CHAPTER 4

RESULT

1. Data collection

During the period of study (April 2001- January 2002), there were 71 patients presented with palpable neck nodes and received FNA biopsy. The demographic characteristics and investigation findings appear in Table 1. Columns 1-4 are data of running number, accession number of the FNAC, sex and age of the patients respectively. Columns 5-8 reveal number, location, size, and duration of the palpable nodes respectively. Column 9 shows the main findings of FNA cytology. AFB detection is informed in column 10 and TT result in column 11. The last column exhibits the final diagnoses that are based on histopathology. The cases are displayed in order of final diagnoses, and cytologic main features accordingly. For each FNA finding, TT values are placed in order from high to low. Thirty-one cases were proven lymph node tuberculosis including one atypical tuberculosis. Of which, 28 cases were classified in the studied group and three others were not. Totally fifteen cases reached conclusive diagnosis by FNA cytology and did not perform tuberculin test. They were comprised of 10 cases of malignant nodes and 5 cases of benign conditions. Most malignant nodes were nodal metastasis. Only one node was lymphoma. The benign lesions were composed of three mycobacterial infections, one histoplasmosis and one cyst. The latter was not lymph node but could not be discriminated clinically. The remaining (56 cases) were the studied population that are further described below.

Table 1: Patients' characteristics and findings

No.	FNA no.	Sex,Age		Node(s),location		Size	Duration	FNA- finding	AFB	TT	Final Dx
1	cp44-1807	M	32	m, b	R, uj	1.5	3 mo	Epithelioid	-	40	TB node
2	cp44-1834	F	23	s	R, sc	2.5	2 wk	Epithelioid	-	40	TB node
3	fna13638	F	58	m	R, a	1.5	3 mo	Epithelioid	-	28	TB node
4	cp44-1633	M	28	m, b	R,p	2	3 mo	Epithelioid	-	18	TB node
5	fna13805	F	43	m, b	R, p	3	1 yr	Caseating	-	42	TB node
6	cp44-968	F	30	m	L, p	1.5	2 yr	Caseating	-	42	TB node
7	cp44-1144	F	23	m, b	L, sc	2	3 wk	Caseating	-	40	TB node

