

Cytological Evaluation of Palpebral Lesions: An Insight into its Limitations Aided with Histopathological Corroboration

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Abstract

Context: Eyelids by virtue of its unique histomorphology give rise to multitudes of different pathological conditions. Appropriate preoperative cytological diagnoses of these cases are necessary to determine their optimal therapy. **Aims:** The aims of this study were to evaluate the utility of various cytological techniques in diagnosing the definite pathology for palpebral lesions and thereby to highlight the drawbacks associated with cytology in this context. **Materials and Methods:** Fine-needle cytology with or without applying the aspiration was the preferable method. Ulcerated lesions were sampled through scrapings. **Results:** Totally 62 cases were examined. Cytologically, 22 lesions were diagnosed as nonneoplastic, 38 lesions were neoplastic, and nondiagnostic material was obtained twice. Malignant tumors predominated among the neoplastic cases. Basal cell carcinoma (BCC) was the most common malignancy observed. On histopathological corroboration, benign skin adnexal tumor was found to be the most frequently misinterpreted entity. Two (out of four cases) of those tumors were confirmed as melanocytic nevus and BCC. A single case of squamous cell carcinoma was also cytodiagnostically erred into sebaceous carcinoma. **Conclusions:** Cytologically palpebral pathologies, including the neoplastic ones, are at times vulnerable to misinterpretation. To avert such dilemma, it is better to readily excise any recurrent lesion, basaloid neoplasm, or any necrohemorrhagic lesion presumptive of overshadowing the neoplastic pathology underneath.

Keywords: Basaloid cells, cytology, histopathology, limitations, palpebral lesions

INTRODUCTION

Structurally, the eyelids engross a complex histomorphology. At its core lies the dense fibroelastic tarsal plate, which is covered externally by redundant skin and internally by smooth conjunctival mucosa. The tarsal plate is impregnated with multiple meibomian-type modified sebaceous glands. Modified sweat glands of Moll and sebaceous glands of Zeis are associated with the eyelashes. Superficially, the tarsal plate is separated from the skin by the orbicularis oculi muscle and the levator palpebrae muscle only in the upper eyelid. The lacrimal glands in its superior palpebral location resemble serous-type salivary glands.^[1] Therefore, quite understandably, a whole diverse lot of pathological conditions infest the eyelids. It may be either infective or inflammatory lesions, cysts, congenital anomalies, local manifestations of some systemic metabolic derangements or any neoplastic

condition of surface epithelia, appendageal structures, lacrimal gland, or even the soft-tissue mesenchyme.^[2] The therapeutic alternatives range from conservative management, incision with curettage, simple enucleation, up to radical excision with or without radiotherapy, or cryotherapy.^[3] In general, surgical maneuver within the eyelids requires extra attention toward future cosmesis, afterward preservation of visual and ocular health, intraoperative accessibility, safety of vital structures, and specialized facilities for anesthesia or operating theatre.^[3-5] Hence, a pretherapeutic knowledge about the nature of palpebral pathology is essential to sequester the patients who really need surgery. Cytological material obtained in this purpose by fine-needle aspiration or nonaspiration technique, by exfoliation or imprint method yields the best

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results with optimum convenience.^[4-7] This latest study of ours was intended to assess the diagnostic utility of cytology for palpebral lesions and also to evaluate its limitations if any there.

