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UPREGULATION OF NON-BUDDING MEGAKARYOCYTES AND DYSREGULATION OF TNF-α AND IL-1β EXPRESSIONS IN BENZENE-INDUCED LEUKEMIC WISTAR RATS

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Background: Thrombocytopenia and leukemia are common features of benzene toxicity and the precise mechanism for these phenomena and the roles of tumor necrosis factor alpha (TNF-α) and interleukin-1beta (IL-1β) are still emerging.

Objective: To compare peripheral blood and bone marrow cell morphology as well as TNF-α and IL-1β concentrations with a view of understanding the possible mechanism of thrombocytopenia and the role of these cytokines in benzene-induced leukamia.

Method: Leukemia was induced in 10 rats by the administration of 100 mg/kg daily for five days a week and for the eight weeks via oral intubation. Ten untreated rats served as control. Peripheral blood and bone marrow smears were prepared appropriately for cytohistological studies; TNF-α and IL-1β concentrations were evaluated in plasma and bone marrow homogenate using ELISA. Data were analyzed using GraphPad software.

Results: The bone marrow smears of rats exposed to benzene showed significant increased frequencies of myelo- and lymphoblastic leukaemic transformations with some dysplastic myeloid series compared with the control. Significant increase (p0.05) in frequencies of non-budding megakaryocytes was also observed. Thrombocytopenia was clearly evident on peripheral blood film. Plasma concentrations of TNF-α and IL-1β were significantly elevated (p0.05) while the bone marrow expressions of these cytokines were significantly decreased (P0.05) compared with the control.

Conclusion: We conclude that modulation of megakaryocyte budding process is a possible mechanism for benzene-induced thrombocytopenia in rats. Upregulation of peripheral expression of TNF-α and IL-1β appears to be a possible host mechanism for mitigating benzene toxicity in the peripheral blood.

Yescarta: A new era for non-Hodgkin lymphoma patients

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The use of conventional therapeutic approaches in patients with lymphoma demonstrates significant drug resistance leading to poor prognosis with reduced median survival period. T-cell immunotherapy has diverted huge attention of the researchers in recent times to engage in the stated research studies in the pool of chemotherapy-refractory lymphoma patients. B-cell antigen CD19-targeted chimeric antigen receptor (CAR) T-cell products are approved for the treatment of non-Hodgkin B-cell refracting or relapsing lymphoma. The aim of this article is to give an idea about the use of FDA-approved anti-cancer gene therapy, Axicabtagene ciloleucel, marketed under the name of Yescarta®. Axicabtagene ciloleucel is developed from the patients' mononuclear peripheral blood cells during which T cells are orchestrated to articulate a CAR that diverts them to identify CD19-expressing cells. It is used in patients with non-Hodgkin B-cell refracting or relapsing lymphoma who had no response to prior therapeutic regiment involving the use of chemotherapeutics. Here, we review the mode of action, safety, and efficacy of Yescarta.

An Unusual Liver Mass

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Background: Extramedullary myeloma (e-MM) is a rare entity. We discuss a case of hepatic involvement by e-MM presenting as multiple hyper-enhancing focal liver lesions on CT and triggering carcinoma of unknown primary (CUP) pathway referral.

Clinical presentation: A 72 year-old previously fit and active man presented with 2-3 months history of fatigue, constipation, reduced appetite and significant weight loss. Physical examination revealed pallor, distended abdomen and hepatomegaly.

Consecutive investigations demonstrated anaemia, hypercalcaemia, raised serum IgG, low IgA and IgM, increased Kappa:Lambda light chain ratio and normal CEA, CA199, AFP, PSA.

A CT scan with contrast identified multiple hyper-enhancing liver deposits and lytic bone lesions. The working diagnosis was that of synchronous malignancies: liver metastasis from a CUP, and myeloma.

A bone marrow aspirate and trephine biopsy showed increased neoplastic plasma cells, confirming diagnosis of plasma cell myeloma.

Liver core biopsies showed vast infiltration by sheets of atypical plasmacytoid cells, which on immunohistochemistry were positive for CD138, CD319, IRF4 and Kappa, whilst negative for Lambda and CD19, confirming the diagnosis of e-MM.

The patient has since successfully completed six planned cycles of VCD (Velcade, Cyclophosphamide and Dexamethasone) chemotherapy.

Conclusion: Liver involvement by e-MM radiologically classically shows diffuse parenchymal involvement. We demonstrate a case with an unusual presentation of e-MM as hyper-enhancing well defined liver deposits and highlight the importance of its consideration in the differential diagnosis of focal liver lesions, in addition to hepatocellular carcinoma and hypervascular metastatic disease to ensure timely, appropriate clinical referral and commencement of appropriate therapy.

Lymphomas: Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Identification of a cellular receptor for bovine leukemia virus infection

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[Background] Bovine leukemia virus (BLV) is the causative agent of enzootic bovine leukosis, which is closely related to human T-cell leukemia viruses. The cellular receptor specifically binds with viral envelope glycoprotein (Env), and this attachment mediates cell fusion to lead virus entry. BLV Env reportedly binds to cationic amino acid transporter 1 (CAT1)/solute carrier family 7 member 1 (SLC7A1).

[Objective] To investigate whether the CAT1/SLC7A1 is an actual receptor for BLV.

[Methods] First, we had constructed bovine CAT1(bCAT1)/SLC7A1-expression plasmid to investigate whether exogenous expression of CAT1 induces BLV infection in CAT1-negative, BLV-resistant cells. Second, we determined the CAT1 and BLV particles binding and colocalizing with BLV-Env in the cells. Third, we analyzed the impacts of CAT1 knockdown on BLV cell-free and cell-to-cell infection and BLV particle binding. Finally, we clarified the species-specific susceptibility of CAT1 for BLV infection.

[Results] Cells expressing undetectable CAT1 levels were resistant to BLV infection but became highly susceptible upon CAT1 overexpression. CAT1 exhibited specific binding to BLV particles on the cell surface and colocalized with the Env in endomembrane compartments and membrane. Knockdown of CAT1 in permissive cells significantly reduced binding to BLV particles and BLV infection. Expression of CAT1 from various species demonstrated no species specificity for BLV infection, implicating CAT1 as a functional BLV receptor responsible for its broad host range.

[Conclusion] CAT1 functioned as an infection receptor, interacting with BLV particles. These findings provide insights for BLV infection and for developing new strategies for treating BLV and preventing its spread.

