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REVIEW

A stepwise approach to fine needle aspiration cytology of lymph nodes

Yosep Chong[1], Gyeongsin Park[1], Hee Jeong Cha[2], Hyun-Jung Kim[3], Chang Suk Kang[4], Jamshid Abdul-Ghafar[1], Seung-Sook Lee[5]

[1]Department of Hospital Pathology, The Catholic University of Korea, College of Medicine, Seoul;
[2]Department of Pathology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan;
[3]Department of Pathology, Inje University Sanggye Paik Hospital, Seoul;
[4]Department of Pathology, Samkwang Medical Laboratories, Seoul;
[5]Department of Pathology, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

The cytological diagnosis of lymph node lesions is extremely challenging because of the diverse diseases that cause lymph node enlargement, including both benign and malignant or metastatic lymphoid lesions. Furthermore, the cytological findings of different lesions often resemble one another. A stepwise diagnostic approach is essential for a comprehensive diagnosis that combines: clinical findings, including age, sex, site, multiplicity, and ultrasonography findings; low-power reactive, metastatic, and lymphoma patterns; high-power population patterns, including two populations of continuous range, small monotonous pattern and large monotonous pattern; and disease-specific diagnostic clues including granulomas and lymphoglandular granules. It is also important to remember the histological features of each diagnostic category that are common in lymph node cytology and to compare them with cytological findings. It is also essential to identify a few categories of diagnostic pitfalls that often resemble lymphomas and easily lead to misdiagnosis, particularly in malignant small round cell tumors, poorly differentiated squamous cell carcinomas, and nasopharyngeal undifferentiated carcinoma. Herein, we review a stepwise approach for fine needle aspiration cytology of lymphoid diseases and suggest a diagnostic algorithm that uses this approach and the Sydney classification system.

Key Words: Cytology; Fine needle aspiration; Lymph node; Lymphoid neoplasms; Diagnosis

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Corresponding Author: Yosep Chong, MD, PhD, Department of Hospital Pathology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 271 Cheonbo-ro, Uijeongbu 11765, Korea
Tel: +82-32-820-3160, Fax: +82-32-820-3877, E-mail: ychong@catholic.ac.kr

Lymph nodes are an essential component of the human immune system. Lymphadenopathy occurs when a lymph node is large in size and number or atypical in consistency [1]. The causes of lymphadenopathy range from benign reactive lymphoid hyperplasia to malignant diseases. Although several conditions present with lymph node enlargement, the most common cause is benign lymphadenopathy (90%), including reactive hyperplasia (60%), followed by infectious or inflammatory lymphadenitis (30%). Infectious or inflammatory lymphadenitis includes Kikuchi-Fujimoto disease (KFD), tuberculosis, sarcoidosis, infectious mononucleosis, toxoplasmosis, human immunodeficiency virus infection, cat-scratch disease, drug (phenytoin) reaction, and others (Fig. 1) [1,2]. Malignant lymphadenopathies only comprise 10% of the cases, which include primary lymphomas (3%), including diffuse large B-cell lymphoma/anaplastic large cell lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), and Hodgkin's lymphoma (HL). Metastatic carcinomas account for 7% of cases and include metastatic papillary thyroid carcinoma, adenocarcinomas primarily from lung or breast, and poorly differentiated squamous cell, small cell, or any primary unknown carcinoma (Fig. 1) [2]. It is very unlikely to diagnose the cause of lymphadenopathy based solely on history, physical examination, or ultrasound alone.

Fine needle aspiration cytology (FNAC) has been vastly utilized as a primary diagnostic tool to examine enlarged lymph nodes and to exclude involvement of alternative organs, such as the salivary gland, head, neck, or other subcutaneous masses. It is a minimally invasive approach that allows fast diagnosis and treatment. There are few complications that have been reported for FNAC, including hemorrhage, nerve damage, and vasovagal reactions in head and neck lymph node procedures [3]. Finally, FNAC is a cost-effective procedure, especially in developing coun-

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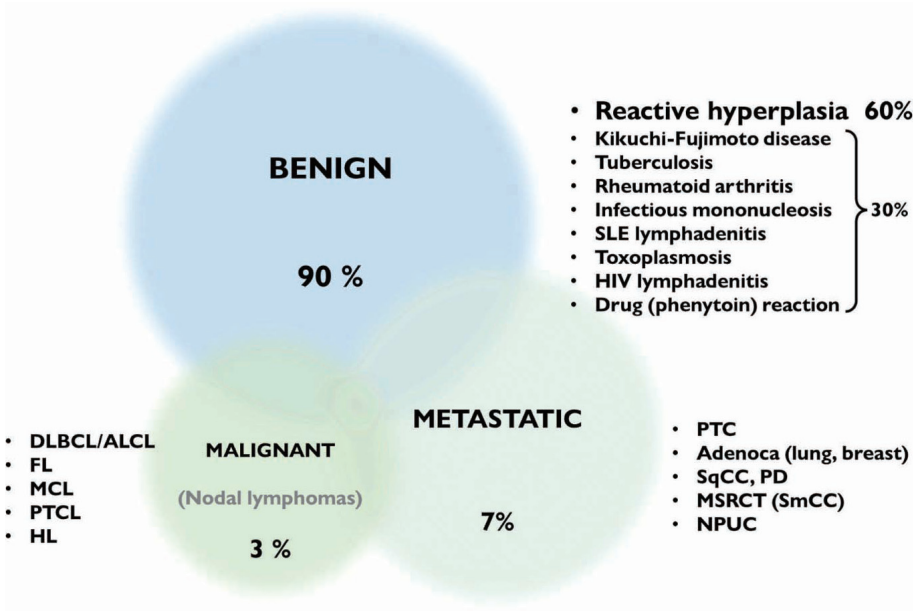

Fig. 1. Disease entity that can be found in lymph node fine needle aspiration cytology. DLBCL/ALCL, diffuse large B-cell lymphoma/anaplastic large cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma; HIV, human immunodeficiency virus; HL, Hodgkin's lymphoma; PTC, papillary thyroid carcinoma; SqCC, squamous cell carcinoma; MSRCT, malignant solitary fibrous tumor of the pleura; NPUC, non-papillary urothelial carcinoma; PD, poorly differentiated; SmCC, small cell carcinoma.

tries where the cost of surgical biopsy can be prohibitive [3]. However, this procedure has limitations.

