Use of UVA1 in the treatment of mycosis fungoides – case report

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Abstract

Mycosis fungoides is the most common form of primary cutaneous lymphoma, with three phases: erythematous, infiltrative and tumour phase. In contrast with Sézary syndrome, the course is often slow and skin lesions may not be distinctive for a longer period of time and may resemble lesions occurring in the course of other dermatoses, such as eczema, large plaque parapsoriasis, atopic dermatitis or psoriasis. The right choice of treatment method seems to be essential in the therapy of mycosis fungoides. According to the consensus by the Cutaneous Lymphoma Section of the Polish Lymphoma Research Group, less aggressive methods of treatment mainly with local administration of corticosteroids and phototherapy should be used in early stages of the disease. The described case is a patient with mycosis fungoides, in whom modern UVA1 therapy proved to be successful. The obtained remission was confirmed by ultrasound imaging of skin lesions before and after the therapy, which may be a new method of monitoring the course of the disease in patients with mycosis fungoides.

Key words: mycosis fungoides, primary cutaneous T-cell lymphomas, UVA1, ultrasonography.

Introduction

Mycosis fungoides (MF) is one of the primary cutaneous lymphomas (cutaneous T-cell lymphoma – CTCL), characterized by malignant proliferation of T cells. The dermatosis was first described by Alibert in 1806, and in 1876 Bazin presented the division into three phases, erythematous, infiltrative and tumour phase, that may turn into each other or occur at the same time in a given patient [1, 2]. Sézary and Bouvrain in 1938 were the first to describe Sézary syndrome as a rare form of CTCL [3]. Sézary syndrome is characterized by a triad of symptoms: erythroderma, enlargement of lymph nodes and presence of Sézary cells in the peripheral blood, lymph nodes and the skin. Due to intense itching of the skin of the whole body and very aggressive course, the disease is very burdensome. According to the WHO/EORTC, the five-year survival rate from the moment of diagnosis is 24% [4]. Primary cutaneous lymphomas are the most common type of non-Hodgkin lymphomas with primary extranodal localization [5]. About 1,000 new cases are noted per year in the USA, and men suffer from the disease more frequently than women – the ratio is 2 : 1. In most cases the age at onset of mycosis fungoides is between the 55th and the 60th year of age [6] and it seems that the prevalence of the disease is similar in Poland.

In the initial stage of the disease, skin lesions from a few to a dozen or so years may not be distinctive and may resemble erythematous and desquamative lesions in the course of eczema, large plaque parapsoriasis, atopic dermatitis, psoriasis, or Devergie's disease [7, 8].

Modern trends in the treatment of mycosis fungoides only with skin lesions are limited to mild dermatological treatment. So far no treatment has been found that would result in a complete cure of a patient with mycosis fungoides. At present it is recommended to administer treatment that is as little toxic as possible, adjusted to the stage of the disease. First-line drugs include local corticosteroids, mechlorethamine or carmustine. Using the last two drugs is problematic due to the need for direct imports of the preparations. Other methods used in stages IA, IB and IIA include photochemotherapy (PUVA), UVB or UVA1 therapy, and total skin electron beam radiotherapy (TSEB).