No.	FNA no.	Sex, Age		Node(s), location		Size	Duration	FNA- finding	AFB	TT	Final Dx
8	fna13761	F	30	s	L	1	1 mo	Caseating	-	40	TB node
9	fna13659	F	38	s, matt	L, p	3	1 mo	Caseating	-	38	TB node
10	fna13771	M*	22	m, b	L, p	4	4 mo	Caseating	-	38	TB node
11	fna13658	F	33	s	R, p	4	1 mo	Caseating	-	37	TB node
12	fna13605	F	57	m	L, p	2	1 mo	Caseating	-	35	TB node
13	fna13657	F	40	m	R, sc	2	1 mo	Caseating	-	30	TB node
14	cp44-1222	F	40	s	L, sc	1.5	1 mo	Caseating	-	30	TB node
15	cp44-1512	F	39	s	R, uj	2.5	1 mo	Caseating	-	30	TB node
16	fna13723	M	24	m	L,p	4	1 mo	Caseating	-	28	TB node
17	fna13495	F	58	s	R,sc	2	1 mo	Caseating	-	28	TB node
18	cp44-26	F	48	s, matt	R, sc	6	1 mo	Caseating	-	20	TB node
19	cp44-1634	F	30	m	R, sc	1	2 wk	Caseating	-	20	TB node
20	c44-1308	F	27	m	L, sc	4	2 mo	Caseating	-	15	TB node
21	fna13749	M*	32	m	L, p	1.5	8 mo	Necrotizing	-	35	TB node
22	fna13645	F	35	s	R,sc	4	2 mo	Necrotizing	-	25	TB node
23	cp44-1232	M	32	s	L, p	2	1 mo	Necrotizing	-	20	TB node
24	cp44-1779	F	29	m	R, p	1.5	3 mo	lymphoid cells	-	70	TB node
25	fna13655	F	37	m, b	R,p	1.5	4 mo	lymphoid cells	-	35	TB node
26	fna13835	M	27	m	R,p	1.5	1 mo	lymphoid cells	-	35	TB node
27	cp44-1795	M*	27	m	L, p	3	1 mo	lymphoid cells	-	19	TB node
28	cp44-1862	F*	63	s	R, sc	1.5	1 mo	Reactive	-	0	TB node
29	cp44-1477	F	29	s	L, p	1.5	1 mo	Epithelioid	-	11	Reactive
30	cp44-1671	F	32	m	L, p	1	2 mo	Caseating	-	8	Reactive
31	fna13862	M	75	s	R, p	5	1 mo	Necrotizing	-	0	Inflam.
32	cp44-2576	F	41	s	R, uj	2.5	1 mo	Necrotizing	-	0	Inflam.
33	cp44-1196	F	25	s	L, p	1	2 mo	lymphoid cells	-	15	Reactive
34	cp44-2507	F	42	m	o	1.5	3 mo	lymphoid cells	-	0	Reactive
35	fna13439	M	40	m, b	R, p	1.5	1 yr	lymphoid cells	-	0	Lymphoma
36	cp44-1836	F	29	s	R, p	1	5 mo	Reactive	-	32	Reactive
37	cp44-2614	F	18	s	R, p	1.5	7 y	Reactive	-	30	Reactive
38	c44-1848	F	45	m, b	R, p	1.5	2 wk	Reactive	-	18	Reactive
39	cp44-1588	M	51	s	R, uj	1	1 mo	Reactive	-	17	Reactive
40	cp44-998	F	26	s	R, p	1	1 mo	Reactive	-	8	Reactive
41	fna13660	F	28	s	R, p	2	2 wk	Reactive	-	0	Kikuchi
42	fna13626	F	60	s	R. p	1	6 mo	Reactive	-	0	Reactive
43	cp44-1342	F	21	s	o	1	1 wk	Reactive	-	0	Reactive
44	fna13649	F	17	s	L, p	1.5	2 mo	Reactive	-	0	Reactive
45	cp44-2430	M	27	s	L, p	1.5	1 mo	Reactive	-	0	Reactive
46	cp44-1716	M	37	m, b	R, p	3	3 mo	Reactive	-	0	Reactive

No.	FNA no.	Sex	Age	Node(s)	location	Size	Duration	FNA- finding	AFB	TT	Final Dx
47	cp44-1545	F	70	s	L, p	1.5	2 mo	Reactive	-	0	Reactive
48	fna13695	F	15	s	L, p	2	1 mo	Reactive	-	0	Reactive
49	fna13806	F	36	s	R, p	1	1.5 mo	Reactive	-	0	Reactive
50	cp44-2434	F	29	m	L, p	1	1 mo	Reactive	-	0	Reactive
51	cp44-2439	F	30	m	R, p	1	1 mo	Reactive	-	0	Reactive
52	fna13781	M	35	s	L, p	1	3 wk	Reactive w. mac.	-	33	Reactive
53	cp44-2429	F	45	s	L, p	1.5	1 mo	Reactive w. mac.	-	15	Reactive
54	cp44-1971	M	55	m	R, p	1	1 mo	Reactive w. mac.	-	5	Reactive
55	cp44-2549	F	45	s	R, p	1.5	6 mo	Reactive w. mac.	-	5	Reactive
56	cp44-1543	F	17	s	L, p	1.5	3 wk	Reactive w. mac.	-	0	Reactive
57	cp44-1607	M	30	s	L, p	4	1 yr	Met papillary ca	NA	NA	Met CA
58	fna13685	M	50	s	R, p	1.5	1 mo	Met sq ca lung	NA	NA	Met CA
59	cp44-1590	F	66	s	L, sc	1.5	3 mo	Met sq ca	NA	NA	Met CA
60	fna13702	M	43	m	L, p	1.5	2 mo	Met nasopha ca	NA	NA	Met CA
61	fna13684	F	30	m	p	1	2 mo	Met adenoca	NA	NA	Met CA
62	cp44-1596	M	64	s	R, p	6	2 mo	Lymphoma?	NA	NA	Met CA
63	cp44-1544	M	59	s	R, p	2	2 mo	Met nasopha ca	NA	NA	Met CA
64	fna13632	M	93	s	L, p	3	2 mo	Met sq ca	NA	NA	Met CA
65	fna13648	M	26	s	L, sc	6	3 mo	Met carcinoma	NA	NA	Met CA
66	fna13716	F	90	m	L, p	4	4 mo	Lymphoma	NA	NA	Lymphoma
67	cp44-1563	M	16	s	o	2.5	3 mo	Hematoma cyst	NA	NA	Cyst
68	fna13626	F*	32	s	R, sm	2	2 mo	Histoplasmosis	-	NA	Histoplasmosis
69	c44-1358	M*	38	s	L, p	1	1 mo	Necrotizing	+	NA	Atypical TB
70	c44-1116	M*	24	m	L, a	1.5	2 wk	Necrotizing	+	NA	TB node
71	c45-294	F	56	s	R, sc	2	1 mo	Caseating	+	NA	TB node

