Fine-Needle Aspiration Cytology in the Follow-Up of Hodgkin Lymphoma

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Hodgkin lymphoma (HL) is characterized by long survival and risk of relapse and second neoplasm. The aim of this study is to evaluate the possibility of improving the accuracy of fine-needle cytology (FNC) in HL follow-up using Power Doppler ultrasound (US) assistance and immediate microscopic evaluation (ICE).

The study was performed in two consecutive groups of 200 FNC in HL patients. In the first group FNC of palpable lymph-nodes or extra lymph-nodal masses were performed without US assistance except for impalpable and/or deep located masses (nonassisted group); In the second group, all the FNC were performed under Power Doppler US assistance with ICE and immediately repeated in inadequate cases (assisted group). Cytological diagnoses were controlled by histology (61) or clinical follow-up (69); sensitivity and specificity were calculated in the two groups and to evaluate the effect of Power Doppler alone, adequate cases were compared with the total number of FNC in each of the two groups.

FNC identified 90 negative cases, 3 false negatives, 70 HL relapse, 16 inadequate and 14 suspicious; second neoplasia were diagnosed in 12 cases and all histologically confirmed. Sensitivity and specificity were 64 and 84% in the nonassisted group and 86 and 94% in the assisted group and there were significant differences between the number of adequate cases v.s. the total number of FNC in each of the two groups.

Sensitivity and specificity in assisted FNC are higher than in nonassisted ones. The main advantage of assisted FNC in the follow-up of HL is to produce accurate diagnoses avoiding invasive biopsies. Diagn. Cytopathol. 2008;36:467–472.

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Hodgkin lymphoma (HL), in its initial and limited stages, is nowadays a curable disease.[1–3] In fact, because of timely diagnoses, accurate staging, and high quality treatments, more than 80% of HD patients may recover from the disease.[1–3] Nonetheless, HD patients, because of their frequent young age and the received treatments, require a special form of extended follow-up.[1,4] This follow-up is aimed at the prevention and detection of HL recurrences and the treatment-related late effects including second neoplasia.[4] Fine-needle cytology (FNC) combined with phenotypic and molecular techniques have progressively gained an important role as first step and follow-up procedure in the diagnosis of lymphadenopathies. In many Institutions, a percentage of non-Hodgkin lymphomas (NHL) are diagnosed and classified by FNC[5–10]; nevertheless this technique has a less relevant and more controversial role in the diagnosis of HL.[3,11,12] In fact, the sensitivity of the method is extremely variable, ranging between 30 and 90% in the series available in literature[11–21] and, from a practical point of view, HL is responsible for at least 30% of the false negatives in FNC diagnoses of lymphoprolipherative processes.[11] Nonetheless, FNC remains a widely used instrument in the diagnosis of lymphoproliferative processes and continues to deal with HL and its diagnostic problems. Moreover HL, in cases of complete remission or in relapsed cases, requires a careful follow-up in which lymphadenopathies, or nonlymphnodal swellings, may arise from different pathologies such as reactive processes, relapses of HL, and even second neoplasms. Other noninvasive instruments are widely used in the diagnosis and staging and follow-up of HL, such as ultrasound (US), computed tomography (CT), and positron emission tomography scan (PET); these tools are

Table I. Baseline Patient Characteristics in the Two Study Groups

FNC characteristic	*Total no.*	*Nonassisted group*	*Assisted group*
No. of cases	200	104	96
No. of patients	130	69	61
Gender (M:F)	69:71	37:32	33:28
Age range (year)	16–74	19–74	16–72
Lymph-nodal	154	78	76
Extra lymph-nodal	46	24	22

Table II. Lymph-Nodal and Non Lymph-Nodal FNC Sites

Lymph-nodal	*No.*	*Non lymph-nodal*	*No.*
Cervical	54	Thyroid	11
Axillary	42	Soft-tissue	10
Supra-clavear	17	Breast	9
Sub-mandibular	4	Liver	3
Parotideal	4	Lung	2
Retronucal	1	Salivary gland	2
Intramammarian	2	Testis	2
Inguinal	27	Abdominal masses	3
		Spleen	2
		Ovary	1
		Kidney	1
Total	154		46

generally highly sensitive but they are not specific, therefore treatment decisions are not based solely on imaging techniques.[22–24] In this perspective, FNC, because of its reliability, handiness and bearably, may contribute to the prebiopsy or presurgical diagnosis of these processes.

