Role of Cytopathology in Eyelid Growth with Histopathological Correlation

*Paul R,[1] Kundu UK,[2] Kabir E,[3] Islam MN[4]

The purpose of this study was to evaluate diagnostic accuracy of cytopathology in different eyelid lesions using fine needle aspiration cytology (FNAC) & scrape cytology with histopathological correlation. Accurate diagnosis of eyelid tumors is necessary to guide ophthalmologists to design optimal management. Fine needle aspiration from 85 eyelid growth and histopathological correlation were studied. Immunohistochemical analysis were done in few cases. A majority of the patients (43 out of 85) were in the 26-50 age group (53.49% male vs 46.51% female). Mean age was 43.22±17.42 (range 19 – 90 years) years. Of the malignant lesions, basal cell carcinoma were highest (12 in number, 36.36%) followed by sebaceous gland carcinoma and squamous cell carcinoma. Less common malignant tumor were Non-Hodgkin's lymphoma. Among benign neoplastic lesions, nevi were most common (14 in number, 43.75%) followed by haemangioma and squamous papilloma. Other less common benign tumors were fibroepithelial polyp, adenoma, lipoma and neurofibroma. Most common benign cystic lesions of eyelid are cyst (10 in number, 50%) of moll/Hydrocystoma/Sudoriferous cyst, followed by Dermoid cyst, Epidermal inclusion cyst and Sebaceous cyst. Present study revealed that accuracy of cytopathological diagnosis of malignant eyelid growths were 97.65%. Cytopathology had a high diagnostic accuracy rate. Aspiration cytology was cost effective and offers rapid diagnosis with minimal discomfort to the patient.

[Journal of Histopathology and Cytopathology, 2018 Jul; 2 (2):134-144]

Key wards: Eye lid growth, Cytopathology, Histopathology, Correlation

Introduction

Eyelid growth is a common cause to be presented to ophthalmologists[1] and many of them can be treated as day care service. At the same time some of the tumors demand emergency surgical intervention and thus early referral.[2] Introduction of cytopathology prior to excision biopsy would contribute to early diagnosis and management plan.[3] Pathologic conditions affecting the eyelid may be inflammatory or neoplastic. Neoplastic lesion may be benign or malignant.[1] It becomes difficult to decide clinically either it is a true neoplasm or an inflammatory lesion. In all such cases, cytopathology (FNAC / scrape cytology) proved to be very useful in quickly determining the nature of the lesion and also deciding the mode of treatment.[4] FNAC has a high diagnostic accuracy rate, if the aspirated material is sufficient for microscopical examination and if it is properly interpreted.[5] Aspiration cytology is also cost effective and offers rapid diagnosis, with minimal discomfort to the patient.[6]

1. **Dr. Rita Paul, Assistant Professor, Department of Pathology, Ibrahim Medical College, Dhaka. ritapaul16@gmail.com*
2. *Dr. Utpal Kumar Kundu, Assistant Professor (Eye), Mugda Medical College, Dhaka.*
3. *Professor Enamul Kabir, Professor, Department of Pathology, Sir Salimullah Medical College, Dhaka.*
4. *Professor Md. Nasimul Islam, Professor and Head, Department of Pathology, Sir Salimullah Medical College, Dhaka.*

**For correspondence*

Method

This was a cross sectional study conducted at the Departmentof Pathology of Sir Salimullah Medical College, Dhaka and National Institute of Ophthalmology and Hospital, Dhaka, Bangladesh from January 2012 to December 2013. 85 adult patients with eye lid growths of both sexes were recruited. Purposive sampling technique was used. FNAC was done using 22 Guage needle without anaesthesia and smears were stained with Papanicolaou's stain. Biopsy was taken by clinician and diagnosis was confirmed by histopathological examination. Inclusion criteria were adult patients with eyelid growth. Exclusion criteria included patients who were clinically diagnosed to have inflammatory eyelid lesions, patients belonging to less than 18 years of age, and very tiny growth <0.5cm in diameter.

