Further Abstracts

1. Epidemiology/Diagnostic/Pathology

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SERUM FERRITIN IN MALIGNANT LYMPHOMA

Introduction: The purpose of this study is to define the clinical significance of the detection of serum ferritin (SPH) in malignant lymphoma (ML).

Methods: The SPH level of 62 patients with pathologically proven ML were detected by RIA.

Results: The mean value and range of SPH value of tested subjects are as follow:

<table>
<thead>
<tr>
<th>Subject</th>
<th>No.</th>
<th>7±SD ug/l</th>
<th>Range ug/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML patient</td>
<td>56</td>
<td>349±325</td>
<td>131-1284</td>
</tr>
<tr>
<td>ML patient</td>
<td>27</td>
<td>363±219</td>
<td>67-780</td>
</tr>
<tr>
<td>ML patient</td>
<td>56</td>
<td>170±125</td>
<td>95-350</td>
</tr>
<tr>
<td>ML patient</td>
<td>27</td>
<td>59±44</td>
<td>22-175</td>
</tr>
<tr>
<td>ML patient</td>
<td>36</td>
<td>139±90</td>
<td>90-371</td>
</tr>
<tr>
<td>ML patient</td>
<td>60</td>
<td>47±31</td>
<td>26-110</td>
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</tbody>
</table>

The results showed the SPH value was significantly higher (P<0.001) in ML patient with clinical tumor than in the patient in disease free period and non-tumor subject. In the long-term followed patients showed a dynamic change of SPH levels in a close correlation with the disease course, the SPH level increased to abnormal higher level in disease progression and decreased to normal level as the disease was suppressed by effective treatment.

Conclusion: The SPH is a marker of ML, the serial follow-up detection of SPH during the treatment of ML patient may offer a diagnostic value, monitor the treatment response and predicate to relapse.

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MICROVESSEL DENSITY IN CHEMOSENSITIVE AND CHEMORESISTANT DIFFUSE LARGE B-CELL LYMPHOMAS
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Introduction: Preliminary reports involving a number of different kinds of tumors have indicated that microvessel quantification may be useful in predicting disease outcome. The aim of this study was to clarify the relationship between microvessel density (MVD) as a parameter of tumor angiogenesis and the response to chemotherapy in diffuse large B-cell (DLBCL) lymphomas.

Methods: A total of 36 DLBCL lymphoma patients were evaluated. Twenty three with a chemosensitive, responsive disease (median survival 8 years) and 13 with a chemoresistant, refractory disease (median survival 8 months). Microvessel quantification was performed by immunohistochemical staining, using monoclonal antibodies against factor VIII related antigen (FVIII) and against platelet/endothelial cell adhesion molecule-CD31.

Results: We found that FVIII stained significantly higher number of blood vessels (about 2.5 times more) than CD31, and 7 samples that were unstaied with CD31 were positive for FVIII. There was no significant difference between the MVD staining of the two groups. MVD in the lymphomas stained for FVIII ranged from 6.6 to 149.3 microvessels per X 200 field (mean 54±36.1) for the chemosensitive DLBCL group, and from 10.8 to 94.5 (mean 43±25.5) for the chemoresistant DLBCL group.

Conclusions: FVIII appears to be more sensitive for staining DLBCL lymphoma microvessels than CD31. We found no correlation of tumor MVD and response to chemotherapy in patients with DLBCL lymphomas.

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IDENTIFICATION AT THE MOLECULAR LEVEL OF INTRANASAL LYMPHOMA
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Primary lymphoma (L) of the breast is rare phenomenon. It is usually evident elsewhere (lymph node) when detected in the breast, lymphoma (L) is a cause of large axillary lymph nodes (L-ADN). Intranasal lymphoma (L) has been described on histologic sectioning in all areas of the breast. The enlargement of breast (L-ADM-UN) is due to L- metastatic spread from intranasal malignancy to TM-ND, or hyperplastic. The ability to invade & metastasize (TM) characterize some but not all malignant cells. To be LM tumors must secrete proteolytic enzymes that can dissolve the type IV collagen that forms the basement membranes that surrounds the duct. A pancreatic Collagenase(Col) which is isolated & its enzymic activities detailed (Makkin & Peters, Kptl,Med, Surgery 20;114-211, 212-226,1985) & is an extracellular protease released from breast cancer cells (Makkin, Cancer Biochem. Biophys. 8;170-185,1980). DKK. #1951,1979). To metastasize cancer cells must have the ability to adhere to and migrate to new sites, thus tumor cells must develop adhesive proteins. To leave the blood & invade a secondary organ, the cells must have the ability to adhere to the blood vessel wall & pass through into the surrounding. Cells from L-ADM-UN, L-ADN, L-ND, L-ND (5), L-ND (6), L-ND (7) & L-ND (8) were examined for expression of oncogenes (O-ERG, ERG, Neu, mutated P53 (Makkin, J, Surg Oncol. 40:35-31,1989) & Diagnostic Clin, Testing 2;30-39,1989) using the well established immunoblotting technique (Makkin, Naturwissenschaften 75:261,1989). P-ERG, P-ERG, Neu & mutated P53 were undetectable in L-UN, L-ADM-UN, L-ADN, ADM-UN. Amplified oncogenes & mutated P53 with mRNA encoding Col, Integrin & IG-PIF were detected in L-ADM-UN, L-UN. Therefore, Col & the adhesion proteins play a role in the invasion of the mammary glands, while the oncogene & P53 identify the malignancy of the invading lymphoma cells.

NODAL CYTOTOXIC LYMPHOMA SPECTRUM:
A CLINICOPATHOLOGIC STUDY OF 64 CASES
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Introduction: The expression of cytotoxic granules-associated protein has been reported in some T- or NK-cell lymphomas of mostly extranodal origin, but rarely of nodal origin except for anaplastic large cell lymphoma (ALCL) and Hodgkin’s disease (HD).

Methods: This study analyzed 64 nodal lymphomas expressing TIA-1 and/or granzyme B, to characterize the clinicopathologic spectrum of these neoplasms.

Results: Four main categories could be delineated. (1) p80/ALC1 (ALCL). The patients were 2 to 50 years of age (median, 13 years), and pursued the relatively indolent clinical course. The tumors were of either T- or null-cell type with constant expression of CD30, EMA, and p80/ALC1, but not CD15 or BCL2. None harbored EBV. (2) Nodal high-grade cytotoxic lymphoma (n=13). The patients were 29 to 72 years in age (median, 53), and pursued an aggressive clinical course. The tumors often showed pleomorphic, anaplastic or centralized morphology, and were featured by either EBV association or CD56 expression. (3) Nodal low-grade cytotoxic lymphoma (n=8). The patients, 3 men and 5 women, were 31 to 75 years old (median, 61). Notably, 6 of them were of lymphoblastic (Lemmet) lymphoma. (4) Cytotoxic Hodgkin’s-related lymphoma (n=9) included two cases of HD and 7 cases of ALCL, Hodgkin’s-related, the latter characterized by the presence of Reed-Sternberg cells and often CD15+ phenotype. The patients were all men but one with age of 24 to 74 years (median, 50).

Conclusions: A significant heterogeneity was seen in the family of nodal cytotoxic lymphomas. The link among these four categories was also reinforced by the presence of a highly characteristic large cell with hoesnroe-like or reifnoid nuclei and the frequent expression of CD30 and EMA, which was helpful in identifying the cytotoxic phenotype.
BILATERAL THREPHINE BIOPSY IN THE DIAGNOSIS OF LYMPHOMA. UNILATERAL BIOPSY IS ENOUGH?

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Purpose: To evaluate the frequency of bilateral bone marrow biopsy performed in the staging of non-Hodgkin's lymphomas compared with unilateral bone marrow biopsy.

Materials and Methods: In our area with about 300,000 inhabitants, 272 patients got the diagnosis lymphoma between January 1992 through December 1996. We examined all medical journals to find out how many bone marrow biopsies there was performed and in how many cases an unilateral bone marrow was done. In all cases where a bilateral bone marrow biopsy was performed an evaluation whether lymphoma involvement was found from both sides. In these cases a second evaluation was performed by a lymphoma pathologist.

Results: Of the 272 patients, a bone marrow biopsy was done in 153 patients, 56% cases, of these a bilateral bone marrow biopsy was done in only 46 cases, 17% of the patients. Involvement of the bone marrow was found in 12 of 46 bilateral biopsies, and of these all have an lymphoma involvement in both of the biopsies.

Conclusion: In the literature there is no consensus about the necessity of performing bilateral bone marrow biopsies. In this small pilot study lymphoma involvement was found in 12/46 and all in both sides when a bilateral biopsy was done. A study is under progress in a larger patient population to answer the question.

ASSOCIATION OF EPITHELIAL GRANULOMAS AND NON-HODGKIN'S LYMPHOMA: REPORT OF TWO CASES.


Granulomatous reactions are well known pathological findings which may occur in association with malignant solid tumors and hematologic neoplasms. In lymphoproliferative disorders epithelial granulomas or granuloma-like features have been more frequently observed in Hodgkin's disease and T-cell lymphomas. By contrast, these findings only occasionally occur in B-cell lymphomas and at times they strikingly affect the clinical manifestations to the extent that they obscure the underlying primary disease. With the exception of infectious granulomatous disease, the occurrence of systemic epithelioid granulomas is highly suggestive of sarcoidosis, but it is very difficult to distinguish whether a generalized sarcoid-like reaction is a primary disorder or an unusual event linked to a neoplasm. Moreover, as suggested by previous researchers, sarcoidosis and lymphoproliferative disease may not be two entirely distinct clinical entities seeing that patients with history of sarcoidosis show a higher than expected incidence of lymphoma. We present two cases of B-cell lymphoma (case 1, 53 year old male; case 2, 49 year old male) with clinical findings characterized at outset by portal hypertension with hepatomegaly and splenomegaly but without lymph node enlargement. In both patients liver biopsies and subsequent bone marrow samples showed a non-caseating epithelioid granulomas consistent with sarcoidosis and without evidence of lymphoma. Steroid therapy induced only a partial and transient improvement of systemic symptoms in both cases. In case 1 a further bone marrow biopsy revealed the involvement by a diffuse large B-cell lymphoma that was later confirmed by a left axillary lymph node biopsy. Patient n. 2 developed a thrombocytopenic purpura and underwent splenectomy after unsatisfactory immunosuppressive treatment.

EXTENDED FIELD RADIOTHERAPY: A GEOMETRICAL SOLUTION FOR THE MATCHING OF DIFFERENT REGIONS USING ASYMMETRIC COLLIMATION.

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Introduction: In extended field radiotherapy as in (Sub)Total Nodal Irradiation, different fields often have to be planned because of the limited maximal field dimensions of the treatment machine (40 cm) or otherwise because of limitations imposed by the acute toxicity of large field radiotherapy.

