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Case Report

Clear cell hidradenoma in a patient with previous glycogen rich clear cell carcinoma of the breast: Diagnostic pitfalls and pearls

Amanda B. Moyer, MD*, Daniel J. Duhon, MD, Mary R. Schwartz, MD, Jae Y. Ro, MD PhD, Ross A. Miller, MD

Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Medical College of Cornell University, United States

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ABSTRACT

Clear cell hidradenoma (CCH) is an uncommon benign dermal-based tumor that typically presents on the head, neck, and upper extremities as a solitary firm nodule. The clear cytoplasm can resemble benign and malignant clear cell neoplasms from multiple sites; thus, a large differential diagnosis is often considered. When CCH is seen in the breast or axilla, glycogen-rich clear cell carcinoma (GRCCC) of the breast enters the differential diagnosis. Although GRCCC is rare, it is important to recognize as a breast carcinoma variant because most reports have suggested that it has a more aggressive course than typical invasive ductal carcinoma. We report a case of CCH in the upper axilla of a 64-year-old woman who also happened to have a remote history of invasive GRCCC to highlight the potential diagnostic pitfalls when evaluating these two histologically similar clear cell tumors. Although immunohistochemical studies can be helpful, overlapping staining patterns can lead to potential confusion and misclassification. Both of our patient's tumors were negative for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and PAX8. ER and PR are typically negative in hidradenomas and can be negative in up to 50% of GRCCC. Although considered a breast marker, GATA-3 can be negative in GRCCC and positive in skin adnexal tumors. p63 can be especially helpful, as it is expressed in skin adnexal tumors, but lost in most (Thike et al., 2010) invasive breast carcinomas. Finally, periodic acid-Schiff (PAS) with and without diastase highlights intra-cytoplasmic glycogen in GRCCC.

1. Introduction

Breast carcinoma is one of the most common primaries of skin metastases in women [1]. The most common clinical presentation is nodules on the trunk [1,2]. There are a variety of breast carcinoma subtypes. Glycogen rich clear cell carcinoma (GRCCC) is a rare variant of invasive ductal carcinoma comprising only 1–3% of all breast carcinomas [3,4].

GRCCC was first described by Hull et al. in 1981 as having two distinct compartments for glycogen and organelles on electron microscopy, and histologically resembling epithelial cells of the mammary gland bud in a 13-week human fetus [5]. Further studies of this entity showed variable architectural patterns including both papillary and solid [6]. Cytologic features on fine needle aspiration (FNA) vary and can include koilocyte-like perinuclear halos, papillary fronds of tall columnar cells with apical cytoplasmic projections, finely granular eosinophilic cytoplasm, or abundant foamy cytoplasm [7]. Atypical hidradenoma can mimic a primary mammary carcinoma on FNA cytology [8]. The histologic findings of GRCCC can be difficult to distinguish from other clear cell malignancies such as signet-ring cell carcinoma, secretory carcinoma, lipid-rich carcinoma, hidradenocarcinoma, apocrine carcinoma, and metastatic clear cell renal cell carcinoma [9]. Benign breast changes, such as the physiologic changes of pregnancy, can also be a consideration in the appropriate clinical context, particularly if a limited amount of material is present for evaluation. Benign clear cell neoplasms including clear cell hidradenoma (CCH) and sebaceous neoplasms are also a consideration [10].

We report a case of CCH in the upper axilla of a 64-year-old woman with a remote history of invasive GRCCC to highlight the diagnostic pitfalls when evaluating histologically similar clear cell dermal based tumors. This case further illustrates the challenge when the patient has been previous diagnosed with a clear cell malignancy. Histology, immunohistochemistry (IHC), and clinicopathologic correlation are required in order to differentiate a new separate primary neoplasm from a metastasis or recurrence of her breast cancer.

