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Value of Fine-Needle Aspiration Cytology in Diagnosis of Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma: One Centre Experience

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ABSTRACT

The aim of the study was to determine the value and limitations of cytology in diagnosis of Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL) as well as differentiation between these two entities. We analysed the FNA cytodiagnoses and histopathological reports, as well as treatment and survival in 89 newly diagnosed consecutive patients with these lymphomas treated in our clinical department. These patients (40 male, 49 female; age range 16–93 years; 44 in clinical stages I–II; 38 with B symptoms) were diagnosed and treated during a period of 64 months (1.1. 2004–1.5.2009). The FNA cytodiagnoses were available in 86 patients and the pathohistological diagnoses were available in 84 patients. Cytology revealed 65 classic HL, 18 ALCL and three patients in which diagnosis was not informative. Among 65 FNA cytodiagnoses of HL, comparison with histopathology was made in 61 cases and the histopathological diagnoses were as follows: 56 (91.8%) HL; three ALCL; one diffuse large B cell lymphoma and one marginal zone B cell lymphoma. In the group of 18 FNA cytodiagnoses of ALCL eight patients (53.3%) had definitive diagnosis of ALCL (either as T-cell or O type), five (33.3%) of HL and in three cases a histopathological diagnosis could not be made. These results confirm the value of FNA in diagnostic procedure in patients with HL and ALCL, especially in HL group of patients. Since we have an almost uniform group of patients according to therapeutic approach, we did univariate analyses and found out that patients with FNA cytodiagnoses of HL, younger than 55 years, with early stage of the disease and without B symptoms had significantly longer overall survival (OS). FNA cytodiagnosis has clinical relevance in differentiation between HL and ALCL.

Key words: *fine-needle aspiration cytology, Hodgkin's lymphoma, anaplastic large cell lymphoma*

Introduction

The role of fine-needle aspiration (FNA) in the diagnostic approach to lymphoma has been widely accepted since 1985[1]. Its success rate usually exceeds 70%, even approaches 100% in some studies[2], but there are still some controversies about its value in diagnosis and differentiation between various subtypes of lymphoma. The current (2008) WHO (World Health Organization) classification[3], as well the previous (2001) WHO classification[4], incorporate individual cell morphology, immunophenotype, genetic and clinical parameters when defining the lymphoma status. Some authors, in their reevaluation of FNA cytodiagnosis of Hodgkin's lymphoma (HL) according to the new WHO classification and with the knowledge that today the therapeutic approach for different subtypes of HL is the same, have concluded that if the cytology diagnosis of HL is confirmed both by morphology and immunostains, no further tissue biopsy is necessary[5]. On the other hand, Jimenez-Heffernan and co-workers have stated that cytology diagnosis of HL is not so easy, especially in differentiation between HL and

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anaplastic large cell lymphoma (ALCL) and T-cell- -rich B-cell lymphoma (TCRBCL)[6]. It is known that morphological and immunological similarities do exist between these entities. Leoncini et al. suggested that HL and CD30-positive ALCL belong to a continuous spectrum of malignant disorders[7] as well as Schmidt and co-workers who speculated that TCRBCL represents a phenotypically different manifestation of lymphocyte rich subtype of HL[8]. A similar treatment approach which is oriented to disease biology appears reasonable to our group and in last five and a half years we have had the same therapeutic approach for patients with HL and T-cell ALCL. We were also interested in the estimation of clinical relevance of cytology diagnoses in these lymphoma groups. To study the value and limitations of cytology, the cytology diagnoses and histopathological reports, as well as treatment and survival, were analysed in 89 newly diagnosed consecutive patients with HL and ALCL treated in our clinical department.

