Clinical significance of FNA and cell block immunocytology as screening tools for pediatric lymphadenopathy in reference to excision biopsy

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Abstract: Background: Childhood peripheral lymphadenopathy is a major health problem annoying parents greatly. Although most patients turn out to be reactive conditions yet surgical excision with all its hazards has been considered as the golden diagnostic tool. In this study we evaluate FNA and cell block immunocytochemistery results with excision biopsy results in children with peripheral lymphadenopathy**. Patients and Methods:** 87 patients with peripheral lymphadenopathy are subjected FNA, cell block combined with immunocytochemistery and excision biopsy. **Results:** There were significant difference between FNA results and post excision results with agreement percent of 37.9%. and significant difference between cellblock combined immunocytologicalresults and post excision results there were them with agreement percent of 72.4%. Cell blocks accuracy percentage was 98.5 % while accuracy percentages of FNA was 74.71 %. **Conclusions** Cell block method improves accuracy of FNA, allows the recovery and processing of minute amounts of cellular material and facilitates the better classification of tumor especially if accompanied with immunostaining**.**
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Keywords: FNA, cell block

1.Introduction :

An enlarging or persistent neck mass in a child is a common source of concern for parents and pediatricians and is a frequent reason for referral to a pediatric surgeon. The etiologies of peripheral lymphadenopathy are numerous but the majority (85%-89%) are benign (1, 2&3). However, a lymphoproliferative or malignant disorder must be ruled out. This latter diagnostic possibility usually raises fears and anxiety among parents and/or patients. Open surgical lymph node biopsy (LNB) is considered the gold standard for diagnosis of suspicious or persistent lymphadenopathy (2,4&5). It is obvious that a delayed diagnosis of a serious, especially malignant, disease may be critical for the patient. On the other hand an unnecessary LNB may increase parent/patient anxiety, is not devoid of complications, is invasive, is associated with a scar and may increase medical costs (6&7). It should be done under general anesthesia especially in infants and young children. It may also decrease the chance of cure and long-term survival if done in patients of LN secondaries from a squamous cell carcinoma. In this latter situation, the diagnosis of metastatic tumor to a LN on cytologic smears is crucial and highly reliable (8&9).

Because of the wide range of causes of lymphadenopathy sometimes fine needle aspiration does not yield sufficient information for precise diagnosis and the risk of false negative or intermediate diagnosis always exists. In order to overcome these problems, cell block technique has been resorted to make the best use of available material (10).

Cell block method allows the recovery and processing of minute amounts of cellular material and facilitates the better classification of tumor when reviewed along with cytological smears. A modified cell block technique offers excellent cytomorphologic features and provides best preservation for histochemical and immunocytochemical techniques (11). The method is simple to perform and no expertise is required to handle the specimen. Therefore the routine preparation of the cell block improves the accuracy of fine needle aspiration cytology diagnosis (12).

We conducted this study to assess the sensitivity of FNA in association with modified cell blocking technique and cell block immunocytology in the diagnosis of lymphadenopathy in children with reference to open surgical LNB.

2. Materials and methods

This study was conducted as a corporate work between Pediatrics, Pathology, and Pediatric surgery departments Tanta University during a period of 2 years from January 2012 to December 2014. An informed written consent was obtained from the parents. Ninety seven children were included in this study. The age ranged from 2 months to 18 years.

Children with persistent or suspicious lymphadenopathy were referred after clinical and diagnostic work up from the department of pediatrics for histopathologic diagnosis. Under general anesthesia pre-surgery cytopathology consisting of FNA and cell block was first performed by the pathologist followed by formal open surgical LNB of the same LN. Only patients with palpable LNs were included in this study. This allowed surgical sampling of the same LN upon which cytology was performed to allow accurate comparison of the results of both techniques. Then cell blocks were subjected to needed immunocytological markers.

- Smearing Technique:

The FNA specimens were obtained. Two to 4 smears were prepared using positively charged slides, fixed immediately in 95% ethanol and H&E stained. Any excessive material, including the needles used in aspiration, was submitted in 50% ethanol (ethanol/water, 1:1) for cell block preparation.