The aim of this study, therefore, has been to assess the role of FNC in the diagnosis of lymphadenopathies and extra lymph-nodal masses in the follow-up of HL and to evaluate the possibility of improving the accuracy of the method through a comprehensive clinical, instrumental, and cytological approach.

Materials and Methods

From the files of the Dipartimento di Anatomia ed Istologia Patologica e Citopatologia of the University of Naples "Federico II," 200 cytological samples from 130 patients with a previous diagnosis of HL in the ten year period from 1997 to 2006 were retrieved. In all patients, the primary diagnosis of HL had been histologically proven and HLs were classified according to the Revised European-American classification of lymphoid neoplasm.[25] The series included for 69 (57%) males and 61 (43%) females, with a median age of 45 years (ranging from 16–74); clinical data are summarized in Table I. After diagnosis and staging, all the patients had received HL therapy in the Haematology Department of the same Medical School according to the standard treatments (early stages: ABVD $\times$ 4 cycles followed by radiotherapy, advanced stages ABVD $\times$ 6 cycles followed by radiotherapy on bulky sites). The new masses appeared after a median time of 36 months (range 9–108) from the initial histological diagnosis of HL. The targeted anatomical sites were:154 lymph-nodes and 46 extra lymph-nodal sites FNC (Table II). Extra lymph-nodal targets concerned thyroid,[11] breast,[9] soft-tissues,[10] liver,[3] lung,[2] salivary gland,[2] abdominal deep located masses,[3] testis[2] spleen,[2] kidney,[1] and ovary[1] (Table II). The study was retrospectively performed comparing two consecutive groups of FNC in HL patients. In the first group FNC of palpable lymph-nodes or extra lymph-nodal masses were performed without US assistance whereas FNC of impalpable and/or deep located masses were performed under US guide in the Radiology Department; in these cases the US procedures were performed using a portable Spazio-Hitachi equipment and a 3.5 HMz curvilinear probe. In the second group all the US procedures were performed with an US Hitachi instrument equipped with harmonic computed technology Power Doppler (EUB 6500; Hitachi, Tokyo, Japan) and a 13–6 MHz broad and linear probe (EUB 54M probe; Hitachi) for superficial targets or a 5–2 MHz broad-band curvilinear probe (EUB 514C probe; Hitachi) for deep-seated targets. All the FNC of the second group were performed under US control using this high resolution Power Doppler equipment by a team made of a hematologist and a cytopathologist. This high resolution US equipment, combining tissue harmonic compound and Power Doppler sonography allows an accurate evaluation of morphology (including size, shape and hilar or cortical deformation) and vascular characteristics of the lymph nodes and hence it is possible to select the areas most suspected of malignancy (Fig. C-1).[26] Because one of the goals of the study was to evaluate the possible benefit of US high resolution and Power Doppler US-assistance, cases in which FNC had been performed under CT control were not considered in the present study. In all the cases of the second group, the first smear was immediately Diff-Quik stained and evaluated (ICE) while the patient was still in the outpatient office; ICE identified four inadequate cases (scantily or non cellular and/or, blood contaminated) which were repeated and classified accordingly. ICE also oriented the application of ancillary techniques; in fact, when possible, another two or more extra slides were prepared, alcohol 95° fixed and used for immunocytochemistry (ICC). In 20 cases in which a NHL was considered in the differential diagnosis, a further pass was flushed in buffer solution and used for flow cytometry (FC). ICC was performed in 28 cases using CD30 and CD15 (LEU-M1) (1:100) (Dakopatts, Glostrup, Denmark). FC was performed using the following combined fluoresceinated antibodies CD3, CD4, CD5, CD8, CD10, CD19, CD23, FMC7, bcl-2, kappa and lambda light chains (Becton Dickinson, San José, California). Cytological diagnostic categories were as follows: positive for malignant cells consistent with HL, positive for malignant cells consistent with another (non-HL) neoplasm, suspicious for HL recurrence, negative for malignant cells and/or reactive hyperplasia in lymph-nodal FNC, negative with or without further specification in other non lymph-nodal

