EORTC
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EORTC Cutaneous Lymphoma Task Force (CLTF) Spring meeting

22 – 23 April 2016

EORTC Headquarters
Brussels, Belgium

PROGRAMME

Friday 22 April

13:15 – 13.30	Opening of the meeting Pietro Quaglino on behalf of Board
13:30 – 14:30	NEW INSIGHTS INTO CUTANEOUS LYMPHOMAS I Moderators: Detlev Klemke, Chalid Assaf, Emilio Berti • Abstract presentations
14:30 – 15:00	Update on EORTC guidelines for CTCL (Franz Trautinger) introduced by Robert Knobler. Moderated Robert Knobler, Rein Willemze, Pietro Quaglino
15:00 – 15:30	SPECTARare (Vassilis Golfinopoulos) introduced by Maarten Vermeer
15.30 – 16.00	**Coffee break**
16:00 – 16:30	EORTC strategy and new trial development (Sandrine Marreaud) Introduced by Julia Scarisbrick
16:30 – 17:30	EORTC clinical trials session, Moderated by Martine Bagot, Pablo Ortiz Romero
16:30 – 16:50	Experience in clinical trials during the last decade (Rudi Stadler)
16:50 – 17:30	Trial Proposals • PD1 trial – Rudi Stadler • PROMPT (ECP) trial – Robert Knobler • Mogalizumab & RT – Pablo Ortiz • JAK1-2 inhibitor and MS/SS – Evangelia Papadavid
17:30 – 18:30	PROCLIPI session, moderated by Robert Knobler, Rudi Stadler, Evangelina Papadavid
17:30 – 17:50	PROCLIPI early stage MF project (Julia Scarisbrick)
17:50 – 18:10	PROCLIPI early stage MF pathology (Rein Willemze)
18:10 – 18:30	OPEN DISCUSSION
18:45	**Coach Transport from EORTC HQ to Restaurant**
19:30	**Drinks**
20:30	**Dinner 'Aux Armes de Bruxelles'**

Saturday 23 April

08:30 – 08:45	Welcome by Denis Lacombe, introduced by Pietro Quaglino – **Members only**
08:45 – 09:00	New TR proposal: CD8 Positive Dermal Lymphoid Infiltrated (Werner Kempf, Alistair Robson)
09:00 – 10:30	EORTC CLTF meets other EORTC groups Moderators: Julia Scarisbrick, Pietro Quaglino, Maarten Vermeer • Wilfried Budach; EORTC Radiotherapy Group • Alex van Akkooi; EORTC Melanoma Group • Paul Meijnders; EORTC Lymphoma Group
10:30 – 11:00	**Coffee break**
11:00 – 12:00	Presentations by Pharma • Mallinckrodt Pharmaceuticals (Therakos (UK) Ltd) – Behlke Susanne • Kyowa / Prostraken – Dmitri Grebennik • Takeda – Meredith Little • 4SC – Susanne Danhauser-Riedl
12:00 – 12:30	**General assembly – Members only**
12:30 – 13:15	NEW INSIGHTS INTO CUTANEOUS LYMPHOMAS II Moderators: Antonio Cozzio, Robert Knobler, Pablo Ortiz-Romero • Abstract presentations
13:20 – 13:30	End of the meeting + prize for best young investigator

ABSTRACT SESSION I

Friday 22 April

13:30 – 14:30

NEW INSIGHTS INTO CUTANEOUS LYMPHOMAS I

Moderators: Detlev Klemke, Khalid Assaf, Emilio Berti
6 Abstracts (7 minutes presentation, 2 minutes discussion)

1. **DIMETHYL FUMARATE INHIBITS XENOGRAFT CTCL TUMOR GROWTH AND METASTASIS IN VIVO.**
   Jan P. Nicolay, Karin Müller-Decker, Markus Möbs, Markus Brechmann, Anne Schroeder, Cyrill Géraud, Chalid Assaf, Sergij Goerdt, Peter H. Krammer, Karsten Gülow. Mannheim Germany.

2. **THE COMBINED LSD1-/HDAC-INHIBITOR 4SC-202 CAUSES CELL CYCLE ARREST WITH CONSECUTIVE CELL DEATH IN CUTANEOUS T-CELL LYMPHOMA CELL LINES.**
   Marion Wobser, Amelie Glunz, Alexandra Weber, Hella Kohlhof, Matthias Goebeler, David Schrama, Roland Houben. Wuerzburg, Germany.