Methods: We developed a technique with a fixed patient position and a fixed table height for the entire treatment. We define hereby a horizontal plane close to the midplane of the patient, which is equivalent to the isocentre of the treatment machine. The junction zone between the superior and inferior part of the treatment volume consists of a zone of 2 cm in a region without visible tumor deposits. Patient and table position are fixed for each of both series of radiotherapy. For the superior field, the lower jaw of the collimator is 16 and 20 cm on alternate days, the upper jaw position is asymmetrically adjusted to the upper limit of the target volume. For the inferior field, the upper jaw of the collimator is 20 and 18 cm on alternate days, while the lower jaw position is adjusted to the lower limit of the target volume. Irradiation of the superior and inferior part of the total target volume is done consecutively with a rest period of 0-3 weeks, depending on acute toxicity, in between the 2 series of radiotherapy.

Results: Because of the fixed patient position and table height for the entire treatment, setup reliability is excellent. The 2 cm. at the junction zone is treated half by the superior field and half by the inferior field, leading to a homogeneous total dose distribution without major under- or overdosages at the junction zone. This obviates the need for shielding blocks as used for the spinal cord at the junction of different radiotherapy fields. A supplementary advantage is a smaller divergence at the non-junctioning field borders.

Conclusions: This technique, as is illustrated by a sagittal treatment plan, enables us to deliver a homogenous dose to the clinical target volume. The technique can be used for all kinds of extended field radiotherapy.
INCIDENCE RATES OF MALIGNANT LYMPHOMA IN A NORTHERN-Spanish Area
Protocol: To determine the incidence rates (IR) and the age-adjusted incidence rates (AIR) of malignant lymphoma (ML) in the Aragon population. The evaluated population showed a regressive demographic pattern and negative-vegetative growth (-1.84 /10 inh) and it seems a good model to justify a prospective study, taking into account the strong relationship between age and lymphoproliferative disorders. This area has a total population of 1,188,817 inh (M:586,750; F: 602,247).
Patients & Methods: From 01/98 to 12/98, among 710 primary malignant hematological disorders, 166 lymphoma (23.4%) were diagnosed according to REAL classification and included in the Aragon registry of haemopathies. Demographic data: age, sex, abode, date and histological subtypes. Epidemiological parameters used: IR, AIR and confidence interval (CI); statistics: descriptive and frequency distribution Results: - NHL 141 (84.9%); M:F ratio 69:72; mean age 60.5±17.5 (range 3-92); abode 80 urban (56.7%), country 61 (43.3%) HD 25 (15.1%); M:F ratio 13/12, mean age: 41.0±18.6 (range 18-77), abode: urban 16 (64.0%), country 9 (36.0%). B-cell NHL 126 (89.4%), M:F 60/66, mean age 60.8±17.0; T-cell NHL 15 (10.6%) M:F 96, mean age 57.7±22.2; Extranodal NHL 25 (17.7%), M:F 9/16,mean age 56.0±15.3.
The incidence rates (cases/10 inh) were the following: Dx Global Males Females
HD 1.9 1.8 0.8 2.0 1.8 1.1 1.8 1.9 1.1
NHL 103.6 6.4 1.2 9.5 6.2 1.7 11.1 6.6 1.8
B-NHL 106.7 6.7 1.3 10.2 6.7 1.8 11.0 6.6 1.8
T-NHL 1.3 0.7 0.4 1.5 0.7 1.0 0.5 0.4
Extranodal 2.1 1.5 0.6 1.5 1.1 0.8 2.7 1.8 0.9
Total 123.8 6.3 1.5 11.6 8.1 2.1 13.0 8.5 2.1
NHL IR and AIR by age a 60 <60 were: 26.3±5.2 and 2.9±3.5.
Remarks: There are a high IR of NHL, specially in patients over sixty.

THREE DIMENSIONAL TREATMENT PLANNING AND CONFORMAL RADIOThERapy FOR LYMPHomas: WHICH SHOULD BE USE It?
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Introduction: Three dimensional treatment planning with inhomogeneities corrections are considered superior than 2-D planning for studying the dose distribution better to the experimental data. New imagers with spiral CT and MRI, are becoming more often implemented in 3-D planning, because thickening the dose to a 3-D volume requires a very good knowledge of its shape, for a safe anatomical and dosimetric coverage of the target volume, avoiding unexpected cold and hot spots. Drawing the inner profiles of sensitive organs and target(s), allows the study of multiple Dose-Volume Histograms showing differential and cumulative dose distribution per organ volume, to be analyzed for the probability of early and late normal tissue complications and local disease control. The probability of local control is actually a function of the mean target dose, but this is limited by normal tissues reactions. Multiple customized beams may concentrate the dose inside the target volume, increasing the gradient between target volume and critical organs.
Three dimensional treatment planning techniques are time and efforts consuming, and normally used to increase the dose to the target, improving local control without excess of toxicity. This is usually needed for epithelial tumours, where higher doses are required than for lymphomas, although often distributed in greater volumes.
Rationale: The rationale for using special radiotherapy techniques in lymphomas is not to increase the total dose but to reduce the toxicity of the treatment, or even allowing the radiotherapy treatment itself for patients otherwise excluded. Concentrating the dose inside the target reduces the toxicity of the treatment, especially toward the haematopoietic tissue, that may be very critical in some cases, conditioning the therapeutic choices. Possible candidates are for example those who should receive high dose chemotherapy or bone marrow transplantation and those who have already been treated with multiple chemotherapy lines.
Conclusions: 3-D planning and special radiotherapy techniques apply for new radiotherapy indications in lymphoma patients.

SOLUBLE CD44 IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA
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Introduction: Soluble CD44 (sCD44) is known to be increased in patients with malignant lymphoma. We evaluate the sCD44 as a prognostic factor in patients with non-Hodgkin's lymphomas (NHL), and correlate with sCD44 and its isoforms, sCD44v5 and sCD44v6.
Methods and Results: The subjects consisted of 18 healthy controls and 122 patients with untreated patients. The disease was low grade NHL in 22 patients, intermediate- to high-grade NHL in 90, and ATLL in 10. The standard sCD44, sCD44v5, and sCD44v6 levels were determined by ELISA. The sCD44 level was 412±112 ng/ml in the controls and 835±713 ng/ml in patients. The level tended to be higher in intermediate- to high-grade NHL than in low-grade NHL. When the NHL patients were classified by the international prognostic index, the level was significantly increased in the high-intermediate and high risk groups. The patients achieved partial remission and non-response had significantly higher sCD44 levels than the cases achieved complete remission. The prognosis was significantly poorer when the sCD44 level was 1200 ng/ml or more. Like the standard sCD44 level, the sCD44v6 level was increased to 281±108 ng/ml in patients with intermediate- to high-grade NHL as compared with 161±65 ng/ml in the controls, but the sCD44v5 levels of patients and controls were not significantly different.
Conclusion: The sCD44 level seems to be of prognostic value in NHL, particularly intermediate- to high-grade NHL. A correlation was demonstrated between sCD44 and sCD44v6.

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PROGNOSTIC FACTORS IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA OF THE HEAD AND NECK IN STAGE I AND II

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PURPOSE: In a retrospective study to establish prognostic factors in patients with head and neck non-Hodgkin's lymphoma (NHL), as well as to determine the role of radiotherapy in treatment of these patients.

Patients and methods: I analysed 116 patients with head and neck NHL in stage I and II treated at the Institute of Oncology between 1983 and 1992. Of these, 80 patients, extranodal sites were involved, 33 were localised in the Waldeyers ring, 8 in the thyroid gland, 8 in the paranasal sinuses, 4 in the parotid gland, 3 in the nose and 2 in the orbit and in 36 nodal sites. The average age for all patients was 63 (range 20 to 87 years). There were 59 men and 57 female patients and of these 65 had stage I and 51 stage II. According to the Ann Arbor classification. The morphologic classification we used Ki67 classification and 81 patients had a high grade NHL (in 89% treated with a combination of chemotherapy and radiotherapy) and 35 low grade (treated locally in 89% - mostly with radiotherapy).

RESULTS: The five years overall survival for all patients was 78%. 10 patients younger than 40 years had a better prognosis than the older ones, but otherwise sex, stage and histology did not significantly affect survival rate. The outcome was also not influenced by site of involvement. 10 patients with a high grade NHL treated only locally had statistically worse survival rate than patients treated with a combination of chemotherapy and radiotherapy. Of these 71 patients with high grade NHL and treated with combined modality therapy, 34 of them received only 20-21 Gy and this survival was equal to the patients irradiated with a higher dose.

Conclusions: Excepting age, no other factors had an influence on survival. We also conclude that patients with a high grade NHL should be treated with a combination of antineoplastic agents and radiotherapy.

WHIPPLE DISEASE: A DIAGNOSTIC ENIGMA. IMPLICATIONS FOR THE DIFFERENTIAL DIAGNOSIS OF VERY SLOWLY PROGRESSIVE LYMPHADENOPATHY.

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A 57 year old man was admitted for evaluation of a para-aortic lymph node seen on chest CT. Three weeks prior to his visit, he had fever and symptoms of an upper respiratory infection. Chest CT revealed a 2cm para aortic lymph node. There was no reported diarrhea, rash or night sweats. He had lost 2kg during the febrile episode, but started gaining them back. He recalled migratory pains of the knees and metacarpophalangeal joints with no tenderness, swelling or deformities. He is a bus driver, does not drink or smoke and had never been out of the country. Physical examination was normal. WBC 4600/μL, Hb 10.8 g/dL, Hct 34.4 ml/dL, Ptt 226000/μL, MCV 77, neutrophils 68%, lymph 27%, mon 5.2%. ESR 60mm/hr, β-2-microglobulin 3000mg/mL (N=2700). CT revealed mesenteric lymphadenopathy 1.5cm diameter. Gallium scan revealed pathologic uptake at the mesenteric location. Bone marrow biopsy and aspirate showed no evidence at the mesenteric location. PCR for 14,18 translocation from the BM was negative. Four months later the patient was asymptomatic. However, he still had microcytic anemia and an elevated ESR. Gallium scan became negative but mesenteric, abdominal and thoracic para-aortic nodes became increased in size to 2x3cm. At that point, the patient had a core needle biopsy from a retroperitoneal lymph node that showed foamy looking macrophages with bacilliform inclusions that stained positive for PAS and negative for acid fast, and diagnostic of Whipple's disease. The patient was treated with trimethoprim sulfamethoxazole and folinic acid. Six weeks later, his hematocrit increased from 32 to 39%, and homoglobin increased from 10.3 to 13.1gm/dL. A year later the patient is in good general condition, gained 5kg and has no evidence of disease. Treporyhma whippelii infection may be another great imitator that should be added to the differential diagnosis of lymphadenopathy. It can be treated successfully when diagnosed early and can be lethal if missed.
DIFERENTIAL DIAGNOSIS OF LYMPHOMAS BY MediASTINAL FINE-NEEDLE ASPIRATION BIOPSY


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Introduction: Fine-needle aspiration biopsy (FNAB) is increasingly being used for the diagnosis of lymphomas and has been shown to be suitable for immunocytochemical analysis. FNAB samples give excellent material for cytomorphological study as well as in paraffin embedded sections. Radiologically guided FNAB provide a reliable method of diagnosis for planning definitive therapy of patients with mediastinal lesions. Material and Methods: FNAB materials from 114 pts with mediastinal masses, between 1996. and 1998., were reviewed. The series was comprised of 62 females and 52 males, mean age 38.8 years, ranged from 14 to 71. All pts underwent a radiologically guided mediastinal FNAB as the initial step in their diagnostic evaluation. Material was analysed cytopathologically and histologically. Immunocytochemical studies were performed on all FNAB specimens to render a definitive diagnosis.