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Case report

The patient, aged 52, has been in the care of the Outpatient Dermatology Department of the Poznań University of Medical Sciences since 1999. The first skin changes (spots) were observed in 1998 on the patient's buttocks, hypogastrium and side areas of the trunk. The clinical diagnosis of large plaque parapsoriasis was made. The patient underwent selective ultraviolet phototherapy (SUP), which resulted in a significant improvement in the clinical condition. Due to deterioration in the clinical condition, the patient reported to the Outpatient Dermatology Department in 2000 – skin changes occurred on the trunk, lower limbs and buttocks and were erythematous and infiltrative. The histopathological examination of the skin specimen revealed a dense inflammatory infiltration adjacent to the epidermis, numerous cells with hyperchromatic and irregular nuclei (so-called "mycosis cells") among the infiltration cells, and epidermotropism and Pautrier's microabscess in the epidermis (Figs. 1-3) [9]. The above examination and the clinical picture resulted in the diagnosis of mycosis fungoides in the infiltrative stage. The patient underwent another series of SUP therapy. However, since no significant improvement was observed, PUVA therapy was administered after ophthalmological consultation. In 2001 hepatitis C was diagnosed in the patient. Further deterioration in the clinical condition was observed in 2003 – infiltrative lesions on the thighs and trunk with a tendency for new lesions. It was decided to administer general treatment with methylprednisolone initially at the dose of 40 mg with periodic reduction of the dose after obtaining a significant improvement in the dermatological condition. At the same time the patient underwent SUP and then PUVA therapy. Immunohistochemical examination performed in April 2006 in the Greater Poland Cancer Centre confirmed the diagnosis of mycosis fungoides. The determined immunophenotype was CD3+, CD4>CD8, CD20– (positive result in B cells), CD 68– (positive result in macrophages). The patient was treated in the Greater Poland Cancer Centre in the Radiotherapy Ward with rotational total skin 6-MeV electron beam radiotherapy – TSEB. The patient received the total dose of 36 Gy/max+boost, which resulted in a decrease in skin infiltrations. However, the assessment of the remission was difficult because of the strong post-radiation reaction. After the treatment, 2-year remission was observed together with intensified epileptic symptoms, from which the patient has been suffering for several years. In 2009 the patient reported to the Outpatient Dermatology Department because of the deteriorated dermatological condition. Numerous infiltrative lesions appeared on the skin of mainly the face, trunk and lower limbs. Further phototherapy resulted in a slight improvement in the clinical condition. In March 2010 the patient was hospitalized in the Clinic of Dermatology because of the deteriorated dermatological condition in the disease stage IIb. Laboratory and imaging examinations performed during the hospitalization found no deviations from the norm. Flow cytometric analysis showed that in the examined population of peripheral blood leuko-

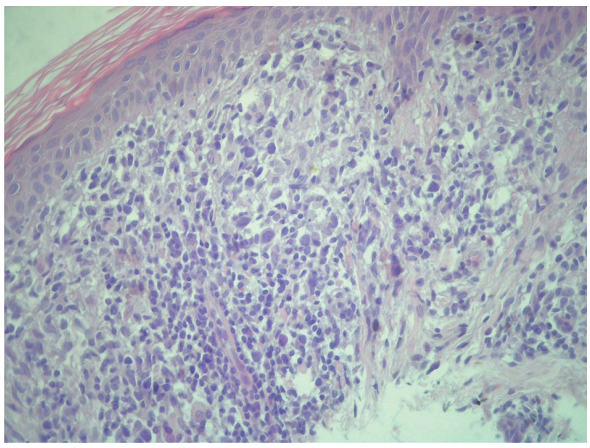

Fig. 2. Numerous cells with hyperchromatic and irregular nuclei – so-called "mycosis cells" among the infiltration cells (H+E staining, magnification 40×)

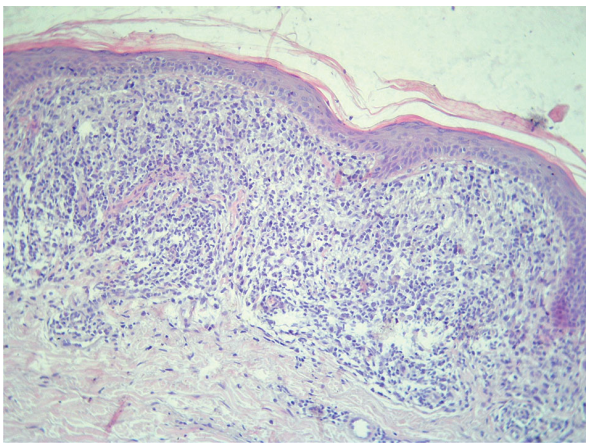

Fig. 1. Dense inflammatory infiltration adjacent to the epidermis (H+E staining, magnification 20×)

