

# Plaque morphea with neurological involvement— an extraordinary uncommon presentation

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## Abstract

Localized scleroderma is traditionally considered to be limited to the skin, subcutaneous tissue, underlying bone, and in the craniofacial subtype, also nervous system involvement. However, recent studies have also described other systemic manifestations in these patients. Despite many reports of neurological involvement in patients with the craniofacial linear localized scleroderma, it is extremely rare in patients with the other subtypes of localized scleroderma. Here, we report an extraordinary case of localized scleroderma *en plaque* (classic morphea), located to the upper trunk and neck, associated with neurological manifestations presented as seizures. Magnetic resonance imaging of the brain showed focal lesions on the contralateral side to the skin involvement. This case is extremely relevant not only due to its rarity, but also because it supports the idea that the pathogenesis of the localized scleroderma is related to a systemic autoimmune process.

## Key points

- Localized scleroderma is known to be related with systemic symptoms.
- To the best of our knowledge, this is the first case report of an exclusive plaque morphea with neurological involvement.
- This case provides support to the concept that the pathogenesis of the disease is a systemic autoimmune process.

**Keywords** Autoimmunity · Central nervous system vasculitis · Localized scleroderma · Plaque morphea

## Introduction

Scleroderma is a broad, often confusing term, used to denote a subset of fibrosing disorders, characterized by thickening and hardening of the skin as a result of an increased collagen production. The term includes a variety of disease subtypes, ranging from localized scleroderma (LS) to systemic sclerosis (SSc).

LS (also called morphea) is traditionally considered to be limited to the skin, and depending on the respective subtypes, it can also involve adjacent tissues such as fat, fascia, muscle and bone, and, in the craniofacial subtype, it may be also associated with nervous system involvement [1]. Recent studies, however, have described malaise, fatigue, arthralgia, and myalgia in the LS. Moreover, rheumatological, ophthalmological, and neurological symptoms and signs have been described in up to 20 % of the patients with LS [1]. Based on these findings, LS ought to be differentiated from systemic sclerosis by the absence of sclerodactylia, Raynaud's phenomenon, and capillaroscopic abnormalities [1]. Neurological involvement is significantly more frequent in patients with linear LS of the face and is rarely observed in patients with the other subtypes [2].

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Here, we report an extraordinary case of a patient with the plaque morphea subtype, located to the upper trunk and the neck, associated with neurological manifestations.

### Case report

A previously healthy 19-year-old young lady presented with skin lesions of the right shoulder, chest, and right neck, clinically compatible with plaque morphea. A biopsy was performed and the diagnosis of LS *en plaque* was determined. No specific therapy was instituted and the progress of the lesions was documented with the development of fibrosis and hyperpigmentation (Fig. 1).

Three years later, at the age of 22, she was admitted to another hospital with generalized tonic-clonic seizures. She was treated initially with phenytoin and later on with lamotrigine. On the initial magnetic resonance imaging (MRI) scan of the brain, several pathological focal lesions were seen in the left frontal region. These lesions were hyperintense on T2/FLAIR-weighted images and showed enhancement following gadolinium, findings suggestive of an active vasculitis (Fig. 2). She was treated with a course of corticosteroids, with full clinical remission, and therefore those were tapered and discontinued. One year later, she was re-admitted to the neurology department in our hospital with generalized epileptic seizure. There were no abnormal laboratory results, including renal function, the erythrocyte sedimentation rate, C-reactive protein, coagulation, and hematological tests. Serological autoimmune markers were negative, including antinuclear, anti-dsDNA, anti-ssDNA, anti-thyroid, antiphospholipid, anti-Ro, anti-La, anticentromere, and anti-Scl-70 antibodies; rheumatoid factor was negative; complement and total gamma globulin levels were in normal range. A repeat MRI was performed which showed a deterioration, with new lesions demonstrated not only in the previously involved left frontal lobe but also in the left peritrigonal and subinsular regions, all in the left hemisphere (Fig. 3). As a result, treatment with corticosteroids (prednisolone 10-mg BID) was re-initiated in conjunction with lamotrigine (250-mg OD) and aspirin (100-mg OD). At this time, the lesions of the morphea were inactive, with residual fibrosis and hyperpigmentation of the skin. She underwent a period of 2 years free of seizures, after which, she presented with recurrent seizures despite the ongoing treatment. It was decided to increase the dose of prednisolone to 60 mg OD, and to initiate azathioprine as a corticosteroid-sparing drug. The prednisolone was tapered to 20 mg OD and the azathioprine dose was increased to 100 mg OD. Repeated MRIs showed mild improvement in the extent of the T2/FLAIR lesions with no enhancement and a year later, there was a reduced number of lesions. The skin lesions were static during this period. Attempts to taper down the dose of steroid resulted in the