Results: Adequate material was obtained with a diagnosis achieved in 106 pts (92.9%). On the basis of cytomorphologic, histopathologic and ancillary studies performed on FNAB material diagnosis were: 60 (56.6%) lymphomas, 10 (9.4%) neuroepithelial neoplasms, 9 (8.4%) Schwannomas, 9 (8.4%) small cell lung cancer, 5 (4.7%) mesenchymal tumors, 3 (2.8%) thymomas, 2 (1.9%) metastases, and 1 (0.5%) tuberculous, chemodectoma, ganglieneuroma, neuroblastoma, dermato竣工, teratoma and extraneous Ewing sarcoma. Fifty seven (95%) of 60 lymphomas were correctly identified according to REAL classification: 39 Hodgkin's disease (33 nodular sclerosis and 6 mixed cellularity), 21 non-Hodgkin's lymphomas (7 primary mediastinal B-cell NHL, 5 precursor T-lymphoblastic NHL, 4 diffuse large B-cell NHL, 1 small lymphocytic NHL, 1 peripheral T-cell NHL and 3 unclassified NHL).

Conclusions: Diagnosis of mediastinal masses can be established with high degree of accuracy on the basis of FNAB material. The FNAB morphology of primary mediastinal lymphomas correlates with the spectrum of morphologic diversity with this entity in the surgical biopsies. Differential diagnosis between small round cell tumors of the mediastinum is still a great problem that can be solved by detailed immunonuropathology.
THE BONE MARROW PARTICLES IN THE STAGING OF LYMPHOMAS

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Introduction: The bone marrow (BM) examination is a key element in the staging of lymphomas. Optimal evaluation of the BM involves examination of the biopsy core and aspirate material. Aspirate sections, known as spicules or BM particles when carefully technically prepared, can give excellent results in morphology. They are particularly useful in immunohistochemistry because the tissue does not go through the decalcification process.

Methods: During the last year, at our Department, 106 sections of BM particles, alone or with biopsy core were examined in staging of lymphomas. Our technique for paraffin embedding accompanied by excellent cooperation with hematologists, contained in 90.5% material that was diagnostic. After the BM aspiration particles were carefully collected and placed into glass tube, fixed in B5 for 30 minutes, dehydrated in grading concentrations of ethyl alcohol, cleared in xylene and embedded in paraffin. During the whole processing tissue specimens are left in the glass tube that is crushed before embedding. In that way no particles are lost. Immunocytochemical analysis with an adequate panel of monoclonal antibodies was performed in all specimens.

Results: 9 BM particles, without core biopsy, were available for analysis in 12 pts. We observed lymphoma’s infiltration (nodular, interstitial and diffuse) in all 12 pts. Nucleo-cytoplasmatic or reactive BM, without infiltration was found in 56 pts in both specimens. Lymphoma’s infiltration of BM was observed in 39 pts, both in particles and in core biopsy. In 9 pts, histological and immunocytochemical analysis showed different findings in particles and in core biopsy: in 7 pts lymphoma’s infiltration (4 small lymphocytic NHL, 2 diffuse large B-cell NHL, 1 peripheral T-cell NHL) was observed only in particles while core biopsy contained only reactive marrow. The pattern of infiltration was interstitial or nodular. In two pts (one with small lymphocytic and one with follicle center NHL) the infiltration was observed in core biopsy while particles did not contain tumor tissue. In both cases the BM infiltration was of pathological pattern. Blood contamination of particles was noticed in 10 pts.

Conclusions: Our results prove that paraffin embedded BM spicules are of value in the staging of lymphomas. By taking both spicules and core biopsies we got more adequate samples of bone marrow tissue, which can be carefully histologically explored in identification of minimal lymphoma infiltration.

PROGNOSTIC SIGNIFICANCE OF BCL-2 AND MDR-1 PROTEIN EXPRESSION IN PATIENTS WITH NON HODGKIN’S LYMPHOMA.

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Introduction: High levels of BCL-2 protein are capable of preventing apoptosis and promote resistance to chemotherapy in lymphoproliferative disorders. Expression of MDR-1 gene is one of the most important mechanism of multidrug resistance in malignant cells treated with cytostatic agents. The purpose of this study was to know the prognostic significance of BCL-2 and MDR-1 protein expression in patients with Non Hodgkin’s Lymphoma (NHL).

Methods: 30 NHL patients treated with CHOP/MINE/ESSAP regimens, were studied. Avidine/Blackine-Peroxidase technique was used with monoclonal antibody C219 (Closencein), for the determination of the mdr-1 phenotype. The BCL-2 rearrangement was determined by the polymerase chain reaction (PCR) and subsequent molecular hybridization of the product. Both were done in peripheral blood. The prognostic factors were evaluated according to the International Prognostic Index (IPI). The actuarial event free survival (EFS) and overall survival (OS) were calculated by Kaplan and Meier method.

Results: The Pgp-170 and BCL-2 proteins expression were found in 9/30 (30%) and 10/30 (33%) of the samples respectively.

Tumor response: CR PR TR Progression
MDR-1(+) 4/6 (66%) 3/6 (50%) 7/6 (12%) 1/6 (16%)
BCL-2(+) 3/10 (30%) 5/10 (50%) 8/10 (80%) 2/10 (20%)
MDR-1(+) BCL-2(+) 8/15 (53%) 4/15 (27%) 8/15 (53%) 1/15 (6%)

Overall Survival: OS was 53% (95% CI, 43-63%) at 5 years, with a median of 40 months.

Event Free Survival: EFS was 41% (95% CI, 31-51%) at 5 years, with a median of 40 months.

No significant differences (p>0.10) in OS and EFS was found.

Conclusions: The presence of overexpression of MDR-1 and BCL-2 proteins in our patients did not have influence on OS and EFS.

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CUTANEOUS INVOLVEMENT IN MANTLE CELL LYMPHOMA

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Introduction: Skin involvement by mantle cell lymphoma (MCL) has been very rarely reported. Both clinical and histopathological features may raise diagnostic problems especially when skin lesions correspond to the extranodal lymphomatous infiltration.

Aim of the study: To describe the clinical and histopathological features of cutaneous MCL and to determine which complementary investigation may contribute to the diagnosis of MCL.

Results: The three patients were male, aged 56, 72, and 89 respectively. The two patients for MCL was previously unknown presented with a maculo-papular eruption of the trunk with purpuric lesions in one case. The third patient with prior diagnosis of MCL presented a diffuse and nodular infiltration in the trunk and the face. The patients had polyadenopathy but no hepatosplenomegaly. Skin biopsies showed either a diffuse and nodular infiltration of the dermis (n=2) or a discrete perivascular infiltration (n=1) by small lymphoid cells. These cells exhibited a B-cell phenotype: CD5, CD23, (2/3), CD19, CD20, CD43, S-IgM (2/3) or S-IgD (1/3). The immunohistochemical detection of cyclin-D1 protein was positive in only one case. Despite normal peripheral blood lymphocytosis (PBL) count, the same monomorphic monoclonal rearrangement of the immunoglobulin heavy chain gene was evidenced in the skin and PBL by PCR in all patients. (11/14) breakpoint was amplified from PBL in 1 patient. RT-PCR study of PBL showed overexpression of cyclin-D1 mRNA in another patient whereas the study of skin biopsies by RT-PCR was not contributive because of constitutive cyclin-D1 expression. The diagnosis of MCL was confirmed on lymph node biopsies in two patients. Our study emphasizes on the need of the parallel study of skin and PBL samples for the diagnosis of small B-cell cutaneous infiltrates.

NON-HODGKIN LYMPHOMAS (NHL) IN SOUTHWESTERN FRANCE: EPIDEMIOLOGICAL DATA FROM A GENERAL HOSPITAL.

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Centre Hospitalier de la Côte Basque, Bayonne, France.

Introduction: The reported incidence of NHL in the Western countries varies between 8 and 18/100000/year. Recently, an unexpected increase in this parameter has been evidenced. HIV is a well established risk factor for NHL while HCV has been implicated only by Italian authors. The purpose of our study was to determine the distribution of NHL cases in our area (300000 inhabitants) including those associated with HIV and HCV seropositivity.

Methods: We collected all the new cases of HIV+ and HCV+ NHL admitted in our day-hospital unit between January 1st, 1991 and October 31st, 1998. The studied population lives in rural or in little urban zones. No nuclear installations, petrol-derived industries, sources of toxic chemicals or insecticides exist in our region. These NHL were classified according to the REAL histological scheme. All the patients were checked for HIV and HCV serology.

Results: During the 41-month study period, one hundred thirty-six new patients were admitted in our department with a diagnosis of NHL. The calculated incidence was 15 cases/100000/year. The sex ratio (MF) was 1/2. The patients age ranged from 7 to 93 (median 62). NHL localized in lymph nodes in 86 cases (63.2%). The main extranodal sites were: stomach (8 cases), spleen (7), bone marrow (6), skin (5), bowel (4), bone (3), tonsil (7), CNS (2), thyroid (2). Our hundred NHL were of B immunophenotype (80.8%) including: diffuse large cell (40 cases / 29.4%), follicular (29 cases / 21.3%), small lymphocytic (11 cases), marginal zone (7) (pleomorphic: 7/MA T: 5), lymphoplasmacytotic (6), mantle cell (5), lymphoblastic (5), Burkitt (7). T- NHL were classified as anaplastic large cell (10 cases / 7.3%), peripheral T-cell (4), angioimmunoblastic (3), mycosis fungoides/sezary syndrome (1). In eleven cases, histologic +/- immunologic types could not be determined.

