poster session II
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pathology

266 A LYMPHOMA INFILTRATING THE SPLENIC RED PULP (SRP) INVOLVES THE BONE MARROW (BM) AND LIVER WITH INTRASINUSOIDAL LYMPHOMATOUS INFILTRATION (ISLI). A PROPOSAL FOR THE BLOOD DEFENSE SYSTEM (BDS) AND RELATED LYMPHOMAS

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Introduction: ISLI is a rare phenomenon observed in classical intravascular lymphomatosis (IVL) and an Asian variant of IVL (AIVL). We recently identified a primary splenic diffuse large B-cell lymphoma (DLBCL) originating from SRP (DLBCL-SRP) as a distinct clinicopathologic entity characterized by the involvement of the BM and liver with ISLI. We also found that ISLI was present in lymphomas diffusely infiltrating the SRP. To clarify the characteristic features of these lymphomas, we analyzed them clinicopathologically.

Patients: We collected lymphomas diffusely infiltrating the SRP; DLBCL-SRP, primary liver DLBCL infiltrating the liver sinusoids (DLBCL-Liver), DLBCL of the BM (DLBCL-BM), splenic marginal zone lymphoma (SMZL) and gamma/delta hepatosplenic T-cell lymphoma (HSTL).

Results: ISLI was observed in all the lymphomas infiltrating the SRP. They infiltrated the BM and liver, but rarely the lymph nodes (LN). The lymphoma cells of DLBCL-SRP, -Liver, -BM, and SMZL also infiltrated cords of the BM and portal areas of the liver. However, those of HSTL were restricted in sinuses of the liver and BM. The presence of ISLI and the involved sites; SRP, BM, and liver were the common features in this group of lymphomas. The SRP acts as a defense system for the blood against microorganisms. Macrophages in the sinus of the BM and liver also play a defensive role against pathogens in bloodstream. The SRP, BM, and liver might form a BDS. The BDS also has the capacity to induce hematopoiesis. Thus, the microenvironments of the BDS differ from those of the LNs and mucosa-associated lymphoid tissues.

Conclusions: ISLI is a common feature of BDS-derived lymphomas, which may form ISLI by different mechanisms of classical IVL. The AIVL might therefore be DLBCL originating from the BDS. In addition, the lymphoma cells involve other tissues of the BDS at the early stage of the disease.

267 RECURRENT GENOMIC ABERRATIONS DEREGULATING THE G1/S TRANSITION COMBINED WITH DELETIONS OF VARIOUS CANDIDATE TUMOR SUPPRESSOR GENES IN CD4+ CD56+ HEMATODERMIC NEOPLASMS CONTRIBUTE TO THE AGGRESSIVENESS OF THE DISEASE AND ITS FATAL OUTCOME

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CD4+CD56+ hematodermic neoplasm (HN) is a rare disease characterized by an aggressive behaviour and a poor prognosis. CD4+CD56+ HN cells represent the leukemic counterpart of the plasmacytoid dendritic cell. Despite the knowledge of the cell of origin of these tumors, the genetic causes and cascades of oncogenic events involved are still unknown. To delineate novel candidate regions and disease-related genes, we analysed CD4+CD56+ HN cases using genome-wide high resolution array-CGH.

Materials and methods: Genome-wide analysis of DNA copy number changes of 9 typical CD4+CD56 HN cases was performed using a high resolution CGH-array. A quantitative multiplex genomic PCR approach was designed to confirm CGH results and to compare gene copy number abnormalities with 11 monocytic variants of acute myeloid leukaemia (AML) cases.

Results: Genomic imbalances, predominantly losses, were constantly detected. The most frequent imbalances were deletions of chromosome 9, 13, and partial losses affecting 17p or 12p. Combination of heterozygous or homozygous deletions of tumor suppressorgenes (TSG), namely *RB1*, *CDKN1B*, *CDKN2A*, or *TP53*, located in commonly deleted regions, were observed in all cases. This genomic pattern was confirmed by PCR and was not observed in AML cases. In addition, deletions involving a large spectrum of TSG, such as *SLIT2*, *AUTS2*, *NF1*, *MSH5*, *HUS1*, *CDKN2D* or *RHOBTB2,* were detected. Furthermore, microRNA containing regions, including miR-15a, miR-16, were frequently involved.

Conclusion: Genes controlling the RB1/E2F pathway are constantly altered by deletional mechanisms in CD4+CD56+HN, a feature that distinguishes this disease from AML-4/5. Candidate genes, known to be involved in solid tumors and miRNA, are frequently deleted, contributing most likely to the chemoresistance observed after frontline therapy.

