Desmoplastic Trichoepithelioma, Infiltrative/Morpheaform BCC, and Microcystic Adnexal Carcinoma: Differentiation by Immunohistochemistry and Determining the Need for Mohs Micrographic Surgery

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Several important cutaneous neoplasms present with basaloid cells in the dermis. Desmoplastic trichoepithelioma (DTE), infiltrative/morpheaform basal cell carcinoma (BCC), and microcystic adnexal carcinoma (MAC) are tumors in this category that may be difficult to differentiate, especially when evaluating thin biopsy specimens. An accurate diagnosis has important clinical implications. While DTE is a benign neoplasm with indolent behavior, infiltrative/morpheaform BCC and MAC can be highly aggressive, leading to substantial local destruction and potential metastasis. We present a patient with an unusual tumor demonstrating basaloid cells in the dermis and discuss the diagnostic approach for these lesions, emphasizing the potential role of cytokeratin 20 (CK20) in determining the need for Mohs micrographic surgery.

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Case Report

A 53-year-old man with a history of psoriasis treated with UV radiation presented to his local dermatologist for evaluation of a right cheek lesion of 2 years' duration. The lesion was a firm scarlike plaque with telangiectasia that was suspicious for basal cell carcinoma (BCC). A shave biopsy was performed. The lesion was histologically described as a basaloid neoplasm with unusual features. The histologic differential diagnosis included an unusual BCC, desmoplastic trichoepithelioma (DTE), and microcystic adnexal carcinoma (MAC). The neoplasm showed some features of each of these tumors on hematoxylin and eosin–stained sections. The tumor extended to the deep margin and complete reexcision was recommended. The patient was referred to the Mohs micrographic surgery clinic for further evaluation.

Examination showed a 14×14-mm, erythematous, depressed, well-healed scar on the right cheek (Figure 1A). Regional lymph nodes were not palpable. Mohs micrographic surgery was completed in 3 layers extending into subcutaneous fat. The overall size at completion was 26×31 mm (Figure 1B). After a tumor-free plane was achieved, the wound was repaired with a bilobed transposition flap. There were no complications.

Microscopic evaluation of the first layer by frozen tissue sections showed basaloid cells involving the deep dermis and subcutaneous tissue. The architectural pattern showed both infiltrative and micronodular invasive characteristics. Peripheral palisading of the basaloid cells was present. There was no artifactual retraction. Perineural involvement was absent. The tumor nests were larger in the

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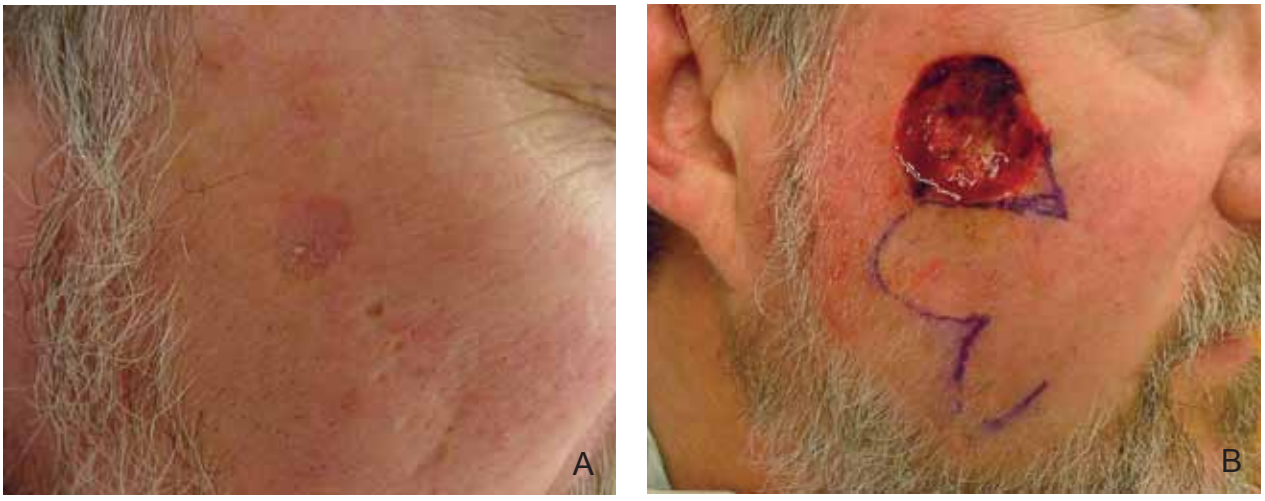

Figure 1. The patient presented to the Mohs micrographic surgery clinic with an atrophic, 14×14-mm scar from a prior biopsy (A). After Mohs micrographic surgery, the final size of the scar was 26×31 mm (B). Three layers, extending into subcutaneous fat, were required to clear the tumor.

superficial reticular dermis, forming small keratin-filled cystic structures that became more strandlike with a morpheaform pattern in the deeper dermis.