HIV+ (8%) among which three extranodal (tumor 2, liver 1). Their histologic types were Burkitt (1), B lymphoblastic (1),T anaplastic large cell (3), diffuse large cell (4), unclassified (2). Two patients (1.4%) presented with HCV+NHL including a 28-year woman with MAHL and a 43-year man with follicular NHL.

Conclusions: In our region, the incidence and the histologic distribution of NHL seem comparable with current published data. We did not evidence, as it is an Italian studies, a high prevalence of HCV infection among patients with NHL. Although HIV+HCV constitutes a relatively frequent entity, it does not explain the growing incidence of NHL in industrialized countries.

1. Epidemiology/Diagnostic/Pathology
ARE FDG-PET AND MRI USEFUL IN THE PREDICTION OF RELAPSE IN LYMHPHOMA RESIDUAL MASSES?

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Introduction: Treatment of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) frequently results in a residual mass (RM) visible radiologically. Such patients may receive radiotherapy unnecessarily because the RM may represent benign fibrotic tissue. Further treatment may be avoided if the nature of such lesions could be more accurately determined. The aim of this study was to compare FDG PET and MRI in the assessment of RM following treatment for lymphoma.

Methods: Patients with NHL/RD who had a RM following chemotherapy were eligible. Patients had a combination of MRI and/or FDG PET. All scans were reviewed within 5 months of the end of treatment. Patients were followed up (FU) for relapse.

Results: Fifty-eight patients were studied. Thirty-four had an MRI only, 2 had a PET only. Twenty-two patients had both investigations. Twenty-seven of the 58 patients with a RM were relapsed with a FU of 11.5 months (IQR 9-24) of whom relapsed within the RM.

<table>
<thead>
<tr>
<th></th>
<th>True +ve</th>
<th>False -ve</th>
<th>True -ve</th>
<th>False +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET all patients</td>
<td>24</td>
<td>4</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>MRI all patients</td>
<td>56</td>
<td>17</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>PET NHL</td>
<td>12</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>MRI NHL</td>
<td>24</td>
<td>4</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>PET HD</td>
<td>12</td>
<td>0</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>MRI HD</td>
<td>12</td>
<td>0</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

PET was performed in 12 patients with HD and 12 with NHL. In patients with HD there were 3 out of 9 false-negatives. In NHL the false-negative result was 1 out of 5. PET had a negative predictive value of 73% and a positive predictive value of 62%.

The results for MRI were 48% and 59% respectively. There was a trend for improved PET negative survival rate (PPS) compared to both MRI and PET.

Conclusions: These results are consistent with previous series of similar size and suggest that a negative PET scan can aid clinical decision making and obviate the need for further therapy in lymphoma RM. In this series it appears that PET is superior to MRI in this setting. The high rate of false positive with PET may be important in the potential change and optimal timing of scanning for relapse.

To date it has not been established whether the sensitivity of PET scanning varies with histology in RM.

DO WALDENSTRÖM'S MACROGLOBULINEMIA AND SPLENIC LYMPHOMA WITH VILLOUS LYMPHOCYTES FORM PART OF THE SAME DISEASE ENTITY?

R. G. Olson,

LA Parusan,
SI Richard,
SJ Morgan,
AS Jack.

The General Infirmary at Leeds and Bradford Royal Infirmary.

Waldenström's macroglobulinemia (WM) and splenic marginal zone lymphomas / splenic lymphoma with villous lymphocytes (SMZL/SVL) are disorders characterised by the presence of IgM paraprotein and variable degrees of BM, splenic, nodal and PB involvement. Furthermore a subgroup of pts exist who exhibit the morphological features of WM but who do not have a detectable IgM paraprotein; this disorder is generally termed lymphoplasmacytoid lymphoma/immunocytoma (LPL/IC). Distinction between these disorders is difficult and sometimes arbitrary. In order to clarify this matter we retrospectively analysed the immunophenotype of 122 pts diagnosed in our laboratory between 5/91 - 11/92. 91 pts were diagnosed as having WM, 17 SMZL/SVL, and 14 LPL/IC. Clinical details of the pts are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Medium age</th>
<th>IgM band</th>
<th>Splenomegaly</th>
<th>Lymphadenopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>60.5</td>
<td>100%</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>SMZL/SVL</td>
<td>68.5</td>
<td>NA</td>
<td>100%</td>
<td>18%</td>
</tr>
<tr>
<td>LPL/IC</td>
<td>70.3</td>
<td>0%</td>
<td>30%</td>
<td>50%</td>
</tr>
</tbody>
</table>

*w* PD lymphocytosis count > 4/10³.

Immunophenotype was determined by three colour flow cytometry in 109/122 (89%) cases while the remaining cases were assessed by immunohistochemistry. Trephine biopsies from 64 cases of WM and 12 cases of LPL/IC were also analysed immunohistochemically to determine the expression of IgM within the lymphoid component and CD138 within the plasma cell component. The results (expressed as the % of cases with positive antigen expression) are summarised in the following:

<table>
<thead>
<tr>
<th></th>
<th>CD20</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD23</th>
<th>CD56</th>
<th>CD38</th>
<th>CD138</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>SMZL/SVL</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>LPL/IC</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

We conclude that the majority of cases classified as WM, SMZL/SVL, LPL/IC are characterised by a pent germinal centre phenotype (CD19+CD20+CD21+CD22+CD35-CD103-CD11b-CD18+) and may therefore arise from splenic marginal zone memory B-cells. Distinction between these disorders is impossible on the basis of immunophenotype. They are however all characterised by variable degrees of splenomegaly, adenopathy and PB involvement. We suggest that it is more appropriate to consider them all as variants of the same disease entity which may be termed 'systemic marginal zone lymphoma'.

CD56+ Non-Nasal Aggressive NK cell lymphoma with Coexpression of Fas and Fas-Ligand

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2) The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Background: CD56+ NK/T-cell lymphomas occur more frequently in Orientals than in Western populations. Many cases of which are sinonasal origin and the cases of non-sinonasal origin are of a rare clinicopathological entity. We report a case of non-sinusal, nodal aggressive NK cell lymphoma with a fulminant clinical course of only 55 days. Present History: The patient admitted to our institution with high fever; generalized lymphadenopathy; severe jaundice; hepatitis; and pancreatitis. Abdominal para-aortic lymph node swelling was also detected. No sinonasal lesions, mediastinal masses and skin rashes were detected. No blastic cells were seen in the peripheral blood.

Morphological analysis: The He-stained specimen biopsied from left cervical lymph node showed diffuse, medium to large, centroblastoid cell proliferation with occasional apoptosis. No angiocentricity and massive necrosis were observed. Giemsa-stained imprint cytology demonstrated characteristic numerous azurophilic granules.

Immunohistochemistry: CD2+, CD56+, surface-CD57+, CD8a+, CD3+, CD16+, CD16+, CD57+, perforin+, TIA-1+, granzyme B+, Fas+, Fas-L+

Molecular analysis: IgV gene mutation, TCR y, TCR C, TCR B: germ line configuration

Discussion: Recent studies have demonstrated the relationship between the occasional necrosis of this group of lymphomas and the expression of cytotoxic molecules. This case, in addition, revealed that Fas and Fas-L pathway may contribute to the subsequent autocrine/paracrine tumor cell apoptosis.

T-cell rich large B-cell lymphoma: a single institute experience

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1) Servizio di Oncologia Medica, "Servizio di Anatomia e Patologia Patologica, Azienda Ospedaliera - Varano"

T-cell rich large B-cell lymphoma (TCRBLCL) is a recently described morphological variant of diffuse large B-cell lymphoma (DLBCL) characterized by a prominent reactive T-cell and histiocytic infiltrate that may obscure the scattered neoplastic cells. At present it is doubtful whether TCRBLCL represents a clinicopathological entity distinct from DLBCL. So in order to define the incidence of TCRBLCL and its clinical features we retrospectively evaluated 183 patients (pts) affected by non-Hodgkin lymphoma (NHL) referred to our center from January '91 to August '98. We excluded cases of chronic lymphocytic leukemia, Waldenström's macroglobulinemia, lymphoblastic lymphoma and HIV pts. We based histologic diagnosis of TCRBLCL on the following criteria: 1) diffuse growth pattern; 2) reactive lymphocytes and histocytes representing more than 50% of the cellular population; 3) scattered large cells with a B-cell phenotype making up less than 20% of cellular population. So in this period we observed 8 cases of TCRBLCL accounting for 4.3% of NHL and for 1% of DLBCL diagnosed in the same period.

Immunohistochemical analysis revealed that in 6/8 cases the reactive infiltrate was prevalently of T-cells (expressing more than 90% of cells in 6/8 cases), while in 2/8 cases histocytes prevailed. The male to female ratio was 1:1. Mean age was 58 years (range 29-85). The disease was usually advanced at onset in 6/8 pts (6/8 had stage III-IV) at clinical presentation. Bone marrow localization was present in 3/8 pts, splenic involvement in 5/8 pts., and extranodal disease in 6/8 pts. No patient complained B-symptoms. High LDH level was only observed in 2 pts. All pts received an anthracycline-containing induction regimen (CEOP) and 2 pts. received a high dose consolidation therapy. At present 6/8 pts. are in complete remission (CR) at a mean follow-up of 6 months (range 1-12). Two pts died, one for progressive disease and one for refractory relapse at 6 months from CR.

Both those 2 pts. had a prevalent histiocytic reactive infiltrate at the immunohistochemical analysis. Conclusion: TCRBLCL is a relative infrequent form of NHL but its recognition is important because it may simulate peripheral T-cell lymphoma or Hodgkin's disease. In our pts. affected by TCRBLCL the incidence of male, advanced stage, splenic involvement and bone marrow localization is higher than that found in DLBCL, suggesting a possible biologic difference between these two entities. Moreover, histiocytic prevalence in the reactive infiltrate, as reported by other authors, might be associated with a poor prognosis.
RISK OF LYMPHOMA AMONG SIBLINGS: A POPULATION-BASED STUDY

O. Paltiel, T. Shimit, H. Adler, P. A. Rachmilewitz, A. Pollack, A. Cohen, N. Haim, M. Ben Shachar, R. Epelbaum, M. Hurwitz, D. Ben-Yehuda. Dept. of Social Medicine and Epidemiology, Hebrew University, Jerusalem, Israel. (Received for publication September 6, 1979, and in revised form March 14, 1980.)

Genetic predisposition to Hodgkin's disease (HD) has been shown in twin and family studies. The familial risk of Non-Hodgkin's lymphoma (NHL) has been less consistently demonstrated. Through recent studies using two population-based sources we estimated the risk of HD and NHL in siblings of lymphoma (LY) cases.