3. **PRIMARY CUTANEOUS CD8-POSITIVE AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA: CLINICOPATHOLOGICAL FEATURES AND GENOMIC ALTERATIONS.**
   Alberti-Violetti S, Fanoni D, Corti L, Tomasini C, Venegon L, Berti E. Milan, Italy.

4. **INEFFECTIVE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN PATIENTS WITH LATE STAGE CUTANEOUS T CELL LYMPHOMA.**
   Emmanuella Guenova, Yun-Tsan Chang, Desislava Ignatova, Antonio Cozzio. Zurich, Switzerland.

5. **DIFFERENTIAL GENE EXPRESSION IN INITIAL SKIN BIOPSIES IN STABLE EARLY STAGE MYCOSIS FUNGOIDES VERSUS LATER TUMOR-STAGE.**
   Ulrike Wehkamp, Ilske Oschlies, Christian Kohler, Michael Weichenthal, Wolfram Klapper. Kiel, Germany.

6. **MYCOSIS FUNGOIDES: NEW ISSUES FROM MICROENVIRONMENT?**
   A Pileri, C Agostinelli, V Grandi, M Sessa, C Delfino, A Patrizi, N Pimpinelli. Bologna, Italy.

ABSTRACT SESSION II

Saturday 23 April

12:30 – 13:15

NEW INSIGHTS INTO CUTANEOUS LYMPHOMAS II

Moderators: Antonio Cozzio, Robert Knobler, Pablo Ortiz-Romero
5 Abstracts (7 minutes presentation, 2 minutes discussion)

7 **MIR-155 EXPRESSION IN PRIMARY CUTANEOUS T CELL LYMPHOMAS (CTCL).**
P. Fava, C. Astrua, M. Bergallo, M. Brizio, I. Galliano, P. Montanari, V. Daprà, M. Novelli, P. Savoia, P. Quaglino and MT. Fierro. Turino, Italy.

8 **TOX1 EXPRESSION IN MYCOSIS FUNGOIDES CASES.**
A. Iliadis, T. Koletsa, A. Patsatsi, E. Georgiou, I. Kostopoulos. Thessaloniki, Greece.

9 **EPSTEIN BARR VIRUS-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA OF THE ELDERLY WITH SKIN AND BRAIN INVOLVEMENT: CLINICOPATHOLOGICAL FEATURES AND GENOMIC ANALYSIS.**
Iberti-Violetti S, Bernareggi S, Bonometti A, Venegoni L, Merlo V, Onida F, Berti E. Milano, Italy.

10 **STAGING PRIMARY CUTANEOUS B-CELL LYMPHOMA – T STAGE LACKS PROGNOSTIC VALUE.**
Chan SA, Shah F, Chiganti S, Stevens A, Amel-Kashipaz R, Vydianth B, Scarisbrick JJ. Birmingham, UK.

11 **PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA: PROGNOSTIC IMPACT OF THE ISCL/EORTC T-CLASSIFICATION FOR NON-MF CUTANEOUS LYMPHOMAS.**
Jördis Hüneke, Artur Gontarewicz, Ulrike Wehkamp, Wolfram Klapper, Ilske Oschlies, Michael Weichenthal. Kiel, Germany.

ABSTRACT SESSION I

Friday 22 April
13:30 – 14:30

NEW INSIGHTS INTO CUTANEOUS LYMPHOMAS I

Moderators

Detlev Klemke, Khalid Assaf, Emilio Berti

1

13.30-13:39
DIMETHYL FUMARATE INHIBITS XENOGRAFT CTCL TUMOR GROWTH AND METASTASIS IN VIVO

Jan P. Nicolay[1,2#], Karin Müller-Decker[3], Markus Möbs[4,5], Markus Brechmann[2], Anne Schroeder[2], Cyrill Géraud[1], Chalid Assaf[4,6], Sergij Goerdt[1], Peter H. Krammer[2], Karsten Gülow[2#]

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Introduction and objectives

Despite intensive efforts in recent years, a curative therapy for cutaneous T cell lymphoma (CTCL) has not yet been developed. Therefore, the establishment of new therapeutic approaches with higher efficacy rates and milder side effects is strongly required. A characteristic feature of the malignant T cell population in CTCL is resistance towards cell death due to constitutive NFκB activation. Therefore, NFκB-dependent cell death resistance represents an interesting therapeutic target in CTCL, as an NFκB-directed therapy would leave bystander T cells widely unaffected. In vitro data already showed that the NFKB inhibitor dimethyl fumarate (DMF) induces cell death in primary CD4+ T cells from CTCL patients and CTCL cell lines.

