

CLINICAL REPORT

Persistent Improvement of Previously Recalcitrant Hailey-Hailey Disease with Electron Beam Radiotherapy

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Hailey-Hailey disease, or familial benign chronic pemphigus, is an autosomal dominant genodermatosis. Disease symptoms may contribute to an adverse impact on quality of life and functional limitation and disability. As Hailey-Hailey disease is chronic and frequently recalcitrant to treatment, multiple therapeutic approaches, including surgical options, have been attempted. We describe here three cases of recalcitrant Hailey-Hailey disease that showed long-term improvement with radiotherapy. Axillary lesions were treated with electron beam at an anti-inflammatory dose (energy 6–8 MeV). Patients received 20 Gy in 10 fractions to 90% isodose, at each axilla. No disease recurrence was observed during a 38 months follow-up of the treated sites. The effect of radiotherapy was thus considered to be locally beneficial, but without any positive influence on the general course of the disease. Key words: Hailey-Hailey disease; electron beam radiotherapy; treatment.

(Accepted October 19, 2009.)

Acta Derm Venereol 2010; 90: 179–182.

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Hailey-Hailey disease (HHD) or familial benign chronic pemphigus is an autosomal dominant genodermatosis characterized by a chronic course (1). Skin lesions, including vesicles and erosions, localize mainly in the

intertriginous areas (groin, axilla, perineum). Associated symptoms (itching, pain, burning) may contribute to an adverse impact on quality of life and functional disability. HHD affects primarily middle-aged persons, but can also develop in elderly people. Although it is a genetic disease, the family history can be negative. Exogenous factors, such as ultraviolet (UV) radiation, heat, sweating, infections and contact allergens can exacerbate the condition (1, 2). Histological examination of typical HHD lesions reveals suprabasal acantholysis with a “dilapidated brick wall” appearance (3). Common therapeutic options consist of systemic or topical treatment with antibiotics, antimycotics and corticosteroids (4–6), dapsone (7), etretinate (8) or methotrexate (9). As HHD is often recalcitrant to treatment, further options, including invasive methods, have been introduced. Psoralen plus ultraviolet A (PUVA) therapy, thalidomide (4, 5), vitamin E (10), cyclosporine (11, 12), topical immunomodulators (tacrolimus) (13–15), vitamin D analogues (16–18), photodynamic (19) or laser therapy (20–24) dermabrasion (25, 26) or skin grafting (27, 28) have been reported as useful in treatment of HHD. However, beneficial effects were observed in only a proportion of treated patients and the duration of improvement was lasted only for a few months on average. In some cases the improvement was confined to the treated site and did not affect the development of skin lesions elsewhere. We describe here three cases of HHD in which various therapeutic regimens were tried without benefit and in which electron beam radiotherapy resulted in protracted local improvement.

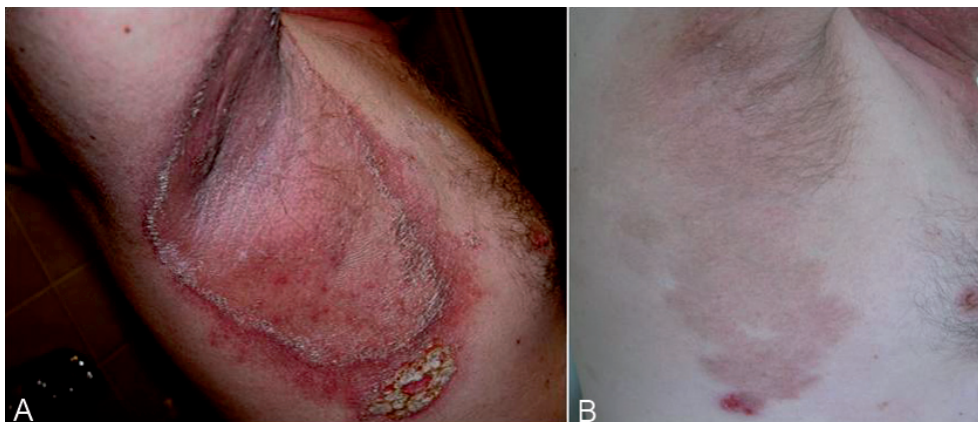


Fig. 1. Case 1. (A) Typical skin lesions within the axilla. (B) Therapeutic efficacy of radiotherapy: right axilla showing only hyperpigmentation after 38 months.

