CHAPTER 5

DISCUSSION

5.1. Discussion on clinical aspect

Lymph node is the most common organs for extra-pulmonary tuberculosis[1]. The involved nodes are mostly located in the neck[2]. Pathogenesis of how the acid-fast bacilli reaching the nodes is not established but some evidences favor for the primary infection in the oral cavity and tonsils[12]. Thirty percent of the patients are shown to have concomitant pulmonary tuberculosis[2]. Hence the hematogenous or lymphatic routes from pulmonary site is also possible, particularly drainage from the mediastinal nodes to the supraclavicular region[12]. In this study, right supraclavicular node tuberculosis is common as well as posterior triangle nodes on the left side of neck. The former is less likely for a reactive hyperplasia lymph node. The common sites for reactive node are in bilateral posterior triangle of neck. A few cases of lymph node tuberculosis had concomitant pulmonary tuberculosis.

Most patients manifested palpable neck lumps as their chief complaint. The average size of infected nodes is 2.41 cm comparing with 1.54 cm of the non-tuberculous lymphadenopathy. The patients in this study in overall come with small tuberculous nodes and mostly solid node. It is quite different from the author's experience in the previous studies[4, 13]. This may explain for the very low detection rate of AFB. In prior experience, many fluctuated large nodes were encountered. Acid-fast bacilli were detected in nearly a half of TB node patients. More cases were HIV positive than this time.

5.2. Discussion on methodology

This is a prospective and descriptive study regarding a diagnostic test. Its aim of design is to be able to implement in an economical way to improve clinical management. On this basis, the author chose tuberculin test that is kind of simple test to be over-looked by people. As mentioned above, the benefit of TT as a

complementary test could be scrutinized into three objectives and needed to analyze in this study. The first and most important aim is to prevent cytologic pitfalls of making wrong diagnosis. Since FNA cytology is at present widely excepted in clinical practice, most patients receive definitive treatment based solely on it's reporting. The second point is to enhance the sensitivity of FNA cytology in diagnosis of lymph node tuberculosis. Chemotherapy is nowadays very effective for treating tuberculosis[12]. To start early is better than late treatment. When the therapy is responsive, the diseased node can be dissolved. There is not any evidence that excision of diseased nodes will benefit any result[12]. On contrary, it causes unnecessary scar and numbness. Therefore, to able to enhance sensitivity will save more cases from surgical excision. The third aim is to show that how it can be really cost-effective. Sometimes, we have to adjust for whom, when and which situation to have the test to achieve the efficiency.

The suitable aim to be put into primary research question was the sensitivity enhancement based on the only one relevant study on review of the English-written literature. The question was followed by the question on economics of the same importance that needed analysis. The aim on cytologic pitfalls was by-product, though it was the very important subject for the cytopathologist like the author.

The separation of conclusive case of positive AFB in the smear is rationale. The use of histology as the solely method for gold standard is practical. Caseating granulomatous inflammation is hallmark for the diagnosis of tuberculosis, particularly in this region of the world. Culture is not routinely performed and therefore ignored from the design. Furthermore, it cannot be regarded as practical gold standard because it does not yield positive results in every case. Although in retrospective study, simple culture method could be achieved in those aspirates with liquefied cheese-like content[13].

Sample size calculation was based on the study in Hong Kong which focus on sensitivity enhancement. In the current study, the number of TB cases in the studied population was less than that expected (TB cases in the studied group had 28 cases comparing with the expected number of 34), though the number of all patients (71 cases) and the prevalence of the disease (50%) were keeping with the expectation (69

cases and 50% respectively). This was because the definitions of inclusion criteria were not exactly the same. In this study, the three AFB detection cases were not included. In the previous study, the investigators had more selective criterion to invite the cases that they thought clinically tuberculosis lymph node. Therefore, they had only 5 malignant nodes in contrast with 10 of this study. In fact, it is difficult to exclude known treated malignant patients coming with neck node that it is not likely TB node. Since treated cancer patients could have any superimposed infection of the nodes. Nevertheless, the sensitivity outcomes of FNA cytology and combined test were keeping in line of sample size estimation.

One weak point of this study was the lack of reliability tests. The measurement of TT was based on single measurement by one staff member of the Chest-Unit for each case. Nevertheless, the discrepancy of TT positive and negative cases was explicit because the values nearby the cut-off, namely $\geq$15 and $\geq$25 mm were few. The cytologic features, should have a second opinion from expert. Though the pictures are clearly illustrated, the pertinent findings in each case could be captured and sent to be confirmed of the features from another expert cytopathologist.

5.3. Discussion on results

The performance of FNA cytology in this study in diagnosis of granulomatous lymphadenitis is in concordance with other[5]. The sensitivity is 71.4%, specificity is 92.8% and accuracy is 82.1%. To treat the patients based on the result of cytology, specificity and positive predictive value of the test are very concerned. Tuberculin test was proved that it could save the two false-positive cases. These were cases no.29 and no.30. Both of them had TT of 11 mm and 8 mm respectively. TT of the true TB node cases varied from 15 to 70 mm. Therefore, if a case to diagnose as granulomatous feature for tuberculosis, it should have TT $\geq$15 mm which is the cut-off value to interpret test as positive for general population in the national guideline[15].

