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Other meeting abstracts

Extranodal lymphomas

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Intravascular large B-cell lymphoma: clinicopathological study of seven cases

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Introduction: Intravascular large B-cell lymphoma (IVLBL) is an extremely rare, aggressive and usually disseminated extranodal lymphoma characterized by the growth of neoplastic B lymphocytes almost exclusively within the blood vessel lumen. The diagnosis of IVLBL is usually delayed, frequently made post mortem, sometimes from surgically removed organs because of enlargement or for unrelated clinical problems. Usually the prognosis is poor, some case reports and few larger studies suggest benefit from the use of Rituximab+ CHOP (R-CHOP) improving the overall survival.
Results: We report seven cases of IVLBL diagnosed in our department in the last ten years: 4 males, 3 females, median age 71 year. The diagnosis were made from biopsy specimens in all cases; two patient had cutaneous involvement, three patient were diagnosed from bone marrow biopsies taken becase of cytopenia and two diagnosis were made incidentally from surgically removed specimens: one patient was operated with prostate hyperplasia and the other with hypophysis adenoma. All patients were treated with R-CHOP. The overall median survival is 30 months, two patients are alive in complete remission after 46 and 48 months, one of them had systemic disease. The relapse in one case was diffuse large B-cell lymphoma clonally related to the primary IVLBL. Detailed immunohistochemical examination revealed non-germinal center origin in five cases.
Conclusion: The histology and immunophenotype of our series of IVLBL were similar, R-CHOP therapy resulted prolonged survival in cutaneous forms and systemic IVLBL as well.

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Primary dural lymphoma: One center's experience

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Primary dural marginal zone B-cell lymphoma (PDMZBL) is rare. Optimal therapy of this lymphoma is discussed. We present the clinicopathologic features and the result of the therapy of 4 patients with PDMZBL treated at our institution from May 2006 to Dec 2009. There were 2 women and 2 men. The mean age at presentation was 47 years (38–52 years). All patients presented with headaches, focal motor deficits, or cranial nerve palsy. Radiologic studies demonstrated well-defined dural cranial mass in 3 and dural spinal mass in 1 patient. Before hospitalization all patients underwent surgical treatment by different reasons (proposal diagnosis – meningioma in 3 and hematoma in 1 case). Pathology revealed small to medium size cells, expressing pan B-cell markers (CD19, CD20 and CD79) but lacking CD10, CD23 and cyclin D1, confirming low-grade MALT lymphoma. Fluorescent in situ hybridization study showed trisomy 3 chromosome in 2 cases. Magnetic resonance imaging revealed residual postoperative tumor mass in all cases. All patients were treated by chemotherapy (4 courses FMCR – fludara 25 mg/m2 i/v 1–3 d, mitoxantrone 10 mg/m2 i/v 1 d, cyclophosphane 200 mg/m2 i/v 1–3 d, rituximab 375 mg/m2 i/v 0 d). All patients achieved complete remissions. Severe complications were not registrated. None of the patients received consolidative radiotherapy. The mean follow-up is 23 months (range 2–39). No relapses have been registered so far.
Conclusion: FMCR chemotherapy is highly effective in PDMZBL. Additional study and longer follow-up are needed to determinate advantage of surgery and radiotherapy.

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Detection of hypermethylation of tumor suppressor genes in ocular adnexal lymphoma using multiplex ligation-dependent probe amplification

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Ocular adnexal lymphomas (OAL) occur in the orbit, lacrimal gland, conjunctiva and eyelid. OAL comprise 8% of all extranodal non-Hodgkin lymphomas (NHL). Extranodal marginal zone B-cell lymphomas (EMZL) are the commonest subtype. Silencing of tumour suppressor genes (TSGs) by promoter hypermethylation has been observed in various tumours, including NHL. To determine if hypermethylation plays a role in OAL development, we examined the promoter methylation status of 36 candidate TSGs in OAL by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) using the ME001 and ME002 assays (MRC-Holland). DNA was extracted from 70 formalin-fixed, paraffin-embedded OAL samples using the Qiagen DNeasy Blood and Tissue kit. Thirty-three EMZL and 37 non-EMZL OAL samples (15 follicular, 13 diffuse large B-cell (DLBL), 6 mantle cell lymphoma (MCL), 2 plasmacytoma and 1 primary T-cell lymphoma) were examined. MLPA peak heights were assessed by capillary electrophoresis using the 3130 Genetic Analyser (Applied Biosystems). Results were

analysed using Excel spreadsheets designed by the National Genetics Reference Laboratory. The 10 most frequently hypermethylated TSGs were the same for EMZL, DLBL and MCL, suggesting a similar epigenetic aetiology. These genes were CDH13, DAPK1, ESR1, GATA5, IGSF4, PAX6, RAR-β, THBS1, TIMP3, and WT1. Patient prognosis is poorer when the OAL develops in the orbit. We hypothesized that more aggressive lymphomas would show greater epigenetic deregulation. For non-EMZL OAL, a greater number of genes showed hypermethylation when the tumour was diagnosed in the orbit. However, it is interesting to note that the opposite was observed for EMZL. Hypermethylation of common TSGs suggests epigenetic deregulation may play a role in the development of OAL. Correlation of hypermethylation data with clinical presentation and follow-up could reveal epigenetic markers of prognostic value in these tumours.