Table III. Cytological Diagnosis of the Whole Series

Hodgkin lymphoma relapse	68
Hodgkin lymphoma suspect	14
Second neoplasm	12
Inadequate	16
Negative	90
Total	200

FNC and inadequate. All the cytological diagnoses were confirmed by clinical follow-up and by histology in 61 cases. FNC were generally well tolerated by the patients without complications even in splenic FNC, which were performed as previously described.[27] Sensitivity and specificity in the two groups were calculated and a statistical analysis was performed to evaluate the different diagnostic efficiency in the two groups. Moreover, to evaluate the effect of Power Doppler alone without the contribute of ICE, we compared the number of adequate cases versus the total number of FNC in each of the two groups using the Chi-square test.

Results

Diagnostic distribution of the two consecutive series (200 samples) was as follows: 90 negative, HL relapse in 68 cases; 14 HL suspects, 16 inadequate and 12 s neoplasm (Table III). The 68 HL relapse cases included 56 lymph-nodal FNC and 12 extra lymph-nodal FNC which included soft tissues,[8] breast,[2] liver,[1] and spleen[1]; in all these cases the diagnosis was based on the identification of Reed-Sternberg (RS) cells in a specific background (Figs. C-2 and C-3), further confirmed by CD15 and CD30 positivity (Fig. C-4) when possible. The cytological diagnoses were confirmed by histological examination in 30 cases and by clinical follow-up in the remaining 38 cases. In these latter negative cases, clinical and US examinations assessed the regression of clinical and instrumental signs mainly represented by lymph-nodal swellings. In 14 cases, diagnosed as suspicious, no classical RS cells were observed in the smears but only scanty or even single atypical mononucleated cells in an inflammatory background. These cases concerned lymph-nodes[11] and soft tissue swellings.[3] In these suspect cases, subsequent histological examination confirmed the cytological suspect of HD in 9 cases (64%), whereas the remaining 5 cases (34%) were reactive processes. Twelve inadequate cases were collected in the nonassisted group; conversely, four inadequate cases of the second group were immediately repeated, evaluated and distributed in the corresponding diagnostic categories (Table IV). Second neoplasm were diagnosed in 12 cases; this was an heterogeneous category which included breast carcinoma,[2] kidney carcinoma,[1] lymph-nodal metastases from carcinoma of the tongue[1] and head, and neck squamous-cell carcinoma,[2] hepatic metastasis from lung adenocarcinoma,

Table IV. Diagnostic Distribution in the Two Study Groups

Cytological diagnoses	*No.*	*Non assisted group*	*Assisted group*	*P*
Reactive hyperplasia	75	35	40	N.S.
False negative	3	3	0	N.S.
Negative, other benign pathologies	12	7	5	N.S.
Hodgkin lymphoma relapse	68	32	36	N.S
Second neoplasm	12	4	8	<0.05
Hodgkin lymphoma suspected	14	9	5	<0.05
Inadequate	16	12	4	<0.05
Total	200	102	98	

