] conducted a retrospective investigation on the efficacy of mycophenolate mofetil (600–1200 mg/m^2/day; mean treatment period, 20 months) in 10 pediatric patients with localized scleroderma (pansclerotic morphea, $n = 2$; generalized morphea, $n = 3$; morphea en coup de sabre, $n = 3$; linear scleroderma of the limbs, $n = 2$; mean age at onset, 8 years; mean duration of disease, 18 months) that was either treatment-resistant (no improvement with 4 months of combined methotrexate and systemic steroid therapy) or had severe extracutaneous symptoms. All patients who were treated

with mycophenolate mofetil had reduced disease activity based on thermography evaluation, and it was possible to reduce the dose or stop methotrexate and steroids. The only adverse drug reaction was mild abdominal discomfort after 27 months.

Therefore, cyclosporin and mycophenolate mofetil may be effective for treating localized scleroderma, and we await further investigation with prospective studies.

In one case report, azathioprine was effective when used in combination with systemic steroid therapy and multiple topical therapies,[90] but there are no reports on its therapeutic effect as monotherapy. A randomized double-blind study was conducted on topical tacrolimus (see CQ14) but no reports have evaluated the efficacy of oral monotherapy. Cyclophosphamide was used in a patient with cranial nerve symptoms (see CQ22) but no reports have examined the effect of monotherapy on skin lesions.

CQ17 Is phototherapy effective for treating skin lesions?

Recommendation: ultraviolet (UV)-A1, broadband UV-A, psoralen plus UV-A therapy (PUVA) and narrowband UVB are effective for treating localized scleroderma lesions of the skin, and are particularly effective for treating circumscribed morphea; therefore, these are proposed as treatment options.

Recommendation level: UV-A1, 2B; broadband UV-A, 2B, PUVA, 2C; and narrowband UV-B (NBUVB), 2C.

Explanation: Numerous investigations have been conducted on the efficacy of phototherapy to treat localized scleroderma, mainly with UV-A1, PUVA, broadband UV-A and narrowband UV-B (NBUVB) as treatment for circumscribed morphea.

The efficacy of phototherapy to treat localized scleroderma was first reported by Kerscher*et al.*[91] in 1994. A report on two patients who were treated with PUVA found marked improvement in histological and ultrasound evaluations. Kerscher *et al.* determined that psoralen may be unnecessary in this action mechanism, and in a follow-up report published the following year on 10 patients treated with UV-A1 alone, they reported improvement in all patients, using a similar evaluation method.[92]

Since 1995, multiple prospective studies on localized scleroderma treated with UV-A1 have been reported.[93–99] These studies include a total of 121 subjects (mainly Caucasian; age range, 3–73 years; duration of disease, 6 months to 20 years; including not only circumscribed morphea, but also circumscribed morphea/deep variant and linear scleroderma), and 70 of these patients were treated with low-dose UV-A1 (20 J/cm^2; 5–20 weeks; total dose, 600–800 J/cm^2). The evaluation of clinical, histological and imaging findings indicated an improvement in 90% of cases. These reports also included two prospective, open-label, randomized controlled studies on the intensity of UV-A1 irradiation and its therapeutic effect. Sator *et al.*[97] conducted a study on 16 patients with circumscribed morphea, selected three active lesions, and separated the subjects into the low-dose UV-A1 treatment group (20 J/cm^2; total dose, 600 J/cm^2), medium-dose UV-A1 treatment group (70 J/cm^2; total dose, 2100 J/cm^2) and non-irradiated control group. They reported that 3, 6 and 12 months after the end of irradiation, a significant improvement was seen in the treatment group compared with the non-treatment group; and with the ultrasound-based evaluation, they found that the medium-dose UV-A1 treatment had a significantly higher improvement effect on dermal thickness than low-dose UV-A1 treatment. Stege *et al.*[93] conducted a study with 17 patients with localized scleroderma (circumscribed morphea, $n = 15$; linear scleroderma, $n = 2$; age, 9–72 years; duration of disease, 9 months to 6 years), comparing high-dose UV-A1 (130 J/cm^2; total dose, 3900 J/cm^2) and low-dose UV-A1 (20 J/cm^2; total dose, 600 J/cm^2). They found that high-dose UV-A1 treatment had significantly better effects on improvement than low-dose UV-A1 treatment in all clinical, histological and imaging findings. In particular, they reported that the skin lesions completely disappeared in four of the 10 patients who were treated with high-dose UV-A1, and in nine patients the therapeutic effect was maintained at 3 months after the end of treatment. Based on the above information, we assume that the therapeutic effect of UV-A1 on localized scleroderma is dose-dependent.

