CASE REPORT

Case Report: Late onset of generalized isomorphic morphea in a postmenopausal woman [version 1; peer review: 2 not approved]

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Abstract

Morphea is an inflammatory, sclerosing skin condition of unknown cause that generally does not present systemic manifestations. A 66-year-old Caucasian Peruvian female patient, who was previously a nurse, presented with a prior history of 4 years of indurated dermal plaque lesions with constant progression. Diagnosis of morphea was made by clinical examination and skin biopsy. The patient started topical treatment with methoxsalen and phototherapy. When no improvement was seen, it was switched to methotrexate. However, due to changes in liver profile, phototherapy was restarted with progressive clinical improvement. It is essential to differentiate all morphea subtypes for proper management.

Keywords

Isomorphic generalized morphea; indurated plaque; postmenopausal woman

Open Peer Review

Approval Status **XX**

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1. **Tasleem Arif** , Ellahi Medicare Clinic, Kashmir, India

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Lazo-Betetta MA: Conceptualization, Data Curation, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; Perez-Vasquez R: Conceptualization, Data Curation, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Sanchez-Boluarte A: Conceptualization, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing; Inga-Berrospi F: Conceptualization, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; Grandez-Urbina JA: Resources, Writing – Original Draft Preparation, Writing – Review & Editing

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Background

Morphea is a rare, sclerosing inflammatory condition of the skin that can involve underlying soft tissues and cause a severe cosmetic and functional defect of unknown etiology. Associated factors, such as genetic predisposition, immune dysregulation, and environmental factors, have been reported^{1,2}. The current classification includes five subtypes: circumscribed, generalized, linear, pan-sclerotic, and mixed (Table 1)^{3,4}. Generalized morphea has two patterns of cutaneous distribution, symmetric distribution and isomorphic distribution, which occurs almost exclusively in postmenopausal patients^{5,6}. The annual incidence ranges between 3.4 and 27 cases per 1,000,000 people, and is more frequent in women than men. This disease has a peak of bimodal incidence, with the age of presentation being between 7 and 11 years in children and 44 and 47 years in adults^{7,8}.

Case presentation

Information of the patient

A 66-year-old postmenopausal Caucasian Peruvian female patient, who was previously a nurse of Swedish ancestry, with prior history of Type 2 Diabetes Mellitus and insignificant family history presented at an outpatient facility of an allergy and immunological center in Lima, Peru. She had a prior history of pathology biopsy report of morphea, she was treated with topical methoxsalen previously (with good outcome) in Sweden.

Clinical findings

The clinical episode began four years ago, starting with indurated, painless skin lesions without erythema in the breast folds, which progressively increased locally. These lesions appeared in other regions, such as the hip and upper and lower extremities, presenting plaques with indurated hiccups and hyperpigmentation (Figure 1–Figure 3). The patient was diagnosed with morphea following clinical examination and a prior pathological biopsy, which reported morphea, in Sweden. A timeline of care is available in Figure 4.

Figure 1. Inactive lesion in left forearm.

Figure 2. Inactive lesion at the level of the right iliac crest.

Figure 3. Inactive lesion at the level of the left iliac crest.

Treatment

Initially, pharmacological treatment was initiated, we use topical treatment with methoxsalen (0.1% lotion applied 30 minutes before phototherapy) and phototherapy (light therapy using artificial ultraviolet A light) the wavelength was 315–400 nm with 3.10–3.94 eV photon energy in lesions five times a week for six months. The patient had good adherence to the treatment. However, no improvement was seen, so the treatment was changed to methotrexate administrated orally (7.5 mg twice a week). Measuring the tolerance of the pharmacological treatment with liver profile (aspartate and alanine transaminases and total, indirect and direct bilirubin were measured). After six weeks, the patient exhibited alterations in liver profile, this being an expected adverse event. Therefore, the medication was discontinued, after which phototherapy was restarted twice a week, without topical treatment. Visible improvement of the lesions was achieved, the upper limbs being the location that was initially remitted. Subsequently, the frequency of phototherapy went from twice a week to once a week, for two years (Figure 1).

Figure 4. Timeline of care.

Follow-up

Currently, the patient has inactive lesions with the presence of dystrophies and atrophic skin, with annual follow-up controls to assess for disease remission and a good prognosis. The patient has a follow-up period of two years after last course of treatment and is seen every year.

