Clinical Case Report

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Pegylated liposomal-encapsulated doxorubicin in cutaneous composite lymphoma

A case report

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Abstract

Background: Cutaneous composite lymphomas are very rare. Their treatment depends upon the different contributing lymphoma entities. Peripheral T-cell lymphoma, not otherwise specified, (PTCL-NOS) represents an aggressive lymphoma subtype. Follicular cutaneous B-cell lymphoma (FCBCL) runs an indolent course. Treatment with pegylated liposomal encapsulated doxorubicin (PLE-DOXO) has yet not been reported in this entity.

Case presentation: A 73-year-old male patient presented with 3 rapidly growing, painful nodules on his left leg. He was diagnosed as composite cutaneous lymphoma consisting of PTCL-NOS and FCBCL. All lesions had been surgically removed. Staging was unremarkable. After 4 months a relapse occurred with involvement of inguinal lymph nodes and systemic treatment with PEL-DOXO 20 mg/m^2 every 3 weeks was initiated. After 6 cycles PLE-DOXO, which were well tolerated without grade 3 or 4 toxicities, a mixed response was obtained with complete remission of cutaneous lesions.

Lymph nodes were treated by radiotherapy. A second relapse occurred after 8 months and various polychemotherapy regimens were applied without remission. The overall survival was 28 months.

Conclusion: PEL-DOXO is a possible initial systemic treatment in case of PCTL-NOS. Whether polychemotherapy offers an advantage for survival remains questionable but further investigations are needed.

Abbreviations: CBCL = cutaneous B-cell lymphoma, CCL = combined cutaneous lymphoma, CHOP = acronym for non-Hodgkin lymphoma chemotherapy with cyclophosphamide, hydroxydaunorubicin (or doxorubicin or adriamycin), oncovin (vincristine), and prednisolone, CR = complete response, CTCL = cutaneous T-cell lymphoma, DOXO = doxorubicin, FBCL = follicular cutaneous B-cell lymphoma, MF = mycosis fungoides, OR = overall response rate, PLE-DOXO = pegylated liposomal encapsulated doxorubicin, PR = partial response, PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified.

Keywords: combined cutaneous lymphoma, follicular cutaneous B-Cell lymphoma, pegylated liposomal-encapsulated doxorubicin, peripheral T-Cell lymphoma – not otherwise specified, polychemotherapy

1. Background

Major groups of cutaneous lymphomas are T-cell (CTCL) and B-cell (CBCL) lymphomas. CTCL belongs to the heterogeneous group of non-Hodgkin lymphomas and is primarily indolent. The most important subtypes of CTCL are mycosis fungoides (MF) and Sézary syndrome. CTCL arises in skin but may spread to lymph nodes, peripheral blood, and visceral organs with significantly worsening of prognosis. Staging of CTCL is based on the involvement of the different tissue compartments.[1]

CBCL are less frequent than CTCL and constitute about 25 % of all cutaneous lymphomas. CBCL are more indolent than their nodal counterparts and usually have a good prognosis. Follicular CBCL (FCBCL) is the most common subtype. Treatment may be surgically for solitary lesions.[2] Cutaneous composite lymphomas (CCL) are very rare. Because of this, no randomized controlled clinical trials have yet been performed for CCL.[3]

Doxorubicin is an active chemotherapeutic agent for CTCL but has the potential of severe cardiotoxicity. Pegylated liposomal encapsulated doxorubicin (PLE-DOXO) increases the concentration of the active compound in skin while reducing cardiac toxicity.[4] Reported overall response rates, that is, complete response (CR) plus partial response (PR), range from 20 % to 44 % in CTCL of MF or Sezary type.[5–9] Interestingly, PLE-DOXO has shown activity in a phase II trial for primary cutaneous B cell lymphoma as well.[10]

No data are available for PLE-DOXO in patients with CCL. Here we report on PLE-DOXO in a patient with CCL.

2. Case presentation

For this case report, an ethical committee approval was not necessary. Patient's informed consent was given.

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Authorship: UW reviewed the data and drafted the manuscript. GH was the pathologist on the case and reviewed and reported the morphology and immunohistochemistry. DL and GH were the treating physicians, drafted and reviewed the manuscript. All authors read and approved the final manuscript.