Note: Size of node measured in cm in greatest dimension, TT induration size measured in mm. Abbreviations are as followings: F= female, M= male, * = HIV sero-positive, s= single, m= multiple, b= bilateral, matt= matted nodes, R= right, L= left, uj= upper jugular, sc= supraclavicular, a= anterior triangle, p= posterior triangle, o= sub-occipital, sm= sub-mandibular, mac.= tingible-body macrophage, Met= metastatic, sq ca= squamous cell carcinoma, nasopha ca= nasopharyngeal carcinoma, adenoca= adenocarcinoma, NA= not applicable.

2. Patients and demographic characteristics

From Table 1, the studied population revealed male : female = 15 : 41 or approximately 1 : 2.7. The tuberculosis group had male : female = 8 : 20 which was approximately 1: 2.5. The non-tuberculosis node patients showed 1: 3 ratio of male : female. Both TB node and non-TB node groups had about 36 average years of age. All HIV sero-positive patients that are marked by an asterisk above the sex determination (4/56 =7.1% of the studied population) had tuberculous lymphadenitis. Three other HIV sero-positive patients that were classified in the conclusive group because acid fast bacilli were identified in the smears were encountered. Therefore, tuberculosis associated with HIV occurred in 7 out of 31 proven tuberculosis cases, accounting for 22.6%. Two of the 7 cases with HIV (28.5%) could be diagnosed as lymph node tuberculosis by acid-fast stain.

Comparison of TB and non-TB patients is illustrated in Table 2. Tuberculous lymphadenitis in the studied population manifested more with multiple nodes than single node (1.5:1). A few cases with single node were in fact matted nodes. Either on unilateral or bilateral neck was found for the multiple nodes group. Bilateral neck nodes had twice more than unilateral multiple nodes. On contrary, the patients with non-tuberculosis nodes presented predominantly with single node than multiple nodes in the neck (2.5:1). Almost all cases were reactive hyperplasia except for one case of lymphoma, another as Kikuchi's lymphadenitis and two others as inflammatory process. Lymph node tuberculosis could be found in all regions of neck, however, left posterior triangle neck and right supraclavicular area were common sites. The latter did not harbor any reactive nodes. Both right and left posterior triangles of neck were common sites for reactive nodes. Suboccipital area was the place for only reactive node in this study.

The average size of tuberculosis lymph nodes was larger than that of the non-tuberculosis group i.e. 2.41 cm comparing with 1.54 cm. The ranges of node sizes were 1-6 cm and 1-5 cm respectively.

All patients were good co-operated and could be followed-up. No severe complications from FNA biopsy procedure, tuberculin reaction, surgical biopsy or drug toxicity were found. All TB node cases except one case responded well to treatment.

The single case (case no.24) developed hypersensitivity 4 months later and had been controllable with steroid addition regimen. She is still on-going treatment with anti-tuberculosis agents.

