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Cytological Diagnosis of Pilomatrixoma and its Diagnostic Pitfalls

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Abstract

Background:

Pilomatrixoma (PMX) is a relatively uncommon benign cutaneous neoplasm arising from skin adnexa. It presents as a subcutaneous asymptomatic nodule mostly in the head and neck region and is frequently misdiagnosed by the clinicians. Although easily diagnosed on histopathology, the cytologic features of PMX are less distinctive, depending on the stage and evolution of disease and may mimic other benign or even malignant lesions.

Aim:

To study the cyto-morphological features of this uncommon neoplasm and identify its potential diagnostic pitfalls on fine needle aspiration cytology (FNAC).

Material and Methods:

Archival records of histopathologically diagnosed Pilomatrixoma were analyzed during study period of 2.5 years. Clinical diagnosis, preoperative FNA characteristics, and histopathological details were studied in each case. Cytologic pitfalls resulting in misdiagnosis of PMX cases on FNAC were evaluated in discordant cases.

Results:

The series showed male preponderance, with head and neck being the commonest site. Out of 21 histopathologically proven cases of PMX, cytological correlation was available in 18 cases. A correct cytologic diagnosis of PMX/adnexal tumor was rendered in 13 cases. Erroneous diagnosis was given in 5 cases mainly because of the predominance of one component over the other or non-representative-aspirated material.

Conclusion:

The present study highlights the importance of careful screening of FNAC smears keeping in mind the variability in the relevant cytologic features of PMX and creates awareness about the lesions that can mimic Pilomatrixoma resulting in diagnostic dilemma.

Keywords: Adnexal tumor, FNAC, pilomatrixoma

Introduction

Pilomatrixoma (PMX) is a benign tumor with differentiation toward the hair matrix cells and is common in head and neck region. First described by Malherbe and Chenantais in 1880 as a benign neoplasm of sebaceous gland origin, it is also known as Calcifying Epithelioma of Malherbe.[1] It is most commonly seen in the first two decades of life, accounting for 20% of pilar tumors. It presents as a solitary, slow growing dermal, or subcutaneous nodule and is rarely diagnosed clinically.[2]

Fine-needle aspiration cytology (FNAC) has been described as an important preoperative diagnostic investigation, though on cytology PMX is difficult to diagnose often resulting in erroneous diagnosis. Despite the characteristic and well recognized histopathological features, the cytological diagnosis of this entity remains problematic with misdiagnosis and false positive diagnosis.[3]

Misinterpretation of the fine needle aspiration cytology (FNAC) diagnosis has been attributed to various factors which include non-representative smears, predominance of one cellular component over the others in a slide and the relative inexperience or lack of awareness of the reporting pathologist regarding these comparatively rarer lesions encountered on cytology. However, limited literature is available on the cytological features of PMX and its diagnostic pitfalls.[4,5]

With this background in mind, this study was planned to characterize the cytological features, evaluate the cytologic histological concordance in PMX, and to highlight the differential diagnosis of these lesions on cytology. Cytopathologists play an important role in the preliminary diagnosis, and therefore, should keep in mind the cytologic differential diagnosis of these types of lesions to avoid misdiagnosis.

Materials and Methods

This study was conducted in the Department of Pathology, Hamdard Institute of Medical Sciences and Research, New Delhi. Archival records of 2.5 years period with respect to clinical findings, FNAC and histopathology of PMX cases were evaluated. During the study period, there were a total of 21 cases of histopathologically confirmed PMX. Histopathology forms were retrieved to access the clinical and histomorphological data of each case. These cases were then investigated for available cytology. FNAC records were available in 18 out of these 21 cases of PMX prior to the surgical resection. Cytology slides were re-evaluated and the cyto-morphological features of each case were characterized. Special emphasis was given to the cases in which cytology and histopathology was discordant.

A detailed analysis of the cytology smears was done for the presence of following type of cells.

1. Basaloid cells: tight clusters or singly occurring small cells having a high nuclear-cytoplasmic ratio, round to oval nuclei with smooth nuclear borders, finely dispersed to slightly granular chromatin, and conspicuous to prominent nucleoli and scant cytoplasm.
2. Shadow cells (ghost cells/anucleate squamous): non-nucleated keratinized squamous cells with distinct cell borders and central pale nuclear zone, present singly, or in clumps.
3. Keratinized squamous cells.
4. Multinucleated foreign body type of giant cells.
5. Chronic inflammatory cells and amorphous debris.