In a review by Rammeh et al. [3], FNAC for head and neck masses was inconclusive in 17.7% of cases, while literature review found a rate range of 3%–30% [4,5]. This rate largely depends on the experience of cytotechnologists and cytopathologists [4,5]. There are fewer inconclusive cases when experienced cytopathologists perform the procedure, evaluate the samples, and recognize inadequate aspirates. Another limitation of FNAC is that the diagnoses of some malignant tumors (e.g., thyroid follicular carcinoma) are based only on histological criteria [2,6,7]. Moreover, the value of FNAC for verifying recurrent or residual lymphoma is well established and accepted. However, the diagnosis of primary lymphoma remains controversial [4].

A stepwise approach is required when using FNAC to diagnose the cause of lymphadenopathy. In general, up to three separate needle puncture passes with aspirates are needed to obtain a sufficient sample. Moreover, microscopic evaluation is associated with the following clinical history: signs and symptoms, radiological findings, presence of systemic inflammatory symptoms, node size and location, enlargement duration, malignancy history, medical and drug history, autoimmune disease, and risk factors for malignancy (including age, sex, race, family history, or presence of other masses in the body) [1,8,9].

In the current study, we introduce a stepwise approach for lymph node FNAC diagnosis along with disease-specific diagnostic clues, clinical information, and ultrasonographic findings. We suggest a diagnostic algorithm that encompasses this stepwise approach and the Sydney classification system published in 2019 [10].

CLINICAL FINDINGS

Fig. 2 summarizes the stepwise approach to lymph node FNAC. Before cytological interpretation, it is important to review the clinical information. In order to formulate a proper differential diagnosis, the following clinical features are needed: age, site (cervical/inguinal), lymph node size, presence of B symptoms (fever, weight loss, night sweating), previous medical history (primary or metastatic), infectious signs, autoimmune disease, and history of drug or chemical exposure.

Radiological findings, including mostly ultrasonographic and positron emission tomography computed tomography (PET/CT) findings, are helpful to narrow the differential diagnosis (Supplementary Table S1, Supplementary Fig. S1). In benign lymphadenopathy, the lymph nodes are relatively small, oval-shaped, and hypoechoic with a regular well-demarcated border. The general architecture is preserved, with a visible hilum without obvious necrosis or calcification. In metastatic lesions, lymph nodes are usually large, round, and hypoechoic with irregular, ill-de-

fined blurred borders that suggest capsular invasion. The architecture can be destroyed by metastatic tumors, leading to a heterogeneous internal structure without a visible hilum. Cortical nodules, cystic tumor necrosis, and calcifications can occur. In malignant lymphomas, lymph nodes are continuously enlarged/conglomerated and hypoechoic with cortical thickening and no visible hilum. On PET/CT, metastatic lesions or malignant lymphomas demonstrate high fluorodeoxyglucose uptake more frequently than do normal lymph nodes.

On microscopic examination, a comprehensive interpretation of low-power patterns, high-power patterns, and disease-specific diagnostic clues is essential for successful differential diagnosis.

LOW-POWER PATTERN OF LYMPH NODE FINE NEEDLE ASPIRATION CYTOLOGY

The first step in lymph node FNAC is to assess the low-power magnification patterns. Lymphadenopathy can be broadly categorized into three patterns: reactive, metastatic, and lymphoma (Fig. 3). The reactive pattern comprises an evenly distributed smear with normal cellularity and some normal lymphoid clusters. Diverse inflammatory cells may be observed according to the type of lymphadenopathy. Necrosis or granulomas may be observed in tuberculosis or KFD. Neutrophilic smears suggest a benign condition.

The metastatic pattern involves an irregularly distributed hypercellular smear with prominent epithelial clusters and is often

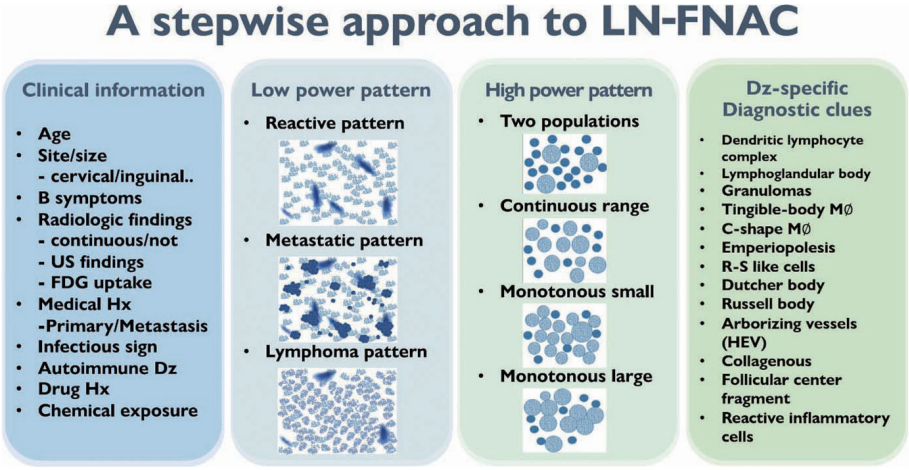

Fig. 2. A stepwise approach to lymph node fine needle aspiration cytology (LN-FNAC) interpretation. US, ultrasonography; FDG, fluorodeoxyglucose; Hx, history; Dz, disease; MΦ, macrophage; R-S, Reed-Sternberg; HEV, high endothelial venule.

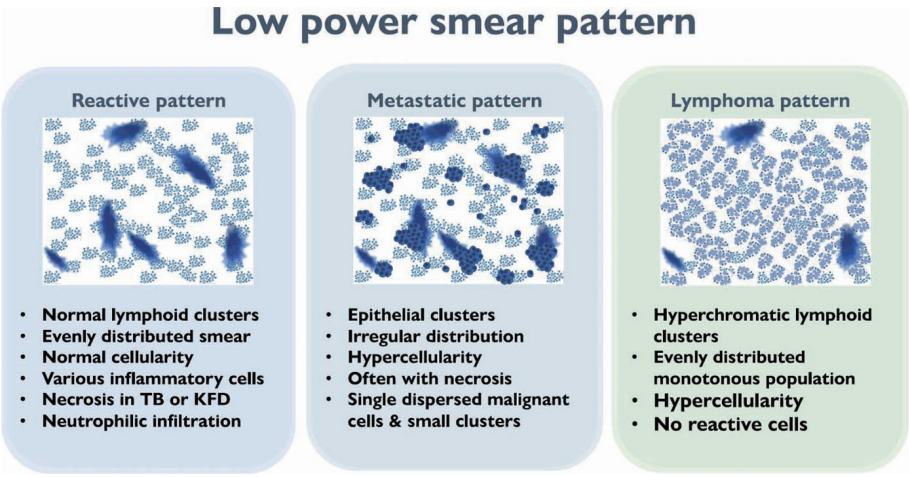

Fig. 3. Low-power smear patterns of lymph node fine needle aspiration cytology interpretation. TB, tuberculosis; KFD, Kikuchi-Fujimoto disease.

