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# UVA1 Phototherapy in the Management of Sclerodermatous Graft-Versus-Host Disease (GVHD): a report of two cases

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## Abstract

Chronic graft-versus-host disease (GVHD) is a frequent complication after allogeneic hematopoietic stem cell transplantation (HSCT). Approximately 10% of patients with GVHD develop sclerodermatous changes, which can cause significant morbidity and are often refractory to standard systemic immunosuppression. We present two cases of sclerodermatous GVHD. The first is a 39-year-old man, who had a matched sibling, undergoing allogeneic HSCT for severe aplastic anemia. The second patient is a 7-year-old boy, who had an allogeneic HSCT from his HLA-identical mother for acute myeloid leukemia (AML). Both patients presented with widespread sclerotic changes, resulting in joint contractures and significant functional difficulties. Studies have shown UVA1 phototherapy to be a promising and well tolerated treatment modality in patients with sclerotic skin diseases. Both of our patients were treated with UVA1, which resulted in a significant skin softening, improvement in joint mobility and quality of life. UVA1 appears to be an effective treatment for refractory sclerodermatous GVHD; however, long-term clinical studies in larger groups are needed to accurately evaluate its efficacy and safety.

Chronic graft-versus-host disease (GVHD) is the most frequent complication after allogeneic hematopoietic stem cell transplantation (HSCT), occurring in about 50% of patients (1). It is a multisystem disorder, induced and maintained by the donor's immunocompetent cells. The clinical presentation is polymorphic and it can affect any organ system, however, the epithelia of fast proliferating tissues such as the skin, gastrointestinal tract and the liver, are most frequently affected. Whilst this graft-versus-lymphoma effect reduces relapse related mortality, there is considerable morbidity associated with chronic GVHD.

The skin is the most frequently affected organ in chronic GVHD. The clinical features are diverse, and may include poikiloderma, lichenoid eruptions, erythroderma, and sclerosis (2). Oral corticosteroids are the first line therapy for chronic GVHD, but most patients require systemic therapy beyond corticosteroids, with a median duration of immunosuppression of 23 months (3). Patients with skin GVHD, without other organ involvement, may be treated with skin directed therapy. This includes potent topical steroids, topical tacrolimus, UVB, PUVA or extracorporeal photopheresis (ECP) (4).

Approximately 10% of patients with GVHD develop sclerodermatous changes which can cause significant morbidity, particularly when generalized, and are often refractory to skin directed therapy and standard systemic immunosuppression (5). Longer wavelenghts in the UVA region can reach subcutaneous tissue. Studies have shown UVA1 phototherapy (peak wavelengths of 370-380 nm) to be a promising and well tolerated modality in patients with sclerotic skin diseases (6). We report our experience with UVA1 in two patients with sclerodermatous GVHD. The first is a 39-year-old man, who had a matched sibling, undergoing allogeneic HSCT for severe aplastic

 

anemia. The second is a 7-year-old boy, who had an allogeneic HSCT from his HLA-identical mother for acute myeloid leukemia. Both patients presented with widespread sclerotic changes, resulting in joint contractures and significant functional difficulties.

## Case 1

A 39-year-old gentleman (Fitzpatrick skin type II), who had a HSCT for aplastic anemia eleven years before, developed after two years sclerodermatous GVHD with complete loss of mobility of the ankles