* Corresponding author at: 6565 Fannin St. M227, Houston, TX 77030, United States.
E-mail addresses: amoyer@houstonmethodist.org (A.B. Moyer), djduhon@houstonmethodist.org (D.J. Duhon), mschwartz@houstonmethodist.org (M.R. Schwartz), jaero@houstonmethodist.org (J.Y. Ro), rmiller@houstonmethodist.org (R.A. Miller).

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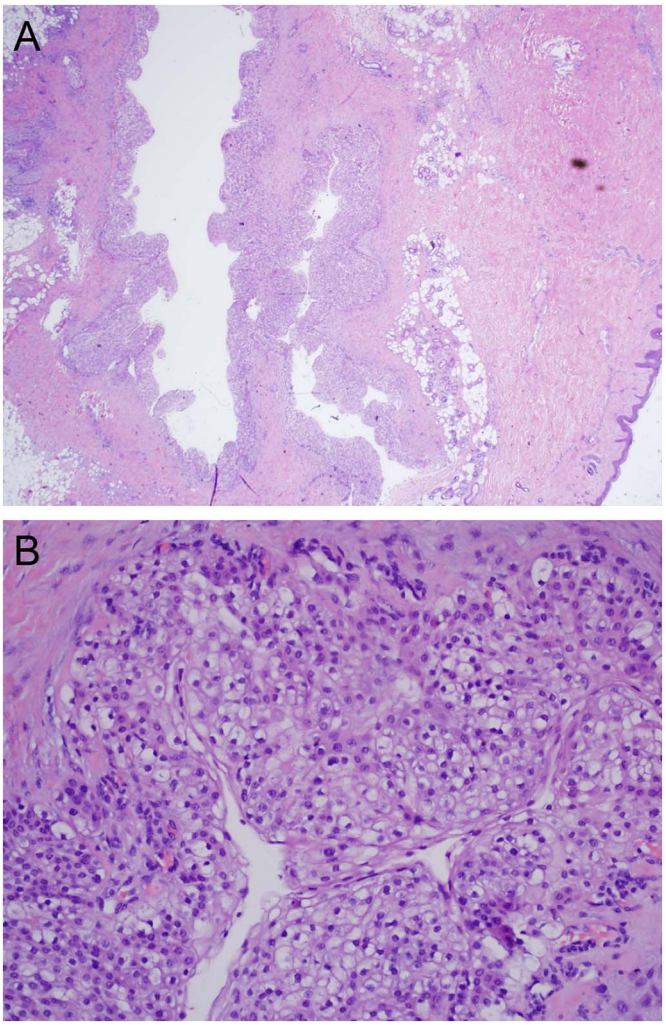

Fig. 1. (A) Low and (B) high power magnification of patient's CCH demonstrating a well-demarcated, dermal cyst lined by multiple layers of polygonal cells with sharply defined cell borders, abundant clear cytoplasm, oval vesicular nuclei and small nucleolus. The tumor has a well-defined boundary with no infiltration, increased mitotic activity or necrosis.

2. Case report

A 64-year-old woman with a remote history of invasive GRCCC of the right breast, status post radiation therapy 10 years prior, presented with a 2 cm, slowly growing, mobile, right upper axillary mass. No lymphadenopathy or systemic symptoms were noted. The main clinical considerations were hemangioma versus metastatic breast cancer. A wide local excision of the mass was performed. The excision had a dermal based 1.5 cm cystic lesion with a smooth lining, filled with brown serous fluid. Microscopic examination showed a well-demarcated dermal cyst lined by multiple layers of polygonal clear cells with sharply defined cell borders, clear cytoplasm, and oval vesicular nuclei with a small nucleolus (Fig. 1). No infiltration into the surrounding tissue, increased mitotic activity, or necrosis was observed. The lesion was immunoreactive for p63, p40, and GATA3 by immunohistochemistry. PAX8, ER, PR, and HER2 immunostains were negative in the tumor cells (Fig. 2). Periodic acid-Schiff (PAS) stain with and without diastase highlights diastase-sensitive intracytoplasmic glycogen.