Table 2: Comparison of demographic characteristics of TB and non-TB cases of the studied population

	TB node patients	Non-TB node patients
Male : Female	8 : 20 (1:2.5)	7 : 21 (1:3)
Average age	35.9	36.4
HIV positive	4	0
Numbers, multiple : single	17 : 11 (1.5:1)	8 : 20 (1:2.5)
Common locations (numbers of cases)	Right supra-clavicle (9); Left posterior triangle (9)	Right posterior triangle (13); Left posterior triangle (11)
Average node size	2.41 cm	1.54 cm

3. Cytologic features and pitfalls

Table 3: Frequency of cyto-features and numbers of case correlation with tuberculosis

Cyto-features	Total	(TB case + Non-TB case)
Epithelioid aggregate	5	(4 + 1)
Caseating pattern	17	(16 + 1)
Necrotizing pattern	5	(3 + 2)
Lymphoid cell	7	(4 + 3)
Reactive	17	(1 + 16)
Reactive with macrophage	5	(0 + 5)

Table 3. exhibits the number of cases belonging to each feature category followed by its corresponding number according to TB or Non-TB node cases. The cyto-feature of epithelioid cell aggregates had appeared in 5 cases, of which 2 were shown granuloma and 2 others elicited only a few tiny aggregated microfragments of

epithelioid cells. Four cases were true tuberculosis whereas one case was reactive hyperplasia of node, therefore, giving (4+1) in the table. Accordingly, caseating necrotizing feature accounted for 17 cases and 16 were true. The single falsely interpreted case showed reactive hyperplasia of lymph node. Necrotizing but non-specific feature accounted for 5 cases. Three cases were TB and 2 cases were not. The latter exhibited cystic structures which were probably related to organizing inflammation. The rest of cyto-features comprised lymphoid cells (7 cases), reactive feature (17 cases) and reactive with tingible-body macrophages (5 cases) were not suggested cytology for tuberculosis. Therefore, 8 cases in total may consider as false-negative by cytology for diagnosing tuberculosis.

There were 2 false-positive cases. The pitfalls are illustrated with corresponding features in true cases. Figure 8 shows the case (case no.29) with false interpretation of plump endothelial cells as epithelioid cells. Figure 9 shows the case (case no.30) with false interpretation of fibrous fragment as caseous necrosis fragment.