There are two different reports on the therapeutic effect of phototherapy in fibrotic skin conditions, investigating if the effect is related to skin type. Jacobe *et al.*[100] conducted a study on 101 patients (localized scleroderma, systemic sclerosis, graft-versus-host disease, atopic dermatitis, nephrogenic sclerosing fibrosis, granuloma annulare, pityriasis rubra pilaris and urticaria pigmentosa) who were treated with high-dose UV-A1, and investigated the therapeutic effect based on Fitzpatrick skin types I–V. They reported that there was no difference in the therapeutic effect between different skin types, both among all the subjects and among the 47 patients with localized scleroderma. On the other hand, Wang *et al.*[101] investigated 18 patients with localized scleroderma, systemic sclerosis and graft-versus-host disease, using high-dose UV-A1 (130 J/cm^2) or medium-dose UV-A1(65 J/cm^2) irradiation three times a week for 14 weeks. They reported that with high dose UV-A1, the expression inhibition effect of type I collagen and type III collagen and the expression induction effect of matrix metalloproteinase differed, depending upon the skin type. Namely, the paler the color of the skin, the greater the effect; and the darker the color, the weaker the effect. They also reported that after the first high-dose UV-A1 treatment, there was reduced expression of type I and type III collagen; however, this effect was not seen after the third dose of irradiation with high-dose UV-A1. Based on the aforementioned results, we suggest that pulse irradiation should be used to increase the therapeutic effect of UV-A1 to prevent the attenuation of suntan.

Investigations into broadband UV-A have examined PUVA or low-dose broadband UV-A. Two prospective studies have been conducted on the therapeutic effect of PUVA[102,103] with a total of 30 subjects (PUVA bath, $n = 17$; oral PUVA, $n = 11$; topical PUVA, $n = 2$), with 80% of cases showing clinical improvement. El-Mofty *et al.*[104,105] conducted two prospective studies on low-dose broadband UV-A. Twelve patients with circumscribed morphea underwent 20 doses of irradiation with

low-dose broadband UV-A (20 J/cm^2), and all treated skin lesions showed improvement compared with non-irradiated lesions. When 63 patients with circumscribed morphea were treated with 20 doses of low-dose broadband UV-A irradiation at 5, 10 and 20 J/cm^2 and the results were compared, there was no difference in the therapeutic effect between the different irradiation doses. These two studies reported that the therapeutic effect was good (77%).

One prospective, open-label, randomized controlled study compared the efficacy of NBUVB and UV-A1. Kreuter *et al.*[106] conducted a study on 64 patients with localized scleroderma (circumscribed morphea, $n = 50$; linear scleroderma of the limbs, $n = 4$; linear scleroderma of the head, $n = 4$; circumscribed morphea/deep variant, $n = 2$; generalized morphea, $n = 3$; age, 5–73 years, duration of disease, 5 months to 39 years), using low-dose UV-A1 (20 J/cm^2), medium-dose UV-A1 (50 J/cm^2) and NBUVB (Fitzpatrick skin type II started at 0.1 J/cm^2, Fitzpatrick skin type III started at 0.2 J/cm^2, and the irradiation dose was increased by 0.1–0.2 J/cm^2 at a time, reaching a maximum irradiation dose of 1.3 and 1.5 J/cm^2, respectively), five times a week for 8 weeks. The authors reported that all 62 patients who completed the protocol in any treatment group had significant improvements, based on both histological and ultrasound evaluation. In a comparison of the therapeutic effect among the three groups, the medium-dose UV-A1 therapy demonstrated a significantly higher therapeutic effect than NBUVB, and there were no significant differences between low-dose UV-A1 and NBUVB, and medium dose UV-A1 and low dose UV-A1. The study concluded that NBUVB, which is relatively easy to use, had an equivalent effect to that of low dose UV-A1.

