Mycosis fungoides: therapeutic difficulties

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Postep Derm Alergol 2015; XXXII (5): 404–408
DOI: 10.5114/pdia.2014.44005

Lymphoma belongs to a heterogeneous group of malignant neoplasms of the lymphatic system developing from lymphocytes, precursor cells, or directly from a multipotent stem cell [1]. Cutaneous T-cell lymphoma (CTCL), including mycosis fungoides, first affects the skin [2].

Mycosis fungoides, first described by Albert in 1806, is a type of lymphoma developing from peripheral T cells, characterised by low malignancy, chronic nature and slow progress [3, 4].

The first skin lesions, in the form of non-specific patchy eruptions, occurred in a 50-year-old male patient in 2004. Initially, patches on the skin were located on the lower extremities, and later also on the abdomen. In 2008, the patient visited the Outpatient Clinic of Dermatology in Poznan due to the exacerbation of skin symptoms. Because of the extent of the skin lesions and an initial suspicion of cutaneous T-cell lymphoma, the patient was referred to the Wielkopolskie Centre of Oncology in Poznan, where a skin biopsy was taken for histopathological examination that confirmed the clinical diagnosis of mycosis fungoides. In addition, a specimen was taken from the left axillary lymph node, and the examination revealed that the image may correspond with lymphonodulitis dermatopathica. The immunohistochemical skin examination revealed CD3+, CD4+ and CD8+ cells and Ki 67 proliferation antigen. Trephine biopsy revealed bone marrow with a reduced cell count containing all cell lines. The patient was treated with total skin electron beam therapy (TSEB), and an improvement in the skin condition was achieved. In December 2008, the therapy was completed and the patient was in remission for almost 8 months. In March 2009, due to the exacerbation of skin lesions, the patient was admitted to the Hospital Department of Dermatology in Poznan, where he was qualified for phototherapy. Starting from April 2010 the patient was treated with UVA1, and received a total dose of irradiation of 1980 J/cm^2 in 30 sessions. Both before the treatment with UVA1, and after completion of the phototherapeutic cycle, the patient was subject to skin tests with a high-resolution ultrasound technique. In addition, histopathological examination of skin biopsy specimens with lesions was done twice (before treatment and after the cycle of irradiation) (Figures 1 and 2). Both methods confirmed that clinical remission was achieved in the patient. About 3 months after the completed UVA1 treatment, a single infiltrative patch in the lumbar area was found in the patient, and 3 months later, the patient presented with four patches of erythematous and infiltrative lesions (Figure 3). Due to the relatively fast progression of skin symptoms, in November 2010 it was decided to repeat the course of UVA1 phototherapy. The patient was again subject to irradiation five times a week and received a total dose of 1750 J/cm^2 in 30 sessions. Clinical and ultrasonographic findings demonstrated no remission, and therefore a decision was made to continue UVA1 therapy according to a one-session-per-week protocol. The patient continued phototherapy according to this protocol for 15 weeks and received another dose of 920 J/cm^2. The patient achieved the target total dose of UVA1 radiation in May 2011. In addition, starting from March 2011 he took methylprednisolone at alternating doses of 16 and 8 mg/day. The patient was closely mon-

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Received: 24.09.2013, **accepted:** 19.01.2014.