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accompanied by necrosis. Single dispersed malignant cells and small-to-large clusters are observed.

The lymphoma pattern shows an evenly distributed hypercellular smear with monotonous hyperchromatic lymphoid clusters. Reactive inflammatory cells (such as neutrophils) are uncommon. Occasional multinucleated, large, atypical cells such as Reed-Sternberg cells and ill-defined granulomas with occasional eosinophils can be found in HL.

HIGH-POWER PATTERN OF LYMPH NODE FINE NEEDLE ASPIRATION CYTOLOGY

The second step for lymph node FNAC is to assess high-power magnification cell population patterns. There are four broad patterns: two-cell, continuous range, monotonously small, and monotonously large population (Fig. 4). The two-cell population pattern is a smear pattern with two distinct cell populations. This pattern can be seen in reactive hyperplasia; metastatic carcinomas; and diverse lymphomas including HL, FL, and anaplastic large cell lymphoma. Rarely, T-cell/histiocyte-rich B-cell lymphoma (TCR-BCL) and lymphomatoid granulomatosis can also present with this cytological pattern [2].

The second pattern is a smear with a continuous range of variably sized cells. In this pattern, there is an obvious dominant cell population of atypical lymphocytes and diverse inflammatory cells such as eosinophils. PTCL and angioimmunoblastic lymphoma, which are representative examples of this pattern, can present with variable inflammatory/reactive cells.

The third pattern is a small cell population that predominantly presents as monotonously small, atypical lymphoma cells with few reactive cells. This category includes malignant small round cell tumors, such as metastatic small cell carcinoma or small round cell sarcoma, and low-grade B-cell lymphoma such as MCL or small lymphocytic lymphoma. However, malignant small round cell tumors generally have slightly larger nuclei than low-grade B-cell lymphomas.

The fourth pattern is a large cell population of mostly monotonously large atypical malignant cells. For metastasis, poorly differentiated squamous cell carcinoma (such as basaloid type) and undifferentiated nasopharyngeal carcinoma are the major differential diagnoses. Diffuse large B-cell and Burkitt lymphoma are common examples of lymphoma.

Two-cell population pattern

Reactive lymphoid hyperplasia without a specific etiology accounts for 60% of all cases and usually demonstrates polymorphic cell populations, including small and large plasmacytoid lymphocytes [11]. This hyperplasia is often accompanied by tingible-body macrophages; dendritic lymphocytic aggregates (intact follicles); and other reactive inflammatory cells, including capillaries, eosinophils, and mast cells (Fig. 5A) [11].

FL is another example of a two-cell population pattern. It demonstrates predominantly small irregular/cleaved and large cleaved/non-cleaved lymphocytes with few tingible-body macrophages,

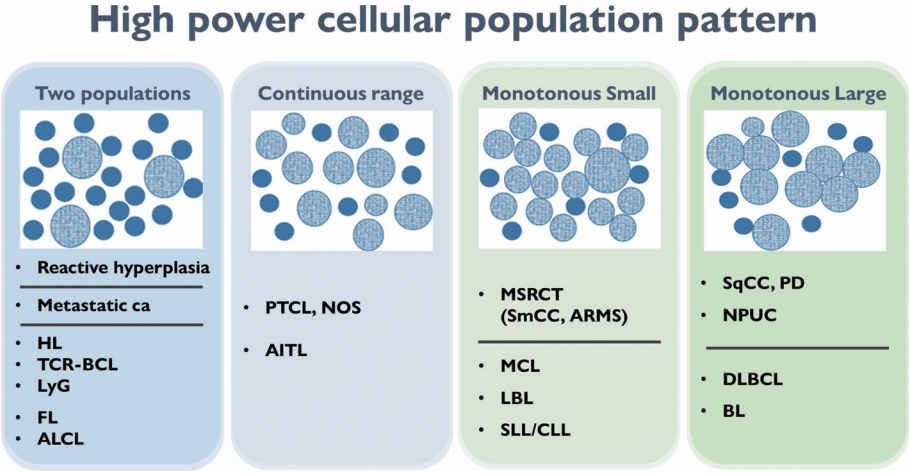

Fig. 4. High-power magnification cellular population patterns of lymph node fine needle aspiration cytology interpretation. HL, Hodgkin's Lymphoma; TCR-BCL, T-cell/histiocyte-rich B-cell lymphoma; LyG, lymphomatoid granulomatosis; FL, follicular lymphoma; ALCL, anaplastic large cell lymphoma; PTCL, NOS, peripheral T-cell lymphoma, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; MSRCT, malignant solitary fibrous tumor of the pleura; SmCC, small cell carcinoma; ARMS, alveolar rhabdomyosarcoma; MCL, mantle cell lymphoma; LBL, lymphoblastic lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; SqCC, squamous cell carcinoma; PD, poorly differentiated; NPUC, non-papillary urothelial carcinoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma.

similar to reactive lymphoid hyperplasia (Fig. 5B). However, FL is more hypercellular, and the small lymphocytes are slightly larger than those in reactive lymphoid hyperplasia. Differential diagnosis can be challenging, although immunocytochemical staining for BCL2 may be helpful [12].

HL also demonstrates two-cell populations comprising large Reed-Sternberg cells in the background of small lymphocytes, plasma cells, and histiocytes (Fig. 5C) [13]. Because the low-power cytologic findings of Hodgkin lymphoma may resemble those of reactive lymphoid hyperplasia, it is important not to miss Reed-Sternberg cells in high-power examinations.

Rarely, differential diagnosis of metastatic carcinoma that demonstrates discohesive tumor cells with poor differentiation can be challenging as it can also present with two-cell populations, as in other examples (Fig. 5D). Tumor cells most often demonstrate adenoid or squamous differentiation, which can be useful for a correct diagnosis using high-magnification fields. Information on the clinical history or presentation of the primary cancer should be carefully verified when interpreting fine needle aspiration (FNA) slides.