The pitfalls of the two cases are a mimic of epithelioid cells in one case and a mimic of caseous necrosis fragment in the other. These pitfalls can be aware after having experience. On comparing with the true features, the mimic of epithelioid cell

lacks appreciable spindle and elongate cells. Just the nuclei look plump and pale. On observation, there are two presentations of epitheliod cells. In small node, few and tiny fragments of epithelioid cells are detected. The cells are likely in a tightly aggregates, not like this case. In node with large caseating grauloma area, the epithelioid cell aggregates often occur together with some necrosis, sometimes typical caseous. The other mimicking feature is the false interpretation of fibrous fragments as caseous fragments. On scrutiny, the matrix of the fibrous is relatively homogeneous dense and the background looks clean. This is in contrast with real caseous necrosis. The fragments will contain distorted and necrotizing elements.

Other pitfalls are mentioned in the cytology textbook and literature. The failure to distinguish epithelioid cells from malignant cells leading to false positive diagnosis as tumor and vise versa. It is not seen in this study. However, to have complementary TT for every difficult case is helpful to re-check.

To employ TT in diagnosis of recent tuberculous infection fraught with some complexity[12]. From this study, the large induration size of tuberculin test (strong reaction) corresponds well with FNA cytology suggesting TB cases. It achieved the sensitivity of 75%, specificity of 89.3%, and positive predictive value (PPV) of 87.5%. The result is different from the study in Hong Kong. With cut-off value of above 24 mm, patients in Hong Kong were proven recent TB cases, and that the PPV achieved 100%. In the present study, if we would like to have this 100% PPV, the cut-off value has to raise up to above 34 mm, ten millimeters more than in Hong Kong.

Combined test can give the higher sensitivity but the lower specificity when compare with cytology alone. There were three cases of reactive node hyperplasia with strong TT reaction, above 30 mm. This was contrary to the finding in Hong Kong. To shift the value of cut-off to be above 34 mm, might be helpful but it is difficult to implement.

The economic evaluation is based on the charges and estimated costs at King Chulalongkorn Hospital setting in the period of the study. This is a patient's perspective evaluation.

On practical viewpoint, detailed cytologic features play role on the certainty of diagnosis of tuberculosis. In this study, the three components that suggest tuberculosis have different frequency and limitations. For analysis purpose, the cytologic features are classified into six categories. The frequency in each category appears in Table 3. There were 5 cases which showed epithelioid cell aggregates. Two of which had the granuloma feature. Two cases showed only one or two epithelioid aggregates which could be easily overlooked. Such cases, it could be doubt and TT confirmation is really needed. Caseous necrosis is reliable feature when it is obvious. The true caseous should comprise necrotic cell debris. Only patchy material have to make differential diagnosis with fibrous fragments and is the cause of false interpretation. Beware of such pitfall will lead to an unequivocal diagnosis of TB.

The epithelioid cell aggregates are subset of granuloma. Its presence in the smear in couple with caseous necrosis fragments is corresponding to the hallmark of tuberculosis in histology. This finding should be the most definite, however, one out of the six cases with the epitheioid cells is wrongly interpreted. This case has few minute clusters of cells that mimic the epithelioid cells. On review with histology, the foci can be prominent endothelial cells. Tuberculin test in this case is 11 mm which is interpreted as negative in the study. So, such a minute foci of epithelioid cell without caseous, TT test may give clue to correct diagnosis.

Necrotizing feature is usually associated in the caseous necrosis category. The feature is called necrotizing nonspecific pattern when the caseous amorphous and patchy microfragments are not apparent. Like caseous necrosis, necrotizing non-suppurative inflammation can also manifest cheesy liquefied content. The source of false positive in this study is due to mis-interpretation of organizing inflammation or abscess and turbid content cyst as tuberculous lymphadenitis with liquefactive necrosis. On scrutiny of the smears, cystic histiocytes are clue to the inflammatory cyst.

Lymphoid cells are components of lymph node. The aspirates showing lymphoid cells are therefore not specified for any diseases. TB nodes that reveal focal lesion can often get only some lymphoid cells. Tuberculin test may alarm us not overlook

tuberculosis. One case of malignant lymphoma was cytologically benign and the smear manifestation was lymphoid cells. In some papers, such finding is considered inadequate or non-diagnostic. So-called reactive lymph node feature is characterized by moderate to high cellularity of lymphoid cells in the smears with polymorphous lymphoid cells and predominant small lymphocytes. The presence of substantial number of tingible-body macrophages will be separate into the category of reactive feature with macrophages. The benefit is that the latter is highly consistent with benignity of lymph node condition. Five such cases are reactive hyperplasia compared with one out of the 17 reactive node feature turned out to be tuberculosis in the biopsy specimen. The finding of reactive lymphoid feature with appreciable tingible body macrophages is proposed to be a criterion that no biopsy confirmation is needed. TT is not useful and may cause confusion.

The proposed model has developed from the above principle. Cytologic features that are obvious, comparable to hallmark feature in histopathology, are rational to treat the patients with anti-tuberculosis drugs and follow-up the therapeutic response. These features include unequivocal epithelioid cell aggregates with granuloma formation and florid caseating necrotizing inflammatory pattern. Cytologic features that will benefit from TT are consisted of limited epithelioid cell aggregates and necrotizing nonspecific inflammation. The latter is particularly concerned when aspirates are cheesy liquefied material. Negative TT and scrutiny of the cytologic details can prevent misinterpretation. Cytologic features that not suggest tuberculosis are reasonable to have biopsy with or without TT. It is remarkable that one case with benign cytology (or inadequate cytology) is malignant lymphoma. Correlation of the cytologic feature with clinical feature is therefore pertinent. The FNAC features described as lymphoid cells, reactive lymphoid feature and reactive feature with appreciable macrophages have the merit of increasing levels of certainty towards benignity as well as excluding tuberculosis.