Furthermore, approximately 50% of patients with localized scleroderma are positive for antinuclear antibodies, but there has not been a single report of photosensitivity in more than 400 subjects; therefore, phototherapy is considered to be a very safe therapy.

Based on the above information, UV-A1, broadband UV-A, PUVA and NBUVB are all effective for treating localized scleroderma, and this treatment is considered particularly effective for circumscribed morphea. UV-A1 has a high degree of therapeutic effect and the effect is dose-dependent. However, few facilities are able to perform UV-A1, and irradiation treatment takes between 30 and 60 min; therefore, this treatment is difficult to implement in clinical practice. Conversely, NBUVB machines are widespread, the treatment requires a shorter irradiation time and it is considered an easier treatment to administrate in clinical practice than UV-A1. However, there are still little clinical data and further evaluation of the efficacy of this treatment is essential.

Phototherapy for localized scleroderma is not covered by insurance, and excessive irradiation may induce phototoxic dermatitis or skin cancer and exacerbate pigmentation. For these reasons, although UV-A1 and broadband UV-A have demonstrated efficacy in controlled studies, the recommendation level is set as 2B, based on the consensus of the committee that created this guideline.

CQ18 Are any therapies other than corticosteroids, immunosuppressants and phototherapy effective for treating skin lesions?

Recommendation: Topical imiquimod, topical calcipotriol hydrate/betamethasone dipropionate ester compound, topical calcipotriene, infliximab, imatinib and photopheresis are proposed as treatment options.

The efficacy of D-penicillamine has been proposed, but using this product is not recommended due to adverse drug reactions.

Topical photodynamic therapy, oral calcitriol and interferon (IFN)-γ have been shown to be relatively ineffective in controlled trials; therefore, these are not recommended for treatment.

Recommendation level: Topical imiquimod, 2C; topical calcipotriol hydrate/betamethasone dipropionate ester compound, 2C; topical calcipotriene, 2C; infliximab, none; imatinib, none; photopheresis, none; D-penicillamine, 2C; topical photodynamic therapy, 1B; oral calcitriol, 1A; IFN-γ, 1A.

Explanation: Trial therapies for localized scleroderma, including imiquimod topical drugs, topical calcipotriol hydrate/betamethasone dipropionate ester compound, topical calcipotriene, infliximab, imatinib, photopheresis, D-penicillamine, topical photodynamic therapy, oral calcitriol and IFN-γ s.c. injection have been reported as case accumulation studies, case reports or controlled studies.

Dytoc *et al.*[107] investigated the effect of 5% imiquimod cream on 12 patients with localized scleroderma. The cream was applied topically three times a week before bed, allowing for an increase in the number of applications if the cream was well tolerated. Six months after starting treatment, all patients had improved skin hardening, erythema and depigmentation, and significant improvement was seen in the treatment group, including two patients who took part in comparisons with their own non-treated control lesions. Dytoc *et al.* reported that inflammation and fibrosis improved in the four patients who took part in histological comparisons before and after treatment. Campione *et al.*[108] conducted a study on two patients with circumscribed morphea, using a topical application of 5% imiquimod cream for 5 days, followed by a 2-day break over a 16-week treatment period, and reported that the lesions completely resolved.

Dytoc *et al.*[69] conducted a prospective open-label study to investigate the efficacy of a topical calcipotriol hydrate/betamethasone dipropionate ester compound. The drug was applied once or twice a day to treat active circumscribed morphea in six subjects (age range, 15–59 years); after 3 months, five of the six participants showed clinical improvement, and Dytoc *et al.* reported that improvement was also seen on ultrasound evaluation.