Continuous range of cell size population pattern

A continuous range population pattern might be the most challenging pattern in lymph node FNA interpretation because it can be easily misinterpreted as reactive lymphoid hyperplasia. This pattern includes peripheral T-cell and angioimmunoblastic lymphoma, which are present in the background of diverse inflammatory cells including histiocytes, plasma cells, and eosinophils.

PTCL demonstrated a marked variation in cell composition, including small, intermediate, and large cells (Fig. 6A) [14]. The biggest obstacle for proper diagnosis of PTCL is its lack of specific diagnostic features and immunocytochemical markers [15-17]. Likewise, there were no cytomorphological features specific to angioimmunoblastic T-cell lymphoma that displayed polymorphous cytomorphology (Fig. 6B). Sometimes, large cells resemble Reed-Sternberg cells and can be Epstein-Barr virus–positive, which leads to a misdiagnosis of HL.

Monotonous small cell population pattern

The third pattern involves a population of monotonously small cells and includes malignant small round cell tumors such as metastatic small cell carcinoma, alveolar rhabdomyosarcoma, and mature B-cell lymphomas (including mantle cell, lymphoblastic, and small lymphocytic lymphoma or chronic lymphocytic leukemia).

Small lymphocytic lymphoma or chronic lymphocytic leukemia demonstrated monomorphous small lymphocytes with scanty cytoplasm, smooth or minimally irregular nuclei with

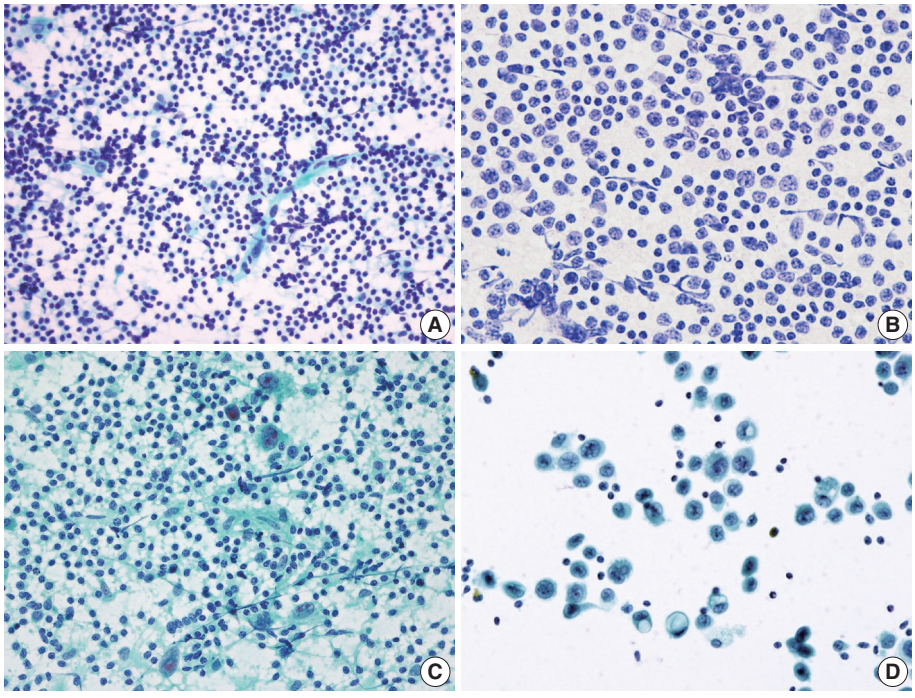

Fig. 5. Exemplary images of the two-cell population pattern. (A) Reactive hyperplasia. (B) Follicular lymphoma. (C) Hodgkin's lymphoma. (D) Metastatic adenocarcinoma.

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clumped (soccer ball-like) chromatin, and inconspicuous or absent nucleoli (Fig. 7A) [18]. Occasionally, large lymphocytes such as prolymphocytes and paraimmunoblasts are observed. MCL demonstrated monomorphous small-to-intermediate-sized cells with scanty cytoplasm and irregular nuclei with fine chromatin and inconspicuous or absent nucleoli (Fig. 7B). Centroblasts or immunoblasts are absent. There may be a few histiocytes with moderately abundant eosinophilic cytoplasm, or so-called "pink histiocytes." Lymphoblastic lymphoma demonstrates monomorphous intermediate-sized cells with scant or moderate cytoplasm and round or convoluted nuclei with finely granular chromatin and inconspicuous nucleoli [19]. The cells look small at low power due to their blastic nature. However, they are 1.5 to 2 times larger than the small lymphocyte at high power. Occasionally, cytoplasmic vacuoles and mitoses are observed (Fig. 7C).

The most common diagnostic pitfalls in this category are malignant small round cell tumors, such as metastatic small cell carcinoma and rarely alveolar rhabdomyosarcoma. Small cell lung carcinoma commonly metastasizes to the cervical lymph nodes and demonstrates diverse cellular clusters and dispersed cells with abundant necrosis (Fig. 7D). Several important differential findings include variable-sized tumor cells with characteristic salt-and pepper-like chromatin including frequent smudging and molding. The differential interpretation of cell aggregation and

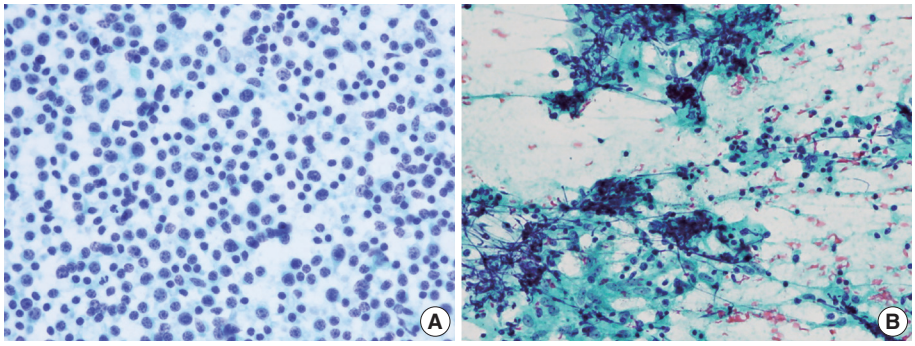

Fig. 6. Exemplary images of continuous range of variably sized cells pattern. (A) Peripheral T-cell lymphoma, not otherwise specified. (B) Angioimmunoblastic T-cell lymphoma.

