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# Role of FNA Cytology in the Diagnosis of Lymph Node Diseases

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**Summary :**

***FNA cytology is indicated for any enlarged abnormal lymph node in any anatomical site. The FNA of deep nodes and other inaccessible lesion can be done by .Applying various radiological imaging techniques. As a rule cytological examination can decide whether the lymphadenopathy is due to reactive hyperplasia, granulomatous inflammation, metastatic malignancy or malignant lymphoma Lymph node clinically suspected of metastatic malignancy constitute one of the commonest indication for FNA***

***Diagnostic accuracy not only depends on the representativeness of aspirate but also on the quality of tile cytological preparation. Diagnostic sensitivity of tile metastatic malignancy and recurring malignancy is usually above 95% Diagnostic sensitivity has generally been found to be significantly lower for lymphoma than for metastatic malignancy. if the cytological diagnosis is malignant lymphoma or suspicious of lymphoma this must be confirmed by open biopsy and histopathological examination and also by immune marker studies necessary for define diagnosis and subtyping that is necessary to select the appropriate treatment regimen. To recall the several advantages of FNA cytology, it can be concluded that FNA cytology should be the first line investigation in a patient with unexplained lymphadenopathy***

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## Introduction:

Fine needle aspiration cytology (FNAC) is a simple traumatic invasive procedure that involves aspirating cells and attendant fluid with a small bore needle followed by cytological examination[1].

This method is applicable to lesion that are easily palpable for example superficial growth of skin, subcutis and soft tissue and organs such as lymph node, thyroid, breast & salivary gland. Aspirates may also be taken from lung, the prostate, and the abdominal, and retroperitoneal organs and tissues by applying internal radiological imaging techniques.

FNA of lymph nodes has been practised in central Europe and in Scandinavia for many years, particularly by haematologists in conjunction with aspiration of bone marrow and spleen. It took longer for the method to become widely accepted in the Anglo-American World. Martin & Ellis of the Memorial Hospital in NewYork were pioneers in this field .[3] Thereafter their work was followed up by Bestill & Hajdu[4].

Fine needle aspiration cytology (FNAC) has its application in lymph node pathology in three major clinical setting: Primary diagnosis, staging of disease and follow up[5].

Primary diagnosis made on FNAC in patient with lymphadenopathy may be requested for:

1. Anatomical purposes (e.g. confirming that the nodule at the angle of mandible is a hyperplastic lymph node, and not a salivary gland lesion).
2. Confirmation of suspected clinical condition. (e.g. metastatic carcinoma).
3. First -line investigation in a patient with lymphadenopathy of unknown cause.

Staging of disease is usually undertaken in patient with known primary tumour (e.g. lymphoma) to establish the extent of disease (e.g. subdiaphramatic)

Follow-up of patients with a history of malignancy (e.g. carcinoma of the breast) provide accurate confirmation of recurrence.

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Thus any enlarged abnormal lymph node in any site constitutes an indication for FNA biopsy. Lymph node clinically suspected of metastatic malignancy constitute one of the commonest indications for FNA biopsy. The accuracy of FNA of lymph node in the diagnosis of metastatic malignancy is influenced by many factors such as the size and site of node, fibrosis, previous irradiation and number of punctures made. As a rule, cytological examination can decide whether the lymphadenopathy is due to reactive hyperplasia, metastatic malignancy or malignant lymphoma. Despite newfound support for using needle aspiration for evaluating unexplained lymphadenopathy, there remains resistance to this application for both pathologists and clinicians. This is related to:

1. Lack of clinician's understanding regarding the application of FNA in the management of lymphadenopathy.
2. Inexperience on the part of the pathologists, who interpret lymph node aspirates (resulting in both false- negative and false-positive interpretations).
3. The relative paucity of reliable, well-defined cytomorphologic criteria for the evaluation of lymph node specimens.
4. A failure to obtain and accurately correlate clinical data with cytologic findings when making the final diagnosis.

Barbara F. Atkinson's experience and as the recent literature suggests, when these factors are controlled, the sensitivity and specificity of lymph node aspiration diagnoses are dramatically improved[6]. There are several advantages to using FNA in the evaluation of unexplained lymphadenopathy:

1. It is an easy, reliable office procedure.
2. It is cost -effective and safe.
3. It helps to distinguish benign from malignant disease
4. It assists in patient management.
5. It reduces patient anxiety.
6. It provides material for additional studies (e.g. surface markers, special stains, culture and flow cytometry).
7. It provides data for appropriate therapy.
8. It eliminates the need for open biopsy in most cases of RLNH.

Morphologic characteristics of lymph node aspirates: The following are the useful morphologic features when evaluating aspiration of lymph node. The single most important feature is lymph node interpretation is the pattern of lymphoid elements present on smear. Since both T and B lymphocytes undergo functional changes when stimulated that produce morphologically distinct cell types of varying maturities, reactive nodes usually contain a mixed or polymorphus population of cells. It is the relative proportion of these cells in the overall pattern that gives one of the best criteria for benignity. These population pattern can best be visualized on Romanovsky-stained slide on low power because of flattening of cells during airdrying. In a benign population, except a greater percentage of small round lymphocyte (either mature mantle B cells or paracortical T cells) than follicular centre cells. (Small cleaved and large non-cleaved) or immunoblast and plasmacytoid cells. This ratio however, is dependent upon the stage of the reaction. In other patterns of reactive lymph node hyperplasia there is a greater relative proportion of immunoblast and plasma cells and a smaller relative proportion of small round and small cleaved lymphocyte. Accurately characterizing this lymphoid population and determining the relative of mix of these cells is the first critical step in interpretating lymph node aspirates[7]. The presence of lymphohistiocytic aggregates (LHAs) is also a significant diagnostic features when defining reactive lymph node hyperplasia. These aggregates are actually fragments of hyperplastic follicles that are held together by dendritic and fibroblastic reticular cells. These reticular cells have oval, histiocyte-like nuclei with micronucleoli and long fragile cytoplasmic processes. Another component of LHAs is the tingible body macrophage (TBM). These phagocytic mobile histiocytes generally have cell debris in their cytoplasm; are easily recognized in lymph node aspirates and are usually but not always associated with benign nodes[8]. Scattered in this LHAs is a mixed population of lymphoid cells, usually follicular central cells varying in size from small round to large non-cleaved cells and rarely plasmacytoid cells. Although LHAs is usually indicate a benign follicular

hyperplasia, they are sometimes associated with some lymphomatous processes (e.g. Burkitt lymphoma) especially in partially involved nodes[9]. Background changes in lymph nodes aspirates are helpful when evaluating reactive process because they may assist in further defining both the type of reaction occurring and the causative agent[10]. Identifying a background of neutrophils suggests a suppurative process perhaps from the microabscesses seen in cat-scratch disease or the abscess associated with and unidentified bacterial infection. The presence or absence of caseating necrosis, with or without giant cell formation and epithelioid cells, is associated with a panorama of granuloma producing processes including tuberculosis, sarcoidosis, toxoplasmosis and tularemia. Culture and special stains are indicated when either of these background patterns predominates.