268 MOLECULARLY DEFINED SUBTYPES OF AGGRESSIVE B-CELL LYMPHOMAS ARE CHARACTERIZED BY DISTINCT CHROMOSOMAL ABERRATION PATTERNS APPLICABLE FOR DIAGNOSTIC CLASSIFICATION

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Introduction: Genetic profiling has significantly contributed the characterization of aggressive B–cell non-Hodgkin lymphomas. Molecular classification into molecular-Burkitt lymphoma (mBL), ABC or GCB like lymphoma has been recently proposed.

Material and methods: In the recently presented dataset of the German network project ''Molecular Mechanisms in Malignant Lymphomas'' we reanalysed 183 aggressive lymphoma samples for a correlation of chromosomal aberrations and molecular disease subtypes to clarify their importance as surrogate markers for a diagnostic classification.

Results: Using ArrayCGH, mBLs had significantly less chromosomal aberrations than non-mBLs (p=0.00014) and frequently showed gains of chromosome arm 1q. Within the non-mBLs group distinct aberration patterns for the subtypes GCB (gains on 1q, 2p, 12q) and ABC (gains on 3q, 18q and losses on 8p, 9p, 17p) were identified. Furthermore, IgH-BCL2 fusions were exclusively associated with the GCB subtype whereas mBLs showed a strong association with breaks of the MYC locus (88%). These aberration patterns were independently confirmed by unsupervised non negative matrix factorization (NMF). Using logistic regression on only five distinct aberrations (breaks on MYC, BCL2, BCL6; gains on 3q, 18q) we were able to build a genomic classification model for the diagnosis of the mentioned molecular subgroups. 113 samples carried a defined molecular diagnosis. 81 (72%) of these having at least one informative aberration and thus were classifiable. 31 of 35 mBL (89%) and 64% of the ABC samples (27/42) were classified accurately. Lowest concordance was seen in the GCB group (53%; 19/36). Overall, only 5% of these cases were classified incorrectly (n=4).

Conclusion: Disregarding unidentified molecular subclasses (type III or intermediate cases) genomic aberration patterns represent surrogate markers for the identification of distinct molecular subtypes in aggressive NHL. Due to the lack of informative genomic aberrations in a subgroup of cases, additional markers e.g. immunohistochemistry are needed for a clinically applicable classification model.

269 AN AGGRESSIVE VARIANT OF GERMINAL CENTRE DIFFUSE LARGE B-CELL LYMPHOMA CHARACTERISED BY ABORTIVE PLASMA CELL DIFFERENTIATION

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Diffuse Large B-cell Lymphoma (DLBCL) is classified by phenotype into germinal centre (GC) and activated B-cell (ABC) subtypes, with the GC type being regarded as having a favourable prognosis. However, the GC subtype is heterogeneous with regard to both phenotypic and genotypic characteristics and this may result in differences in clinical outcome. This point is illustrated by the following series of patients. The 7 patients presented acutely (5M:2F age 36-74); five with bone marrow replacement and two with generalised nodal and extranodal disease. Two patients had a preceding follicular lymphoma and a third patient had DLBCL with GC phenotype but without the additional characteristic described below. All of the tumours showed expression of CD19, CD10 and CD38 but with down-regulation of CD20, sIg and sCD79 and weak expression of CD22 and CD45. All cases showed absence of BCL6 with strong IRF4 and PRDM1. CD138, CD34 and TdT were not expressed. 6 tumours showed rearrangement of *cMYC* and in five cases a t(14;18) was present. 5 patients were initially treated with CHOP-R, one with CODOX-M IVAC and 1 with ALL induction. 6/7 have died with a median survival of 4 months (1.5- 9). The immunophenotype of these tumours strongly suggest they are derived from GC B-cells that have undergone partial

plasma cell differentiation. This is confirmed by the presence of a preceding 'conventional' GC lymphoma in 3 cases. Given the loss of pan-B cell markers it is important to distinguish these cases from acute lymphoblastic leukaemia, particularly in those presenting with bone marrow infiltration. These cases have a very poor clinical outcome and illustrate the need to consider additional phenotypic and genotypic prognostic factors within the GC type of DLBCL

270 PRIMARY CYSTIC LUNG LIGHT CHAIN DEPOSITION DISEASE: A CLINICOPATHOLOGIC ENTITY DERIVED FROM UNMUTATED B CELLS WITH A STEREOTYPED IGHV4-34/IGKV1 RECEPTOR

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We have recently described a new form of light chain deposition disease (LCDD) presenting as a severe cystic lung disorder requiring lung transplantation. There was no bone marrow plasma cell proliferation. Because of the absence of disease recurrence after bilateral lung transplantation and of serum free light chain ratio normalization after the procedure, we hypothesized that monoclonal light chain synthesis occurred within the lung. The aim of this study was to look for the monoclonal B-cell component in three patients with cystic lung LCDD. Histological examination of the explanted lungs showed diffuse non-amyloid k light chain deposits associated with a mild lymphoid infiltrate composed of aggregates of small CD20+, CD5-, CD10- B lymphocytes reminiscent of bronchus-associated lymphoid tissue. Using PCR, we identified a dominant B-cell clone in the lung in the three studied patients. The clonal expansion of each patient shared a unmutated antigen receptor variable region sequence characterized by the use of IGHV4-34 and IGKV1 subgroups with heavy and light chain CDR3 sequences of more than 80% amino acid identity, a feature evocative of an antigen-driven process. Combined with clinical and biological data, our results strongly argue for a new antigen-driven primary pulmonary lymphoproliferative disorder.