Methods: We identified 2,500 siblings of 2,500 consecutive LY cases. The risk of NHL was compared between HD and NHL probands treated between 1970 and 1975 in 3 major hospitals in Israel and the Population Registry using the unique identity population of the proband case. This file was then linked with the Israel Cancer Registry where notification of all malignancies is required by law. The observed number of cases was compared with expected rates controlling for age, sex, calendar year, and continent of origin (standardized incidence ratio - SIR) using a person-time analysis.

Results: 22 cancer cases were identified among siblings of LY cases. Of these, 11 were hematopoietic - 7 leukemia, 1 NHL, and 5 HD. Mean age at diagnosis of all probands was 48 years, whereas for those with affected siblings it was 20 (and 25 for their siblings). There were 4 HD/HD pairs, 1 NHL/NHL pair, and 3 NHL/HD pairs. For HD/HD and NHL/NHL pairs the interval between LY occurrence in proband and sibling was 1.4 years, whereas for HD/NHL pairs this ranged from 16-21 years. SIRs among siblings with an A.LY proband were as follows:

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Observed cases</th>
<th>Expected SIR</th>
<th>Survival*</th>
<th>95% CI</th>
<th>* E=Estimated, * L=Unkown-Lowest Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>22</td>
<td>17.3</td>
<td>1.27</td>
<td>1.17</td>
<td>0.80-1.92</td>
</tr>
<tr>
<td>Hodgkin's</td>
<td>5</td>
<td>1.60</td>
<td>3.12</td>
<td>0.04</td>
<td>1.01-7.29</td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>13</td>
<td>1.10</td>
<td>1.27</td>
<td>1.80</td>
<td>0.46-3.11</td>
</tr>
<tr>
<td>All Lymphomas</td>
<td>2.20</td>
<td>2.68</td>
<td>0.10</td>
<td>0.79</td>
<td>1.55-27</td>
</tr>
<tr>
<td>Leukemias</td>
<td>1.44</td>
<td>2.08</td>
<td>0.17</td>
<td>0.14-4.07</td>
<td></td>
</tr>
<tr>
<td>All hematopoietic</td>
<td>11</td>
<td>4.47</td>
<td>2.46</td>
<td>0.06</td>
<td>1.23-4.4</td>
</tr>
</tbody>
</table>

* E=Estimated, L=Unknown-Lowest Interval

Conclusions: Using a non-biased population-based reporting system we found a 2.5 fold increase in risk of HD among siblings of LY probands compared to the general population. The uncontrolled patient of HD/NHL pairs argue for an environmental as well as genetic clasticity which requires further exploration.

PROGNOSTIC SIGNIFICANCE OF SERUM CA-125 LEVELS IN PATIENTS WITH HODGKIN'S DISEASE AND N.H. LYMPHOMA.


University of Patras Medical School, Patras, GREECE.

Introduction: CA-125 is an epithelial antigen/glycoprotein which serves as an index of tumor activity in patients with ovarian cancer. Increased serum levels have been also reported in other cancers and in N.H. lymphomas. The purpose of this study was to investigate the prognostic significance of serum CA-125 levels in patients with Hodgkin's disease (HD) and in N.H. lymphomas (NHL).

Methods: Serum CA-125 levels were determined at diagnosis and after treatment completion in 36 patients with HD and 106 with NHL.

Results: Five patients with HD and 32 with NHL had a minor to moderate elevation, 1 with HD and 15 with NHL exhibited a substantial increase (> 100 IU) of CA-125 levels. Three pts had mixed cellularity and 2 nodular sclerosis HD. Thirty one pts had nodal and 16 extranodal NHL. There were 27 D1C, 7 DM, 4 DS, 4 JM, 2 lymphoblastic and only 3 with indel NHL. Two pts had Ki-1+ ALCL and additional 2, mantle cell NHL. There was no T- or B- phenotype preponderance. Patients with elevated CA-125 had more frequently B symptoms (24/47 vs. 18/59, x^2=3.81, p=0.053), monocytic anemia (13/47 vs. 17/59, x^2=16.37, p=0.000) and an acute phase reaction (20/47 vs. 13/39, x^2=4.22, p=0.039) than those with normal levels. The majority of them had extensive abdominal disease with pleural or peritoneal effusions. Moreover they had significantly increased γ-globulins (1.07 ± 0.3 vs. 0.90 ± 0.03 g/dl, p=0.004), CRP (6.6 ± 0.5 vs. 2.8 ± 0.5 mg/dl, p=0.037) LDH (392 ± 38 vs. 271 ± 22 IU, p=0.008) and β2-microglobulin levels (3831 ± 377 vs. 2658 ± 220 μg/l, p=0.018). A good correlation between LDH and CA-125 levels was found. Finally treatment response was not different, but patients with high CA-125 had shorter DFS and more frequent relapses. Median survival was 16 months for pts with high and 34 months for those with normal CA-125 levels.

Conclusions: Elevated CA-125 levels is a common finding in patients with NHL and less common in those with HD. A substantial increase is found mainly in patients with aggressive disease and lymphomatous effusions, and constitutes a bad prognostic factor.

THE UTILITY OF FLOW CYTOMETRY IN THE DIAGNOSIS OF B-CELL LYPHOPROLIFERATIVE DISORDERS IN LYMPH NODES AND EXTRANODAL BIOPSY SPECIMENS.


Aim of the study: to evaluate the utility of flow cytometry (FC) immunophenotypic analysis in lymph nodes and extranodal tissues suspension cells obtained from patients with suspected lymphoma.

Patients and Methods: From January 1996 to December 1998, 185 biopsy specimens were tested at our FC laboratory with an Epics-XL cytometer (Coulter). They included 156 lymph nodes, 22 spleens, 3 tonsils, 2 liver biopsies, 1 skin biopsy and 1 gastric biopsy. A panel of paired antibodies conjugated directly to either fluorescein isothiocyanate (FITC) or phycoerythrin (PE) was used. Antibodies were: CD45, CD3, CD4, CD8, CD19, CD20, CD22, CD79b, CD23, CD10, CD5, CD43, FCMC7 and polyclonal (Fab) anti-kappa and anti-lambda. The immunophenotypic results were compared with the final pathological diagnosis.

Results: 12 samples (6.48%) were neocitic and excluded. The pathological diagnoses were B non-Hodgkin lymphoma (97 cases), T cell lymphoma (4), Hodgkin disease (29), reactive lymphoid hyperplasia (36) and metastatic lymph node (7). The FC studies showed a sensitivity of 83.5% and a specificity of 93.4% for B-cell lymphoma. The reliability was 87.9%. The positive predictive value and negative predictive value were 92.4% and 81.6% respectively. The highest diagnostic sensitivity was for indolent lymphoma (90.2%) and the lowest for aggressive lymphoma (72.5%).

Conclusions: FC analysis in lymph node biopsy specimens is an accurate ancillary diagnostic tool for B-lymphoproliferative disorders. FC analysis is a fast and easy technique, and could play a role in the initial evaluation when B-cell lymphoma is suspected. In our experience the results obtained in aggressive B-cell lymphomas were not as accurate as in the low-grade lymphomas.

Diagnostic significance of histomorphological, immunohistological and molecular biological analyses in parapsoriasis en plaques: 10 year follow-up and reevaluation of 35 cases

Andreas C. Höffner, MD; Karoline Zepter, MD; Poch Lor, MD; and Günter Burg, MD

Department of Dermatology, University Hospitals of Zurich, Zurich, Switzerland.

In order to assess the diagnostic significance of distinct phenotypical, histological and genetic criteria in parapsoriasis en plaques and to further define its position within the spectrum of inflammatory and malignant dermatoses, as well as to determine its tendency to transform into malignant T-cell lymphoma, clinical and laboratory data (history, clinical course, histology, immunohistochemistry and molecular clonality assessment) of 35 patients seen between 1979 and 1996 in the department of Dermatology, University Hospital of Zurich, were reevaluated and updated to current status by mailed questionnaire and by clinical reevaluation. After 10 to 17 years, none of our patients showed transformation into cutaneous T-cell lymphoma. In five patients, skin involvement remained constant during the observation interval, one patient showed progressive disease.

No single clinical, histomorphological or immunohistochemical test proved powerful enough to distinguish between cutaneous lymphomas and parapsoriasis en plaques on its own. A unifying feature of the parapsoriasis cases examined, however, was the polyclonal nature of the infiltrating T-cells as assessed by PCR-DGGE (Polymerase chain reaction / denaturing gradient gel electrophoresis). In contrast, similar inferences of early Cutaneous T-cell lymphomas could be shown to be clonal. Our study demonstrates the benign clinical course of Parapsoriasis en plaques and reveals the significance of PCR-DGGE as a tool to discriminate this entity from early CTCL.
Non Hodgkin's Lymphoma : is Thyminde kinase serum level is a predictive factor for response and relapses rates?

G Cartron, L. Broussolle, C. Linossier, M. Delain, C. Valeri, T. Lefrancois, Z. Tellier, J.P. Lamagnere, Ph Colombat. Department of Medical Oncology, CHRU Bruxenanne, Tours, France.

Introduction: Serum thyminde kinase (s-TK) have been found to provide useful therapeutic and prognostic informations in various hematological disorders. The aim of this study was to evaluate the prognostic relevance of s-TK in Non Hodgkin's Lymphomas (NHL). Methods: s-TK levels was measured at diagnosis in 120 pts with NHL. There were 62 male and 55 women with a median age of years (26-89). Sixty six pts were high grade and 44 low grade NHL. Ann Arbor stages : IV in 61 cases (25 pts had more than one extra nodal site involved), III in 16 cases, II in 17 cases and I in 26 cases. B-symptoms were present at diagnosis in 28 cases and a bulky mass was found in 28 pts. All patients were homogeneously treated according to the GOELAMS protocols. Results: s-TK levels was averaged (\(\geq 10^{10}/L\)) in 57 cases (48%) and was closely related to the stage of the disease (\(p=10^{-4}\)). One hundred eighteen patients were evaluable for response to induction therapy.

\[
\begin{array}{cccccc}
\text{s-TK (U/L)} & \text{LDH (U/L)} & \text{N} & \text{AA} & \text{NA} & \text{AA} \\
\hline
\text{< 10} & 26 & 54 & 18 & 44 & 12 & 16 \\
\text{\geq 10} & 50 & 10 & 16 & 19 & 9 & 7 \\
\text{p} & 10^{-5} & 10^{-5} & 10^{-5} & 10^{-4} & 10^{-4} \\
\end{array}
\]

Conclusion: With these preliminary results, we conclude that the s-TK level could be a good predictive factor in pts with NHL and predictive for response and relapse after first line chemotherapy.

MANTLE CELL LYMPHOMA - A HOMOGENOUS ENTITY?

G.Hopfner, H. Nowotny, A. Grutter, A. Nader, M. Veese, P. Eitermann, R. Heinz. 3th Med Dept and Ludwig Boltzmann Institute for Leukemia Research and Hematology, Hannover Hospita1, Dept of Pathology, Hannover Hospital, Vienna, Austria.