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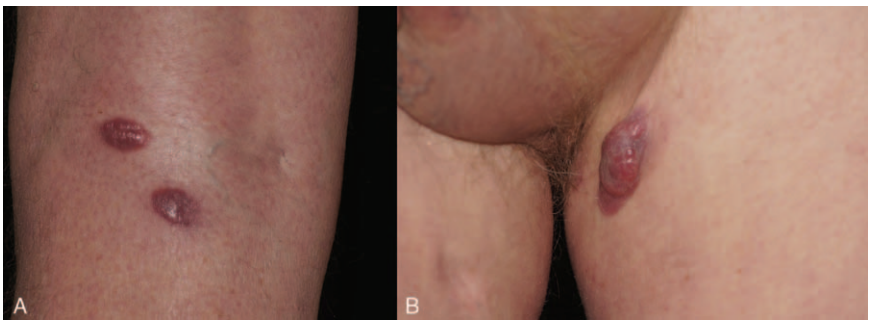

Figure 1. Initial clinical presentation of the patient with composite lymphoma of skin. (A) Nodules in the popliteal fossa of the left leg. (B) Tumor growth in the right groin.

A 73-year old male patient presented in April 2014 with 3 painful nodules on the left upper leg (knee and near the groin) that developed with the last 6 weeks (knee) and the last 3 days (groin). He denied night sweat, fever, weight loss, or loss of appetite. He suffered from several co-morbidities such as arterial hypertension, presbyakusis, cataract of the left eye, embolism of his left ocular artery, and relapsing vertigo due to spine problems. His medication consisted of amino salicylic acid, naftidrofuryl oxalate, and metoprolol succinate.

On clinical examination, we observed 3 flat nodules, well circumscribed, with a size between 1.5 × 1.1. cm to 2.8 × 1.8 cm. Their color was pink-brownish around the knee and flesh-like near the groin. The tumor near the groin was the largest and the fastest growing (Fig. 1). Our primary working diagnoses were dermatofibroma or cutaneous metastases of CUP syndrome.

We performed several skin biopsies. Histological examination revealed a dense inflammatory infiltrate composed of lymphoid and blastic cells intermingled with histiocytes, mast cells, plasma cells, and mature lymphocytes. We observed atypical mitoses. There was minimal epidermotropism. The epidermis was papillomatous, with alternating hypo- and hypertrophic sections (Fig. 2 A and B). Immunohistochemistry identified a mixed T- and B-cell population. Medium-sized and large atypical T-lymphocytes expressed CD2, CD3, CD4, CD5, Programmed Cell Death 1 (PD1) protein, and beta-F1 (anti-T-cell receptor beta chain antibody) (Fig. 3 A and B). They were negative for T-cell receptor gamma and mostly negative for ICOS (CD278). There was a mixed reaction to B-cell lymphoma (Bcl) 6 protein, chemokine ligand 13 (CXCL13), and CD30. B lymphocytes were arranged in irregular follicular networks and expressed CD20, CD21, CD79a, paired box-5 (PAX-5), and partially Bcl6. In situ hybridization for Epstein–Barr virus remained negative. Monoclonality was proved for B cells but not for T-cells (Dermatopathology Reference Center, Medical University of Graz, Austria —Prof. Lorenzo Cerroni, MD).

Bone marrow histology and immunohistology provided no evidence for specific infiltrates of a lymphoma. X-ray of the thorax, abdominal, and lymph node sonography were unremarkable.

Laboratory investigations revealed lymphopenia of 13% (normal range 20–45%), increased lactate dehydrogenase of 5.37 μkat/L (2.25–3.75 μkat/L), elevated thymidine kinase of 6.5 U/L (0–6.1 U/L), an increased CD3/CD4 ration of 5.25 (1.0–2.3), and slightly elevated percentages of $CD7^+$ cells of 82% (49–75%), $CD20^+$ cells of 14.0% (2–12%), and $HLA\text{-}DR^+$ cells with 19.0% (0–12%).

The diagnosis of CCL, composed of peripheral T-cell lymphoma, not otherwise specified (NOS) and follicular B cell lymphoma, pT2N1M0B0, stage IIA was confirmed.

The patient was classified for prognosis by Prognostic Index for PCTL-NOS (PIT).[11] The patient was older than 60 years of life and laboratory analysis demonstrated increased LDH. Performance status was 0; bone marrow involvement had been excluded. This resulted in PIT group 3 with an estimated 5-year survival rate of 32.9%.