Cunningham *et al.*[109] reported that there was a significant improvement in erythema, pigmentation, telangiectasias and capillary infiltration in 12 patients with active morphea or linear scleroderma after 3 months of taking calcipotriene as an ODT twice a day.

Diab *et al.*[110] administrated infliximab 5 mg/kg per month to a 66-year-old patient with generalized morphea, and reported that progression of the skin lesions halted after the second dose. Histological improvements in the lesion were seen after the fourth dose.

Three case reports have evaluated the effect of imatinib. Moinzadeh *et al.*[111] administrated imatinib 200 mg/day for 6 months to a patient with generalized morphea (74 years old; duration of disease, 12 months) who was resistant to treatment including PUVA, cyclosporin, systemic steroid therapy and azathioprine. They reported improvement in the clinical and ultrasound evaluation at 3 months after starting treatment, but the patient's condition relapsed 6 months after stopping treatment. Inamo *et al.*[112] started treatment for a child (3 years old) with generalized morphea, using prednisolone 1 mg/kg per day, methotrexate 9.5 mg/m^2/week and imatinib 235 mg/m^2/day. The dose of prednisolone was tapered and then stopped after 3 months, imatinib was stopped after 1 year, and methotrexate therapy was continued for 4 years. They reported marked improvement in the patient's skin lesions and improvement in joint range of motion at 1 year after starting treatment, and there was no relapse 1 year after stopping all treatments. Coelho-Macias *et al.*[113] administrated imatinib to an adult patient (50 years old; duration of disease, 10 years) with generalized morphea and multiple skin ulcerations, for 12 months (200 mg/day for 3 months, 300 mg/day for 9 months). They reported that the skin lesions improved based on histological and ultrasound evaluations, the skin ulcerations healed and joint range of motion improved.

Three case reports have evaluated the effect of photopheresis. Cribier *et al.*[114] performed photopheresis on two patients with severe localized scleroderma. Treatment was abandoned in the patient with generalized morphea 3 months after starting because it was no longer possible to secure a peripheral blood vessel. However, the patient with linear scleroderma continued treatment for 16 months, and Cribier *et al.* reported that the skin lesions had improved. Schlaak *et al.*[115] administrated mycophenolate mofetil 2 g/day to a patient with treatment-resistant, bullous, generalized morphea and implemented photopheresis for 2 days consecutively every 2 weeks. After the sixth course of treatment, the authors gradually increased the intervals between treatments. They reported that the pain improved beginning at 4 weeks after starting treatment, all the ulcerations healed by 10 weeks after starting treatment and no new ulcers formed in the following 6 months.

Falanga *et al.*[116] evaluated the efficacy of D-penicillamine 2–5 mg/kg per day in 11 patients with lesions over a broad area and severe localized scleroderma. They reported that seven of the 11 patients (64%) experienced improvement within 3–6 months, all seven patients no longer had any active lesions, five patients had softening of the skin, two of the three pediatric patients achieved normal growth in the limb that was affected by a lesion, and joint stiffness and contracture also improved. The improved cases were treated with a dose of 2–5 mg/kg for 15–53 months. One patient developed renal syndrome and three other patients developed mild, reversible proteinuria. There are no controlled studies on the efficacy of D-penicillamine, and it is currently almost never used due to concerns about adverse drug reactions.

Karrer *et al.*[117] administrated topical photodynamic therapy using 5-aminolevulinic acid (5-ALA) to five patients with treatment-resistant, localized scleroderma. The patients were treated with photo-irradiation once or twice a week after topical application of 3% 5-ALA gel for 3–6 months, and the skin lesions improved. Temporary pigmentation was reported as an adverse drug reaction. Conversely, Batchelor *et al.*[118] implemented a prospective, single-blinded, controlled study on six adult patients with morphea and two or more active lesions. Treatment involved an ODT application of 20% 5-ALA cream for 5 h, followed by photo-irradiation that was implemented once a week for a total of six treatments. After 6 weeks, at the end of treatment, no significant therapeutic effect was seen in clinical evaluation. They reported that while histological improvement was seen in one patient, the remaining five patients did not improve.