- Cell Blocking:

Following smear preparations, the needles and syringes used to obtain fine-needle aspirates were rinsed in 10 Ml of 50% ethanol in a specimen container. Any residual clot or tissue in the hub of needles was removed carefully in the laboratory with the aid of another needle and rinsed in 50% ethanol. The entire material was centrifuged in a 10-mL disposable centrifuge tube at 4,000 rpm for 6 minutes to create 1 pellet (13).

The deposit was fixed in freshly prepared Nathan alcohol formalin substitute (NAFS) consisting of 9 parts of 100% ethanol and 1 part of 40% formaldehyde. The fixed cell pellets, at the end of 45 minutes' fixation, were recentrifuged at 4,000 rpm for 6 minutes. These pellets should detach themselves or can be removed easily with a disposable Pasteur pipette following centrifugation. The cell pellets were wrapped in crayon paper, placed in a cassette, and stored in 80% ethanol until ready for processing in the automatic tissue processor. The cell blocks were embedded in paraffin and sectioned at 4 μm thickness(13).

Staining:

Routine H&E (Harris H&E) staining was used on all cell block sections. Kappa and Lambda (Kappa and Lambda (mRNA) PNA Probes,Code No. Y 5202, Dako), range of monoclonal antibodies CD3, CD20, CD15, CD30 &cytokeratin. According to the manufacturer's instructions for the kits (Dako Denmark) was applied in patients requiring identification or phenotyping of tumor cells using the streptavidin-biotin method.

Statistical analysis:

Sensitivity of accuracy (detecting benign from malignant) and agreement (reaching the final diagnosis) between different technique were calculated on the basis of the true-positive and true-negative.Statistical analysis was performed with software (StatView, version 5.0.1). Chi- square test SPSS version 20 for windows statistical package. p – value <0.05 was considered statistically significant.

3. Results :

This study was conducted on 87 patients age ranged from 2 months and 18 years old.

- FNA results : (Table1)

Sixty eight patients were diagnosed as benign aspirate: 23 patients were reactive lymphadenitis, 8 patients were reactive with microgranulomata (Fig 1) 32 patients were reactive with atypical monocytoid cells (Fig 2), 2 patients were diagnosed as chronic sialadenitis and 3 patients were diagnosed as necrotizing granuloma mostly tuberculous lymphadenitis (Fig 3).

19 patients were diagnosed as malignant aspirate; 6 patients HL (Fig 4), 6 patients NHL, 3 patients anaplastic lymphoma (Fig 5) and 4 patients were diagnosed as round cell malignancy

- Cell blocks combined with immunocytological results (Table 2)

55 patients were diagnosed as benign smear : 31 patients were reactive lymphadenitis proved by polycolonal reaction for kappa and lambda, 12 patients were reactive with microgranulomata, 5 patients were reactive with atypical monocytoid cells supported by negative immunostaining for CD15&CD30, 2 patients were diagnosed as chronic sialadenitis and 5 patients were diagnosed as tuberculous lymphadenitis(Fig 6).

32 patients were diagnosed as malignant aspirate; 13 patients were HL proved by positive immunostaining for CD15&CD30 (fig7&8), 9 patients were diagnosed as NHL (proved by monoclonal reaction for kappa and lambda and positive immunostaining for CD20 (Fig 9)and lymphoblastic lymphoma proved by positive CD3 (figures 10&11), 6 patients were diagnosed as anaplastic lymphoma proved by positive immunostaining for CD30 (Fig 12) and negative staining for CD15, and 4 patients were diagnosed as metastatic carcinoma proved by positive cytokeratin immunostaining (Fig 13).

- Excision biopsy results(Tables 1&2)

51 patients were diagnosed as benign conditions: 17 patients were reactive with follicular hyperplasia, 12 patients were reactive with sinus histiocytosis, 13 patients were diagnosed as reactive with microgranulomata, 2 patients were diagnosed as chronic sialadenitis, 2 patients were reactive expanded zone and 5 patients were T.B lymphadenitis.