itored by the Outpatient Clinic of Dermatology (visits once a month). Results of laboratory tests were normal, but the skin condition was clearly deteriorating. In October 2011, a decision was made to include methotrexate for systemic treatment, starting from a 12.5 mg dose per week, and increasing it later to 20 mg per week. After 4 months of treatment no clinical improvement was achieved and methotrexate was discontinued. Dermatological examination revealed new disseminated erythematous and infiltrative skin lesions on the abdomen and extremities. The decision to introduce phototherapy was made once again. Because the patient had tolerated the treatment with UVA1 radiation well in the past, and had a history of ophthalmological disorders (corneal degeneration in the left eye and corneal graft in the right eye in 1998), the UVA1 therapy was considered a safer option than PUVA. The patient completed another cycle of 30 UVA 1 phototherapeutic sessions (five-times-per-week protocol) with a very good outcome, receiving a total dose of UVA1 radiation of 1590 J/cm^2. Again remission was achieved, and it was confirmed in physical examination, histopathological examination of skin lesions, and by high-resolution ultrasound imaging. Unfortunately, skin lesions recurred 4 months after the completed phototherapy, despite the fact that the patient was taking methylprednisolone in a 8 mg/day dose. The dose of metoxalen was increased to 16 mg/day and topical treatment with high potent glucocorticosteroids was maintained. In January 2012, the patient was hospitalized again at the Department of Dermatology in Poznan due to a clear exacerbation of skin lesions. During hospitalization the patient started PUVA therapy three times a week, and before that he was administered Oxsoralen in a dose of 4 tablets 1 h before the phototherapeutic session. The patient tolerated the treatment well and the clinical outcome was satisfactory. Laboratory and imagining tests carried out at that time did not reveal significant deviations from normal. The patient receives regular care at the Outpatient Clinic of Dermatology.

Primary cutaneous lymphomas account for 2% of all lymphomas, and as much as 75% of those are T-cell lymphomas [5]. Mycosis fungoides, which is the most common form of CTCL, with a prevalence estimated at 0.3–0.5%/100 000 people [3], is characterised by slow, years-long stationary course, and usually affects men (M : F – 2 : 1) aged 40–50 years [6]. Itchiness, intensifying as the disease progresses, is another characteristic symptom of MF [7].

However, many patients with mycosis fungoides present at the same time with skin lesions typical of