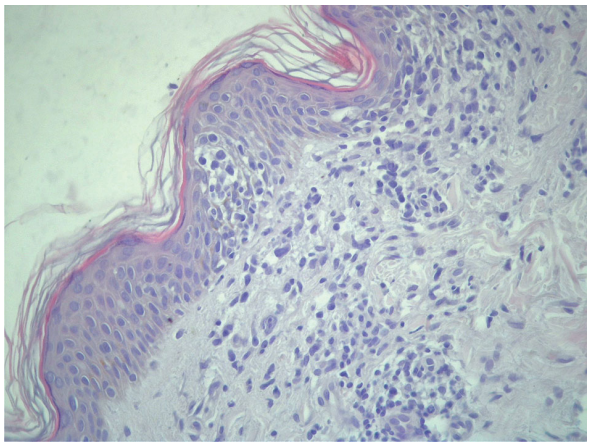

Fig. 3. Epidermotropism and Pautrier's microabscess in the epidermis (H+E staining, magnification 40×)

cytes, lymphocytes accounted for 45% and their immunophenotypic distribution as to the subpopulations of B, T and NK cells showed no significant deviation. During the patient's stay in the ward, UVA1 irradiation was employed (GP-24H Cosmedico apparatus, Germany). Already after 10 irradiations the old lesions flattened or partially regressed. Unfortunately, some new single lesions appeared, so the cycle of treatment with UVA1 was extended up to 30 irradiations. During the 24th irradiation, Metypred at the dose of 32 mg per day was administered. The therapy was finished on 15 April 2010 with the total dose of 2,710 J/cm^2. The patient received one irradiation at the dose of 10 J/cm^2, one at the dose of 20 J/cm^2, one at the dose of 40 J/cm^2, seven at the dose of 60 J/cm^2, six at the dose of 90 J/cm^2 and fourteen irradiations at the dose of 120 J/cm^2. After the treatment with UVA1, the patient reported for follow-up examinations once a month and except for a single lesion on the left cheek, no other mycosis fungoides-like lesions were observed. The patient's examination in the Clinic of Dermatology before the onset of UVA1 therapy also included skin ultrasound examination. The USG examination of healthy skin revealed entrance echo in the form of a thin and echo-rich line, the dermis as a wide layer rich in echoes with scattered reflections and the echo-poor hypodermis (Fig. 4). The USG examination showed a hypoechogenic band just below the entrance echo and decreased skin echogenicity in the pathologically changed skin when compared to healthy skin (Fig. 5). After the end of the irradiations, ultrasound examination of the pathologically changed skin was performed again, which demonstrated that the USG image, together with improvement in the patient's clinical condition, showed fading of the described band and an increase in skin echogenicity (Fig. 6).

The patient constantly received Metypred at the dose of 32 mg with periodic reduction to 24 mg per day. In