FNA Features of different Eye-lid lesions

Smears from nevus showed single and small clusters of cells with rounded or oval nuclei and indistinct cytoplasm.[7] Smears from haemangioma showed only blood, with a few cases showing an occasional cluster of endothelial cells. Smears from squamous papilloma showed degenerated squamous epithelial cells along with mature superficial squamous cells. Smears from neurofibroma showed cohesive spindle-shaped cells within fibrillary mesenchymal background material. Smears from hidrocystoma / Sudoriferous cyst / Cyst of Moll showed foamy macrophages in the background of proteinecious material. Smears from epidermal inclusion cyst showed high cellularity with numerous nucleated squamous cells and anucleated squames in a background of keratinous debris.[8] Smears from dermoid Cyst showed anucleated and nucleated squamous epithelium and keratin debris.[9] Smears from chalazion showed a polymorphic picture with neutrophils, plasma cells and macrophages. The granulomas are more of histiocytic cells with abundant vacuolated cytoplasm; the backround is generally dirty with nuclear debris and fat spaces.[10] Smears from molluscum contagiosum showed Molluscum bodies, in the enlarged superficial cells of the epidermis.[11] Molluscum bodies, also called Henderson-Patterson bodies, were large, round cytoplasmic inclusions (within the enlarged cells of epidermis), which push the nucleus to the periphery.[12] Smears from Rhinosporidiosis showed many scattered basophilic rhinosporidial endospores and rhinosporidial spores in a background of amorphous eosinophilic material.[13] Smears from basal cell carcinoma showed tightly cohesive small clusters of uniform hyper-chromatic basaloid cells with high nuclear-cytoplasmic ratio and absence of cytoplasmic vacuolation. Peripheral palisading of nuclei may be evident in some clusters. Squamous, sebaceous and adenoid differentiation may be seen and pigmented variant may be seen.[14] Smears from sebaceous gland carcinoma showed large pale cells and vacuolated cytoplasm however another type is poorly differentiated cells with dark and irregular nuclei. The smears of squamous cell carcinoma showed markedly enlarged hyper-chromatic nuclei of variable size and keratinization.[10] Smear from cutaneous melanoma showed atypical dispersed population of cells with abundant cytoplasm, eccentric uniform hyperchromatic nuclei, internuclear inclusions in the background of melanin pigment.[15] In Non-Hodgkin's lymphoma, cytology smears showed a monotonous population of lymphocytes with round nuclei having coarse granular chromatin. Histopathological examination of biopsied tissue confirmed the diagnosis[16] and in a few cases by the help of immuno-histochemical analysis using specific antibodies.

Results

Age distribution of the patients presented with eyelid growths showed almost half (50.59%) of the patients comprised of middle age group (26-50 years) with a little more than one-fourth (30.59%) above 50 years of age. Gender distribution of the patients presented with eyelid growths showed slightly male preponderance (50.59%) and female constituted 49.41%. Mean age was 43.22±17.42 (range 19 – 90 years) years.

Among benign neoplastic lesions, nevus was most common, followed by vascular lesion and squamous papilloma. Others were adenoma, lipoma and hamartoma. Correlation with cytopathological and histopathological examination were done. Cytopathologically diagnosed fourteen (14) cases of Nevus were confirmed by histopathological examination. Cytologically diagnosed Vascular Lesion in eight (8) cases were histologically confirmed in seven (7). The other case was histologically diagnosed as Hamartoma. Five (5) cases of squamous papilloma corresponded cytologically and histologically. One (1) case of cytologically diagnosed lipoma was also confirmed histologically. Both (2) cases of histologically diagnosed Fibroepithelial Polyp were cytologically diagnosed as benign Mesenchymal lesion. One (1) case of histologically diagnosed Neurofibroma was cytologically diagnosed as a malignant peripheral nerve sheeth tumor (False positive; Table III).

Cytologically diagnosed Cyst of Moll/ Hydrocystoma/ Sudoriferous Cyst corresponded histologically in all ten (10) cases. Five (5) cases of cytologically diagnosed Dermoid Cyst were confirmed histologically. Cytologically diagnosed three (3) cases of Epidermal Inclusion Cyst corresponded histologically. Two (2) cases of cytologically diagnosed Sebaceous Cyst were later on confirmed histologically (Table IV).

