**Immunodeficiency lymphoma**

483  **EPSTEIN-BARR VIRUS (EBV) DNA MONITORING BY QUANTITATIVE REAL-TIME POLYMERASE CHAIN REACTION IS A USEFUL SURROGATE MARKER OF DISEASE ACTIVITY IN BOTH MONOMORPHIC AND POLYMORPHIC POST TRANSPLANTATION LYMPHOPROLIFERATIVE DISEASE (PTLD)**

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**Background:** PTLD is a rare but aggressive complication of solid organ transplantation. Epstein-Barr virus (EBV) reactivation is predictive for development of PTLD. Monitoring of EBV DNA levels post-transplant allows for early pre-emptive immuno-modulation for high-risk patients (pts), and also assists in diagnosis of PTLD in symptomatic pts. There is however a paucity of data on the utility of EBV DNA levels to follow disease activity once PTLD has been diagnosed.

**Aims:** To evaluate the role of EBV DNA levels as a surrogate marker of disease activity in PTLD.

**Methods:** Consecutive patients with newly-diagnosed PTLD at a major transplant centre were prospectively followed with serial EBV viral load monitoring using a quantitative real-time polymerase chain reaction (PCR) targeted at the conserved region of EBNA-1 gene of EBV from whole-blood samples. The tests were paired and correlated with imaging studies done at diagnosis, for assessment of response (by IWG criteria) and upon relapse of disease.

**Results:** From 2005-2010, a total of 11 pts with newly-diagnosed PTLD post-renal transplantation were included. The mean age of pts was 59 years. Histology was centrally reviewed for consistency according to WHO 2008 classification of PTLD. Of these, 9 pts had monomorphic PTLD (8 with diffuse large B-cell lymphoma [DLCL], 1 peripheral T-cell lymphoma [PTCL]), while 2 had CD20 negative polymorphic PTLD. 8 pts with EBV-associated PTLD (based on histological staining for EBER and LMP1) had elevated EBV DNA titters at diagnosis. Among 3 pts with EBV- negative PTLD, 2 pts (DLCL) had negative EBV DNA titters while 1 (PTCL) had detectable levels at diagnosis. Treatment which included the tapering of immunosuppression, rituximab and CHOP chemotherapy was administered at the discretion of the treating physician. At a median follow-up of 8.4 months, 8 of 11 patients had achieved complete remission, and there were 3 relapse/regression events documented by CT or PET imaging. The negative predictive value of a normal EBV DNA titer with CR was 0.88, while the positive predictive value of a reappearance of an elevated EBV titer after achieving a response was 1. A diminution of EBV titters correlated with partial responses at interim staging.

**Conclusion:** In our patients with a positive EBV DNA at diagnosis, monitoring these levels accurately predicted clinical response for all entities of EBV-associated PTLD. Larger studies are needed to show whether this approach translates into a meaningful clinical standard.

484  **AGE-RELATED EBV-ASSOCIATED LYMPHOPROLIFERATIVE DISORDER – A CLINICOPATHOLOGICAL SPECTRUM**


**Background:** We describe a series of age-related EBV-associated lymphoproliferative disorders (AR-EBVLPD). This spectrum of reactive hyperplasia, indolent "EBV-positive mucocutaneous ulcer" (EBVMCU) and aggressive B-cell lymphoma is underreported.

**Patients and Methods:** Cases were identified from files of the All Wales Lymphoma Panel and studied by immunochemistry, EBER in situ hybridisation and PCR for IgH/TcR clonality.

