

## Unilateral generalized morphea: First case report in Taiwan

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### Abstract

Generalised morphea (GM) is a subtype of localised scleroderma that usually manifests with bilateral involvement. Unilateral generalised morphea (UGM) is a rare variant of GM. This is a case report of a Taiwanese girl with UGM over the left side of her body. She presented with hyperpigmentation, tightness, and skin atrophy over the left extremities and trunk. Mild range of motion (ROM) limitation over the left knee was also noted. At the clinic, the patient was given oral prednisolone, oral methotrexate (MTX), and oral D-penicillamine. Topical emollient and topical glucocorticoids were also given. The dose of oral prednisolone was tapered gradually. All symptoms were improved under the treatment and regular rehabilitation program. To date, there is very little evidence to form the basis for treatment recommendations. This case report provides a treatment option for UGM in the paediatric group without the use of intravenous methylprednisolone pulse therapy.

**Key words:** child; generalised morphea; localised scleroderma; morphea; paediatrics; scleroderma

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### Introduction

The Paediatric Rheumatology European Society (PREs) has proposed a classification of localised scleroderma that includes five subtypes: circumscribed morphea, linear scleroderma, generalised morphea (GM), pansclerotic morphea, and mixed morphea.<sup>1</sup> Most patients with GM have bilateral involvement, whereas unilateral lesions are most frequently found in the circumscribed and linear disease. It is rare for GM to have unilateral involvement.<sup>2</sup>

Unilateral GM (UGM) has been proposed as an extreme variant of GM, usually beginning in childhood.<sup>1,2</sup> In the seventh edition of the Textbook of Pediatric Rheumatology, the term "unilateral generalized morphea" is mentioned as a variant of GM.<sup>1</sup> After Nagai and colleagues<sup>3</sup> reported the first case of UGM, several researchers have also reported cases. The accurate percentage of UGM among the GM population is still uncertain due to its rarity. To our knowledge, only 10 cases have been previously reported and our new case is the first case in Taiwan. The mean onset age is around 13 years old in these 11 cases. Here, we report a case of UGM with a brief review.<sup>2-8</sup>

### Report of Case

A nine-year-old Taiwanese girl presented to the clinic with a one year history of a dark-coloured skin rash over the left side of her body (**Figure 1**). Itchy erythematous plaques were noted over her left shin after one episode of upper respiratory tract infection (URTI) about one year prior. The lesions on her left shin spread, became hyperpigmented, and hardened. It gradually progressed to her left thigh, left lower abdomen, chest, back, and left forearm within one year. Skin atrophy with tightness was also noted together with tenderness. Examination revealed passive range of motion (ROM) limitation of 10 to 100 degrees with her left knee joint. There was no lesion on her face. There was no burning sensation, no numbness, no swelling, and no warmth over the lesions. She did not have Raynaud's phenomenon, arthralgia, difficulty swallowing, dyspnea, or chest discomfort. Localised scleroderma was diagnosed clinically. The final diagnosis was then confirmed by skin biopsy, which showed thickened and hyalinised collagen bundles in the dermis, with lymphoplasmacytic infiltration around the eccrine glands.



**Figure 1. Skin lesions on the abdomen, forearms and the lower extremities, the left side and the right side**

- (A) Right forearm: normal skin
- (B) Left forearm: hardened and hyper-pigmented skin
- (C) Abdomen: normal skin at right side and hardened and hyper-pigmented skin at left side
- (D) (E) Right knee and leg: normal skin
- (F) (G) Left knee and leg: hardened and hyper-pigmented skin

Laboratory studies showed that her anti-nuclear antibody (ANA) level was 1:160 (cutoff point at 1:40 serum dilution) with a speckled pattern and anti-dsDNA Ab was 239.5 IU/mL (negative: < 10 IU/mL). C3 was 82.5 mg/dL (normal range: 90–180 mg/dL) and C4 was 27.0 mg/dL (normal range: 10–40 mg/dL). Anti-cardiolipin IgM was low positive, 34.36 MPL-U/mL (negative: < 20 MPL-U/mL; low Positive: 20 to 40 MPL-U/mL), while anti-cardiolipin IgG was negative. Rheumatoid factor was 155 IU/mL (negative: < 20 IU/mL). Other routine laboratory workup results and autoantibody screening were unremarkable.