Among the malignant lesions encountered during the present study, Basal cell carcinoma was the most common malignancy, followed by Sebaceous Gland Carcinoma and Squamous Cell Carcinoma. Non-Hodgkin's lymphoma (NHL) was found to be less common. Cytological diagnosis was confirmed by histopathological examination in the present study. Eleven (11) cases of cytologically diagnosed Basal Cell Carcinoma were confirmed histologically. One (1) case of cytologically diagnosed Nevus (False negative) was histologically diagnosed as Basal Cell Carcinoma. Sebaceous Gland Carcinoma corresponded cytologically and histologically in all nine (9) cases. Nine (9) cases of cytologically diagnosed Squamous Cell Carcinoma were also confirmed histologically. Lymphoma corresponded cytologically and histologically in both (2) cases, which was later on confirmed by immuno-histochemical study as Non-Hodgkin's lymphoma of 'B' cell origin. One (1) case of cytologically diagnosed Small Cell Tumor was confirmed histologically (Table V).

Comparison of diagnosis between cytopathology with histopathology among the malignant eyelid growths

Among 85 eyelid growths, 32 cases were cytopathologically and histopathologically true positive for malignant lesions. The comparison between cytopathology and histopathology were statistically highly significant ($p < 0.0001$; Table VI). Out of 85 (100%) patients of eyelid growths 32 (37.64%) were positive for malignancy, 51(60.00%) were negative for malignancy, 01(1.18%) was false positive(1.18%) and 1 (1.18%) was false negative (Table VII). The validity of cytopathology to diagnose malignant eyelid growths, Sensitivity, Specificity, PPV, NPV and Accuracy were 96.97%, 98.08%, 96.97%, 98.08% and 97.65% respectively (Table VIII).

Out of a total 33 histologically confirmed cases of malignant tumor, thirteen (13) cases were ulcerated. From these ulcerated lesions, samples were collected by scraping. Out of these, nine (9) cases were Basal Cell Carcinoma, three (3) cases were Squamous Cell Carcinoma and one (1) case was found to be Sebaceous (Meibomian) Gland Carcinoma.

Table I: Distribution of different eyelid lesions with Cytological and Histological Diagnosis (n=85)

Eyelid Growth	Cytological Diagnosis	Histological Diagnosis
Nevus	15 (17.65)	14 (16.47)
Vascular Lesion	8 (9.41)	7 (8.23)
Squamous Papilloma	5 (5.88)	5 (5.88)
Adenoma	1 (1.18)	1 (1.18)
Lipoma	1 (1.18)	1 (1.18)
Hamartoma	0 (0.00)	1 (1.18)
Benign Mesenchymal Lesion	2 (2.36)	0 (0.00)
Fibroepithelial Polyp	0 (0.00)	2 (2.36)
Neurofibroma	0 (0.00)	1 (1.18)
Cyst Of Moll/ Hydrocystoma/ Sudoriferous Cyst	10 (11.76)	10 (11.76)
Dermoid Cyst	5 (5.88)	5 (5.88)
Epidermal Inclusion Cyst	3 (3.52)	3 (3.52)
Sebaceous Cyst	2 (2.36)	2 (2.36)
Basal Cell Carcinoma	11 (12.94)	12 (14.12)
Sebaceous Gland Carcinoma	9 (10.58)	9 (10.58)
Squamous Cell Carcinoma	9 (10.58)	9 (10.58)
Lymphoma	2 (2.36)	2 (2.36)
Small Cell Tumor	1 (1.18)	1 (1.18)
Malignant Peripheral Nerve Sheath Tumor (MPNST)	1(1.18)	0 (0.00)
Total	85 (100)	85 (100)

Table II: Age distribution of the patients of all types of eyelid lesions with percentage (n=85)

Age	Frequency	Percentage
Up to 25	16	18.82
26 – 50	43	50.59
Above 50	26	30.59
Total	85	100.0