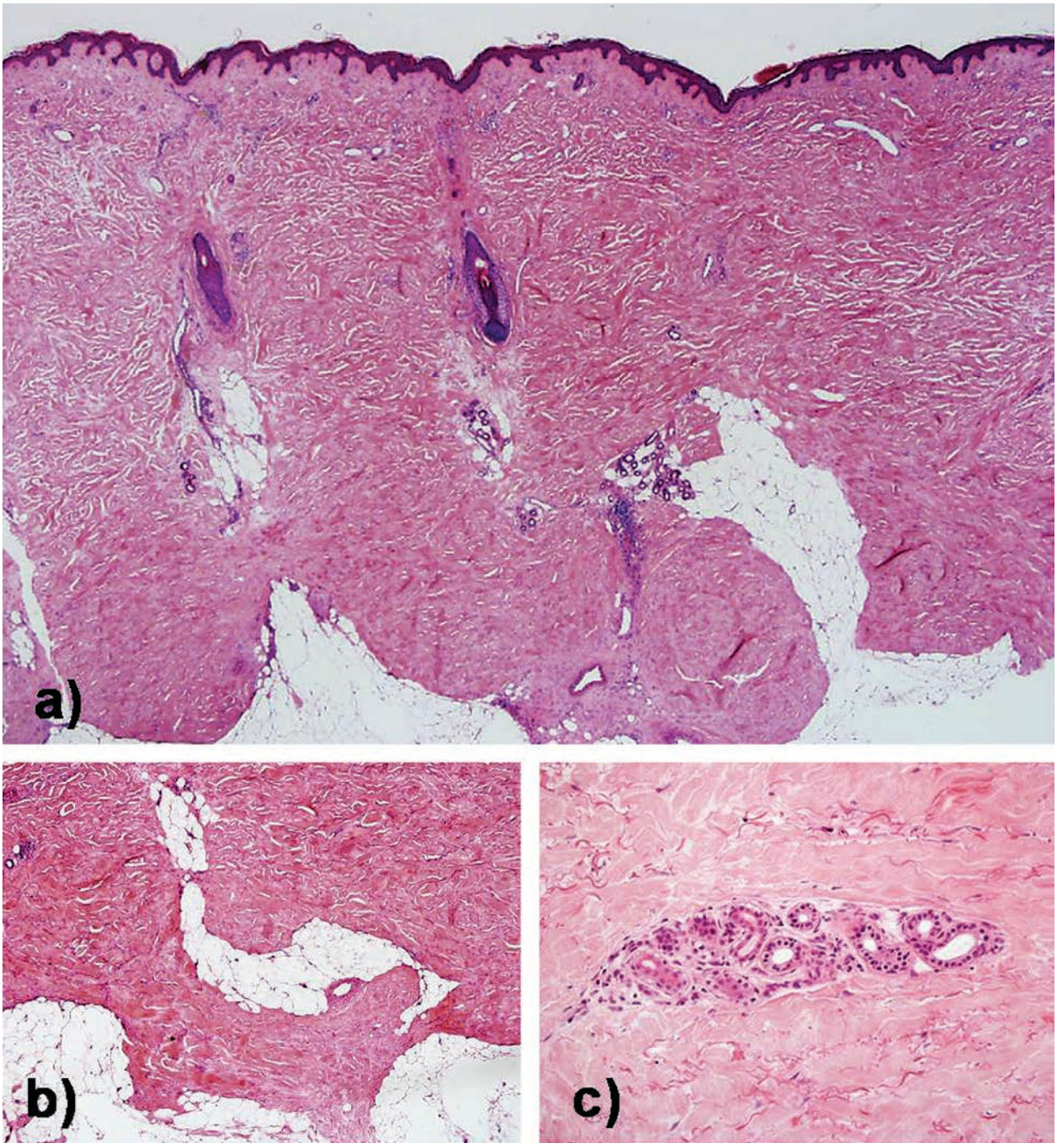


**Figure 1.** A skin biopsy demonstrated: a) deep dermal sclerosis; b) entrapment of the superficial subcutis by hyalinized collagen; c) peri-eccrine fat pad loss, confirming the diagnosis of sclerodermatous GVHD

and marked thickening of the skin. Apart from the cutaneous changes, he had no evidence of active GVHD elsewhere. Skin biopsy demonstrated sclerosis of the deep dermis (Figure 1a), with entrapment of the superficial subcutis by hyalinized collagen (Figure 1b), with peri-eccrine fat pad loss (Figure 1c), confirming the diagnosis of sclerodermatous GVHD.

The patient was initially treated with oral prednisolone, which was helpful, but resulted in avascular necrosis of both hips requiring replacements. Despite mycophenolate and cyclosporin, the disease continued to progress. A course of UVB phototherapy was used, but without benefit. Then he had a course of oral PUVA, up to three times per week, initially at 13.2 J/cm$^2$ and subsequently up to 21.2 J/cm$^2$ (total: 83 treatments, 740 J/cm$^2$). PUVA treatment showed mild benefits, but the response was very slow and there were concerns about the cumulative dose, particularly in view of his fair skin and previous immunosuppression with cyclosporin. The therapy was switched over to UVA1 phototherapy (SELLAMED 24,000 System, Sellas, Germany). Following 4 months of treatment (with a total number of 70 sessions, maximum single dose of 75 J/cm$^2$, cumulative dose of 5235 J/cm$^2$) the patient reported a >70% improvement from his waist up, however, his legs were still very tight. Therefore he received a course of high dose UVA1 on the legs (up to a maximum dose of 120 J/cm$^2$) (total: 70 treatments, 5235 J/cm$^2$).

The patient reported that UVA1 helped his skin changes, enabling him to play golf again for the first time in years. The therapeutic benefit has been longstanding, with quality of life and without side effects. His GVHD is currently in remission.

## Case 2

A 7-year-old boy (Fitzpatrick skin type II) received an allogeneic HSCT from his HLA-identical mother, two years before, for relapsed AML. After one year he developed severe and extensive sclerodermatous skin GVHD. He did not have any problems with his liver, gastrointestinal tract, chest or eyes. He received two courses of rituximab, which enabled him to gradually reduce, and ultimately discontinue oral prednisolone, and was on oral tacrolimus treatment (1.5 mg twice daily) when he was first referred for UVA1.

