Scleroderma (morphea) en Coup de Sabre

Subjects: Dermatology
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Definition

Scleroderma (morphea) en coup de sabre is a localized subtype restricted to the frontoparietal region of the head. Localized scleroderma/morphea en coup de sabre (LScs) is a rare form of localized scleroderma that typically affects predominantly children and women. It manifests by presence of linear atrophy and/or hardening of the skin, subcutis, occasionally involving muscles and bones. The early phase lesions appear as an erythematous or violaceous linear indurated mild atrophic plaque and subsequently lesions progress to hypopigmented or depigmented sclerotic deep furrow. It usually starts at the level of the upper eyebrow ridge and reaches the scalp, where a cicatricial alopecia focus appears. There are known descriptions of patients with localized scleroderma en coup de sabre, in whom lesions spread below the eyebrows involving the eyelids, eyelashes, or the skin on the nose. The disease may manifest with ophthalmologic (deformation of eyelids, uveitis, episcleritis) and neurological (convulsions, migraine, trigeminal neuralgia, vascular malformations) symptoms. In some cases neurological symptoms preceded the appearance of skin lesions. Parry Romberg syndrome (also known as progressive facial hemiatrophy), which is a distinct entity within craniofacial linear subtype involving subcutaneous tissue and bones, coexists in 20–40% of patients with en coup de sabre lesions.

1. Pharmacological Treatments

1.1. Methotrexate

Methotrexate, a folic acid antagonist, is an immunosuppressive agent which inhibits cytokines that play an important role in sclerotic skin disease such as interleukin 2, 4 and 6 [1][2].

Systemic methotrexate was the most commonly reported monotherapy and combined with glucocorticosteroids for localized scleroderma en coup de sabre, achieving a favorable responding rate of 100% [1][3][4][5][2][6].

Rattanakaemakorn et al. conducted a retrospective study on the efficacy of methotrexate in seven patients with localized scleroderma en coup de sabre (six children and one adult). The starting dose of methotrexate was 2.5 mg weekly in pediatric patients and 10 mg weekly in the adult patient. All seven patients improved with methotrexate monotherapy. No adverse events were observed, except in one patient (14%), who developed nausea. Patients were followed for an average of 24 months [1].

Hardy et al. performed study including 12 children (<18 years) with active localized scleroderma en coup de sabre treated with methotrexate for a minimum 4 months. Methotrexate dosage ranged from 7.1 to 15 mg/m^2/week. At evaluation, performed at a median time of 11 months after methotrexate initiation, four patients improved and eight patients remained stable [4].

Polcari et al. reported four pediatric patients with localized scleroderma en coup de sabre, who were treated methotrexate (15–25 mg/week) combined with glucocorticosteroids (prednisone, prednisolone, or methylprednisolone). Therapy slowed disease progression in all patients, but in one of them the worsening of skin lesions after tapering of medications was observed [5].

Anderson et al. reported the case of a 10-year-old girl with localized scleroderma en coup de sabre who was treated with methylprednisolone 1000 mg weekly for 12 weeks with transition to a prednisone taper and 25 mg weekly subcutaneous methotrexate with transition to oral therapy. Her skin lesion became smaller and softer with regression of the violaceous border. Methotrexate was discontinued after nearly 3

years [2].

Niklander et al. described a case of a 13-year-old girl with localized scleroderma en coup de sabre. A treatment of prednisone 15 mg/day, methotrexate (MTX) 20 mg/week (intramuscular), and folic acid 5 mg daily after the dose of methotrexate was administered. The patient reported no adverse side effects. The drug therapy described above was maintained for 15 months. No other lesions appeared during this period and the existing ones underwent no change or became smaller [3].

Van der Veken et al. reported a case of a 19-year-old woman with mixed scleroderma (en coup de sabre and circumscribed scleroderma) who was treated with methotrexate. An initial dose of 7.5 mg/week was well tolerated and therefore increased to 15 mg/week after 2 weeks. This treatment was continued for 12 months. The goal of the treatment was to stop progression of the skin lesions. The only adverse effects were a subjective feeling of fatigue and abdominal discomfort.

1.2. Systemic Glucocorticosteroids

Glucocorticosteroids have anti-inflammatory and immunosuppressive effects and also anti-proliferative effects on keratinocytes. Furthermore, they can suppress collagen synthesis by fibroblasts [7].

A study performed by Joly et al. revealed that systemic glucocorticosteroids were effective in 100% (7/7) patients with localized scleroderma en coup de sabre. Patients were given doses of 0.5–1 mg/kg prednisone per day for 6 weeks, followed by a progressive decrease of the dosage. Treatment lasted 5 to 70 months (mean, 18.3 months); four patients improved and three patients remained stable. The follow up period lasted at least 18 months after the initiation of therapy. There were no data how many patients with localized scleroderma en coup de sabre had recurrence of skin lesions after treatment discontinuation [8].

