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Atypical Clear Cell Hidradenoma: Case report and a brief review of the literature

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Abstract

Clear cell hidradenoma (CCH) is an uncommon adnexal neoplasm that usually behaves in a benign fashion. However, it may present diagnostic and therapeutic challenge when atypical histologic features and persistent clinical progression are present. We report the case of a 39-year-old woman with a slowly enlarging left shoulder lesion that had initially been diagnosed on superficial shave biopsy as benign eccrine poroma. Despite this benign interpretation, the tumor enlarged over 18 months, developed violaceous discoloration, and bled intermittently after minor trauma. Magnetic resonance imaging (MRI) demonstrated a well-circumscribed, enhancing, solid-cystic dermal and superficial subcutaneous mass. Wide local excision revealed a clear cell hidradenoma with atypical features, including solid and cystic architecture, clear glycogen-rich cells, poroid cells, focal necrosis, scattered mitotic activity, subcutaneous extension, and positive deep and peripheral margins. Immunohistochemistry (IHC) supported adnexal differentiation, and molecular testing was negative for MAML2 rearrangement.

This case illustrates the limitations of superficial sampling, the importance of correlating pathology with continued clinical change, and the need for complete excision and close surveillance when hidradenoma demonstrates worrisome but not frankly malignant features. It also reinforces the value of multidisciplinary review in guiding definitive management.

Keywords: Clear cell hidradenoma; Immunohistochemistry; Adnexal neoplasm; Atypical; Shave biopsy; Wide local excision

1. Introduction

Clear cell hidradenoma (CCH) is a rare benign skin tumor arising from eccrine sweat glands that can occur on the head, neck, and extremities. [1] While most cases are slow-growing and benign, atypical variants can present with more concerning features, including rapid enlargement, cellular atypia, and increased mitotic activity, and may carry a risk of recurrence. When a CCH exhibits such worrisome histopathological features but lacks the definitive invasive, destructive growth pattern of a cancer, it is designated as an atypical hidradenoma. [2] Because these features can resemble those of malignant tumors, such as hidradenocarcinoma, distinguishing between them can be difficult and may complicate management. The clinical features of these lesions include erosion or ulceration and, in rare cases, malignant transformation. [3] The appearance of brown, blue, or red discoloration, together with superficial ulceration and serous discharge, can sometimes be mistaken for malignancies. [4]

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Given CCHs' potential to mimic other lesions, accurate diagnosis is challenging. Superficial biopsy samples may fail to capture the full architectural and cytological complexity of the lesion, increasing the risk of misdiagnosis or underestimation of its biological behavior. [1] While atypical hidradenoma is not always classified as a separate, distinct entity from malignant hidradenocarcinoma in all grading systems, it is recognized as a "borderline" or "low-grade" lesion with an increased risk of recurrence. [2] This underscores the importance of clinicopathological correlation and, when necessary, complete excision for definitive evaluation.

In this report, we present a case of atypical clear cell hidradenoma in a 39-year-old woman with progressive lesion growth and initial biopsy findings that did not correlate with her clinical presentation. We highlight the diagnostic challenges, the multidisciplinary management approach, and the histopathologic features of this case, along with a brief review of the literature to emphasize key considerations in evaluation and treatment.

2. Case Presentation

2.1. Clinical Presentation

A 39-year-old woman presented for evaluation of a gradually enlarging mass over the left shoulder, first noticed approximately 18 months earlier. Initially, the lesion appeared as a small, flesh-colored papule that was occasionally tender when in contact with clothing. Over the preceding six months, it had progressively increased in size, developed a violaceous discoloration, and began to bleed intermittently following minor friction. The patient denied systemic symptoms, unintentional weight loss, or similar lesions elsewhere on the body. Her past medical history was otherwise unremarkable.

Eighteen months prior, a dermatologist had performed a shave biopsy, which revealed features consistent with a benign eccrine poroma. Despite this diagnosis, the lesion continued to enlarge and became increasingly symptomatic, prompting referral to a surgical oncologist for definitive management.

2.2. Physical Examination, Imaging, and Differential Diagnosis

On physical examination, there was a solitary, well-circumscribed, dome-shaped dermal nodule on the anterior aspect of the left shoulder, measuring 3.2 cm × 2.5 cm. The lesion was firm to palpation with a smooth surface, scattered telangiectasias, and a centrally eroded, crusted area. No palpable axillary lymphadenopathy was identified.