Discussion

Morphea is a rare disease, with an estimated incidence of 27 cases per million people. It is suggested that it has an

autoimmune origin. In relation to pathophysiology, little is known until now. However, some risk factors have been proposed, the most reported being: trauma, radiation, *Borrelia burgdorferi* infection, and certain medications^{9,10}. The age of presentation of this disease in childhood and adulthood, is the age range of 4–62 years, with a mean age of presentation of 35–37 years; in addition, it is more frequent in women than in men, with a ratio of 3:1.^{9,11}. The presentation is characterized by erythematous or violaceous skin lesions, with the progression of the disease sclerotic plaques develop in the center of these lesions. In some patients,

one of the predominant characteristics is the development of hyperpigmentation, and sclerosis may be limited or absent^{7,12}. Generalized morphea is characterized by superficial, long, and coalescing plaques in multiple parts of the body. This type of morphea is more common in adults than in children, and sclerosis usually occurs in the trunk, upper and lower limbs, with preservation of the face, hands, and feet^{7,13}.

Regarding the complications of this disease, the injuries caused to the skin can generate functional deterioration and limitation of the motility range of the affected area. The disease can also produce arthralgia, edema, and contractures in the extremities. Initially, sclerotic plaques are formed, which after months and years become hypopigmented or hyperpigmented atrophic plaques that manifest as a depressions in the skin^{14,15}. In patients with compromised dermis, subcutaneous tissue and muscle, squamous cell carcinoma may be formed due to the present of chronic inflammation^{16,17}.

In many patients, the diagnosis can only be achieved using clinical findings. However, some imaging studies such as ultrasound, 2-D shear wave elastography and magnetic resonance imaging would be useful in assessing and quantifying morphea extension. In other and histopathological changes, such as compromised dermis, subcutaneous tissue and muscle, may be useful to confirm the diagnosis and evaluate the extent of the disease. Skin biopsy can provide additional information in those patients where the physical examination is inconclusive, also allows us to have information on the depth of the condition and the activity of the disease. Walker *et al.* assessed a cohort of 83 adults and children with morphea, where they sought to systematize morphological changes and determine the association between histopathological and clinical findings¹⁸. In total, 91 biopsies were performed in 83 patients, and they found three patterns of dermis involvement: superficial, deep, and total sclerosis, which can occur in the different morphea subtypes. For example, in the generalized symmetric morphea, a pattern of deep affection of the dermis predominates; in the generalized isomorphic morphea, a pattern of superficial affection is often presented; on the other hand, lichen sclerosis morphea involves a pattern of linear and superficial affection. In this case, after having carried out a detailed study, skin biopsy was performed, which confirmed the diagnosis of morphea¹⁸.

Dharamsi *et al.*¹⁹ conducted a cohort study of 181 patients vs controls with the objective of determining the prevalence of antinuclear antibodies, anti-histone antibodies and anti-single-strand DNA antibodies finding that the prevalence of morphea is 34% antinuclear antibodies, 12% anti-histone antibodies and 8% anti-single-strand DNA antibodies. Concerning the patient discussed in this case study, we did not have the results of autoantibodies, so it is not possible to stratify it in any of the groups mentioned above.

The differential diagnosis for morphea is usually systemic sclerosis, this being a systemic disease characterized by progressive

dermal sclerosis with the involvement of internal organs. The typical cutaneous manifestations are evidenced symmetrically at the proximal level, presenting as sclerodactyly, Raynaud's syndrome, facial, trunk and/or limb sclerosis with significant functional limitation, sometimes accompanied by pulmonary and cardiac involvement. Regarding the patient, the condition was exclusively cutaneous without systemic manifestations and without compromising the proximal part of the hands, as happens in systemic sclerosis, also taking into account that the condition is currently in remission without treatment²⁰.

It should be taken into account that the patient was previously diagnosed and had received treatment in Sweden. The patient therefore had access to an advanced health system and did not encounter present economic limitations; it was possible to have timely diagnosis and treatment, which positively affected prognosis. However, within the limitations of the study, it was not possible to have access to the patient's complete medical history; only the information provided adequately by the patient was used. At present, there are various treatment options for active lesions in generalized morphea, whether superficial or deep²¹. Concerning superficial lesions, it is possible to initially use phototherapy as the first line of treatment throughout the body²². If phototherapy is ineffective, a systemic treatment that includes methotrexate or mycophenolate, alongside systemic glucocorticoids, should be used²³. If the lesions are deep, immediate use of systemic treatment is recommended and phototherapy should be avoided due to poor penetration of ultraviolet light in the deep tissues²⁴. There is also topical therapy in which corticosteroids, vitamin D, and tacrolimus are used. However, it has not proven to be useful in cases of generalized morphea²⁵.

