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 lymphono-dulitis 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/cm² 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/cm² 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/cm². 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...
Mycosis fungoides: therapeutic difficulties

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...
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-II: 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      |
| Date                            | 10 J/cm²         | 20 J/cm²         | 50 J/cm²         |
| Date                            | 30 J/cm²         | 40 J/cm²         | 60 J/cm² – 19×   |
| Date                            | 40 J/cm²         | 50 J/cm²         | 60 J/cm² – 3×    |
| Date                            | 60 J/cm² – 19×   | 70 J/cm² – 2×    | 80 J/cm² – 4×    |
| Phototherapy protocol           | 10 J/cm²         | 20 J/cm²         | 30 J/cm²         |
| Phototherapy protocol           | 40 J/cm²         | 50 J/cm²         | 60 J/cm² – 3×    |
| Phototherapy protocol           | 60 J/cm² – 3×    | 70 J/cm² – 2×    | 80 J/cm² – 4×    |
| Total dose                      | 1980 J/cm²       | 2670 J/cm²       | 1590 J/cm²       |
| Number of sessions              | 30               | 45               | 30               |

Figure 3. Skin lesions before the introduction of UVA1 therapy
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 carbamustine 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 (II B, 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.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Weiss-Rostkowska W, Biedka M, Placek W, et al. T-cell lymphoma – case report. Contemp Oncol 2008; 12: 192-5.
2. Yamashita T, Abbade LP, Marques ME, Marques SA. Mycosis fungoides and Sézary syndrome: clinical, histopathological and immunohistochemical review and update. An Bras Dermatol 2012; 87: 817-28.
3. Braun-Falco Dermatology. Polish edition. Czelej, Lublin 2010; 1510-74.
4. Grajewska A, Orlowski M, Wilk M, et al. D’emblee form of mycosis fungoides – case report. Dermatol Klin 2009; 11: 42-5.
5. Polakiewicz-Gilowska A, Mrochen-Domiń I, Nowara E. Mycosis fungoides – case report and references review. Onkol Prakt 2010; 6: 195-201.
6. Sokolowska-Wojdyło M, Maciejewska-Radomska A, Trzebiak M, et al. Treatment outcomes of CTCL patients in Medical University of Gdańsk between 1997-2008. Dermatol Klin 2009; 11: 141-6.
7. Weisshaar E, Szeptiwotski JC, Darsow U, et al. European guideline on chronic pruritus. Acta Derm Venereol 2012; 92: 563-81.
8. Barcos M. Mycosis fungoides diagnosis and pathogenesis. Am J Clin Pathol 1993; 99: 452-8.
9. Morales Suarez-Varela MM, Llopis Gonzalez A, Marquina Vila A, et al. Mycosis fungoides: review of epidemiological observation. Dermatology 2000; 201: 21-8.
10. Toro JR, Stoll HL, Stomper PC, et al. Prognostic factors and evaluation of mycosis fungoides and Sézary syndrome. J Am Acad Dermatol 1997; 37: 58-67.
11. Weinstock MA, Horn JW. Mycosis fungoides in the United States: increasing incidence and descriptive epidemiology. JAMA 1988; 260: 42-6.
12. Wojewoda K, Sokolowska-Wojdyło M, Barańska-Rybak W, et al. Treatment of primary cutaneous lymphoma with reference to the latest therapeutic consensus of the Polish Lymphoma Research Group (PRLG). Postep Derm Alergol 2012; 2: 63-8.
13. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998; 134: 949-54.
14. Silny W, Osmola-Markowska A, Czarnecka-Operacz M, et al. Wąskozakresowa fototerapia UVA-1 w lecznictwie dermatologicznym – pierwsze polskie doświadczenia. Postep Derm Alergol 2010; 27: 1-10.
15. Malinowska K, Sysa-Jędrzejowska A, Woźniacka A. UVA1 phototherapy in dermatology. Postep Derm Alergol 2011; 28: 53-8.
16. Godar DE. UVA1 radiation mediates singlet-oxygen and superoxide anion production rich tigger two different final apoptotic pathways: the S and P site of mitochondria. J Invest Dermatol 1999; 112: 3-12.
17. Willemze R, Jaffe ES, Burg C, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 106: 3768-85.
18. Prince HM, Whitaker S, Hoppe RT. How to treat mycosis fungoides and Sézary syndrome. Blood 2009; 114: 4337-53.
19. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 1997; 90: 354-71.

20. Goujon E, Truc G, Petrella T, et al. Total skin electron beam therapy for early-stage mycosis fungoides: immediate results and long-term follow-up in 68 patients. Ann Dermatol Venereol 2009; 136: 249-55.

21. Talpur R, Ward S, Apisarnthanarax N, et al. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 2002; 47: 672-84.

22. Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. Arch Dermatol 2002; 138: 325-32.

23. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. J Clin Oncol 2001; 19: 2456-71.

24. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001; 137: 581-93.

25. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003; 16: 311-21.

26. Foss FM, Ihde DC, Linnoila IR, et al. Phase II trial of fludarabine phosphate and interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol 1994; 12: 2051-9.

27. Olsen EA, Rosen ST, Vollmer RT, et al. Interferon alfa-2a in the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 1989; 20: 395-407.

28. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol 2003; 49: 873-8.

29. Cheeley J, Sahn RE, DeLong LK, Parker SR. Acitretin for the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 2013; 68: 247-54.

30. Chmielowska E, Studziński M, Giebel S, et al. Follow-up of patients with mycosis fungoides after interferon alpha2b treatment failure. Postep Derm Alergol 2015; 32: 67-72.

31. Gardner JM, Evans KG, Musiek A, et al. Update on treatment of cutaneous T-cell lymphoma. Curr Opin Oncol 2009; 21: 131-7.

32. Prince HM, Whittaker S, Hoppe RT. How we treat mycosis fungoides and Sezary syndrome. Blood 2009; 114: 4337-53.

33. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD 52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003; 101: 4267-72.

34. Ernengo MG, Quaglini P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007; 92: 784-94.

35. Kaye FJ, Bunn PA, Steinberg SM, et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med 1989; 321: 1784-90.