At first, the lesions did not improve under topical corticosteroid therapy at another clinic. She was once treated with 1 mg/kg/day oral prednisolone, maximum 40 mg/day, for 2 months and then tapered off. Topical 50 µg calcipotriol (as hydrate)/0.5 mg betamethasone (as dipropionate) ointment, topical 0.1%

adapalene gel, and oral hydroxychloroquine, at around 6 mg/kg/day, were administrated at another medical center for 6 months. Because of the poor response with progression of lesions, she was then referred to our clinic for further treatment.

At our clinic, the patient was given 0.5 to 1 mg/kg/day oral prednisolone, maximum 20 mg per day, for 2 weeks and then tapered off within one year, 15 mg/m<sup>2</sup>/week oral methotrexate (MTX) for one year and tapered to 10 mg/m<sup>2</sup>/week, and 5 mg/kg/day oral D-penicillamine. Topical emollient and as-needed topical 0.05% fluticasone propionate cream were also given if skin itching occurred. Her lesions softened gradually. The passive ROM limitation of her left knee joint also improved to 0 to 130 degrees under the treatment and regular rehabilitation program. She is still improving under 10 mg/m<sup>2</sup>/week oral MTX and 5 mg/kg/day D-penicillamine treatment and tolerates them well without any observed side effects.

## Discussion

The term “unilateral generalized morphea” (UGM) was first described by Nagai and colleagues<sup>3</sup> in 2002. The term also appeared in the seventh edition of the Textbook of Pediatric Rheumatology in 2016 under the classification of generalised morphea.<sup>1</sup> The diagnosis mainly follows the diagnostic criteria of localised scleroderma. No laboratory abnormality is diagnostic.<sup>9</sup> There are very few case reports on unilateral generalised morphea to date. After Nagai and colleagues<sup>3</sup> reported the first case of UGM in 2002, Appelhans<sup>2</sup> added four additional cases in 2006 and described UGM as a rare variant of localised scleroderma. Since then, additional cases describing UGM have been reported.<sup>4-8</sup> This case report is a modest contribution to the existing literature. We summarised the total 11 cases (Table 1) to reveal the differences between the studies.

According to the classification<sup>1,9</sup> by the PReS, GM is described as skin indurations starting as individual plaques (four or more and larger than 3 cm) that become confluent and involve at least two out of seven anatomical sites (head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, and posterior trunk). In this case, some erythematous rashes were first noted over the left shin. These then progressed to the left thigh, left abdomen and lower back, and left forearm. Thus, the symptoms and signs fulfilled the diagnostic criteria of GM.

The cause and pathogenesis of the localised scleroderma and unilateral distribution remain poorly understood. There was a hypothesis that both transformation of CD34<sup>+</sup> fibrocytes to CD34<sup>+</sup> myofibroblasts and an increase in Factor XIIIa<sup>+</sup> cells