CASE REPORTS

Case 1

A 54-year-old Caucasian man with HHD has been treated in the outpatient Dermatology Clinic, Medical University of Lodz, Poland, for more than 10 years. The patient presented with persistent flexural blistering skin lesions localized mainly to the axillae, groin, scrotum, and lower part of the neck (Fig. 1A). The lesions evolved into eczematous plaques with crusting and fissuring. The skin eruptions first appeared when the patient was 41 years old. His family history was negative for HHD. Histological examination of an axillary lesion, performed 10 years ago, revealed an acanthotic epidermis with prominent suprabasal clefting and widespread acantholysis with a "dilapidated brick wall" appearance. In the overlying epidermis, focal dyskeratotic changes of the keratinocytes (corps ronds) were present. Perilesional direct immunofluorescence and indirect immunofluorescence for pemphigus/basement membrane zone (BMZ) antibodies were negative. The clinical and histological findings were compatible with a diagnosis of HHD.

During a 10-year course of the disease, the patient was hospitalized several times in our department because of severe course of the disease. Initially the disease was controlled with systemic antibiotics (amoxicillin) and topical treatment including antibiotics, antimycotics and steroids. Skin lesions healed rapidly, but complete clinical remission never occurred. Next systemic therapy with steroids (prednisone) was tried, followed by dapsone and etretinate; the latter with no clinical improvement. As the best result was achieved with systemic steroids, this therapy was continued with tapering doses of prednisone for 2 years. It was then withdrawn due to side-effects of hypertension, obesity and diabetes mellitus. Other therapeutic approaches were used, including topical calcineurin inhibitors and vitamin D analogues, without benefit. Indeed tacrolimus application led to the exacerbation of the skin lesions. In 2002, excision of the involved areas within the groin with split-thickness grafting was performed. This therapy brought some improvement, and during the 3-year follow-up, milder skin lesions in this area developed. However, the patient was dissatisfied due to protracted healing time, development of contractures, and severe pain.

Four years ago, because of the worsening of the skin lesions, especially in the axilla, which resulted in disability (the patient was a taxi driver and was unable to work) we searched for an alternative treatment and radiotherapy was tried. After providing written informed consent from the patient, the skin lesions on the right axilla were treated with external beam irradiation in the Department of Radiation Therapy, Copernicus Memorial Hospital, Lodz, Poland. An electron beam of energy 7.5 MeV was used. The patient received in total 20 Gy administered in 10 fractions to 90% isodose. Conventional fractionation was used consisting of 2 Gy once daily 5 days per week. The patient experienced a grade 1 (ac-

ording to Radiation Therapy Oncology Group (RTOG) criteria) skin reaction, i.e. erythema, "dry desquamation" without epilation, which was assessed as mild and transient and did not require further treatment (29). As we revealed a satisfactory outcome with no new lesions and only hyperpigmentation after 2 months, this encouraged treatment of the left axilla also. The same therapeutic regimen was applied with the same result.

In radiotherapy-treated sites, no recurrence of the disease was observed during a 38-month follow-up of the right axilla (Fig. 1B) and a 36-month follow-up of the left axilla. Only hyperpigmentation was apparent. To confirm the positive effect of radiotherapy, a punch biopsy from the treated right axilla was taken, which demonstrated slight suprabasal clefts and mild features of acantholysis, considerably less intense than before radiotherapy.

Case 2

A 60-year-old Caucasian man had previously been treated in the outpatient Dermatology Clinic for 8 years. He denied any history of skin disease in his family. The personal history revealed diabetes mellitus and arterial hypertension. The skin lesions were localized mainly in intertriginous areas: axillae, groin and sacrum (Fig. 2A). The skin eruptions were characteristic for HHD; erythematous plaques with overlying crust and secondary impetiginization associated with burning and itching. A skin biopsy from axillary lesions demonstrated acantholysis with dilapidated brick wall appearance of the epidermis and mixed inflammatory infiltrate in the papillary dermis, confirming the diagnosis of HHD. Direct and indirect immunofluorescence tests were negative. One year later, the patient presented with erythematous scaly plaques and guttate lesions scattered on the trunk and limbs, which were diagnosed clinically and histologically as psoriasis. The psoriatic plaques were mild and required only topical treatment. HHD lesions were treated with systemic and topical antibiotics (cefuroxime, tetracycline), antimycotics and steroids. Applying topical calcineurin inhibitors led to short-lived remission while vitamin D analogues gave no satisfactory response. Because of disease worsening, methotrexate was administered. However it was ceased because of side-effects, specifically elevated liver enzymes.