Lymphomas: Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Oxidative/Nitrosative Metabolism in T Lymphoma Cells: Functional Consequences of Cellular Redox Imbalance

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Background: Thyroid hormones (THs) have direct effects on metabolism and cell growth. We characterized the presence of receptors for THs in T lymphoma cells. THs have dual effects on cell proliferation depending on the culture time and the doses tested. Objectives: To evaluate *in vitro* the effect of THs on the oxidative/nitrosative metabolism of T lymphoma cells, analyzing their consequences on cellular functionality. Methods: BW5147 cells were incubated with or without T4 ($1x10^{-6}$ M) for 5 or more days. Proliferation was evaluated by the [^{3}H]-thymidine technique. Reactive oxygen species (ROS) were evaluated using the DCFH-DA probe and flow cytometry. Inducible NOS expression and protein nitration were evaluated by Western Blot and the production of nitric oxide (NO) was determined by the Griess technique. Apoptosis was assessed by DNA ladder and Hoechst 33258 staining. Mitochondrial depolarization was evaluated by staining with Rhodamine-123 and active caspase-9 was determined by Western Blot. Results: Lymphoma cells incubated with T4 showed lower proliferation compared to controls, which was correlated with an increase in ROS and NO production. Cells showed increased levels of iNOS expression and protein nitration. Incubation with T4 induced DNA fragmentation and changes in nuclear morphology consistent with apoptosis. The role of mitochondria in apoptosis was corroborated by the loss of mitochondrial membrane potential and the activation of caspase-9. Conclusion: T lymphoma cells incubated with T4 (5 days) showed an increase in cellular metabolism and a greater production of ROS and NO. Oxidative/nitrosative stress produced damage to macromolecules and induced apoptosis through the intrinsic mitochondrial pathway.

Mechanisms of Regulation of Oxidative Balance in T Lymphoma Cells *versus* Normal T Cells. Effects of Oxidative Metabolism Induced by Thyroid Hormones on Mitochondria

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Background: T lymphoma cells differ from normal T cells by uncontrolled cell proliferation and increased metabolism. Both cell types have receptors for thyroid hormones on the outer membrane of the mitochondria, the main ROS-producing organelle. Thyroid hormones have direct effects on metabolism. Objectives: 1-To study the mechanisms involved in the regulation of oxidative balance in T lymphoma cells versus normal T cells. 2-Analyze the effects of oxidative metabolism induced by tiroxine on mitocondria. Methods: BW5147 T lymphoma cells and murine normal T lymphocytes were treated with thyroxine. ROS were evaluated using the DCFH-DA probe and flow cytometry. The expression of catalase, glutathione peroxidase-1, superoxide dismutase and p-Nrf-2 was determined by Western Blot. The translocation of p-Nrf-2 to the nucleus was evaluated by confocal microscopy. Nitric oxide (NO) production was determined by the Griess method. The expression of NOS and the nitration of PKCζ was evaluated by Western Blot. Mitochondrial morphology was evaluated by electron microscopy. Apoptosis was evaluated by Annexin V-FITC/PI labeling and flow cytometry. Results: The thyroxine-induced increase in ROS production was greater in T lymphoma cells than in normal T cells. Thyroxine also induced phosphorylation and translocation of Nrf-2 to the nucleus. Both cell types had an increased expression of antioxidant enzymes. Lymphoma cells showed a high expression of iNOS and NO production that was correlated with the nitration of PKCζ. The morphology of the mitochondrial crests was altered in both cell types, however apoptosis was observed only in tumor cells. Conclusion: Both normal and tumor cells showed antioxidant defense mechanisms against thyroxine-induced oxidative stress. However, the increase in NO caused the nitration and loss of function of PKCζ, an enzyme essential for the survival of lymphoma cells.

MULTIPLE MYELOMA AND RENAL IMPAIREMENT: DESCRIPTIVE STUDY ABOUT 53 CASES IN NEPHROLOGY DEPARTEMENT

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Background: Renal impairement is a severe complication in multiple myeloma (MM); it remains a poor prognostic factor. Methods:We performed a retrospective study on 53 patients diagnosed multiple myeloma with renal impairement at nephrology departement in University Hospital in Tunisia. Objective:We determined the clinical, biological, and the evolution features of kidney injury related to myeloma.Results:The mean age of our patients was 63.53 years +/- 11.49 years with extremes ranging from 41 years to 85 years. A maximum of frequency is observed in the age group between 46 years and 59 year. Renal involvement was inaugural in 75,5%.The most commen clinical features were :Anemia symptoms in 71,7%, impaired general condition in 67,3%, bone pain in 41,5%,deshydratation in 34,4% , inection in 34% , oligoanuria 24,5% .The mean serum creatinine was 693.47umol / L. The mean eGFR was 13.94 ml / min / 1.73 m2. CKD was found in 52.8%. ARI on admission was found in 81.1%. 35.8% of patients underwent dialysis on admission and 41, 5% pregressed to terminal stage of chronic kidney disease. The mean proteinuria was 3.11g / 24h +/- 2.79. Nephrotic syndrom was present in 22, 6% of patiens. Renal biopsy was performed in 23 cases It showed myeloma cast nephropathy in 14 patients, AL amyloidosis in 9 patients,a case of membranoproliferative glomerulonephritis(MPGN) and a case of membranous nephropathy(MN).The majority of patients received a chemotheray (80,8%),only 7 patients had a graft of hematopoietic stem cells .26,4% of cases showed a favorable renal evolution and 73,6% had a bad evolution of renal function.The mean of overal survival was 17,97months .The major cause of death was infectious complications and progression of the disease.Conclusion:Renal impairement in MM is a commen complication that worsen the prognosis of the disease. Treating early with new chemotheray drugs can stop the progression and improve survival outcomes.

A Rare Case of Central Nervous System Involvement in Mantle Cell Lymphoma.

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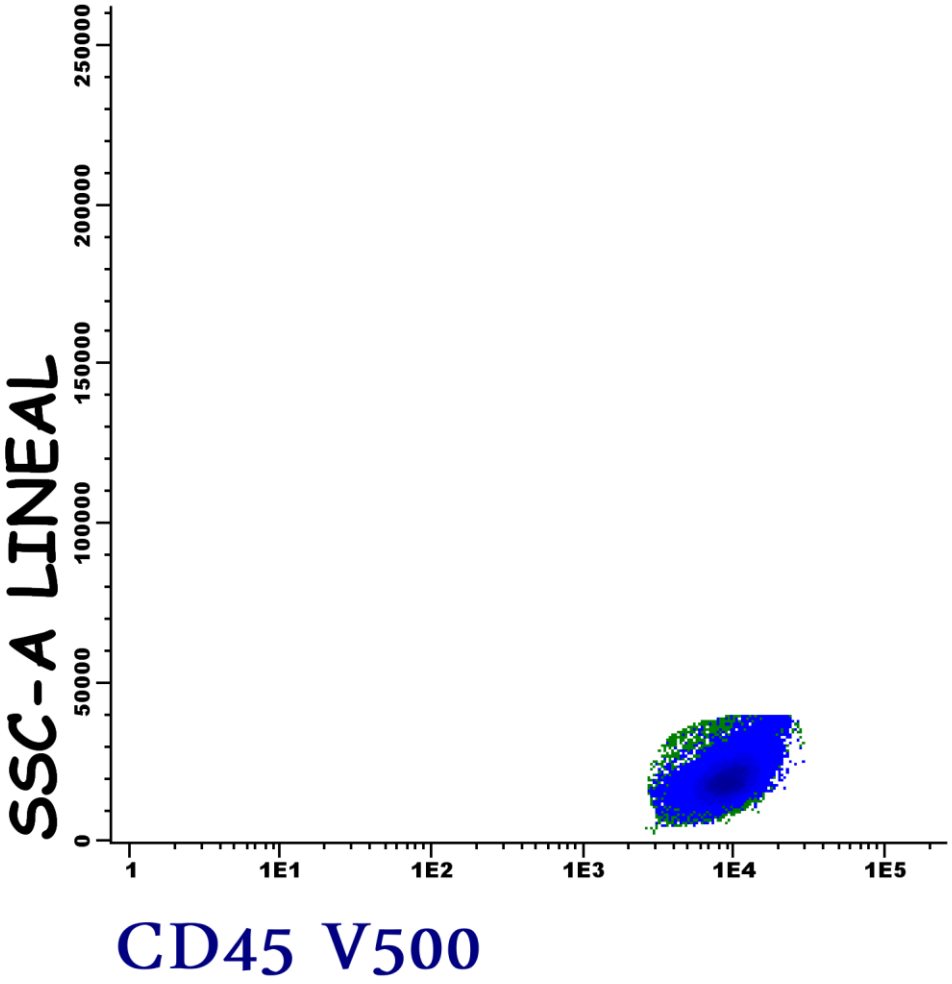
Mantle cell lymphoma (MCL) accounts for approximately 3-6% of all Non-Hodgkin Lymphomas (NHL). The patients are predominantly male, with a median age at diagnosis of 68 years and a median survival time of 4-5 years. Extranodal manifestations are common. CNS involvement is not precisely defined and it is most commonly detected at the time of relapse.