Introduction: Mantle cell lymphoma (MCL), formerly defined only by histological criteria according to the Kiel classification, appeared with the introduction of the REAL classification as a well characterized entity of Con-Hodgkin lymphomas. MCL completely replaces the grade centrocytotic lymphoma and its blastic variant. Furthermore, the definition of MCL led to inclusion of the high grade centroablasticcentrocydctic subtype in some cases. Materials and Methods: To test homogeneity of MCL, we reevaluated clinical and cytogenetic data of 16 patients with high grade centroablasticcentrocydctic (C/B/c) lymphoma, 29 patients with centroablastic/centrocydctic (C/CC) and 82 patients with centroablastic lymphoma (CC) treated at our institution. The clinical observation time ranged from 1977 to 1998; cytogenetic analyses were carried out from 1992.

Results: The median age was as follows: C/B/c 67 yrs., C/CC 63 yrs. and CC 67 yrs. Bone marrow involvement was similar in all three groups: 43%, 55% and 61%. Involvement of the spleen was as follows: 25%, 12% and 23%. Concerning the International Prognostic Index, the three groups were well balanced. Complete response rate was as follows: 7/16 (43.5%), 9/23 (39%) and 28/32 (87.5%). First line therapy was a regimen containing anthracyclines in most cases. The median overall survival was 25 months for C/B/c, 11 months for C/CC and 30 months for CC.

To date, histopathological reevaluation of 716 patients with centroablasticcentrocydctic has confirmed MCL. However, in 4 cases, one case was reclassified as follicular center lymphoma/grade III and two as diffuse large B lymphoma. Our cytogenetic findings in ten cases of CC (including blastic variants) showed the typical stem line aberration [t(11;14)] in all cases. The [t(11;14)] appeared as a consistent marker for mantle cell lymphoma. The inclusion of the blastic variant (r6) was supported by the typical [t(11;14)] found in all cases of this subgroup. In five cases of C/B/c lymphoma analyzed, we found [t(11;14)] in two cases.

Conclusion: Our data suggest that the inclusion of the blastic variant of centroablastic lymphomas based on cytogenetic and clinical findings supports the REAL classification. The inclusion of [t(11;14)] in centroablastic lymphoma into MCL was supported in some cases by clinical features. However, a histopathological and molecular biological review is mandatory.

INFECTION, ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS IN THE ETIOLOGY OF LYMPHOMAS: INTERNATIONAL CASE-CONTROL STUDY EPIBLUE.


Institutes: Case de Cadi d'OncoLog, Count Senaver Universiti de Bolytge, Barcelona; Spain; Free University Hospital, Amsterdam, Holand; International Agency for Research on Cancer, Lyon, France.

The incidence of all types of lymphomas has been rising in the last 30 years in Europe at an annual rate of approximately 4%. Recent data support that this rise is confined to some subgroups of lymphomas such as follicle center cell type, extranodal B-cell and nodal T-cell. The reasons for this increase are unknown and do not appear to be explained solely by better diagnosis. It has been recently postulated that the increase in incidence may be due to altered immune reactions to identifiable viral exposures. The project is a multicentric case control study in 6 European countries aiming to identify specific risk factors in the occurrence of lymphoid neoplasms. The study aims are: to identify the contribution of different infectious agents (Epstein-Barr virus, EBV, Hepatitis C virus (HCV) and Herpes virus 8 (HHV-8)) occupational exposures and UV solar radiation to the occurrence of lymphoid neoplasms with update technology. The study will be conducted in France, Spain, Italy, Germany, Finland and Ireland and aims to enroll 2000 cases and 40 controls. Risk estimates will be obtained for the different infectious agents and potential interaction effects between environmental and occupational exposures with the different viral agents will be estimated. A core protocol has been designed to be adapted to other potential participant countries. We present the feasibility study carried out in Barcelona, Spain that includes 60 lymphoma cases and 40 controls.

Methods: All incident cases of lymphoid neoplasms typed according to the REAL classification diagnosed at the CSUI, Barcelona during May-September 1999 are included. For each case, one hospital control has been selected frequency matched to the cases by age, sex and hospital. All patients were personally interviewed. Blood samples have been obtained from cases and controls. Tumoral tissue was obtained from cases. The data presented are acceptance rates, together with the success rates in obtaining biological samples and a complete exposure questionnaire. Serological results on HHV-8 and Hepatitis C virus tissue detection of EBV related proteins are presented.

Results: During the 4 month period 78 cases of lymphomas were identified and 52 were finally confirmed as lymphoma cases. These patients refused to participate and 3 did not have mental conditions to be interviewed: 30 NHL, 12 LLC, 7 MM and 3 HD. Three patients were HIV positive and 8 out of 33 lymphomas were EBV positive. No HCV cases were identified. 46 controls were identified and 36 included with a referral rate of 22%. Personal interviews last for about 2 hours and are well accepted.

Conclusion: The study is ongoing and updated information on this first phase of the study will be provided. We concluded that the study is feasible and can be extended to other settings.

CONTRIBUTION OF FLOW CYTOMETRY IN HEMATOPOIETIC BIOPSYES

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Background: Immunophenotyping is routinely performed by immunohistochemistry (IHC) in lymphoid pathology. The use of fresh cells obtained from tissue samples and its analysis by flow cytometry (FC) could enhance the panel of antibodies, improve the assessment of clonal restriction, and reduce the time of phenotypical studies.

Design and Methods: Samples from 128 lymph node biopsies, 8 spleens, and 7 other tissues were analysed. Fresh cells were obtained by repetitive infiltration of culture medium (RPMM 1640) with a fine needle. A panel of 10 markers was selected and samples were studied using Flow-sight softaware.

Results: The final diagnosis of cases was: 75 NHL (18 GLL, 6 MCL, 14 FL, 20 DGL, 12 Lymphomasomocytotic, 2 MLL, 1 Burkitt, 3 B NHL, 6 T-NHL, 1 true histocytocytic, 1 composite T and B NHL); 10 Hodgkin; 12 metastatic; 20 follicular hyperplasia; 18 granulomatous lymphaditis; and 8 others. Enough cellularity to perform FC study was obtained in 122 cases (85.3%) with a higher proportion in malignant hematological diseases (85.3%) than in other diagnosis (70.7%) (p<0.0001). Immunophenotype results were obtained within 4 hours after biopsy. Flow cytometry was considered normal in 45 cases, inconsistent in 6 (0 NHL, 1 reactive) and abnormal in 71 cases. A concordant phenotype between FC and IHC was obtained in 60 of B cell origin, 5 T cell, 1 monocytic and 4 epithelial tumors. A composite B and T lymphoma could be diagnosed by FC but not by IHC. A normal FC phenotype was detected in 12 cases with a final diagnosis of malignancy: Hodgkin’s disease (6/9), metastatic lymph node (2/7), NHL (1/3). Cytolical light chain restriction was observed in 5/100 samples, all B-NHL, in 2 B-NHL no clonal restriction was detected and in 5 no light chain was detected (all DGL). Reactive follicular hyperplasia showed higher percentage of T cells (51.9% ± 11.3 vs 29.8% ± 14.6, p<0.0001), lower percentage of cells with CD10 expression (2.5% ± 7 vs 36.5% ± 26.8, p<0.0001), and a lower percentage of FL. Accuracy of FC study was 65.5% (95.5% excluding Hodgkin’s disease) and sensitivity 100%.

Conclusion: Immunophenotype of lymphoid samples by FC in the diagnosis of NHL shows a good accuracy and sensitivity. It is a simply and fast method to discriminate follicular hyperplasia, and is very useful to detect clonal B cell population.
Effect of Marrow Flow Cytometry (FC) on NHL Staging

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Introduction: Morphological examination of trephine biopsy is standard practice in staging of patients with NHL. It can affect prognosis and treatment strategies used, especially in stage I and localized stage II disease. The purpose of this study is to see the frequency with which FC will advance the stage of morphologically staged NHL.

Methods: A review of all trephine biopsies submitted for conventional morphological and immunophenotypic staging of confirmed NHL was performed. Biopsy morphology was reviewed separately and independently by two investigators for adequacy of specimen and involvement by NHL, and disagreements resolved by third party morphological assessment. A chart review determined the clinical stage of disease at diagnosis. FC was performed using 3- and 4-color multi-parameter flow cytometric analysis with individualized gating strategies.

Results: Of 106 cases, 32 had stage I disease, 28 stage II, 28 stage III, and 18 stage IV(E). Two of the stage I cases were reclassified as stage IV on the basis of marrow positivity by FC despite negative morphologies. Five cases that were initially stage II were reclassified as stage IV based on FC. The majority of stage III cases had marrow involvement, half (14/28) morphologically with a further 5 involved by FC.

Clinical Stage  
No. (%) Stage modified by morphology alone Stage modified by morphology + FC
Stage I 32 (30) 28 (26) 26 (24)
Stage II 28 (26) 23 (21) 17 (16)
Stage III 28 (26) 14 (13) 9 (8)
Stage IV(E) 18 (17) 41 (39) 54 (51)

Conclusions: A number of early stage NHL cases with negative marrows will be reclassified to stage IV on the basis of FC results. The clinical importance of this finding with respect to treatment outcomes needs further evaluation.

T-CELL-RICH B-CELL LYMPHOMA - A CLINICOPATHOLOGIC STUDY OF EIGHT CASES

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INTRODUCTION: Although T-cell rich B-cell lymphoma (TCRBCL) is a recently recognized form of Hodgkin's lymphoma (NHL), limited information regarding its incidence, cellular origin, morphologic spectrum and biological behaviors is currently available. The study is aimed at investigating clinical/biological characteristics of 8 TCRBCL pts.

METHODS: During the period 1996-1998, the total of 8 TCRBCL pts were treated (MR ratio 6/2, median age 52 years [26-67]). One of the pts was Ann Arbor stage II, one stage III and six stage IV pts. The pts presented with generalized lymphadenopathy (head, splenomegaly and/or hepatomegaly [three], and bone marrow involvement [six]). The diagnosis of TCRBCL was initially established in 6 pts, while immunohistochemistry of the lymph node evidenced in all six pts polymorphic cellular composition with small, lymphocytes of T-cell origin (CD45RO and CD2) being the most predominant (more than 80% lymphoid elements). The percentage of the strophic large cells was lower (up to 20%) with rare Reed-Sternberg-like (CD20, CD20a) and (CD15, CD30) cells. The remaining two pts were initially diagnosed as having Hodgkin's disease (of mixed cellularity in one patient and lymphocyte predominance in another). Revision of the samples and immunohistochemistry enabled diagnosis of TCRBCL. B-cell clonality was evidenced in all 8 pts by restriction of Ig light chains.