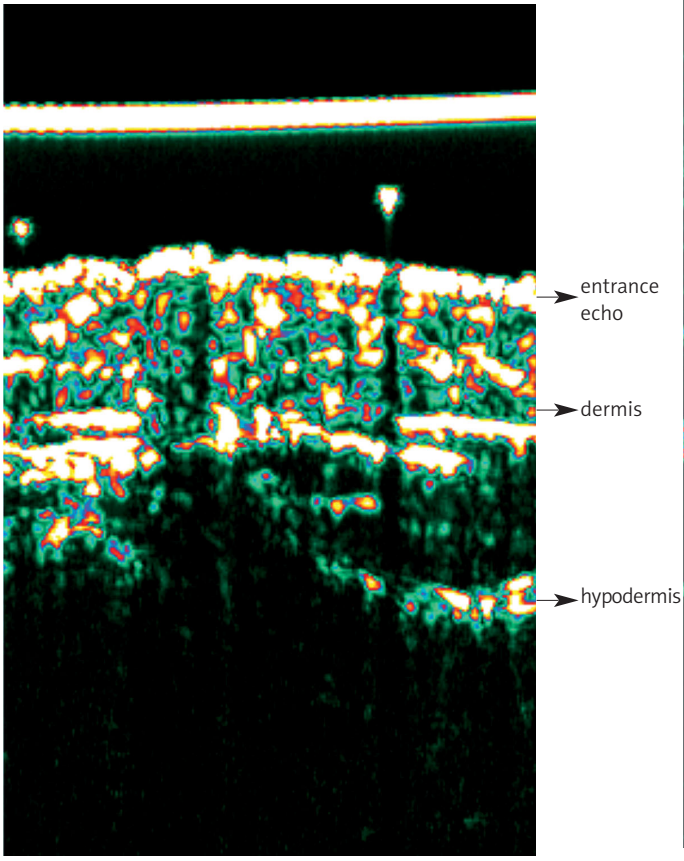

Fig. 4. The USG examination of healthy skin: entrance echo in the form of a thin and echo-rich line, the dermis as a wide layer rich in echoes with scattered reflections and the echo-poor hypodermis

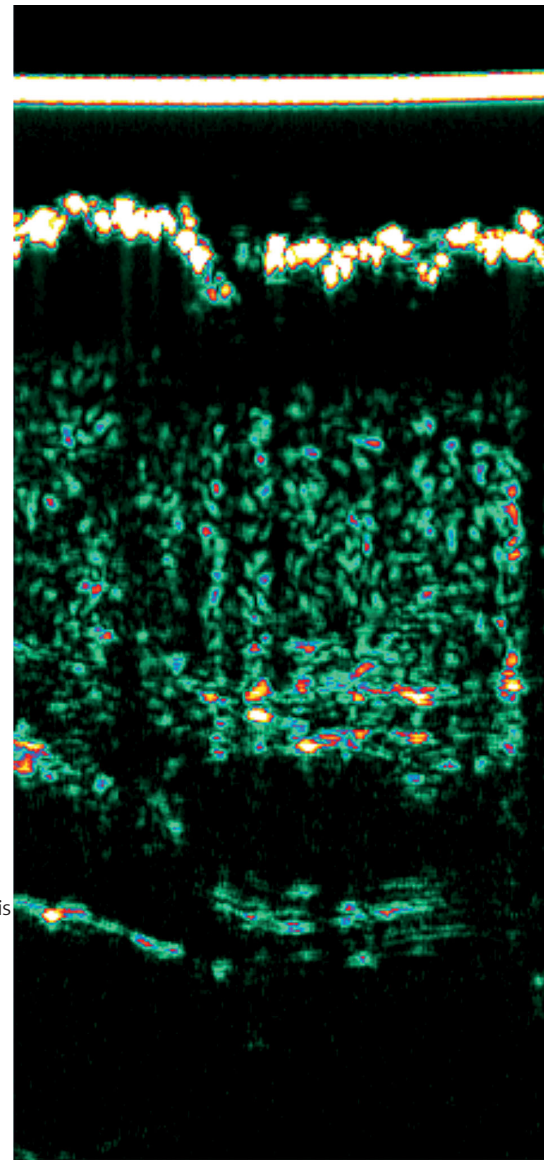

Fig. 5. The USG examination of the pathologically changed skin showed a hypoechogenic band just below the entrance echo and decreased skin echogenicity when compared to healthy skin

August 2010, a distinct increase in AFP was observed, and the patient was subjected to CT examination of the abdominal cavity, which showed an oval lesion, 8 mm in diameter, in segment 2 of the left liver lobe, invisible before administration of a contrast medium that homogeneously strongly enhanced in the arterial phase and became isodense in the venous phase. The image is ambiguous – presumably primary hepatocellular carcinoma or adenoma. In addition, horseshoe kidney and a cyst 1 cm in diameter in the right part can be seen. Other organs of the abdominal cavity and lymph nodes are normal. Magnetic resonance imaging of the abdominal cavity was recommended. During the last follow-up visit at the end of October 2010, new single infiltrative lesions were observed. The patient has constantly been receiving Metypred at the dose of 24 mg per day and externally applying steroid preparations.