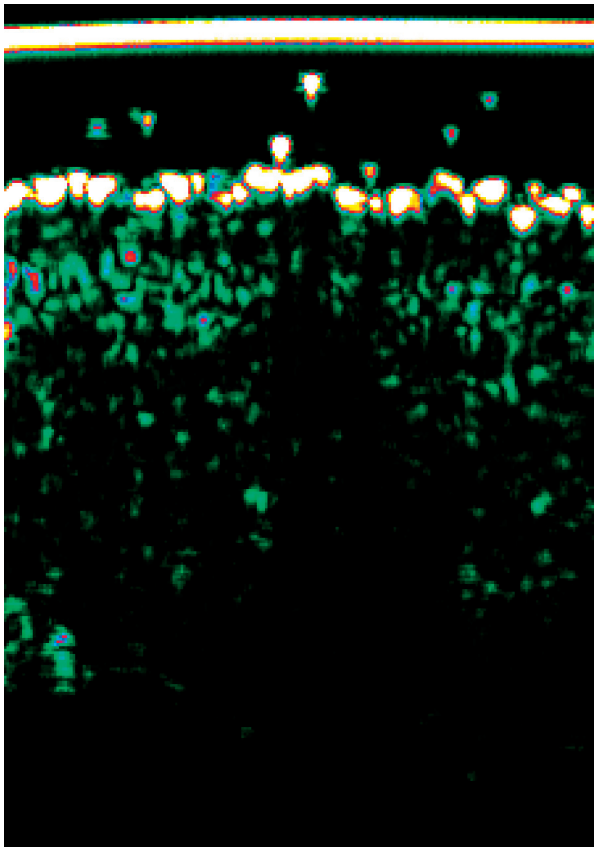

Figure 1. Ultrasound scan before UVA1 irradiation

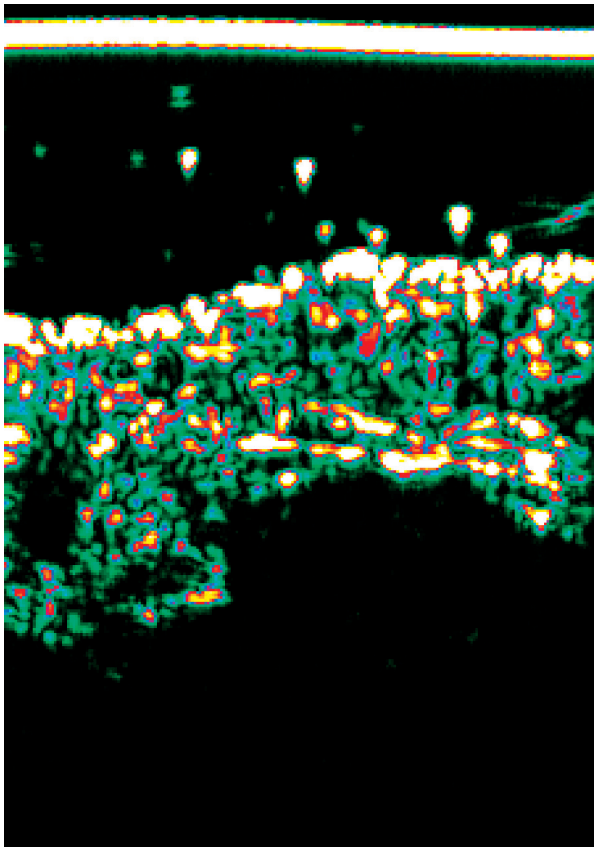

Figure 2. Ultrasound scan after UVA1 irradiation

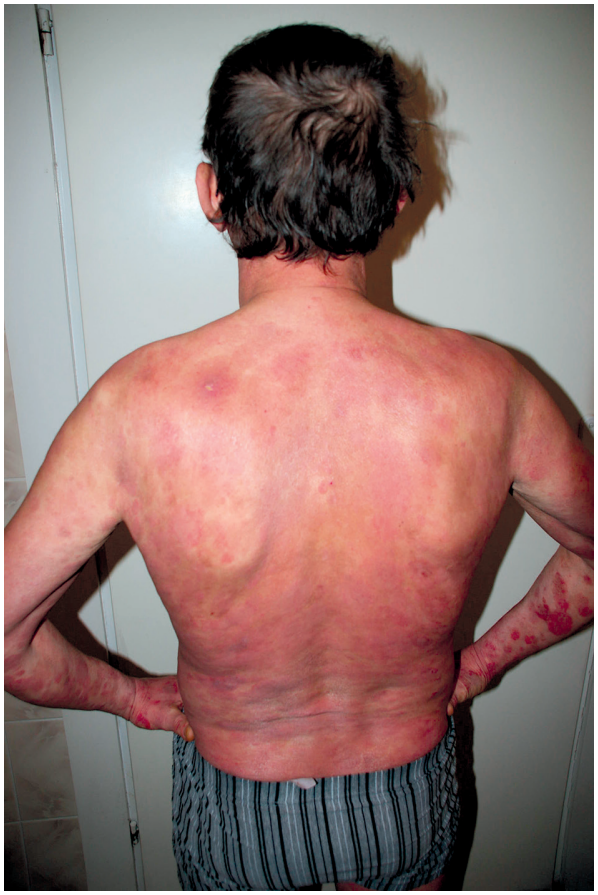

Figure 3. Skin lesions before the introduction of UVA1 therapy

various disease stages, and sometimes the disease becomes aggressive. For these reasons, WHO considers that the term "mycosis fungoides" should be used only for variants characterised by a standard clinical course, i.e. evolving from erythematous skin lesions through infiltrative and nodular patches to the systemic disease, in which lymph nodes and internal organs finally become affected [3, 6].

Many authors indicated smoking, alcohol, various medications and exposure to ultraviolet or X rays as potential factors contributing to the development of the disease. However, clinical studies have not confirmed these suggestions. Therefore, the pathogenesis of mycosis fungoides still remains unknown [8–11].

Because CTCL is a rare disease there have been very few randomized clinical studies carried out to help determine the optimum treatment procedure. So far, no widely-acceptable algorithm for the treatment of CTCL has been established. The choice of therapy depends on the disease stage, and factors that appear to have the strongest effect on prognosis in patients with CTCL include the extent of skin lesions and the presence of disease manifestations in organs other than the skin (involvement of internal organs or lymph nodes) [12]. According to the TNMB classification system (tumour-nodes-metastasis-blood), 4 disease stages are identified, including early phases (IA, IB and IIA) and advanced phases (IIB, III and IV) [5]. An overview of the available literature reveals two treatments of choice for phase I-IIB: strong topical glucocorticosteroids (in monotherapy up to stage IIA, and as an adjuvant in more advanced stages), or phototherapy [6, 13].