Our patient, an 81-year-old man, was referred to the Emergency Room in November 2020 from the neurologists' office due to a history of apraxia, and agnosia. Fourteen years earlier, he had been diagnosed with MCL and was then treated with four lines of systemic chemoimmunotherapy during multiple relapses. After the fourth remission under chemoimmunotherapy, he was treated with Rituximab every 8 weeks for two years, finalizing treatment in April-2018.

After the beginning of these symptoms, an analysis by flow cytometry of the cerebrospinal fluid (CSF) revealed a cell count of 285 cells/µL (mostly mononuclear cells) and an increased protein level (400 mg/dL; reference range, 15-45 mg/dL). The cells expressed CD19+, CD20+, sIg lambda, CD5+, CD10-, CD43+, CD79B+, CD200+, CD23-, CD38+. The t(11;14)(q13;q32) translocation between an IGH gene and CCND1 was also found in the lymphocytes of the CSF.

We performed four lumbar punctures (LP), in which we infused Methotrexate (MTX) and ARA-C until the cell count in the CSF fell to 1 cells/µl. However the clinical condition of the patient did not improve.

We then started ibrutinib at complete dose with good initial tolerance. Despite this our patient suffered early hematological toxicity, further complicated with sepsis and rapid deterioration which eventually resulted in the patients' death.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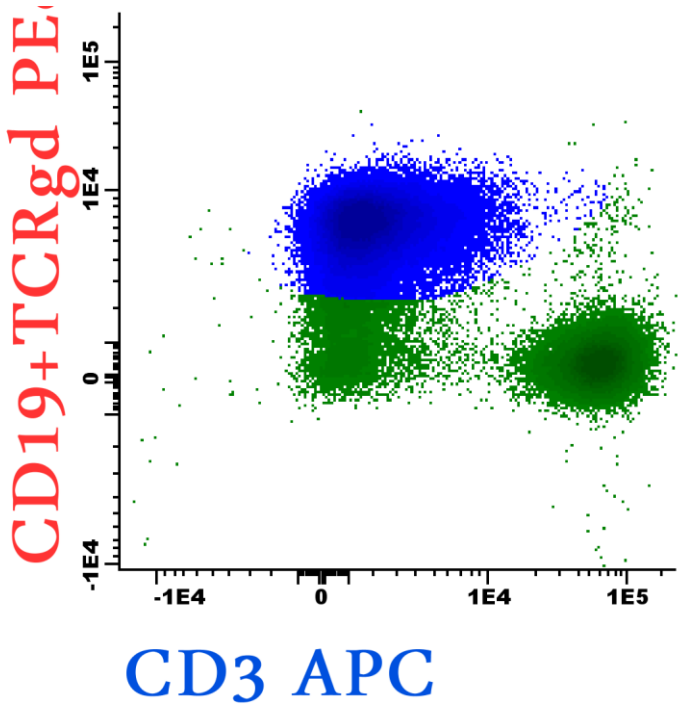
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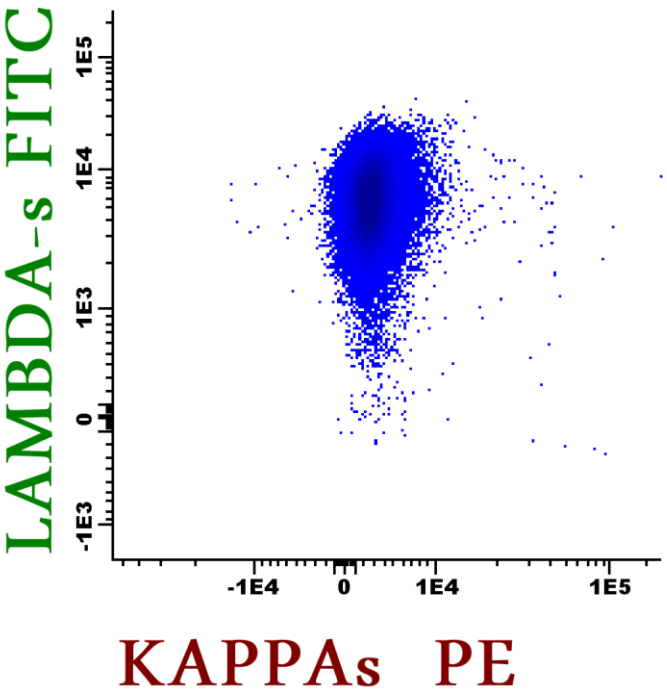
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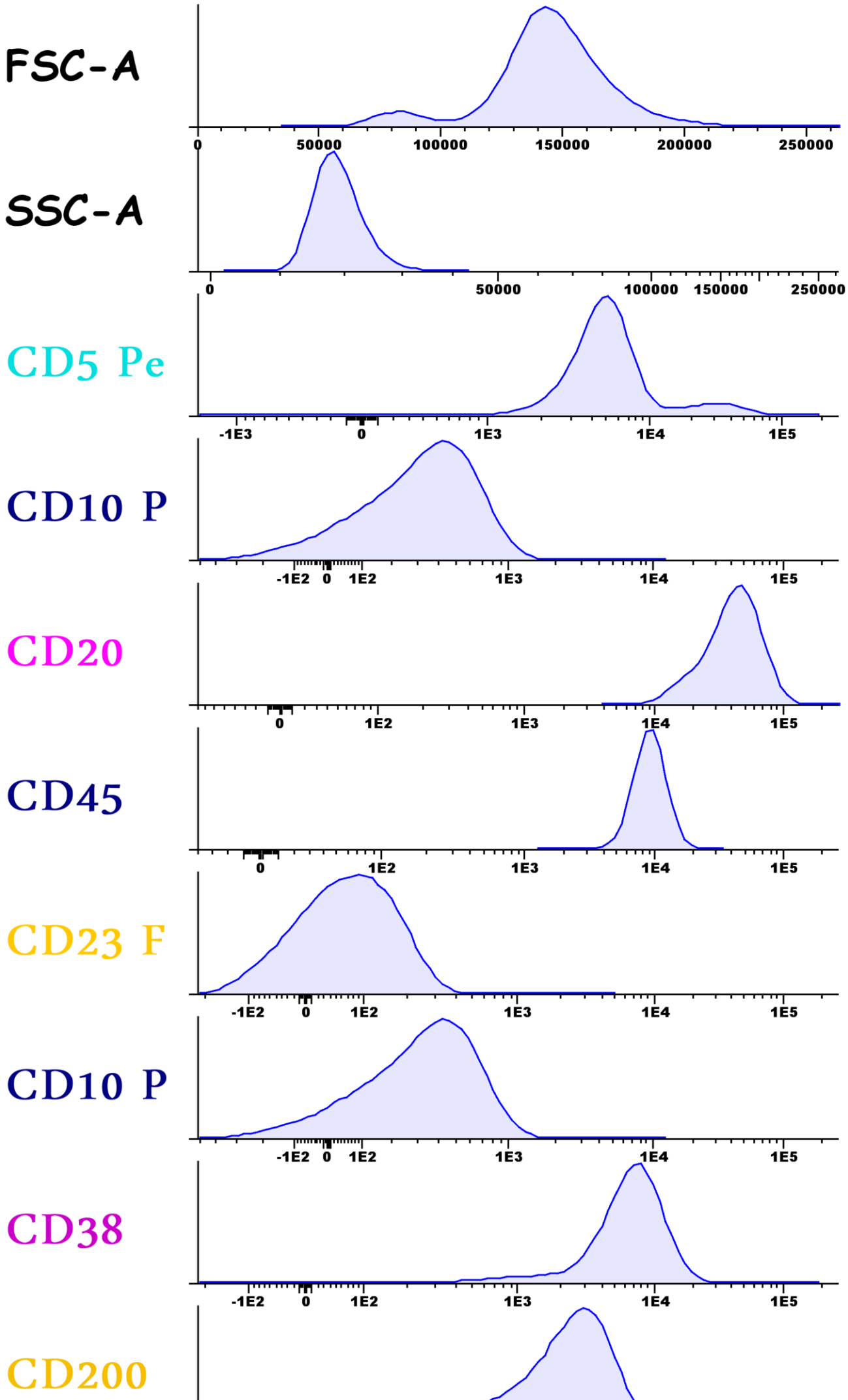
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CLL: Chronic Lymphocytic Leukemia and Hairy Cell Leukemia