Lymphoglandular bodies (fragments of lymphocyte cytoplasm) are seen in nearly every Romanovsky-stained aspirate containing lymphocytes and are useful in distinguishing malignant epithelial from lymphoid (benign or malignant) processes. It is important to be able to recognize and distinguish other nonlymphoid and lymphoid cell types in lymph node aspirates since they help distinguish benign from malignant processes and assist in specifying the aetiology of RLNH. These cell types include ephitheloid-histiocytes, giant cells (e.g. Warthin-Finkeldey and Langhans), eosinophil, plasmacytoid cells and mast cells.

Technical considerations: Both reactive nodes and nodes involved by metastatic malignancy or lymphoma are highly cellular and moderately vascular tissues. Sufficient material is therefore easily obtained using a 27-23 Gauze needle, except in the presence of fibrosis. Multiple pricking of the needle in different direction within the node for wider sampling do not usually cause admixture with blood to the same extent as when aspiration is used. An abundance of blood in the sample adversely affects cell fixation and tends to distort the cells. During aspiration syringe should be mounted in a pristol grip so that one hand is free to hold the node firmly during puncture. Local anaesthetic is not used and simple skin disinfection as for an injection is adequate. Two or more samples may be necessary to secure enough material for both smears and for special investigations and to reduce sampling error in focal disease. The use of gloves and extreme care in handling the used needles are important safety precautions in many circumstances. The FNA of deep nodes and other inaccessible lesion can be done by applying various radiological imaging techniques. The major internal imaging techniques are computed tomography (CT) and ultrasonography (US) and more recently magnetic resonance imaging (MRI), plus development of stereotactic guidance, particularly for brain and breast biopsies.

If the standard technique does not yield sufficient material, for example due to fibrosis (nodular sclerosing Hodgkin's disease and some sclerosing non-Hodgkin's lymphomas, a 22 Gauze cutting core needle may be tried[11]. An airdried smear has to dry quickly for optimal fixation and therefore has to made thin. The smearing pressure must be finely balanced to obtain a thin smear and at the same time avoid crush artefacts. This can be achieved by pulling the cell sample behind the smearing cover glass. If the flat of the glass is used as in subsequent steps, the movement should be quick and no pressure applied. A wet-fixed smear must be fixed immediately to minimise drying artefacts. Only those part of the smears in which the cells are evenly dispersed, well fixed and not distorted by the trauma of smearing should be chosen for diagnostic evaluation. Areas in which cells show crush and/or drying artefacts, usually at the tail of smear are better ignored. Whenever possible, both airdried and wet fixed smears should be made. Extra smears to allow special stains are often of great value. Staining for microorganisms (Ziehl-Neelsen, PAS, silver impregnation techniques etc.), for mucin (PAS/D, alcian blue), for melanin (Masson, Formalin-induced fluorescence), for acid phosphatase, and for immunocytochemical purposes are those most commonly used. Immunocytochemical staining for demonstration of a variety of tissue specific cell product is one of the most useful "special stains" in diagnostic cytology. Immunocytochemistry is helpful in tracing the origin of metastatic malignancy, in the differentiation of lymphoma from reactive process and from anaplastic carcinoma or melanoma and in the classification of lymphoma[12].

Accuracy of lymph node disease diagnosis: Diagnostic accuracy not only depends on the representativeness of aspirate but also on the quality of the cytological preparations. This is particularly the case in the diagnosis of certain reactive lymphadenopathies and in the diagnosis and classification of lymphoma, which depends on the study of fine cytological detail and on an estimate of proportions of various cell types in the smear[13]. If the biopsy material is adequate, diagnostic sensitivity is occasionally limited by the fact that small metastatic deposits, metastases confined to the subcapsular sinus and single cell metastases can be missed even by multiple aspiration. However, early (micro) metastases rarely produce significant lymph node enlargement and if a lymph node is palpable it is likely to contain enough tumour tissue to be easily detectable by FNA. Although the diagnostic sensitivity of metastatic and recurring malignancy reported in the literature varies, it is usually above 95%[14]. Failure to obtain a representative sample is no doubt responsible for most false negative diagnosis. Interpretation of a representative aspirate can be a problem, but by far more often in lymphoma than in metastatic malignancy. For example, without immunophenotyping follicular lymphoma can be mistaken for reactive follicular hyperplasia[15]. Thus, although a negative cytological report makes malignancy unlikely, it cannot be taken as diagnostic on its own[16] and if the lymphadenopathy does not show sign of regression within a few weeks of observation, FNA should be repeated or a node should be excised for histology. Diagnostic specificity, on the other hand is high. False positive diagnoses are rare[17] if particular caution is observed in the interpretation of smears from nodes in the fields of previous irradiation and in the presence of necrosis. Most false positive diagnoses reported in the literature are the cases of reactive lymphadenopathy reported as suspicious of lymphoma. Conflicting opinions are expressed in the literature regarding the accuracy of cytological diagnosis and of typing of malignant lymphoma[18]. Diagnostic sensitivity has generally been found to be significantly lower for lymphoma than for metastatic malignancy[19]. If the cytological diagnosis is malignant lymphoma or suspicious of lymphoma, this must be followed by surgical excision of the node. The exact diagnosis and classification of malignant lymphoma is necessary to select the appropriate treatment regimen can in most cases only be reached by histological and immunological examination of whole node. As a rule FNA biopsies from malignant lymphoma are cellular. If indicated, an extensive immune marker typing can be performed on cytospin preparations of suspected cells to prove the neoplastic or reactive nature of a nodal or extranodal lymphoid proliferation. Other supplementary techniques such as cytogenetic analysis, morphometry, and gene rearrangement studies may be applied to cell samples obtained by FNA[20].