RESULTS: Two pts (initially diagnosed as having Hodgkin's disease) were treated according to the standard ABVD protocols and partial remission, lasting 30 and 24 mos was achieved. Five pts were treated according to the protocols intended for large-cell lymphomas and complete remission was achieved in 2 pts (lasting 12 and 16 mos, respectively). Partial remission was achieved in 1 patient (22 mos), while in 2 pts the treatment is still in progress. In one patient lethal outcome ensued one month after diagnosis. Median survival for the whole group was 14 mos (3-30 mos), with 5 pts being still alive while 3 pts died.

CONCLUSIONS: Akin the situation in histopathology, views on TCRBCLs is difficult to separate from those of Hodgkin's lymphoma and peripheral T-cell lymphomas. It can be thus concluded that immunohistochemistry in conjunction with histomorphology will allow a conclusive diagnosis of TCRBCLs. This distinction from prognostic and therapeutic standpoint is of the utmost importance. The rarity of TCRBCL (approximately 1% of NHL) studies on larger series of pts are necessary.

CLINICAL RELEVANCE OF GALLIUM SCAN IN LYMPHOMA BEFORE AND AFTER THERAPY


Introduction: The clinical impact of gallium scan (GS) before and after therapy of lymphoma remains controversial. The aim of the present study was to examine whether GS could find additional sites and could change the pre-therapeutic clinical stage of the disease by comparison with conventional imaging (CI), and to evaluate the ability of GS to predict the long-term outcome of patients with or without residual radiologic abnormalities.

Methods: From March 1995 to November 1998, 86 GS were performed in 62 patients with Hodgkin's disease (n=52) or Non-Hodgkin's lymphoma (n=10). GS was performed at diagnosis (n=44) or after therapy (n=42) in standardised conditions, using 185-220 MBq gallium-67 citrate.

Results: For individual suspected sites of disease before treatment, an agreement between CI and GS was observed in 25/44 patients (57%). CI showed more sites than GS in 12 patients (27%) and GS demonstrated more sites than CI in 5 patients (11%). Although the number of sites showed by CI and GS were identical in 2 patients (5%), the localisations were different. The clinical stage defined by GS and CI were identical in 35 patients (79%). Compared with CI, GS 'downstaged' 7 patients (16%) and 'upstaged' 2 patients (5%). GS 'downstaged' mainly because of a limited value below the diaphragm and 'upstaged' owing to a good sensitivity in the chest. After therapy, CI and GS were normal in 11/42 patients. All but one were in complete remission (CR) after a median follow-up of 26 months. In contrast, radiological residual mass was observed in 31/42 patients. GS was normal in 25/32 (78%); 17 of these were in CR after a median follow-up of 26 months and 4 relapsed to 8 to 43 months later. The cause of death was unknown in 1 patient. GS showed an abnormal uptake in 9/31 patients; active disease was demonstrated in 8 patients, of whom 5 died and 1 patient was in CR 18 months after GS.

Conclusion: GS cannot substitute for CI in the staging work-up, but can demonstrate additional individual sites in more than 10% of patients and can lead to a clinical 'upstage' in some of them. After therapy, GS has a clinical impact when radiological abnormalities persist because it can either avoid useless complementary treatment or confirm the necessity of changing treatment modalities.

EVALUATION OF RESPONSE TO THERAPY WITH 67Ga SCINTIGRAPHY, CT SCAN AND MAGNETIC RESONANCE IN MALIGNANT LYMPHOMAS


The aim of this study was to evaluate the usefulness of the 67Ga Scintigraphy in the management of patients with malignant lymphomas after treatment, and in particular to assess the nature of residual masses seen on Computed Tomography (CT Scan) and/or Magnetic Resonance (MR) and to detect recurrence during remission.

To 33 patients (14 M, 19 F, median age 28 yrs, 15-67 yrs) were studied; 23 had HD and 10 NHL high grade. 11 patients had only mediastinal disease, 16 had mediastinal and extra mediastinal disease, 4 only extra mediastinal disease. In 21 patients 67Ga scan, CT scan and/or MR were performed after the completion of conventional chemotherapy, in 2 after intermediate dose chemotherapy and in 12 after high dose chemotherapy with peripheral blood stem cell support. Twenty-two/33 patients received consolidation radiotherapy as part of treatment strategy. Clinical score was deaths (D), continuous disease (CD) and continuous complete remission (CCR).

Results concerning the upper diaphragm disease are:

<table>
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<tr>
<th></th>
<th>Ga+</th>
<th>Ga-</th>
<th>CT+</th>
<th>CT-</th>
<th>MR+</th>
<th>MR-</th>
</tr>
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<tbody>
<tr>
<td>D</td>
<td>6/8</td>
<td>28/31</td>
<td>66/66</td>
<td>0/66</td>
<td>1/6</td>
<td>1/6</td>
</tr>
<tr>
<td>CD</td>
<td>2/3</td>
<td>1/3</td>
<td>3/3</td>
<td>0/3</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>CCR</td>
<td>11/18</td>
<td>17/18</td>
<td>12/16</td>
<td>4/16</td>
<td>5/9</td>
<td>4/9</td>
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</table>

In the group of 9 patients with 67Ga scan positive 6 died and two showed continuous disease while in the group of 20 subjects in whom 67Ga was negative 2 deaths were recorded (one patient died for secondary leukaemia). 1 showed continuous disease and 17 remained in continuous complete remission.

Conclusions: Ga-scintigraphy seems to be an accurate indicator for detecting the presence of active disease and viable tumor in residual masses and is able to differentiate between tumor and fibrosis or scarring. It has also been demonstrated that it can evaluate and predict the long term effects of therapy.
ROLE OF CD79b AND CD43 IN A DIAGNOSTIC SCORING SYSTEM (MCSS) FOR CHRONIC B-CELL LYMPHOPROLIFERATIVE SYNDROMES
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Introduction: The continuous advances being made in the definition of new lymphocytic antigens continue to stimulate the search for immunophenotype markers capable of distinguishing chronic lymphoproliferative diseases in leukemic phase. We evaluated the reactivity of CD79b (recently proposed by Catovsky for the CLL scoring system) and CD43 (included in the REAL classification) with the aim of evaluating their diagnostic impact in patients with leukemic forms of chronic B-cell lymphoproliferative syndromes.

Methods: CD79b and CD43 expression was evaluated in a series of 110 pts with mature B-cell chronic leukemias of extracoludicular origin (CD10+), subdivided into 4 groups in accordance with our scoring system based on Slg intensity and CD19/CD20 reactivity group (133 pts had cytoremorphological and immunophenotypical characteristics compatible with classical CLL, group 2 (21 pts) had characteristics compatible with what we call variant CLL (CLL-ve) because of its 567 intensity and atypical morphology (significantly more frequent than in cluster 1: p<0.002); group 3 (15 pts) had characteristics compatible with mantle cell lymphoma, and group 4 included 21 pts with leucemic immunoctoma and splenic marginal zone lymphoma, HCL and prolymphocytic leukemia. Marker positivity was expressed as grade 0 (0% of CD19+ cells), grade 1 (€ 20% - 60%), grade 2 (60% - 80%), and fluorescence intensity as the difference in the log scale distribution of the median value of positive cells and that of the negative control.

Results: In group 1 CD79b positivity was much less (but present) than in the other groups (grade 2 reactivity: 26% vs > 90%; p < 0.001; CD43 was constantly dim (median 222 vs 400). Moreover, in group 1, variant or non-CLL morphology was more frequent in the CD79b+ patients (p <0.08), there was a close correlation between the fluorescence intensity of CD79b and IgD (Pearson test, 0.99) and not in CD79b+; and correlated well with Slg intensity and CD23 expression (Pearson test r = 0.53, respectively).

Conclusions: CD79b and CD43 were useful in distinguishing CLL from cLL-ve, but not the non-CLL forms. The results support the significance of our scoring system, although more patients need to be studied and biological, molecular, clinical and prognostic features need to be evaluated.

DIFFUSE LARGE B CELL LYMPHOMAS: REPRODUCIBILITY OF THE KIEL CLASSIFICATION HISTOLOGIC SUBTYPES
I. Soubeyran*, A. De Mascred, E. Labouyrie, M. Trepars
Departments of Pathology, Institut Bergonié and Hôpital Libourne University Hospital, Bordeaux, France.

Among non-Hodgkin’s lymphomas, diffuse large B cell lymphoma (DLCL) (REAL Classification) represents a large heterogeneous group of tumors recognized until now in different categories (Kiel and WP). The main reason to group them were: 1) no difference between treatment strategies among subgroups; 2) reproducibility among observers is not good enough to be reliable. However, this group of tumors is morphologically, molecularly heterogeneous and clinically heterogeneous from a prognostic point of view. The aim was to devise a grading system that would reflect the biological differences within this group.

Method: Each of the 4 pathologists reviewed cases independently without knowledge of the clinical information. We studied a series of 136 primary DLCL treated at the Institut Bergonié from 1990 to 1993.

Results: The proportion of the different subtype among pathologists were as follows: monomorphic centroblastic (CB) 43.5 to 58%, multilobulated CB 6.5 to 12%, polymorphic CB 12 to 19%, immunoblastic 1.5 to 9%, anaplastic large B cell 0.7 to 1.5%, unclassifiable 9 to 13% and other subtypes of NHL 5 to 8%. The median concordance for DLCL versus other NHL was 95%. In the group of DLCL, median concordance was 77% (73-85%) with a median Kappa test of 0.66 (0.59-0.76). In a same team, concordance increased to 83 and 85% with Kappa test of 0.70 and 0.74. Median concordance for all categories was 56% (47-69%) with a median Kappa test of 0.39 (0.25-0.53).

Conclusions: DLCL is a reliable diagnosis. Inside the group, reproducibility is correct but insufficient. There is a need to define reliable and reproducible morphological, immunohistochemical and molecular criteria. This work was supported by the Ligue Nationale contre le Cancer, Comité Départemental des Pyrénées Atlantiques.

COMPUTER TOMPOMAGRY, MAGNETIC RESONANCE AND GALLIUM-67 SPECTROGRAPHR AND GALLIUM-67 SPECTROGRAPHY IN THE EVALUATION OF REMISSION IN PATIENTS WITH MEDIATINAL LYMOPHOMA
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Magnetic Resonance (MR) and Gallium-67 scintigraphy (Ga-67) have been proposed as alternative and potentially more accurate procedures than Computer Tomography (CT) for differentiating between residual active lymphoma and fibrotic scar after therapy (especially for mediastinal disease). Nevertheless there is no general consensus on the role of these radiological techniques for monitoring residual masses in patients with Hodgkin’s disease (HD) and non Hodgkin’s lymphomas (NHL). We have compared the imaging data of CT, MR and Ga-67 after treatment in a selected group of patients (pts) with high risk HD and NHL. All pts had mediastinal involvement at diagnosis (bulky 40%) and were consecutively entered on chemotherapy (6 courses of ABVD for HD and 6 courses F-MACHOP for NHL) radiotherapy on residual disease and autologous stem cell transplantation (ASCT) (conditioned with BEAM for HD and BAVC for NHL, respectively). CT, MR and Ga-67 were evaluated as positive respectively when a residual mass more than 2 cm of diameter was present (CT), when the residual mass was hypointense in T2-weighted images (MR), and when the residual mass had a Gallium uptake. Median follow up after ASCT was 41 months (range 24-96). Data here reported are those relative to the evaluation performed 6 months after ASCT.