Treatment and course: After complete surgical excision of the 3 tumor nodes, a relapse occurred after 3 months with nodules on the left malleolus medialis, scrotum, and mons pubis. These

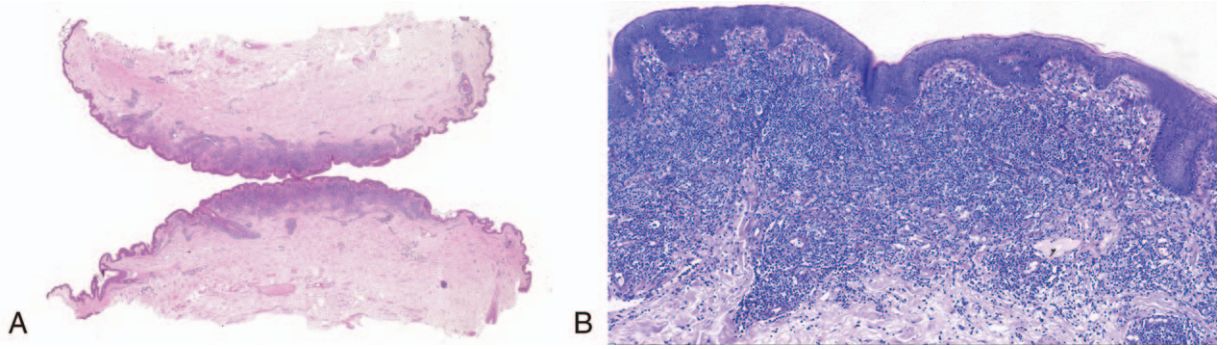

Figure 2. Histopathology of composite lymphoma of skin demonstrating a dense inflammatory dermal infiltrate composed mainly of lymphoid and blastic cells without significant epidermotropism. (A) Overview (HE ×2). (B) Giemsa stain (×4). HE = hematoxylin-eosin.

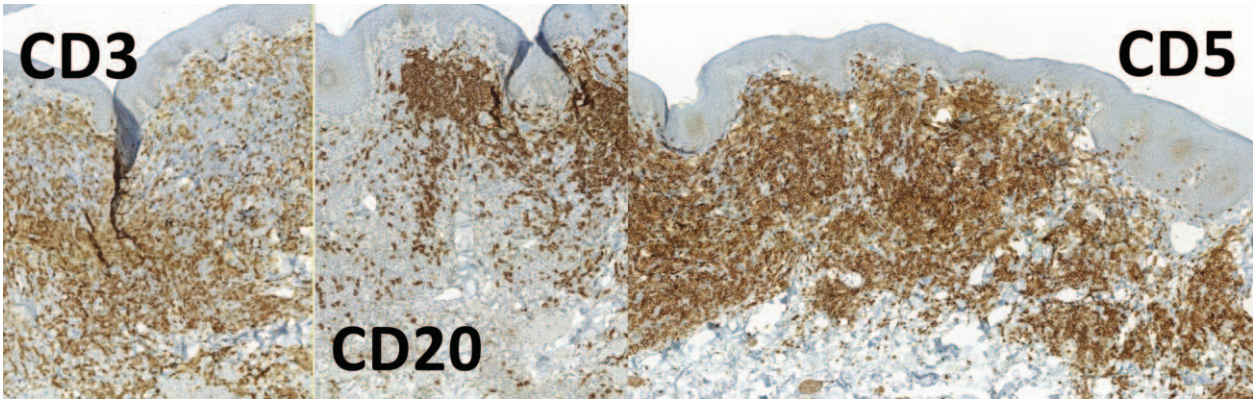

Figure 3. Characterization of the inflammatory dermal infiltrate by immunohistology with monoclonal antibodies against CD3, CD20, and CD5 (Immunoperoxidase stain, ×4).

lesions were biopsied. Histopathologic examination proved the primary diagnosis. As he had enlarged lymph nodes in the left groin, 2 lymph nodes had been taken for restaging. In both nodes, T-cell infiltrates of the NOS lymphoma could be identified with polymorphous T lymphocytes that strongly expressed CD3 and CD4 but were negative for CD10 with multiple $CD8^+$ cells intermingled with some plasma cells and $PAX5^+$ B lymphocytes. The proliferation rate as measured by Ki67-labeling was high (> 70%).

Computerized tomography (CT) disclosed enlarged lymph nodes in the groins of both sides.

The case was discussed in the interdisciplinary tumor board. Because of the dominant T-cell component in the composite lymphoma systemic and due to the pre-existent cardiovascular risk factors and co-morbidities, PLE-DOXO was recommended due to lower cardiotoxicity and higher drug concentrations in skin.

The treatment with PLE-DOXO 20 mg/m^2 was initiated in September 2014 and performed every 3 weeks.[5] The patient received premedication with ondansetron 8 mg per session. A total of 6 treatment cycles was performed. After the 3rd PLE-DOXO therapy, skin lesions became regressive. No signs of lymph node involvement were observed except for both groins with enlarged nodes of 2.3 × 3.3 cm and 2.5 × 2.2 cm, respectively. After 6 cycles of PLE-DOXO, the cutaneous lymphoma lesions completely disappeared. Inguinal lymph node involvement was stable and no further progression of disease had been observed.