Outcome of Imatinib-Treatment in Chronic Myeloid Leukemia (CML) Patients of Different Food Habits

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Background: CML is characterized by Philadelphia (Ph)-chromosome that originates from t(9q34;22q11) and carries the chimeric/mutant BCR-ABL oncogene. The oncogene causes overproduction of tyrosine kinase (TK), and thus, targeted for therapeutics. Imatinib is the first such TK-inhibitor (TKI) and considered for front-line therapy for its efficacy to render fast elimination of Ph-positive clone. However, delay in treatment outcome/relapse of the disease was reported due to occurrence of point mutation within BCR-ABL and/or individual genetic composition. Similar outcome was apparently noticed among 1136 patients known two have distinct food habits in the present study.

Methods: From the heterogeneous treatment-group, 232 patients receiving imatinib were considered for bone-marrow cytogenetics with a view to understanding the effect of food habit on treatment outcome. The patients were known to consume two distinct types of food such as one never consumes beef (Group1) and the other consumes more of beef than other items (Group2). Analysis of G-banded metaphase chromosomes or BCR-ABL signals following FISH has collected data on partial response (100% Ph+ve), no response (100% Ph+ve) and complete cytogenetic remission (CCR; 100% Ph-ve), which was considered for X2-statistics.

Results: In all, Group2 patients (60%) didn't exhibit any response till one year of treatment compared to Group1 (42%), which was significant in males and for the cumulative data. However, the difference between the two genders was not significant since the females of the two food-groups have achieved similar outcome.

Conclusion: Food, especially red meat interferes in treatment outcome and that is aggravated by smoking and other factors in males.

Comparative Assessment of Clonal Evolution by Whole Exome Sequencing at Diagnosis and on Progression in Multiple Myeloma

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Background: Clonal proliferation of malignant plasma cells is a hallmark of Multiple Myeloma (MM). Somatic mutations may be acquired prior to diagnosis and expand subsequently depending on selection pressures imposed by treatment/ microenvironment. Clonal trajectories drive myeloma genesis, regulate drug refractoriness and clinical outcomes. There are limited studies on clonal propagation of genomic aberrations in MM and their clinical relevance.

Objective: To evaluate clonal somatic mutational profiles in MM patients at diagnosis in comparison to progression and identify mutated drivers / actionable genes.

Method: Paired DNA was extracted from purified plasma cells (CD134+) of 62 MM patients at diagnosis and at progression. Whole exome libraries were generated with Nextera Exome kit and sequenced on Illumina HiSeq 2500.

Results: A significant reduction in total somatic mutations (20%), Single base substitution (CA) (16% to 8%) and total mutation burden (TMB) (average 14 NS mutations to 7) was observed on progression. Most patients (70%) developed branching clonal evolution. Unique mutations in 563 and 90 genes were observed at diagnosis and progression, respectively. Certain mutated drivers showed a decrease (n=32) (e.g. IRF4, FAT4, TET2) or an increase (n=20) (e.g. NRAS, CYLD, TP53) in their frequencies with progression.

Conclusion: There is intraclonal heterogeneity across patients. A decline in TMB and the predominance of branching evolution are indicative of response to therapy. Identification of driver and actionable genes at more than one time points may be beneficial in decision making on targeted therapy and prognosis.

EPIDEMIOLOGICAL AND HISTOPATHOLOGICAL FEATURES OF LYMPHOMAS IN TUNISIA

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Background

Epidemiological and histopathological features are important data to assess the course of a disease and for a better understanding of its characteristics.

Objective

The aim of our work was to study the epidemiological and histopathological features of lymphomas in Tunisia.

Method

It was a multicentric, retrospective study including cases of cancer diagnosed between 2015 and 2016 in the governorate of Medenine, Tunisia. Hereby we report the results concerning lymphomas.