Patients and Methods

During the period of 64 months (1.1.2004–1.5.2009) 89 untreated patients were admitted in our clinical department with a diagnosis of HL or ALCL. Age of the patients ranged from 16 to 93 years; the median age was 33 years. Male to female ratio was 40:49. The diagnostic procedure was done according to the Croatian consensus of diagnosis and therapy of lymphoma[9]; clinical stage was determined according to Ann-Arbor criteria[10]. 44 patients were in clinical stages I–II and 38 had B symptoms at time of diagnosis. Patients were treated with various chemotherapeutic regimens: ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine), CHOP regimen (cyclophosphamide, hydroxydaunomycin, vincristine and prednisone), LVPP (chlorambucil, vinblastine, procarbazine and prednisone) and with CHOP-R therapy (CHOP-rituximab). Response to treatment was assessed according to the standard criteria[9]. Overall survival (OS) was measured from the point of inclusion into the study until the time of death for any reason, or losing the patient for the follow up.

The FNA cytodiagnoses were available in 86 patients; three patients were admitted with histopathological diagnoses and without enlarged lymph nodes suitable for FNA. Cytological samples were analysed on the standard May-Grünwald-Giemsa stained smears and determination of cellular markers by smear immunocytochemistry, applying a panel of CD3, CD15, CD20, CD30, EMA and ALK (anaplastic lymphoma kinase) monoclonal antibodies.

Histopathology reports and immunohistological results were available in 84 patients; in one patient with massive mediastinal lymphadenopathy surgery was not possible; four patients with enlarged abdominal lymph nodes refused the surgical procedure. Tissue samples were fixed in formalin, embedded in paraffin, stained with haematoxylin and eosin, Giemsa, periodic acid--Schiff and Gomori. Immunohistochemical staining was performed for CD3, CD4, CD15, CD20, CD30, EMA, ALK, PAX5, EBV-LMP and MUM1.

The FNA cytodiagnoses of HL and ALCL were compared with the corresponding histopathology reports. The univariate analyses were used on statistical data processing, and Kaplan-Meier method for the analysis of survival (Statistica 7.1, StatSoft Inc.,Tulsa, USA).

Results

Overall, FNA cytodiagnoses included 65 classical HL, 18 ALCL and three cases in which diagnosis was not informative due to inadequate material. Among the 65 FNA cytodiagnoses of HL comparison with histopathology was done in 61 cases (in three cases a biopsy of lymph node was not possible and in one case there was no tumour infiltration in the analyzed lymph node). The histopathological diagnoses were as follows: 56 (91.8%) HL; three ALCL; one diffuse large B-cell lymphoma and one marginal zone B cell lymphoma (Table 1). FNA cytodiagnosis of mixed cellularity (HL-MC) was made in 31 (55.4%) cases; in 21 (67.7%) cases the FNA cytodiagnosis of HL--MC was in agreement with the histopathology report, while in 10 cases the histological diagnosis was nodular sclerosis. In the group of 18 FNA cytodiagnoses of ALCL two patients did not have a lymph node biopsy; in one case no tumour was found in the biopsy; eight patients (53.3%) had definitive diagnosis of ALCL (either T-cell or 0 type), five (33.3%) as HL and two as T-cell non-Hodgkin's lymphoma (Table 1). These results confirm the value of FNA

TABLE 1
CORRELATION OF FNA CYTODIAGNOSES WITH HISTOPATHOLOGICAL DIAGNOSES

FNA cytodiagnosis	Number of cases	Histopathological diagnosis		
		HL	ALCL	Other + (*)
HL-MC	34	31	1	(2)
HL-NS	13	12	1	–
HL-NS II	5	3	–	1 + (1)
HL-MC/NS II	1	1	–	–
HL-LR	7	4	1	1 + (1)
HL NOS	5	5	–	–
ALCL 0	11	3	6	(2)
ALCL T	4	–	2	1 + (1)
ALCL	3	2	–	1
Total HL	65	56	3	2 + (4)
Total ALCL	18	5	8	2 + (3)
HL/ALCL	3	2	1	–
Total	86	63	12	4 + (7)

HL – MC – Hodgkin's lymphoma – mixed cellularity, HL – NS – Hodgkin's lymphoma – nodular sclerosis, HL – LR – Hodgkin's lymphoma – lymphocyte rich, HL NOS – Hodgkin's lymphoma, not otherwise specified, ALCL – anaplastic large cell lymphoma
* histopathological diagnosis was not available and/or there was no tumour infiltration