Cytological findings: FNA samples of lymphoid tissue, nodal or extranodal, benign or malignant are as a rule characterised by a very high cell content. This is obvious to naked eye as the aspirate is smeared. It appears as a film of slimy material which becomes grey on drying. The cytoplasm of lymphoid cell is fragile. Many cells appear as naked nuclei or with a small rim of cytoplasm and a variable number of round cytoplasmic fragments measuring up to 8 micrometer in diameter are seen in the background. Such cytoplasmic fragments - so called 'lymphoid globules' or 'lymphoglandular bodies' which stain an even pale-blue with Giemsa stain, are characteristic of lymphoid tissue, both neoplastic and non-neoplastic. The recognition of 'lymphoid globule' is of great diagnostic value, for example in distinction of lymphoma from anaplastic carcinoma. Most of the lymphoid cells in smears are seen as single cells but dense clumps or aggregates may also occur especially in bloody smear. Cell detail is obscured in such clumps and they are of no diagnostic value as they can be found in both reactive and malignant nodes. However a characteristic aggregation of cells tends to occur in some follicular centre cell lymphomas[21] or CD30 positive large cell lymphomas[22].

A. The cytological features of reactive lymphadenopathy: The reactive pattern is variable depending on the degree of stimulation, the number and size of germinal centres and on whether the sample derives mainly from a germinal centre, or from interfollicular or paracortical tissue. A smear which derives mainly from interfollicular tissue consists predominantly of lymphocyte with a variable

number of scattered immunoblast, plasma cell, non-specific histiocytes and endothelial cells. Germinal centre tissue is represented by poorly defined loose tissue fragments. These fragments include centroblasts, centrocytes, and a smaller number of lymphocytes which adhere to the syncytial cytoplasm of dendritic reticulam cells. The following criteria are used for the diagnosis of reactive lymphadenopathy.

1. A mixed population of lymphoid cells.
2. A predominance of small lymphocytes.
3. Centroblasts, centrocytes, immunoblasts and plasma cells in variable but 'logical' proportion.
4. Dendritic reticulam cells associated with centroblasts and centrocytes (representative germinal centres)

Scattered histiocytes with intracytoplasmic nuclear debris (tingible body macrophages)

6. Pale histiocytes, interdigitating cells, endothelial cells, eosinophils and neutrophils (variable).

The important features which distinguished a reactive process from lymphoma are:

I. A mixed population of lymphoid cells representating the whole range of lymphocyte transformaton from small lymphocytes to immunoblasts and plasma cells.

II. A predominance of small sometimes slightly larger 'stimulated lymphocytes' which have small round nuclei and a characteristic chromatin pattern of large ill-defined chromatin condensations.

III. Centroblasts and centrocytes associated with dendritic reticulam cells derived from germinal centres and tingible body macrophage[23].

The presence of macrophages with tingible bodies favour reactive hyperplasia but does not rule out lymphoma. Especially in high grade lymphomas like Burkitt's lymphoma with a high turnover of cells, a considerable number of starry sky macrophage may be present. The cytological pattern of reactive hyperplasia in which plasma cells are prominent but without other distinguishing features can be seen for example in cases of secondary syphilis and of rheumatoid arthritis.

The differential diagnosis between follicular hyperplasia and follicular lymphoma of mixed cell type (centroblastic/centrocytic) can be very difficult in FNA smear. In follicular lymphoma the predominant cell type may appear small but the nucleus is of intermediate size and has an irregular shape and more granular chromatin similar to centrocytes. Immunoblasts, plasma cells and tingible body macrophages are usually absent or few in number. The difficulty in distinguishing the two conditions is largely due to the fact that the dendritic reticulam cells associated with centroblasts and centrocytes are seen in both and that interfollicular areas in lymphoma may contain large number of small lymphocytes. Immunological demonstration of poly or monoclonality may be necessary to solve the problem. A prominent immunoblastic and plasmacellular reaction is found in several conditions. In viral lymphadenitis particularly in infectious mononucleosis, immunoblasts, plasmacytoid cells, mature plasma cells and atypical lymphocytes can be numerous[24].

Immunoblastic cells can cause differential diagnostic problems; the main differential diagnoses are T-cell immunoblastic lymphoma and Hodgkin's disease (atypical binucleate immunoblasts closely resembling Reed-Sternberg cells can occasionally can be seen). In mononucleosis, the diagnosis is usually already suggested by the clinical presentation and can be confirmed by serological tests. Prominent immunoblasts and sometimes Reed-Sternberg like cells also occur in postvaccinal lymphadenitis and dilantin hypersensitivity. Immunobalstic reaction such as angioimmunoblastic lymphadenopathy (AILD) are difficult to distinguish from T-cell lymphoma and in many cases progress to lymphoma. An increased number of histiocytes without specific features can be seen in smears from non-specific reactive nodes, perhaps indicating some degree of sinus histiocytosis. Histiocytes are particularly prominent in nodes sampled within a few days of lymphangiographic examination. Their cytoplasm contains lipid droplets, multinucleated histiocytic giant cells are common and there is often a conspicuous number of eosinophils. Another condition with prominent histiocytes and multinucleated giant cells as a reaction to foreign materials is silicon lymphadenopathy, occasionally seen in axillary nodes of women with silicon breast

prostheses. Scattered small cluster of histiocytes which have ovoid, pale nuclei and resemble epithelioid cells with a background of follicular hyperplasia are suggestive of toxoplasmosis. The cytological pattern is not diagnostic in itself and needs to be confirmed by serological tests. Microcysts and organisms are hardly ever seen in smear[25].

Numerous non-chohesive, pale histiocyte -like cells are present in dermatopathic lymphadenopathy. Some macrophages contain pigment-either haemosiderin or melanin. These have smaller and more consistently oval-non-folded- nuclei and have a better defined cytoplasm. Some eosinophils are usually present. The background is predominantly of small lymphocytes which may appear slightly atypical with small pale, central nucleoli and blast forms are less common.

In histiocytosis X and malignant histiocytosis, the nuclei of Langerhans histiocytes are large and can have a very irregular shape: folded convoluted, lobulated and grooved. Mitotic activity may be seen and sometimes necrosis. Such cells seen in lymph node

aspirate especially in absence of eosinophils may raise a suspicion of metastatic malignancy such as melanoma. However the nuclear chromatin of Langerhans histiocytes is bland and finely granular. If suspected, the diagnosis may be confirmed by immunochemistry[27] and/or by EM. The cytological finding in sinus histiocytosis with massive lymphadenopathy have been described by Lampert and Lennert and by Van Heerde[28.] They diagnosed the entity by observing large histiocytes with intracytoplasmic lymphocytes and plasma cells.