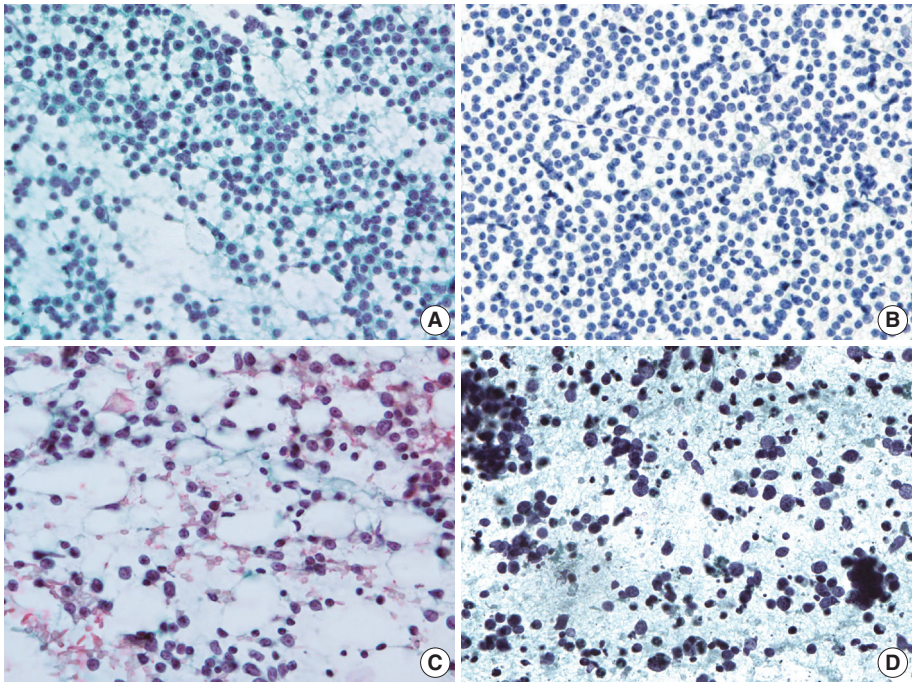

Fig. 7. Exemplary images of monotonously small population pattern. (A) Small lymphocytic lymphoma/chronic lymphocytic leukemia. (B) Mantle cell lymphoma. (C) Lymphoblastic lymphoma. (D) Metastatic small round cell tumor (small cell carcinoma).

clusters is important. Rarely, alveolar rhabdomyosarcoma can simulate the cytological features of malignant lymphomas. Therefore, the clinical presentation and history are important to avoid misdiagnosis.

Monotonous large cell population pattern

The last pattern is a monotonously large cell population pattern. This pattern can be seen in high-grade lymphomas, such as diffuse large B-cell and Burkitt lymphoma, and other metastatic carcinomas, such as poorly differentiated squamous cell and nasopharyngeal undifferentiated carcinoma. The smear of diffuse large B-cell lymphoma demonstrated a moderately to highly cellular smear of predominantly large, atypical cells that were 2.5–5 times larger than small lymphocytes or histiocytes (Fig. 8A) [20]. The tumor cell has a round or irregular nucleus with a single prominent nucleolus and scant or abundant cytoplasm. However, these cells sometimes have multiple abnormal pleomorphic nuclei that resemble those of Reed-Sternberg cells. As reactive T-cells and histiocytes are few, they usually demonstrate a monotonously large cell population. Tingible-body macrophages are variable in number, lymphoglandular bodies are common, while dendritic lymphocytic aggregates are rarely seen.

Burkitt lymphoma is another example of this pattern when the lesion involves extranodal sites. The tumor cells were typically uniform with intermediate-sized round nuclei, coarse chromatin, two–five small nucleoli per nucleus, and scant blue cytoplasm with small intracytoplasmic vacuoles (Fig. 8B). Several characteristic features of Burkitt lymphoma include apoptosis and brisk mitoses, along with frequent tingible-body macrophages.

In this pattern, the major challenging differential diagnoses were poorly differentiated metastatic squamous cell and undifferentiated nasopharyngeal carcinomas that predominantly demonstrated singly dispersed tumor cells (Fig. 8C, D). It is important to identify tumor cells in clusters, which are uncommon in lymphoma.

DISEASE-SPECIFIC DIAGNOSTIC CLUES

In addition to the low- and high-magnification power patterns, several characteristic findings are specific or pathognomonic for certain diseases (Fig. 2). One famous example is the occasional presence of Reed-Sternberg cells in Hodgkin lymphoma, which are large, atypical cells with multiple prominent nuclei and nucleoli intermixed with diverse inflammatory cells (Fig. 9A). Another example is the Russell body or Mott cells that can be found in mature B-cell lymphomas, including lymphoplasmacytic or extranodal marginal zone lymphoma (Fig. 9B) [21]. These findings are critical for proper diagnostic use of FNA samples. There-

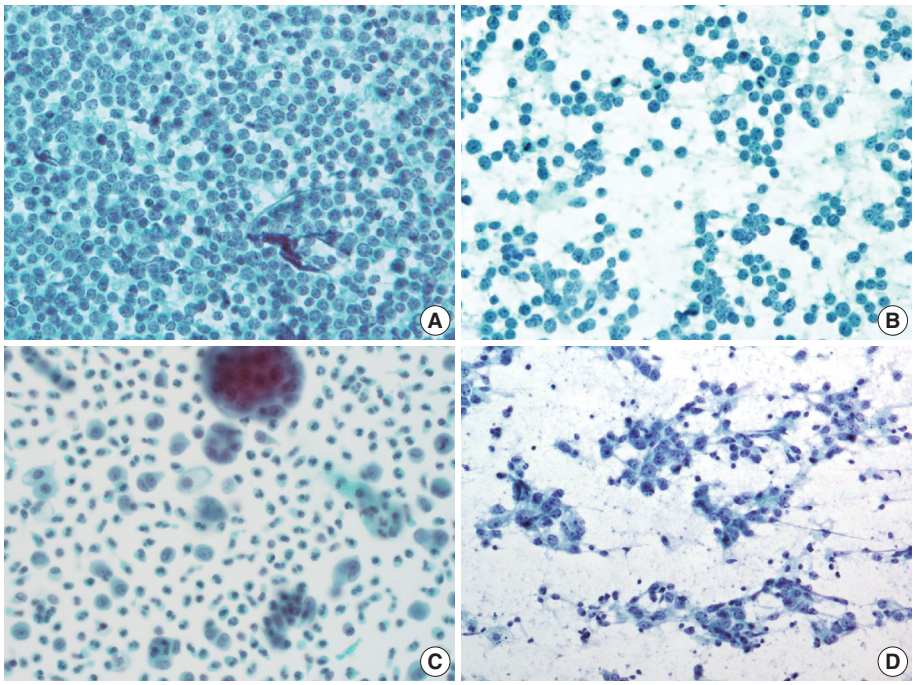

Fig. 8. Exemplary images of monotonously large population pattern. (A) Diffuse large B-cell lymphoma. (B) Burkitt lymphoma. (C) Squamous cell carcinoma, poorly differentiated. (D) Undifferentiated carcinoma, nasopharynx.