Arif et al. described a 17-year-old girl with concomitant localized scleroderma en coup de sabre and plaque type scleroderma. Treatment for the patient was prednisolone 30 mg/day and topical tacrolimus ointment 0.1% to be applied twice daily. After 1 month of treatment, there were no new lesions and the existing lesions over the scalp and thigh showed improvement with respect to thickness and pigmentation [9].

Unterberger et al. reported a 24-year-old woman in the 33rd week of pregnancy who developed right-sided hemiparesis and progressive neurological complications in association with localized scleroderma en coup de sabre. The patient was treated with a pulsed intravenous methylprednisolone, 1 g daily for three days, followed by 500 mg daily for a further three days, and a consecutive tapering period with oral methylprednisolone. During the following two weeks this treatment led to a rapid improvement in the neurological symptoms. The patient recovered well and was discharged five weeks after the onset of her neurological symptoms [10].

1.3. Cyclosporine

Cyclosporine (a calcineurin inhibitor) selectively inhibits the release of IL-2 from activated lymphocytes [11].

There is one case report of a 7-year-old girl with localized scleroderma en coup de sabre, who was treated with oral cyclosporine 3 mg/kg/day for 3 months. Skin lesions improved 3 months after starting treatment but relapsed 18 months after she completed treatment. Adverse drug reactions were not reported [12].

1.4. Mycophenolate Mofetil

Mycophenolate mofetil exerts an inhibitory effect on T- and B-lymphocyte proliferation. It showed expression of inhibit type I collagen to enhance the expression of matrix metalloproteinase-1 and to alter both the migratory and contractile functions of fibroblasts. Thus, mycophenolate mofetil has direct

antifibrotic properties in addition to its well-known immunosuppressive effects.

Martini et al. conducted a retrospective study on the efficacy of mycophenolate mofetil in 10 pediatric patients with localized scleroderma, of which 2 had en coup de sabre lesions. In one patient (3-year-old boy) with en coup de sabre lesions, mycophenolate mofetil was chosen as the first therapy because besides skin lesion activation, concomitant cerebral and ocular vasculitis was present. In second patient (6.5-year-old boy) the first treatment was intravenous methylprednisolone, oral prednisone, and methotrexate (15 mg/m^2). The mean duration of treatment with mycophenolate mofetil, at the last follow-up evaluation, was 20 months. The daily dose was 600–1200 mg/m^2/day, twice daily. In both patients, arrest of disease progression and reduction of erythema were observed. The patient with scleroderma en coup de sabre associated with ocular and cerebral vasculitis exhibited markedly improved ophthalmological examination and an arrest of progression of cerebral vasculitis as shown by MRI (Magnetic Resonance Imaging) [13].

1.5. Hydroxychloroquine

Hydroxychloroquine has antithrombotic and antifibrotic properties [14][15]. Kumar et al. investigated the effect of hydroxychloroquine in a group of five patients with localized scleroderma en coup de sabre (four of them were younger than 18 years). The daily dose for adult patients was 400 mg and 5 mg/kg for children. Treatment with hydroxychloroquine monotherapy lasted for a minimum of 6 months. Clinical outcomes of treatment were classified as follows: complete response indicated total resolution of active skin lesions and lack of new lesions, or at least 95% improvement as qualitatively graded by the physician; partial response indicated persistence of some active skin lesions (with or without the development of new lesions), with resolution of some lesions such that extent or severity was decreased (partial response was graded as >50% or ≤50%); no response indicated persistence, worsening, or increase in skin lesions; and relapse was defined as the appearance of skin lesions at the same sites or at different sites 1 year or more after complete response. Two patients with localized scleroderma en coup de sabre had a partial response greater than 50%, two had partial response less than or equal to 50%, and one had no response [16]. No side effects or relapses were reported in patients with localized scleroderma en coup de sabre treated with hydroxychloroquine.

1.6. Abatacept

Abatacept is a soluble recombinant fusion protein that inhibits T-cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28 [17].

Fage et al. presented data concerning two patients with localized scleroderma en coup de sabre treated with abatacept intravenously (500–750 mg/day on days 1, 15, 30, and thereafter every 4–6 weeks) for 3–21 months.

A significant reduction of lesions, approximately 50%, of the area (measured in cm^2) was observed in both patients. Adverse events associated with abatacept use were reported in 1 patient and included oral aphthous ulcers [18].

1.7. Tocilizumab

Tocilizumab is a monoclonal antibody raised against the soluble receptor for interleukin 6. IL-6 inhibition can be an effective target in localized scleroderma, as serum levels of soluble IL-6 receptor have been found to be increased in patients with localized scleroderma compared with healthy controls [19][20]. In two published case reports and one case series, which included three patients with en coup de sabre, subcutaneous (162 mg/weekly in one patient) [21] or intravenously (8–10 mg/kg every 3–4 weeks in two patients) [22][23], tocilizumab was effective in all of them. Adverse drug reactions and relapse rate were not reported.