A retrospective review and categorization of the above components was done in all the cases by carefully reexamining the FNAC smears and histological sections. The cytological features for each case were recorded and the final impression was compared with the histopathological diagnosis. Histopathological diagnosis was considered as the definitive diagnosis. This comparative methodology highlighted the features that were missed on cytological smears.

Results

In our study, there were a total of 21 cases of histopathologically diagnosed PMX, out of which 18 had undergone preoperative FNAC. Among these 18 cases, there were 14 males and 4 females; the mean age was 32.7 years with age range of 8-62 years. Size of the lesion varied from 0.9 to 5 cm (mean = 1.6 cm). Six (33.4%) lesions were located in the head and neck region, five (27.8%) on the back, and scalp each and two (11%) on the arm. Preoperatively, in all the 18 cases of PMX in which cyto-histological correlation was available, clinical impression was varied ranging from sebaceous cyst to soft tissue tumors and even metastatic lymph node [Table 1].

In our series, a correct cytological diagnosis of PMX was possible in 13 cases while 5 were misdiagnosed on FNAC. Details of the cytological and histopathological features in 18 cases of PMX is shown [Table 2]. Unfortunately, not all the morphological aspects of the cytological picture of PMX were disclosed in smears.

Histopathologically, all the cases had distinctive population of basaloid epithelial cells and shadow cells in varying proportions. Basaloid cells had round to oval hyperchromatic nuclei and scanty cytoplasm. Shadow cells had eosinophilic cytoplasm and a central unstained zone, corresponding to the site previously occupied by nucleus. Areas revealing apparent evolution of basaloid cells into shadow cells were also noticed [Figure 1]. In addition to the characteristic epithelial component, in some cases the tumor stroma showed variable degree of granulomatous reaction with keratin debris, foreign body giant cells, calcium deposits, and inflammatory cells with no areas of ossification seen in any case.

A confident first hand diagnosis of PMX/adnexal tumor possibly PMX, on FNAC smears was possible in 13 cases as they exhibited diverse cell types including basaloid, squamous, shadow, and foreign body giant cells, although the proportion varied from case to case. On review, basaloid cells were seen lying singly or in sheets. They were mostly round with scant cytoplasm and indistinct cell borders. Ghost cells having abundant cytoplasm with distinct cell borders and central unstained area were seen in clusters [Figure 2].

In five cases, erroneous diagnosis was rendered on FNAC which included keratinous cyst (2 cases), lipoma (1 case), granulomatous lesion (1 case), and atypical epithelial cells (1 case). In these erroneous cases (case no. 14-18), gradation was done and reasons for misdiagnosis were reviewed [Table 3]. These were mostly due to predominance of one component over the other and also non-representative material.

In case no. 14 and 15, there was predominance of anucleated squamous cells in the absence of basaloid cells which led to a mistaken diagnosis of keratinous cyst. Even careful review of the smears did not reveal graded findings to render a diagnosis of PMX, but on histopathological examination it showed an abundance of basaloid cells, areas of calcification with very few areas of shadow cells. Non-representative material was the reason for erroneous diagnosis of keratinous cyst in these cases.

Aspiration was performed twice in case no. 16 in which cytological diagnosis was lipoma. There was a boggy sensation on needling the swelling from the back. Even on review of the smears, only occasional fibrofatty fragments were found with the absence of basaloid cells and shadow cells [Figure 3a]. However, scant occasional anucleated squamous were seen which were considered to be a contaminant on initial diagnosis. Histological sections revealed mainly large areas of calcification in addition to the basaloid cells, shadow cells, and foreign body giant cells. The presence of calcification could be the possible reason for poor yield on FNAC smears.

Aspiration in case no. 17 yielded fluid mixed aspirate. The smear showed macrophages and inflammatory cells, multinucleated giant cells, histocytes, and lymphocytes [Figure 3b-d]. Cytological diagnosis of granulomatous lesion was made. On reexamination of the FNAC smears, few areas showing singly lying and groups of keratinized squamous epithelial cells were seen almost obscured by the inflammation, which were missed initially. Histological section revealed ruptured cystic areas lined by collections of macrophages, giant cells, and inflammatory cells and in the periphery abundance of basaloid cells with few shadow cells.