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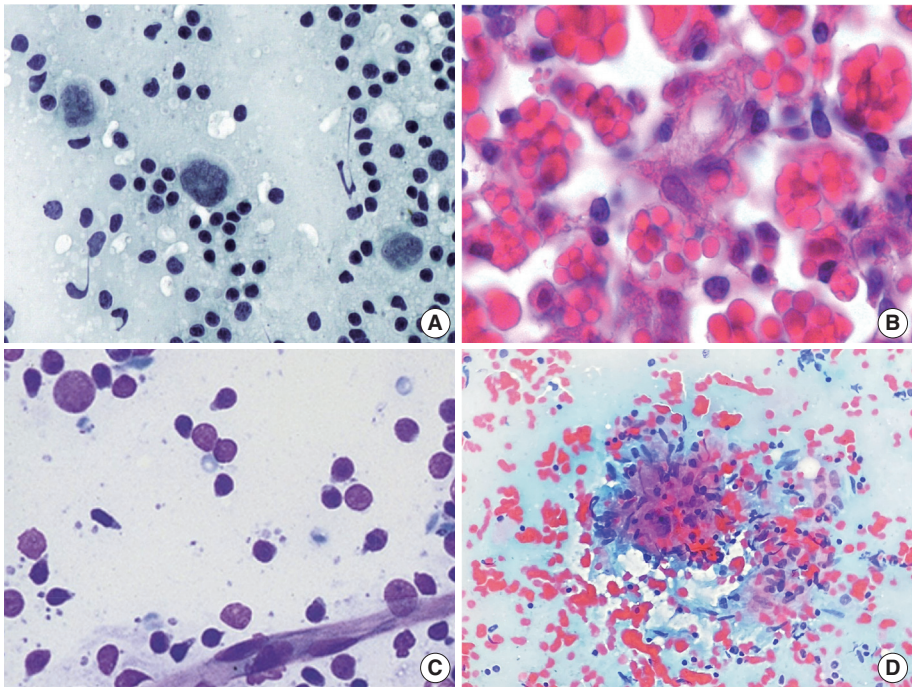

Fig. 9. Disease-specific diagnostic clues. (A) Reed-Sternberg cells in Hodgkin's lymphoma. (B) Russell body (Mott cells) in mature B-cell lymphoma such as lymphoplasmacytic lymphoma. (C) Lymphoglandular bodies in reactive hyperplasia. (D) Ill-defined granuloma in tuberculosis.

fore, it is important to be familiar with these disease-specific diagnostic clues. Lymphograndular bodies, also called hyaline bodies or lymphoid globules, are round, pale, basophilic fragments of cytoplasm with smooth borders in lymphoid tissues. Francis et al. [22] reported that lymphograndular bodies were found in >90% of non-Hodgkin lymphomas, 86% of reactive lymphadenitis, and 66% of Hodgkin lymphomas (Fig. 9C). Granulomas with caseous necrosis are suspicious for tuberculosis, while those that are small tight granuloma clusters without necrosis are suspicious for sarcoidosis (Fig. 9D). Granulomas can also be found in toxoplasmosis, cat-scratch disease, and HL. Other diagnostic clues include dendritic lymphocyte complexes in reactive hyperplasia, tingible-body macrophages in highly proliferative lymphomas such as Burkitt lymphoma, C-shaped macrophages in KFD, emperiopolesis in Rosai-Dorfman disease, and melanin-containing macrophages in dermatopathic lymphadenopathy. Additionally, Dutcher bodies are intranuclear inclusions of cytoplasm (pseudoinclusions) found in plasma cells and were originally described in Waldenstrom macroglobulinemia and IgA multiple myeloma. Arborizing vessels (high endothelial venules) can be found in the lymph node FNA of follicular dendritic cell-derived tumors, such as Castleman disease. A necrotic background is a common finding in several high-grade malignant lymphomas and metastatic carcinomas including diffuse large B-cell lymphomas or metastatic squamous cell carcinomas and in benign lymphadenopathies such as tuberculosis and necrotizing histiocytic lymphadenitis (KFD) [23].

SYDNEY CLASSIFICATION

In 2019, a steering committee of international cytopathologists involved in lymph node FNAC developed a system for reporting lymph node FNAC in the International Cytology Congress in Sydney. They ultimately published The Sydney system after five rounds of circulation among committee members based on a review of the international literature and the expertise of the members (Table 1).

This system defined the following five diagnostic reporting categories according to the cytological findings: inadequate/non-diagnostic (L1), benign (L2), atypical, undermined significance/atypical lymphoid uncertain significance (AUS/ALUS) (L3), suspicious (L4), and malignant (L5) [2]. The inadequate/non-diagnostic category includes cases that cannot be diagnosed properly owing to scant cellularity, extensive necrosis, or technical limitations that cannot be overcome. Repeat FNAC, core needle, or excision biopsy was recommended in these cases. The benign category includes cases of suppurative and granulomatous inflammation and specific infections that demonstrate a heteroge-