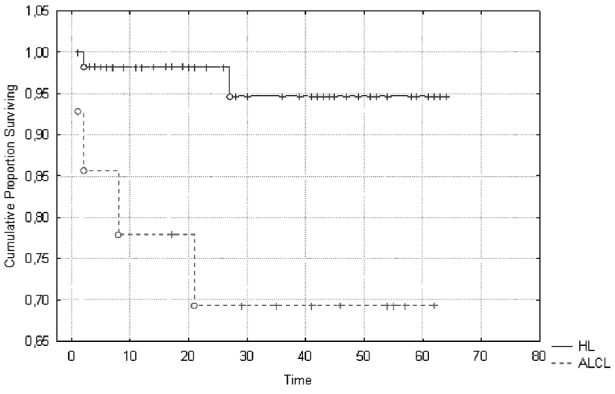

Fig. 1. Cumulative survival according to FNA cytodiagnosis. HL – Hodgkin's lymphoma, ALCL – Anaplastic large cell lymphoma, p=0.00328 (p<0.01).

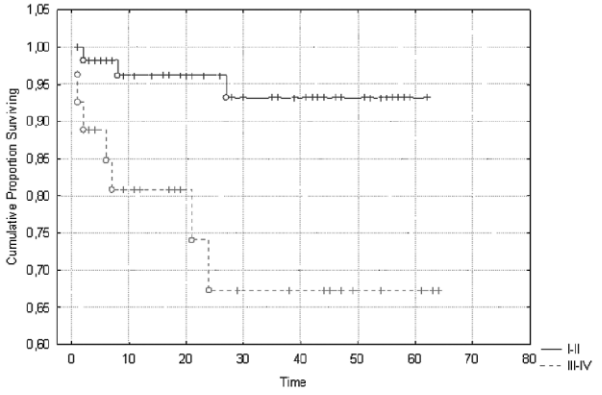

Fig. 2. Cumulative survival according to disease stage. I–II – early stage disease, III–IV – late stage disease, p=0.0467 (p<0.5).

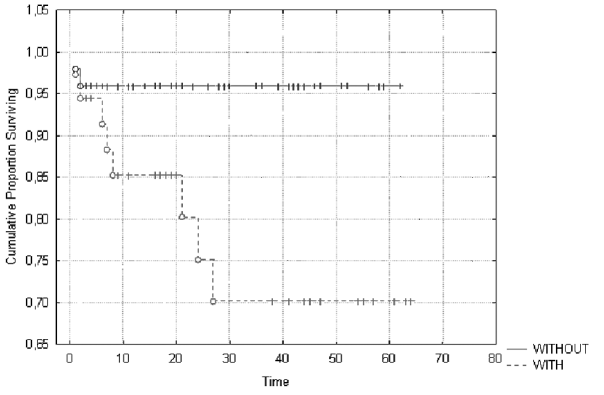

Fig. 3. Cumulative survival according to presence of B symptoms, p=0.03697 (p<0.05).

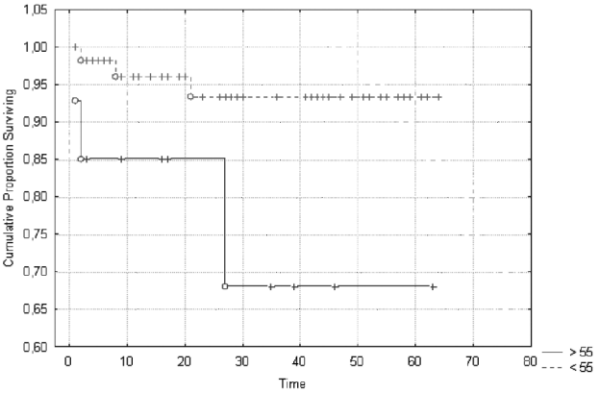

Fig. 4. Cumulative survival according to age at time of diagnosis, p=0.0368 (p<0.05).

in diagnostic approach for patients with HL and ALCL, especially in HL group of patients.