Continuous progression of HHD and previous positive outcome with radiotherapy in case 1, encouraged us to offer external beam irradiation to this patient. After providing informed consent, the same therapeutic regimen of irradiation was applied to affected sites of both axillae with similar positive results as in the first case. The energy of electron used was 6 MeV. The patient also experienced a grade 1 (according to RTOG) skin reaction, which was transient and required no further medication (29). At 33-month follow-up, no new lesions characteristic for HHD were observed and the treated sites remained quiescent. Currently we observed only hyperpigmentation in irradiated areas and periodic waxing and waning of psoriatic lesions (Fig. 2B).

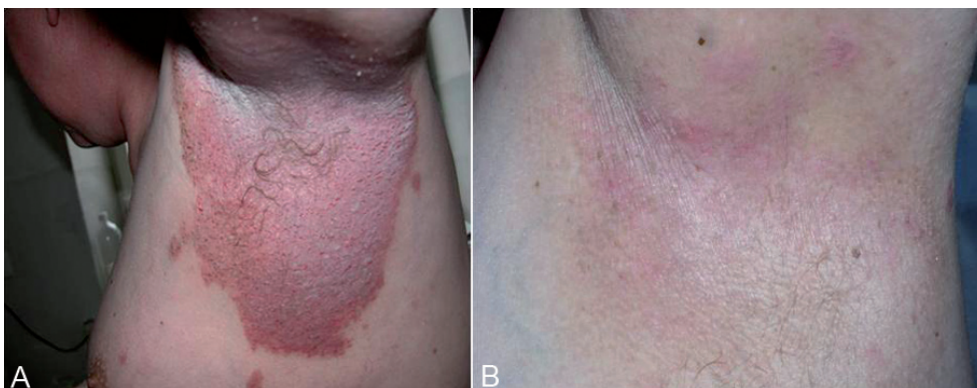


Fig. 2. Case 2. (A) Typical skin lesions within the axilla. (B) Therapeutic efficacy of radiotherapy within the left axilla showing hyperpigmentation after 33 months.

Case 3

A 47-year-old Caucasian woman with HHD had been treated for 3 years in the outpatient Dermatology Clinic in Lodz and had been hospitalized on several occasions at the Department of Dermatology in Lodz. Her family history was negative for HHD. The first skin lesions occurred in the flexural regions, mainly in axillary and inframammary folds (Fig. 3A). Dermatological examination revealed erythema, lamellar scaling and superficial erosions with impetiginization. The skin lesions were accompanied by intense subjective symptoms; pain and itching. Biopsy from the axilla showed typical suprabasal acantholytic clefts. Perilesional direct immunofluorescence and indirect immunofluorescence tests for pemphigus/BMZ antibodies were negative. We observed initially good but short-lived response to multiple topical corticosteroids, antibiotics and antimycotics, but helpful only during exacerbations but did not abate their frequency. Topical treatment with vitamin D analogues and oral tetracycline were not tolerated by the patient. We observed the greatest benefit with administration of prednisone, which was continued for 3 years. However, the development of telangiectasias and Cushing's syndrome necessitated discontinuation. In March, 2008 after consultation with the Department of Radiation Therapy, Medical University of Lodz and providing informed consent, the patient underwent electron beam radiotherapy at an anti-inflammatory dose. She received 20 Gy in 10 fractions of electron beam irradiation simultaneously to both axillae. The electron beam energy used for treatment was 6 MeV. To decrease the exposure of underlying tissues and to provide a more homogeneous dose on the skin surface the wax bolus was applied. To exclude the risk of radiation to breast tissue, treatment of inframammary regions was avoided. At 9-month follow-up, treated sites at both axillae were in clinical remission, with hyperpigmentation as the only residual effect after radiotherapy (Fig. 3B). However, periodic relapses of HHD continued at the inframammary folds.

DISCUSSION

Ionizing radiation therapy used to be applied frequently in dermatology in the Roentgen rays era. Very early after its discovery, it was recognized as a useful treatment of skin cancer, mycosis fungoides and Sezary's syndrome, and also for inflammatory skin diseases and even bacterial inflammation (30). The introduction of new surgical techniques, antibiotics and other therapeutic modalities markedly decreased the use of

ionizing radiation therapy in dermatology. Currently its use is limited to a small number of applications for selected patients.

