Case Series

Pilomatricoma: A Case Series Highlighting Cytological Diagnostic Pitfalls

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Abstract

Pilomatricoma (PMX) is an uncommon benign skin adnexal tumor that frequently poses diagnostic challenges on fine-needle aspiration cytology (FNAC) due to its variable morphological spectrum. We present six histologically confirmed cases of PMX from our institution, emphasizing the cytological diagnostic pitfalls. The series included three females and three males (age range: 28-52 years) presenting with subcutaneous nodules at various locations. Clinical diagnoses include lipoma, sebaceous cyst, and tuberculosis. Correct cytological diagnosis was achieved in four cases (66.7%), while two cases were misdiagnosed as metastatic adenocarcinoma and small round cell tumor due to focal sampling and predominance of basaloid cells. All cases were confirmed as PMX on histopathology with uneventful follow-up. This series highlights the importance of recognizing the dual cell population (ghost cells and basaloid cells), performing multiple needle passes from different sites, and awareness of cytological mimickers to avoid misdiagnosis. PMX should always be considered in the differential diagnosis when primitive-appearing cells are aspirated from subcutaneous nodules, particularly to prevent unnecessary aggressive workup for malignancy.

Keywords: pilomatricoma; fine needle aspiration cytology; ghost cells; basaloid cells; diagnostic pitfalls; skin adnexal tumor.

Introduction

Pilomatricoma (PMX), also known as *pilomatrixoma*, is an uncommon benign tumor showing differentiation towards hair matrix cells. First described by Malherbe and Chenantais in 1880 as "calcifying epithelioma," it was later renamed by Forbis and Helwig in 1961 to reflect its true origin from hair matrix cells.[1] The tumor most commonly occurs in the head and neck region, followed by upper extremities, and rarely in lower extremities. It shows a bimodal age distribution with peaks in the first and sixth decades of life, with slight female preponderance.[2, 3]

Despite well-described cytological features consisting of ghost cells (anucleated squamous cells) and basaloid cells, *pilomatricoma* remains a diagnostic challenge on FNAC.[4, 5] The variability in cellular composition, focal sampling, and overlapping features with various benign and malignant lesions contribute to diagnostic errors. Misdiagnosis as malignancy has significant clinical implications, particularly in young patients where it may lead to unnecessary investigations and aggressive treatment.[6]

This case series specifically addresses the gap in literature regarding systematic analysis of misdiagnosis patterns, their underlying causes, and their clinical consequences in *pilomatricoma*, with emphasis on providing actionable recommendations to improve diagnostic accuracy.

We present six cases of *pilomatricoma* with detailed clinico-cyto-histopathological correlation to highlight the diagnostic pitfalls and emphasize the importance of recognizing this entity on cytology.

Case Report

Pilomatricoma Misdiagnosed as Metastatic Adenocarcinoma

A 35-year-old male presented with a slowly growing subcutaneous swelling on the lateral aspect of right leg for six months. Examination revealed a 1.5×1 cm, soft, freely mobile, non-tender nodule with no overlying skin changes. Clinical possibilities of sebaceous cyst and lipoma were considered.

FNAC yielded blood-mixed aspirate. Cytology smears were moderately cellular showing few clusters of atypical cells with hyperchromatic nuclei, high nuclear-to-cytoplasmic ratio, finely dispersed chromatin, visible nucleoli, and scant cytoplasm. Focal glandular/acinar pattern was noted (1). The background showed cellular debris and few degenerated cells. No mitoses were identified. Based on these findings, a cytological diagnosis of metastatic adenocarcinoma was rendered, and the patient was advised evaluation for primary malignancy.

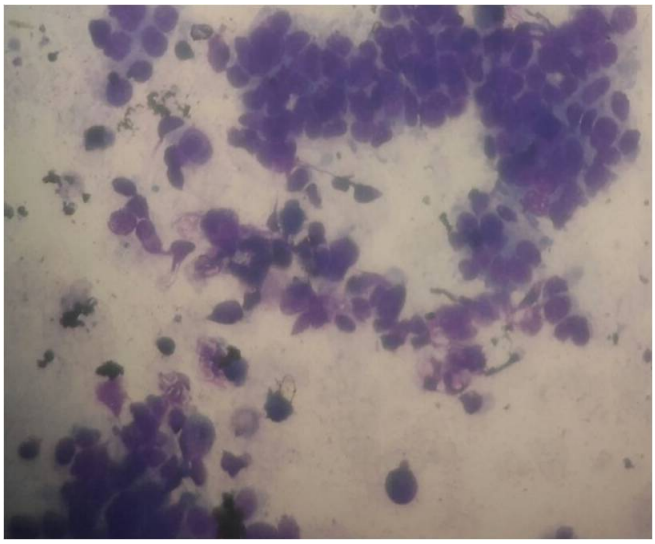

Figure 1: FNAC smear from case 1 showing clusters of basaloid cells with focal acinar pattern and high nuclear-to-cytoplasmic ratio, misinterpreted as metastatic adenocarcinoma (Giemsa, $\times 400$).