Materials and methods

To study the effects of DMF on CTCL cells in vivo we developed a subcutaneous and an intradermal (orthotopic) CTCL xenograft mouse model. After detection of tumor growth we treated the mice orally or intraperitoneally with DMF or placebo and evaluated the tumors and organs morphologically and microscopically. In addition the tumor growth dynamics were evaluated.

Results

CTCL xenograft tumors of DMF-treated mice grew significantly slower than those of vehicle-treated animals. This finding correlated with higher apoptosis and necrosis rates of xenografted cells in the DMF-treated mice compared to the vehicle-treated animals. This effect was dependent on NFκB activity and inhibition, respectively. In addition we found massive hepatic and splenic metastasis of the xenograft

tumors in the vehicle-treated animals, but hardly in the DMF-treated mice. In the metastases we also detected increased xenograft cell death upon DMF treatment. The cell death inducing effect of DMF was independent of the way of application.

Conclusion

DMF induces CTCL cell death not only *in vitro*, but also in a xenograft mouse model. This hints towards an antineoplastic effect of DMF on CTCL cells *in vivo*. As DMF is already in save clinical use for psoriasis and multiple sclerosis we propose DMF as a realistic therapeutic option for CTCL.

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13:39-13:48

THE COMBINED LSD1-/HDAC-INHIBITOR 4SC-202 CAUSES CELL CYCLE ARREST WITH CONSECUTIVE CELL DEATH IN CUTANEOUS T-CELL LYMPHOMA CELL LINES

Marion Wobser[1], Amelie Glunz[1], Alexandra Weber[1], Hella Kohlhof[2], Matthias Goebeler[1], David Schrama[1], Roland Houben[1]

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Introduction and objectives

Targeting of epigenetic events such as histone methylation and acetylation has been proven to be effective in several malignancies including systemic and cutaneous lymphomas (CTCL). De-repression of growth-inhibitory proteins is considered as one of several important mechanisms mediating anti-tumor activity. In this regard, 4SC-202 is a novel compound, which has been demonstrated to dually inhibit class 1 histone deacetylases (HDAC) as well as the lysine (K)-specific demethylase 1A (LSD1). 4SC-202 has recently been investigated in a phase I trial (TOPAS) in patients with advanced hematologic malignancies including CTCL.

Results

In MTS assays all six different CTCL cell lines tested were strongly inhibited by 4SC-202, irrespective of the levels of LSD1 or HDAC expression as determined by qPCR, whereas fibroblasts or peripheral blood lymphocytes were largely resistant. DNA staining demonstrated that growth inhibition of CTCL cell lines was associated with an accumulation of cells in G2/M followed by induction of massive cell death. In contrast to the well-studied HDAC class I inhibitor FK228, which does not induce a G2/M arrest in CTCL cell lines, 4SC-202 had only minor effects on the global histone acetylation pattern with respect to functionally relevant sites (H3K9ac) and even the minor increase of dimethyl H3K4 levels was less pronounced than the increase observed for FK228 at concentrations resulting in similar levels of cell death. Moreover, in nanostring nCounter® and qPCR analysis, the gene expression profile of key oncogenic genes was only marginally affected by 4SC-202. Moreover, the capability of this compound to sustain a G2/M arrest, which had been pre-induced by nocodazole, was not affected by inhibition of transcription indicating that gene expression is not required for this effect. To further explore the process of cell division and cell death under 4SC-202, we analyzed adherent HeLa cells, which detach during mitosis, by time-lapse microscopy. 4SC-202 provoked a profound prolongation of the detachment phase which was followed by either complete lack of cytokinesis,

failed abscission or cell death suggesting that mitotic failure is the primary consequence of 4SC-202 treatment.