MATERIALS AND METHODS

It was a 4-year-spanning prospective study accomplished during 2014–2017. Totally 62 patients underwent cytological evaluation of their palpebral lesions in the department of pathology, North Bengal Medical College and Hospital. Prior approval was obtained from the same Institutional Ethics Committee (Ethics Committee Pathology 2014, SI no. 07). After securing written informed consent from each participating patient the research proceedings were commenced in accordance with the guidelines laid down in Declaration of Helsinki, 2013. Supervision of an ophthalmologist was asked whenever required. The lesions were preferably sampled with fine-needle aspiration cytology (FNAC) while pulling them away from the globe as much as feasible. However, for the minute lesions and also those in close vicinity to the eyeball, nonaspiration fine-needle cytology (NAFNC) was exercised. In case of ulcerated lesions, materials were scraped from its surface through exfoliation. Cytological smears were routinely stained with Leishman–Giemsa and Papanicolaou stains. All the neoplastic and nondiagnostic lesions were excised. The recurrent nonneoplastic lesions and the cysts that persisted after initial aspiration were operated. Histopathological specimens were processed for conventional staining with hematoxylin and eosin. A simple sensitivity and specificity analysis of overall cytotechniques in separating benign lesions from the malignant ones was done using the XLSTAT add-on statistical software available in Microsoft Excel 2016 for Windows 10.

RESULTS

During the current study, totally 10 children, 9 adolescents, and 43 adults were examined from the age group of 1½ years to 72 years. Males (44 patients) became the dominant cohort. On cytology, malignancy was detected in 25 cases (40.3%). Thirteen (20.9%) lesions were cytologically categorized as benign neoplasms, and 22 cases (35.5%) were recognized as either cystic or inflammatory lesions. Two tiny nodules yielded paucicellular blood-rich aspirates and remained undiagnosed on cytology. These were identified as lipoma and fibroepithelial polyp on histopathology. Besides also, singular lesions of dermoid cyst, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) were miscued as epidermal cyst, benign skin adnexal tumor, and sebaceous carcinoma, respectively. Therefore, in this present study, the sensitivity of cytological methods in diagnosing malignant palpebral lesions remained 96.2%, and the specificity was 100%. The detailed cytological and histological diagnoses of all examined cases are summated in Table 1.

Totally 36 lesions were sampled with FNAC. Out of there, 29 pathological lesions underwent biopsy, followed by histopathological examination. On FNAC, none of the benign pathological lesions were misinterpreted as malignancy and *vice versa*. Hence, the sensitivity and specificity of FNAC in the

current study were 100%. Exfoliative cytological preparation was made with the scrapings from the ulcerated surface of five eyelid patches. All of these lesions were diagnosed as BCC both on the smears and on the histopathology, thereby the scrapings also had a high sensitivity and specificity value at 100%. During the present study, 21 palpebral nodules had to be sampled with NAFNC, 17 of which were excised for histopathological examination. Although the specificity of NAFNC came out as 100%, its sensitivity turned out to be low at 91%.

Cytologically both the epidermal and dermoid cysts consisted of numerous anucleated squames. In addition, there were presence of hair shaft fragments, sebaceous cells, and many admixed oil droplets within the dermoid cysts [Figure 1a and b]. Other benign cystic lesions generally appeared paucicellular, with few epithelial sheets and occasional macrophages on a serous or mucoid background [Figure 1c].

Smears from the granulomatous lesions showed syncytial histiocytic aggregates, foamy macrophages, occasional multinucleate giant cells, and varying proportions of polymorphonuclear and lymphoplasmacytic inflammatory infiltrates over the dirty background containing lipid debris. Two of these lesions were excised, which were diagnosed as chalazion. Histopathology revealed foci of chronic granulomatous inflammation surrounding empty lipid spaces [Figure 2a]. A 38-year-old woman suffering from chronic xerostomia and xerophthalmia presented with bilateral mechanical ptosis caused by multinodular firm swellings in the upper eyelids. Identical nodules were also palpable at bilateral submandibular regions. FNAC diagnosed these masses as chronic dacryoadenitis and chronic sialadenitis, respectively. The smears were comprised by regenerating population of many lymphoid cells with few sheets of ductal epithelial