Table III: Distribution of different benign neoplastic eyelid growths

Final Histological Diagnosis					Cytological Diagnosis						
	Total (Final Histology)	Nevus	Haemangioma	Squamous Papilloma	Adenoma	Lipoma	Hamartoma	Benign Mesenchymal Lesion	Fibroepithelial Polyp	Neurofibroma	MPNST
Nevus	14	14	0	0	0	0	0	0	0	0	0
Haemangioma	7	0	7	0	0	0	0	0	0	0	0
Squamous Papilloma	5	0	0	5	0	0	0	0	0	0	0
Adenoma	1	0	0	0	1	0	0	0	0	0	0
Lipoma	1	0	0	0	0	1	0	0	0	0	0
Hamartoma	1	0	1	0	0	0	0	0	0	0	0
Fibroepithelial Polyp	2	0	0	0	0	0	0	2	0	0	0
Neurofibroma	1	0	0	0	0	0	0	0	0	0	1
Total =	32							Total= 32			

Table IV: Distribution of different benign cystic eyelid lesions

Final Histological Diagnosis		Cytological Diagnosis			
	Total Final Histology	Cyst of Moll	Dermoid Cyst	Epidermal Inclusion Cyst	Sebaceous Cyst
Cyst of Moll	10	10	0	0	0
Dermoid Cyst	5	0	5	0	0
Epidermal Inclusion Cyst	3	0	0	3	0
Sebaceous Cyst	2	0	0	0	2
Tolal	20			Total = 20	

Table V: Distribution of malignant eyelid lesions (total of 85 cases each)

Final Histological Diagnosis			Cytological Diagnosis				
	Total Final Histology	Basal Cell Carcinoma	Sebaceous Gland Carcinoma	Squamous Cell Carcinoma	Lymphoma	Small Cell Tumor	Nevus
Basal Cell Carcinoma	12	11	0	0	0	0	1
Sebaceous Gland Carcinoma	9	0	9	0	0	0	0
Squamous Cell Carcinoma	9	0	0	9	0	0	0
Lymphoma	2	0	0	0	2	0	0
Small Cell Tumor	1	0	0	0	0	1	0
Total =	33				Total = 33		

TableVI: Comparison of diagnosis between Cytopathology with Histopathology among the Malignant Eyelid Growths

Cytopathology	Histopathology		Total
	Malignant	Benign	
Malignant	32 (37.64)	1 (1.18%)	33 (100.0%)
Benign	1 (1.18%)	51 (60.00%)	52 (100.0%)
Total	33 (38.82%)	52 (61.18%)	85 (100.0%)

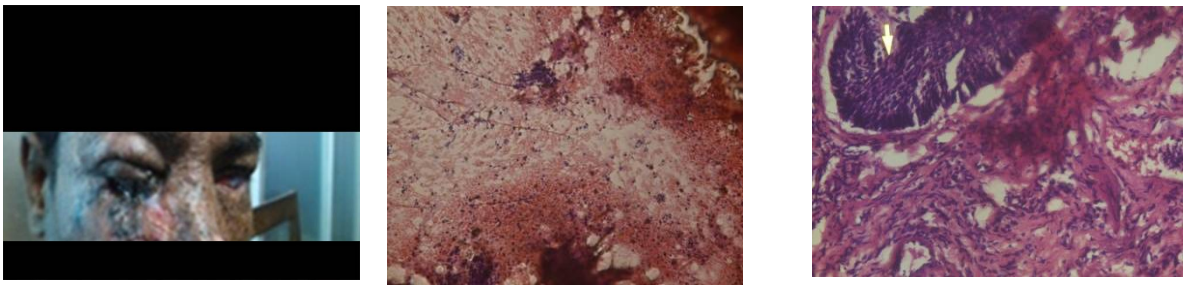
* p value < 0.0001

Table VII: Assessment of diagnostic accuracy of cytopathology of eyelid growths

Cytopathological Diagnosis	No. of cases	Percentage
Positive for Malignancy	32	37.64%
Negative for Malignancy	51	60.00%
False Positive	1	1.18%
False Negative	1	1.18%
Total	85	100%