There were 8 false-negative cases. The pitfalls were the failure to obtain the suggestive features.
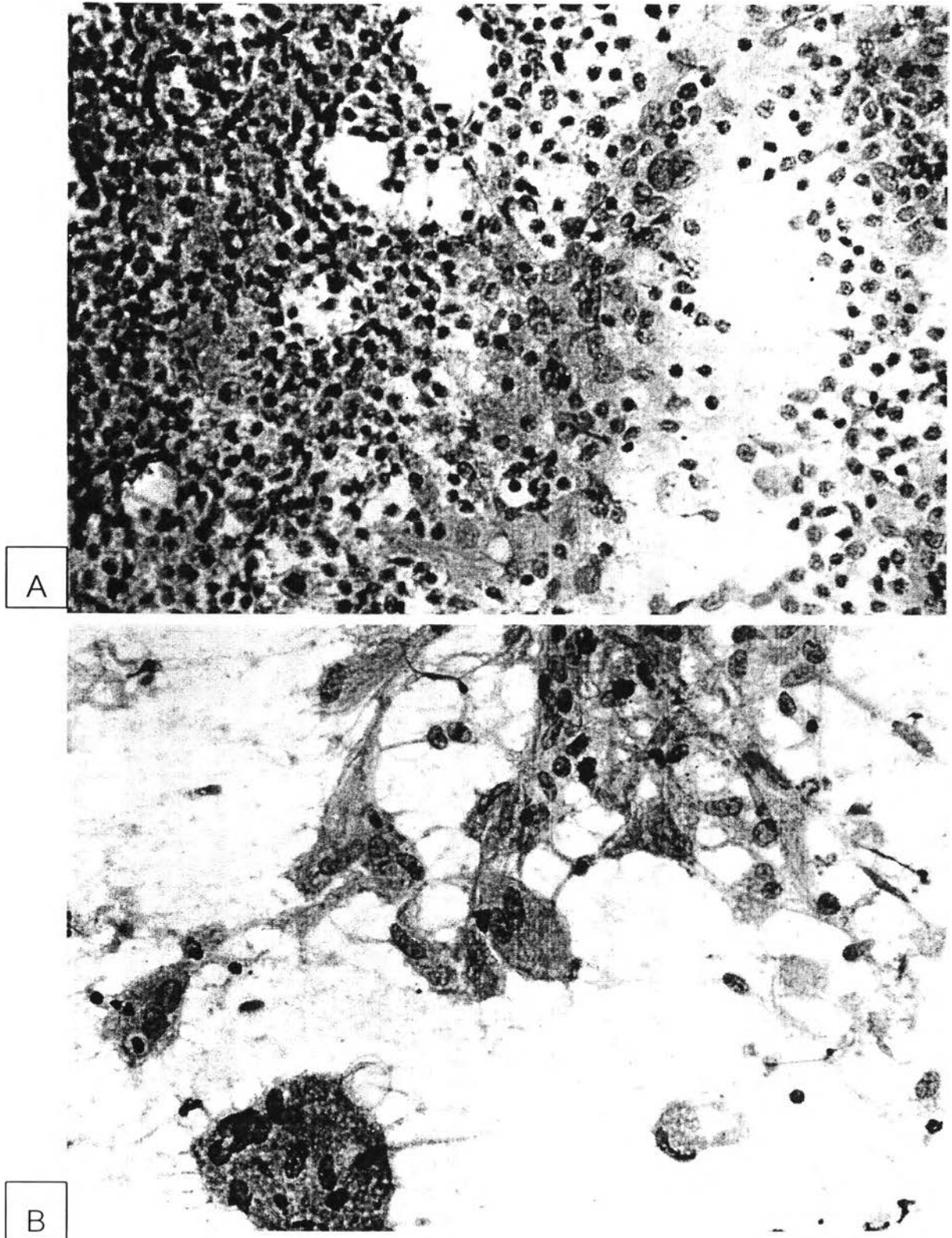
Figure 8: Pitfall of false interpretation on epithelioid cells feature, A. mimic of epithelioid cells (case no.29), B. true epithelioid cells (case no.1) (Both pictures are Papanicolaou stain, original magnification x400)
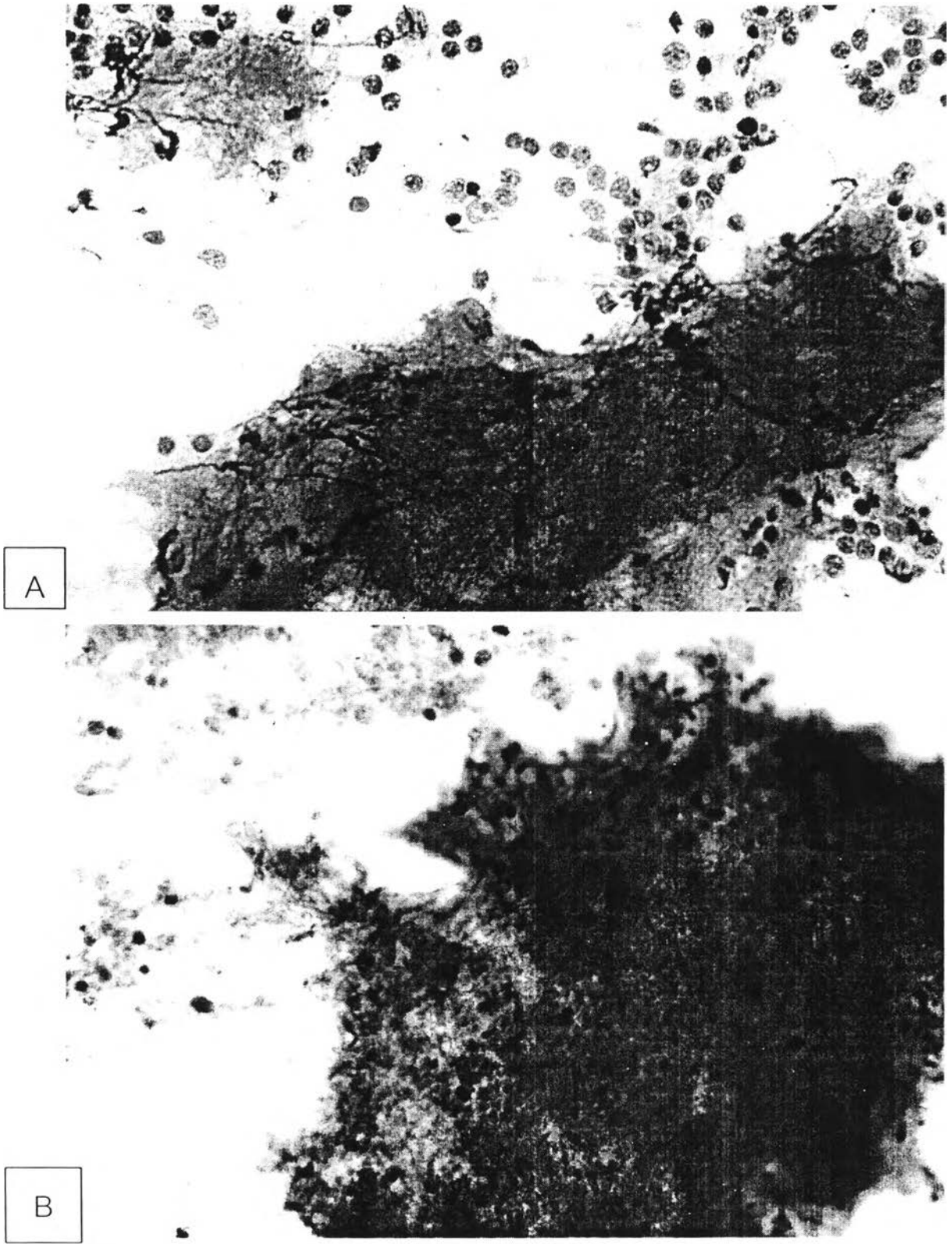
Figure 9: Pitfall of false interpretation on caseous necrosis fragments, A. mimic of caseous necrosis fragment (case no.30), B. true caseous necrosis fragment (case no.5) (Both pictures are Papanicolaou stain, original magnification x400)