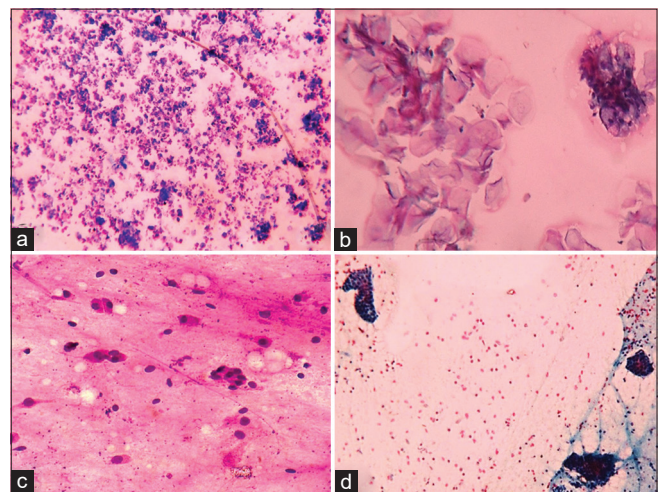


Figure 1: Cytologically, dermoid cysts expressing (a) hair shaft (LG, ×40) and (b) sebaceous cell cluster (Pap, ×400); (c) Small columnar epithelial cells within mucoid background of mucus retention cyst (LG, ×400); (d) Ductal sheets and scattered lymphocytes represent chronic dacryoadenitis (Pap stain, ×100)

Table 1: Cytological and histopathological distribution of all palpebral lesions (n=62)

Diagnostic categories		Cytological diagnosis/findings	Number of cases	Sampling method (number of lesions)	Cases correlated on histopathology	Histopathological diagnosis	
Nonneoplastic	Cysts (totally 14 lesions)	Dermoid cyst	5	FNAC	4	Dermoid cyst	
		Epidermal cyst	4	FNAC	4	3 epidermal cysts, 1 case of dermoid cyst	
		Benign cyst	4	FNAC	1	Mucus retention cyst	
		Inflamed epidermal cyst	1	FNAC		Not done	
	Inflammatory (totally 8 lesions)	Granulomatous inflammation	4	FNAC (2) NAFNC (2)	2	Chalazion	
		Chronic nonspecific inflammation	2	NAFNC		Not done	
		Suppurative lesion	1	NAFNC		Not done	
		Bilateral chronic dacryoadenitis	1	FNAC		Not done	
Neoplastic	Benign (totally 13 lesions)	Benign skin adnexal tumor	4	FNAC (2) NAFNC (2)	4	1 each of trichilemmoma, syringoma, melanocytic nevus, and BCC	
		Benign keratinocytic tumor	3	FNAC (1) NAFNC (2)	3	Benign squamous papilloma	
		Pleomorphic adenoma	3	FNAC	3	Pleomorphic adenoma	
		Vascular lesion	3	FNAC	3	Hemangioma	
		Malignant (totally 25 lesions)	BCC	9	FNAC (1) NAFNC (3) Scraping (5)	9	BCC
			Sebaceous carcinoma	8	FNAC (3) NAFNC (5)	8	7 sebaceous carcinomas, 1 case of SCC
	SCC		4	FNAC	4	SCC	
	ACC		2	FNAC	2	ACC	
	ERMS		1	NAFNC	1	ERMS	
	Nondiagnostic (totally 2 lesions)	Melanoma	1	NAFNC	1	Malignant melanoma	
		Paucicellular smears, scattered adipocytes, blood components	1	NAFNC	1	Lipoma	
Paucicellular aspirates, blood elements, spindle cells, short stromal fragments		1	NAFNC	1	Fibroepithelial polyp		

FNAC: Fine-needle aspiration cytology, NAFNC: Nonaspiration fine-needle cytology, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, ACC: Adenoid cystic carcinoma, ERMS: Embryonal rhabdomyosarcoma

