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Single Case

Immediate Response to Brentuximab Vedotin in a Patient with Localized MF-LCT

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Mycosis fungoides · Cutaneous lymphoma · Brentuximab vedotin

Abstract
The large cell transformation of mycosis fungoides (MF-LCT) is a phenomenon observed in the advanced stages of mycosis fungoides (MF), which is the most common primary cutaneous lymphoma. The diagnostic criteria of MF-LCT are a minimum of 25% of large cells or a formation of microscopic nodules of them in the histological examination of skin samples. The clinical outcomes for MF-LCT are poor, as less than 20% of patients survive 5 years after diagnosis, but the expression of the CD30 antigen is generally considered to be associated with a better prognosis. We present a case of a patient with the diagnosis of MF with LCT, with an ulcerated tumor lesion approximately 30 × 20 cm in size on the right lateral abdominal wall. Brentuximab vedotin (BV) treatment was started due to the presence of the CD30 antigen, with a quick and impressive regression of the cutaneous lesion and tumor mass and good treatment tolerance. After follow-up of 20 months, patient remains in complete remission. A schedule of treatment for MF-LCT is directed mainly by the clinical stage of the disease and the comorbidities; the more severe clinical course of the disease requires systemic treatment. If at least 5% of the cells found in the skin lesions biopsy sample express the CD30 antigen, a beneficial effect of BV treatment could be expected. It may seem that the use of BV is one of the optimal therapeutic options in patients with advanced MF-LCT showing expression of CD30.

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Introduction

The term primary cutaneous lymphomas (PCLs) refers to a heterogeneous group of neoplasms classified histologically as non-Hodgkin extranodal lymphomas, as described in the updated WHO-EORTC classification (2018) [1]. In contrast to nodal lymphomas, PCLs are T-cell lymphomas in approximately 75% of cases [2], while the most common type of PCL is mycosis fungoides (MF, up to 50% of cases) [3]. The disease is more common in men, and the incidence increases with age. Large cell transformation of MF (MF-LCT) is observed in about 20–50% of advanced cases of MF.

MF presents with the characteristic pattern of evolution of lesions, including the patch stage and plaque stage (which localize in areas unexposed to the sun and may persist for months or years), followed by the development of ulcerated tumors (tumor stage). Diagnostic procedures include a skin biopsy with histopathological assessment with immunostaining and blood tests with flow cytometry to exclude the presence of Sezary cells [4]. Usually, the lymph nodes and bone marrow remain free of the disease in its early stage. Histopathological and immunohistochemical examinations are necessary to determine the histological subtype of the disease. Typically, LCT is recognized after the clinical progression of the disease. To meet the diagnostic criteria of MF-LCT, a minimum of 25% of large cells or the formation of microscopic nodules of them must be found in the histological examination [5].

The clinical outcomes of MF-LCT are poor, as less than 20% of patients survive 5 years after diagnosis [6]. The three main factors that are of prognostic significance are the stage of the disease at the moment of transformation, folliculotropism, and low expression of the differentiation 30 cluster antigen (CD30) antigen (<10%). Other characteristics of patients that worsen the prognosis include older age, elevated serum lactate dehydrogenase levels, the need for polychemotherapy, and the presence of generalized skin lesions [7, 8]. Some studies reported that the time period of less than 2 years from the diagnosis of MF to the transformation negatively impacts survival, although this statement remains controversial [8].

The diagnosis of MF-LCT with CD30 antigen expression is generally considered to be associated with a better prognosis [7]. This is a rare disease subtype, as it comprises about 20% of cases; however, if the CD30 positivity is recognized, usually more than 75% of cells are CD30+ [8]. In such cases, an effective treatment with brentuximab vedotin (BV) could be introduced [9]. The agent consists of a chimeric monoclonal antibody, brentuximab, directed against the CD30 antigen, which is linked via a cathepsin-digestible covalent linker to the molecule of an antimitotic drug auristatin E. Current reports indicate that BV therapy results in an overall objective response for at least 4 months (OOR4) of approximately 90% in patients diagnosed with cutaneous CD30+ lymphoma [2].