Case no. 18 was earlier categorized as atypical epithelial cells on the basis of predominance of few aggregates of epithelial cells with round to irregular hyperchromatic nuclei. Careful re-evaluation of smears showed occasional shadow cells with predominance of aggregates of darkly stained hyperchromatic basaloid cells which were misinterpreted as atypical cells [Figure 4]. Specific diagnosis of PMX was possible on review of the FNAC smears. Moreover, report was biased in favor of atypical cells diagnosis as the clinical diagnosis in this case was of metastatic lymph node and the patient was a 62 year old male. On histopathological examination, the lesion showed abundance of basaloid cells and scant shadow cells and the final diagnosis of PMX was rendered.

Discussion

Pilomatrixoma is a relatively infrequent tumor, with a highly variable incidence. Malherbe and Chenantais coined the term Calcifying Epithelioma of Malherbe describing its origin as sebaceous glands. However in 1961, Forbis and Helwig gave the term PMX describing its cell of origin and Arnold coined the term pilomatricoma.[6,7] PMX is a benign cutaneous adnexal tumor having differentiation toward the hair follicle matrix. Head-neck region is the most common affected region followed by upper limbs, chest, and the lower extremities.[8]

While pilomatrixoma can develop at any age, two maximum frequency peaks have been identified: one in the pediatric age range and the other in the sixth decade of life.[9] In our study, the lesion was noted in the age group ranging from 8-62 years with the mean age of presentation being 32.7 years which is in concordance with other investigators.[5,6,7,8] With regard to the gender distribution of these tumors, we recorded a slight male predilection, unlike other authors who reported a predominance among females.[10,11] The most frequent locations were the head and neck region, in agreement with other case series.[12,13,14] The other locations in decreasing order of frequency were the upper limbs, legs, and trunk.

The diagnosis of pilomatrixoma is mainly clinical, though it needs to be differentiated from other lesions such as dermal and subcutaneous masses (sebaceous cysts, epidermoid cysts, basal cell epitheliomas, and neurofibromas), calcified lesions (calcified epidermoid cyst, foreign body reactions or calcified hematomas) and in the specific case of preauricular lesions, and primary and secondary parotid gland tumor pathology.[15] In the literature, some 60 cases of malignant transformation in PMX have been documented to date. In our series, no malignant variants were diagnosed. Distant metastases are rare, with only 6 cases described till date in the literature.[16]

Excisional biopsy is the preferred method of diagnosis for majority of cutaneous nodules. However, FNAC is being increasingly used preoperatively due to its ease of performance and rapid diagnosis. The histological features of pilomatrixoma are well recognized, but cytological recognition poses a problem. Studies in the literature reveal a relative scarcity of FNAC exposure in cases of pilomatrixoma, which could be a cause for misdiagnosis.[17] In our study, on cytology, case no. 1-13 were correctly diagnosed as pilomatrixoma corroborating with the histopathology. The most consistent finding was the presence of shadow cells, basaloid cells, and giant cells, which was further supported by the presence of calcification and nucleated squamous cells in variable proportions. However, other features like inflammatory cells and background debris were not present in majority of the cases.

There was erroneous diagnosis in case no. 14-18, because the pathognomic components were not present in every case. Secondly, the predominance of one component over the other in the smears led to the misinterpretation. A review of the literature revealed several cases of pilomatrixoma misinterpreted as trichilemmal cyst, epidermal inclusion cyst, granulomatous lesions, squamous and basal cell carcinoma, lymphomas, small round blue cell tumor, salivary gland, and other appendageal tumors.[18,19,20]

We observed that the smears were most commonly misinterpreted as benign lesions. Dominance of anucleate squamous cells, inflammatory cells, multinucleated giant cells, and absence of basaloid cells led to a misdiagnosis of keratinous cyst in case no. 14 and 15. Keratinous cyst consists of well delineated anucleated squamous cells occurring singly or in clumps. Basaloid cells and calcification are rarely seen. However, a ruptured cyst with presence of inflammation and foreign body giant cells can be confused with pilomatrixoma.[21]

The cytological diagnosis in case no. 16 was lipoma. Even after repeated aspirations from back swelling, the smears showed scant fibrofatty fragments. On review scattered anucleated squamous were also seen in the smears and were considered as a contaminant at initial diagnosis.