B. The cytological features of granulomatous lymphadenitis: The criteria used for the diagnosis of granulomatous lymphadenitis includes.

I. Histiocytes of epithelioid type forming cohesive cluster.

II. Multinucleated giant cells of Langhans type.

III. With or without necrosis (Caseous type).

Epithelioid cells are quite characteristic seen in smear from lymph node. They have elongated nuclei, the shape of which can be described as resembling the sole of a shoe. The nuclear chromatin is finely granular and pale. The cytoplasm is pale without distinct cell borders. The most commonly encountered granulomatous lymphadenitis with necrosis is tuberculous. The tuberculous lymphadenitis contains aggregates of epithelioid cells, multinucleated giant cells against a necrotic (caseous) 'dirty' background. The FNA procedure should include sending material for culture. Ziehl-Neelsen stain shows sparse acid-fast bacilli particularly within necrotic areas. Caseous material appears granular and eosinophilic in smear and usually lacks recognizable cell remnants. Smear from tuberculous lymph node may sometimes show only polymorphs and necrotic debris without histiocytes particularly in immunocompromised patients. Cohesive clusters of epithelioid cells in absence of necrosis are suggestive but not diagnostic of sarcoidosis. However, tuberculosis remains in the differential diagnosis whether necrosis is present or not.

Cat scratch disease often present as a rapidly developing swelling in preauricular area and neck region of children[29]. FNA reveals a 'dirty' aspirate composed of a mixture of lymphocytes, plasma cells, eosinophils and a number of polymorph in a necrotic background. Aggregation of epithelioid and/or giant cells can be seen. Warthin-starry stain can be attempted to demonstrate causative bacteria. Sometimes only a few epithelioid cells are found in small groups or as a single cells or the histiocytes may not quite have the typical appearance of epithelioid cells. The pattern then approaches that of non-specific, reactive lymphadenitis with prominent histiocytes. This may be the case in toxoplasma lymphadenitis and in the early stage of sarcoidosis. Lymphogranuloma venereum clinically present as enlarged inguinal lymph node. FNA shows 'active histiocytic' cells scattered in background of neutrophils and debris. Endothelial cells can sometimes also closely resemble epithelioid histiocyte. Also deposits of kaposi's sarcoma in lymph node may be mistaken for granulomatous lymphadenitis, although the nuclei are more elongated and spindle shaped and the nuclear chromatin is darker and coarser than in epithelioid histiocytes[30.] Clusters of epithelioid cells are

sometimes found in cases of malignant lymphoma particularly in Hodgkin's disease and in Lennert's lymphoma. They can also occur in metastatic seminoma and in lymph node regional to carcinoma. One must therefore look carefully for abnormal lymphoid cells and for metastatic cancer cells in smear containing epithelioid histiocyte. Full knowledge of the clinical presentation is obviously essential.

The cytological features of Non-Hodgkin's lymphoma: Cytological subtyping of non-Hodgkin's lymphoma (NHL) in FNA smear is difficult and requires extensive experience. It can only be successful in centre with a team of oncology experts and with a regular flow of material. However, the diagnostic criteria of lymphoma in cytological preparations vary with the histological subtypes. It is therefore necessary to describe the main subtypes in some detail. Of all current classification of non-Hodgkin's lymphoma, the Kiel classification can most readily applied to cytological preparation and is therefore used in this presentation. The various cell types and cytological, histological and immunological patterns of malignant lymphomas were recently illustrated by Van Heerde et al in Amsterdam[31]. The cytological criteria for the diagnosis of non-Hodgkin's lymphoma are as follows:

1. A monotonous population of small lymphoid cells.
2. Mainly round nuclei slightly larger than those of normal small lymphocytes.
3. Characteristically coarse granular nuclear chromatin; nucleoli absent.
4. A varying number of prolymorphocytes; larger size, more cytoplasm, pale chromatin, single central nucleolus.

Immunophenotype: Pan B, faint SIg, CD5 & CD23.

The typical well-differentiated lymphocytic lymphoma of CLL type is readily recognized by monotonous population of cells resembling of small lymphocytes. Difficulties can arise if the process contains numerous proliferation centres with many large and intermediate size cells- paraimmunoblast and prolymorphocytes. A large B-cell lymphoma may develop in patients with B-CLL, the so-called Richter syndrome[32]. Low grade non-Hodgkin's lymphoma yield a monotonous population of small lymphocytes (chronic lymphocytic leukaemia type), lymphocytes with plasmacytoid or plasma cells differentiation (lymphoplasmacytoid type, plasmacytoma), or centrocytes (centrocytic lymphoma) and centroblasts (centrobastic/centrocytic lymphoma).

High grade B-cell lymphomas show a monotonous population of centroblasts (centroblastic non-Hodgkin's lymphoma), lymphoblasts (lymphoblastic, including Burkitt's), or immunoblast (immunoblastic non-Hodgkin's lymphoma). T-cell lymphomas are usually diagnosed after immunochemistry confirm the cell of origin. Of interest is human T-lymphotropic virus type I (HTLV-I) associated cutaneous Tcell lymphoma. FNA smears contain a population of small lymphocytes, eosinophils, small convoluted blasts and plasma cells. Pleomorphic high grade T-cell lymphomas must be distinguished from anaplastic carcinoma and large cell anaplastic CD30 (Ki-I) positive lymphoma by means of immunochemistry[33].

Burkitt's lymphoma is endemic and Epstein-Bar virus associated in African children, the jaws often being involved. In non-African cases most patients present with abdominal localisation. FNA smear of Burkitt's lymphoma show the following characteristic features.

a) A relatively uniform cell population with a high mitotic rate.
b) Round nuclei of variable but predominantly intermediate size.
c) A granular or speckled chromatin pattern; multiple small but prominent nucleoli.
d) A variable, mostly thin rim of dense blue cytoplasms with small lipid vacuoles (MGG).
e) Starry Sky macrophages often prominent.