Results

We collected 1061 cases of cancer, diagnosed between 2015 and 2016, in the governorate of Medenine, Tunisia. Non-Hodgkin lymphomas represented 5.18% of all cancers (55 cases). They represented 5.90% of cancers in men (30 cases) and 4.48% of cancers in women (25 cases). The Age-Standardized Incidence Rate was estimated at 5.18/100,000 inhabitants. The sex ratio is 1.2. The mean age at diagnosis was 60.6years. The crude incidence increased with age. It increased from less than 2/100,000 for patients under 35 to 54.3/100,000 for patients over 80. The most frequent localizations were lymph node (29.1%) and the stomach (23.6%). The most frequent histological type was Diffuse Large B-Cell Lymphoma (65.5%).

Hodgkin lymphoma represented 1.22% of all cancers (13 cases). The Age-Standardized Incidence Rate was estimated at 1.37/100,000 inhabitants. The crude incidence reached 2.79 /100,000 for the age group between 10 and 14 years and 2.78 /100,000 for the age group between 15 and 19 years. The mean age at diagnosis was 31.2years and the sex ratio was 0.86. In all cases, Hodgkin`s lymphoma is of the classic type.

Conclusion

Relative proportions of different types of lymphoma vary geographically. In Tunisia, Non-Hodgkin lymphomas represents 5.18% of all cancers with a mean age at 60.6years. The most frequent histological type is Diffuse Large B-Cell Lymphoma. Hodgkin lymphoma is rare and represents 1.22% of all cancers with a mean age at 31.2years.

INTRAVENTRICULAR CHEMOTHERAPY IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA WITH COGNITIVE DYSFUNCTION AFTER INTRACRANIAL SURGERY

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Background : Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal non-Hodgkin lymphoma and only 0.3-1.5% of intracranial neoplasm, involving the neuro-axis without systemic involvement. It has specific characteristic aggressive course, unsatisfactory outcome and poor prognosis.

Case Presentation : A 56 years old man presented with a severe headache that poor respond to any medication and left hemiparesis. Brain MRI studies showed multiple lesion located in right-temporal lobe pressing the right lateral ventricle and midline shifting to the left and shows signs of increased intracranial pressure. Following the surgical procedure, the results of pathological and immunohistochemistry revealed a PCNSL. Lumbar puncture results which revealed normal appearance. Cognitive dysfunction occurs after intracranial surgery.

Discussion : High-dose methotrexate (MTX) systemic still plays a crucial role in the chemotherapy on PCNSL because it crosses the blood-brain barrier. Frontline treatment for these patients was De Angelis protocols with intraventricular chemotherapy for MTX by ommaya reservoir showed effectively improve clinical response. WBRT was administered to a total dose of 45 Gy and high dose Ara-C after radiotherapy.

Conclusion : Primary central nervous system lymphoma is highly aggressive non-Hodgkin lymphoma but it is sensitive to both chemotherapy backbone HD-MTX and radiotherapy to provide a better outcome and improve survival.

Keywords : PCNSL De Angelis Protocols Intraventricular chemotherapy

Chronic Lymphocytic Leukemia: Molecular Diagnostics, Epigenetics, and New Treatments

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Background

CLL, the most common form of leukemia in Western European countries, displays a varied clinical course and different sensitivity to treatment. As a still incurable disease, CLL remains a great challenge to researchers looking for new, more effective and safe therapies.

Objective

The aim of the study was to assess the effect of chlorambucil (CLB) and valproic acid (VPA) used separately and in combination on the viability and apoptosis of CLL cells in vitro.

Method

CLL cells were isolated from peripheral blood of 17 previously untreated patients from Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, and examined after 24 and 48 hours of culture with CLB and VPA used alone, and in combination. For negative control of apoptosis, CLL cells were cultured with no treatment (media alone). Cell viability was evaluated with a trypan blue exclusion assay and the assessment of apoptosis was performed with the use of Annexin V-Cy3TM Apoptosis Detection Kit according to producers' instructions. Gene expression profiling of genes involved in apoptosis process in CLL, such as *BCL2*, *MCL1*, *p21*, *HDM2*, and *GAPDH* as a control gene, was achieved using qPCR technique. Assessment of cytogenetic prognostic factors, i.e. trisomy 12, del13q, del17p and del11q was completed by fluorescent *in situ* hybridization method.

Results

The combination of presented drugs showed ability to induce apoptosis effect in CLL cells, and potentially to reduce the toxicity of the treatment.

Conclusion

The present study strongly suggests further investigations on CLB and VPA combination in CLL treatment.

Lymphomas: Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Expression of RUVBL1 component of R2TP complex correlates with poor prognosis in DLBCL.

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Abstract

DLBCL is the most prevalent subtype of non-Hodgkin's lymphoma (NHL) accounting for 30% of adult NHL worldwide. Recently identified HSP-90 co-chaperone complex R2TP has been shown to contribute towards DNA damage and Myc induced transformation which are well known in DLBCL. The aim of this study was to compare the immunohistochemical expression of R2TP complex components RUVBL1, PIH1D1 and RPAP3 in FFPE DLBCL patients. Surprisingly, the overexpression of RUVBL1 component of R2TP complex turned out to be associated with relapse and poor survival.

Objective

To check the immunohistochemical expression of the components of R2TP complex and their correlation with the patient survival.

Methods

Immunohistochemical staining of R2TP complex components RUVBL1, PIH1D1 and RPAP3 was performed on FFPE tissue samples of 54 tumours patients of. The immunohistochemical staining was assessed by two pathologists who were blinded to all clinicopathological and cytogenetic details. Based on a scoring system, expression of these components was graded as high or low.

Results

There were total of 54 tumour tissues out of which 32 (59.26%) cases strongly stained for RUVBL1 and none of the reactive lymph node stained for RUVBL1. The RUVBL1 expression was correlated with the clinicopathological features and positive statistical significance was observed with progression free survival (p=0.0146); overall survival (p=0.0328) and bone marrow involvement (p=0.0525). Kaplan-Meier survival analysis showed a statistically significant difference in progression free survival those in RUVBL1 positive and negative (21 vs 39 months, respectively, p=0.008).

Conclusion

RUVBL1 over expression in DLBCL is associated with relapse and poor survival.

A functional FAM46C/FNDC3A complex predicts sensitivity to autophagy and sphingosine kinase inhibition in multiple myeloma cells.

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Recently, we have thoroughly characterized the novel FAM46C/FNDC3A tumour suppressor complex, which is frequently inactivated in multiple myeloma (MM).

We found that, by altering intracellular vesicle trafficking, FAM46C/FNDC3A affects protein secretion and indirectly inhibits autophagy, an event which in turn causes accumulation of misfolded proteins, endoplasmic reticulum (ER) stress and cell death through apoptosis.

To exploit our findings in the context of MM treatment, we tested the crosstalk between FAM46C/FNDC3A and autophagy modulators. We found that a functional FAM46C/FNDC3A complex senthysizes cells to treatment with Bafilomycin and Chloroquine, two classic inhibitors of autophagy.