**Results:** 14 patients (8 male, 3 female; median age 76y, range 68-82) were classified as 2 EBVMCU, 4 polymorphic B-cell lymphomas (Poly-BCL) and 8 diffuse large B-cell lymphomas (DLBCL). EBVMCU were circumscribed tongue lesions. Poly-BCL and DLBCL presented with lymphadenopathy (7), thyroid (1), stomach (1), bone marrow (1) or brain involvement (1) (stage I-FV (8%-50%)). 75% had B-symptoms. EBVMCU and Poly-BCL showed Hodgkin-like and PTLD-like histological features, respectively. 37% of DLBCL were of NOS type and 63% were Hodgkin-like. 79% showed non-germinal centre phenotype. 14% co-expressed CD30 and CD15. EBER was absent in all cases. 87% (7/8) had clonal IgH rearrangements. 50% (3/6), 17% (1/6) and 33% (2/6) showed polyclonal, clonal and restricted T-cell patterns, respectively. Of 2 EBVMCU, 1 had a complete response to interferon-α-2b. In the second, the ulcer regressed spontaneously but died directly after with donally unrelated EBV-negative CNS DLBCL. Patients with Poly-BCL and DLBCL received chemotherapy with CVP (3), R-CVP (4), R-GCVP (1), R-CHOP (1), CCEP (1) and high dose methotrexate (1), combined with radiotherapy in 3 cases. 1 patient received supportive care only. 2 (17%) achieved complete remission, 6 (50%) partial remission and 4 (33%) progressed. 6 (50%) died of disease, 1 (8%) died of unrelated causes and 5 (42%) are alive (median follow up 4 months (range 2-14)).

**Conclusion:** Indolent EBVMCU may respond to conservative and immunomodulatory treatment. Age-related Poly-BCL and DLBCL are aggressive lymphomas responding poorly to conventional therapy. Restricted and clonal T-cell responses suggest defective T-cell surveillance of EBV due to immunosenescence. Novel approaches including adoptive immunotherapy with EBV-specific allogeneic cytotoxic T-cells should be considered.

485  **EBV POSITIVE MUCOCUTANEOUS ULCER – A NOVEL IMMUNOSUPPRESSION-ASSOCIATED LYMPHOMA-LIKE ENTITY REQUIRING CONSERVATIVE MANAGEMENT**

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**Background:** We describe a series of Epstein-Barr virus (EBV)-positive mucocutaneous ulcers (EBVMCU) associated with immunosuppression (IS) of different causes. Clinical course is indolent but historically patients have received aggressive treatments for lymphoma. Material and methods: Cases were identified from files of the All Wales Lymphoma Panel and studied by immunochemistry, EBER in situ hybridisation and PCR for IgH/TcR clonality.

**Results:** The study group comprised 8 patients (4 males, 4 females), median age 74 years (range 52-84). 6 received IS with azathioprine, methotrexate or cyclosporin-A for ulcerative colitis (1), autoimmune hepatitis (1), rheumatoid arthritis (2) or post transplant setting (2). 2 had age-related immunosenescence. Patients presented with sharply circumscribed, solitary and localised ulcers in skin (2), oropharynx (3) and colon (3). 1 had a concomitant lung lesion. The same Hodgkin-like histological features were seen regardless of etiology or site of presentation. The atypical B-cell blasts showed strong CD30 and EBER positivity in a background of abundant T cells. 43% (3/7) co-expressed CD5 and CD30. PCR revealed 75% (3/4) clonal IgH rearrangements with 25% (1/4) and 75% (3/4) of clonal and restricted T-cell patterns, respectively. 6 patients with iatrogenic IS were treated with reduction of IS, one having had hemi-nectectomy for suspected lymphoma. 1 patient addition received chlorambucil. 2 post transplant cases also received rituximab. 5 of 6 iatrogenic cases had a complete treatment response and are alive without disease (median follow up 8 months (range 3-24)). 1 patient showed regression of ulcer but died of unrelated causes. Of 2 age related cases, 1 had a complete response to interferon-α-2b. In the second, the ulcer regressed spontaneously but he died shortly after with clonally unrelated EBV-negative CNS DLBCL.

**Conclusion:** EBVMCU is a new clinicopathological entity with Hodgkin-like features and indolent clinical course, responding well to conservative management and reduction of IS in iatrogenic cases. In patients with age-related immunosenescence, immunomodulatory treatment may be beneficial. Restricted and clonal T-cell responses point to abnormal T-cell surveillance of EBV.