Conclusion

Besides methylation and acetylation of respective histone marks and, thus, the consecutive alteration of gene expression, epigenetic modifiers may demonstrate more complex, pleiotropic modes of action. These include the epigenetic modification of non-histone proteins and, as evidenced by 4SC-202, the induction of mitotic defects, presumably by regulating the recruitment and/or activity of core molecules involved in mitotic segregation. Currently ongoing experiments will uncover the underlying mechanisms of efficient growth inhibition and mitotic defects of 4SC-202 on CTCL cell lines.

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13:50-13:59

PRIMARY CUTANEOUS CD8-POSITIVE AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA: CLINICOPATHOLOGICAL FEATURES AND GENOMIC ALTERATIONS.

Alberti-Violetti S,[1] Fanoni D,[1] Corti L,[1] Tomasini C,[2] Venegon L,[3] Berti E[1,4]

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Introduction

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (AETCL) is a rare peripheral T-cell lyphoma with an aggressive behavior (overall survival 12-32 months). Differential diagnosis, made with other indolent CD8 positive lymphomas, such as Lymphomatoid papulosis type D and CD8 positive Mycosis fungoides, is important because of prognosis and therapeutic choices.

Materials and methods

We retrospectively evaluated clinical aspects and histological features in 20 patients affected by AETCL. Kaplan-Meier estimate was used to determinate the overall survival (OS). Array-comparative genomic hybridization (aCGH) analysis was performed to evaluate the genomic profile.

Results

Two clinical presentations were found: 1) diffuse ulcerated and eruptive papules, nodules and tumors; 2) localized nodules, tumors or plaques, especially on acral sites. Histologically, the typical cytotoxic CD8+ neoplastic infiltrate showed a lichenoid pattern with marked epidermotropism in the diffuse variant, but it is more dense and deeper with less epidermotropism in the localized variant. Median OS was 10 months, without any significant differences between two groups. Seventeen patients (85%) died for lymphoma, 1 died for heart failure. One patient

is lost to follow-up and only 1 patient is alive with the disease. aCGH analysis revealed a complex profile mainly characterized by numerous gains, whose frequency was higher than 80% on chromosome 7q and 17q. The most frequent loss (>80%) was on 9p21 region, in particular on CDKN2A and CDKN2B loci.

Conclusion

AETCL is characterized by two clinicopathological variants but the same aggressive course. Genomic analysis showed numerous alterations as reported in aggressive neoplasms and the same and peculiar profile in all cases. Identification of this profile can be usefull to differentiate AETCL from other CD8+ indolent lymphomas.

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13:59-14:08

INEFFECTIVE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY IN PATIENTS WITH LATE STAGE CUTANEOUS T CELL LYMPHOMA

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Introduction

Targeted therapies and immune modulators are currently changing our understanding for the treatment of solid tumors, and promise to open a new perspective in the management of cutaneous T-cell lymphoma (CTCL) as well. The mechanisms of action of therapeutic antibodies in vivo is not fully elucidated in all cases, antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer (NK) cells often being presumed to be a key mode of action. However, since progressive impairment of cellular immunity is a hallmark of CTCL, we questioned the fact that patients with late stage CTCL will still be in a possession of fully functional ADCC.

Objective

To investigate the mechanism of ADDC in CTCL patients.

Materials and methods

NK cells were isolated from patients with MF stage I-IV, Sézary Syndrom (SS) patients and healthy individuals. An aCella-TOX GAPDH assay was used to detect the amount of endogenous glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the level of ADCC in each individual patient.

Results

In vitro ADCC in patients with MF stage I was comparable to that of healthy individuals, but severely abrogated in all MF Stage IV and SS patients included in the study. The percentage of NK cells in the blood of CTCL patients was within normal limits. Trogocytosis, a mechanism of cellular communication that can hamper ADCC by cleaving the surface of the tumor cells from the targeted molecule, seemed not to play an essential role in CTCL. However, overexpression of MHC I on the malignant tumor cells in CTCL was important factor in helping tumor cells escape NK-cell activity and MHC I blockade could restore impaired ADCC.

Conclusion

Impaired ADCC may pose some problems when choosing a targeted drug therapy for the treatment of late stage CTCL. Understanding of the immunological mechanisms behind it will help improve NK cell activity in CTCL patients and overcome resistance to treatment.