The sclerodermatous skin changes resulted in fixed flexion deformities of at least 20º at both elbows (Figure 2a), clawing of the hands (Figure 2b), and inability to keep his heels on the ground, due to fixed flexion deformities of his lower legs, which affected his mobility (Figure 2c). He had several superficial

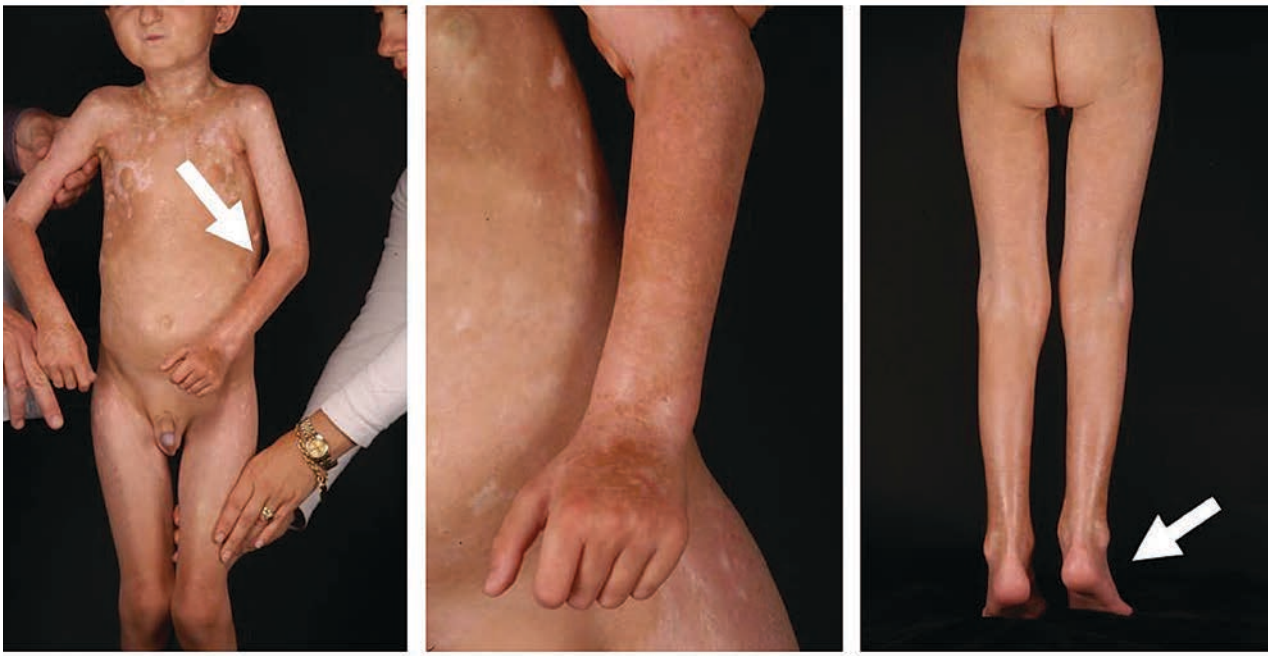

**Figure 2.** A child with sclerodermatous GVHD: a) fixed flexion deformities of at least 20º at both elbows; b) clawing of the hands; c) inability to stand with heels flat on the ground due to fixed flexion deformities of his lower legs

 

ulcerated areas over his scalp with associated scarring alopecia. Due to skin changes he was unable to manage activities of daily living. He had difficulty dressing up, and he was unable to feed independently.

He was treated with UVA1 phototherapy (SELLAMED 24,000 System, Sellas, Germany) three times per week for 10 weeks (up to a maximum dose of 30 J/cm$^2$) (total: 30 treatments, 800 J/cm$^2$). Other skin treatments included regular emollients, topical tacrolimus and physiotherapy. Within 4 weeks of treatment, there was a significant improvement,wihtout side effects. His skin became softer, with better joint flexibility and improved joint mobility, and he was able to go upstairs for the first time. After a month, methotrexate, 10 mg per week, was introduced with continuing improvement.

## Discussion

Equipment capable of delivering long-wavelength UVA (340-400 nm; UVA1) has been available since the early 1980s (7), but only in the last decade, there have been published studies investigating UVA1 as a potential treatment modality for various dermatological conditions. Therapeutic effects of UVA1 therapy have been shown in patients with atopic eczema, *lichen sclerosus et atrophicus, keratosis licehnoides chronica, prurigo nodularis,* cutaneous T-cell lymphoma, *granuloma annulare* and scleroderma (8).