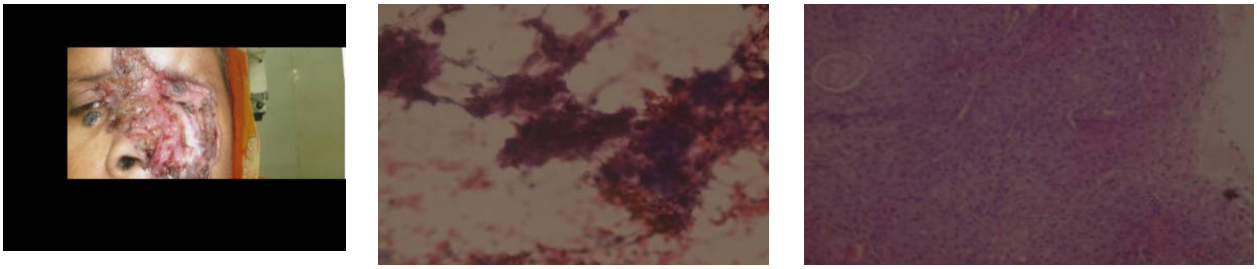
Table VIII: Cytopathological validity of different malignant eyelid growths

Sensitivity	Specificity	Positive Predictive	Negative Predictive Value	Accuracy
96.97%	98.08%	96.97%	98.08%	97.65%



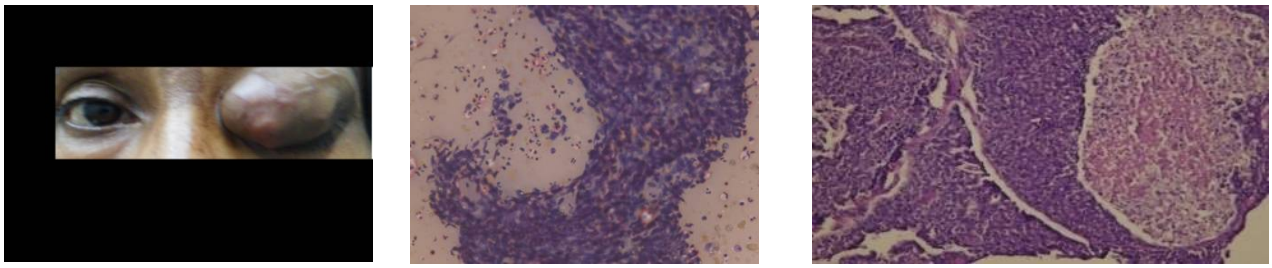
A B C

Figure 1. (A) Case 1. Basal cell carcinoma, (B) Photomicrograph of cytology smear of basal cell carcinoma showing tightly cohesive small clusters of uniform hyperchromatic basaloid cells (Pap's, x200), (C) Photomicrograph of Basal cell carcinoma showing atypical basaloid cell with retraction artifact (H&E, x400)