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14:10-14:19

DIFFERENTIAL GENE EXPRESSION IN INITIAL SKIN BIOPSIES IN STABLE EARLY STAGE MYCOSIS FUNGOIDES VERSUS LATER TUMOR-STAGE

Ulrike Wehkamp[1], Ilske Oschlies[2], Christian Kohler[3], Michael Weichenthal[1], Wolfram Klapper[2]

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Introduction and objectives

Mycosis fungoides (MF) is the most common cutaneous T-cell- lymphoma (CTCL) accounting for approximately 50% of all CTCL with a wide range of initial disease presentation and evolution over time. However, in early disease stages biomarkers as indicators of a later progression have not yet been identified.

Materials and methods

Our study cohort included 248 patients from the Department of Dermatology, University Kiel, (1995-2015). 173 patients were identified with confirmed parapsoriasis en plaques (PP) or MF. All patients were staged retrospectively according to the latest EORTC-ISCLclassification in TNMB and clinical stages. Clinical course of disease was analyzed for every patient and only cases with either long-term stable stage MF or progression to tumor-stage MF were included in the evaluation. Initial biopsies that were obtained at the time of first diagnosis/disease presentation were analyzed. We identified 17 patients with stable disease MF ('MF stable') defined as T1aN0M0B0 or PP over a period of more than 5 years and compared to 20 patients with later evolution to tumor-stage MF ('MF tumor') for histological features. A subgroup of 11 selected biopsies of each group and 2 control biopsies of normal skin with sufficient material available for molecular analysis were used for gene expression profiling for 770 different genes related to immunological mechanisms and cancer (Nanostring/nCounter) with a protocol optimized for formalin fixed paraffin embedded tissue.

Results

The histopathological comparison of the two groups revealed higher infiltrate density and depth, a higher amount of blasts and higher proliferative index for the 'MF tumor' group. The gene expression profiling identified 16 genes with a statistically significant differential expression between 'MF stable' and 'MF tumor' specimen ($p \leq 0{,}05$). One of the differentially expressed genes was CD207 (langerin), a protein specifically expressed in Langerhans cells. Semiquantitative analysis of immunohistochemistry for langerin in fact confirmed a higher number of Langerhans cells in lesions of 'MF stable' compared to 'MF tumor'.

Conclusion

We identified genes in initial biopsies of MF that differ between diseases with a long stable course and those with progression to a tumor stage. Our data might provide future perspectives for routine diagnostic biomarkers that could guide clinical follow-up andtreatment recommendations. Further validation of our results in an independent cohort is required.

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14:21-14:30

MYCOSIS FUNGOIDES: NEW ISSUES FROM MICROENVIRONMENT?

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[4] Section of Pharmacology, Department of Experimental Medicine, Pharmacoepidemiology and Pharmacovigilance Centre of the Campania Region, Second University of Naples, Italy

Introduction and objectives

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL). Clinical outcome is stage-related: while early stages show an indolent behaviour, the disease become aggressive in advanced ones. Tumour immune escape response mechanisms are well-known strategies involved in tumour growth and metastasis in many neoplasms as melanoma, lung and breast cancer. Many cytokines and cells are involved in tumour spread as plasmacytoid dendritic cells (pDCs), T-Reg lymphocytes, Langerhans cells (LC), myeloid derived suppressor cells (MDSCs) and macrophages. However, little is known in CTCL. Our aim is to evaluate, LC, pDCs as well as MDSCs distribution in early and advanced MF lesions.

Materials and methods

Sixty-eight MF cases in various disease stages (26 IA/B, 22 IIB, 5 IIIA, 7 IIIB and 8 IVA stage) from databases of Turin, Bologna and Florence Cutaneous Lymphoma Units were retrieved. In order to investigate LC, pDCs and MDSCs distribution, sections were cut from the blocks and placed on electrically charged slides. They were tested with specific antibody against Langherin, CD303 as well as Arginase.

Results

Preliminary data seem to suggest that Langherin expression decreases from early to advanced stages, while CD303 and Arginase do not show substantial changes from a statistic point of view. Furthermore, in early stages Langherin seems to be related to patients' age.