Case Report

We present a 70-year-old man in good general condition, with the Eastern Cooperative Oncology Group (ECOG) score 1, who was referred to the Department of Hematology with the diagnosis of MF. About 2 years earlier, in the area of the present changes in MF skin on the right side of the trunk, numerous nonconfluent erythema lesions appeared, which resolved spontaneously afterward. About a year later, erythematous infiltrative changes appeared, and after another few months, in their place, an ulcerated tumor lesion was systematically growing. The patient reported pain in a tumor skin lesion with a severity of 2/10 when moving. Additionally, the patient had no B symptoms, no comorbidities, a negative family history, and no environmental exposure. We found him neglected with an advanced ulcerated tumor.

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Physical examination revealed a massive polycyclic ulcerated skin lesion, approximately 30 × 20 cm in size, on the right lateral abdominal wall (shown in Fig. 1, 2). The remaining skin area was clear, without pathological eruptions. Peripheral lymph nodes, liver and spleen, were not enlarged. Histopathological examination of ulcerated skin tumor sections revealed diffuse lymphoma infiltration from medium and large lymphocytes with the immunohistological profiles: CD3+, CD4+, CD30+, CD8−, CD7−, ALK− were visible in the dermis. In the context of the entire clinical presentation compatible with MF (previous erythematous lesions with tumors formed on their basis, subsequently ulcerated), the microscopic image and the immunohistochemical profile of the infiltrate support the diagnosis of MF with LCT.

The computed tomography (CT) of the thorax revealed a skin infiltration in the area of the right epigastrium, about 2 cm wide. On the abdominal CT, the liver was enlarged. Enlarged lymph nodes were not visible in both the thorax and abdomen. In the lateral abdominal wall, the mesogastrium and the lower abdomen, the ulcerative skin area and subcutaneous tissue defect were visible, not reaching the level of muscle fascia. Bone marrow biopsy was not performed. The results of complete blood counts remained within the normal range, except for decreased total lymphocyte count ($0.76 \times 10^3/\mu L$, reference range 1.00–5.00) and hemoglobin (12.3 g/dL, reference range 13.5–18.0). The tumor burden marker lactate dehydrogenase was in normal range, inflammatory – C-reactive protein was elevated to 37.32 mg/L, reference range <5.00. Liver and kidney function tests were within the normal range.

The clinical stage of the tumor was established as Modified Severity-Weighted Assessment Tool (mSWAT) score 36. According to the International Society of Cutaneous Lymphomas (ISCL) and EORTC Cutaneous Lymphoma Group, stage T3N0M0, i.e., IIB, was found. Body surface area coverage (% BSA) was 9%.

The large skin involvement due to an ulcerating tumor and the high risk of severe infectious complications during chemotherapy treatment, associated with a poor prognosis, prompted the consideration of all possible therapeutic options. Due to the presence of the CD30 antigen on tumor cells, it was decided to start BV treatment as first-line treatment, after the patient's informed consent to the proposed treatment. The treatment plan consisted of BV in a standard dose used every 3 weeks – up to 16 doses, and after a good response to the qualification of the treatment for allogeneic hematopoietic stem cell transplantation. Prophylactic antibiotic therapy in the form of ciprofloxacin was also administrated, as in the swab of the ulcer were found *Proteus vulgaris* (confluent growth), *Pseudomonas aeruginosa* (confluent growth), and *Corynebacterium striatum* (abundant growth). Additionally, acyclovir was included in the prophylaxis of Herpes simplex infection and wound care was assigned to a qualified dermatologist with recommendation of topical therapy: chinosol compresses, clostridiopeptidase, and mechanical debridement with a surgical spoon, metronidazole in spot powder, PermaFoam dressings (Hartman), PermaFoamTM Cavity dressings (Hartman), Sorbalgon dressings (Hartman), fixation dressings, and spray Argotiab.

After the first administration of BV, regression of the cutaneous lesion was observed. On the abdominal skin on the right side, two skin tumors were visible, without signs of infection, and a massive inflammatory infiltrate. The recommended local therapy was maintained.