The patient was discussed in the interdisciplinary tumor board again. Radiotherapy for the inguinal lymph nodes was recommended. Radiotherapy was performed with a linear accelerator and a total dose of 36 Gy in January and February 2015. At the end of this treatment, a new perianal tumor mass had developed. That was followed by cutaneous lesions in groins, gluteal, and on his left foot with tumors and plaques (Fig. 4). He received a combined chemotherapy in the oncology outpatient clinic with gemcitabine, oxaliplatin, and bendamustine. After 2 chemotherapy cycles, he developed a severe leukopenia.

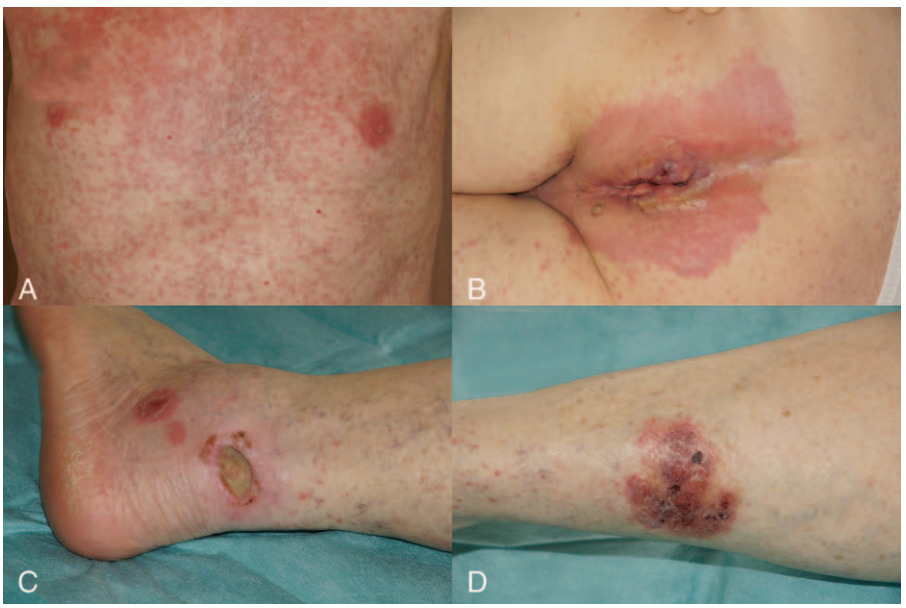

Figure 4. Relapse of composite lymphoma of skin after radiotherapy. (A) Maculo-papular rash on the trunk. (B) Tumor-like mass with surrounding erythema in the anal fold. (C) Hyperpigmented patch and ulceration on the left foot. (D) Ill-defined hyperpigmented scaly plaque on the left lower leg.

Chemotherapy had to be interrupted and recombinant granulocyte growth factor (Filgrastim®) was given s.c. with a daily dosage of 48 mio U for 5 days. On the last day, he was sent to the emergency department because of fever, general malaise, and an acute generalized pruriginous erythema. We treated the patient with systemic (starting dose 100 mg/d) and topical corticosteroids and desloratidin 3 × 5 mg/d. With 1 week, a complete remission of the acute rash was achieved. Our working diagnosis was Filgrastim®-induced exanthema with fever. A DRESS-syndrome was not confirmed, as eosinophils were not increased. In April and May, chemotherapy was intensified to CHOEP q 14 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone – 14 days cycle). Due to further progress, the protocol was changed in June 2015 to bendamustine, etoposide, and pixantrone until July 2015. He developed fever. The pneumonia was diagnosed and treated by systemic antibiosis. The lymph node involvement was progressive with enlargement of axillary, mediastinal, iliacal, and retroperitoneal involvement.

Safety: During PLE-DOXO therapy the patient was monitored by regular laboratory investigations and electrocardiography (ECG). Treatment was well tolerated. The performance status was 0–1 during the whole time of PLE-DOXO. No major toxicities were observed neither in the laboratory nor by ECG. The treatment had been given continuously without any interruption. The wounds in the left groin and on the left foot needed a revision due to delayed wound healing in October 2014. The patient developed a papular rash in November 2014 treated by topical corticosteroids. We observed palmo-plantar hyperkeratosis on erythematous skin diagnosed as hand–foot syndrome (palmo-plantar dysesthesia) that was treated by topical ointment containing urea 10%. After the 6th PLE-DOXO treatment, he developed a papulo-macular rash treated with topical prednicarbate ointment.