Conclusion

Our data are in line to those reported by Schwingshackl et al, that showed an increased number of CD303+ cells in MF lesions compared to healthy donor ones. However, no correlation between CD303 expression intensity and MF stage was observed. In agreement with Schwingshackl et al and Luftl et al, in our cases we observed a decrease in Langherin expression from early to advanced lesions. For the first time, we analysed

MDSCs distribution in MF. No significant changes in Arginase distribution was observed. This finding seems to suggest that MDSCs are not involved in MF progression. Moreover, our data contribute to deeper investigation of the relationships between MF cells and microenvironment, in order to develop tailored therapies.

ABSTRACT SESSION II

Saturday 23 April
12:30 – 13:15

NEW INSIGHTS INTO CUTANEOUS LYMPHOMAS II

Moderators
Antonio Cozzio, Robert Knobler, Pablo Ortiz-Romero

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12:30-12:39
MIR-155 EXPRESSION IN PRIMARY CUTANEOUS T CELL LYMPHOMAS (CTCL)

P. Fava, C. Astrua, M. Bergalloʃ, M. Brizio, I. Galliano, P. Montanari, V. Daprà, M. Novelli, P. Savoia, P. Quaglino and MT. Fierro.
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Introduction and objective
Mycosis Fungoides (MF) and Sézary Syndrome (SS) are the most frequent cutaneous T-cell lymphomas (CTCL). MicroRNAs are a class of short length double strand genome-encoded RNAs produced to repress post-transcriptionally the expression of cellular mRNAs. In this study we performed miR-155 analysis on blood samples of MF and SS patients to evaluate the miR-155 expression in CTCL.

Materials and methods
Peripheral blood mononuclear cells from 50 MF/SS patients were analysed; total RNA was extracted and amplified with RT-PCR. Results were compared with those obtained in a cohort of 20 healthy donors.

Results
miR-155 resulted significantly over-expressed in SS patients when compared with healthy donors (p 0.0004) and MF. No differences in the overall amount of miR-155 were found in MF vs healthy subject.

Conclusion
These data suggest that microRNAs are involved in SS pathogenesis and could provide new options for disease diagnosis and for clinical outcome definition.

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12:39-12:48
TOX1 EXPRESSION IN MYCOSIS FUNGOIDES CASES

A. Iliadis[1], T. Koletsa[1], A. Patsatsi[2], E. Georgiou[3], I. Kostopoulos[1]
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[3]*Cutaneous Lymphoma Clinic, Papageorgiou' General Hospital, Thessaloniki, Greece*

Introduction and objectives

Recently it has been reported that the thymocyte selection-associated high mobility group box family member 1 protein (TOX1) is expressed in mycosis fungoides (MF) T-cells, even in early stages, and it is thought that this may prove useful for MF diagnosis and management in the future. The purpose of this study was to investigate TOX1 protein expression in MF cases immunohistochemically as well as its possible association with disease stage and patient outcome.

Materials and methods

From 34 patients having been diagnosed with MF 37 paraffin blocks containing formalin-fixed skin specimens were included in the study. Specifically, 1 patient had folliculotropic MF, 5 patients were erythrodermic, 12 in patch stage, 15 in plaque stage, and 1 patient contributed both specimens from tumor stage and large cell transformation. All but 4 had a CD4+ immunophenotype. Clinical data were available for 13 patients. Seven of them responded to treatment and 6 had partial or no response. TOX1 immunostaining was performed. Lymphocytes with TOX1 nuclear positivity were counted as a percentage of the total lymphoid cell population in the dermis. TOX1+ cells in the epidermis were classified as none, few solitary or many.

Results

Dermal TOX1+ cells were found even in small number in all cases, but positivity in three of the specimens was <5%. Thirteen of the cases showed ≤20% of the total lymphoid cell population, while in 21 cases the percentage was >20%. In CD8+ cases a TOX1 positive dermal T-cell population was observed and seems to belong to reactive T4 cells. Almost 50% of the cases presented many intraepidermal TOX1+ cells. The highest positivity percentage was observed in tumor stage and transformation, although there was no association between TOX1 expression and the clinical presentation or the stage. However, two of the three cases with no response showed TOX1 expression in >20% of the neoplastic population (x^2, p=0.012). No significant differences in staining intensity were found between cases in different stages.