We continued the treatment plan with rapid and impressive regression of the tumor mass. Currently, the patient is after administration of the last, 16th dose of the drug, with a result of a very good response to treatment, complete remission of the disease (shown in Fig. 3). Treatment tolerance was good, the patient reported only slight foot paresthesia – peripheral neuropathy after BV grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) and fatigue grade 1 (CTCAE v4.0). No infectious complication was observed. Treatment was administered as scheduled. As planned, after a good response to treatment, the patient was qualified for the alloHSCT procedure but did not

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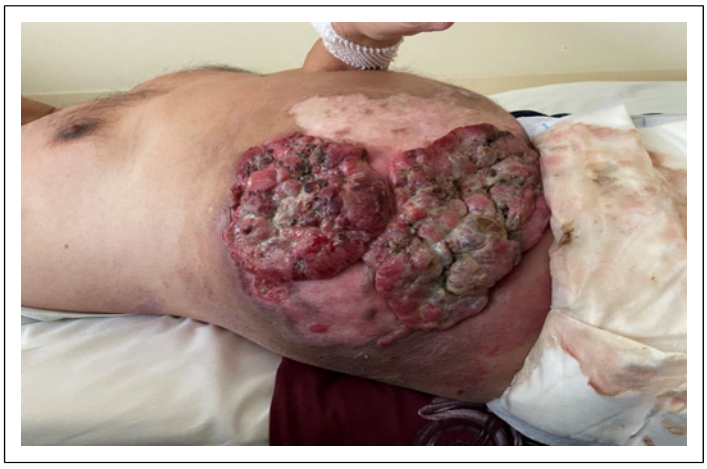

Fig. 1. Photos of the lesion at the time of diagnosis.

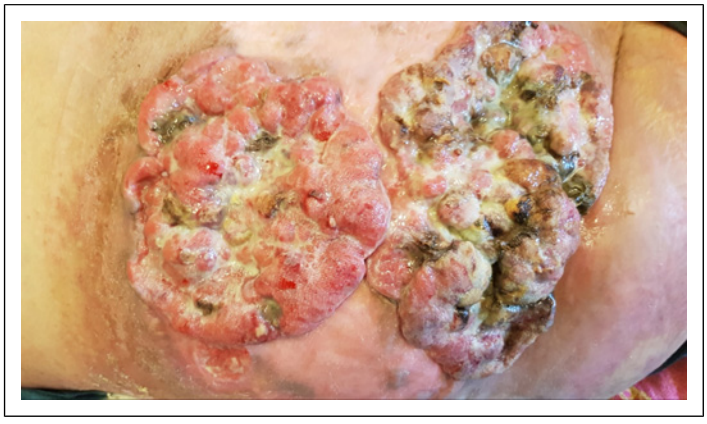

Fig. 2. Photos of the lesion at the time of diagnosis.

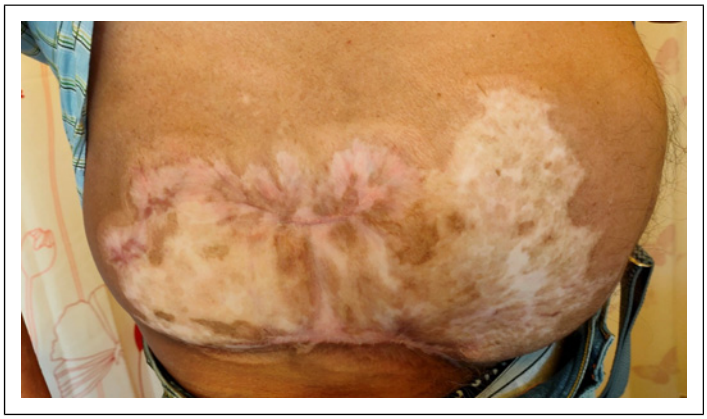

Fig. 3. Skin lesions after 16 administrations of brentuximab vedotin.

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consent to a transplant consultation. Therefore, after 20 months of follow-up, the patient remains in complete remission.

Discussion

The median survival time in MF-LCT is between 19 and 36 months [6]. Factors such as male sex, age over 60 years, involvement of lymph nodes (N2/N3) and visceral organs, and the presence of Sezary cells in the blood are generally considered to be poor prognostic factors in MF [10]. The disease course with the development of large, ulcerated tumors and accompanying infiltration of the visceral organs poses a challenge in choosing a treatment that would provide a chance of cure with minimal toxicity and infectious complication.