Discussion

Primary cutaneous lymphomas are a heterogeneous group of lymphoproliferative hyperplasias of various degrees of malignancy, of which 75% derive from T cells or less often from B cells. In the diagnosis, absence of lymphoma cells in lymph nodes, bone marrow and visceral organs is highly significant. The current classification of primary cutaneous lymphomas combines the WHO classification (the World Health Organization) and the EORTC classification (the European Organization for Research and Treatment of Cancer) (Tab. 1) [10]. The course of lymphomas is usually chronic with periods of remissions and recurrences. They are dermatoses that pose an interdisciplinary problem in the diagnostics and treatment. So far the causes and risk factors of mycosis fungoides remain unclear. Although environmental and occupational factors were analysed to find out if exposure to them causes primary cutaneous lymphomas, the conducted large studies failed to confirm these assumptions [11]. A viral background of mycosis fungoides was also suggested. Several studies present descriptions of cases where human T-cell lymphotropic virus type 1 (HTLV-1) was found both in the patients' blood and in tissues [12]. There are also some studies that contradict the role of this virus in the aetiopathogenesis of mycosis fungoides [13]. Therapeutic procedures in cutaneous lymphomas are subject to tumour histopathological diagnosis and staging, assessed according to the TNMB classification (Tab. 2) [10].

According to the current medical knowledge and the consensus of the Cutaneous Lymphoma Section of the Polish Lymphoma Research Group, the treatment of mycosis fungoides in stages IA and IB should be limited to local administration of glucocorticosteroids, PUVA, UVB or UVA1 therapy. Generally, external application of strong glucocorticosteroids to erythematous lesions has a very beneficial effect. If skin lesions are very disseminated, the treatment of choice includes irradiation, which induces apoptosis of T lymphocytes. Photochemotherapy using psoralens (8-MOP) combined with UVA (320-400 nm) is a standard treatment in the early stages of mycosis fungoides. In the case of higher stages of mycosis fungoides, the therapy is not satisfactory, so the method may be combined with treatment with retinoids or interferon α-2a [14]. Obviously, there are numerous contraindications against this treatment method, and the most significant include pregnancy, melanoma or non-melanoma skin cancer also in the medical history of a patient, systemic or cutaneous lupus, severe liver and kidney disorders, age under 12 (in the case of PUVA therapy) or xeroderma pigmentosum. Theoretically, UVA1 therapy seems to be an alternative to PUVA therapy in patients with mycosis fungoides. UVA1 radiation has a similar range of effect on skin as PUVA therapy [15]. The precise mechanism of action of UVA1 radiation in patients with primary cutaneous lymphomas is not well known. On the basis of *in vitro* and *in vivo* research to date on specific T lympho-

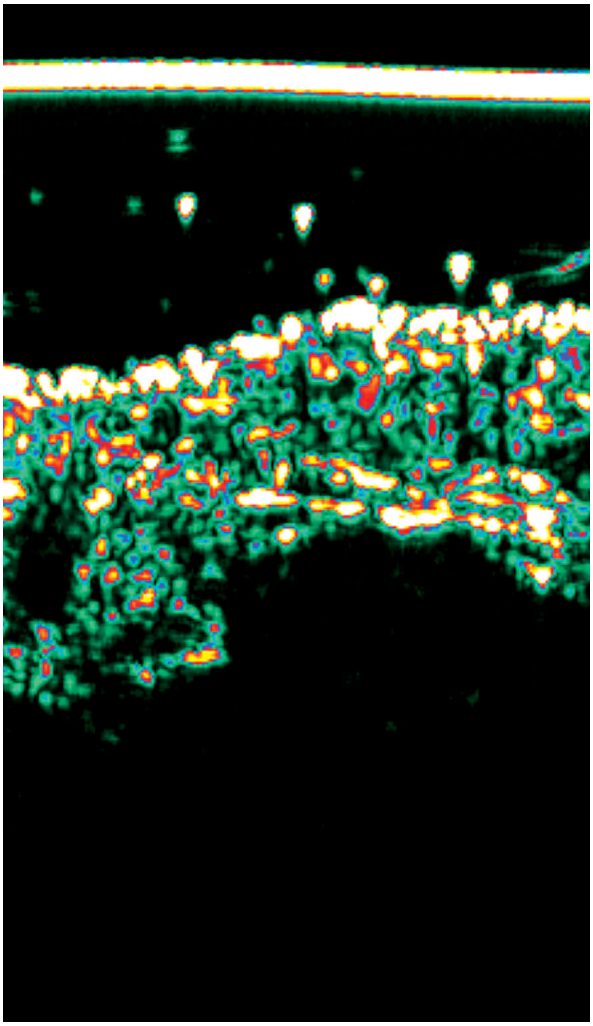

Fig. 6. The USG examination showed fading of the described band and an increase in skin echogenicity together with improvement in the patient's clinical condition