MRI of the left shoulder demonstrated a well-defined, enhancing solid-cystic mass confined to the dermis and superficial subcutaneous tissue, without evidence of deep fascial involvement or perineural extension. Based on clinical and radiologic findings, the differential diagnosis included recurrent eccrine poroma, clear cell hidradenoma, pyogenic granuloma, and a primary cutaneous adnexal malignancy such as hidradenocarcinoma or malignant eccrine spiradenoma.

2.3. Multidisciplinary Tumor Board Discussion

The case was reviewed at the multidisciplinary tumor board, where discussion focused on the discrepancy between clinical progression and the initial benign pathology, as well as surgical planning. The pathologist noted that the prior shave biopsy was superficial and may have sampled only a benign portion of a larger, more atypical tumor.

Given the history of progressive enlargement and spontaneous bleeding, and the known potential for local recurrence in clear cell hidradenoma, the team reached consensus that complete excision was essential. The surgical oncologist proposed a wide local excision, and the discussion centered on optimal margin width. Because the lesion was located on the shoulder—allowing for adequate margins with acceptable cosmetic and functional outcomes, the board recommended a 1.0–1.5 cm clinical margin encompassing the previous biopsy site, with intraoperative evaluation of deep margins given the propensity for subcutaneous extension.

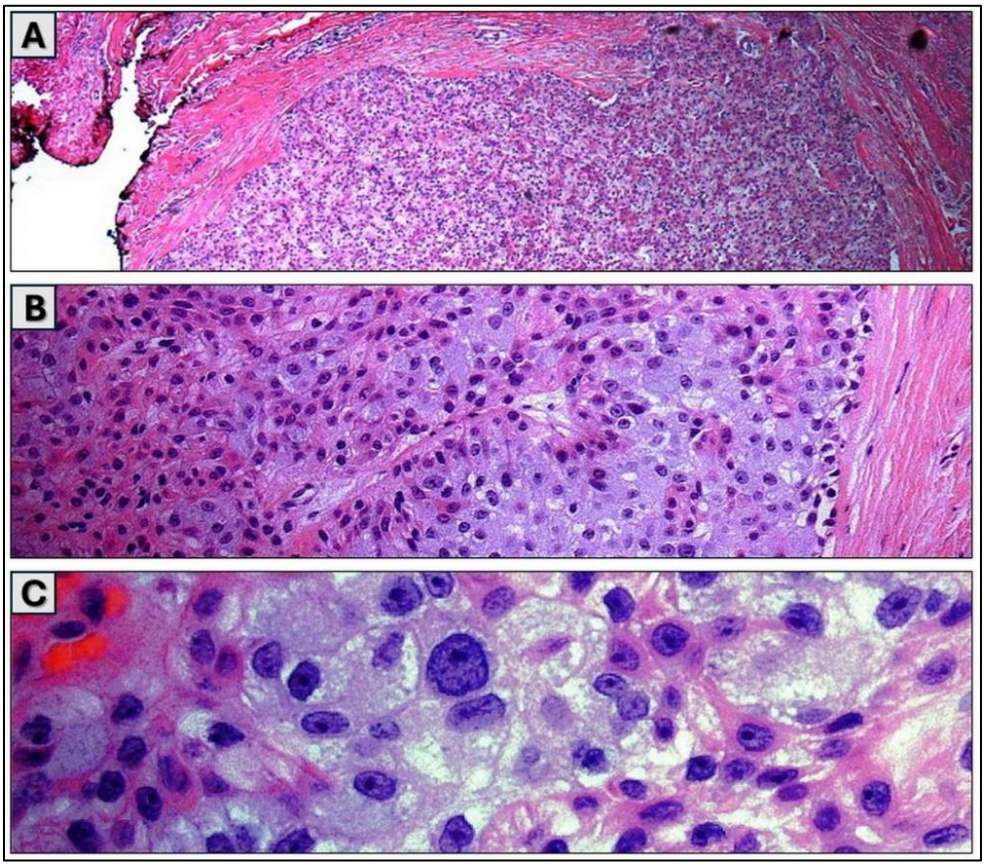
2.4. Special Studies, Pathology, Immunohistochemistry (IHC), and Molecular Findings