1.8. Interferon Gamma

Interferon gamma (IFN-ϒ) is a dimerized soluble cytokine, which has a strong inhibitory effect on collagen synthesis by normal dermal and scleroderma fibroblasts in vitro. In addition, inhibition of growth and chemotaxis fibroblasts, and decrease of fibroblasts adhesion to collagens I, IV, VI, fibronectin, and laminin has been described [24]. One case report described a patient with localized scleroderma en coup de sabre complicated by orbital involvement who was successfully treated with interferon gamma (100 mg 3 times a week subcutaneously—52 mg/m^2 body surface area). Adverse drug reactions and relapse rate were not reported [25].

1.9. UVA1-Therapy

The specific mechanism of action of ultraviolet therapy in the treatment of localized scleroderma is unknown. Studies indicate that UVA1 causes apoptosis of epidermal Langerhans cells and T cells. UVA1 also affects fibroblasts, increasing synthesis of collagenases and decreasing synthesis of collagen. It is also thought to impair collagen cross linking. UVA1 also affects levels of local cytokines. It causes a decrease in interleukin-6, which decreases collagen and glycosaminoglycans, a decrease in transforming growth factor beta (TGFb), which decreases fibroblast growth, and an increase in IFN-ϒ, which increases matrix metalloproteinase-1 [26].

Su et al. described three patients with localized scleroderma en coup de sabre in which UVA1-therapy (30 J/cm^2 3–5 times a week for 10–15 weeks) was effective. In two patients, relapse was observed after stopping the therapy [27]. Kowalzick at al. reported the case of a 13-year-old girl who was treated with a combination of topical calcipotriol 0.005% twice a day and 30 daily whole-body irradiations each of 30 J/cm^2 UVA-1. After that treatment, a stop of the progression and a softening of the lesion was achieved [28]. Side effects were not reported.

1.10. PUVA-Therapy

PUVA may suppress collagen synthesis and induce collagenase activity, resulting in clinically observed softening of former sclerotic lesions. Gambichler et al. described two patients with localized scleroderma en coup de sabre treated with topical calcipotriol and cream psoralen plus ultraviolet A. The initial UVA dose was 0.3 J/cm^2. The treatment was performed three times weekly and the UVA dose was increased at the earliest after 3 days with 0.2 J/cm^2. In addition, calcipotriol ointment was applied twice daily. Three months after beginning therapy, a considerable softening of sclerotic lesions was observed in both patients. Forty treatments resulted in a cumulative UVA dose of 71 J/cm^2. No side effects were observed [29].

1.11. NB-UVB Therapy

Narrow-band (NB-UVB) phototherapy is used to treat inflammatory and T-cell mediated dermatoses. Browned et al. investigated the effect of narrow-band ultraviolet B (NB-UVB) phototherapy combined with antimalarials in one 32-year-old female with localized scleroderma en coup de sabre. Therapy slowed disease progression and reversed hair loss. One year after stopping NB-UVB therapy, the progression of her condition with the onset of alopecia of the affected scalp was noted. No adverse effects were observed [30].

1.12. Pulsed Dye Laser (595 nm)

Pulsed dye laser is the gold standard for treatment of port wine stains. These lasers selectively target hemoglobin, resulting in destruction of dilated ectatic capillaries in the upper dermis, while sparing the surrounding tissue [31]. Kakimoto et al. reported the case of a 6-year-old girl with localized scleroderma en coup de sabre who was given an initial diagnosis of acquired port wine stain and treated with a pulsed dye laser (595 nm) [32]. Pulsed dye laser therapy combined with topical clobetasol helped to alleviate initial erythema. Two years later, a relapse of skin lesions was noted. The side effects included blistering and hypopigmentation.

2. Reconstructive Treatments

2.1. Fat Grafting

Reconstructive treatment is proposed as an option for lesions with settled disease activity to improve the cosmetic aspect of lesions [33]. Structural fat grafting is ideal for the correction of localized tissue atrophy or craniofacial deformities. Adipose tissue contains the highest percentage of stem cells, and therefore structural fat grafting creates new vascularization and real structural alterations [34]. According to the present review, fat grafting were effective in all patients (6/6). No side effects or relapses were reported in patients with localized scleroderma en coup de sabre treated with fat grafting [35][36][37][38][39].

2.2. Hyaluronic Acid Filler

Hyaluronic acid filler is particularly well suited for soft tissue augmentation because of its tolerability, availability, relatively low cost, reversibility, and efficacy in volumization. In addition to these benefits, it plays a role in cell growth, membrane receptor function, and adhesion [40]. Upon review of the literature, we encountered two cases in which hyaluronic acid filler was utilized in the correction of patients with localized scleroderma en coup de sabre with successful improvements [41][42].

2.3. Polymethylmethacrylate

Polymethylmethacrylate is a permanent filler, biocompatible, non-toxic, non-mutagenic, and immunologically inert. After polymethylmethacrylate application, there is a reaction of a foreign body type that induces the onset of giant cells that wrap each particle of the product, leading to new collagen and blood vessels formation [43]. Franco et al. reported the case of a 14-year-old male patient with localized scleroderma en coup de sabre who was treated with polymethylmethacrylate. After the treatment, they observed raising of the depressed portion and partial hair regrowth in the alopecia area of the scalp [44].

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Keywords

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