271 PROPOSAL FOR A NEW CLINICAL ENTITY, IGG4-POSITIVE MULTI-ORGAN LYMPHOPROLIFERATIVE SYNDROME: ANALYSIS OF 64 CASES OF IGG4-RELATED DISORDERS

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Background: Mikulicz's disease (MD) has been considered as one manifestation of Sjögren's syndrome (SS). Recently, MD is also known as one of the IgG4-related disorders.

Objective and Patients: To determine the differences between IgG4-related disorders including MD and SS, we investigated patients with MD and IgG4-related disorders registered from all over Japan, and set up provisional criteria for the new clinical entity: IgG4-positive multi-organ lymphoproliferative syndrome (IgG4+MOLPS). The diagnostic preliminary criteria include elevated serum IgG4 (>135 mg/dl) and infiltration of IgG4+ plasma cells in the tissue (IgG4+/IgG+ plasma cells >50%) with fibrosis or sclerosis. We compared 64 patients with IgG4+MOLPS and 31 patients with typical SS in clinical features, laboratory data and pathologies.

Results: The incidences of xerostomia, xerophthalmia and arthralgia, RF and ANA, A-SSA and A-SSB antibodies were significantly lower in IgG4+MOLPS than typical SS. Allergic rhinitis and autoimmune pancreatitis were significantly more frequent and total IgG, IgG2, IgG4 and IgE were significantly elevated in IgG4+MOLPS. Histological specimen from patients with IgG4+MOLPS revealed marked IgG4+ plasma cell infiltration. Many patients with IgG4+MOLPS showed lymphocyte follicle formation, but lymphoepithelial lesions were rare. Few IgG4+ cells were seen in the tissue of typical SS. Thirty-eight patients with IgG4+MOLPS treated with glucocorticoids showed marked clinical improvements.

Conclusion: Despite similarities in the involved organs, there are marked clinical and pathological differences between IgG4+MOLPS and SS. Based on the clinical features and good response to glucocorticoid, we propose a new clinical entity: IgG4+MOLPS. Furthermore, some IgG4+MOLPS have monoclonal lymphocytes, and relationship between IgG4+MOLPS and lymphoma is discussing.

272 MOST OF THE LYMPHOPROLIFERATIVE DISORDERS (LPD) OCCURRING IN INFLAMMATORY BOWEL DISEASES (IBD) PATIENTS RECEIVING AZATHIOPRINE BELONG TO THE SPECTRUM OF IMMUNODEFICIENCY-ASSOCIATED LPD (ID-LPD)

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Introduction: There is an increased risk of LPD in IBD patients treated with azathioprine. Our objective was to characterize their clinicopathological features.

Patients and Methods: CESAME is a French cohort designed to determine prospectively the risk of cancers associated with the use of immunosuppressive therapy (IT). Between 2004 and 2005, 821 gastroenterologists included 20,802 IBD (Crohn (CD) and ulcerative colitis) patients. Investigators had to report all the incident cases of cancers. Clinical and histological characteristics of all cases of LPD were reviewed. LPD were looked for EBV (systemic EBV viral load (PCR) and/or presence of viral RNA or proteins).

Results: One case of EBV+ Hodgkin disease occurred in a patient receiving azathioprine. Among the 16 non Hodgkin (NH)-LPD, 3 cases (no death) occurred in patients naive to IT. One fatal case of LBCL occurred in a patient who previously received azathioprine. The 12 remaining cases (5 deaths) occurred in patients receiving azathioprine at the time of diagnosis of NH-LPD. Nine cases belonged to the spectrum of immune disorders (ID)-LPD of the WHO classification. Among them, 7 involved extranodal sites and 7 out of 8 cases tested were EBV+, including 4 fatal cases (1 brain LPD, 1 intestinal B-cell lymphoma and 2 early post-mononucleosis with LPD affecting the inflamed small intestine in 1 case). In 4 patients out of 7 with CD, LPD involved intestinal segments damaged by CD.

Conclusion: Most of the LPD occurring in IBD patients receiving azathioprine affect young patients, belong to the spectrum of ID-LPD, are often associated with EBV and fatal issue and tend to involve extranodal sites, including damaged intestinal segments of CD. The eventuality of fatal early post-mononucleosis LPD must also be underlined.