36 patients were diagnosed as malignant consisting of 15 patients were diagnosed as HL two of them were of lymphocytic predominance type, 11

Table (1) comparison between FNAC results and excision biopsy results

Post Excision Biopsy		FNAC									
		Reactive	Microg-ranuloma	Reactive with atypical monocytoid cells	Hodgkin lymphoma	Chronic sialadenitis	T.B Lymphadenitis	Non Hodgkin lymphoma	Anaplastic lymphoma	Round cell malignancy	Total
Reactive with follicular hyperplasia	N	17	0	0	0	0	0	0	0	0	17
	%	19.54	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	19.54
Reactive with sinus histocytosis	N	4	0	7	1	0	0	0	0	0	12
	%	4.60	0.00	8.05	1.15	0.00	0.00	0.00	0.00	0.00	13.79
Microgranuloma	N	0	8	4	1	0	0	0	0	0	13
	%	0.00	9.20	4.60	1.15	0.00	0.00	0.00	0.00	0.00	14.94
Hodgkin lymphoma	N	2	0	8	4	0	1	0	0	0	15
	%	2.30	0.00	9.20	4.60	0.00	1.15	0.00	0.00	0.00	17.24
Chronic sialadenitis	N	0	0	0	0	2	0	0	0	0	2
	%	0.00	0.00	0.00	0.00	2.30	0.00	0.00	0.00	0.00	2.30
Reactive with Expanded T zone	N	0	0	2	0	0	0	0	0	0	2
	%	0.00	0.00	2.30	0.00	0.00	0.00	0.00	0.00	0.00	2.30
T.B Lymphadenitis	N	0	0	3	0	0	2	0	0	0	5
	%	0.00	0.00	3.45	0.00	0.00	2.30	0.00	0.00	0.00	5.75
Non Hodgkin lymphoma	N	0	0	5	0	0	0	6	0	0	11
	%	0.00	0.00	5.75	0.00	0.00	0.00	6.90	0.00	0.00	12.64
Anaplastic lymphoma	N	0	0	3	0	0	0	0	3	0	6
	%	0.00	0.00	3.45	0.00	0.00	0.00	0.00	3.45	0.00	6.90
Metastatic	N	0	0	0	0	0	0	0	0	4	4
	%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.60	4.60
Total	N	23	8	32	6	2	3	6	3	4	87
	%	26.44	9.20	36.78	6.90	2.30	3.45	6.90	3.45	4.60	100.00
Chi-Square	X^2	203.87									
	P	<0.001*									
Agreement (%)		37.93%									

Table (2) comparison between cell block combined immunostainig results and excision biopsy results

Post Excision Biopsy		Cell block									
		Reactive	Microg-ranuloma	Reactive with atypical monocytoid cells	Hodgkin lymphoma	Chronic sialadenitis	T.B Lymphadenitis	Non Hodgkin lymphoma	Anaplastic lymphoma	Metastatic	Total
Reactive with follicular hyperplasia	N	17	0	0	0	0	0	0	0	0	17
	%	19.54	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	19.54
Reactive with sinus histocytosis	N	12	0	0	0	0	0	0	0	0	12
	%	13.79	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	13.79
Microgranuloma	N	0	12	1	0	0	0	0	0	0	13
	%	0.00	13.79	1.15	0.00	0.00	0.00	0.00	0.00	0.00	14.94
Hodgkin lymphoma	N	0	0	2	13	0	0	0	0	0	15
	%	0.00	0.00	2.30	14.94	0.00	0.00	0.00	0.00	0.00	17.24
Chronic sialadenitis	N	0	0	0	0	2	0	0	0	0	2
	%	0.00	0.00	0.00	0.00	2.30	0.00	0.00	0.00	0.00	2.30
Reactive with Expanded T zone	N	2	0	0	0	0	0	0	0	0	2
	%	2.30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.30
T.B Lymphadenitis	N	0	0	0	0	0	5	0	0	0	5
	%	0.00	0.00	0.00	0.00	0.00	5.75	0.00	0.00	0.00	5.75
Non Hodgkin lymphoma	N	0	0	2	0	0	0	9	0	0	11
	%	0.00	0.00	2.30	0.00	0.00	0.00	10.34	0.00	0.00	12.64
Anaplastic lymphoma	N	0	0	0	0	0	0	0	6	0	6
	%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.90	0.00	6.90
Metastatic	N	0	0	0	0	0	0	0	0	4	4
	%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.60	4.60
Total	N	31	12	5	13	2	5	9	6	4	87
	%	35.63	13.79	5.75	14.94	2.30	5.75	10.34	6.90	4.60	100.00
Chi-Square	X^2	301.46									
	P	<0.001*									
Agreement (%)		72.413									