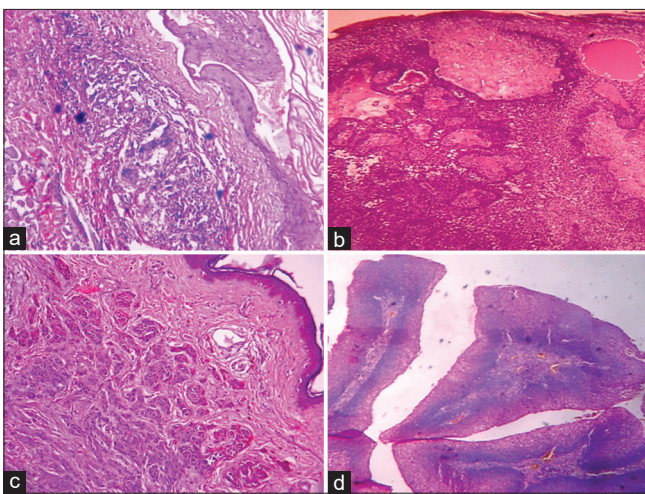


Figure 2: Histopathologically, (a) clear lipid spaces surrounded by giant cells and inflammation characterize the chalazion (H and E, $\times 100$); (b) lobules of uniform clear-to-basaloid epithelial cells descend from surface epidermis in trichilemmoma (H and E, $\times 100$); (c) melanocytic nevus with sporadic presence of melanin granulation (H and E, $\times 100$); (d) benign squamous papilloma (H and E, $\times 40$)

cells [Figure 1d]. Further investigation confirmed the patient to be suffering from Sjogren syndrome.

Four palpebral nodules were cytologically categorized as benign skin adnexal tumors. The smears thereof featured tightly cohesive sheets and clusters of uniform small basaloid cells bearing scanty indistinct cytoplasm and indiscernible nucleoli. Stromal substances were present occasionally [Figure 3a]. Histomorphologically, these tumors were confirmed as trichilemmoma, syringoma, melanocytic nevus, and BCC [Figure 2b and c]. This BCC occurred in a nonulcerative nodular form. It was sampled by NAFNC, showed moderate cellularity, and lacked the signature peripheral nuclear palisading. Aspirates from the benign keratinocytic tumors expressed predominantly superficial-type mature squamous cells with few anucleated squames in clumps and dispersal [Figure 3b]. On biopsy examination, these were proved as squamous papillomas [Figure 2d]. Pleomorphic adenomas of the lacrimal glands resembled their salivary counterparts. The highly cellular smears consisted of plasmacytoid myoepithelial cells in singles and clusters within

the background of ample fibrillary chondromyxoid ground substances [Figure 3c]. Vascular lesions emitted copious amount of blood components with occasional aggregates of spindly endothelial cells. Color Doppler and then the histopathology corroborated these lesions as hemangioma.

BCCs were cytomorphologically characterized by tightly cohesive, overlapping aggregates of small basaloid cells, which bore hyperchromatic ovoid nuclei, indistinct nucleoli, and scanty ill-defined cytoplasm. The basaloid nuclei often produced a palisaded arrangement at the edge of cell groups [Figure 3d]. Smears from the SCCs were characterized by the presence of large clusters and isolated population of keratinized and nonkeratinized tumor cells. Their nuclei varied from coarsely granular hyperchromatic, enlarged to pyknotic spindly in shape. The cytoplasm remained glassy dense and sometimes orangeophilic. Background contained necroinflammatory debris and keratin flakes. Cellularities were very high within the aspirates from sebaceous carcinomas. Grossly atypical neoplastic cells appeared in three-dimensional clusters and singles. They contained large pleomorphic nuclei, with uneven coarse chromatin, prominent nucleoli, and abundant vacuolated foamy cytoplasm [Figure 4a]. FNAC from the adenoid cystic carcinomas also yielded high cellularity. The uniform hyperchromatic basaloid tumor cells appeared in singles, compact fragments, and also adherent to hyaline globules or strands of varying size [Figure 4b]. Cytologically, the embryonal rhabdomyosarcoma showed the characteristic presence of well-differentiated rhabdomyoblasts in dispersal. These tumor cells possessed eccentrically placed 1–2 rounded nuclei and abundant dense inclusion-like cytoplasm. Undifferentiated small round tumor cells were present though in fewer numbers [Figure 4c]. The only case of melanoma also produced hypercellular aspirates. The tumor cells were mostly isolated singly, contained eccentric round-shaped

nuclei with marked anisonucleosis, uniform hyperchromasia, and prominent macronucleoli. Melanin pigmentation was noticeable both intracellularly and extracellularly. Binucleation, multinucleation, and intranuclear inclusions were also frequent [Figure 4d].