Moreover, by connectivity map analysis, we intriguingly found that the signature induced by re-constituting a functional FAM46/FNDC3A complex in MM cells resembles inhibition of Sphingosine kinase (SK) activity. SKs are involved in the metabolic pathway of ceramide conversion and their inhibition is known to cause alterations in the lipid structure of the ER, consequently causing ER stress.

We found that reconsitution of a functional FAM46C/FNDC3A complex senthysizes cells to treatment with SKI-I, an inhibitor of both SK1 and SK2, indicating that FAM46C/FNDC3A alteration of ER stability/homeostasis is synergistic with SKI-I treatment.

In conclusion, by modulating in MM those pathways affected by the FAM46C/FNDC3A complex, namely autophagy and ER homeostasis, we were able to test novel therapeutic avenues. In particular, the possibility of stratifying patients based on the presence of a functional FAM46C/FNDC3A complex should be taken in account for future clinicals implementations of MM therapies relying on autophagy and/or ER stress modulators.

Functionalized microgels as a disease model for Multiple Myeloma

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Background: The development of three-dimensional environments to mimic the in vivo cellular response to treatment is one of the current problems in the building of disease models. One of the key points is to develop a culture medium in which tumour cells develop the same type of drug resistance as in vivo.

Objective: The aim of this work was the synthesis and validation of a three-dimensional support for culturing monoclonal plasma cells (mPC) as a disease model for multiple myeloma (MM).

Method: The three-dimensional (3D) environment is a biomimetic microgel formed by alginate microspheres, produced on a microfluidic device, whose surface has been functionalized by a Layer-by-Layer process with hyaluronic acid (HA) and collagen type I (COL), components of the bone marrow's extracellular matrix (BMECM), that will interact with mPC.

Results: Synthesis of a 3D culture system based on alginate microspheres coated with HA and COL. As a proof of concept, by culturing RPMI 8226 cells in our 3D culture platform, it has been proven that the microgel that exhibit HA in the microparticles surfaces significantly increases cell proliferation and corroborates its role in inducing resistance to dexamethasone while COL has no effect on proliferation and yet, it also generates significant resistance to dexamethasone.

Conclusion: These results encourage the use of biomimetic microgels as a 3D culture system that simulates the interaction between tumoral cells and the BMECM, which could be a valuable culture system to test antitumoral drugs efficiency in MM.

Keywords: Multiple Myeloma, Microgel, Hyaluronic Acid, Collagen, Dexamethasone.

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Increased total number of CD34+ peripheral blood cells by curcuminoids plus Aphanizomenon flos-aquae (blue-green algae extract) treatment in patients.

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The mobilization of stem cells into the circulation is enhanced by AMD-3100 or plerixafor (a CXCR4 human antagonist). CD34 is a maker of hematological stem cells (HSC). However, stem cell mobilizers have shown side effects in patients. Consequently, the search of new active principles from plants could be useful to induce the peripheral mobilization of CD34+ cells. Curcumin is the active principle from Curcuma longa extract and Aphanizomenon flos-aquae (AFA algae extract) is a species of cyanobacteria (blue-green algae), which is commercially processed into a dietary supplement.

In the present study, we measured the total number of CD34+ cells into peripheral blood from healthy subjects; they were long-term supplemented with curcumin plus sulforaphane during 38 consecutive days (120 mg/day of curcuminoids plus 30 mg/day of sulforaphane).

Curcuminoids plus sulforaphane enhanced hematopoietic stem cells mobilizatioin into peripheral blood by increasing CD34 total levels after 38 days of curcumine plus AFA extract supplementation. CD34 levels were measured by flow cytometry into peripheral blood and compared to their basal levels (before any supplementation) as well as placebo-treated subjects. Curcumine has shown beneficial effects in leukemia cells. Further studies will evaluate whether these active principles from plants could promote beneficial effect/s in leukemic patients.

Lymphomas: Hodgkin Lymphoma and Non-Hodgkin Lymphoma

SUCCESFULL TPE (THERAPEUTIC PLASMA EXCHANGE) FOR TUMOR LYSIS SYNDROME

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Background

Treatment for HL has been associated with adverse late effects, such as increased risks of secondary malignant neoplasms and cardiovascular diseases. Endocrine paraneoplastic syndromes can complicate the patient`s clinical course, response to treatment, impact prognosis, and even be confused as metastatic spread

Case presentation

A 19 old women present with multiple lymphadenopathies, mild LDH increase, Chest X-ray suggested mediastinum mass with pleural effusion, Lymph node biopsy suggested a lymphocyte rich classical Hodgkin lymphoma. The treatment includes thoracentesis and ABVD chemotherapy ongoing. After the second chemotherapy, this patient made shortness of breath and edema all their body including the breasts, increased uric acid 8,4 mg/dl, calcium 2,65 mmol/l and echocardiography revealed obtained dilated left ventricular ejection fraction 25 %. Chemotherapy was delayed. This patient was treated with spironolactone, allopurinol, and 3 cycles of TPE. Post third TPE edema disappeared, calcium and uric acid found repair.

Discussion

Patients who are receiving chemotherapy must be aware of the therapeutic effect on the tumor itself. the tumor lysis syndrome process which can have a wide effect both on neurological, hematological, or endocrinological effects. One of the therapies for tumor lysis syndrome in this patient is plasmapheresis and it is proven that there is a significant improvement.

Conclusion

Chemotherapy must be considered carefully the effects that may occur either the effect on the tumor or the chemotherapy drugs that we were given it. plasmapheresis has been shown to provide significant benefits to tumor lysis syndrome that occurs.

Keywords: Hodgkin lymphoma, cardiomyopathy, tumor lysis syndrome, TPE

Multiple Myeloma and AL Amyloidosis

Immunoprecipitation in IgD multiple myeloma with hidden light chains: paving the way in a complex diagnosis.

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Background

IgD multiple myeloma (MM) with "hidden" light chains (LC) is an extremely infrequent subtype of MM with few cases described. Serum immunofixation (IF) is very difficult to interpret in some patients with this disease.

Objective

To present a case report of IgD MM with hidden LC and describe a trouble-free IF method to elucidate its diagnosis.

Methods

Data were collected from electronic history and clinical records. All procedures were performed according to ethical standards. Complete diagnosis work-up included clinical findings, morphology, IF and immunophenotyping by flow cytometry (FC).

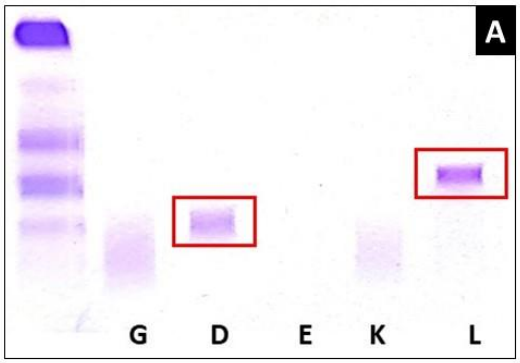
Results

A 72-year-old caucasian male was referred for osteolytic lesions and Bence-Jones proteinuria without decreased glomerular filtration. First serum IF revealed an isolated lambda monoclonal band, not correlated with serum free LC levels. Second IF showed an IgD monoclonal band with a lambda monoclonal band migrating at different heights (Figure 1a). Third IF was performed with the supernatant obtained after incubating the patient serum with anti-human lambda immunoglobulin for 48h at 4 . No presence of lambda monoclonal band and a remarkable decrease of the IgD monoclonal band were detected. These results showed that heavy and light chains belonged to the same monoclonal paraprotein.