NHL,[2] thyroid papillary carcinoma[2] thyroidal Hurthle cell adenoma,[1] and ovarian cystic serous tumor.[1] The remaining 90 cases, diagnosed negative, included 78 lymph-nodal FNC diagnosed as reactive hyperplasia and 12 extra-nodal FNC samples diagnosed negative for HD. These latter included other benign processes such as breast steatonecrosis,[2] gynecomastia,[2] spermatocele[1] and thyroidal nodular goiter.[4] Among these cytological negative cases there were three false negatives: two in deep located abdominal lymph-nodes and one case of hydrocele caused by testicular neoplasm. Diagnostic distribution of FNC in the two study groups is summarized in Table IV. As for the temporal and clinical distribution of cytological diagnosis, in most of the cases just one FNC was performed. In 19 patients, two or more FNC were performed during the 10-year period; seven of these cases developed two relapses of HL. Three patients underwent to three FNC with two diagnosed relapses, another three patients underwent three FNC with three relapses in two cases. In six patients, two FNC in two distinct sites were performed at the same time: in four cases both the FNC concerned palpable lymph-nodes whereas the other two cases concerned lymph-nodes and soft tissues (buttock and scapular soft tissue swellings, respectively). Sensitivity and specificity were then calculated in the two different groups with the following results: 64 and 84% in the nonassisted group and 86 and 94% in the assisted group, respectively ($P < 0.05$). As far as the effect of Power Doppler concerns, there were significant differences in the frequencies between the number of adequate cases versus the total number of FNC in each of the two groups ($P < 0.05$).

Discussion

Although cytological features of HL are well known and extensively described,[11–20] the role of cytology in the diagnosis of HL is still controversial. Low diagnostic sensitivity and difficult or impossible identification of specific sub-types represent the main limitations of the technique.[11–13] Nonetheless, FNC is extensively used in the diagnosis of lymphadenopathies and lymphoproliferative processes, and as HL is part of these processes, inevitably