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**Introduction:** Lymphomatoid granulomatosis (LG) is a rare, EBV-associated B-cell lymphoproliferative disorder. Treatment that includes...
corticosteroids, chemotherapy, interferon-alpha and Rituximab only shows modest results.

**Patients and Methods:** To describe the results of intensive therapy and stem cell transplantation (SCT) in patients with LG, a retrospective survey was conducted among centers belonging to the EBMNT. As LG is not reported as a histological entity to the EBMNT database, a questionnaire was sent to the centers identifying 9 patients (8 ASCT, 1 allo-SCT). In addition, we collected follow-up data of a patient with LG, who was sent a case report (Lemerieux et al., Hematology 2002 Vol 7 (6), pp. 355-358).

The patient cohort finally consisted of 5 males and 4 females with a median age of 41 (range 14–52) years. Two patients had localized disease (stage I-II), 8 patients had stage IV disease. The lungs were the most frequently involved extranodal site (8 patients).

**Results:** Nine patients had received ≥ 2 lines of therapy before SCT including Rituximab in 6 patients, the median time interval from diagnosis to SCT being 10 (range 5–52) months. All patients had active disease at the time of SCT; 7 patients had a partial remission, 2 had stable disease and 1 progressive disease (PD). Seven of the 9 ASCT patients were conditioned with the BEAM regimen, 1 patient with thiopeta, melphalan and carboplatin and the remainder with fludarabine, busulphan and cyclophosphamide. A reduced intensity-conditioning regimen (fludarabine and alkylating agent) was used prior to allo-SCT. One ASCT patient died of NRM (S. salvator) at day 7, 1 patient died of acute leukemia at autograft. No patient except for allograft disease-free 19 months after SCT and 1 patient died of PD 10 days post ASCT. The remaining 7 patients (6 ASCT, 1 allo-SCT) are alive and disease-free with a median follow up of 43 (range 25–57) months.

**Conclusions:** Hematopoietic SCT shows very promising results for patients with relapsed LG.

**487 NON HODGKIN LYMPHOMA IN HIV PATIENTS – SINGLE INSTITUTION EXPERIENCE**

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**Introduction/background:** The aim of this study was to evaluate characteristics of patients with HIV related lymphoma (HRL) treated in Clinical Center Belgrade.

**Material and methods:** A retrospective study of 25 patients with HRL treated between January 2000 and December 2010 was conducted.

**Results:** Diffuse large B cell lymphoma (DLBCL) was the most observed histological type (72%) while Burkitt lymphoma was diagnosed in 28% patients (p<0.05). The median CD4 lymphocyte count at lymphoma diagnosis was 178 cells per microliter while median LDH level was 561 U/L. Significant differences in LDH level between histological subtypes of lymphoma was not observed. HAART was applied in median LDH level was 581 U/L. Significant differences in CD4 count and LDH level were observed between histological subtypes of lymphoma (p=0.62). Also, patients on HAART regimen with Burkitt lymphoma had higher LDH levels than other subtypes. HAART was given to 19 patients, and 6 patients were on HAART and HAART-free regimens. Median time of follow up of 43 (range 25–57) months.

**Conclusions:** Our results showed that the reduced OS observed could be explained by poor immune status seen in our population of HIV-positive patients.
on treatment with ARV. The mean CD4 count was 31.2%, with a mean viral load of 220,124 copies (0-7,561,180). 51(86.4%) had stage 3 or 4 disease; 21(35.5%) had extramedullary disease at presentation and 8(13.5%) had performance status of 3 or 4. 48(90.5%) were receiving ARV at the completion of chemotherapy. 3 patients died during treatment and 6 patients were lost to follow-up. 48(90.5%) achieved a complete remission and 45(84.9%) were alive at a median follow up of 854(0-4184) days.