**Fig. 1** Lesions of plaque morphea after years of evolution with fibrosis and hyperpigmentation, localized to the right shoulder, chest and right inferior neck

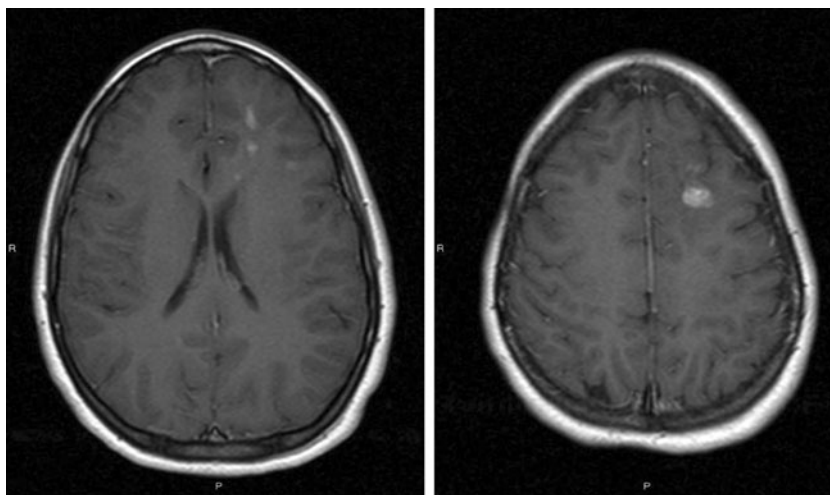
appearance of active lesions in brain MRI. Last MRI performed 2 months before showed mild elongation of one of the frontal lesions with extension of the enhancement into adjacent subcortical white matter. The dose of azathioprine was increased from 100 to 125 mg and prednisolone was increased to 10 mg daily (before she was on alternating daily between 5 and 10 mg).

### Discussion

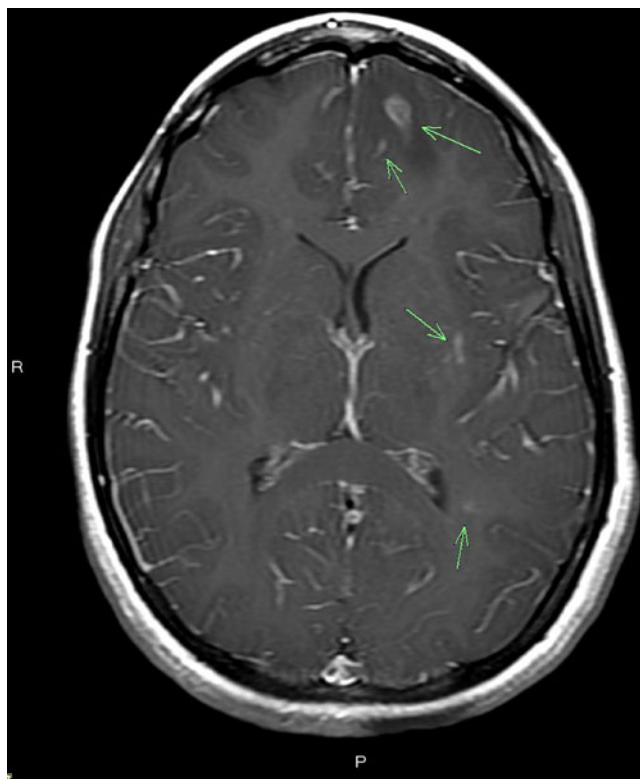
LS incidence ranges from 0.4 to 2.7 per 100,000 people. Females are more affected, and distribution is similar between children and adults. In adults, the disease incidence peaks in the fifth decade of life, whereas 90 % of the children are diagnosed between 2 and 14 years of age [1].