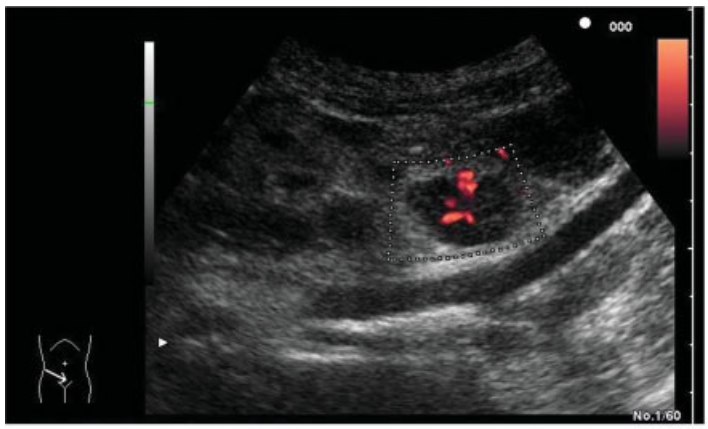

Fig. C-1

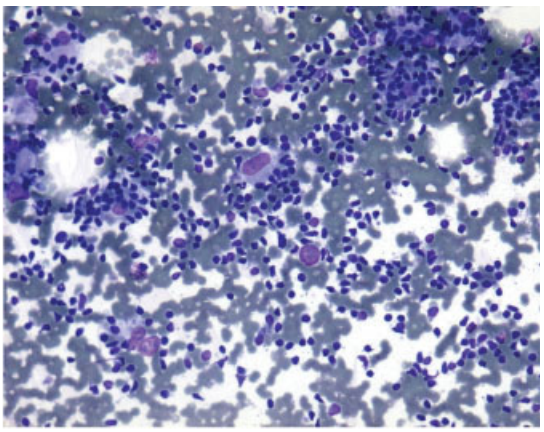

Fig. C-2

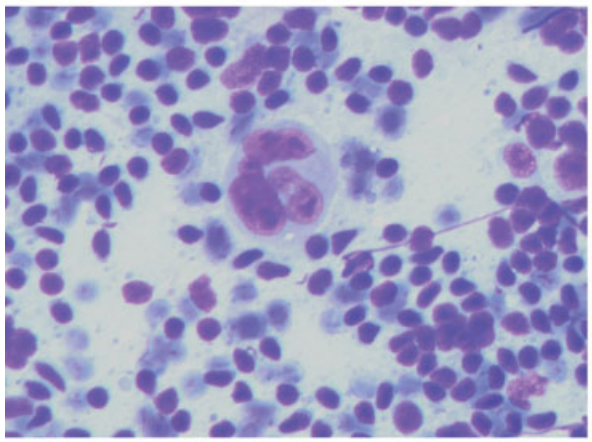

Fig. C-3

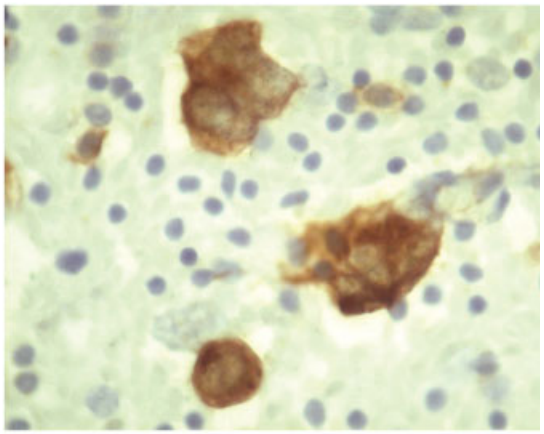

Fig. C-4

Figs. C-1–C-4. Fig. C-1. Localized neoangiogenesis in a lymph-node partially involved by Hodgkin's lymphoma as revealed by Power Doppler US. **Fig. C-2**. HL cytological features: atypical mononucleated and multinucleated nucleolated cells in a proper background (Diff-Quik stain ×106). **Fig. C-3**. Classical RS cell in lymphocytic background (Diff-Quik stain ×430). **Fig. C-4**. Immunocytochemical stain of HL: C-CD30 positive RS cells confirming the cytological diagnosis of HL (APAP ×430).

cytologists face HL with its diagnostic problems. Apart from the role in the primary diagnosis, FNB has another role in the follow-up of HL which may be of great clinical relevance. In fact, combination chemotherapy (CT) and extensive radiotherapy (RT) have greatly improved the survival rate and increased complete remissions of HL.[1–3] Nonetheless, these patients require a careful follow-up in which any lymph-nodal enlargement or other clinical process are approached with a greater attention compared with that reserved to non-HL patients and, in general, to nononcological patients even when they arise in an evident and/or reassuring clinical context. On the other hand, advanced stage HL has a high risk of new lymph-nodal or extra-lymph-nodal localizations.[28–30] Finally, HL patients, as late effects of treatment, have an increased risk of hematological and nonhematological second malignancies, which increases through time and requires prolonged clinical-pathological survival.[31–33] In hematological dedicated Institutions, FNC is generally considered insufficient for the primary diagnosis of HL and histology is always required[3] but there are divergent opinions regarding the diagnostic strategies in HL patients who develop lymphadenopathies or swellings whether they are or are not suspected of HL relapse. In fact, in these cases, surgical biopsies may be either "too much" or "too little" especially when the targets are deeply located or not easily reachable; conversely FNC may produce a definite diagnosis avoiding useless and more invasive diagnostic procedures. Therefore reactive processes, HL relapses and second malignancies represent the main targets of FNC when dealing with HL patients. As reported in the literature,[11–20] the cytological diagnosis of HL may be hampered by different factors such as specific histological sub-type, shortage of diagnostic cells, hidden or masked diagnostic cells, and possible unspecific ICC. In fact in nodular sclerosis, which represents the most common histological subtype of HL, fibrosis and random distribution of diagnostic RS cells may hamper the cyto-