Conclusion: A high proportion of patients with lymphoma in our catchment area were found to be HIV positive at presentation, and HIV screening should become mandatory for all newly diagnosed cases of lymphoma. Patients on ARV are still at significant risk of developing lymphoma in spite of low viral copy number and high CD4 counts. ARV treatment with standard dose chemotherapy can be given with high RR and expectation of prolonged free OS.

Shared care and management plans between HIV specialists and Haematologists is crucial for this outcome.

491 LONG-TERM FOLLOW-UP OF RITUXIMAB AND INFUSIONAL CYCLOPHOSPHAMIDE, DOXORUBICIN AND ETOSPODPIDE (CDE) IN COMBINATION WITH HAART IN HIV-RELATED NON-HODGKIN’S LYMPHOMAS (NHL)


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Background: The combination of Rituximab plus chemotherapy (CT) is more effective than CT alone in the treatment of high grade NHL. Objective: To report the long-term follow-up of CDE plus Rituximab in HIV-NHL.

Method: In June 1998, we started a phase II study using infusional CDE (Cyclophosphamide 187.5 mg/m2/day, Doxorubicin 12.5 mg/m2/day and Etoposide 60 mg/m2/day) administered by continuous intravenous infusion for 4 days every 4 weeks and Rituximab 375 mg/m2 i.v. on day 1. HAART was given concomitantly with CT.

Results: Seventy-four patients (pts) have been enrolled. The median CD4+ cell count was 161 (range 3-691) and the median Performance Status was 1 (range 0-3). Diffuse large B-cell NHL was diagnosed in 72% of pts and Burkitt in 28%. Seventy seven cent of pts had advanced stage (III-IV) disease and 57% of pts had an age-adjusted international prognostic index >2. Fifty-two out of 74 pts (70%) achieved a complete remission (CR), 47 (63.5%) had a partial remission and 18 pts progressed. With a median follow-up of 61 months, only 17% of CRs have relapsed and 47/74 pts are alive. The overall survival, disease free survival and time to treatment failure (TTF) at 5 years were 56%, 81% and 52%, respectively. Four cases of secondary tumours have been observed. No case of late pulmonary or cardiac toxicity has been reported.

Conclusion: The combination of Rituximab and CDE in HIV-NHL treated concomitantly with HAART is very active. CR rate (70%) and TTF at 5 years (52%) are comparable to those observed in high grade NHL of the general population. Our data support the use of adequate prophylaxis. Liposomal cytarabine has shown a significant activity in lymphomatous meningitis, but there are limited data in HIV prophylactic setting.

493 HODGKIN’S DISEASE AND HIV INFECTION (HD-HIV): PROGNOSTIC FACTORS IN 596 PATIENTS (PTS) WITHIN THE EUROPEAN GROUP FOR THE STUDY OF HIV AND TUMOURS (GECAT)


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Background: Hodgkin’s disease (HD) is the most common non-AIDS defining tumour diagnosed in HIV setting. The introduction of highly active antiretroviral therapy (HAART) has opened a new prospective in the treatment of pts with HD-HIV as the better control of the underlying HIV infection allows the use of more aggressive chemotherapy regimens, including high dose chemotherapy. However, up to now prognostic factors on overall survival (OS) or time to treatment failure (TTF) have not been identified yet.

Methods: in order to identify prognostic factors, we analyze data on 596 pts with HD-HIV diagnosed and treated in 90 different Institution from 6 European countries from October 1983 to March 2010. All factors were analyzed for OS and TTF.

Results: 86% of pts were male and the median CD4 cell count was 224/dl (range 3-1274); 52% of pts had mixed cellularity subtype, stages III-IV were diagnosed in 72% of cases and 55% of pts had extranodal involvement (bone marrow 35%, spleen 21%, liver 14%). Table 1 summarized the results of multivariate analysis.

Conclusion: We identified a new “European Score” for HD-HIV able to predict different outcomes in these patients. This score should be considered for future prospective studies.