Table 1. The Sydney classification system

Diagnostic reporting categories	Explanation	Post–LN-FNAC management recommendations	Exemplary findings
Inadequate/non-diagnostic (L1)	Low cellularity	LN-FNAC repetition and/or CNB or excision	-
Benign (L2)	Reactive hyperplasia Benign lymphadenitis	Clinical F/U or specific Tx depending on the Dx	-
AUS/ALUS (L3)	Possibly benign, not fully supported by cytology and ancillary technique	LN-FNAC repetition with acquisition of material for ancillary studies and/or CNB or excision	Two-cell population that cannot exclude follicular lymphoma Monotonously small cell population that cannot exclude low-grade B-cell lymphomas such as marginal zone B-cell lymphoma, small cell lymphoma/chronic lymphocytic leukemia, mantle cell lymphoma, and lymphoblastic lymphoma
Suspicious (L4)	Possibly malignant, not fully supported by cytology and ancillary technique	LN-FNAC repetition with acquisition of material for appropriate ancillary studies and/or CNB or excision	Monotonously small and/or medium-sized, monomorphic atypical lymphoid cells suspicious of lymphoma, but cytomorphology alone is not sufficient for diagnosis, polymorphous lymphoid smears in which few Reed-Sternberg-like cells are detected, large cell or Burkitt lymphomas with scantly cellular, and smears in which atypical cells suspicious for metastasis are detected but are too scant to be diagnostic
Malignant (L5)	(NHL, HL, metastases)	Histological biopsy requested (not requested for HL/NHL relapses or metastasis from known or clearly indicated primary tumor, etc.)	Small-to-medium-sized cells of non-Hodgkin lymphomas supported by evidence of clonality and all the entities in which cytopathological features alone are sufficient to identify malignancy as large cell non-Hodgkin's lymphoma. This category also includes Hodgkin's lymphoma in which there is an appropriate cellular background and diagnostic Reed-Sternberg cells as well as metastatic neoplasms

LN-FNAC, lymph node fine needle aspiration cytology; CNB, core needle biopsy; F/U, follow-up; Tx, therapy; Dx, diagnosis; NHL, non-Hodgkin lymphoma.

neous lymphoid population (two-cell population). The AUS/ALUS category includes cases with two-cell populations in which the features suggest a reactive process; however, FL cannot be excluded; or the atypical cells are not lymphoid cells (AUS); or there is a monotonously small cell population for which low-grade B-cell lymphomas cannot be excluded. The suspicious category includes cases with small and/or medium-sized monomorphic atypical lymphoid cells that are suspicious of lymphoma, but cytomorphology alone is insufficient to make the diagnosis. The suspicious category includes polymorphous lymphoid smears containing a few Reed-Sternberg-like cells, large cell or Burkitt lymphomas with scantly cellular cells, or atypical cells that are suspicious for metastasis are detected but are too scant to be diagnosed. The malignant category includes small- to medium-sized cells of non-HLs supported by evidence of clonality and all cases in which cytopathological features alone are sufficient to identify large cell non-HLs. This category also includes HL in cases in which there is an appropriate cellular background, diagnostic Reed-Sternberg cells, and metastatic neoplasms.

The authors of the Sydney system proposed that this standardized system may improve the quality of the procedure, the handling of material for diagnostic ancillary testing, the understanding of the report, and the communication between the cytopathologist and the clinician. Recently, an Indian research group evaluated the malignancy risk in 6,983 lymph node FNACs by retrospectively reviewing cases with the Sydney system [24]. The diagnoses using the Sydney system were discordant in 10.7% of histologic diagnoses. The overall diagnostic accuracy of this system was 89.3%. The malignancy risk was 11.5% and 99.6% for the benign and malignant categories, respectively. Inter- and intraobserver variabilities were noted for categories 3 and 4, respectively. The authors reported a relatively high malignancy risk of 27.5% in the inadequate/non-diagnostic categories. For these cases, they recommended a repeat FNAC according to the Sydney system recommendations. Collectively, the authors concluded that application of the Sydney system can help achieve uniformity, reproducibility, and risk stratification in lymph node FNAC. However, multicenter studies with larger samples are needed to validate the utility of the Sydney system.

SUGGESTED DIAGNOSTIC ALGORITHM FOR LYMPH NODE FINE NEEDLE ASPIRATION CYTOLOGY

Herein, we suggest a diagnostic algorithm for lymph node FNAC that encompasses a stepwise approach and the Sydney

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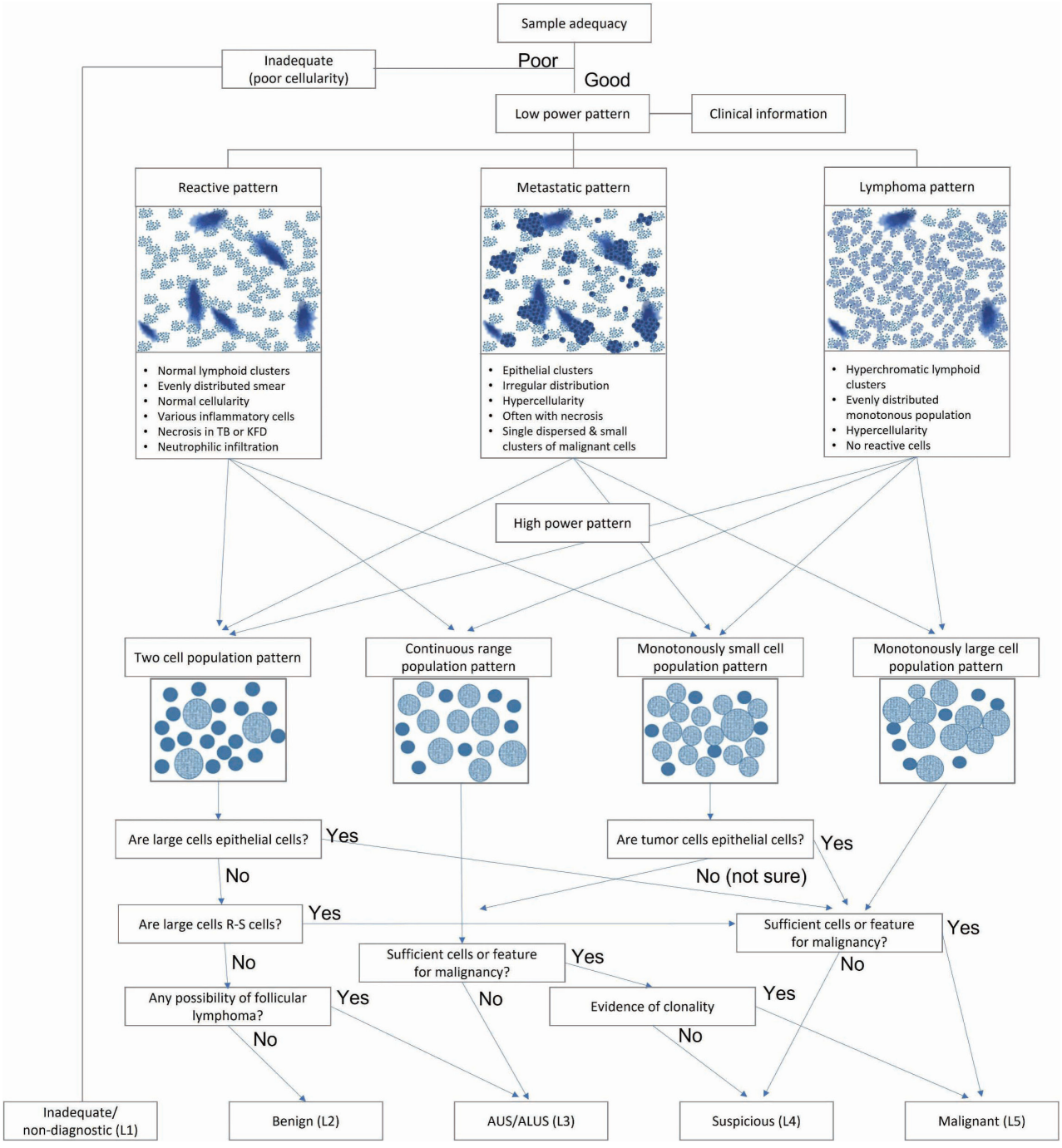