The patient underwent a wide local excision with a 1.5 cm margin extending to the underlying deep fascia. Histopathologic examination of permanent sections showed a well-circumscribed but unencapsulated dermal neoplasm featuring both solid and cystic components. Two cellular populations were identified: large polygonal cells with clear, glycogen-rich cytoplasm (clear cells) and smaller cells with eosinophilic cytoplasm (poroid cells). Foci of necrosis and scattered mitotic figures were present. The tumor extended into subcutaneous fat, with involvement of both peripheral and deep margins. (Figure 1 A, B, C) IHC analysis demonstrated diffuse positivity for cytokeratin 7 (CK7), epithelial

membrane antigen (EMA), and p63, consistent with adnexal origin and myoepithelial differentiation. Carcinoembryonic antigen (CEA) staining highlighted luminal borders of rare ductal structures. The Ki-67 proliferation index was approximately 10–15% in the most active regions.

The diagnosis of CCH with atypical features was established based on the tumor's morphology, predominance of clear cells, and IHC profile. Although hidradenomas are commonly associated with MAML2 gene rearrangements, molecular testing was negative, confirming this as a sporadic, conventional clear cell variant. A negative molecular test for the MAML2 rearrangement does not exclude a diagnosis of hidradenoma but rather identifies it as a sporadic, conventional, or "wild-type" case, distinguishing it from the rearranged subtypes.

Following a wide local excision with 2 cm margins, the patient showed no evidence of recurrence at the 14-month follow-up.



1A: Low power view showing large dermal mass extending into the surgical margin (Left side) (H&E X20); **1B:** Intermediate power view showing two cellular populations, clear cells and eosinophilic cells (H&E X40); **1C:** High power view showing cellular details, large polygonal cells with clear, glycogen-rich cytoplasm (clear cells) and smaller cells with eosinophilic cytoplasm (poroid cells). Focal atypia is noted (H&E X60).

Figure 1 Microscopic findings of Clear Cell Hidradenoma

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

CCH, also known as nodular hidradenoma or eccrine acrospiroma, is a benign tumor of the sweat glands. CCH, first recognized in the mid-1900s, has been associated with other eccrine tumors. [5] Earlier, it was thought that these tumors arose solely through eccrine differentiation. However, subsequent studies using IHC and ultrastructural methods have identified features of both eccrine and apocrine origins, highlighting the intricate biology of adnexal-type tumors. [6]

CCH is a rare cutaneous neoplasm that most commonly affects adult patients in their third to sixth decades of life and shows a slight female predominance. [6,7] Lesions most often occur on the head, trunk, and proximal extremities and

are usually slow-growing, solitary nodules. These tumors are usually benign but can recur if not completely removed; rare cases of malignancy have been reported as hidradenocarcinoma. [7]

The most recent World Health Organization (WHO) Classification of Skin Tumors [8] places hidradenoma in the second category of benign adnexal tumors with sweat gland differentiation, alongside poroid and hidradenomatous neoplasms. The classification highlights morphologic diversity, including clear cell variants with glycogen-rich cytoplasm and dual cell populations. [9]

CCH is an important adnexal tumor with significant diagnostic importance given its overlapping clinical and histological features associated with both benign and malignant entities.

3.2. Pathogenesis, Pathophysiology

CCH is a benign tumor that originates from the distal excretory ducts of the eccrine glands. Hidradenomas are believed to develop from eccrine gland progenitor cells that can differentiate into clear and poroid cells, resulting in tumors with both cell types. [10] The clear appearance of these cells is due to their glycogen content, and the presence of poroid cells indicates that the tumor is related to other tumors originating from eccrine glands.

MAML2 gene rearrangements have been identified in a subset of hidradenomas, leading to dysregulation of the Notch signaling pathway and contributing to tumor pathogenesis. [11] The absence of this genetic rearrangement in this tumor suggests that the hidradenoma developed sporadically. The Ki-67 proliferation index, which measures the rate of tumor cell proliferation, is high at 10-15%, with some areas of the tumor exhibiting necrosis and undergoing cell division. These features suggest that, although the tumor is benign, it exhibits atypical features.