The cytological diagnosis in case no. 17 was granulomatous inflammation. The smears were composed of few multinucleate giant cells, histiocytes, and lymphocytes. Multinucleate giant cells and histiocytes in dermal aspirates may be observed in conditions like panniculitis, tuberculosis, and infectious and noninfectious granulomatous conditions. The presence of multinucleate giant cells should be evaluated in the context of accompanying cells. In pilomatrixoma these cells correspond to a foreign body giant cell reaction adjacent to shadow cells. Despite the abundance of shadow cells in histological sections, they might not be present in the cytological smears due to difficulty in detaching these cells during aspiration.

The most dangerous mistake in FNA diagnosis of pilomatrixoma is with regard to a diagnosis of neoplastic lesion. In our study, there was one false positive case [Case no. 18]. A cytological diagnosis of metastatic carcinoma was made which was supported by clinical suspicion of malignancy in an elderly patient with history of neck swelling. Studies show that pilomatrixoma has been very often misdiagnosed as primary malignant or metastatic lesions.[22,23] The differentiation from metastatic deposits may not be easy, especially in neck swelling in cases which are predominantly composed of basaloid cells and devoid of other diagnostic features of PMX on FNAC, leading to a false diagnosis of malignancy.[22]

The diagnostic accuracy of FNAC for pilomatrixoma in our study was found to be 72% which was much more than Ieni *et al*.[21] who gave it as 44%. This could be due to awareness of the lesion and its cytology among our reporting pathologists. In 5 discordant cases even on review of slides later, it was not possible to give a conclusive diagnosis due to non-representative material or predominance of one component over another. However, on review of the literature, it was found that there is relative scarcity of FNAC material which could be one of the reasons that pure adnexal tumors are underreported or misdiagnosed very often by the cytopathologists.[24]

There are very few studies on Pilomatrixoma available in the literature, mostly limited to single case reports. A study conducted in 2003 reviews an 11-year experience at a tertiary children's hospital, examining the cause, clinical and histopathological presentation, management, and treatment outcomes of 346 cases of pilomatrixoma.[25] In another study, clinical and pathologic features of 51 cases of pilomatrixoma found in archives from 1990-1999 were reviewed, with emphasis on the cytopathologic features of the 22 cases.[26] In an Indian study by Kumar *et al*,[27] 15 cases with initial cytodiagnosis of pilomatrixoma or benign skin appendage tumor were reviewed. Table 4 describes various studies on the cytological features of Pilomatrixoma till date.

Conclusions

This study highlights the importance of careful screening of FNAC smears and creates awareness about the lesions that can mimic Pilomatrixoma cytologically usually due to predominance of one component over another resulting in diagnostic dilemma. Knowledge of the complete spectrum of the cytological findings in PMX and a thorough search for these can help in achieving an accurate cytologic diagnosis. Cytopathologists play an important role in the preliminary diagnosis and should keep in mind the variability of the cellular composition seen in Pilomatrixoma to avoid misdiagnosis.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

Clinical profile of 18 cases of pilomatrixoma

[A] Age of the patients		
Age	**Male**	**Female**
0-10 years	1	-
11-20 years	5	2
21-30 years	2	2
31-40 years	3	-
41-50 years	1	-
51-60 years	1	-
61-70 years	1	-
[B] Site of the lesion		
Site	**Male**	**Female**
Arm	1	1
Scalp	4	1
Back	3	2
Head and Neck	6	-
[C] Clinical diagnosis		
Provisional diagnosis	**Males**	**Females**
Sebaceous cyst	4	3
Hemangioma	1	-
Reactive lymph node	1	-
Metastatic lymph node	1	-
Neurofibroma	3	1
Lipoma	1	-
Abscess	1	
Schwannoma	1	-
Salivary gland tumor	1	-