In true histiocytic lymphoma, it is difficult to recognize correctly in routine cytological smears. A very pleomorphic cell population with multilobed nuclei and multinucleated cells which may resemble Reed-Sternberg cells are usually present. The main differential diagnosis include large cell non-Hodgkin's lymphoma (especially large cell anaplastic CD30 positive lymphoma) and Hodgkin's disease.

There are certain problems in diagnosis of lymphoma. The problems are :

a) Suboptimal cytological preparation.

b) Variable pattern in one node.

c) Distinction from reactive lymphadenopathy.

d) ML with few neopalstic cells in a dominant population of reactive lymphoid[34]cells, e.g. T-cell rich B lymphomas.

e) Small cell anaplastic carcinoma and other small cell tumours particularly versus ML mantle cell and lymphoblastic type.

f) Large cell undifferentiated carcinoma and melanoma versus large cell lymphoma, especially ML CD30 positive.

g) Effects of chemotherapy and radiotherapy.

Direct smears must be made expertly, since poor preparation makes accurate diagnosis impossible. It has been emphasized that suboptimal smear are the commonest cause of diagnostic difficulties and misinterpretations. In general airdried MGG-stained smears are recommended for the diagnosis of lymphoproliferative lesions, but a combination with alcohol fixed smear stained by Pap or by H&E provide complementary information. Smears of a cell suspension prepared in the cytocentrifuge, in addition to routine smears are very helpful in the diagnosis and classification of NHL and are well suited for immune marker studies[35]. The difference between normal lymphocyte and the neoplastic cells of ML lymphocytic lymphoma (well differentiated) is relatively subtle and the most obvious diagnostic features is the monotomy of the cell population. However, a sample including proliferation centres does not appear monotonous since there can be many cells of intermediate and large size (prolymorphocytes and paraimmunoblast) mixed with the typical cells of CLL type[36]. Such a case can be mistaken for reactive lymphadenopathy unless close attention is paid to the cytological detail of the lymphocyte and the result of immunocytology. ML lymphoplasmacytoid can also be mistaken for reactive lymphadenopathy in view of the sometimes pleomorphic character of the smear population. Immunocytochemical, clinical and biochemical data are of utmost diagnostic importance. In ML centrobastic/centrocytic there may be high proportion of small lymphocytes to suggest a benign reactive process. However, the small cleaved cells of some follicular lymphomas can be difficult to distinguish from lymphocytes in a reactive process particularly if smears are not technically optimal. Nuclei must be studied carefully in high power to appreciate the slightly larger size, irregular shape and granular chromatin. Occasionally, non-Hodgkin's lymphoma of larger cell type may have few neoplastic cells scattered in a background of reactive lymphoid cells[37]. In FNA smears, large centrocytic lymphoma cells have a tendency to clump together into aggregates showing some moulding of nuclei. Rows and Palisades of closely apposed, ovoid nuclei which appear columnar through moulding may simulate small cell anaplastic carcinoma or even adenocarcinoma. However, the proportion of isolated cells is usually larger in lymphoma and may of these have the typical appearance of lymphoid cells with the rim of basophilic cytoplasm and a nuclear chromatin pattern which is different from that of carcinoma cells. Importantly, nuclei of lymphoma cells of a similar size to those of small cell anaplastic carcinoma usually have prominent nucleoli. This is a helpful but not infallible features: nuclei of large centrocytes and of small cell carcinoma of intermediate type may be very similar in size and may have similar nucleoli. Nuclear moulding and well-formed single files of tumour cells are more obvious in small cell carcinoma and other metastatic small cell tumours. The pale-blue, uniformly rounded cytoplasmic fragments characteristic of lymphoid tissue (lymphoid globules/lymphoglandular bodies) are different from the cytoplasmic and nuclear fragments of tumour necrosis in smears of carcinomas[38].

Immunocytochemical staining for cytokeratin and panleukocyte marker can usually solve the problem of distinguishing between small cell carcinoma and lymphoma in difficult cases. Smears of large cell undifferentiated carcinoma and of melanoma may show total dissociation of the tumour cells, nuclei may be larger, with fine chromatin, prominent nucleoli and abundant basophilic cytoplasm. This pattern can be indistinguishable from large cell

lymphoma particularly from immunoblastic or large anaplastic CD30 positive lymphoma and from Hodgkin's disease. The presence of cytoplasmic fragments (lymphoid globules) in lymphoma and lobulated nuclei is helpful. Well-formed sharply delineated aggregates of tumour cells are not seen in lymphoma. Again in difficult cases, immunological staining for cytokeratin and lymphoid markers is usually decisive. However, the commonly used immune markers may not solve the problem of distinguishing large cell anaplastic CD30 positive lymphoma from large cell carcinoma and this may require extensive immune marker studies or even electron microscopical examination[39].

Chemotherapy and radiotherapy may cause changes to lymphoma cells which render typing more difficult. In particular, treatment seems to cause an increased irregularity of the nuclear shapes.

The cytological criteria for the diagnosis of Hodgkin's disease: Hodgkin's disease (HD) is a malignancy of lymphoid tissue characterised by the Reed-Sternberg (R-S) cell or a variant of R-S cell (atypical mononuclear cells/Hodgkin's cells). Usually a background of reactive lymphoid cells, granulocytes (especially eosoniphils), plasma cells and histiocytes is present. The R-S cell is of unknown origin, but some data previously suggests origin in the dendritic reticulum cells. Recently the cell of origin is very probably a lymphocyte. The lymphocyte predominant subtype is in fact a B-cell proliferations, sternberg ('Popcorn') cells and most of the small lymphocytes being B-cells. The other subtypes nodular sclerosing, mixed cellularity and lymphocyte depletion variants - are called classic Hodgkin's disease in which the background lymphocytes are T cells. According to the recent immune marker analysis, the lymphocyte depletion subtype appeared to be a large cell anaplastic CD30 positive non-Hodgkin's lymphoma in most instances[40]. The patients with Hodgkin's disease usually present with painless lymphadenopathy (subdiaphragmatic in 90%, cervical >> mediastinal > axillary), fever, night sweats, pruritus, malaise or weight loss. Later in the course patients have retroperitoneal lymph node, spleen, liver and/or bone involvement. About 50% of the cases occur in patients between 20 & 40 years of age. Less than 10% of cases occur before the age 10 and less than 10% after age of 60. The male to female ratio is 4:3 (males also have worse prognosis). Hodgkin's disease accounts for 30 to 40% of all lymphomas.