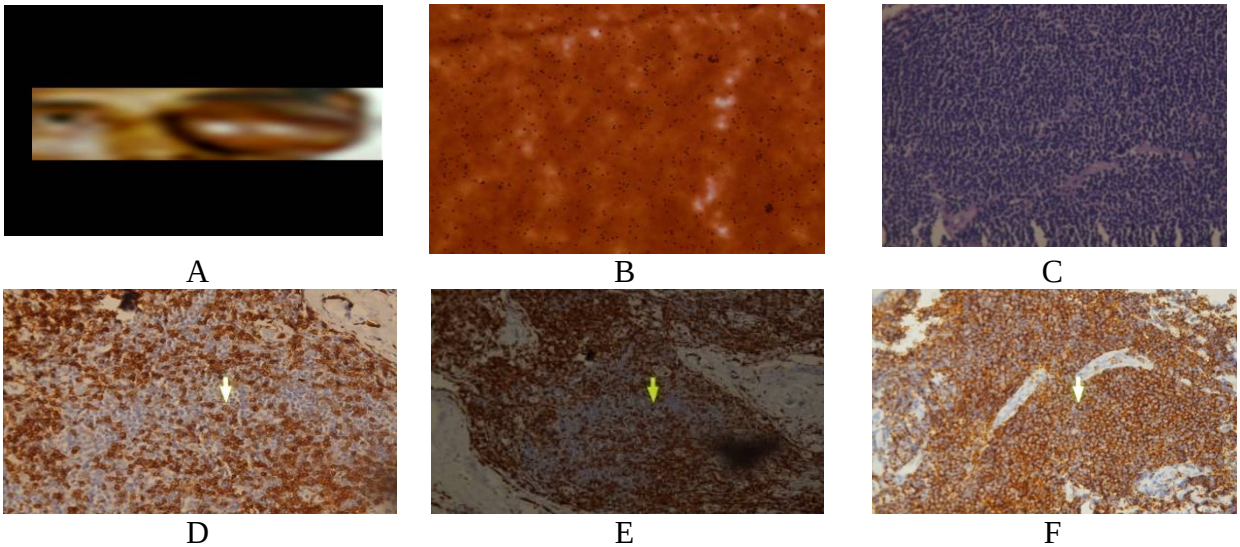
A B C

Figure 2. (A) Case 2. Squamous cell carcinoma, (B) Photomicrograph of cytology smear of Squamous cell carcinoma showing enlarged hyper-chromatic nuclei of variable size and keratinization (Pap's, x400), (C) Photomicrograph of Squamous cell carcinoma (Grade-I) showing atypical squamous cell invading deeply into the dermis. It also shows squamous pearl. (H&E, x200)



A B C

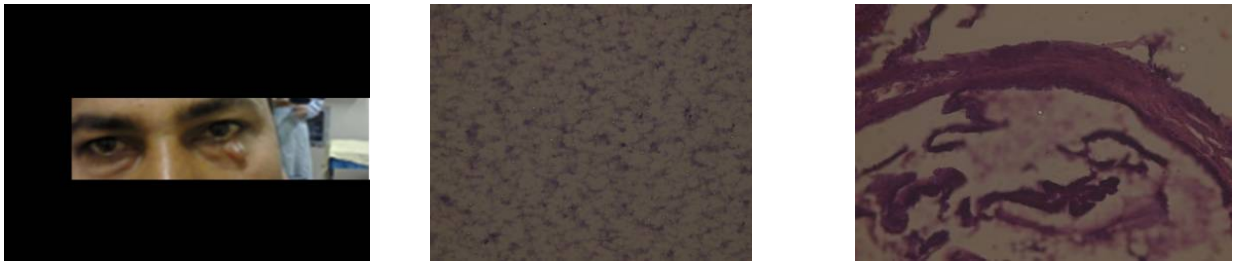
Figure 3. (A) Case 3. Sebaceous (meibomian) gland carcinoma, (B) Photomicrograph of cytology smear of sebaceous (meibomian) gland carcinoma showing atypical tumor cells arranged in clusters and singly with foamy eosinophilic cytoplasm (Pap's, x400), (C) Photomicrograph of sebaceous (meibomian) gland carcinoma showing atypical tumor cells and necrosis (H&E, X200).



A B C

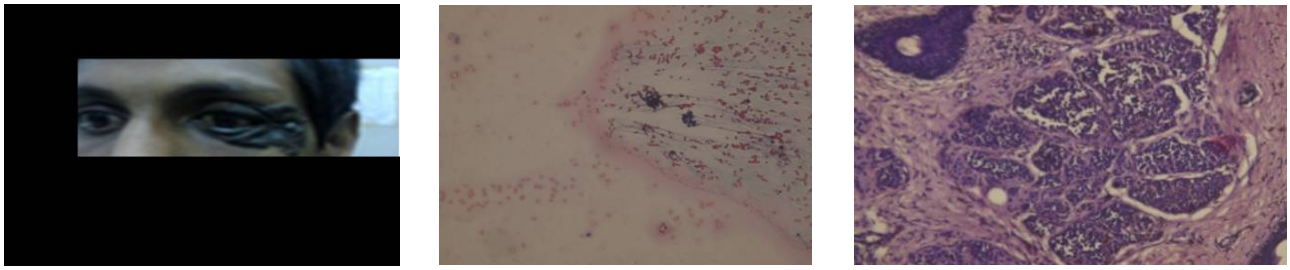
D E F

Figure 4. A. Case 4. Non-Hodgkin's Lymphoma, B. Photomicrograph of cytology smear of Non-Hodgkin's Lymphoma showing monomorphous population of atypical lymphoid cells, scanty cytoplasm with clumped chromatin. (Pap's x200), C. Photomicrograph of Non-Hodgkin's Lymphoma showing hypercellular proliferations. Most of the tumor cells are monotonous in appearance, having large nuclei with condensed chromatin. (H&E, x400), D. Photomicrograph of IHC study showing lymphoid cells with positive staining for LCA. (IHC, x400), E. Photomicrograph of IHC study showing scattered lymphoid cells with positive staining for CD3. (IHC, x400), F. Photomicrograph of IHC study showing majority of atypical lymphoid cells with positive staining for CD20 (IHC, x400) Conclusion: Immunostaining results favor the diagnosis of Non-Hodgkin's Lymphoma of " B" cell origin.