cytes in patients with atopic dermatitis, one can assume that UVA1 improves skin condition in patients with primary cutaneous lymphomas by inducing apoptosis of neoplastic T lymphocytes in skin infiltrations. The observed clinical improvement in dermatological condition correlates with a decrease in skin infiltration. Both PUVA and UVA1 therapy cause apoptosis of neoplastic T lymphocytes. However, the type of apoptosis in each of the methods differs qualitatively. UVA1 therapy results in the stimulation of synthesis of T lymphocyte-dependent and independent proteins in comparison with PUVA therapy, in which the activation is exclusively dependent (programmed cell death) [16, 17]. Irradiation of patients with UVA1 enables one to avoid undesirable effects related to the use of psoralens during PUVA therapy. If a patient is intolerant of psoralens and lesions in the course of mycosis fungoides are very superficial, UVB irradiation may be used (290-320 nm). There are some studies on the use and effectiveness of UVA1 therapy in the treatment of

Tab. 1. The classification of primary cutaneous lymphomas according to the WHO-EORTC [10]

Primary cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
Variants of mycosis fungoides: • Folliculotropic mycosis fungoides • Pagetoid reticulosis • Granulomatous slack skin
Sézary syndrome
Leukaemia/adult T-cell lymphoma
Primary cutaneous CD30+ T-cell lymphoproliferative hyperplasias • Primary cutaneous CD30+ anaplastic large T-cell lymphoma • Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphomas, unclassified • Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma • Cutaneous γ/δ T-cell lymphoma • Primary cutaneous small/medium CD4+ T-cell lymphoma
Primary cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicular lymphoma
Primary cutaneous diffuse large-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other types
Intravascular large B-cell lymphoma
Neoplasms of precursor cells
Blastic plasmacytoid dendritic cell neoplasm

Tab. 2. The TNMB classification of mycosis fungoides and Sézary syndrome according to the ISCL/EORTC [10]

Skin	
T1	Patches, papules and/or plaques covering < 10% of the body surface area
T1a	– Only patches
T1b	– Patches and plaques
T2	Patches, papules and/or plaques covering ≥ 10% of the body surface area
T3	Tumour (one or more, ≥ 1 cm diameter)
T4	Erythroderma (≥ 80% of the body surface area)
Lymph nodes	
N0	No clinically abnormal peripheral lymph nodes (cervical, supraclavicular, epitrochlear, axillary, inguinal; central lymph nodes are not classified); biopsy not required
N1	Clinically abnormal (firm, irregular, clustered or > 1.5 cm diameter) lymph nodes, histopathology: according to NCI – LN0-2 or Dutch classification – grade 1
N1a	– Molecular examination: clone negative
N1b	– Molecular examination: clone positive
N2	Clinically abnormal lymph nodes, histopathology: according to NCI – LN3 or Dutch classification – grade 2
N2a	– Molecular examination: clone negative
N2b	– Molecular examination: clone positive
N3	Clinically abnormal lymph nodes, histopathology: according to NCI – LN4 or Dutch classification – grade 3-4; clone positive or negative
Nx	Clinically abnormal lymph nodes; no histopathological examination
Visceral organ involvement	
M0	No visceral organ involvement
M1	Visceral organ involvement
Peripheral blood involvement	
B0	≤ 5% of peripheral blood lymphocytes are atypical Sézary cells
B0a	– Clone negative
B0b	– Clone positive
B1	> 5% of peripheral blood lymphocytes are atypical Sézary cells; the amount does not meet the criteria of B2
B1a	– Clone negative
B1b	– Clone positive
B2	≥ 1000/µl Sézary cells with clone positive in peripheral blood or Proliferation of CD3+ or CD4+ cells in the ratio CD4/CD8 > 10 or Proliferation of CD4+ cells with abnormal phenotype (without CD7 and CD26)