4. Diagnostic performance of cytology

There were cytology suggested granulomatous feature in 22 cases, 2 cases were proven false positive. Thirty-four cases were cytology not-suggested, eight of which were lymph node tuberculosis. The 2x2 diagnostic test table is shown in Table 4.

Table 4: FNA cytology and TB lymph node correlation

Biopsy FNACytology	TB -Node	Non TB -Node	Sum
Granulomatous	20	2	22
Non-granulomatous	8	26	34
Sum	28	28	56

The diagnostic performance of cytology suggesting granulomatous lymphadenitis was as following:

Sensitivity	= 71.4 %
Specificity	= 92.8 %
Positive predictive value	= 90.9 %
Negative predictive value	= 76.5 %
Likelihood ratio	= 10
Accuracy	= 82.1%

5. Diagnostic performance of tuberculin test

Using cut-off point = above 24 mm, there were TT strongly positive in 24 cases but three cases were proven false positive. Thirty-two cases were considered here as test negative, seven of which were lymph node tuberculosis. The 2x2 diagnostic test table is shown in Table 5.

Table 5: TT and TB lymph node correlation (TT cut-off ≥25 mm)

Biopsy / TT	TB -Node	Non TB - Node	Sum
Test Positive	21	3	24
Test Negative	7	25	32
Sum	28	28	56

The diagnostic performance of cytology was as following:

Sensitivity = 75%

Specificity = 89.3 %

Positive predictive value = 87.5%

Negative predictive value = 78.1%

Likelihood ratio = 7

Accuracy = 82.1%

6. Diagnostic performance of combined test

Combined test gave positive test in 28 cases but three of them were false positive. There were equal numbers of false negative cases. The 2x2 diagnostic test table is shown in Table 6.