DISCUSSION

Eyelids give rise to a widespread variety of lesions, which one can experience anywhere from head to toe. Even the tiniest of these lesions cause appreciable facial imperfection. Therefore, patients suffering from palpebral swellings present early for the diagnostic interventions.^[8] Cytological techniques not just infer into their primary diagnosis, but simultaneously it also segregates those lesions which could be preferably managed through conservative therapy. The inflammatory/infective lesions and nonoperable/lymphoid tumors fall into this category.^[9] In this subject, FNAC carries certain possible drawbacks related to globe perforation and hemorrhage. Hence, the alternate cytological methods by scraping, NAFNC, squash, or imprint preparations are also very much useful.^[8] Recently, the precision of cytology in differentiating benign palpebral lesions from the malignant ones has been documented as 87%–100%.^[10] Quite comparably, in this current study, the sensitivity and specificity of overall cytological techniques were 96.2% and 100%, respectively. When compared individualistically, both the FNAC and scraping methods earned a perfect sensitivity and specificity value at 100% each. However, the NAFNC technique had a bit lower sensitivity of 91%.

Two (3.2%) benign tumors in this present study could not be diagnosed because of inadequate samples. This result is at par with prior observations in which around 2.85%–27.4%

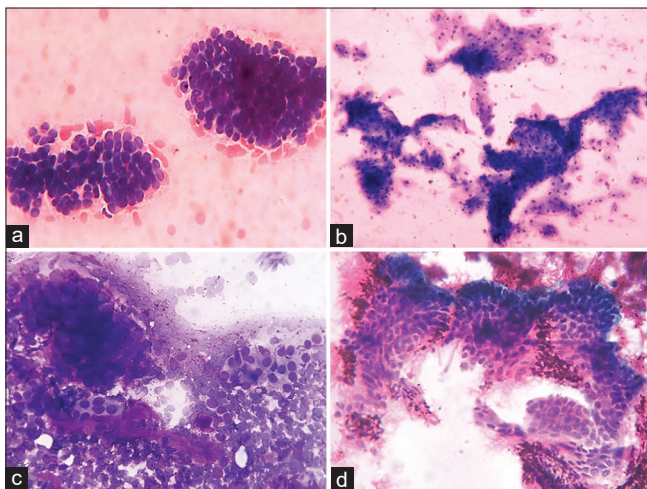


Figure 3: Representative cytology of (a) benign skin adnexal tumors (Pap, ×400); (b) benign keratinocytic tumor (LG, ×100); (c) pleomorphic adenoma characterized by plasmacytoid myoepithelial cells and chondromyxoid stroma (LG, ×400); (d) basal cell carcinoma imparting palisaded arrangement of tumor cells at the edge of clusters (Pap, ×400)