The following cytologic criteria are recognized as diagnosis of Hodgkin's disease.

1. Reed-sternberg cells
2. Atypical mononuclear cells (Hodgkin's cells)

A variable number of eosinophils, plasma cells and histiocytes.

A background population of lymphocytes.

5. Immunophenotype: 'classic' Hodgkin's disease: Reed-sternberg cells CD30, CD 15; small lymphocytes pan T. Lymphocyte predominant type: Reedsternberg cells pan B, CD45, EMA; small lymphocyte pan B.

A confident diagnosis of Hodgkin's disease can only be made in the presence of typical Reed-sternberg cells with a background of lymphocyte and reactive cells (e.g. eosinophil, plasma cell and histiocytes). Reed-sternberg cells have large lobulated nuclei which may appear symmetrically double (mirror nuclei) or complex and multiple. The nuclear chromatin is coarse and irregularly distributed in a reticular fashion with clear areas in between which give the nucleus an overall pale appearance. Nucleoli are large often huge, eosinophilic in H&E preparations; pale or basophilic in MGG-stained smear. The cytoplasm is abundant and pale so that nucleus often appears to be surrounded by an empty spaces. Sometimes the characteristic nucleoli are not well demonstrated and in some cases only mononuclear Hodgkin's cells which have a nuclear structure similar to the typical Reed-sternberg cells are present. In such cases the definite diagnosis must await histological examination, except in recurrent disease when classic Reed-sternberg cells are not essential for diagnosis.

In lymphocyte-predominant subtype HD, the patient is generally a child with a single large spherical node and no other symptoms. The aspirate contains a monotonous population of slightly irregular small lymphocyte with scattered, scanty large multinucleated giant cells, corresponding to the 'popcorn' cells in histology, usually without distinct

nucleoli. Mixed cellularity HD the nodes are clinically soft and aspirates are very cellular. This variant most readily diagnosed because of presence of numorous R-S cells and their variants scattered in a background of many eosinophil, plasma cell and histiocytes[41]. Lymphocyte depletion HD is the least common type and the affected node may be fibrotic or cellular. It is characterised by very pleomorphic R-S cells in a limited lymphoid background. Nodular sclerosing subtype is the most common variant form of HD. The tough consistency of the node felt with the needle, a scanty aspirate and the presence of fibroblast and collagen fragments in smear are features suggestive of nodular sclerosing type. In this type aspirate contains many typical R-S cells and mononuclear variants. In fibrotic areas the fragile R-S cells often lose their cytoplasm and may present as bare nuclei. The background is usually a population of lymphocyte, eosinophils and plasma cells. Occasional cases have areas of suppurative necrosis.

There are certain problem in the diagnosis of Hodgkin's disease:

1. Poor biopsy yield
2. Reed-sternberg look-alike cells in other conditions.
3. Epithelioid histiocyte suggestive of granulomatous lymphadenitis.

Poor biopsy yield is a problem mainly in the nodular sclerosis subtype. Not in frequently, smear show only a few lymphocytes, fibroblast and fragments of collagen which may suggest a chronic inflammatory process. Multiple biopsies or the use of a cutting core needle may be necessary to obtain sufficient material.

2. Large, multilobated nuclei resembling R-S cells can be seen in a variety of conditions. Atypical immunoblasts in non-neoplastic reactive lymphadenopathy, for example in infectious mononucleosis, in rheumatoid arthritis-associated and drug induced lymphadenopathy may have nuclei of this type. They usually differ from the typical Reed-sternberg cells by having smaller and darker nucleoli, a denser chromatin and a basophilic cytoplasm. Multinucleated giant cells in small or large cell nonHodgkin's lymphoma, e.g. ML lymphoplasmacytoid, ML pleomorphic T-cell and especially large cell anaplastic CD30 positive lymphoma, can also have large nucleoli similar to Reed-sternberg cell4[2.] The distinction is particularly difficult in presence of eosinophils, plasma cells and epithelioid cells which is not unusual in T-cell lymphoma. Immunological studies may be necessary to solve the problem. In some cases of large malignant cells with very large nucleoli and with many eosinophils and reactive lymphoid cells in the background, representating single malignant cells of metastatic especially nasopharyngeal carcinoma, which were misdiagnosed as Hodgkin's disease.
3. Cluster of epithelioid histiocytes are sometimes seen in smears of Hodgkin's disease and in some non-Hodgkin's lymphomas which could suggest granulomatous lymphadenitis. The lymphoid cells must therefore always be carefully scrutinized in lymph node smear containing epithelioid cells.

Cytological criteria for the diagnosis of lymph node necrosis: Extensive or total necrosis /infarction of lymph nodes occur in some inflammatory processes, in metastatic malignancy, in malignant lymphoma and rarely in relation to vasculitis and to trauma. If necrosis is extensive, FNA smears may not include any well-preserve cells necessary for diagnosis. Completely amorphous, granular material without identifiable cell remnants suggest caseous necrosis and smear should be searched for acid-fast bacilli and other microorganism. In acute inflammatory necrosis, the aspirate and smears have a purulent character. Necrotizing lymphadenitits (kikuchi's disease) is a condition of unknown but most probably viral etiology seen in young women, in which there is focal necrosis in cervical lymph node[43]. In FNA smears, the characteristic findings are of large number of pale phagocytosing histiocytes with eccentric nuclei, debris with nuclear fragments, absence of neutrophils and a reactive background of lymphoid cells. The presence of large mononuclear cells in such nodes may cause a suspicion of malignant lymphoma. Smears from areas of coagulation necrosis in lymph nodes show numerous cell shadows, some with preserved but pyknotic nuclei. Unless there is a clear history of trauma, such findings raise a strong

suspicion of either metastatic carcinoma or malignant lymphoma. Nodal metastases of small cell anaplastic carcinoma of lung, melanoma and breast carcinoma are prone to necrosis and the necrotic cells with pyknotic nuclei can be indistinguishable from necrotic lymphoid cells. Extensive necrosis/infarction is not uncommon in malignant lymphoma, both non-Hodgkin's and Hodgkin's. Total infarction of a lymph node can sometimes precede manifest lymphoma[44] FNA biopsy should be repeated, if possible from other abnormal nodes and if a diagnosis can still not be made, surgical excision is indicated.