Extensive investigations including contrast-enhanced computed tomography of chest, abdomen, and pelvis, whole-body positron emission tomography-computed tomography (PET-CT) scan, serum tumor markers (CEA, CA19-9, PSA), upper gastrointestinal endoscopy, and colonoscopy, as advised during multidisciplinary tumor board evaluation, failed to identify any primary tumor. This extensive workup caused considerable patient anxiety and delayed definitive treatment for three months. The multidisciplinary team decided to perform a wide local excision. Histopathological examination revealed a well-circumscribed tumor composed of sheets of anucleated keratinized cells (ghost cells) with central pale nuclear zones, rimmed by clusters of basaloid cells. Foreign body giant cell reaction and focal calcification were present (2). The final diagnosis was PMX.

A retrospective review of cytology smears revealed that the atypical cells with focal glandular patterns were actually misinterpreted basaloid cells with clustering artifacts. The nucleoli, while visible, were uniform and not truly atypical as initially interpreted. The ghost cells were misidentified as under stained/degenerated cells, and the dirty background represented cellular debris with calcific material rather than tumor diathesis. The patient had an uneventful postoperative recovery with no recurrence at 24-month follow-up.

Pilomatricoma Clinically Suspected as Tuberculosis

A 28-year-old female presented with progressive enlargement of a swelling on the left arm for five months. There was no history of trauma, but family history of tuberculosis was present. Examination revealed a 1×1 cm, soft, well-defined nodule. Clinical suspicion of tuberculous lymphadenitis (Koch's infection) was considered, and FNAC was performed.

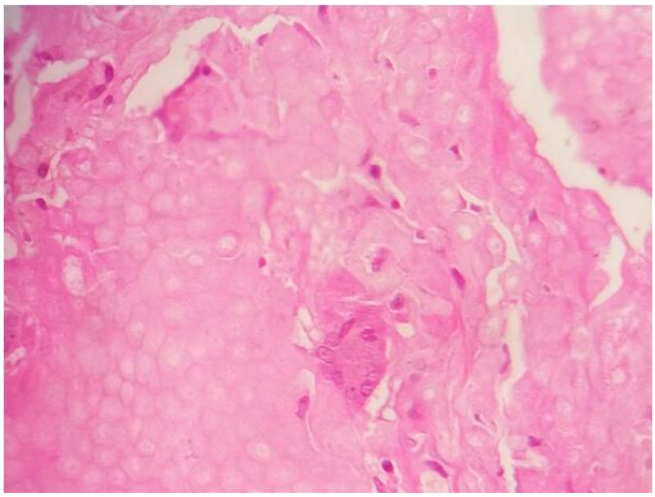

Figure 2: Histopathology showing characteristic features of *pilomatricoma* with basaloid cells rimming sheets of anucleated ghost cells with central calcification (H&E, ×400).

Cytology smears were cellular showing clusters of compact basaloid cells with focal calcification. Scattered anucleated squames (ghost cells) with central pale zones were noted. The background showed cellular debris and foreign body giant cell reaction. No granulomas or caseation necrosis were seen. Ziehl-Neelsen stain for acid-fast bacilli was negative. A cytological diagnosis of *pilomatricoma* was made based on the characteristic dual cell population.

Histopathological examination following excision confirmed the diagnosis of *pilomatricoma*. The patient remained disease-free at 24-month follow-up.

Pilomatricoma Misdiagnosed as Small Round Cell Tumor

A 30-year-old female presented with a subcutaneous swelling on the right forearm for two months. Examination revealed a 2×2 cm, firm, mobile, non-tender, well-defined nodule. Clinical diagnoses considered were sebaceous cyst or lipoma.

FNAC yielded cellular smears showing round to ovoid cells, both dispersed and in clusters, with occasional rosette-like arrangement (3). The cells had high nuclear-to-cytoplasmic ratio and hyperchromatic nuclei. Based on these findings, a cytological diagnosis of small round cell tumor was made. The patient was advised further evaluation including immunohistochemistry.