Hulshof *et al.*[119] administrated oral calcitriol (0.75 μg/day for 6 months and 1.25 μg/day for 3 months) or an oral placebo to 20 patients with localized scleroderma for 9 months, and conducted follow up 6 months after the end of treatment. They reported that there was no difference in the improvement rate of the skin scores between the two groups, and there was no change in the serum markers that were involved in metabolism of collagen.

Hunzelmann *et al.*[120] conducted a randomized, double-blind study on 24 patients with progressive lesions, administrating an IFN-γ s.c. injection (100 mg for 5 days consecutively for 2 weeks, followed by 100 mg once a week for 4 weeks, followed by an 18-week observation period). They reported that there was no significant difference in the lesion size, degree of fibrosis and type I collagen mRNA between the treatment and control groups.

CQ19 Is there any effective treatment for muscle spasms?

Recommendation: Anticonvulsants are proposed as an option for muscle spasms with linear scleroderma skin involvement. Local injection of botulinum toxin is proposed as an option for muscle spasms in the head and neck.

Recommendation level: 2D.

Explanation: Localized scleroderma may be associated with musculoskeletal spasms. There have been seven case reports to date[121–125] on patients with linear sclerodermas (linear scleroderma/limbs: $n = 5$; Parry–Romberg syndrome: $n = 2$). Various muscle contraction abnormalities (e.g. muscle convulsions, muscle contracture, calf cramps) appeared at the same time that lesions appeared in the skeletal muscle underlying the lesion. All patients were evaluated with electromyography and the abnormalities were highly varied, ranging from dystonia, neuropathy, continuous muscle fiber activity and neuromyotonia to no abnormality. Therefore, it is assumed that there is no single mechanism for muscle spasms in patients with localized scleroderma.

As reported by Taniguchi *et al.*,[24] inflammatory cell infiltration around the neurons is a characteristic finding in linear

scleroderma skin biopsies, but in cases in which Kumar *et al.*[123] were able to confirm neuromyotonia with electromyogram, they reported that they found perineuronal cell infiltration in histological imaging of skin lesions directly above the diseased muscle. Given that muscle contraction abnormalities are found even in cases in which the inflammation does not necessarily reach the muscle, neurological disorder may be the main cause of muscle symptoms, at least in some patients.

One theory suggests that adipose tissue and muscle atrophy in linear scleroderma is caused by sympathetic nervous system disorders, and there has been exhaustive investigation on the muscle and nerve lesions that are found in this disease. Saad Magalhaes *et al.*[126] evaluated electromyograms for nine patients with juvenile linear scleroderma (linear scleroderma/limbs, $n = 7$; Parry–Romberg syndrome, $n = 2$) and found myogenic changes in the muscle underlying the lesions in eight patients (both patients with Parry–Romberg syndrome had myogenic changes in the masticatory muscles), while one patient had neurogenic changes. In an investigation on the conduction velocity of limb motor neurons and sensory nerves, they reported that they found abnormalities in a patient with linear scleroderma in whom a lesion extended deep into the thigh. None of these patients had active lesions and there were no muscle symptoms on electromyography. The authors assumed that in linear scleroderma, the presence of subclinical secondary muscle lesions that are caused by neurological disorders are widespread and, rarely, some of these lesions cause muscle contraction disorders.

On the other hand, localized scleroderma can be complicated by inflammatory myopathy, and to date there have been 10 case reports of localized scleroderma with inflammatory myopathy in which myositis findings were confirmed with muscle biopsy (linear scleroderma/limbs, $n = 4$; circumscribed morphea, $n = 2$; linear scleroderma/head, $n = 4$).[127–134] Muscle symptoms commonly include muscle weakness, fatigue and muscle atrophy, but muscle convulsions were reported in one out of 10 patients.[133] Therefore, if muscle contraction abnormalities are seen in patients with localized scleroderma, direct muscle injury must be considered in the pathology of this disease and tests must be implemented accordingly.