Table 6: FNAC+TT and TB lymph node correlation

Biopsy / FNA+TT	TB -Node	Non TB -Node	Sum
Test Positive	25	3	28
Test Negative	3	25	28
Sum	28	28	56

The diagnostic performance of FNA+TT was as following:

Sensitivity = 89.3%

Specificity = 89.3 %

Positive predictive value = 89.3%

Negative predictive value	= 89.3%
Likelihood ratio	= 8.3
Accuracy	= 89.3%

7. Economic evaluation

    7.1 Patient expense items

    Direct cost

        Medical charges

FNAC	400	Baht
TT	50	Baht
Biopsy with Histology	1,200	Baht

        Non-medical cost

Travelling expense	50	Baht

    Indirect cost

for work absence	162	Baht

    Intangible cost

Serious complications	none

    7.2 Incremental cost effectiveness ratio of Combined test over FNA

Incremental cost $\quad$ = (Cost of TT + Expense generated by more days visit) x
$\qquad\qquad\qquad\qquad$ number of patient

(C1 –C2) $\qquad$ = (50 + 1.5* (162 + 50)) x 56

$\qquad\qquad\qquad$ = (50 + 1.5x 212) x 56

$\qquad\qquad\qquad$ = 368 x 56

$\qquad\qquad\qquad$ = 20,608 $\qquad$ Baht

Note * 1.5 more days visit was based on the fact that some patients had the test on the same day of getting the report of cytology, so save one day visit. Others had the test

on the other day and the next two days to measure the induration (wheal) as well as to see the doctor.

Table 7: Incremental effectiveness of Combined test over FNA

Protocol	TP	TN	FP	FN	False case	E1-E2
Cytology (FNA)	20	26	2	8	10	-
Combined test	25	25	3	3	6	4

Incremental effectiveness = False case by FNA – False case by combined test

$$ (E1 - E2) \quad = 10 - 6 \quad \text{cases} $$

$$ = 4 \quad \text{cases} $$

$$ \text{Incremental cost- effectiveness ratio} \quad = \frac{C1 - C2}{E1 - E2} $$

$$ = 20608 / 4 $$

$$ = 5{,}152 \quad \text{Baht per one save-case from misdiagnosis.} $$

Comment: Incremental cost-effectiveness ratio is more expensive than the charge of biopsy plus expense generated by more days visit, paid by individual person which can be calculated as following.

$$ \text{Biopsy charge + Expense of more days visit} = 1{,}200 + (212 \times 2) \quad \text{Baht} $$

$$ = 1{,}624 \quad \text{Baht} $$

Therefore, to prescribe all patients to have combined test is NOT efficient.

7.3 Sensitivity analysis: Incremental cost-effectiveness ratio of components of suggestive cytologic features

Assumption: If TT was performed only for patients with suggestive cytologic features as confirmatory test of cytology, it would be more efficient.

Refer to 7.2, if all studied population had TT, there were 56 cases. The total incremental cost = 368 x 56= 20,608 Baht. Incremental effectiveness = 4.

Refer to Table 3, when cases with suggestive cytologic feature are prescribed to have complementary TT, the incremental cost and the incremental effectiveness will be as shown in Table 8.

Table 8: Incremental cost-effectiveness ratio of suggestive cytologic features to have TT

Cyto-features	No. of cases	Incremental cost of TT (Baht)	Incremental effectiveness (Case)	Incremental cost-effectiveness ratio (Baht / Case)
Epithelioid aggregate	5	1,840	1	1,840
Caseous necrosis pattern	17	6,256	1	6,256
Necrotizing pattern	5	1,840	3	613
Epithelioid and Necrotizing	10	3,680	4	920

Comment: 1. As confirmatory test, TT cut-off value is $\geq$ 15 mm.

2. Suggestive cytologic features consist of epithelioid cell aggregates caseous necrosis and necrotizing liquefaction.

3. Incremental cost-effectiveness ratio is efficient for epithelioid cell aggregates and necrotizing liquefaction categories.

4. The epithelioid cell aggregates and necrotizing liquefaction pattern together could save 4 cases from wrong diagnosis, therefore it gave the most effectiveness model of the four categories.