As a standard, UVB or PUVA therapy is recommended, although UVA1 therapy appears to be an alternative method to PUVA, particularly in cases when contraindications, such as severe liver diseases, exclude the option of introducing conventional photochemotherapy. The mechanism of action of UVA1 radiation in patients with CTCL has not been identified in detail, but most likely it involves the induction of apoptosis in neoplastic T-cells in skin infiltrates. Both PUVA and UVA1 induce apoptosis, but in different pathways. UVA1 radiation induces the synthesis of proteins dependent on and independent of T-cells, while PUVA only induces programmed cell death in the dependent pathway [14, 15].

Single patches can also be treated with radiotherapy (the method was shown to be effective in erythematous, infiltrative and nodular phases) [5] or with total skin electron beam therapy (TSEB) with a good clinical outcome, as demonstrated for the reported patient [6, 17–19]. According to other authors, TSEB is a safe treatment and in

Table 1. Phototherapy protocol

Variable	1st cycle	2nd cycle	3rd cycle
Date	04–05.2010	11.2010–05.2011	03–04.2012
Phototherapy protocol	10 J/cm^2 20 J/cm^2 40 J/cm^2 – 3× 50 J/cm^2 60 J/cm^2 – 19× 80 J/cm^2 – 4×	10 J/cm^2 20 J/cm^2 30 J/cm^2 40 J/cm^2 50 J/cm^2 60 J/cm^2 – 39× 90 J/cm^2 – 2×	10 J/cm^2 20 J/cm^2 30 J/cm^2 40 J/cm^2 50 J/cm^2 60 J/cm^2 – 24×
Total dose	1980 J/cm^2	2670 J/cm^2	1590 J/cm^2
Number of sessions	30	45	30

a short time makes the achievement of persistent remission possible in about 95% of patients [20].

Second-line treatments suggested for early stages of the disease include topical carmustine or mechlorethamine, combined with PUVA plus α-interferon or bexarotene therapy, or inclusion of low doses of methotrexate [17–19, 21–30].

If the above-listed therapies provide no expected clinical outcome, the patient's referral to clinical oncologists should be considered in order to introduce systemic chemotherapy (with gemcitabine, chlorambucil plus prednisolone, or doxorubicin) [6, 17–19, 31–33]. Because of the immune background of the disease much hope is seen in biologic medical products, such as denileukin diftitox (ONTAK), an engineered protein combining diphtheria toxin with an IL2 receptor-binding domain, or alemtuzumab [34]. However, the poor availability of this therapeutic method is a problem.

Treatment of advanced stages (IIB, III, IV) is an even more complicated process, but also in this phase systemic chemotherapy, according to WHO-EORTC guidelines of 2006, is recommended as the second-line therapy because studies demonstrated that it is associated with a high number of adverse events and does not have a significant effect on extending the remission period [35].

In the case reported in this paper the age of the patient at onset of first disease symptoms, the classical slow and stationary course of the disease, and clinical image allowed for the fast preliminary diagnosis. With the interdisciplinary cooperation of doctors (dermatologists, oncologists and haematologists), the patient was in a short time subject to a number of necessary diagnostic tests that enabled final diagnosis and introduction of a modern therapy relevant for the specific phase of the disease. Despite all these efforts, the ongoing progression of the disease was observed.

The high-resolution ultrasound scan that was done twice (before introducing UVA1 therapy and after the completed cycle of 30 sessions) proved to be very helpful in the assessment and monitoring of the therapeutic outcome in the described patient (Table 1). Results of imaging tests obtained for the patient helped in making a decision on the termination of phototherapy. However, it should be noted that although this method allows for the estimation of infiltrate thickness, it does not enable the identification of its type. In our opinion, this brings us to the cautious conclusion that in the future this imaging method could be an alternative to histopathological tests carried out to confirm clinical remission in patients with CTCL.

Acknowledgments

We are grateful to all members of the Department of Dermatology, Poznan University of Medical Sciences, Poland for their excellent technical assistance and encouragement.

Conflict of interest

The authors declare no conflict of interest.

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