In terms of treatment, the efficacy of anticonvulsants and local injection of botulinum toxin has been proposed. In previous reports, anticonvulsants (phenytoin, $n = 2$; tizanidine, $n = 1$) were reported to be markedly effective for three out of five cases of linear scleroderma of the limbs with muscle contraction abnormalities.[121,123,124] Furthermore, other reports indicated that convulsions were well controlled in two patients with Parry–Romberg syndrome with local injections of botulinum toxin.[122,125]

Muscle contraction abnormalities when there are active lesions in patients with linear scleroderma suggest that the lesion extends deep into the muscle, and this may serve as a reference when determining whether systemic steroid therapy or immunosuppressants are indicated. The therapeutic effect of systemic steroid therapy and immunosuppressants on muscle convulsions is unknown, but in the two aforementioned case of Parry–Romberg syndrome, in which convulsions were well controlled with local injections of botulinum toxin, in one of those patients, combined systemic steroid therapy and methotrexate was reported to be completely ineffective for treating convulsions.[125] If myositis can be confirmed clearly, systemic steroid therapy and immunosuppressants are indicated, but in the above 10 cases, nine patients were administrated prednisolone (5–70 mg/day), two of whom responded to treatment; and five were administrated methotrexate, three of whom responded to treatment.[124]

CQ20 What is the treatment for joint flexion contracture and limited range of motion?

Recommendation: Systemic therapy is recommended for active lesions.

Physiotherapy is proposed as an option for inactive lesions.

Surgical treatment is not recommended for active lesions.

Recommendation level: Systemic therapy, 1D; physiotherapy, 2D; surgical treatment, 2D.

Explanation: Circumscribed morphea/deep variant, linear scleroderma, generalized morphea and pansclerotic morphea that develop around joints are associated with joint flexion contractures and limited range of motion. If these symptoms develop progressively, promptly introducing systemic therapy is vital to inhibit progression of the symptoms (see CQ12).[38,68] The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

On the other hand, many studies recommend physiotherapy for already complete joint flexion contractures and limited range of motion.[2,17,135,136] Rudolph and Leyden[137] reported that range of motion of the elbow joint normalized and there was marked improvement in the range of motion of the wrist and finger joints after 1 year of passive and active stretching twice a day at home in a patient with juvenile linear scleroderma (14 years old) with flexion contractures of 3–5 fingers, radial deviation of the wrist joint and severely limited range of motion in the elbow joint 6 years after onset of the condition. To date, there has not been a controlled study on the efficacy of physiotherapy. Although its true efficacy is unknown, the efficacy of physiotherapy has been demonstrated for finger flexion contractures in patients with systemic sclerosis, which is a similar fibrotic disease.[138] Therefore, physiotherapy should be proactively introduced to prevent and improve joint flexion contractures and limited range of motion in patients with localized scleroderma.

Surgical treatment has not been fully investigated and its efficacy is unknown. However, surgical treatment may exacerbate active lesions and performing surgery for this condition requires very careful consideration. Chazen *et al.*[139] investigated seven cases of localized scleroderma in which surgical treatment such as fasciectomy and skin grafts were performed for limited range of motion in joints, and reported that these surgical treatments either had no effect or exacerbated the joint's range of motion.

CQ21 Is surgical treatment effective for improving the cosmetic aspect of skin lesions on the face and head?

Recommendation: Surgical treatment is proposed as an option for lesions with settled disease activity to improve the cosmetic aspect of the lesions.

Surgical treatment is not recommended for active lesions.

Recommendation level: Lesions with settled disease activity, 2D; active lesions, 2D.

Explanation: The cosmetic issues that are associated with morphea en coup de sabre and Parry–Romberg syndrome cause patients considerable psychological anguish, and significantly disrupt both physical and psychological quality of life. Therefore, cosmetic surgery is performed to repair the cosmetic aspect of the lesions.