Discussion

TOX1 is expressed in CD4+ MF neoplastic population of the dermis and epidermis, in Pautrier microabscesses. Reactive CD4+ cells are immunoreactive to TOX1 in CD8+ MF. TOX1 protein level overexpression is found in cases with adverse prognosis. Further investigations are needed to confirm this preliminary data and reach safe conclusions.

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12:48-12:57

EPSTEIN BARR VIRUS-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA OF THE ELDERLY WITH SKIN AND BRAIN INVOLVEMENT: CLINICOPATHOLOGICAL FEATURES AND GENOMIC ANALYSIS

Alberti-Violetti S[1], Bernareggi S[2], Bonometti A[3], Venegoni L[4], Merlo V[1], Onida F[5], Berti E[1,2]

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Introduction

Epstein Barr Virus (EBV)-positive diffuse large B cell lymphoma (DLCBL) is a rare lymphoma which by definition affects elderly patients (over 50 years), without previous immunosuppression, and is characterized by detection of EBV infection in tumor cells. It is more frequent in Easter than in Western populations. Clinical features include lymphadenopathy, B-symptoms and extranodal involvement, usually skin, lung, tonsils and stomach. Histologically, large atypical pleomorphic lymphocytes, expressing B-cell markers, are mixed to reactive cells.

Materials and methods

We collected a case of 65-year-old woman with an ulcerated tumor on the left leg, developed during the last 3 months and histologically diagnosed as DLCBL. In the past, she was discontinuously treated with oral cyclosporine and methotrexate for a diffuse dermatitis. Because of a short episode of aphasia and syncope, a computed tomography scan of the brain was performed, showing an intracranial mass in the occipital region. Histologically, a diagnosis of cerebral DLBCL was made. Both biopsies were evaluated by in situ hybridization (ISH) for EBV. Genomic analysis was performed by array genomic comparative hybridization (aCGH) on DNA extracted by skin biopsy.

Results

ISH showed the presence of EBV in both specimens. Genomic profile was different from that of DLCBL, showing a peculiar profile. The patient started a multi-agent chemotherapy but unfortunately died for acute respiratory distress syndrome.

Conclusion

This is an interesting and rare case of EBV positive DLCBL, showing skin and brain involvement.

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12:57-13:06

TNM CLASSIFICATION IN PRIMARY CUTANEOUS B-CELL LYMPHOMA – T CLASSIFICATION LACKS PROGNOSTIC VALUE

Chan SA, Shah F, Chiganti S, Stevens A, Amel-Kashipaz R, Vydianth B, Scarisbrick JJ
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Introduction and objectives

Primary Cutaneous B-Cell Lymphomas (CBCL) are rare with an estimated annual incidence of 2-2.5 per 1,000,000 persons1. Their management and prognosis varies significantly from systemic lymphomas and is now better understood with the introduction of the World Health Organisation – European Organisation for Research and Treatment of Cancer (WHO-EORTC) Classification in 20052. In 2007 a TNM classification system to include all primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome was proposed by

the EORTC Cutaneous Lymphoma Task Force and International Society of Cutaneous Lymphomas (ISCL). We present the subtypes. T classification, treatment and outcomes of patients with CBCL from our region.

Materials and methods

All patients diagnosed with CBCL were identified from our cutaneous lymphoma database. These patients were either referred directly from primary care to our tertiary centre or referred from other dermatology departments within the region. Diagnoses were confirmed at our multidisciplinary cutaneous lymphoma meeting with the aid of immunohistochemistry, clonality and radiology. Patients without a confirmed clinicopathological diagnosis were excluded. All patients' histology were reviewed by 2 independent histopathologists.

Results

We identified 44 patients with primary cutaneous CBCL (23 females, 21 males) with histological subtypes: Marginal Zone B-Cell Lymphoma (MZL) (n=20) ; Follicular B-Cell Lymphoma (FCL) (n=19) and Diffused Large B-Cell Lymphoma (DLBL) (n=5). The mean age at diagnosis for patients with MZL, FCL and DLBL were 50.1, 60.4 and 64.6 years old respectively. Their cumulative mean age at diagnosis was 56.2 years old (range 22-90yrs).