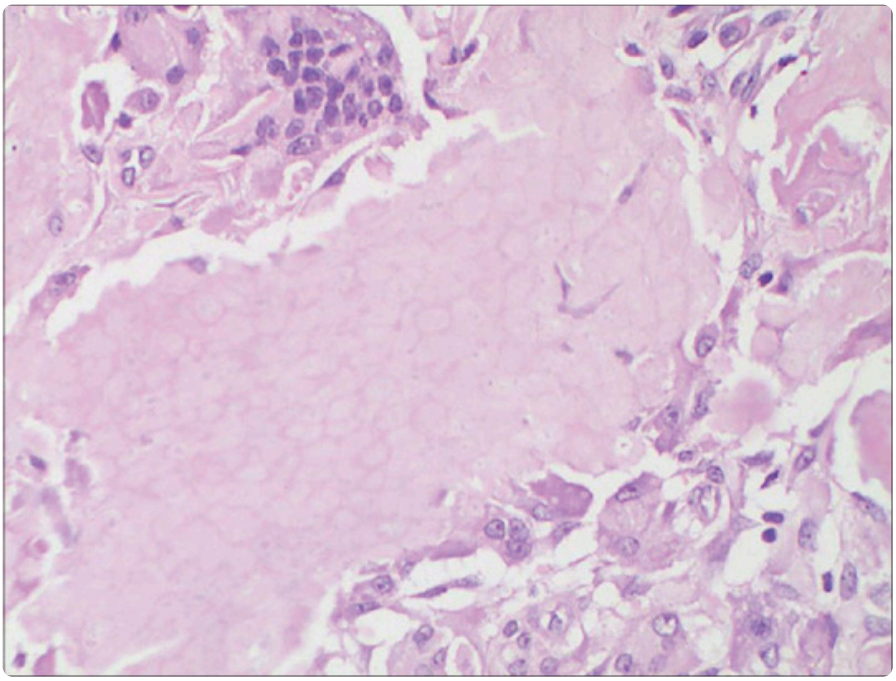
Table 2

Predominant cytological patterns in 18 cases of pilomatrixoma with histopathological correlation

Case No.	Predominant Cytologic patterns							Cytological Diagnosis	Histological Diagnosis
	BC	SC	NSC	MNGC	IC	Calci	AD		
1	++	+	+	-	-	-	-	PMX	PMX
2	+	++	+	+	-	+	-	PMX	PMX
3	++	-	+	+	-	-	-	PMX	PMX
4	++	+	-	+	-	-	-	PMX	PMX
5	++	+	-	+	-	-	-	PMX	PMX
6	+	+++	+	+	+	+	+	PMX	PMX
7	+	+++	+	+	+	+	+	PMX	PMX
8	+	+++	-	+	+	+	-	PMX	PMX
9	++	-	-	-	++	-	+	PMX	PMX
10	-	+++	-	+	-	-	+	PMX	PMX
11	++	+	+	-	-	-	+	PMX	PMX
12	++	+	+	+	-	-	-	PMX	PMX
13	++	+	-	-	+	-	-	PMX	PMX
14	-	-	++	-	++	-	-	Keratinous cyst	PMX
15	-	-	+	++	+	-	-	Keratinous cyst	PMX
16	Only fibrofatty fragments were seen(++)							Lipoma	PMX
17	-	-	-	+	++	-	-	Granulomatous inflammation	PMX
18	Cells with high nuclear – cytoplasmic ratio, hyperchromatic nuclei, moderate amount of ill-defined cytoplasm, debris, inflammatory cells							Atypical epithelial cells	PMX

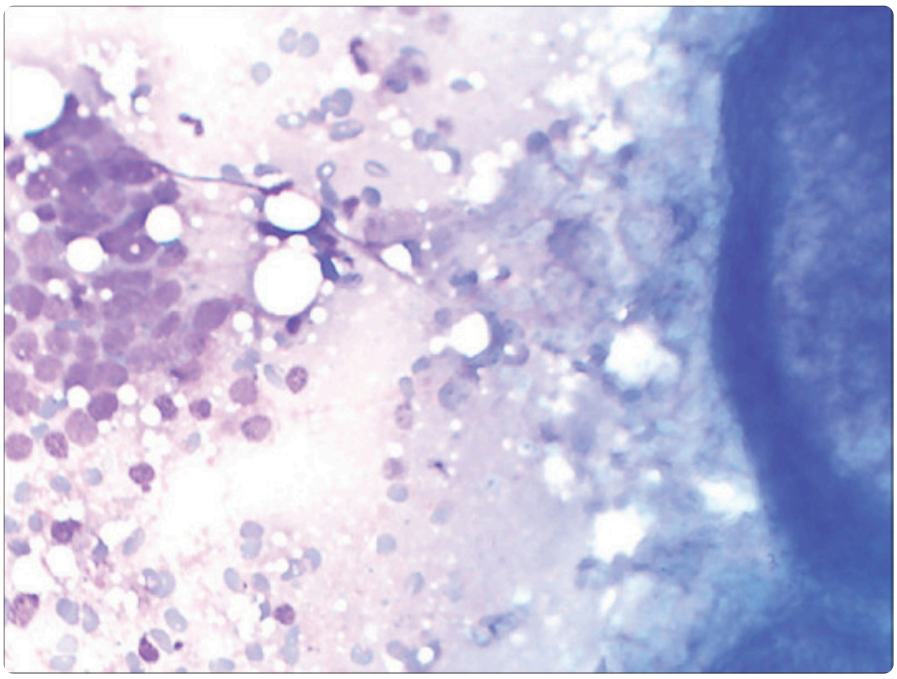
BC-Basaloid cells; SC- Shadow cells; NSC- Nucleated squamous cells; MNGC- Multinucleated giant cells; IC-Inflammatory cells; Calci- Calcification; AD- Amorphous/keratinous debris, PMX- Pilomatrixoma