A complete bone marrow work-up was performed. FC identified: CD38+/CD138+/CD19-/CD56-/CD27+/CD28+/CD81-/+/CD45-/cylambda+/cyIgD+ confirming the previous finding by IF (Figure 1b). Cytomorphological assessment showed massive infiltration by small plasma cells (Figure 1c).

Conclusions

It is worth developing a method to solve the difficulties of interpretation in the IF to distinguish IgD MM with hidden LC from other diseases.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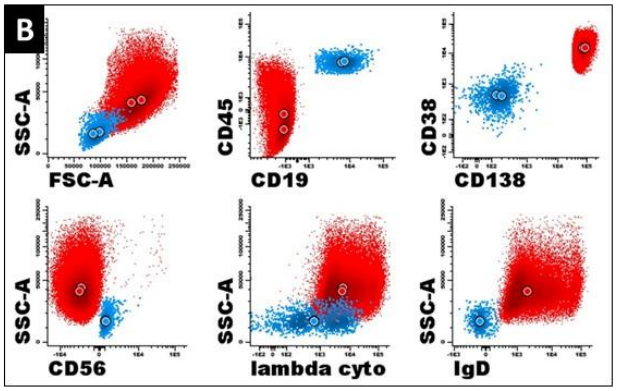
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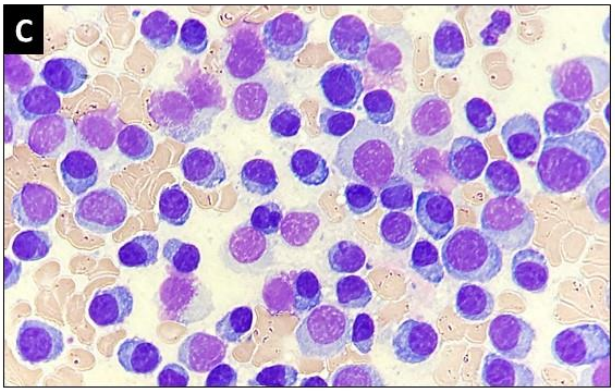
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What is the Role of Global DNA and APC 2 Gene Promotor Hypermethylation in Multiple Myeloma?

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Introduction: Hypermethylation is one of the new approach parameters in Multiple Myeloma (MM). We aimed to demonstrate the effect of hypermethylation in MM. Material and method: In our study,38 patients and 50 healthy people were included.Patients in first group underwent autologous stem cell transplantation. Patients in the second group were not eligible for transplantation.Results:Hypermethylation was significantly higher compared to control group;post-treatment global hypermethylation were significantly increased(p0.05). Both OS and PFS were significantly lower in patients;with higher IPI score;who had not been through transplantation and whose response was below partial remission(p0.05). Conclusion:Our study is first in the literature with initial hypermethylation results and the increase in hypermethylation post-treatment.

A New Parameter in Multiple Myeloma: CYP3A4 * 1B Single Nucleotide Polymorphism

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Introduction: Multiple myeloma (MM) is a disease caused by malignant plasma cells, causing free light chain release accompanying the increase in monoclonal immunoglobulin. Cytochrome P450 (CYP) is one of the large and functional enzyme families composed of various hemoproteins. This protein network has been shown to play a role in many treatment steps in current practices. We aimed to investigate the relationship between genotypes of CYP3A4*1B and treatment response and prognosis of MM. Material and Methods: Seventy-two patients diagnosed with MM between January 2016-2020 and 100 healthy people to create a control group participated in our study. Genotypes were classified in 3 separate groups as NN, MN and MM. Results: Both PFS and OS were significantly higher in the NN genotype(p= 0.001, p=0.014). Being under the age of 65 was 27.988 times more protective for OS and 4.496 times for PFS(p=0.006, p=0.017). NN genotype was shown to be 41.666-fold protective for OS and 3.144-fold protective for PFS(p=0.004,p=0.030). Discussion and Conclusion: This study demonstrated that CYP3A4*1B NN genotype, which is an important cytochrome p450 member for the treatment of MM, was 41.666-fold protective for OS and 3.144-fold protective for PFS. It was shown in this study for the first time in the literature as a valuable contribution.

Vitamin E induces transcription factor C/EBP alpha and G-CSFR in K562 cells

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Background: Chronic myeloid leukemia (CML) is leukemic stem cell-derived disease with the progression of the phase of blast stem cell crisis. However, p210BCR-ABL1 tyrosine kinase inhibitors as imatinib, dasatinib and nilotinib, may induce complete cytogenetic or even molecular responses, but it is unlikely that they will cure CML because blast stem cells are saved as the acquired resistance. Numerous strategies have been tested to avoid and overcome the blast crisis resistance but is unsuccessfully. Objective : The aim of our study to develop the strategy of the leukemic stem cell phenotype reprogramming by targeted inducing the myeloid differentiation pathway through master regulator C/EBP alpha (CCAAT/enhancer-binding protein α) in the process of granulocytic differentiation. The progression of CML to blast crisis is correlated with down-modulation of C/EBP alpha . Therefore, C/EBP alpha may be considered as a putative target in differentiation therapies in myeloid leukemias. Methods: RNA extracted from K562 cells cultured with vitamin E and valproic acid (in comparison) was converted to cDNA which was diluted to 2 ng/μL for quantitative SYBR Green qRT-PCR analysis using 0.3 μM forward primer and reverse primer.. Samples were cycled using the standard SYBR Green protocol on an Q5 Bio-Rad StepOne qPCR instrument and analyzed using the comparative cycle threshold (CT) method to obtain relative expression quantities. Results: We are first found that vitamin E targeted induces the mRNA transcription factor C/EBP alpha and consequently G-CSFR (granulocyt-colony stimulation factor receptor) genes in K562 leukemic blast stem cell line. We have not found detectable expression of C/EBP-alpha in K562 cells by real-time RT-PCR assay. Upon 48-h culture with vitamin E at a dose of 100 μM, K562 cells targeted increased the expression of both C/EBP-alpha and G-CSFR in comparison to control and valproic acid. Conclusion: These findings may suggest the vitamin E-prevention role in the blast pase chronic myeloid leukemia via restored the C/EBP alpha /G-CSFR - potential of granulopoiesis in K562 and consequently in leukemic blast stem cell phenotype.