During polychemotherapy toxicities, grade 3 and 4 were observed. Bone marrow toxicity needed intensified application of GMCSF. Skin toxicity needed hospitalization. Severe infection (pneumonia) occurred. Performance status deteriorated from 0–1 to 3 and temporary to 4. Although an initial response of cutaneous lesions was noted in February 2015, the disease progressed to stage T3N3B0M0 (Stage IVB). He died in August 2015 due to pneumonia and aggressive lymphoma.

Overall survival was 28 months. Progression-free survival after PLE-DOXO initiation was 5 months. There was no progression-free survival thereafter.

3. Discussion

CCL are very rare cutaneous malignancies. In a series of 1200 cutaneous lymphoproliferative diseases, only 15 cases of CCL could be identified.[3] Our patient suffered from a combination of PTCL-NOS and FBCCL. PTCL-NOS is the most common subtype of PTCL that runs an aggressive course.[12] FBCCL is an indolent lymphoma with good prognosis.[13,14]

Negative prognostic factors for PCTL-NOS include peripheral neutropenia and thrombocytopenia, high tumor proliferative index (Ki67), age > 60 years of life, poor performance status, bone marrow involvement, and increased LDH.[15] Increased thymidine kinase serum levels are a marker of aggressive lymphomas.[16] Our patient had a high proliferative index, increased LDH, and was > 60 years of life. Serum thymidine kinase was only slightly increased. Lymphopenia was present from the beginning. For such patients, a median overall survival of 7.6 months has been calculated.[17] Lymphopenia, on the other side, will have a negative impact on the response to classical DOXO-based chemotherapies.[17]

Treatment of PCTL-NOS is not well standardized due to the rareness of this disease. Indeed PCTL-NOS is the rarest type of CTCL.[18] CHOP regimen consisting of cyclophosphamide, DOXO, vincristine, and prednisolone has been used in cutaneous T-cell lymphomas including PTCL-NOS. In a retrospective trial including 56 patients with PTCL-NOS, DOXO has been compared to pirarubicin, a less cardiotoxic DOXO-derivate, as part of CHOP. Complete remission rates in both groups were identical with 52%. The 3-year overall survival was in favor of pirarubicin-CHOP, that is, 67% versus 52% for DOXO-CHOP. The 3-year progression-free survival for pirarubicin-CHOP was 75% versus 33% with DOXO-CHOP.[19] The 5-year survival rate with CHOP is only 19% in PCTL-NOS.[20] Adjuvant radiation therapy to DOXO-based chemotherapy in early stage PCTL-NOS may improve the 3-year survival significantly, that is, 49.7% versus 23.1% (DOXO-based chemotherapy alone).[21]

Gemcitabine, cisplatin, dexamethasone regimen as salvage therapy of relapsed or refractory PTCL (n=25) resulted in a complete response in 48% and in partial response in 24%. Progression-free media survival was 9.3 months.[23] Patients with relapse or progression have a poor outcome despite chemotherapy or radiotherapy.[22]

CHOP and other polychemotherapy regimens such as DOXO, cyclophosphamide, vincristine, prednisolone or gemcitabine, oxaliplatin, bendamustine, and so on, may result in significant toxicities without improvement of overall survival.[12,22]

In contrast, PLE-DOXO has a favorable safety profile with proven efficacy in CTCL in particular at a dosage of 20 mg/m^2.[5–9] This is the first case report on PLE-DOXO as initial chemotherapy in PCTL-NOS. In a patient with PIT risk group 3, a stable disease with complete response of cutaneous lesions could be achieved. No grade 3 or 4 toxicities were observed. The treatment was well tolerated. Palmo-plantar dysesthesia, however, is a common adverse effects observed in about 50% of patients. Overall survival was about 4 times of the median survival of grade 3 PTCL-NOS with 28 months.[11] Despite escalating polychemotherapy, no remission or further progression-free survival could be achieved. Would the patient have been benefited from a second PLE-DOXO course alike MF patients? We do not know. Further investigations for an optimal treatment algorithm are needed.

4. Conclusions

We report a case of a 73-year-old male patient who presented with painful cutaneous nodules identified by histology and immunohistology as CCL composed of PTCL-NOS and FCBCL. We obtained a stable disease with complete remission of cutaneous lesions during 6 cycles of low-dose PEL-DOXO every 3 weeks. The use of PEG-DOXO has yet not been described for this entity although controlled and uncontrolled trials documented clinical efficacy for MF and Sézary syndrome and even in CBCL. Whether escalating polychemotherapy provides benefits for such patients in sense of quality of life, relapse-free, and overall survival has yet not been proven. Further studies are needed to substantiate the positive impression of this well-tolerated treatment in CCL with PTCL-NOS and FCBCL.

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