Figure 1



Area revealing apparent evolution of basaloid cells into shadow cells (H&E,40X)

Figure 2



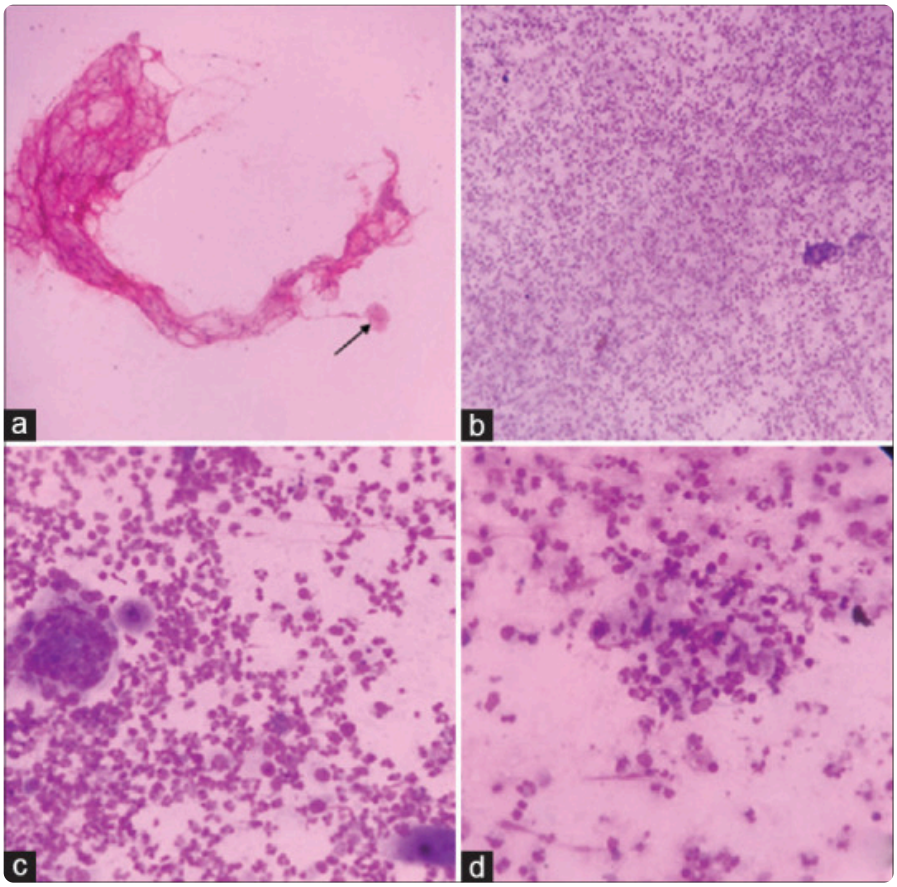
Cluster of ghost cells having abundant cytoplasm with distinct cell borders and central unstained area (Giemsa, 40X)