T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene

patients with mycosis fungoides. A group of German and Japan researchers published the results of research on a group of 3 patients with MF. Two patients were irradiated with high doses of 130 J/cm and one patient underwent treatment with the average dose of 60 J/cm. In all the patients complete remission of skin lesions was observed after 20 irradiations [18]. Zane *et al.* demonstrated that UVA1 irradiation is also an effective method of treatment in stage IIb or III of mycosis fungoides. They found complete remission in 11 patients of a group of 13 MF patients; no improvement was observed in two patients. The patients received a dose of 100 J/cm for 5 days a week, except for one patient who received a dose of 70 J/cm, and the average time of irradiation was 22 days [19]. In the case of the presented patient treated in the Clinic of Dermatology, complete remission of the lesions in the course of mycosis fungoides was observed after UVA1 therapy at the dose of 120 J/cm 5 times a week. The administered treatment was actually the only possible way of treatment due to the complicated medical history of the patient when the liver was considered. The patient has suffered from hepatitis C and the conducted additional imaging examination confirmed the presence of a lesion 8 mm in diameter in segment 2 of the left liver lobe. Due to complete remission after 30 UVA1 irradiations, it was decided to introduce general steroid therapy with Metypred as the treatment continuation to extend the remission period. So far the treatment has been successful. The patient periodically reports for follow-up examinations to the Outpatient Clinic.

High-frequency ultrasound examination in the assessment of lesions in patients with primary T-cell lymphomas seems to be a useful method of monitoring of the course of the disease in patients with cutaneous T-cell lymphomas, not only those treated with UVA1. Hypoechogenic band and a decrease in skin echogenicity observed in the USG image probably indicate inflammatory infiltration of the dermis, characteristic of cutaneous T-cell lymphomas. It should be emphasized that the method is safe, non-invasive and repeatable at every stage of the diagnostic and treatment process.

Apart from irradiations, also treatment with total skin electron beam (TSEB) may be administered in patients in stages IA, IB or IIA. The method is mainly reserved for patients in whom fast disease progression is observed, or for patients who do not respond to other treatment methods. The complete dose amounts to 36 Gy, received in a 10-week cycle with a one-week interval after 18-20 Gy. Complete remission is obtained on average in 80-90% of patients. However, because of the possibility of a range of adverse effects, the method should generally be used only in patients in stages IB and IIA with infiltrative lesions covering over 10% of the body surface area, resistant to the previously used treatment methods. The most common complications include telangiectasias, vesicular lesions on the feet and hands, infertility in men, hand and foot oedema, nail dystrophy and chronic or temporary hair loss. The presented case description also confirms the available data on very positive therapeutic effects in patients after TSEB. Nevertheless, due to a very high post-radiation reaction, it was difficult to precisely determine the dermatological condition after the finished treatment.

Other methods used in this stage of lymphoma include external or oral administration of retinoids, and external administration of mechlorethamine or carmustine. Using the latter two drugs requires direct imports of the preparations. At present the use of rexinoids brings hope since they have a selective effect on the retinoid X receptor (RXR), and high rexinoid doses also affect the retinoic acid receptor (RAR). The currently available drug from this group is bexarotene. The optimum therapeutic dose is 300 mg per day, and the treatment should include monitoring of the parameters of lipid metabolism and following the procedure algorithm developed by Gniadecki *et al*. [20].

It should be emphasized once again that a right choice of therapeutic method is very important in the case of patients with primary cutaneous lymphomas. Dermatologists lean towards non-aggressive treatment using mainly modern phototherapy methods in the early stages of mycosis fungoides. It was demonstrated that polychemotherapy administered from the very beginning of the disease does not extend the survival time, and may lead to pre-term death due to immunosuppressive and myelosuppressive effects [21, 22]. The presented case shows the possibility of monitoring and treatment in patients with mycosis fungoides. Especially the use of UVA1 therapy seems to be an alternative to the other methods of phototherapy so far used in primary cutaneous T-cell lymphomas, and high-resolution ultrasound examination can confirm the clinically observed improvement in dermatological condition.