Table (3) Accuracy percentage FNAC results in comparison with excision biopsy results

			Post Excision Biopsy		Total
			Benign	Malignant	
FNAC	Benign	N	49	19	68
		%	56.32	21.83	78.15
	Malignant	N	2	17	19
		%	2.30	19.55	21.85
Total		N	51	36	87
		%	58.63	41.37	100.00
ROC curve	Sens.	Spec.	PPV	NPV	Accuracy
	89.19	64.00	64.71	88.89	74.71
Chi-Square	X^2	27.31			
	P	<0.001*			

Table (4) Accuracy percentage cell block results in comparison with excision biopsy results

			Post Excision Biopsy		Total
			Benign	Malignant	
Cell block	Benign	N	51	4	55
		%	58.62	4.59	63.21
	Malignant	N	0	32	32
		%	0	36.79	36.79
Total		N	51	36	87
		%	58.62	41.38	100.00
ROC curve	Sens.	Spec.	PPV	NPV	Accuracy
	100.00	98.00	97.37	100.00	98.85
Chi-Square	X^2	109.40			
	P	<0.001*			

patients were NHL, 6 patients were anaplastic lymphoma, and 4 patients were metastatic malignant tumor.

On comparison between FNA results and post excision results there was a significant difference between them with an agreement percent of 37.9%.

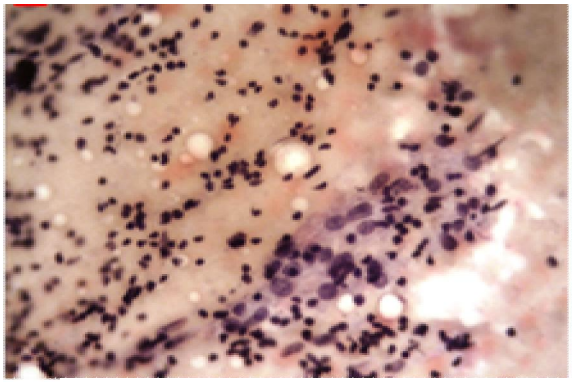

Fig.(1): FNAC showing epithelioid cells admixed with mature lymphocytes suggesting microgranuloma (H&E x400)

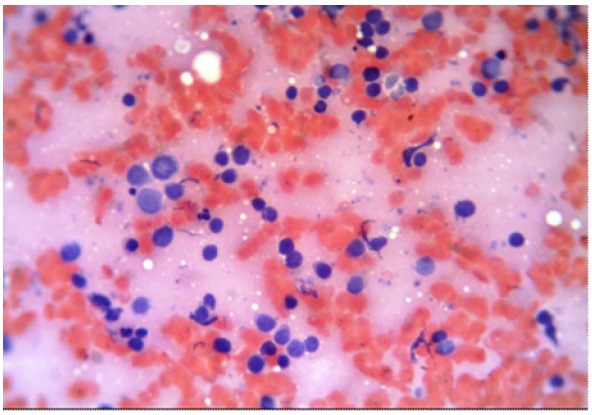

Fig.(2): FNAC showing reactive aspirate with atypical monocytoid cells (H&E x400)

On comparison between cell block combined immunocytological results and post excision results there was a significant difference between them with an agreement percent of 72.4%.

Regarding accuracy in ▮ Tables 3&4 ▮ cell blocks contained diagnostic cellular material in 51/55 patients were diagnosed as benign and atypical with monocytoid cells, and 32/32 patients of malignant cells present with accuracy percentage of 98.5 %.

FNA contained diagnostic cellular material in 49/68 patients were diagnosed as benign and atypical with monocytoid cells., and 17/19 patients of malignant cells present with accuracy percentages of 74.71 %.