Table 3

Causes for misdiagnosis in 5 cases of pilomatrixoma

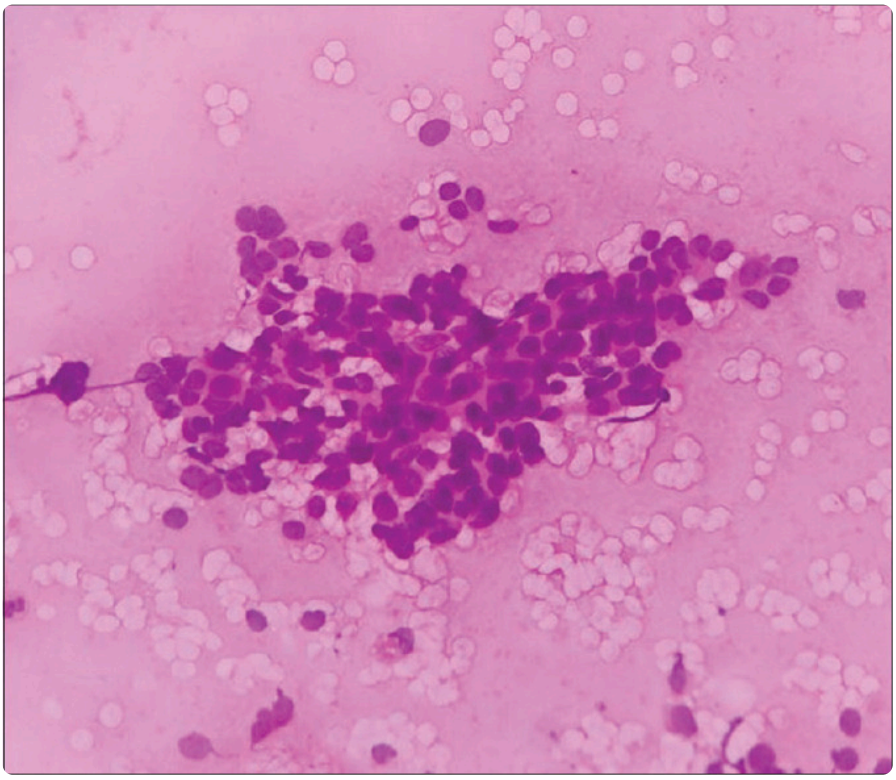
Case No.	Causes for misdiagnosis	Cytological diagnosis	Histopathological Diagnosis
Case 14	Anucleate, (++) Nucleated squamous (+) No basaloid cells were seen	Keratinous Cyst	PMX
Case 15	Anucleated/nucleated squamous cells (+) inflammatory cells (++) , Multinucleated Foreign body giant cells (++) No basaloid/shadow cells	Keratinous Cyst	PMX
Case 16	Scant cellularity of Adipose fragments (++) only	Lipoma	PMX
Case 17	Inflammatory cells (+), Multinucleated giant cells (++), Histiocytes (+) and Lymphocytes(+) Squamous cellularity masked	Granulomatous lesion	PMX
Case 18	Few aggregates of epithelial cells round to irregular with hyperchromatic nuclei(++). No shadow cells	Atypical epithelial cells	PMX

Figure 3



(a) Low power microphotograph showing fibrofatty fragment and occasional anucleated squamous cells.(arrow) (H&E stain, 10X). (b) Smear shows predominantly inflammatory cells, cystic macrophages and multinucleated giant cells (Giemsa stain, 10X). (c), (d) High power view showing multinucleated giant cells with many inflammatory cells (Giemsa stain, 40X)

Figure 4



Predominance of aggregates of darkly stained hyperchromatic epithelial cells with round to oval nuclei, irregular margins, and scant cytoplasm (H&E stain, 40X)

Table 4

Summary of various studies available on cytology of pilomatrixoma

Authors (year)	Total number of PMX cases studied	No of PMX cases misdiagnosed as Malignancy on Cytology
Woyke S *et al*. (1982)[28]	6	6
Bhalotra *et al*. (1990)[29]	2	1
Gomez Aracil *et al*. (1990)[30]	4	2
Ma KF *et al*. (1991)[5]	1	-
Kumar N *et al*. (1996)[27]	15	1
Sanchez SC *et al*. SC (1996)[3]	9	1
Domanski HA *et al*. (1997)[31]	9	-
Thinakaran V *et al*. (1997)[32]	1	-
Tulbah *et al*. (1997)[33]	3	-
Viero RM *et al*. (1999)[34]	14	-
Lemos MM *et al*. (2001)[23]	9	4
Wang J *et al*. (2002)[26]	22	1
Sanyal *et al*. (2004)[4]	1	1
Sivakumar S *et al*. (2007)[35]	1	1
Preethi TR *et al*. (2007)[36]	1	1
Thapiyal N *et al*. (2008)[22]	1	1
Barui GN *et al*. (2009)[37]	1	1
Bansal *et al*. (2011)[24]	14	-
Ieni *et al*. (2012)[21]	25	5
Sharma D *et al*. (2014)[38]	1	1
Nigam JS *et al*. (2014)[39]	3	1
Bax *et al*. (2018)[40]	1	1