

# Primary Cutaneous CD30+/ALK- ALCL with Transition into sALCL: Favourable Response after Systemic Administration with Brentuximab Vedotin! Unique Presentation in a Bulgarian Patient!

Tanya Naskova Popova<sup>1</sup>, Atanass Radinov<sup>1</sup>, Konstantin Stavrov<sup>2</sup>, Ivanka Temelkova<sup>2</sup>, Ivan Terziev<sup>3</sup>, Ilija Lozev<sup>4</sup>, Detelina Lukanova<sup>5</sup>, Hristo Mangarov<sup>2</sup>, Uwe Wollina<sup>6</sup>, Georgi Tchernev<sup>2,7\*</sup>

<sup>1</sup>Department of Clinical Hematology, University Multiprofile Hospital for Active Treatment "Sveti Ivan Rilski", Sofia 15, Acad. Ivan Geshov Blvd., Sofia 1431, Bulgaria; <sup>2</sup>Department of Dermatology, Venereology and Dermatologic Surgery, Medical Institute of Ministry of Interior (MVR-Sofia), General Skobelev 79, 1606 Sofia, Bulgaria; <sup>3</sup>Universitetska Mnogoprofilno Bolnitsa za Aktivno Lechenie "Tsaritsa Yoanna", Common and Clinical Pathology, Sofia, Bulgaria; <sup>4</sup>Medical Institute of the Ministry of Interior, Surgery, Sofia, Bulgaria; <sup>5</sup>National Hospital of Cardiology, Clinic of Vascular surgery and Angiology, Sofia, Bulgaria; <sup>6</sup>Städtisches Klinikum Dresden, Department of Dermatology and Allergology, Friedrichstrasse 41, Dresden, Germany; <sup>7</sup>Onkoderma, Polyclinic for Dermatology and Dermatologic Surgery, General Skobelev 26, Sofia, Bulgaria

## Abstract

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**\*Correspondence:** Georgi Tchernev. Department of Dermatology, Venereology and Dermatologic Surgery, Medical Institute of Ministry of Interior (MVR-Sofia), General Skobelev 79, 1606 Sofia, Bulgaria; Onkoderma - Polyclinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606, Sofia, Bulgaria. E-mail: [georgi\\_tchernev@yahoo.de](mailto:georgi_tchernev@yahoo.de)

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**BACKGROUND:** Modern drugs could sometimes be a good solution even to problematic patients. The cutaneous and systemic forms of the CD30 positive anaplastic large T-cell lymphoma could often be described as a suitable target for therapy with Brentuximab vedotin.

**CASE REPORT:** We present the first case of a Bulgarian patient with a histologically confirmed primary cutaneous T-cell CD30+/ALK- large anaplastic cell lymphoma-cALCL (therapeutically resistant to therapy with Methotrexate, radiation therapy and systemic corticosteroid therapy) who was successfully treated with Brentuximab vedotin. In several years, the patient has developed a comparatively fast skin progression as well as an initial systemic one which impacts inguinal and mediastinal nodes. After the implementation of 4 therapy cycles with Brentuximab vedotin, complete regression of the described by previous hospitalisations lymph nodes as well as 80% reduction of the cutaneous and subcutaneous located tumour formations were observed.

**CONCLUSION:** The therapy of CD30+/ALK- anaplastic large T-cell lymphoma is a significant challenge for oncologists and dermatologists because it requires maximally efficient and minimally traumatic treatment in parallel. Therapy with Brentuximab is a new direction which shows extremely good clinical results and can be applied to the cutaneous as well as to the systemic form of anaplastic large-cell CD30 positive lymphoma. The key element by treatment with Brentuximab is suppression of the CD30- expression which, in turn, could be the cause of relapses. On that ground, patients with these lymphomas should be strictly monitored.

## Introduction

Cutaneous lymphoma treatment is a challenge for the clinician and requires an accurate assessment of the therapy to achieve optimal

therapeutic results and a minimum rate of side effects [1]. CD-30 and ALK positivity in lymphomas is important for the prognosis and choice of treatment regimen [1].

## Case Report

We at this moment report the case of a patient with histologically confirmed primary cutaneous T-cell CD30+/ALK- anaplastic large cell lymphoma with an available histological verification from 2 years ago. From the immunohistochemical tests, CD45+, CD3+, CD2+, CD30+, CD20+, EMA+, ALK- and Ki67+ reactions were detected.

Complaints initially began with wide-surface erythema in the right lower leg area. Subsequently, tumorous papules and a pigmentary solitary tumour formation appeared which were treated surgically. Concomitant computer tomographic scans did not reveal any initial data on the transition to systemic lymphoma. Over the last 2 years, 1) 2 corticosteroid treatment regimens, 2) 3 radiotherapy courses with a total focal dose of 30Gy, and 3) attempted Methotrexate 20 mg/week therapy over a total period of approximately 2.5 months, were performed, all of the currently listed options not leading to any symptomatic improvement. Clinical evidence from the latest outpatient examination indicated a progression of skin symptoms and a slight worsening of the general status expressed in subfertility, weakness, and severe pain in the muscles and joints.