Palmero *et al.*[140] conducted a retrospective survey on 10 patients who underwent cosmetic surgery for juvenile morphea en coup de sabre or Parry–Romberg syndrome (autologous fat injection, Medpor implant, cranioplasty with bone cement or free inguinal flap). The patients' main motivation for undergoing surgery included unhappiness with their appearance, loss of confidence and being subjected to bullying, and they stated that their physical appearance had the greatest impact on their quality of life. Therefore, all patients investigated undergoing further surgery and stated that they would recommend surgery to other patients.

It is difficult to objectively evaluate the degree of improvement in terms of esthetic appearance, but the main aim of this surgery is to remove the patients' mental anguish. From that perspective, cosmetic surgery is considered an effective treatment option. Postoperative relapses have been reported, and it is important to embark on surgery once the disease activity has settled adequately.

CQ22 Is there any effective treatment for brain lesions?

Recommendation: Antiepileptic drugs are recommended for mild epileptic seizures that are caused by brain lesions.

Combined systemic steroid therapy and immunosuppressants are proposed as options for active brain lesions in patients with moderate or severe seizures, including those with generalized tonic clonic seizures or treatment-resistant epileptic seizures.

Recommendation level: Antiepileptic drugs, 1D; combined systemic steroid therapy and immunosuppressants, 2D.

Explanation: Epilepsy is the most frequently seen neurological symptom of localized scleroderma, and various antiepileptic drugs are used to treat epileptic seizures.[141–151] The drugs include carbamazepine, oxcarbazepine, phenobarbital, sodium valproate, topiramate, clobazam, pregabalin, nitrazepam, vigabatrin, sultiame and lamotrigine. Antiepileptic drugs were reported to be effective at controlling epileptic seizures in 78% of mild cases.[152]

Immunosuppressant therapy is essential for generalized tonic clonic seizures or treatment-resistant epileptic seizures. The most frequently used drugs are corticosteroids, used in 80% of previously reported cases with a reported 90% efficacy.[127,142,143,145–147,153,154] However, only one case has been treated with corticosteroid monotherapy,[111] while four were treated with steroids and methotrexate,[142,143,146,154] three were treated with corticosteroids combined with azathioprine,[125,129,131] two were treated with corticosteroids combined with cyclophosphamide,[147] and one each were treated with corticosteroids combined with mycophenolate mofetil,[142] IFN-γ[145] or high-dose Ig i.v. therapy.[153] Improvement of symptoms was reported for all the treatments, other than high-dose Ig i.v. therapy.[153,155]

There has been one case in which functional cerebral hemispherectomy was performed for epilepsia partialis continua,[156] and two cases in which a partial corticectomy was performed for treatment-resistant epileptic seizures,[153,157] and the symptoms improved in all cases. There are also reports of cases in which progressive multifocal encephalopathy, stroke and peripheral neuropathy were well controlled with corticosteroids.[158–160] There was also one case in which steroid pulse therapy effectively treated hemiparesis, and one case in which steroid pulse therapy and high-dose Ig i.v. therapy were reported to be ineffective.[153,161] There have been case reports in which corticosteroids, methotrexate and mycophenolate mofetil effectively treated recurrent headaches and cranial nerve lesions.[142,143,162,163] There have also been reports indicating that anticonvulsants and antidepressants effectively mitigated symptoms.[144,164,165] One case report indicated that corticosteroids and azathioprine were ineffective for treating optic papillitis.[145] One case of cerebral vasculitis, which improved with mycophenolate, has been reported.[162]

Based on the above information, antiepileptic drugs are effective for treating mild epileptic seizures that are caused by brain lesions, while combined systemic steroid therapy and immunosuppressants is considered to be effective for moderate or worse epilepsy, including generalized tonic clonic seizures or treatment-resistant epileptic seizures. The evidence level on antiepileptic drugs is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

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