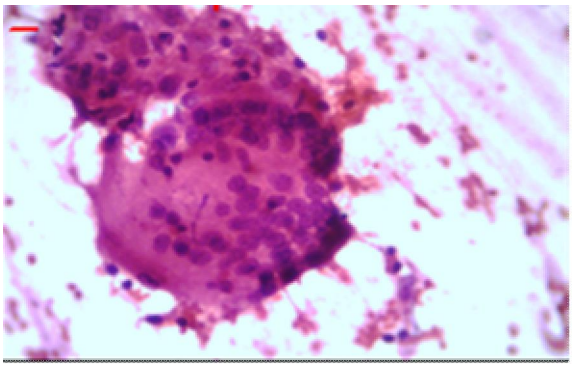

Fig.(3): FNAC showing giant cells suggestive of granulomatous lymphadenitis(H&E x400)

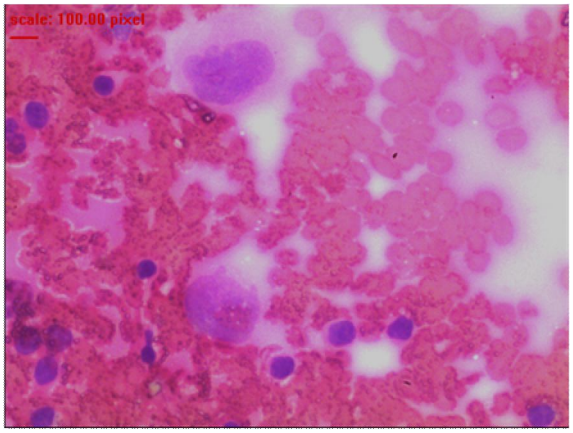

Fig.(4): FNAC showing atypical cells with eosinophilic nucleoli suggesting HL (H&E x400)

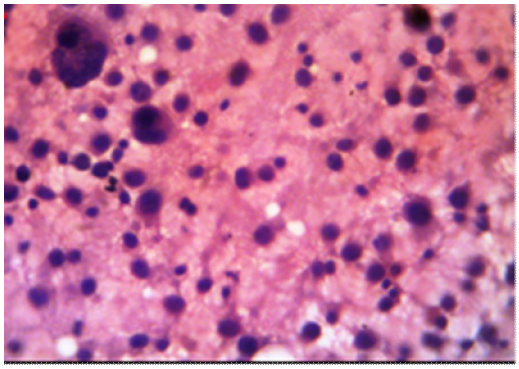

Fig.(5):FNAC showing large atypical cells with horse shoe shaped nuclei suggesting anaplastic lymphoma(H&E x400)

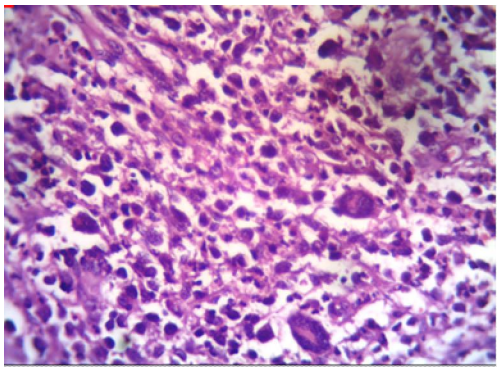

Fig.(6): cell block showing Langhans giant cells suggestive of tuberculous lymphadenitis(H&E x400)

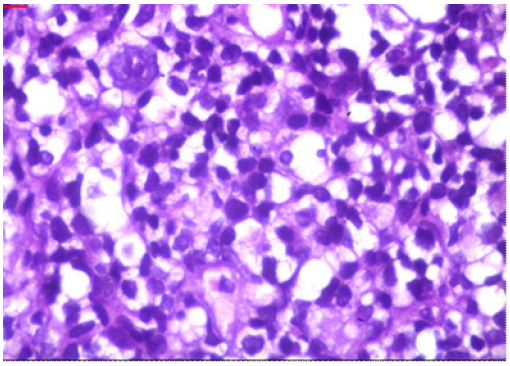

Fig.(7): cell block showing R-S shaped cells in mature lymphocytes suggestive of HL (H&E x400)