A B C

Figure 5. A. Case 5. Hydrocystoma. B. Photomicrograph of cytology smear of benign cystic lesion showing foamy macrophages in the background of proteinecious material (Pap's, x200), C. Photomicrograph of hydrocystoma showing cyst wall lined by a double layer of columnar cells with eosinophilic cytoplasm and prominent papillary projections. (H&E x400)



A B C

Figure 6. A. Case. Nevus, B. Photomicrograph of cytology smear of nevus showing single and small clusters cells with rounded or oval nuclei and indistinct cytoplasm (Pap's x200). C. Photomicrograph of nevus showing nests of round cells in the underlining dermis. (H&E, x200)

Discussion

The present study was conducted with an aim to assess the cytopathological and histopathological correlation of different types of eyelid growths. It was a hospital based cross sectional study which enrolled 85 clinically suspected eyelid growths. Out of them 52 (61.18%) were benign and 33 (38.82%) were malignant. A recent study by Mondal and Dutta,[8] Fine needle aspirates from 80 eyelid swellings were studied. Forty eight cases of benign and 32 cases of malignant lesions were diagnosed by FNAC.

Mean age in the present study was 43.22 years (SD ±17.42) (range 19 – 90 years). Pombejara et al.[17] reported mean age of presentation 52.4 years ± SD 21.8 years in Thailand. Most benign growths were within the age group 26-50 years and malignant eyelid lesions were in patients above 51 years of age.Mondal and Dutta[8] studied 80 eyelid lesions by FNAC, in which 32 cases were malignant. In that study most common malignant lesion was basal cell carcinoma (12 cases, 15%) followed by sebaceous gland carcinoma (nine cases, 11.25%) and squamous cell carcinoma (eight cases, 10%). In the present study, malignancy were 38.82% (33 out of 85), and the most frequent malignant tumor was basal cell carcinoma (12 out of 33, 36.37%) followed by sebaceous gland carcinoma (09, 27.27%), squamous cell carcinoma (09, 27.27%), Non-Hodgkin's lymphoma (2, 6.06%) and small cell carcinoma (1,3.03%).

Among benign lesions, in the present study, nevus was most common in 14 cases (43.75%), followed by haemangioma 7 cases (21.88%) and squamous papilloma in 5 cases (15.64%). Other less common lesions were fibroepithelial polyp, adenoma, lipoma, neurofibroma and hamartoma. In the present study, among benign cystic lesions (20 cases) of eyelid, sudoriferous cyst was most common in 10 cases (50.00%) followed by dermoid cyst in 5 cases (25.00%), epidermal inclusion cysts in 3 cases (15.00%), and sebaceous cysts in 2 cases (10.00%). In a recent study by Toshida et al.,[18] the most frequent diagnosis among 106 benign lesions were nevus in 23 cases (21.7%). The second common was squamous cell papilloma in 18 cases (17.0%), followed by seborrheic keratosis in 14 cases (13.2%). Less common causes were epidermal cyst in 10 cases (9.4%) and dermoid cyst in 7 cases (6.6%).

Ulcerated skin of eye-lid can be scraped safely and it is recommended to combine FNAC with scrape cytology for any ulcerated lesions of eyelid skin and conjunctiva (Rai, 2007). In the present study, out of a total 33

histologically confirmed malignant tumors, thirteen (13) ulcerated cases were taken by scraping. Of these, nine (09) were Basal Cell Carcinoma, three (3) were Squamous Cell Carcinoma and one (1) was found to be Sebaceous (Meibomian) Gland Carcinoma.

In recent studies by Mondal and Dutta [8] and Arora et al.[5] showed accuracy of cytological diagnosis of eyelid growths were 83.87% and 89.4% respectively. In the present study, accuracy of cytological diagnosis of malignant eyelid growths was 97.65%. These comparisons are clearly emphasizing need for cytopathology and histopathology of all surgically removed specimens.[19,20] The present study also compared cytopathological and histopathological diagnosis of all specimens.When comparing cytopathology with histopathology of the clinically suspected malignant eyelid growths, the comparison between cytopathology and histopathology was statistically highly significant ($p<0.0001$).In the present study, Sensitivity, Specificity and Accuracy of cytopathology to diagnose malignant eyelid growths were 96.97%, 98.08% and 97.65% respectively.