Fig. 10. Diagnostic algorithm for lymph node fine needle aspiration cytology.

classification system (Fig. 10). Sample adequacy should be evaluated; if there is insufficient cellularity for proper evaluation or the smearing condition is poor due to dry artifacts, then the sample can be categorized as inadequate/non-diagnostic (L1). Once the clinical information is reviewed, the low-power pattern can be evaluated under a microscope. Reactive patterns can present as two-cell populations, a continuous range, or a monotonously small cell population. Metastatic patterns can present as two-cell populations of monotonously small or large cell populations. Lymphoma can present with all kinds of patterns at high-power magnification. A large cell population in the two-cell population pattern should be thoroughly reviewed if it has epithelial features to

exclude the possibility of a metastatic lesion. If there is no chance of metastasis, FL remains a possibility. FL should be considered in cases of multiple enlarged lymph nodes in elderly patients with hypercellular smears and several small lymphocytes that are slightly larger than usual. Immunocytochemical staining for BCL2 can be helpful for diagnosis in such cases. When FL cannot be excluded and immunocytochemical staining is unavailable, an ALUS diagnosis can be made.

If there are large cells are clearly epithelial, and cytologic atypia is evident, the case can be diagnosed as malignant or suspicious according to the level of evidence. This is true regardless of the high-power pattern of a two-cell, monotonously small, or large cell population. A monotonously large cell population is mostly found in high-grade B-cell lymphomas, such as diffuse large B-cell or Burkitt lymphoma; however, such cases can also be diagnosed as malignant or suspicious according to the level of evidence. Monotonously small cell population patterns can be quite challenging because certain features can be difficult to distinguish between lymphomas and small cell carcinoma (such as mild cytologic atypia in lymphoma). If there are enough cytological features for small cell carcinoma, a case can be diagnosed as malignant or suspicious according to the level of evidence. If there is no definite evidence that the tumor cells are epithelial, lymphomas or other rare mesenchymal malignant tumors should be excluded. In such cases, cytological findings and additional IHC or molecular studies might be required. These cases can be diagnosed as AUS/ALUS, suspicious, or malignant according to the level of evidence. The continuous range population pattern is predominantly from possible T-cell lymphomas. Clonality tests, such as TCR gene rearrangement, are required for a more conclusive diagnosis.

The Sydney system has an inevitable limitation in that the epithelial or lymphomatous nature of the lesion is not clearly separated into different categories and is not emphasized due to the ambiguity of the lymph node features on FNAC. In other words, even though a diagnosis was made on a certain case using the Sydney system, it is still unclear whether the case is lymphoid or metastatic. The L3 category, which includes AUS and ALUS, is a good example. It is often quite challenging to discriminate a certain lesion as lymphoid or epithelial in origin. The aforementioned study by the Indian group mentioned intra- and interobserver variabilities in the diagnosis of category III. However, further in-depth knowledge of lesion nature might be warranted. In cases in which the FNAC features favor certain diseases, the cases should be described specifically as "AUS, favor poorly differentiated carcinoma," "ALUS, favor atypical lymphoproliferative disease (Infectious mononucleosis, Kikuchi-Fujimoto disease, Rosai-Dorfman disease)," or "ALUS, cannot exclude low-grade lymphoma." Since the previous study reported a high malignancy rate of 66.7% in the AUS/ALUS category, it is important to deliver any evidence that supports either lymphoid or metastatic lesion. However, it is also important not to conduct unnecessary excisional biopsy.

CONCLUSION

Lymph node FNAC encompasses diverse diseases, including benign and malignant lymphoma and metastasis, whose cytologic findings often resemble each other. A stepwise diagnostic approach combining clinical findings (age, sex, site, multiplicity, ultrasonography findings), low-power pattern (reactive, metastatic, lymphoma pattern), high-power population pattern (two-cell, continuous range, monotonously small, and monotonously large population patterns), and disease-specific diagnostic clues (granulomas, etc.) can help in comprehensive FNAC diagnosis. It is important to remember representative traits of each diagnostic category, including diagnostic pitfalls that share the cytologic findings of other categories.

Supplementary Information

The Data Supplement is available with this article at https://doi.org/10.4132/jptm.2023.06.12.

Ethics Statement

This study was reviewed and approved by the Institutional Review Board of the Catholic University of Korea College of Medicine (UC21ZISI0138).

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Code Availability

Not applicable.

ORCID

Yosep Chong https://orcid.org/0000-0001-8615-3064
Gyeongsin Park https://orcid.org/0000-0002-9727-5566
Hee Jeong Cha https://orcid.org/0000-0001-8744-5747
Hyung-Jung Kim https://orcid.org/0000-0002-6617-4578
Jamshid Abdul-Ghafar https://orcid.org/0000-0002-6575-8870

Author Contributions

Conceptualization: YC, SSL, CSK. Data curation: YC, JAG, CSK, SSL, HJC, HJK, GP. Funding acquisition: YC. Investigation: YC, SSL. Methodology: YC. Project administration: YC. Resources: YC, CSK, SSL, HJC, HJK, GP. Supervision: SSL, GP, CSK. Validation: YC, JAG. Visualization: YC, JAG. Writing—original draft: YC, JAG. Writing—review & editing: YC, SSL, HJC, HJK, CSK, GP. Approval of final manuscript: all authors.

Conflicts of Interest

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