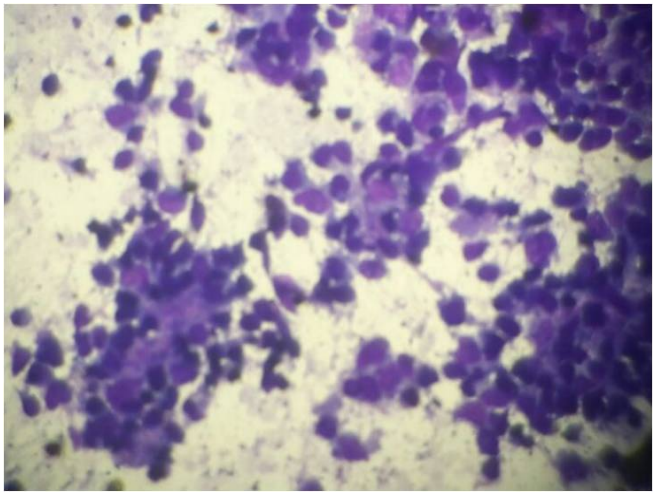

Figure 3: FNAC smear from case 3 showing small round to ovoid cells in clusters with occasional rosette-like arrangement, misdiagnosed as small round cell tumor (Giemsa, ×400).

However, excision biopsy revealed characteristic features of *pilomatricoma* with basaloid cell clusters, ghost cells, and calcification (2). No features of malignancy were identified.

Retrospective cytology review showed that the rosette-like pattern was formed by basaloid cells, and ghost cells were not adequately sampled in the initial aspirate. The patient had an uneventful recovery with no recurrence at 24-month follow-up.

Pilomatricoma on Face

A 52-year-old male presented with a 1×1 cm nodule on the face for one month. Clinical diagnosis was sebaceous cyst. FNAC showed characteristic ghost cells and basaloid cells. Cytological and histological diagnosis confirmed *pilomatricoma*. No recurrence at 24 months.

Pilomatricoma on Trunk

A 34-year-old female presented with a 1.2×1 cm nodule in the trunk for one year. Clinical diagnosis was lipoma. FNAC demonstrated typical features of *pilomatricoma*. Histopathology confirmed the diagnosis. No recurrence at 24 months.

Pilomatricoma on Forearm

A 38-year-old male presented with a 1×1 cm nodule in the left forearm for ten months. Clinical diagnosis was lipoma. Cytology and histopathology confirmed *pilomatricoma*. No recurrence at 10 months.

The clinico-cyto-histopathological details of all six cases are summarized in 1. Written informed consent was obtained from all patients for publication of this case series and accompanying images.

Table 1: Detailed clinical findings with clinico-cyto-histopathological correlations.

Case No.	Age/Sex	Clinical Findings	Cytological Diagnosis	Clinical Diagnosis	Histological Diagnosis
1	35/M	1.5×1 cm, soft, mobile, non-tender subcutaneous nodule at lateral side of right leg from 6 months	Metastatic adenocarcinoma	Lipoma/Sebaceous cyst	PMX
2	28/F	1.0×1.0 cm, soft, well-defined on left arm from 5 months	PMX	Koch's	PMX
3	30/F	2.0×2.0 cm, firm, mobile, non-tender, well-defined nodule in right forearm from 2 months	Small round cell tumor	Sebaceous cyst/Lipoma	PMX
4	52/M	1.0×1.0 cm, firm, mobile, non-tender nodule on face from 1 month	PMX	Sebaceous cyst	PMX
5	34/F	1.2×1.0 cm, soft, mobile, non-tender, well-defined nodule in trunk from 1 year	PMX	Lipoma	PMX
6	38/M	1.0×1.0 cm, soft, mobile, non-tender, well-defined in left forearm from 10 months	PMX	Lipoma	PMX

PMX = *Pilomatricoma*

Discussion

PMX is a benign skin adnexal tumor that frequently leads to diagnostic challenges both clinically and cytologically. Misdiagnosis as malignancy has significant clinical and psychological consequences, as exemplified by Case 1, where the patient underwent extensive imaging, invasive endoscopic procedures, and experienced considerable anxiety over a three-month period before the correct diagnosis was established. This is particularly concerning young adults and children who comprise a significant proportion of *pilomatricoma* cases.

In our series of six cases, clinical misdiagnosis was common with most lesions suspected as lipoma (n=4), sebaceous cyst (n=3), or tuberculosis (n=1), reflecting the non-specific presentation of PMX as a subcutaneous nodule.