According to the standard therapeutic approach in our clinical department, all patients with diagnosis of HL and T-cell ALCL are treated with the same regimen-ABVD. LVPP regimen is reserved for older patients with serious comorbidity. 86 of our patients were treated with chemotherapy: 74 received ABVD, four received LVPP, seven received CHOP and one patient received CHOP- R; two patients refused therapy because of age (one patient was 79 and the other one was 93 years old) and one patient died during the diagnostic procedure.

The overall survival was 89%. Since we had an almost uniform group of patients according to therapeutic approach (the majority of patients received ABVD), we did univariate analyses and found out that some tested parameters (age, clinical stage, presence of B symptoms and FNA cytodiagnosis) proved to be clinically significant. Patients with a FNA cytodiagnosis of HL had a better prognosis (p=0.003, Figure 1). Patients who were diagnosed in the early stage of the disease (p=0.047) as well as patients without B symptoms (p=0.037) had significantly longer overall survival as is shown in Figures 2 and 3, respectively. Also, according to our results (Figure 4) patients younger than 55 years at time of diagnosis also had a better prognosis (p=0.037).

Discussion and Conclusion

FNA cytology offers a rapid, first-level diagnostic approach for patients with lymphadenopathies. Many authors emphasize the reliability of this method in making an accurate initial recognition of lymphomas, especially that of Hodgkin's lymphoma[2,5,11]. Jimenez-Heffernan and co-workers, in a review of 170 cytodiagnoses of HL evaluated the diagnostic accuracy and pitfalls of FNA in the initial evaluation of this lymphoma by comparing the results during two periods (first period 1982–1990; second period 1991–1999)[6]. They found that 15 cytology diagnoses of HL were followed by different histology diagnoses and that the sensitivity of the method varied from 79.3% in the first period to 84.9% in the second. Diagnostic errors with major consequences for patient management diminished from 14 in the first period to five in the second, probably because of wider implement of immunostaining. Zhang and Raza, in their analysis of 42 patients with FNA cytodiagnoses of HL, found 100% agreement with the pathohistologic results and even proposed

that FNA cytodiagnosis of HL, confirmed both by morphology and immunostaining, is enough for the diagnosis[5]. Our results (91.8% in agreement with the histological diagnosis in 61 analysed cases) confirm the value of FNA in diagnostic approach for patients with HL. The cytologists are aware that FNA cytodiagnosis of HL can be more difficult in some cases: lymphocyte-depleted HL[12], hypocellular and nondiagnostic aspirates of nodular sclerosis, presence of Reed-Sternberg (R-S) cells and R-S like cells in other lymphoma subtypes and nonlymphomatous lesions, paucity of diagnostic R-S cells in FNA smears[13]. In our study analysis of HL subtypes showed that the highest agreement with histopathology reports was in the group of patients with mixed cellularity (67.7%). Interestingly, during this period of almost five and a half years there were no FNA cytodiagnoses of lymphocyte-depleted HL. FNA cytodiagnosis of nodular sclerosis was made in 18 cases (13 as NS and five as NSII subtype) and in seven (41.2%) patients the histopathology report confirmed that subtype. In their study of Jogai et al. proposed presence of numerous lacunar- type cells along with fibroblasts and colagenous material as useful pointers toward diagnosis of nodular sclerosis variant[14].

In two cases of HL (nodular sclerosis type II and lymphocyte rich variant) the histopathology report was B cell lymphoma (one diffuse large cell and one marginal zone lymphoma) and that lead to the change of therapeutic plan. These patients received CHOP and CHOP-R therapy.

The FNA cytodiagnosis of ALCL can be a difficult task, but the results of Rapkiewicz and co-workers have showed that this lymphoma entity can be accurately diagnosed by this method[15]. They stressed the importance of obtaining adequate material, keeping a wide differential diagnostic procedure and utilization both immunochemistry and molecular techniques. The morphologic clue is a careful evaluation of hallmark cells and wreath-like multinucleated giant cells, including the necessary staining for ALK. In our study 18 FNA cytodiagnoses of ALCL were made and comparison with the pathohistological reports was possible in 15 patients. Eight patients (53.3%) had definitive diagnosis of ALCL (either T-cell or 0 type), five (33.3%) as HL and two as T-cell non-Hodgkin's lymphoma. These results are expected because we are all aware of morphological and clinical overlapping between HL, ALCL and T-cell lymphoma[16]. Some authors have suggested that proper interpretation of cytological features together with judicious use of immunocytochemical results can help in reducing errors in diagnosing these subtypes[1].