**Table 1. Summary of all reported unilateral generalized morphea cases.**

Authors [Origin]	Onset age/Sex	Lesion characteristics	Possible trigger	Extra-cutaneous manifestation	Effective treatment
Nagai Y et al. <sup>3</sup> [Japan]	5/M	right multiple lesions from arm to leg	unknown	no	topical corticosteroid
Appelhans C et al. <sup>2</sup> [German]	13/F	right half body wide-spreading limb atrophy	unknown	no	oral MTX and prednisolone low dose UVA1 lymphatic drainage
	17/F	right half body	unknown	unilateral Raynaud's phenomenon	PCMT
	8/F	right limbs and torso limb atrophy	unknown	right fingers stretching deficit	PCMT Low dose UVA1 physiotherapy
	4/F	left multiple lesions from neck to leg limb atrophy	unknown	left digits contraction	PCMT emollients physiotherapy lymphatic drainage.
Kraigher O et al. <sup>4</sup> [Italy] *	18/F	right, along Blaschko lines head, shoulder, thorax, leg,	ibuprofen	no	cessation of ibuprofen
Gerceker-Turk B et al. <sup>5</sup> [Turkey]	25/M	Left diffuse lesions from face to leg	vibration and silica	left hand sensori-motor polyneuropathy	oral MTX and methylprednisolone
Fleming KF et al. <sup>6</sup> [America]	5/M	left half body multi-segmental morphea	unknown	no	Not mentioned
Fernández-Rodríguez AM et al. <sup>7</sup> [Spain]	12/F	right half body mottled lesions	trauma	right knee, hip joints ROM limitation	pulse 6-MP oral MTX and prednisolone
Adamska U et al. <sup>8</sup> [Poland]	32/M	right half body, limb atrophy	unknown	no	not found yet under cyclosporine 3.45 mg/kg daily
Our case [Taiwan]	8/F	left half body, skin atrophy	URTI	left knee joint ROM limitation	oral D-Penicillamine oral MTX and prednisolone topical corticosteroid emollients physiotherapy

Abbreviations: M, male; F, female; URTI, upper respiratory tract infection; ROM, range of motion; MTX, methotrexate; UVA1, ultraviolet radiation A light; PCMT, pulsed high-dose glucocorticoid therapy and low-dose methotrexate; 6-MP, 6-mercaptopurine

\* indicates that the patient is a Jewish of Yemenite origin

acting by cross-linking the newly formed collagen and matrix molecules contribute to the fibrotic process.<sup>9,10</sup>

In children with juvenile localised scleroderma, articular symptoms were the most common extra-cutaneous manifestations.<sup>9</sup> In our case, the patient had ROM limitation of the left knee joint. She had no other extra-cutaneous manifestations.

Among the reported cases in PubMed,<sup>2-8</sup> duration of disease activity was not mentioned. An adult case reported by Adamska et al. showed poor improvement.<sup>8</sup> Other reported cases started to improve or lacked further progression, within 0.5–2 years, especially the skin status.<sup>2-7</sup> There was no evidence of disease progression in this case report; however, long-term follow-up is needed.

There is paucity of good evidence on which to base treatment recommendations for localised scleroderma.<sup>1,9,11</sup> Various regimens, including systemic treatment with methotrexate in combination with corticosteroids, are reported to provide a good response and tolerability.<sup>9,12,13</sup> To date, the treatments for children supported by the highest quality of evidence are phototherapy and the pulsed high-dose glucocorticoid therapy and low-dose methotrexate (PCMT) regimen.<sup>9</sup> Physiotherapy is also suggested for treatment of flexion contractures.<sup>1</sup> D-penicillamine is commonly used for systemic sclerosis and for some localised scleroderma.<sup>12,14</sup> The drop in use of D-penicillamine might be associated with the introduction of MTX for treatment.<sup>15</sup>

In conclusion, there are no established guidelines or protocols for localised scleroderma treatment or for its subvariant, UGM, to date. Clinicians should choose a customised treatment for each patient. This case report provides a treatment option for UGM in the paediatric group without the use of intravenous methylprednisolone pulse therapy.

### Ethical Approval of Studies and Informed Consent

This case report was approved by the Institutional Review Board, or ethics committee, of Taipei Medical University. Informed consent was obtained from the patient for the use of this de-identified, retrospective case study.

### Conflicts of interest

The authors have no conflicts of interest relevant to this article.

### Author contributions

- Meng-Che Lu - interviewed the patient and drafted the manuscript.
- Shyh-Dar Shyur - reviewed the manuscript, obtained patient permission, designed the study, and performed patient diagnosis.
- Lee-Wen Lee - coordinated the study and reviewed the manuscript.
- Timothy Hsu - reviewed the manuscript and drafted necessary corrections.
- All authors read and approved the final manuscript

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