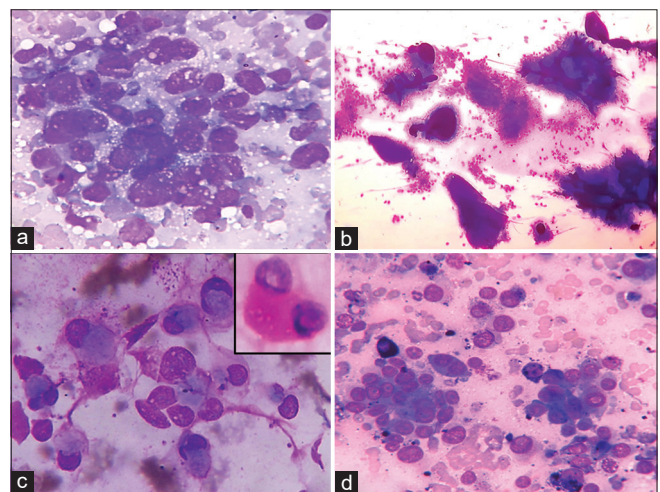


Figure 4: Cytologically, (a) syncytial clusters of pleomorphic tumor cells with vacuolated foamy cytoplasm in sebaceous carcinoma (LG, ×400); (b) beads and globules of hyaline material mantled by basaloid cells indicative of adenoid cystic carcinomas (LG, ×100); (c) characteristic rhabdomyoblasts of embryonal rhabdomyosarcoma (LG, ×400), with occasional binucleated forms (inset: Pap, ×400); (d) melanoma cells bearing macronucleoli, intranuclear inclusions, binucleation, also heavy intra- and extracellular pigment deposition (LG, ×400)

aspirates were unsatisfactory. Cellular inadequacy on the smears mostly occurs with fibrotic lesions.^[5,9] Akpe *et al.*^[11] histopathologically diagnosed one each case of fibroma and fibroepithelial polyp during their study on palpebral lesions. However, both tumors were initially aspirated unsatisfactorily. In the same way, inadequate aspirates bemused Khan and her associates in two respective cases of inflammatory pseudotumor and angiofibroma.^[5] Other less common factors associated with insufficient cytodagnostic material include lack of expertise in the operating cytopathologist, minute size or an aberrantly insecure location of the lesion, and intralesional high vascularity.^[5,9] Any vascular pathology like hemangioma or vascular malformation is difficult to diagnose accurately on cytology for its extensive hemorrhagic contents. Clinicroadiological correlation is required for their distinction.^[4,5,12] Identically, the three hemangiomas described presently could only be depicted as vascular lesions on cytology. Then, radiology and subsequent histology confirmed their definite pathology. Sometimes, malignant tumors such as SCCs also carry high intratumoral vascularity. Cytologically, such masses are hard to interpret as cancers due to the obliteration caused by blood elements. Successive sampling from alternative zones generally fixes the issue.^[13]

Imprint cytology and scrape cytology are two useful preparations for ulcerative eyelid malignancies. However, the diagnosis of SCC often poses troublesome there. Excessive keratin, necrosis, or inflammatory exudate from its surface frequently overshadows the dysplastic cells.^[12,14] Out of same adversity Kane^[15] also missed 2 out of 11 SCCs, which she examined on exfoliative cytology. However, the outcome with imprint cytology is furthermore catastrophic. Sen *et al.*^[16] processed imprint smears from 32 established cases of malignant eyelid tumors. However, in only 9 tumors, they succeeded in rendering a definite diagnosis. During the current study, imprint methods were never practiced anyway. Though with the scrapings, such complication also did not arise at all.

Sebaceous carcinoma and poorly differentiated SCC are often interchangeably misdiagnosed into each other on palpebral cytology. It happens mainly with scanty aspirated material and also due to their overlapping cytomorphology.^[10] Cellular pleomorphism, cytoplasmic abundance, and background necrosis are present in both conditions. In addition, the presence of nonspecific cytoplasmic vacuolization and the absence of cytoplasmic orangeophilia in a poorly differentiated SCC mislead it into a sebaceous carcinoma, whereas in the sebaceous carcinoma, the lack of typical sebaceous differentiation, as well as the coexistent basaloid or squamous cells, complicates its definite categorization. Even the small biopsy specimens from sebaceous carcinomas are also misinterpreted at times. Such dilemma has been reported to happen in about 50%–77.5% of cases. Histological examination of *en masse* resected specimen, often with additional application of fat stains, is required for its proper recognition.^[10,17,18] During the discussed study, none of the sebaceous carcinomas were missed on cytology. However, out of the same adversities described above, one of

the poorly differentiated SCCs was though cytopathologically misinterpreted as sebaceous carcinoma.