References

1. Abdi U, Tyagi N, Maheshwari V, Gogi R and Tyagi SP. Tumors of eyelid: A clinicopathologic study. J Indian Med Assoc, 1996;94: 405-9.
2. Cook BE Jr. and Bartley GB. Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted county, Minnesota. Ophthalmology, 1999; 106: 46-50.
3. Hughes MO. A Pictorial Anatomy of the Human Eye/Anophthalmic Socket: A Review for Ocularists. The Journal of Ophthalmic Prosthetics, 2004; 51-53.
4. Jakobiec FA, Bonanno PA and Sigelman J. Conjunctival adnexal cysts and dermoids. Arch Ophthalmol, 1978;96: 1404-1409.
5. Arora R, Rewari R and Betheri SM. Fine needle aspiration cytology of eyelid tumors. Acta cytol, 1990; 34(2): 227-32.
6. Dey P, Radhika S, Rajwanshi A, Ray R, Nijhawan R and Das A. Fine needle aspiration biopsy of orbital and eyelid lesions. Acta Cytol, 1993; 37: 903-7.
7. Brooks Christine, Scope, Alon, Braun, Ralph, P,Marghoob and Ashfaq A. Dermoscopy of nevi and melanoma in childhood. Expert Review of Dermatology, 2011; 6 (1): 19–34.
8. Mondal SK and Dutta TK. Cytohistological study of eyelid lesions and pitfalls in fine needle aspiration cytology. J Cytol, 2008; 25(4):133-7.
9. Baschinsky D, Hameed A, Keyhani-Rofagha S. Fine-needle aspiration cytological features of dermoid cyst of the parotid gland: a report of two cases.diagncytopathol, 1999; 20(6): 387-8.
10. Vemuganti GK and Rai NN. Neoplastic lesions of eyelids, eyeball and orbit. J Cytol, 2007; 24: 30-36.
11. Brown ST, Nalley JF, Kraus SJ. Molluscum contagiosum. Sex Transm Dis. Jul-Sep, 1981; 8(3), pp227-34.
12. Stulberg DL, Hutchinson AG.Molluscum contagiosum and warts. Am Fam Physician. 2003; 67(6): 1233-40
13. Pathak D and Neelaiah S. Disseminated cutaneous rhinosporidiosis: diagnosis by fine needle aspiration cytology. Acta Cytol, 2006; 50: 111-2.
14. Baron K, Curling OM, Paridaens AD and Hungerford JL. The role of cytology in the diagnosis of peri-ocular basal cell carcinomas.OphthalPlastReconstr Surg, 1996; 12: 190-4.
15. Saqi A, McGrath CM, Skovronsky D and Yu GH. Cytomorphologic features of fine-needle aspiration of metastatic and

recurrent melanoma.Diagn Cytopathol, 2002; 27: 286-290.
16. Pugh WC, Manning JT and Butller JJ. Paraimmunoblastic variant of small lymphocytic lymphoma/leukemia. Am J Surg Pathol, 1988; 12: 907-917.
17. Pombejara FN, Tulvatana W and Pungpapong K. Malignant tumors of the eye and ocular adnexa in Thailand: A six-year review at King Chulalongkorn Memorial Hospital. Asian Biomed, 2009; 3: 551-5.
18. Toshida H, Mamada N, Fujimaki T, Funaki T, Ebihara N, Murakami A andOkisaka S. Incidence of Benign and Malignant Eyelid Tumors in Japan, Int J Ophthalmic Patho, 2012; l1(2): 112-14.
19. Kerstern R, Ewing-Chow D, Kulwin DR. and Gallon M. Accuracy of clinical diagnosis of cutaneous eyelid lesions. Ophthalmology, 1997; 104: 479-484.
20. Margo CE and Waltz K. Basal cell carcinoma of the eyelid and periocular skin, Survey of ophthalmol, 1999; 38(2):169-192.