Patients with MZL presented with lesions on the head and neck region (n=5), trunk (n=9), upper limbs (n=9) and lower limbs (n=3). T classification at diagnosis was T1a (n=12), T1b (n=2), T2b (n=1), T3a (n=3) and T3b (n=2). 8/20 patients received first line expectant therapy, 2 patients received Dermovate, 9 radiotherapy and 1 received phototherapy. Eight patients had one or more cutaneous recurrences with T classification of T1a (n=4) and T3 (n=4) during a mean follow-up of 5.5years (range 1-13yrs). There were no lymphoma specific deaths.

Patients with FCL presented with lesions on the head and neck region (n=6), trunk (n=10), upper limbs (n=4) and lower limbs (n=1). One patient in this cohort also had concurrent mycosis fungoides receiving systemic treatment with interferon-alpha and bexarotene. T classification at diagnosis was T1a (n=16) and T1b (n=3). During mean follow-up of 5.5 years (1-15yrs) there were 4 cutaneous recurrences but no nodal or metastatic spread; 2 patients died neither from systemic progression of lymphoma. Of note 5/19 patients had secondary cutaneous malignancies including BCC (n=3) and SCC (n=2).

Patients with primary cutaneous DLBCL presented with lesions on the lower leg (n=3), head and neck (n=1) and forearm (n=1). T classification at diagnosis was T1a (n=2), T1b (n=1), T2b (n=1) and T2c (n=1). All 5 patients received systemic chemotherapy (3 with CHOP-R) and 3 received further courses of chemotherapy during 2.5year mean follow-up, one patient died from systemic spread of lymphoma (T2c) 12 months from diagnosis.

Conclusion

It is well recognised patients with MZL and FCL have a good prognosis. No patients at our centre developed nodal or visceral spread but cutaneous relapse was frequent. DLBCL patients have a worse prognosis and may succumb to systemic disease. TNM classification in cancers is generally used to stratify patients for prognosis and used to decide treatments. In our CBCL cohort T classification did not have any prognostic value for survival nor predict cutaneous recurrences which were as common in T1 compared to T2-3. We propose prospectively studying prognostic factors in CBCL to further improve TNM classification.

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13:06-13:15

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA: PROGNOSTIC IMPACT OF THE ISCL/ EORTC T-CLASSIFICATION FOR NON-MF CUTANEOUS LYMPHOMAS

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Introduction and objectives

Primary cutaneous follicle center lymphomas (pcFCL) belong to a group of indolent non-Hodgkin B cell lymphomas. Their clinical appearance as well as their prognosis favorably differs from nodal disease and is mostly treated by local means only resulting in a long term complete remission in most of the cases. However, a proportion of patients will present with relapsing cutaneous disease. The International Society of Cutaneous Lympoma (ISCL)/European Organization for Research and Treatment of Cancer (EORTC) have published a proposal for TNM stages in primary cutaneous lymphomas other than Mycosis fungoides/Sézary syndrome.

Materials and methods

In an attempt to validate the prognostic value of the ISCL/EORTC T stage classification, a single center cohort of 29 patients (11 females, 18 males) where classified accordingly with 16 cases belonging to T1a (single lesion <5cm), 9 cases T2a (regional dissemination <15cm), 2 cases T2b (regional dissemination 15-30 cm), and one case each T3a (generalized, 2 body regions) and T3b (generalized, >2 body regions). All cases were N0 M0 B0, as by definition of primary cutaneous B cell lymphomas.

Results

After a mean follow-up of 5.7 years relapses occurred in 13 (44.8 %) patients. All relapses were limited to the skin. There were no systemic progressions or lymphoma related deaths. Cases with initial T1a lesions were significantly less likely to relapse than cases with T2 or T3 disease (25.0% vs. 69.2%). Among those with limited disease, all relapse occurred in patients treated by initial surgery only.

Conclusion

The ISCL/EORTC proposal for the T-classification of non-MF cutaneous lymphomas showed significant prognostic value on relapse free survival in a single center cohort of pcFCL.

Dinner venue

Coach transport from EORTC HQ to restaurant:
Shuttle will leave the EORTC around 18h45

Aux armes de Bruxelles
13 rue des Bouchers, 1000 Bruxelles

Métro : De Brouckère or Gare Centrale (Lines 1-3-4-5)
Phone number : 00 32 (0)2 511 55 98/50

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