Basaloid tumors of cutaneous origin are often difficult to categorize appropriately on cytology. This problem arises especially when the tumor is minute in size, its classic clinical appearance is absent and the material aspirated is scarce in amount. Even the malignant adnexal tumors are sometimes mistaken for benign.^[19,20] Actually, on cytological smears, the difference between benign and malignant skin adnexal tumors is subtle. The small basaloid epithelial cells and their arrangement are similar everywhere. However, there are often accompanying squamoid cells, keratinized squames, glandular formations, and stromal hyaline material, which, in turn, favor the benign tumors.^[21] Similarly, in our present study, one of the BCCs was misinterpreted as benign skin adnexal tumor, as there was a lack of its characteristic cytomorphology. Previously, Mondal and Dutta^[13] and Kusumastuti and Rahniayu^[22] also faced the same problems. Sometimes, such a dilemma hardly resolves even on histopathology and therefore requires immunohistochemical staining as well.^[23]

Melanocytic nevus is another condition frequently erred into tumors of epidermal or appendageal origin. Cytologically, the nevus cells form aggregates. They mostly appear epithelioid in shape with ample well-defined cytoplasm. Small monomorphous rounded or spindly melanocytes appear in few numbers. Intracytoplasmic melanin granules are variable. If the pigment granules are not demonstrable at all, the cytodagnosis of a nevus is easily missed.^[13,24] Earlier, in their respective studies, Akpe *et al.*^[11] and Mondal and Dutta^[13] biopsied two melanocytic nevi, respectively. However, out of the same malign one, each of them was misdiagnosed during preoperative cytological examination. In this present study also, the lone case of melanocytic nevus was misdiagnosed as benign skin adnexal tumor.

It is so difficult to diagnose the benign epidermal tumors of palpebral location definitively on mere clinical and cytological examination. Squamous papilloma is most common of such lesions, followed by seborrheic keratosis, other forms of keratoses, acanthomas, and pseudoepitheliomatous hyperplasia.^[6,25] Regardless of the cytotechnique applied, all these lesions yield a variable amount of keratinized and mature squames in general. Therefore, cytopathologists frequently fail to impose their definite diagnosis.^[11,13] During the discussed study, a general terminology was used in conformity with the World Health Organization-recommended histopathological classification of skin tumors. Accordingly, both the squamous papillomas were cytologically interpreted as benign keratinocytic tumors.^[26]

Chalazion is a common lipogranulomatous inflammatory lesion of the eyelids. It results from the obstruction of meibomian gland ducts.^[27] On the smears, it mimics any other granulomatous pathology. Hence, a presumptuous cytological interpretation of chalazion carries a significant risk of false diagnosis.^[13] Majority lesions are cured after primary

incision and curettage. Only the recurrent chalazions need surgical enucleation.^[8] In the present research work, similar lesions on cytology were simply reported as “granulomatous inflammation.” Two recurrent lesions were excised, which expressed characteristic histomorphology of the chalazion. Cutaneous cysts of epidermal origin are barely discriminable through their cytomorphology. However, on eyelids, their differential possibilities come down to epidermal and dermoid cysts only.^[6,7] Their clinical presentation, location, and consistency of the aspirates become helpful. Like the existence since birth, fixation to underlying skull bone, yellowish greasy aspirates, and presence of hair shafts or mature sebaceous cells are indicative of dermoid cysts.^[28] In the current study, the cutaneous cysts were identically imposed with definite cytological diagnoses. Cytohistological corroboration was achieved in 7 of those cysts, except one dermoid cyst that was cytologically misrecognized as an epidermal cyst.

CONCLUSIONS

Despite the proven efficacy of cytological methods in determining the nature and management protocol for various pathological lesions on eyelids, still sometimes, cumbersome situation arises on account of spurious necrohemorrhagic contamination and scanty or nonrepresentative diagnostic material due to small size or vulnerable location of the lesion. This may lead to the underdiagnosis of any underlying malignant neoplasm as well. Therefore, to end up on a safe side, any recurrent lesion, the basaloid tumors, and the suspected neoplastic lesions expressing necrohemorrhagic aspirates should better be treated *prima facie* by excision.

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Conflicts of interest

There are no conflicts of interest.

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