Chemotherapy Management in Acute Myeloblastic Leukemia During Covid-19

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Introduction

COVID-19 possesses several challenges on management of oncologic patients. Cancer patients are frequently immunosuppressed by their disease and treatment. Cancer patients with COVID-19 have a high risk of becoming critically ill. Case fatality rate of cancer patients with COVID-19 is: 5,65 vs 2,3% and cancer patients had severe events: 39 % vs 8%.

Case Presentation

Mr. STP 36 years old was diagnosed AML on June 30, 2020, with Myeloblast was 34%. Induction chemotherapy 7+3 was carried out from July 31 - August 6, 2020 and experienced complications of anemia, neutropenia and thrombocytopenia. During supportive treatment, patient complained of productive cough and fever. On August 8, 2020, RT PCR was carried out and has a positive result for COVID-19 and chest Xray with mild pneumonia. A negative RT PCR COVID-19 conversion occurred on September 5, 2020. Complete remission (CR) 2% Myeloblast was reached on October 13, 2020. From October 27, 2020 patient underwent consolidated chemotherapy with High-dose cytarabine 3000 mg/m2/12 hours on days 1, 3 and 5. Because the patient had febrile neutropenia, chemotherapy was currently postponed.

Discussion

Cancer patients with neutropenic conditions are susceptible to COVID-19 infection. Our patient was remained CR after induction chemotherapy despite COFID-19 infection. It has an impact on delaying the provision of consolidated chemotherapy because of prolonged neutropenia. Testing of all patients for COVID-19 prior to any hospital admission and/or procedure, even in the absence of symptoms is recommended. Consolidation therapy with high-dose cytarabine should continue to be offered to patients in complete remission, but consider of lowering the dose of cytarabine to 1.5g/m2 instead of 3g/m2

Conclusion

Patient AML was remained CR after induction chemotherapy despite COFID-19 infection. COFID-19 has an impact on prolonged neutropenia. Need to change management by lowering the dose to reduce complications.

Key word:

AML, COVID-19, Neutropenia, CR

Succesfull Management of Tumor Lysis Syndrome in Patient with Lymphoma Hodgkin

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Background. Tumor lysis syndrome (TLS) is characterized by rapid and massive destruction of tumor cells.[1,2,3] TLS occurs typically after initiation of cancer treatment.[4] Acute Kidney Injury is central to the development of TLS.[5] ABVD is the most commonly used treatment for Hodgkin Lymphoma.[6]

Case Presentation. A 29-year-old female with Lymphocyte rich-classic Hodgkin lymphoma admitted for a second chemotherapy of ABVD. Laboratory results: Hemoglobine 10 g%, Leukocytes 12.100/mm^3, Platelets 593,000/mm^3, Kalium 3 mmol/L, Uric acid: 5 mg/dL, Urea: 25 mg/dL, Creatinine: 0,8 mg/dL, CD45 (+), CD3 (+), CD20 (-), CD30 (+), CD15 (+). One day after chemotherapy, patient complained: short of breath, and weakness. On physical examination: the lungs were dim, and lower limbs oedeme. Laboratory results: uric acid 8,4 mg/dL, urea 77 mg/dL, creatinine 1,5 mg/dL, potassium 5,5 mmol/L. We gave therapeutic plasma exchange (TPE) 3 times, and allopurinol 300 mg/24 hours, sodium bicarbonate 500 mg/8 hours. Patient complaints were reduced and laboratory results were normal.

Discussion. A patient got a tumor lysis syndrome based on the presence of acute events such as complaints of short of breath and weakness accompanied by increased results of urea, creatinine, uric acid, and hyperkalemia. Patients' risk factors include lymphoma and chemotherapy regimen.

Complaints of shortness of breath, weakness, and edema decreased after undergoing TPE.

Conclusion. ABVD has effect for tumor lysis syndrome. The implementation of the TPE measures can resolve this event.

Keyword: Tumor Lysis Syndrome, TPE

Infectious Complications in HIV-positive and HIV-negative Patients with Diffuse Large B Cell Lymphoma at a Third Level Mexican Hospital

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Background: The type and frequency of infections in patients with HIV and Diffuse Large B Cell Lymphoma (DLBCL) and their impact on survival are unknown. Objective: To compare the frequency of infectious complications in DLBCL between HIV-negative and HIV-positive patients Methods: An observational, retrospective, longitudinal study in HIV-positive and HIV-negative patients with DLBCL, treated with chemotherapy from 2010-2019 at the Instituto Nacional de Cancerología, México. Results: We analyze data of 170 patients, 56 HIV-positive patients, and 114 HIV-negative. Male gender and advanced clinical stages predominated. During the first year of chemotherapy, 46% of HIV-negative patients and 70% of HIV-positive had one infectious complication ($p = 0.0001$). Pansusceptible gram-negative enterobacteria predominated. The bivariate analysis associated hypoalbuminemia, high ECOG, EPOCH scheme, and the HIV infection with infections. Infections were associated with a decrease in Event Free Survival (EFS) (RR 2.14, $p = 0.007$) and Overall survival (OS) (RR 2.5, $p = 0.001$), in both groups. In the multivariate analysis for OS, infections at diagnosis and CNS infiltration were independent prognostic factors. In the multivariate analysis for infections, ECOG and hypoalbuminemia were independent factors for developing infections. Conclusion: Patients living with HIV and lymphoma present a higher number of infections than patients HIV negative. However, the presence of HIV infection does not impact the survival of these patients. We observed an association between the low functional and nutritional status with the development of infections in the entire cohort. Infections had an impact on EFS and OS, regardless of HIV status.

IMPROVED CLINICAL RESPONSE IN A 21 YEAR OLD MALE WITH RELAPSE OF ACUTE LYMPHOBLASTIC LEUKAEMIA WHO DEVELOP CENTRAL NERVOUS SYSTEM RECURRENCE

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Abstract : Central nervous system (CNS) involvement is identified at the time of diagnosis in 5% of children with acute lymphoblastic leukaemia (ALL). Without adequate CNS prophylaxis, 50–75% of patients eventually develop CNS disease. CNS recurrence occurs in 5–10% of patients who are treated with contemporary induction protocols.
Case presentation : A 21-year old male was diagnosed with ALL-L1. The patient underwent standard risk chemotherapy with intensification and consolidation phase for 1 year, also given CNS prophylaxis and from the bone marrow evaluation found complete response. The patient was treated with maintenance therapy. After 3 months in maintenance phase, the patient suddenly felt blurry vision and legs were weaken. From the lumbar puncture we found lymphoblast cells and then diagnosed with isolated CNS relapse. Patient then was treated with methotrexate 12.5 mg intrsatechal twice weekly for 4 weeks, followed by weekly for 1 month and maintenance every month. After 1 month therapy with methotrexate intrsatechal, the patient condition was improved and he started to walk again.
Conclusion : Patients with isolated CNS recurrences should be treated with intensive, systemic, reinduction therapy. Effective CNS prophylaxis remains the best strategy for potential long-term survival.
Key Words : Acute Lymphoblastic Leukaemia, Relapse, CNS Involvement