References

1. Alibert JL. Description des maladies de la peau observes a l'hospital St Louis. Barrois L'Aine et Fils 1806; 413-46.
2. Bazin PA. Maladies de la peau observes a l'hospital St Louis. 1876.
3. Sézary A, Bouvrain Y. Erytroderme avec pesence de cellules monstruenses dans le derme et le sang circulant. Bull Soc Fr Dermatol Sypholigr 1938; 45: 254-60.
4. Willemze R. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105: 3768-85.
5. Smith BD, Wilson LD. Cutaneous lymphoma. Curr Probl Cancer 2008; 32: 43-87.
6. Massone C, Kodama K, Kerl H, Cerroni L. Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients. Am J Surg Pathol 2005; 29: 550-60.
7. Elmer KB, George RM. Cutaneous T-cell lymphoma presenting as benign dermatoses. Am Fam Phisician 1999; 59: 2809-13.
8. Jankowska-Konsur A, Maj J, Woźniak Z, et al. Ocena angiogenezy u chorych na ziarniniaka grzybiastego. Post Dermatol Alergol 2009; XXVI: 186-9.

9. Lever WF, Schaumburg-Lever G. Histopathology of the skin. 7th ed. J.B. Lippincott Company, Philadelphia 1990.
10. Sokołowska-Wojdyło M, Lech-Mareńda E, Placek W, et al. Leczenie pierwotnych chłoniaków skóry – rekomendacje Sekcji Chłoniaków Skóry Polskiej Grupy Badawczej Chłoniaków (PLRG). Onkol Prakt Klin 2010; 6: 29-47.
11. Whittemore AS, Holly EA, Lee IM, et al. Mycosis fungoides in relation to environment al exposures and immune response: a case-control study. J Natl Cancer Inst 1989; 81: 1560-7.
12. Hall WW, Liu CR, Schneewind O, et al. Deleted HTLV-1 provirusin blond and cutaneous lesions of patients with mycosis fungoides. Science 1991; 253: 317-20.
13. Wood GS, Salvekar A, Schaffer J, et al. Evidence against a role for human T-cell lymphotrophic virus type I (HTLV-1) in the pathogenesis of American cutaneous T-cell lymphoma. J Invest Dermatol 1996; 107: 301-7.
14. Zackheim HS. Cutaneous T cell lymphoma: update of treatment. Dermatology 1999; 199: 102-5.
15. Gruss C, Strucker M, Kobyletzki G, et al. Low dose UVA1 phototherapy in disabling pansclerotic morphoea in childhood. Br J Dermatol 1997; 136: 293-4.
16. Godar DE. UVA1 radiation mediates singlet-oxygen and superoxide anion production rich trigger two different final apoptotic pathways: the S and P site of mitochondria. J Invest Dermatol 1999; 112: 3-12.
17. Silny W, Osmola-Mańkowska A, Czarnecka-Opreacz M, et al. Wąskopasmowa fototerapia UVA1 w lecznictwie dermatologicznym – pierwsze polskie doniesienie. Post Dermatol Alergol 2010; XXVII: 1-10.
18. Plattenberg H, Stege H, Megahed M, et al. Ultraviolet A1 (340-400 nm) phototherapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 1999; 41: 47-50.
19. Zane C, Leali C, Airo P, et al. High-dose UVA1 therapy of widespread plaque-type, nodular, and erythrodermic mycosis fungoides. J Am Acad Dermatol 2001; 44: 629-33.
20. Gniadecki R, Assaf C, Bagot M, et al. The optimal use of bexarotene in cutaneous T-cell lymphoma. Br J Dermatol 2007; 157: 433-40.
21. Duvic M. Systemic monotherapy vs combination therapy for CTCL: rationale and future strategies. Oncology 2007; 21 (2 Suppl 1): 33-40.
22. Batycka-Baran A, Reich A, Jankowska-Konsur A, Maj J. Nowe trendy w leczeniu ziarniniaka grzybiastego i zespołu Sezarego. Post Dermatol Alergol 2009; XXVI: 41-55.