Conclusions

1. Early diagnosis is essential to prevent disease progression, complications, and improve the patient's quality of life.
2. Likewise, it is of high relevance to determine the form of presentation of the disease to achieve optimal response to treatment and a favorable prognosis. Similarly, the possibility of atypical cases whose age of presentation is not expected should be taken into account.
3. Because there are currently no specific guidelines for the management of Morphea, we recommend that physicians should customize the treatment according to the clinical characteristics of each patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and clinical images were obtained from the patient.

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Takamitsu Makino

Department of Dermatology, Kumamoto University, Kumamoto, Japan

This case report shows that the phototherapy using UVA is effective for a patient with generalized morphea.

1. Please show the clinical photography of the active skin lesions and time-course of phototherapy.
2. Please show the clinical examination for the diagnosis, such as anti single-stranded DNA antibody, anti-histone antibody, rheumatoid factor, IgG and soluble IL-2 receptor. The authors should distinguish from the *Borrelia* infection.
3. The authors should discuss why the second phototherapy was more effective for skin lesions.

Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Scleroderma

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 24 August 2020

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Tasleem Arif

Dermatology, Venereology and Leprosy, Ellahi Medicare Clinic, Kashmir, India

The authors have tried to present a case of generalized morphea in a postmenopausal woman in which they showed how a treating physician can face therapeutic challenge while treating a case of generalized morphea. However, there are major issues with this manuscript.

1. Authors have labelled it as isomorphic morphea which is not correct. Isomorphic morphea (after the isomorphic phenomenon of Koebener) occurs at the sites of repetitive trauma like bra line, waistband, inguinal creases, etc. As per authors patient had lesions on arm, and lower extremities which can't explain the isomorphic phenomenon.
2. The examination part is very deficient. "Painless skin lesions without erythema" Authors should mention the type of lesion like macule, papule or plaque rather than using word skin lesion. Authors have not given detailed examination about the plaques present on lower extremities and what was the size of plaques. The broad term like lower extremities should be avoided. Authors have to actually describe the location of plaques, feet, leg or thighs.
3. The language used to describe the examination is not precise. Instead using words like "presenting plaques with indurated hiccups and hyperpigmentation" authors can simply say "hyperpigmented indurated plaques".
4. Authors need to mention what was in the report of biopsy rather than simply mentioning that reported morphea. As there are depigmented areas in the plaques, Lichen sclerosus et atrophicus provides a good differential for such lesions.
5. Images are of poor quality especially Fig 3. Authors have used "Inactive lesion in left forearm, Inactive lesion at the level of the right iliac crest, etc for illustrating figures which is not correct. Just visualizing a plaque you can't state that it is inactive. There can be subclinical activity going on inside the plaque. It must be corrected.
6. How was phototherapy given? Authors have not mentioned which protocol was used, based on skin phototype or what. The dose of UVA 3.10–3.94 eV looks strange as the usual doses

of UV light are in mj or joules. The dose needs to be standard one. Sun protection and sun blocks have not been recommended after phototherapy for the patient. Since patient had disseminated plaques, was any special advice given to protect the face of patient during phototherapy.

7. When patient received phototherapy 5 times a week she didn't get the benefit but once it was used twice a week patient got benefit. Can authors throw light on this phenomenon?
8. How was the improvement of lesions assessed? Authors have not used any objective tool (like durometer, cutometer, USG, The Localized Scleroderma Cutaneous Assessment Tool) to assess the change in the lesions. Even the authors have not commented on the induration or pigmentation or size reduction of lesions. Then how was the improvement measured?
9. Methotrexate was administrated orally (7.5 mg twice a week). Was folate given along with it? Which regimen was followed by authors in giving methotrexate twice a week? Was once weekly safer option and might not have impaired patients liver profile. I feel authors have been very superficial in most of the clinical part of the case.
10. For diagnosing generalized morphea authors must have stated the actual number of lesions and their size as per the classification system which they have mentioned (Laxer and Zulian).
11. The manuscript has several language and grammatical errors and needs to be written by an expert medical writer. There are incomplete sentences with many having punctuation mark mistakes.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Morphea, Systemic sclerosis, Linear atrophoderma of Moulin, Erythromelanosis follicularis faciei et colli, idiopathic atrophoderma of pasini and Pierini, Nanotechnology in dermatology and cosmetics

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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