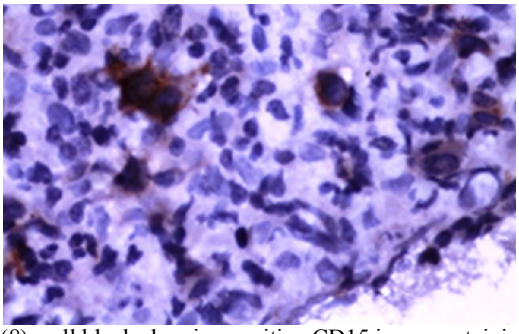

Fig.(8): cell block showing positive CD15 immunostaining of R-S like cells(streptavidin biotin x400)

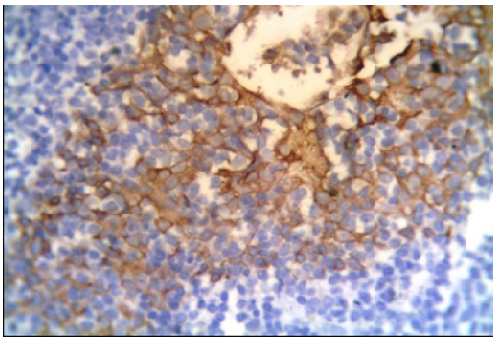

Fig.(9): cell clock showing positive CD20 immunostaining of neoplastic large cells(streptavidin biotin x400)

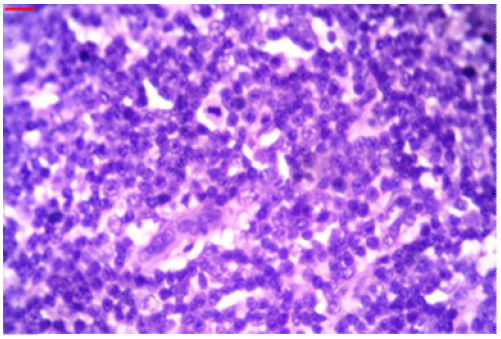

Fig.(10): cell block showing neoplastic lymphocytes with atypical mitosis suggestive of lymphoblastic lymphoma (H&E x400)

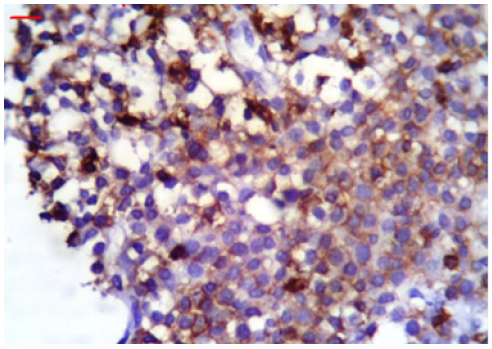

Fig.(11):cell block of lymphoblastic lymphoma showing positive CD3 immunostaining in neoplastic lymphocytes (streptavidin biotin x400)

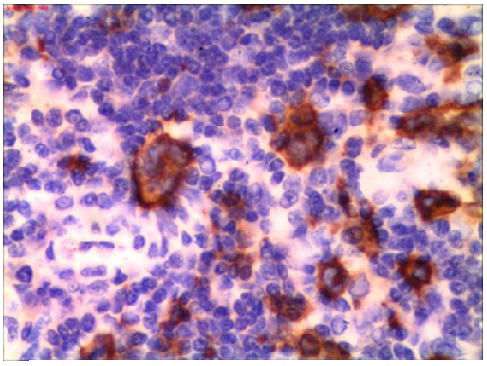

Fig.(12): cell block showing positive CD30 immunostaining in anaplastic lymphoma(streptavidin biotin x400)

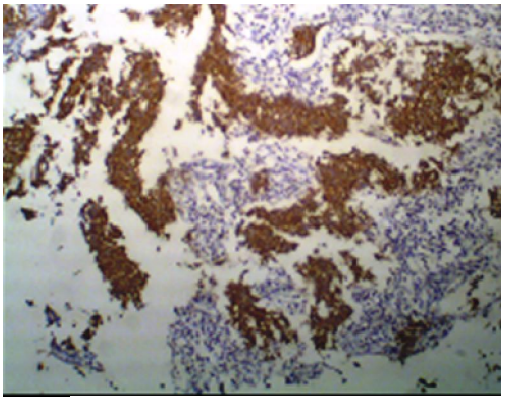

Fig.(13): cell block showing positive cytokeratin immunostaining in metastatic carcinoma (streptavidin biotin x100)

