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.

Discussion: The complete color transformation of the entire skin due to hemosiderin accumulation is to the best of our knowledge the first reported observation in CD30+ lymphoproliferation/ALCL patient. We speculate that hemosiderin loaded macrophages resulted from the paraneoplastic process by some still unknown mechanism.

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Primary mediastinal B cell lymphoma

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A 51 year old male presented with a one month history of progressive facial and chest swelling, hoarseness and dry cough. He developed acute onset anterior chest pain and presyncope. He had no weight loss or sweats and no haemoptysis. He was a non-smoker with no significant past medical history. On examination he had facial swelling and distended neck and chest wall veins. Breath sounds were reduced at the right apex. There was no peripheral lymphadenopathy or hepatosplenomegaly. Clinically the impression was of superior vena caval obstruction syndrome. Full blood count, biochemistry and LDH were normal. CT scan showed a 10.6 by 6.4 cm anterior mediastinal mass (image available). There was no other lymphadenopathy. Biopsy revealed a diffuse, moderately large lymphoid cell infiltrate with diffuse sclerosis (image available). Immunohistochemistry was positive for CD20, CD79a, BCL2, BCL6 and MUM1. CD5, CD30, cyclin D1, CD21 and CD23 were negative. Proliferation fraction was 70%. A diagnosis of primary mediastinal B cell lymphoma was made, stage 1AX. He was commenced on dexamethasone prior to starting definitive chemotherapy in the form of R-CHOP. CT scan after 3 courses showed >50% reduction in the mass which now measured 6.6 by 2.5 cm. Following a further 3 courses of R-CHOP the mass reduced to 5.2 by 1.5 cm. A PET/CT scan on completion of chemotherapy showed a complete metabolic response (image available). In view of this result, radiotherapy was omitted. The patient remains well in clinical remission 9 months post presentation. Potential points for discussion: 1. Is primary mediastinal B cell lymphoma a distinct histological entity? 2. Optimal first line chemotherapy for primary mediastinal B cell lymphoma 3. The role of rituximab 4. The utility of PET/CT imaging 5. The role of consolidation radiotherapy

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Relapsing multiple myeloma with difficult peripheral blood stem cells mobilization and uncommon adverse effects of novel agents

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A 53-year-old man presented in November 2008 with left sided chest wall swelling and was diagnosed as multiple myeloma, Durie-Salmon Stage III and serum beta2-microglobulin 3.2 mg/L). Investigations confirmed left fourth rib plasmacytoma with 20% abnormal plasma cells in bone marrow and monoclonal protein in serum of IgA lambda subtype. Following 5 cycles of VAD regime from November 2008 till March 2009, he attained complete remission and planned for autologous PBSCT and thalidomide. However, he failed twice peripheral blood stem cells (PBSC) mobilizations using high dose cyclophosphamide and refused bone marrow harvesting. In October 2009, he had successful PBSC mobilization with filgastrim and plerixafor yielded 3.7×106 CD34+ cells/kg in 3 leukapheresis sessions. Two days after the mobilization, he developed worsening renal function, detection of urine Bence Jones, abnormal plasma cells in peripheral blood and raised serum free light chain. There were also severe thrombocytopaenia, multiple lytic lesions, myelomatous deposits in the pelvic muscles and pleura and cardiogenic shock with diastolic dysfunction secondary to suspected early amyloid cardiomyopathy. He was treated with bortezomib, dexamethasone and thalidomide dose was continued but was later withheld due to intolerable adverse effects. It was complicated by severe peripheral neuropathy NCI-CTAE Grade III and deterioration in cognitive function with MMSE of 13. This occurred about 2 weeks after second cycle of VD which was thought to be associated with bortezomib. Other possible causes of deterioration in cognitive functions were excluded. A week later, he developed severe pneumonia and massive haemorrhagic pleural effusion after which he succumbed. In this case, we would like to highlight the uncommon adverse effects of novel agents, namely subcutaneous plerixafor in mobilizing patients with multiple myeloma and bortezomib. Further management of these issues are to be discussed.

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Six cases of ABO discrepancies after intensive chemotherapy for B cell lymphoma

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In ABO blood typing, the discrepancies between forward (cell) grouping and reverse (serum) grouping are observed in the cases of disease-related immunosuppresion. However, it is obscure that these phenomena are related to some types of treatment, such as intensive chemotherapy for malignant diseases. We retrospectively analyzed 2156 specimens for ABO blood typing in our hospital between January 2005 and December 2005, and compared forward and reverse typing tests in each case. ABO typing was performed by gel column centrifugation method at room temperature. Anti-A or anti-B antibodies were negative (zero), trace (w+) and weakly positive (1+) in 30 specimens of 24 cases (19 cases of group A, 4 cases of group B and one case of group O). In these cases, 12 cases were examined for the first time and the other 12 cases (11 in group A and one in group O) had been examined before. In latter 12 cases, decrease of anti-B antibodies was observed in eight cases (seven in group A and one in group O), including six cases of B-cell lymphoma (B-NHL) in group A. All these cases of B-NHL received intensive chemotherapy with rituximab. Decrease of serum immunoglobulin (IgG, IgA and IgM) was observed in all the cases after B-NHL treatment. The ABO discrepancies in these cases may be related to decrease of anti-B antibodies caused by treatment-related severe immunosuppression (decrease of serum immunoglobulin). Anti-B agglutination reaction might be influenced more easily than anti-A, as the amount of group B antigen on red blood cells is less than that of group A antigen. Further studies are needed to clarify between this phenomenon and other complications (such as severe viral infections).

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Anaplastic large T/null cell lymphoma (ALCL) while treating Langerhans cell histiocytosis (LCH)

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We report a case of a 27 year-old woman, previously healthy, with the diagnosis of a LCH and an ALCL. In Jun/2007 the patient (pt) noted a left parasternal lump, with progressive