There have been a small number of case reports and uncontrolled studies in the treatment of the sclerodermatous form of GVHD with UVA1 phototherapy. They have shown promising results in the treatment of these patients who were previously resistant to systemic immunosuppressive therapies (5,9-11).

Unlike UVB radiation that can penetrate at the most into the papillary dermis, longer wavelengths in the UVA region have the capacity to reach the subcutis as well (12). UVA1 radiation induces T-lymphocyte apoptosis, as well as reduction of the number of Langerhans cells and mast cells in the dermis, which may contribute to its effect in acute atopic dermatitis (13). In skin sclerosis, the dermis is compacted from the epidermal layer to the sweat glands, and the collagen bundles are thicker with decreased space between them (14). UVA1 irradiation induces collagenase activity, which results in degradation of collagen in sclerotic lesions (15-17).

UVA1 is usually well tolerated with very few side effects. Erythema, tanning polymorphous light eruption, itching and recrudescence of herpes simplex infection are the main acute adverse effects. The major potential chronic adverse effects are photo-aging and skin cancer, and only long-term follow-up of a large number of patients will be able to quantify the risk (18).

Both of our patients were treated with UVA1. In the 39-year-old patient, PUVA therapy showed limited benefits. However, UVA1 phototherapy significantly softened the sclerotic changes, improving joint mobility, allowing the patient to play golf for the first time in a number of years. In the case of the 7-year-old boy, UVA1 was used as an adjunct to methotrexate. It was difficult to define whether the clinical benefit was due to methotrexate, in regard to the UVA1, but there was an obvious skin improvement prior to the introduction of methotrexate. Prior to treatment, he had clawing at his hands, was unable to keep his heels on the ground, and found activities of daily living challenging. Treatment with UVA1 markedly improved the appearance and texture of his skin.

## Conclusion

UVA1 appears to be an effective treatment for refractory sclerodermatous GVHD and other sclerotic skin diseases; however, long term clinical studies in larger groups are needed to accurately evaluate its efficacy and safety.

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## Abbreviations

GVHD – graft-versus-host disease
HSCT - hematopoietic stem cell transplantation
ECP – extracorporeal photopheresis
UVA – ultraviolet A
UVB - ultraviolet B
PUVA – psoralen and ultraviolet A
HLA - human leukocyte antigen
AML – acute myeloid leukemia

# UVA1 fototerapija u lečenju sklerodermatoznog oblika hronične GVHD: prikaz dva slučaja

## Sažetak

Uvod: Sklerodermatozne promene u okviru hronične *graft-versus-host disease* (GVHD; eng. reakcija transplantata protiv domaćina) javljaju se kod oko 10% obolelih i dovode do značajnog morbiditeta. Ovaj oblik GVHD je veoma rezistentan na terapiju, uključujući sistemsku primenu imunosupresiva, PUVA fotohemoterapiju, UVB fototerapiju, ekstrakorporalnu fotoferezu, kao i lokalnu primenu koristikosteroida i takrolimusa. Za razliku od UVB zraka, zraci većih talasnih dužina unutar UVA spektra, prodiru od hipodermisa i u sklerozom zahvaćenoj koži, putem aktivacije kolagenaze izazivaju sledstvenu degradaciju kolagena. Dosad je objavljen manji broj radova o primeni UVA1 fototerapije (340-400 nm) u lečenju ovog oboljenja.

Cilj rada: Prikazujemo naša iskustva u lečenju dva pacijenta sa sklerodermatoznim oblikom GVDH: kod tridesetdevetogodišnjeg muškarca je u cilju lečenja aplastične anemije, pre jedanaest godina, izvršena transplantacija matične hemopoetske ćelije sa HLA-kompatibilnog donora; kod sedam godina starog dečaka, obolelog od akutne mijeloidne leukemije izvršena je pre dve godine transplantacija matične hemopetske ćelije od HLA-identičnog donora, majke.

Klinička slika: Oba pacijenta su imala diseminovane sklerotične promene na koži, izražene kontrakture zglobova i značajne funkcionalne abnormalnosti. Promene su se javile dve godine nakon transplantacije kod tridesetdevetogodišnjeg muškarca i godinu dana nakon transplantacije kod sedmogodišnjeg dečaka i u oba slučaja su bile diseminovane.

Lečenje: Oba pacijenta su lečena UVA1 fototerapijom što je dovelo do omekšanja sklerotičnih plakova, povećanja pokretljivosti zglobova i do ukupnog

 

poboljšanja funkcionalne sposobnosti, bez neželjenih efekata.

Zaključak: UVA1 fototerapija je pokazala obećavajuće rezultate u lečenju naša dva pacijenta obolela od sklerodermatozne forme hronične GVHD. Dalja istraživanja su potrebna kako bi se precizno evaluirala njena efikasnost i bezbednost u terapiji ovih pacijenata.