For HHD, previous reports (31, 32) indicated an initial beneficial response to superficial radiotherapy in two cases. The irradiated sites included the axilla, low back, groin and perineum. Unfortunately, only temporary improvement was achieved.

In cases of HHD in which conservative therapy gives only partial or temporary improvement, one suggestion of invasive treatment is split-thickness skin grafting (27, 28). This procedure can lead to many complications, such as infection, with possible graft rejection, or contractures of the excised areas. Grafting was undertaken on the groin region of our patient 3 years ago, but the result was considered only semi-satisfactory, with impaired wound healing and the appearance of skin lesions, although less intense than before grafting.

Our first patient was irradiated at the axilla with an electron beam of energy 7.5 MeV (the lowest available energy) generated in a linear accelerator. The therapeutic dose is achieved at depth of 2.0–2.5 cm, and thereafter decays rapidly up to a depth of 3.0–3.7 cm. Accordingly, the spectrum of potential effect ranges from the epidermis to underlying dermis and fatty tissue. As the result of equipment upgrading, we were later able to apply lower doses to minimize the dose to underlying tissues. In the last case we also applied individually fitted wax bolus to receive a higher dose on the skin surface and decrease the depth of the therapeutic isodose. Although the changes in HHD are limited to the epidermis, the exact effects of the irradiation on the underlying tissue are unknown. Previous reports of using radiation therapy classic Roentgen beams in HHD treatment did not include long-lasting effects. Roentgen beams are seldom used in European Radiotherapy Departments for superficial skin therapy and were replaced by electron beam therapy. Electrons are the particles which cause direct ionization, resulting in intracellular function disturbance, inhibition of epidermal cell proliferation and immunosuppression (31). These effects may be one



Fig. 3. Case 3. (A) Typical skin lesions within the axilla. (B) Therapeutic efficacy of radiotherapy: axillary left region with hyperpigmentation after 9 months.

explanation of long-lasting response of HHD to electron beam therapy.

During the follow-up period, new lesions developed in other body sites (trunk and neck, lumbar region) untreated by electron beam therapy, while the irradiated areas remained quiescent. Based on these results we conclude that radiotherapy has a local beneficial effect in the treatment of HHD providing prolonged remission, but that it does not influence the general course of the disease. It will be interesting to study more patients with chronic and resistant HHD in order to further validate this treatment. However, it is necessary to remember that use of radiotherapy might be linked with oncogenesis; hence, individual therapeutic decisions must be made in each case.

ACKNOWLEDGEMENTS

We would like to thank Dr Jerry Tan from Windsor Clinical Research Inc. and University of Western Ontario, Windsor, Ontario, Canada, for critical review of the manuscript and providing constructive comments. The study was supported by research project of Medical University of Lodz, Poland (nr 503-11-52-1).

The authors declare no conflict of interest.