The cytological diagnosis was accurate in four cases (66.7%), while two cases (33.3%) were misdiagnosed as metastatic adenocarcinoma and small round cell tumor.[4, 5, 7] 2 summarizes the initial versus retrospective cytological interpretations in these misdiagnosed cases, highlighting the specific features that led to errors. The main causes of misdiagnosis were focal sampling and predominance of one cellular component.

Table 2: Comparison of initial versus retrospective cytological interpretation in misdiagnosed cases.

Case No.	Initial Cytological Interpretation	Retrospective Interpretation
1	Metastatic adenocarcinoma	*Pilomatricoma*
3	Dispersed basaloid cells, high N/C ratio, rosette-like structures	*Pilomatricoma*

N/C = Nuclear-to-cytoplasmic

The diagnostic cytological features include ghost cells (anucleated keratinized squamous cells with central pale nuclear zone), basaloid cells (small cells with basophilic nuclei and small to inconspicuous nucleoli), calcification, and foreign body giant cell reaction. [4, 5] The presence of both cell types is virtually diagnostic. However, when sampling is focal and only one component is aspirated, diagnostic difficulty arises.

Ghost cells are frequently missed or misinterpreted for several reasons: (1) they may be understained on cytology smears and resemble cellular debris or background material, (2) when degenerated, they lose their characteristic pale central zones and appear as amorphous material, (3) in focal sampling, ghost cells may be sparse or absent from the aspirated material, (4) the accompanying calcific debris and inflammatory background can obscure ghost cells, making them difficult to identify, and (5) inexperienced cytopathologists may not actively search for these cells when faced with a predominant basaloid population.

Our two misdiagnosed cases illustrate important pitfalls. In Case 1 (1), basaloid cells with acinar pattern mimicked adenocarcinoma. The nuclear hyperchromasia and visible nucleoli were misinterpreted as malignant features, while absence of ghost cells and "dirty" background (calcific debris) suggested tumor diathesis. In Case 3 (3), basaloid cells with rosette-like arrangement mimicked round cell tumors.

The cytological mimickers detailed in 3 include epidermal inclusion cysts, adnexal tumors, squamous cell carcinoma, basal cell carcinoma, round cell tumors, small cell carcinoma, and metastatic adenocarcinoma. These entities have been well-documented in cytological literature as potential diagnostic pitfalls. [7, 8, 9]

Table 3: Cytological mimickers of *pilomatricoma*: Overlapping and distinguishing features on FNAC.

Cytological Mimicker	Overlapping Features with PMX	Distinguishing Features of the Mimicker	Key PMX Features to Look For
Metastatic Adenocarcinoma	Basaloid cells with visible nucleoli, acinar pattern	True gland formation, significant nuclear pleomorphism, prominent macronucleoli, single dissociated malignant cells	Ghost cells, uniform basaloid cells, calcification, foreign body giant cells
Small Round Cell Tumor	Dispersed basaloid cells, high N/C ratio, rosette-like structures	Nuclear molding (small cell carcinoma), lymphoglandular bodies (lymphoma), specific IHC markers	Biphasic population, ghost cells, association with skin/subcutis
Squamous cell carcinoma	Squamous differentiation, keratin debris, inflammation	Marked nuclear atypia, atypical mitoses, nucleated pleomorphic squamous cells	Basaloid cell component, well-defined ghost cells without nuclear atypia
Epidermal Inclusion Cyst	Anucleated squames, debris	Lack of basaloid cells, presence of nucleated squamous cells, cholesterol crystals	Dual population is key; basaloid cells are essential for PMX diagnosis
Basal Cell Carcinoma	Compact basaloid cell clusters, peripheral palisading	Tight cohesive clusters, peripheral nuclear palisading, stromal mucin, clefting artifact	Ghost cells, looser cohesion, calcification, saw-toothed edges of basaloid clusters
Trichilemmal Cyst	Anucleated squames, keratin material	Dense orangeophilic keratin, absence of basaloid cells, abrupt keratinization	Basaloid cells present, calcification common, foreign body giant cell reaction
Adnexal Tumors (cylindroma, spiradenoma, hydradenoma)	Clusters of epithelial cells with mild pleomorphism, occasional nucleoli	Specific architectural patterns, hyaline material (cylindroma), stromal features	Ghost cells, dual population, calcification, subcutaneous location