4.Discussion

Peripheral lymphadenopathy is a major health problem during the period of childhood. FNA of LN has become an integral part of the initial diagnosis and management of patients with lymphadenopathy due to its minimal trauma, less complications, simplicity, cost effectiveness and early availability of its results (14). Although reliable and preferable in the diagnosis of metastatic tumor to LN, the role of FNA in the diagnosis and subclassification of primary lymphoid disease is still controversial and is very often followed by open biopsy in many cases; excision biopsy is considered the gold standard for these cases (2, 4, 9 &15). However, surgical LNB is not devoid of complications, LN are located in the vicinity of important neurovascular structures in the neck and axilla especially the internal jugular vein and spinal accessory nerve. Although injuries of such structures are rare they can have serious consequences. Fixed and matted LN add to the surgical difficulty and increase the possibility of complications (3). LN located deep in the body e.g. intra-abdominal or mediastinal LN may need major surgeries to retrieve them and radiology guided FNA can be a good initial diagnostic tool with less morbidity and costs. The same holds true for poor surgical risk patients. Open LNB from LN harboring meatstic SCC is a grave error (3&16). Also most lymphadenopathies in children are benign (2, 3&17).Therefore FNA remains an optimal initial step for diagnosing LN disease. Modifying the technique by adding the cell block technique can increase the accuracy of FNA whilst keeping its safety and advantages.

In this study we tried to evaluate FNA, and cell block immunocytology results in reference to excision biopsy results.

Regarding FNA showed accuracy of 74.71% in comparison to post excision biopsy and an agreement of 37.93%. The 21.83% false negative results can be attributed to sampling and detection errors. These findings were in accordance with Koen Creemers *et al.* (18). On the other hand false positive percentage of 2.3% in our study may be due to lack of adequate sampling material, this was in agreement with Meda BA, *et al.* (19).

Regarding cell block with immunocytology an accuracy percentage of 98.85% in comparison to post excision biopsy and an agreement percent of 72.4% for exact sub classification of the disease. False negative results in 4.5% of patients,this was due to insufficient sampling and in one case that proved to be lymphocytic predominance HL that was negative for CD15 and 30 immunostaing.There is no false positive results which may be explained by the concept of Thapar *et al.* (20), who pointed out that the cell block technique has the added advantage that multiple sections of the same material can be obtained for special stains and immunohistochemistry. Apart from this concept, morphological details can also be obtained with cell block method, which includes preservation of the architectural pattern, excellent nuclear and cytoplasmic details, and individual cell characteristics.Moreover, fragments of tissue can easily be interpreted in a biopsy-like fashion.

Few studies have compared the value of cell blocks with smears. Keyhani-Rofaga *et al.* (21) reported that in a study of 85 patients, 55% of the original smears diagnoses were improved after the cell blocks were examined. The sensitivity of cell blocks varied from 60% to 86%, depending on sampling type and size, type of specimens, and aspiration techniques used. However Axe et al (22) showed that the sensitivity of Papanicolaou-stained smears (79%) was slightly superior to cell blocks (73%). Kern and Haber (23) studied 393 patients using cell block preparation and found that 60.3% of cases were confirmatory to FNA results, and in 26.2% the cell blocks provided additional information for diagnosis.

So finally combined FNA and cell block with immunocytology might be sensitive indicators to discriminate between lymphoma and reactive conditions, this may help the physician start proper treatment, while avoiding child a surgical procedure that might have complications and increase the parents' anxiety. But still excision biopsy for assessment of the pattern of expression of immunomarker is necessary in some patients as in some lymphoma patients who remain challenging to diagnose by FNA even with the help of cell block immunohistochemistry (24).

From this study we concluded that FNA alone doesn’t yield sufficient information for precise diagnosis. Cell block method improves accuracy of FNA, allows the recovery and processing of minute amounts of cellular material and facilitates the better classification of tumor especially if accompanied with

immunostaining. However excision biopsy remains the golden methods for diagnosis of lymph node biopsy especially for better architecture phenotyping of lymphoma.

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