LS is classified based on the clinical presentations. So far, no uniformly accepted classification for LS exists, but the classification published by Peterson et al. in 1995 is widely accepted, and distinguishes plaque, generalized, deep, bullous, and linear types as the five main groups of LS [3]. Morphea, the classical plaque type, is by far the most frequent subtype of LS, especially in adults. In the early active phase, morphea usually presents with oval-shaped lesions

**Fig. 2** Axial T1 weighted post contrast images showing several enhancing subcortical foci in the left frontal lobe



surrounded by an erythematous border (the so-called lilac ring). In the later stage of the disease, morphea lesions become hard and sclerotic in the center, with a whitish or ivory color. Older lesions may also become atrophic, hypo- or hyperpigmented and, depending on the location of fibrosis, may also lead to hair loss and loss of the skin appendages. It is frequently located to the trunk, especially to the submammary region, and the transitional area between the hip and inguinal regions [4]. Linear LS is, by far, the most common subtype of LS in childhood. It is characterized by longitudinally arranged



**Fig. 3** Axial T1 post contrast image showing several new enhancing vasculitic foci in the left hemisphere. These were accompanied by T2 FLAIR signal changes (not shown)

linear, band-like lesions that are predominantly located to the extremities. There are two rare subtypes of linear LS, both involving the face, in which neurological involvement is not uncommon. The first one, known as LS *en coup de sabre*, is located on the frontoparietal region of the head, usually ranging paramedian from the eyebrows into the hair-bearing scalp where it may cause scarring alopecia. The second one, progressive facial hemiatrophy (also called Parry-Romberg syndrome), is clinically characterized by a primary atrophy of the subcutaneous tissue, muscle, and bone. Skin fibrosis is rare in this particular subtype. Progressive facial hemiatrophy often occurs in childhood or adolescence and may result in severe facial asymmetry [4]. Some authors speculate that progressive facial hemiatrophy and LS *en coup de sabre* are variants of the same condition [4].

Extracutaneous manifestations in morphea are not uncommon; they are most likely in patients with generalized morphea and include myalgia, arthralgia, and fatigue [1, 2]. Neurological manifestations are the second most frequent extracutaneous manifestation (17 %) reported in children with linear scleroderma of the face (LS *en coup de sabre*/progressive facial hemiatrophy), after articular involvement (47 %) [5]. The proportion of adults with these findings is uncertain. Otherwise, neurological findings are rarely observed in patients with the other subtypes of LS [2]. Neurological symptoms and signs in LS *en coup de sabre* are variable and include epilepsy, headache, focal neurologic deficits, and movement disorders, as well as neuropsychiatric symptoms and intellectual deterioration [6]. Nervous system involvement does not usually correlate with skin activity and may present years after the initial presentation of the disease [7]. Neuroradiological abnormalities demonstrated on MRI in morphea include T2 hyperintensities in the subcortical white matter and corpus callosum, focal tissue atrophy, and calcifications [8].

Here, we described an extraordinary case of LS classic plaque type that presented with epilepsy as a manifestation of neurological involvement, and with MRI showing multiple

pathological focal lesions of the contralateral hemispheres, compatible with vasculitis. There are two previous case reports describing *LS en coupe de sabre* in association with plaque morphea and neurological complications [9]. To the best of our knowledge, this is the first case report of an exclusive plaque morphea with neurological involvement.

The pathogenesis of morphea is poorly understood. A variety of factors, including autoimmunity, genetics, and vascular dysfunction may all play a role. Clinical and pathological data support the hypothesis that vasculature is the primary target in LS. Early skin biopsies revealed damaged endothelial cells preceding the development of fibrosis by months or years. Increased vascular permeability is associated with a mononuclear cell infiltration, leading to perivascular inflammatory cell infiltrates, vascular intimal thickening, and vessel narrowing. Progressively, the vessels lose their elasticity; media and adventitia become fibrotic and more prone to small-artery occlusion. The latter is further exacerbated by thrombotic events driven by platelets activation, resulting in fibrosis and end-organ damage. The inciting event for microvascular damage remains unknown [6, 10]. It has been hypothesized that certain stimuli, such as infections, trauma, radiation, or drugs might cause microvascular injuries that subsequently result in a release of various adhesion molecules [4, 10]. Pathogenesis of central nervous system involvement in *LS en coup de sabre* seems to be due to perivascular infiltrate and vasculitis; however, biopsies are not routinely performed and histological findings are available only for patients with severe neurological findings. Gliosis, suggesting chronic inflammatory process, leptomeningeal band-like sclerosis, and thickened blood vessels' walls, as well as intraparenchymal calcification, have also been described in the few available studies [6]. In the past, neurological changes were noted on the same side as the skin lesion. However, in Zulian et al.'s review [2], neurological findings were unrelated to the side of the skin involvement in one third of the patients. This may support the hypothesis that a systemic autoimmune process rather than a dysgenetic process of both cerebral and facial structures could be responsible for such an association, as suggested by some investigators [2]. The case we present also supports the idea of an autoimmune systemic disease: first, cutaneous lesions are located on the opposite site of the neurological lesions; second, lesions are the classic plaque type and anatomically located in a different site in contrast to those in craniofacial disease.