N/C = Nuclear-to-cytoplasmic; PMX = *Pilomatricoma*; IHC = Immunohistochemistry

Literature review reveals multiple recent misdiagnoses. Jung et al (2018) reported *pilomatricoma* misdiagnosed as carcinoma on PET/CT and FNAC.[10] Kurose et al (2018) documented proliferating *pilomatricoma* misdiagnosed as parotid malignancy.[11] Khan et al (2023) found 27.8% misdiagnosis rate in 18 cases, mainly due to predominance of one cellular component.[12] Shelgaonkar et al (2020) reported misdiagnosis as pancreatic carcinoma metastasis.[13] Lee et al (2018) found 71.4% diagnostic accuracy, identical to ours, emphasizing that ghost cells were often inconspicuous.[14] Recent studies from 2020-2024 continue to document similar diagnostic pitfalls, demonstrating that *pilomatricoma* remains a challenge despite increased awareness.[15, 16] Earlier, large clinicopathological series remained relevant for defining the epidemiological and morphological characteristics of *pilomatricoma*, while recent studies highlight the persistent nature of

diagnostic pitfalls in cytological practice.

Our diagnostic accuracy of 66.7% is comparable to recent rates (Lee: 71.4% [14], Khan: 72.2% [12]). The unusual location in Case 1 (lateral leg) contributed to diagnostic difficulty.[2, 3] Our case series showed an age range of 28-52 years, which does not reflect the typical bimodal distribution with a pediatric peak, representing a limitation of our small sample size and institutional case selection.

Immunohistochemistry can serve as a valuable adjunct in diagnostically challenging cases, particularly when small round cell tumor or other malignancies are in the differential diagnosis. Markers such as β-catenin (nuclear positivity in basaloid cells), CD10, and BerEP4 can help confirm the diagnosis of *pilomatricoma*. However, immunohistochemical studies require either cell block preparation or tissue biopsy. Cell block preparation was not performed in any of our cases, which represents a technical limitation. For future cases with diagnostic uncertainty, we recommend requesting cell block preparation at the time of FNAC, particularly for lesions larger than 1.5 cm or when only one cellular component is present.

While *pilomatricoma* is typically benign, awareness of *pilomatrix carcinoma* (malignant *pilomatricoma*) is important. This rare malignant variant shows features of true malignancy including infiltrative growth, significant nuclear pleomorphism, atypical mitoses, and necrosis, beyond the mere nuclear atypia that can be seen in basaloid cells of benign *pilomatricoma*.[17]

Based on our experience and literature review, we recommend the following specific measures to improve diagnostic accuracy: Perform a minimum of 3-4 needle passes from different areas of the lesion, particularly for nodules larger than 1.5 cm. Actively and systematically search for ghost cells in every microscopic field at scanning magnification before high-power examination. Avoid overinterpretation of visible nucleoli in basaloid cells; assess the overall nuclear features and look for true cytological atypia. Request cell block preparation at the time of FNAC for lesions with diagnostic uncertainty or predominance of one cellular component. Correlate cytological findings with clinical features (age, subcutaneous location, firm consistency) which may suggest *pilomatricoma*. When uncertainty persists despite adequate sampling, recommend repeat FNAC or direct excisional biopsy rather than extensive staging investigations. Maintain a high index of suspicion for *pilomatricoma* when encountering primitive-appearing cells in subcutaneous lesions.

When facing diagnostic uncertainty, repeat FNAC or proceeding directly to an excisional biopsy is preferable to initiating expensive and invasive staging workups for suspected malignancy.

Conclusion

PMX remains a diagnostic challenge on fine-needle aspiration cytology (FNAC). Our series demonstrates 66.7% diagnostic accuracy, with two cases misdiagnosed as malignancies. The dual cell population of ghost cells and basaloid cells is diagnostic; however, focal sampling and predominance of one component lead to misdiagnosis. Critical factors include inadequate sampling, failure to actively search for ghost cells, overinterpretation of nucleoli in basaloid cells, understaining of ghost cells causing them to be mistaken for debris, and unusual anatomical locations. Specific recommendations include performing minimum 3-4 passes from different sites, systematic screening for both cellular components at scanning magnification, cell block preparation for lesions $>$1.5 cm or with diagnostic uncertainty, correlation with clinical features, and appropriate use of immunohistochemistry when tissue is available. When uncertainty persists, direct excisional biopsy is preferable to extensive staging investigations. Awareness of the morphological spectrum and familiarity with cytological mimickers are essential to prevent unnecessary aggressive management in young adults and children.

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