CCH typically grows slowly. However, they often grow expansively within the dermis and lack encapsulation. The tumors contain both solid and cystic portions. The presence of cystic portions of hidradenomas is thought to result from the tumor's ductal differentiation. [13] The expansive growth of the tumor accounts for the increasing size of the lesion. Erosion of the lesion's surface and the presence of blood within the lesion are thought to be due to trauma to the lesion. Additionally, the lesion's violaceous color is suggestive of increased tumor vascularity. [8]

The presence of both clear and poroid cells, as well as the necrotic and proliferative portions of the tumor, correlates with tumor behavior. The lack of encapsulation explains how it has invaded the adjacent subcutaneous tissue. Positive biopsy margins show how much of the tumor remains and suggest the risk of recurrence if not fully removed. The positivity of the lesion for CK7, EMA, and CEA indicates differentiation toward eccrine glands, supporting the tumor's origin and its true structure. [14] These findings directly relate to the differentiation of the tumor.

Though there are no specific therapies for CCH, knowledge of MAML2 gene rearrangements in other hidradenomas can help guide potential therapies for these tumors in the future.

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

The present case shares several features with previously reported nodular or CCH, including occurrence in a woman, slow enlargement over many months, intermittent bleeding, and a well-circumscribed solid-cystic morphology with dual cell populations on histology. [8,10] As in other reports, the lesion was clinically nonspecific and overlapped with a wide differential diagnosis that included benign adnexal tumors, vascular lesions, and primary cutaneous malignancies. [8,16] The shoulder location was also compatible with the known distribution of hidradenoma on the trunk and extremities. However, many series described a predominance in the head and neck region. [8,9]

What distinguishes this case is the discordance between an initially benign superficial shave biopsy and the subsequent clinically aggressive behavior, which prompted multidisciplinary reassessment. This pattern echoes recent reports emphasizing that limited sampling may miss focal atypical or malignant areas, particularly in heterogeneous tumors with both cystic and solid components. [4,16] Histologically, our case showed necrosis, mitotic activity, and subcutaneous extension, findings that overlapped with atypical hidradenoma described by Nazarian et al., who proposed that atypical lesions may recur yet are less likely to metastasize than hidradenocarcinoma. [12] However, unlike frankly malignant lesions, our case lacked definitive infiltrative carcinoma-level features such as marked pleomorphism, high mitotic burden, angiolymphatic invasion, or metastatic disease. [12,16] Consistent with prior literature, complete excision with margin control and structured follow-up remain the most appropriate management strategy in the setting of atypical histology and prior incomplete sampling. [8,15,16]

4. What Have We Learned from This Case?

This case offers several practical lessons for clinicians. First, a benign result on superficial biopsy should not end the diagnostic evaluation if the lesion continues to enlarge, change color, ulcerate, or bleed. In adnexal tumors with architectural heterogeneity, limited sampling may capture only a less atypical portion of the neoplasm, leading to false reassurance. [4,14,16] Second, red-flag features such as persistent growth, spontaneous bleeding, focal necrosis, mitotic activity, and extension beyond the dermis should prompt renewed concern for atypical hidradenoma or early malignant transformation, even when classic hidradenocarcinoma criteria were not fully met. [14,16] Third, management should prioritize complete excision with careful margin assessment, because local recurrence has repeatedly been linked to incomplete removal. [8,10,15] Finally, this case reinforced the importance of clinicopathologic correlation and multidisciplinary review. In future practice, lesions with discordant clinical and histologic findings should be re-biopsied, excised more definitively, or both, rather than followed conservatively based solely on a limited initial specimen.

Abbreviations:

- Clear cell hidradenoma (CCH);
- Immunohistochemistry (IHC)

5. Conclusion

This case was reported because it illustrated an atypical clear cell hidradenoma in which benign initial sampling did not reflect the lesion's subsequent clinical behavior or its more worrisome excision pathology. It added to the literature by highlighting the diagnostic limitations of superficial biopsy, the importance of recognizing progressive bleeding and enlargement as warning signs, and the value of multidisciplinary decision-making in selecting definitive treatment. For the medical community, the case reinforced a simple but important message: when clinicopathologic discordance persisted in an adnexal tumor, complete excision and close follow-up were warranted, even in the absence of unequivocal hidradenocarcinoma.

Compliance with ethical standards

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Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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