logical integrity, the harvest and examination of diagnostic cells. RS cells may also be scanty and the presence in a cytological sample of variants such as "atypical mononuclear nucleolated" or "hyperlobated" may suggest HL but might not be sufficient for a definitive diagnosis of HL. These difficulties are enhanced in the "lymphocytic predominance" variant in which there is a prevalence of lymphocytes and absence of classic RS cells.[34] In ordinary cases, RS cells and their variants are generally interspersed in a reactive back-ground made-up by lymphocytes, plasma cells, eosinophils, neutrophils, histiocytes, and epithelioid cells; their amounts varying from case to case.[16,17,35–40] This complex background may hide the RS cells giving rise to false-negative.[17,35,36,38] Conversely atypical cells, mimicking RS cells may be observed in reactive lymph-nodes or NHL such as anaplastic "K1" lymphoma, melanoma and some undifferentiated carcinomas.[39] All these difficulties may probably cause the extreme variability of sensitivity in the different experiences reported in the cytological diagnosis of HL.[11–20] In this study, sensitivity and specificity obtained in the assisted group are higher than those obtained in the non-assisted group as well as those reported in literature,[11–20] and different factors may have determined this improvement. First of all, clinical history has probably influenced the whole procedure determining a higher and probably "dedicated" attention; moreover, in cases of HL relapse, diagnostic criteria may be less strict compared with those ones requested for primary diagnosis of HL[34] resulting in an general diagnostic advantage. Moreover modern high resolution US instruments equipped with harmonic computed technology and Power Doppler, other than to guide the needle in the impalpable masses, enables to select the most significant areas to biopsy. Abnormalities of morphologic structures (abnormal shapes, hypoechogenicity, hilar asymmetry, irregular margins) and vascular structures (chaotic vascular pattern) are US findings suspected for malignancy in lymphadenopathies and become selected targets for US-guided FNC. In fact, as reported above, in this study the use of US Power Doppler has determined a significant improvement of efficiency ($P < 0.05$). As far as the second malignancies, because of their clinical and histological heterogeneity, they may cause diagnostic difficulties in Institutions mainly or totally dedicated to hematological pathologies. These difficulties are enhanced in case of "unusual" second malignancies or nonlymphomatous processes. In fact "typical" second malignancies closely related to the iatrogenic effects such as leukemia, head and neck tumors or breast carcinomas are well known and in some way "expected." Conversely "atypical" second neoplasm such as in this series, renal carcinoma and other nonmalignant processes such as inflammatory psedotumour or gynecomastia were unexpected and correct FNC diagnoses changed the clinical planning and increased the sensitivity. As far as the ancillary techniques are concerned, according to other experiences,[11,12] ICC may be helpful in the cytological diagnosis of HL with some limitations. In fact in nodular sclerosis, mixed cellularity and lymphocyte depletion variants, diagnostic cells are generally CD30 and CD15 positive but in the lymphocytic predominance sub-type they are CD30 negative but CD45 and B-markers (CD20, CD19) positive. These cells, apart from their phenotype, may mimic follicular-centre cells on cytological samples and therefore may be missed causing a percentage of false-negative in our as well as in other series.[11–14,18] As far as the other sub-types are concerned, others ICC studies have demonstrated the reliability of CD30 and CD 15 on cytological samples to detect RS cells[11,12] whereas bad preservation and shortage of diagnostic cells may hamper ICC even in these subtypes. In our study ICC has been utilized in a limited number of cases[28] which represents just 14% of the whole series mainly because of the above reported limitations. Nonetheless, when utilized, ICC has been highly effective either in the identification of diagnostic cells or in confirming negativity. FC has dramatically changed the cytological diagnosis of NHL, but as foreseeable, does not contribute in the same manner to the diagnosis of HL.[11] In fact diagnostic cells are too scanty to form an identifiable gate of cells; moreover they are too large and probably get broken or stick to the tubes along the procedure. As for the reactive lymphoid cells in HL, some FC studies have observed a prevalence of CD4+ T-lymphocytes and a small amount of polyclonal B-cell.[41,42] In our four cases, we obtained similar same results with CD4 prevalence in three out of four of the tested cases, but we think this phenotypic pattern may contribute to the exclusion of a NHL but does not help the HL diagnosis. As reported above, we did not perform cytological classifications of specific subtypes; some studies have tried to with variable results.[21,40] Nonetheless, LH sub-classification has a limited value in post-primary HL in which staging and clinical data are more relevant therefore, in HL follow-up, the simple diagnoses of positive or negative for HL may be sufficient for clinical management.[1,2] In conclusion, FNC is a simple and accurate tool to use in the follow-up of HL and it is improved by US Power Doppler guide and ICE. Among the ancillary techniques, ICC is the most useful provided that a sufficient number of diagnostic cells are present. The relevance of FNC in HL patients is related to the determination of diagnostic-therapeutic decisions, avoiding mainly in cases of relapse or in reactive processes, more invasive and expensive diagnostic procedures.

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