The tumor was compared with the patient's primary GRCCC of the breast. The breast primary had large clear cells with abundant glycogen, high mitotic activity, and focal necrosis, with overall histologic grade 3 features. PAS stain with and without diastase highlighted diastase-sensitive intracytoplasmic glycogen (Fig. 3). Immunophenotypically, this tumor was also negative for PAX8, ER, PR, and HER2. Unlike the newer dermal tumor, it was not immunoreactive for p63, p40, and GATA3 (Table 1).

3. Discussion

CCH presents as a solitary, firm, mobile nodule [11,12]. Grossly, it is a well-demarcated dermal mass with a cystic component. Histologically, the tumor is composed of polyhedral cells with a rounded low-grade nucleus and abundant clear cytoplasm, and may form small ductular lumens [11]. The current best classification of this tumor is as an aprocine hidradenoma [13].

CCH usually does not show infiltration into the surrounding tissue, increased mitotic activity or necrosis. Although morphology can help distinguish CCH from other clear cell neoplasms, a potential pitfall is that histology does not predict disease progression in the malignant counterpart of CCH, hidradenocarcinoma [14].

CCH can mimic metastatic clear cell neoplasms. Morphologic comparison with the original tumor is valuable. For metastatic GRCCC, metastatic tumors may be more heavily glycogenated than the primary [1]. It is critical to recognize that there is variability of prognostic markers ER, PR and HER2 in breast carcinomas [15] and GATA3 in GRCCC. Special stains for PAS and PAS with diastase will highlight the diastase labile material in both CCH and GRCCC [5,7].

Other malignant clear cell carcinoma mimics of GRCCC, such as signet-ring cell carcinoma and secretory carcinoma, have mucin containing vacuoles. Lipid-rich carcinoma has finely granular fat containing vacuoles. GRCCC, however, has neither mucin nor fat [5].

Clear cell renal cell carcinoma metastasizes to the skin in only 3.3% of cases, predominantly in male patients, and most commonly to the scalp. The majority of patients with skin metastasis already have involvement by additional organ(s) at the time of cutaneous manifestation [16]. Hidradenoma can be further distinguished from metastatic RCC by small ductular lumens, a less prominent vascular pattern, and negative staining for PAX8, CD10 and vimentin [11].

Immunohistochemical staining for p63 is a critical marker in distinguishing primary skin adnexal tumors from metastases as it is expressed in primary adnexal tumors, including in our patient's skin tumor, and is negative in metastasis, including those of breast origin [1]. Variable staining patterns of p63, GATA3, ER, PR and HER2 in triple negative breast carcinomas can cause diagnostic pitfalls. Focal nuclear staining with p63 can be seen in some triple negative breast carcinomas [17]. Staining for GATA3 can be negative in some triple negative breast carcinomas [18] and expressed in skin adnexal tumors [19]. Similarly, in triple negative breast cancer, ER, PR, and HER2 will not help distinguish a metastasis from a benign adnexal tumor that is also negative for these markers. In addition to morphologic differences, comparison of the primary GRCCC immunophenotype to the new axillary mass was very helpful in our case.

The prognosis of GRCCC is debated [15]. Some researchers claim it has a worse prognosis than conventional invasive breast cancers [6,20–22], while some report that with stage-matched comparison, the prognosis is the same [5,23]. In either case, prognosis and treatment of metastatic breast cancer are different from hidradenoma. Nodular hidradenoma is a benign adnexal tumor and transformation into hidradenocarcinoma is extremely rare [11,14]. Thus, complete surgical excision is curative [12]. Treatment of cutaneous involvement by breast carcinoma is variable depending on the extent of involvement. Various treatment options include surgical excision, hormonal therapy if indicated by prognostic markers, radiation if not previously irradiated, or systemic chemotherapy [2].

4. Conclusion

IHC is a useful tool, particularly p63 which is generally positive in