HL and ALCL have a similar biological pathway and in our clinical department the same therapeutic approach is established for patients with classic HL and T-cell ALCL: ABVD. LVPP regimen is reserved for older patients with serious comorbidity. 86 of our patients were treated with chemotherapy and 78 (90.6%) received either ABVD (74) or LVPP (four). Two patients refused therapy because of age (one patient was 79 and the other one was 93 years old) and one patient died during the diagnostic procedure. The overall survival was high, 89%, as we expected. Since we have an almost uniform group of patients according to therapeutic approach we did univariate analyses to find out which of the tested parameters (age, clinical stage, presence of B symptoms and FNA cytodiagnosis) could be clinically significant. The patients younger than 55 years, who were diagnosed in the early stage of the disease as well as patients without B symptoms had significantly longer overall survival. Also, patients with an FNA cytodiagnosis of HL had a better prognosis.

These results confirm the value and accuracy of FNA cytology in initial diagnostic approach for patients with HL and ALCL, as well as its clinical relevance in the differentiation between these lymphoma entities.

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VAŽNOST CITOLOŠKE ASPIRACIJSKE PUNKCIJE TANKOM IGLOM U DIJAGNOSTICI HOGKINOVOG LIMFOMA I ANAPLASTIČNOG VELIKOSTANIČNOG LIMFOMA: ISKUSTVO JEDNOG KLINIČKOG CENTRA

S A Ž E T A K

Cilj studije bio je procijeniti vrijednost i ograničenja citologije u dijagnostici i razlikovanju Hodgkinovog limfoma (HL) i anaplastičnog velikostaničnog limfoma (ALCL). Analizirali smo početne citološke dijagnoze, rezultate patohistološke obrade, učinke terapije i preživljenje u 89 novodijagnosticiranih bolesnika s tim limfomima koji su liječeni na našem kliničkom odjelu. U 89 bolesnika (40 muškaraca, 49 žena; u dobi od 16 do 93 godine; 44 u kliničkom stadiju I–II, 38 s B simptomima) bila je postavljena dijagnoza i liječeni su u vremenskom razdoblju od 64 mjeseca (1.1.2004.–1.5. 2009. god.). Citološka dijagnostika bila je moguća u 86 bolesnika, a patohistološku dijagnozu bilo je moguće postaviti kod 84 bolesnika. Citološka aspiracijska punkcija otkrila je 65 klasičnih HL-a, 18 ALCL-a, a u 3 bolesnika dijagnoza nije bila informativna. U skupini 65 citoloških dijagnoza HL-a, usporedba s patohistologijom je napravljena u 61 slučaju, a pripadajuće patohistološke dijagnoze bile su: 56 (91,8%) HL-a, tri ALCL-a, jedan difuzni velikostanični B limfom i jedan B- stanični limfom marginalne zone. U grupi od 18 citotoških dijagnoza ALCL-a, patohistološke dijagnoze bile su sljedeće: osam bolesnika (53,3%) imalo je definitivnu dijagnozu ALCL-a (bilo T-stanični ili 0-tip), pet bolesnika (33,3%) imalo je dijagnozu HL-a, dok u tri slučaja nije bilo moguće postaviti patohistološku dijagnozu. Ti rezultati potvrđuju vrijednost citološke dijagnostike u dijagnostičkom postupku kod bolesnika sa HL-om i ALCL-om, naročito kod bolesnika sa HL-om. S obzirom da imamo gotovo jednoliku skupinu bolesnika s obzirom na primijenjenu terapiju, napravili smo univarijatne analize koje su pokazale da pacijenti s citološkom dijagnozom HL-a, mlađi od 55 godina, u ranom stadiju bolesti i bez B simptoma imaju znatno duže ukupno preživljenje. Citološka dijagnostika ima kliničku važnost u razlikovanju HL-a i ALCL-a.