Treatment schedules are primarily based on the clinical stage of the disease and comorbidities. The more severe clinical course of the disease requires systemic treatment. Some new treatment options with different to chemotherapy mechanism of action have been introduced in recent years, including romidepsin, alemtuzumab, and pembrolizumab. Nowadays, the systemic chemotherapy should stay reserved as the last treatment possibility [11]. Local radiotherapy can also be considered as a treatment option – in our case, due to the extensive area of lesions and the high risk of infectious complications, this therapeutic option was abandoned.

If at least 5% of cells found in the biopsy specimen of skin lesions express the CD30 antigen, a beneficial effect of BV treatment could be expected [4]. It should be noted that the threshold for the introduction of BV is arbitrary (some authors suggest the possibility of using it even in the absence of CD30 expression), especially taking into account the fact that the determined level of expression of CD30 often differs in two histological sections taken from the same patient.

BV is a novel therapeutic option that found application in the treatment of tumors which cells express CD30 antigen (including anaplastic large cell lymphoma and Hodgkin's lymphoma). The drug acts in a sequence of events initiated by binding of a brentuximab molecule with the CD30 antigen on the surface of the tumor cell. The entire complex is then internalized and undergoes lysosomal digestion, which leads to intracellular release of auristatin E. Ultimately, this antimitotic drug causes damage to microtubules, cell division arrest, and apoptosis.

As found by Duvic et al. [12], in the case of MF, 50% of patients with expression of CD30 expression <10%, 58% of patients with expression 10–50%, and 50% of patients with expression >50% responded to treatment with BV, respectively (overall response in 54% of patients). It is worth noting that BV is particularly effective in MF with the presence of LCT, as it was established after the sub-analysis of the results of the ALCANZA study in the group of 17 patients [13]. A superior objective response of 4 months (ORR4) was observed compared to the choice of physicians (64.7% vs. 17.6%), similar to progression-free survival (15.5 months vs. 2.8 months). It is worth highlighting that in patients without LCT treated with BV ORR4 was achieved only in 38.7% of cases.

The most serious side effects that limited further treatment options are peripheral neuropathy and fatigue. It is of high importance as the standard therapeutic options commonly adopted for the management of advanced MF-LCT, i.e., methotrexate or CHOP, associated with multiple, sometimes serious, complications that reduce quality of life and alter the future management.

One of the first reports of successful use of BV in MF-LCT was provided by Goggins et al. [14] in 2019. They discussed the case of a patient with oral MF-LCT CD30+ from the IIB stage who presented an excellent response to the initial dose of BV and ~60% improvement of the

lesions (according to the physician's global assessment) after the second dose. Treatment did not induce any toxicity during the 8 months of follow-up.

The new single-center retrospective study by O'Donnel et al. [15] showed, after 8 years of observations, the superiority of BV compared to oral bexarotene, skin-directed therapy, and chemotherapy, as BV treatment reduced the mSWAT score by a mean of 20.53 (skin-directed therapy reduced it by 5.93, while the remaining regimens ended with higher mSWAT than at baseline). It was effective regardless of the early or advanced stage of the disease [15].

The standard BV treatment protocol was used in the described patient with advanced MF-LCT (stage IIB) expressing the CD30 antigen. Treatment resulted in a spectacular improvement in skin lesions with resolution of extensive ulcerated tumors and partial remission of the disease. It should be noted that the therapy was perfectly tolerated. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000529576).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Agnieszka Giza, Dagmara Zimowska-Curyło, and Andrzej Jaworek performed clinical patient care. Grzegorz Dyduch performed a histopathological examination. Agnieszka Giza, Karol Miklusiak, Przemysław Hałubiec, and Andrzej Jaworek contributed to the idea of the case report and design of the manuscript. Agnieszka Giza, Karol Miklusiak, and Przemysław Hałubiec drafted the manuscript, acquired, analyzed, and interpreted the data, reviewed the literature, revised the work for important intellectual content. Tomasz Sacha revised the manuscript critically. All 7 authors approved of the final version of the manuscript to be submitted.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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