<table>
<thead>
<tr>
<th>Category</th>
<th>Positive</th>
<th>True positive</th>
<th>False positive</th>
<th>Negative</th>
<th>True negative</th>
<th>False negative</th>
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<tbody>
<tr>
<td>CT</td>
<td>29</td>
<td>22 (75%)</td>
<td>7 (25%)</td>
<td>10</td>
<td>19 (95%)</td>
<td>1 (5%)</td>
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<tr>
<td>MR</td>
<td>25</td>
<td>16 (64%)</td>
<td>9 (36%)</td>
<td>10</td>
<td>9 (90%)</td>
<td>1 (10%)</td>
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<tr>
<td>Ga67</td>
<td>23</td>
<td>20 (87%)</td>
<td>3 (13%)</td>
<td>10</td>
<td>9 (90%)</td>
<td>1 (10%)</td>
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</table>

These results confirm the persistence of residual mass in the mediastinum in a significant amount of pts after therapy. In our experience all 3 techniques showed a very low-predictive significance for positive cases (94 to 100% of false positive) without any difference between categories, with or without bulky disease at diagnosis. In fact only 1 of the 16 pts with positive MR, none of the 9 pts with positive CT and none of 6 pts with positive GaGa67 relapsed. On the contrary all 3 techniques were highly predictive for negative outcomes, since only 1 of the 22 pts with negative CT, none of the 9 pts with negative MR and none of the 17 pts with negative GaGa67 relapsed.

This data supports the need of a particular caution in the interpretation of radiological positivity after treatment, furthermore points out the necessity for a comparison, laboratory and radiological findings for a better evaluation of response status.

1. Epidemiology/DiagnosticPathology
PREDICTIVE POTENTIAL OF DISEASE PROGRESSION BY DIFFERENT LABORATORY TECHNIQUES IN FOLLICULAR NON HODGKIN'S LYMPHOMA.

Unit of Clinical Hematology, European Institute Oology, Milan, Italy

Introduction: Follicular non Hodgkin's Lymphoma (FLNH) is an indolent disease characterized, in up to 90% of the cases, by the presence of the (t(14;18)) translocation and the positivity of B-lymphocyte (CD20+) for the Calla antigen (CD10). We studied our patients bone marrows (BM) and peripheral blood (PB) by molecular biology (MB) and flow cytometry (FC) analysis in order to evaluate the possible relationship between these two techniques and the clinical stage, remission or progression of the disease.

Patients and Methods: 14 FLNH patients were tested for the presence of the major breakpoint of the (t(14;18)) translocation by nested PCR and the co-expression for CD20 and CD10 by flow-cytometry. The MB sensitivity was 1x10^5 cells, while FC evaluation was considered pathologic when more than 50% of total cells analyzed co-expressed the two antigens. 10 patients were treated with Rituximab (IDEC CD20-Mabthera), 3 with sequential high dose chemotherapy including 3 cycles of Cladribine followed by a myeloablative regimen with stem cell support, while 2 received Leukeran and Prednisone.

Results: Out of 51 determinations on BM and PB, 39 showed a correlation between BM and FC, while 8 were positive for BM and negative for FC and 4 viceversa. The correlation with the clinical stage of the disease (remission or progression) were of 45/51 for MB and 41/51 for FC. Moreover 6/14 patients had at least one positive sample evaluated by MB and 7/14 by FC. PCR positivity had a direct correlation with the progression of the disease.

Conclusion: Both MB and FC can help in the diagnosis and disease monitoring of FLNH patients, showing a good correlation for the presence of circulating or BM malignant cells and the remission or progression of the disease. However, the high sensitivity showed by nested PCR in detecting the (t(14;18)) translocation, was predictive for progression of disease, even in those cases in which clinical and instrumental examination were still negative.

DIAGNOSTICS OF B-CELLULAR CHRONIC LYMPHOCYTED LEUKEMIA USING TWO-COLOURFLOW CYTOFLUORIMETRY

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We studied the immunophenotype of peripheral blood lymphocytes in 78 patients with mature cell lymphoproliferative diseases and determined the density of surface antigens (CD4, CD8, CD19, CD5, CD20, CD23, kappa and lambda chains, CD24, CD43, CD45, CD61+56, CD34, HLA-DR).

The CD45 concentration on the surface of B Orbital chronic lymphocytic leukemia. No reduction of CD45 concentration was revealed though in the overwhelming majority of patients with other B Orbital highly differentiated lymphoproliferative diseases. The low density of CD45 is an important diagnostic sign of BCLL among other immunomorphologic characteristics. For monitoring of BCLL therapy efficacy, a simultaneous detection of lymphocytes with low density CD45+CD19+ can serve as a more sensitive indicator of small amounts of chemotherapy surviving leukemic cells than detection of CD19+CD5+ lymphocytes.

Key words: B Orbital chronic lymphocytic leukemia (BCLL), lymphoma, immunophenotyping, flow cytometry, CD45.

LYMPHOPROLIFERATIVE SYNDROME, AUTOIMMUNE HEMOLYTIC ANEMIA AND KAPOSI SARCOMA IN HIV NEGATIVE PATIENT

S. Storni, R. Marra, M. Mezzabotta, Maresca M, Gaeta A, M. Rotoli*, G. Leone
Istituti di Scienze Mediche e Clinica Dermatoloica - * Universita Cattolica Roma

In September 1991 a sardinian man (B.F.), aged 48, HIV+, was admitted to our Hospital for Kaposi Sarcoma (KS) of the legs. A CT scan showed multiple hyperdense lesions of the lungs with enlarged lymphnodes (LN) in midsternum and at the hilum of the liver. Blood lymphocyte subpopulations were CD4 41%, CD8 26%, CD3 9%, CD20 32%, CD19 46%, CD10 3%, DR 45%, Sfag 50%, Sflg 21%. A bone marrow biopsy showed a polymorphic lymphoid nodules with centrocytes, centroblasts and plasmaetcs. During the hospitalization he presented a severe hemolytic anemia Coombss (AH)+ with HB decreasing until 3 gdl. For this reason he was treated with PBD and high dose native Ig (HD Ig) with partial and transient improvement. Splenectomy and abdominal LN biopsy performed with the histologic finding of red pulp hyperplasia and aspecific lymphoedematopathy. In the following weeks 4 courses of CVP-Bleo regimen were administered with a progressive improvement of the AHA even though the Coombs test was still +. Three months later the fever came back and the anemia worsened again. We treated the patient with HD Ig and azathioprin obtaining a clinical and hemorhologic improvement. In August the renewal of the fever and the presence of circulating atypical lymphocytic cells led us to evaluate again the marrow histology that showed a sustensive picture resembling a lymphoproliferative disease of lymphomamonocytic type. We started ProMACE-CytoBOM regimes (6 courses) with regression of the fever and improvement of the anemia, but with the Coombs still +. The KS lesions grew up. In the following months the patient worsened again and died for the progression of the lymphoma, as confirmed at the autopic study, and of AHA.

The association of KS and LPS is well known in HIV+ subjects, and, even though with a lower incidence, in other immunological disorders. In our patient it is possible to hypothesize a primitive immunologic disorder determining KS, AEA and LPS. Yet we cannot rule out that the LPS may play a primitive pathogenetic role. The control of the anemia and of the fever needed very aggressives therapies, but the CR was never achieved.
Diagnostics and prediction Hodgkin's and Non-Hodgkin's lymphomas by detected threshold concentrations of sCD30 and IL-10 in sera of the patients.

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Earlier we have detected having prognostic and diagnostic value threshold concentrations (TC) of sCD30 and IL-10 in sera of the patients with HD and NHL (B-diffuse large cell, T-large cell anaplastic (ALCL) and B-, T-lymphoblastic Lymphomas). The level of sCD30 reduced after treatment, but its TC depended on sensitivity to chemotheraphy (CT). Values of TC of sCD30 during CT, after the 2-nd course and further: 1) at the patients with remission more than 1 year - 8-18.5 U/ml (at N=5 U/ml), 2) at the refractory patients - 55 ± 8 pg/ml. The initial level of sCD30 at HD at I-II stages was lower, than at the IV (about: 40 and 110 U/ml accordingly) and was lower, than at NHL at I-II and IV stages (about: 60 and 270 U/ml). 2 patients with mantle cell lymphoma had the level of sCD30 which didn't reduce after 2, 5, 7 courses of CT and remained at initial level (120, 190U/ml). Thus, the prognosis of sensitivity to CT can be made already after the 2-nd course of CT, that allows changing tactics of treatment of the refractory patients opportunely. Measurement of sCD30 levels before and during CT allows determining character of lymphomas. The level of IL-10 at HD and at NHL did not depend on quantity of courses of CT, the threshold concentration of IL-10 was equalled 32 pg/ml. The concentration of IL-10 was lower, than threshold at 100 % of the patients with HD and at half of the patients with NHL and only in 50% with NHL IL-10 were higher TC. In this work we managed to correct, to update or to place the diagnosis at 8 patients with the help of of threshold concentration sCD30 and IL-10: 1) 3 patients with the primary diagnosis HD, IV stage, without remission, died in 1.5-2.5 years. The cytokines data: IL-10 is higher than TC concentration, before treatment - level sCD30 > 200 U/ml, after the 2-nd course - 60-70 U/ml. The final diagnosis - ALCL. 2) 2 patients with the primary diagnosis - NHL, are alive (3 and 7 years after disease beginning), without remission, after 2 courses of CT the initial level of sCD30 (200 and 90 u/ml) was not reduced. Immunophenotype CD5 +, CD10 - (D10), CD23 -. The final diagnosis: mantle cell lymphoma. 3) Two patients with undifferentiated lymphomas, IV stage, IL-10 > 200 pg/ml, the initial level of sCD30 reduced after treatment. Conclusion - NHL. 4) 1 patient with primary diagnosis NHL, IV stage, term of life without remission 20 months. Initial level of sCD30 was 25 U/ml. Immunophenotype CD5 +, CD10 -. Conclusion - MCL or CD5 + B-cell lymphoma.