Leukaemias

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BCR-signaling profiles associated with prognosis and progression in B-CLL

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Several biological parameters have been shown to be associated with clinical outcome in CLL. Among them, the most reliable markers are represented by the absence of somatic mutations within the immunoglobulin variable heavy chain genes (IGHV), the expression of CD38 antigen, the presence of the ZAP-70 tyrosine kinase. These parameters of poor clinical outcome are structurally and/or functionally linked to B-cell Receptor (BCR) expressed by CLL cells, thereby strengthening the hypothesis that antigenic stimulation mediated by the BCR represents a driving event in the onset and progression of the malignant B cells. To investigate whether different BCR signaling networks may distinguish clinical-biological groups of CLL patients, we applied a "network level" analysis of BCR signaling by measuring single-cell profiles of phosphoprotein networks by flow cytometry. We evaluated the response to BCR engagement in primary cells isolated from 27 CLL patients by analyzing the phosphorylation states of 5 phosphoproteins on the route of BCR signaling, including p-Syk, p-NF-kappaB, p-Erk1/2, p-p38 and p-JNK. BCR was cross-linked by incubating cells with anti-IgM antibodies. The unsupervised clustering analysis distinguished BCR response profiles of phospho-proteins that differentiated cases of CLL with mutated IGHV from those with unmutated IGHV ($P = 0.0003$), cases with low levels of CD38 expression from those with high levels ($P = 0.0004$) and cases with ZAP-70-negative leukemic cells from cases that were ZAP-70-positive ($P = 0.001$). Furthermore, the same BCR response profiles were also associated with time to progression ($P = 0.0014$) and with overall survival ($P = 0.049$), as assessed by Kaplan–Meier curves and the log-rank test. Independent survival analysis of time to progression via fitting Cox proportional hazards models comprising clinical covariates and/or BCR network response to modulation demonstrated that measuring modulated BCR network signaling can yield improved prognostic information compared to CD38 status alone (likelihood ratio test 5.8 for CD38 versus 10.6 for signaling) and enhance prognostic assessment using IGHV status (likelihood ratio test for IGHV = 14.8 versus for IGHV + signaling = 17.9).
This study shows that single-cell profiles of BCR phosphoprotein networks are associated with prognostic parameters, disease progression and overall survival in CLL.

Lymphomas and myeloma

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Cytomegalovirus (CMV) retinitis post rituximab therapy: A case report

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Rituximab, a chimeric monoclonal antibody against CD20 antigen is used in combination with chemotherapy to treat most B-cell non-Hodgkin's lymphoma. Several serious viral infections have been reported in association with rituximab use. We report a case of acute retinal necrosis secondary to cytomegalovirus (CMV) reactivation in a 59 year old male patient nine weeks following completion of six courses of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) and rituximab regimen for stage 3b diffuse large B-cell lymphoma. Diagnosis of CMV retinitis was confirmed on polymerase chain reaction (PCR) performed on vitreous fluid sample. Peripheral blood was negative for PCR amplified CMV deoxyribonucleic acid (DNA) in serum. While several infections have been reported in the literature, this is the first case report of CMV retinitis following rituximab therapy. In patients undergoing treatment with rituximab, the clinician should be vigilant of this rare but treatable cause of blindness. The case report and review of the literature are presented.

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Diffuse skin hyperpigmentation in CD30+ lymphoproliferation: A case report

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Introduction: CD 30+ T-cell lymphoproliferative disorders (LD) comprise two main groups of diseases: CD30+ LD of the skin and systemic anaplastic large cell lymphoma. The main feature of these disorders is the expression of CD30. We report on a patient with an unusual clinical presentation of CD30+ lymphoproliferative disease.
Case report: A 54-year old Caucasian male was transferred to our hospital with generalized lymphadenopathy and pronounced skin hyperpigmentation. At admission patient was anemic, with hepatosplenomegaly, generalized lymphadenopathy and with low performance status (ECOG 3). The most prominent feature was his skin color. Whole skin was purple-brownish, except his palms and soles, dry and atrophic with desquamation. He stated that his skin started to get brownish 18 months ago. In the lymph nodes and skin CD30+ lymphoproliferation – anaplastic large cell lymphoma – was diagnosed. Prussian blue staining identified that pigment, responsible for skin color, was hemosiderin. Chemotherapy was started but patient's condition was progressively worsening and he died a week after the first cycle.