The patient was hospitalised for a second reevaluation of the diagnosis, ruling out a transition to systemic lymphoma, and recommendations for introducing a more effective treatment regimen.

During the clinical examination, multiple, partially grouped, as well as single standing nodular tumor-like formations with a diameter of between 0.5 and 3 cm were observed on the skin of the right lower leg, which were elastic and dense at palpation, most of them with a centrally ulcerated surface, located on an erythematous base (Figure 1a). The primary skin large anaplastic cell lymphoma (pALCL) diagnosis was confirmed again in histologically and immunohistochemically. Bone marrow puncture/bone marrow flow cytometry analysis showed evidence of normocellular and hypercellular bone marrow with no immunomorphologic evidence of the involvement of the latter from lymphoma. Paraclinical examinations showed the following results that made an impression: ESR - 22 mm/h; uric acid-plasma - 471.0  $\mu\text{mol/l}$ ; glycated hemoglobin% - HbA1C - 8.4%; cholesterol-6.6 mmol/l; LDL - 4.6 mmol/l.

Computer Tomography scan showed the presence of a single 14/11mm paraesophageal lymph node, while in the previous scan the latter had a size of 18 mm. Additionally, bilaterally enlarged inguinal lymph nodes were observed. Primary skin anaplastic CD30+ T cell lymphoma was diagnosed with possible involvement of the regional lymph nodes. The patient received a systemic Brentuximab vedotin therapy, and within 3 cycles (each at a 21-day interval), he showed a significant improvement of the clinical symptoms

and involution of the nodular formations in the lower limb, as well as normalisation of the lymph node dimensions (Figure 1a, 1c). A total of 12 Brentuximab cycles were planned.



Figure 1: a) Clinical picture before starting therapy in a patient with Methotrexate resistant anaplastic large CD 30 positive ALK-negative primary cutaneous T cell lymphoma; b) Clinical picture after the second Brentuximab infusion; c) Clinical picture after the 3 Infusion with Brentuximab showing significant clinical improvement of the tumorous formations

## Discussion

Anaplastic large cell lymphomas comprise a group of CD30-positive non-Hodgkin lymphomas that generally are of T-cell origin and share common morphologic and phenotypic characteristics [2].

The World Health Organization recognises 3 entities: 1) primary cutaneous ALCL (pcALCL), 2) anaplastic lymphoma kinase (ALK)-positive ALCL, and, provisionally, 3) ALK-negative ALCL [2]. pcALCL presents in the skin and, while it may involve locoregional lymph nodes (as in our case suspected), rarely disseminates [2]. Outcomes typically are excellent [2].

Anaplastic large-cell lymphoma (ALCL), especially anaplastic lymphoma kinase-negative (ALK<sup>-</sup>) ALCL (as in the case described by us), is a rare CD30-expressing aggressive subtype of peripheral T-cell lymphoma [3]. The CD30 expression on the cell surface of ALCL is creating the unique possibility for anti-CD30 therapy with Brentuximab (3). Brentuximab vedotin (BV; Adcetris<sup>®</sup> Takeda Pharmaceuticals) is a CD30-directed antibody-drug conjugate that received FDA approval in August 2011 for the treatment of systemic ALCL (sALCL) [3].

The advantage of Brentuximab therapy is that it is available to patients with both cutaneous and systemic form of anaplastic large-cell CD-30 positive lymphoma [4] [5]. Both indications (systemic and cutaneous) for introducing systemic treatment are of significant importance about the clinical management

in “problematic patients” [4] [5]. The patient we have described did not agree to a biopsy of the paraesophageal-localized lymph node and bilaterally localised inguinal enlarged lymph nodes.

During the comparisons of the CT images, it was found that the case was most likely related to a transition from the cutaneous to the systemic form of ALCL. Meanwhile, the two indications for treatment of ALCL ensured some freedom of action relating to the initiation of innovative Brentuximab therapy, as well as optimal clinical outcomes (with complete regression of the paraesophageal and bilateral inguinal located lymphatic nodes) after 4 cycles with Brentuximab vedontin.

The lack of effectiveness due to the loss of CD-30 expression in the course of the targeted treatment is a possible reason for relapses in ALCL patients, as well as a serious obstacle to continued Brentuximab therapy [6].

Therefore, the progression of the disease during the therapy or discontinuation of treatment in patients treated with Brentuximab should be accompanied by re-testing for CD30 expression in the lesional tissue and redefine the therapeutic strategy [6]. The patients should be closely monitored.

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