F. Cytological criteria for the diagnosis of metastatic malignancy: Since clinical enlargement of a lymph node by a metastasis usually invokes more than a fourfold increased in mass, the majority of the node is replaced by metastatic malignancy when it present as lymphadenopathy. Two important criteria are used a diagnostic tool for metastatic malignancy.

1. Foreign cells amongst normal/reactive lymphoid cells
2. Cytological criteria of malignancy.

The cytological pattern seen in routinely stained smear often give clues to the site of primary tumour. Columnar cells with elongated nuclei arranged in palisades, stringy mucus and necrosis suggest a primary in the large bowel; while mucin containing signet ring cells suggest the stomach as the most likely primary site among several other possibilities. Glandular cells, moderately pleomorphic, arranged in a gland-in-gland or cribiform pattern suggest prostatic carcinoma. Large cells with abundant pale, granular or finely vacuolated cytoplasm and a low N:C ratio suggest a renal cell carcinoma. Very large central nucleoli are typical of less well-differentiated forms of this tumour and are also seen in large cell anaplastic carcinoma of lungs and nasopharynx and in hepatocellular carcinoma. Pulmonary and pancreatic adenocarcinoma can have a variety of pattern. They usually show a moderate degree of glandular differentiation, prominent nuclear pleomorphism and obvious mucin secretion. As a rule, the presence of intracytoplasmic mucin excludes renal, adrenal, hepatocellular and thyroid carcinoma. Breast cancer usually displays poor glandular differentiation while cell balls and single files of cells are more common. Some tumours form a monolayer of dispersed cells with intact cytoplasm. Nuclear pleomphism is often relatively mild.

The cells of small cell anaplastic carcinoma of lung are closely packed together in aggregates or as single files with prominent nuclear moulding. Pyknotic nuclei and nuclear debris are commonly seen between preserved cells, in the absence of massive necrosis. 'Tear-drop' nuclear artefacts caused by smearing are characteristic. Smears of malignant melanoma may show total dissociation of cells, well-defined cytoplasm, eccentric nuclei, prominent anisokaryosis, uniformly dense chromatin, often large nucleoli, binucleate cells, intranuclear vacuoles and in most cases some cells with intracytoplasmic pigments or at least a dark staining paranuclear area. Malignant melanoma can occasionally mimic lymphoma in FNA smears. Testicular tumours may clinically occult and present with metastases to pelvic, paraaortic or supraclavicular nodes. The cytological pattern of seminoma is characteristic. The tumour cells are mainly dissociated and are mixed with lymphocytes and epithelioid cells. They have large rounded vesicular nuclei and evenly distributed nuclear chromatin. Nucleoli are prominent. The cytoplasm is pale and both cytoplasm and nuclei are very fragile, the dispersed cytoplasm forming a 'tigroid' background to the nuclei[45]. Cells from a transitional carcinoma may also be dispersed, resembling a large cell lymphoma, or may form solid and sometimes papillary groups. The cells have abundant, relatively dense cytoplasm with distinct borders and pleomorphic nuclei which are often eccentic. A tendency to squamous differentiation or spindle cell pattern may be seen.

Special stains are often helpful and the cell sample can be divided to provide spare slides for this purpose. Squamous differentiation is most obvious in alcohol-fixed papstained smear but can also be distinguished in MGG-stained preparation. The histochemical demonstration of intracytoplasmic mucin droplets is important in adenocarcinoma. Strong positivity for acid phosphatase by the enzymatic method or positive immunocytochemical staining for prostatic acid phosphatase and/or prostatespecific antigen in an adenocarcinoma supports a prostatic origin. Distant

metastases particularly to supraclavicular lymph nodes are sometimes the first manifestation of prostatic cancer preceding any urinary symptoms. Immunocytochemical staining for S 100 and especially HMB45 for melanoma is more reliable. Differential cytokeratines (CK7, CK20) may be helpful in suggesting the origin of metastatic carcinoma. In some cases, electron microscopical examination of the aspirate can be helpful, particularly in small round cell tumour and in some mesenchymal tumours.