In SSc, highly specific antibodies exist for limited (anticentromere antibodies) and diffuse (anti-Scl-70 antibodies) disease, otherwise, such parameters are absent (or still unknown) in LS. However, depending on the clinical subtype, a high incidence of autoimmune phenomena has been reported in LS patients. Serum antinuclear antibodies, most of them with a homogenous pattern, have been detected in 20 to 80 % of LS patients, as well as several other antibodies, namely

anti-ssDNA, but their role remains to be elucidated [4, 11] [12]. In the case we presented, the patient had no serological markers.

Given the rarity of localized scleroderma, there are no randomized studies on the treatment of the disease. So far, the most robust data is available for ultraviolet A1 phototherapy in the disease that is restricted to the skin, and methotrexate alone or in combination with systemic corticosteroids in more severe disease that additionally affects extracutaneous structures [4]. D-penicillamine, methylprednisolone, mycophenolate mofetil, and methotrexate may be considered in the treatment of neurological involvement of *LS en coupe de sabre*. In reported cases, treatment with a combination of methotrexate or mycophenolate mofetil and steroids appeared to have a significant impact in controlling previously intractable seizures and stabilizing central nervous system damage [6]. In the patient that we reported, systemic treatment was required to control the neurological manifestations, and still, it has not been possible to reduce immunosuppression.

## Conclusion

Once believed to exclusively involve the skin, subcutaneous tissue, and bone; LS has been associated with systemic symptoms. Rheumatological, ophthalmological, and neurological manifestations seem to be presented in around 20 % of the patients, and, in those with *LS en coupe de sabre*, nervous system disorders are the most prevalent extracutaneous presentation. Here, we presented an extremely rare case of plaque morphea of the trunk and neck with neurological involvement; clinically presented as epilepsy and with MRI showing focal lesions on the contralateral hemisphere to the skin involvement. This case is extremely relevant as it provides support to the concept that the pathogenesis of the disease is a systemic autoimmune process, in spite of the fact that all the serological studies performed were interpreted as negative.

**Disclosures** None.

## References

1. Fett N, Werth VP (2011) Update on morphea: part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol* 64(2): 217–228
2. Zulian F, Vallongo C, Woo P, Russo R, Ruperto N, Harper J, Espada G, Corona F, Mukamel M, Vesely R et al (2005) Localized scleroderma in childhood is not just a skin disease. *Arthritis Rheum* 52(9): 2873–2881
3. Peterson LS, Nelson AM, Su WP (1995) Classification of morphea (localized scleroderma). *Mayo Clinic Proc Mayo Clinic* 70(11): 1068–1076
4. Kreuter A (2012) Localized scleroderma. *Dermatol Ther* 25(2):135–147

5. Zulian F, Athreya BH, Laxer R, Nelson AM, de Feitosa Oliveira SK, Punaro MG, Cuttica R, Higgins GC, Van Suijlekom-Smit LW, Moore TL et al (2006) Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology* 45(5):614–620
6. Amaral TN, Marques Neto JF, Lapa AT, Peres FA, Guirau CR, Appenzeller S (2012) Neurologic involvement in scleroderma en coup de sabre. *Autoimmune Dis* 2012:719685
7. Menni S, Marzano AV, Passoni E (1997) Neurologic abnormalities in two patients with facial hemiatrophy and sclerosis coexisting with morphea. *Pediatr Dermatol* 14(2):113–116
8. Kister I, Inglese M, Laxer RM, Herbert J (2008) Neurologic manifestations of localized scleroderma: a case report and literature review. *Neurology* 71(19):1538–1545
9. Unterberger I, Trinkka E, Engelhardt K, Muigg A, Eller P, Wagner M, Sepp N, Bauer G (2003) Linear scleroderma "en coup de sabre" coexisting with plaque-morphea: neuroradiological manifestation and response to corticosteroids. *J Neurol Neurosurg Psychiatry* 74(5):661–664
10. Katsumoto TR, Whitfield ML, Connolly MK (2011) The pathogenesis of systemic sclerosis. *Ann Rev Pathol* 6:509–537
11. Falanga V, Medsger TA Jr, Reichlin M (1987) Antinuclear and anti-single-stranded DNA antibodies in morphea and generalized morphea. *Arch Dermatol* 123(3):350–353
12. Arkachaisri T, Fertig N, Pino S, Medsger TA Jr (2008) Serum autoantibodies and their clinical associations in patients with childhood- and adult-onset linear scleroderma. A single-center study. *J Rheumatol* 35(12):2439–2444