REFERENCES

- Peluso AM, Bonifas JM, Ikeda S, Hu Z, Devries S, Waldman F. Narrowing of the Hailey-Hailey disease gene region on chromosome 3q and identification of one kindred with a deletion in this region. *Genomics* 1995; 30: 77–80.
- Peppiatt T, Keefe M, White JE. Hailey-Hailey disease – exacerbation by herpes simplex virus and patch tests. *Clin Exp Dermatol* 1992; 17: 201–202.
- Haber H, Russel LB. Sisters with familial benign chronic pemphigus. *Br J Dermatol* 1950; 62: 458–460.
- Burge SM. Hailey-Hailey disease: The clinical features, response to treatment and prognosis. *Br J Dermatol* 1992; 126: 275–282.
- Galimberti RL, Kowalczyk AM, Bianchi O, Bonino MV, Garcia Garcia A. Chronic benign familial pemphigus. *Int J Dermatol* 1988; 27: 495–500.
- Ikeda S, Suga Y, Ogawa H. Successful management of Hailey-Hailey disease with potent topical steroid ointment. *J Dermatol Sci* 1993; 5: 205–211.
- Sire DJ, Johnson BL. Benign familial chronic pemphigus treated with dapsone. *Arch Dermatol* 1971; 103: 262–265.
- Bonafe JL, Fontan B, Pieraggi MT, Divoux D. Action positive de l'etretinate (RO 10.9359) dans un cas de pemphigus benin familial. *Ann Dermatol Venereol* 1983; 110: 151–153.
- Fairris GM, White JE, Leppard BJ, Goodwin PG. Methotrexate for intractable benign familial chronic pemphigus. *Br J Dermatol* 1986; 115: 640.
- Ayres S Jr. Hailey-Hailey disease: response to vitamin E therapy. *Arch Dermatol* 1983; 119: 450.
- Berth-Jones J, Smith S, Graham-Brown R. Benign familial chronic pemphigus (Hailey-Hailey disease) responds to cyclosporine. *Clin Exp Dermatol* 1995; 20: 70–72.
- Ormerod A, Duncan J, Stankler L. Benign familial pemphigus responsive to cyclosporin, a possible role for cellular immunity in pathogenesis. *Br J Dermatol* 1991; 124: 299–305.
- Lafitte E, Panizzon RG. Is topical tacrolimus really an effective therapy for Hailey-Hailey disease? *Arch Dermatol* 2004; 140: 1282.
- Rabeni EJ, Cunningham NM. Effective treatment of Hailey-Hailey disease with topical tacrolimus. *J Am Acad Dermatol* 2002; 47: 797–798.
- Sand C, Thomsen HK. Topical tacrolimus ointment is an effective therapy for Hailey-Hailey disease? *Arch Dermatol* 2003; 139: 401–402.
- Bianchi L, Chimenti MS, Giunta A. Treatment of Hailey-Hailey disease with topical calcitriol. *J Am Acad Dermatol* 2004; 51: 475–476.
- Rajpara SM, King CM. Hailey-Hailey disease responsive to topical calcitriol. *Br J Dermatol* 2005; 152: 816–817.
- Aoki T, Hashimoto H, Koseki S. 1- α ,24-dihydroxyvitamin D₃ (tacalcitol) is effective against Hailey-Hailey disease both in vivo and in vitro. *Br J Dermatol* 1998; 139: 897–901.
- Ruiz-Rodriguez R, Alvarez JG, Jaen P, Acevedo A, Cordoba S. Photodynamic therapy with 5-aminolevulinic acid for recalcitrant familial benign pemphigus (Hailey-Hailey disease). *J Am Acad Dermatol* 2002; 47: 740–742.
- Touma DJ, Krauss M, Feingold DS, Kaminer MS. Benign familial pemphigus (Hailey-Hailey disease). Treatment with the pulsed carbon dioxide laser. *Dermatol Surg* 1998; 24: 1411–1414.
- McElroy JA, Mehregan DA, Roenigk RK. Carbon dioxide laser vaporization of recalcitrant symptomatic plaques of Hailey-Hailey disease and Darier's disease. *J Am Acad Dermatol* 1990; 23: 893–897.
- Kartamaa M, Reitamo S. Familial benign chronic pemphigus (Hailey-Hailey disease). Treatment with carbon dioxide laser vaporization. *Arch Dermatol* 1992; 128: 646–648.
- Collet Villette AM, Richard MA, Fourquet F, Monestier S, Gaudy C, Bonerandi JJ, Grob JJ. Treatment of Hailey-Hailey disease with carbon dioxide laser vaporization. *Ann Dermatol Venereol* 2005; 132: 637–640.
- Beier C, Kaufman R. Efficacy of erbium: YAG laser ablation in Darier disease and Hailey-Hailey disease. *Arch Dermatol* 1999; 135: 423–427.
- Hamm H, Metz D, Brocker EB. Hailey-Hailey disease. Eradication by dermabrasion. *Arch Dermatol* 1994; 130: 1143–1149.
- Zachariae H. Dermabrasion of Hailey-Hailey disease and Darier's disease. *J Am Acad Dermatol* 1992; 27: 136.
- Sonck RE, Rintala A. Treatment of familial benign pemphigus by skin grafting. *Acta Derm Venereol* 1975; 55: 395–397.
- Crotty CP, Scheen SRIII, Masson JK, Winkelmann RK. Surgical treatment of familial benign chronic pemphigus. *Arch Dermatol* 1981; 117: 540–542.
- Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; 47: 13–47.
- Sarkany I. Grenz-ray treatment of familial benign chronic pemphigus. *Br J Dermatol* 1959; 71: 247–252.
- Roos DE, Reid CM. Benign familial pemphigus: little benefit from superficial radiotherapy. *Australas J Dermatol* 2002; 43: 305–308.
- Roos DE. Radiotherapy for benign familial pemphigus. *Int J Radiat Oncol Biol Phys* 2003; 56: 908.