**References:**


1. Cotran RS, Kumar V, Robbin SL. Pathologic Basis of Diseases. Sixth edition. NewYork: WB Saunders. 1999. pp290-291.
2. Lopes Cardozo P. The cytologic diagnosis of lymph node punctures. Acta cytol. 1964; 8 : 194-205.
3. Martin HE, Ellis EB. Aspiration Biopsy. Surg. Gynaecol Obstet 1934; 59 : 578589.
4. Bestil WL, Hajdu SI. Percutaneous aspiration biopsy of lymph nodes. Am J Clin Pathol 1980; 73 : 471-479.
5. Kocjan GIL. Atlas of Diagnostic Cytopathology. Second edition. Newyork. Churchill Livingstone 1997. pp 225-235.
6. Atkinson FB. Atlas of Diagnostic Cytopathology. Third edition. Philadelphia: WB Saunders. 1992. pp 480-486.
7. Feldman P, Covell J, Kardos T. Fine needle aspiration cytology of Lymph Node, Thyroid and salivary gland. ASCP press, Chicago. 1989. pp 710-715.
8. Jaffe ES. Surgical pathology of lymph node and related organs. Fourth edition. Philadelphia: WB Saunders. 1985. pp 312-315.
9. Stani J. Cytologic diagnosis of reactive lymphadenopathy in fine needle aspiration biopsy specimen. Acta Cytol. 1987; 31 : 8-13.
10. Tani EM, Christenson B, Powit A, Skoog L. Immunocytochemical analysis and cytomorphologic diagnosis on fine needle aspirates of lymphoproliferative disease. Acta Cytol 1988; 32 : 209-215.
11. Wotherspoon AL, Norton AJ, Lees $W_r$, Shaw P, Isaacson PG. Diagnostic fine needle core biopsy of deep lymph nodes for the diagnosis of patients unfit for surgery. J Pathol. 1989; 158 : 115-121.
12. Robey SS, Caffarty LL, Beschozner WE, Gupta PK. Value of lymphocyte marker studies in diagnostic cytopathology. Acta cytol. 1987; 31 : 453-459.
13. Spieler P, Schmid U. How exact are the diagnosis and classification of malignant lymphomas from aspiration biopsy smears? Path Res Pract. 1978; 163 : 232-250.
14. Ramzy I, Rone R, Schultenover SJ, Buhaug J. Lymph node aspiration biopsy. Diagnostic reliability and limitations -- an analysis of 350 cases. Diagn Cytopathol. 1985; 1 : 39-45.
15. Cartagena N, Katz RL, Hiresch-Ginsberg C, Childs CC, Ordonez NG, Cabanillas F. Accuracy of diagnosis of malignant lymphoma by combining fine needle aspiration cytomorphology with immunocytochemistry and in selected cases, southern blotting of aspirated cells - a tissue controlled study of 86 patients. Diagn Cytopathol. 1992; 8 : 456-464.
16. Zajdela A, Ennuyer A, Bataini P, Poncet P. Valeur du diagnostic cytologique des adenopathies par ponction aspiration. Confrontation of cyto-histologique de 1756 cases. Bull Cancer (Paris). 1976; 63 : 327-340.
17. Behm FG, O'Dowd CJ, Frable WJ. Fine needle aspiration effects on benign lymph node histology. Am J Clin Pathol 1984; 82 : 195-198.
18. Erwin BC, Brynes BK, Chan WC et al. Percutaneous needle biopsy in the diagnosis and classification of lymphoma. Cancer 1986; 57 : 1074-1078.
19. Martelli G, Pilotti S, Lepera P et al. Fine needle aspiration cytology in superficial lymph nodes-an analysis of 266 cases. Eur J Surg Oncol 1989; 15 : 13-16.
20. Hu E, Horning S, Flynn S et al. Diagnosis of B cell lymphoma by analysis of immunoglobulin gene rearrangement in biopsy specimens obtained by fine needle aspiration. J Clin Oncol 1986; 4 : 778-783.
21. Zajicek J. Aspiration biopsy cytology. Cytology of supradiaphragmatic organs (Part I). Third edition. Basel: Karger. 1974. pp 92-96.
22. Noorduyn LA, Van Heerde P, Mayer CJLM. Cytology of Ki-I (CD-30) positive large cell lymphoma. Cytopathology. 1990; 1 : 297-304.
23. O'Dowd GJ, Frable WJ, Behm FG. Fine needle aspiration cytology of benign lymph node hyperplasias. Diagnostic significance of lymphohistiocytic aggregates. Acta Cytol 1985; 29 : 554-558.
24. Kardos TF, Kornstein MJ, Frable WJ. Cytology and immunocytology of infectious mononucleosis in fine needle aspirates of lymph nodes. Acta cytol 1988; 32 : 722-726.
25. Christ ML, Feltes-Kennedy M. Fine needle aspiration cytology of toxoplasmic lymphadenitis. Acta Cytol 1982; 26 : 425-428.
26. Layfield LJ, Bhuta S. Fine needle aspiration cytoloty of histiocytosis-a case report. Diagn Cytopathol 1988; 4 : 140-143.
27. Van Heerde P, Egeler RM. The cytology of Langerhan's histiocytosis (histiocytosis x). Cytopathology 1991; 2 : 149-158.

Lampert F, Lennert K. Sinus histiocytosis with massive lymphadenopathy. Fifteen new cases. Cancer 1976; 37 : 783-789.

29. Silverman JF: Fine needle aspiration cytology of cat scratch disease. Acta Cytol 1985; 29 : 542-547.
30. Hales M, Bottles K, Miller T et al. Diagnosis of kaposi's sarcoma by fine needle aspiration biopsy. Am J Clin Pathol 1987; 88 : 20-25.

31. Van Heerde P, Meyer CJLM, Noorduyn LA et al. An atlas and text book of malignant lymphomas. Cytology, histology and immunochemistry. Fifth edition. Oxford university press. 1996. pp105-112.

32. Harris NL, Jaffe ES, Stein H et al. A revised European-American classification of lymphoid neoplasm-Proposal from the international lymphoma study group. Blood 1994; 84 : 1361-1392.

33. Oertel J, Oertel B, Kastner M et al. The value of immunocytochemical staining of lymph node aspirates in diagnostic cytology. Br J Haematol 1988; 70 : 307-316.

34. De Jong D, Van Gorp J, Sie-GOD et al. T-cell rich B-cell non-Hodgkin's lymphoma - a progressed from of follicle centre cell lymphoma and lymphocyte predominance Hodgkin's disease. Histopathology 1996; 28 : 15-24.

35. Katz RL. Cytologic diagnosis of leukaemia and lymphoma. Values and limitations. Clin Lab Med 1991; 11 : 469-499.

36. Van Heerde P, Go DMDS, Koolman-Schellekens MA, Peterse JL. Cytodiagnosis of non-Hodgkin's lymphoma. A morphological analysis of 215 biopsy proven cases. Virchows Arch (Pathol anat) 1984; 403 : 213-233.

37. Feinberg MR, Bhaskar AG, Bourna P. Differential diagnosis of malignant lymphomas by imprint cytology. Acta Cytol 1980; 24 : 16-25.

38. Turner RR, Martin J, Dorfman RF. Necrotizing lymphadenitis. A study of 30 cases. Am J Surg Pathol 1983; 7 : 115-123.

39. Tani E, Lowhagen T, Nasiell K, Skoog L. Fine needle aspiration cytology and immunochemistry of large cell lymphoma expressing the Ki-1 antigen. Acta cytol 1989; 33 : 359-362.

40. Jaffe ES, Harris NL, Chain JKC et al. Introduction to WHO classification. Am J Surg Pathol 1997; 21 : 114-121.

41. Moriarty AT, Banks ER, Blotch T. Cytologic criteria for subclassification of Hodgkin's disease using fine needle aspiration. Diagn Cytopathol 1989; 5 : 122125.

42. Strum SB, Park JK, Rappaport H. Observation of cells resembling sternbergReed cells in conditions other than Hodgkin's disease. Cancer 1970; 26 : 176190.

43. Tsang WYW, Chan JKC. Fine needle aspiration cytologic findings of Kikuchi's lymphadenitis - an analysis of 24 cases. Mod Pathol 1993; 6 : 32.

44. Cleary KR, Osborne BM, Butler JJ. Lymph node infarction foreshadowing malignant lymphoma. Am J Surg Pathol 1982; 6 : 435-442.

45. Highman WJ, Oliver RT. Diagnosis of metastases from testicular germ cell tumours using fine needle aspiration cytology. J Clin Pathol 1987; 40 : 1324-1333.

46. Wang NP, Zee S, Zarbo RJ et al. Coordinate expression of cytokeratins 7 and 20 defines unique subsets of carcinomas. APPI Immunohistochem 1995; 3 : 99107.