The deep tissue specimens were submitted to dermatopathology for paraffin sections. At low power, sections showed irregular angular aggregates of basaloid cells in the dermis and tumor with rounded cystic differentiation and slightly elongated and irregular areas of ductal differentiation (Figure 2). Higher-power sections demonstrated several areas with focal separation between tumor epithelium and stroma, more characteristic of BCC (Figure 3). Sections were stained with BCL2 and showed focal positivity. The working diagnosis was infiltrative/morpheaform BCC versus MAC; however, the absence of reliable immunohistochemical markers made this tumor difficult to distinguish from DTE. A literature review was performed, focusing on recent advances in the role of immunohistochemistry in delineating these tumors. Cytokeratin 20 (CK20), a marker for Merkel cells, has demonstrated utility in distinguishing DTE from MAC and infiltrative/morpheaform BCC (discussed below). Cytokeratin 20 staining was performed and was negative, suggesting that the lesion was an infiltrative/morpheaform BCC or MAC, both indications for Mohs micrographic surgery.

Comment

Desmoplastic trichoepithelioma, infiltrative/morpheaform BCC, and MAC can present as

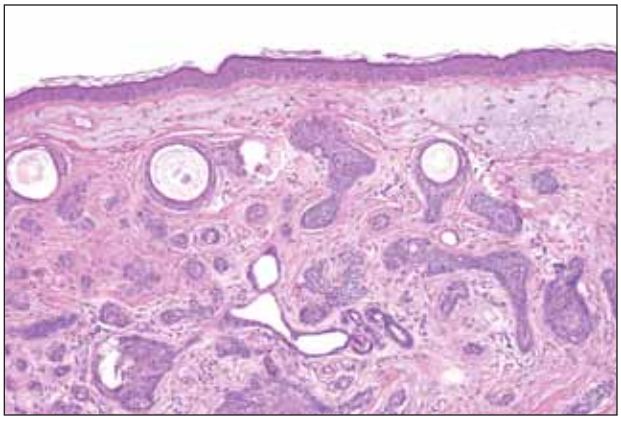

Figure 2. Tumor with rounded cystic differentiation and slightly elongated and irregular areas of ductal differentiation. Notice the contrast between solar elastosis (bluish tinge in superficial dermis) and eosinophilic hyalinized stroma. No connection with the epidermis is present (H&E, original magnification ×40).

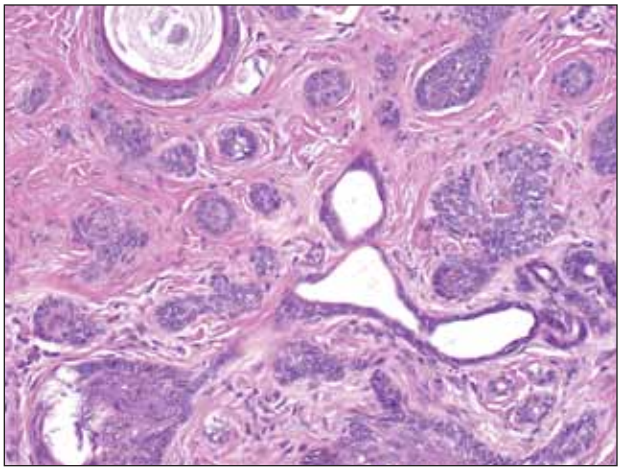

Figure 3. Cystic and ductal differentiation were demonstrated. Note several areas with focal separation between tumor epithelium and stroma, characteristic of basal cell carcinoma (H&E, original magnification ×100).

Table 1.

Histopathologic Differentiation of DTE and Infiltrative/Morpheaform BCC

Reference	Clinical Feature[a]
Brownstein and Shapiro[2]	Horn cysts, epidermal hyperplasia, squamous aggregations, calcifications
Takei et al[10]	Depression in the center, papillated surface, symmetry, no clefts between aggregations of cells and stroma, neoplastic cells connected to the infundibula, no bizarre shapes of aggregations, follicular differentiation, no perineural invasion, solar elastosis above the stroma, shadow cells in cysts
Costache et al[11]	Depression in the center; symmetrical; connection to the infundibula; well-circumscribed infundibular, sebaceous, or follicular differentiation; granulomas around ruptured cysts; calcification; combination with a melanocytic nevus; no solar elastosis beneath the lesion; no clefts between aggregations of cells and stroma

Abbreviations: DTE, desmoplastic trichoepithelioma; BCC, basal cell carcinoma.
[a]Features present in DTE and usually absent in infiltrative/morpheaform BCC.

indistinguishable facial lesions. Desmoplastic trichoepithelioma, first described by Zeligman[1] in 1960 and definitively characterized by Brownstein and Shapiro[2] in 1977, is a benign, slow-growing tumor that occurs with a female to male ratio of 6 to 1. Desmoplastic trichoepithelioma almost exclusively occurs on the face and presents as an annular plaque with a raised border and central dell.[2] Reported treatment options include excision, laser ablation, dermabrasion, electrosurgery, and observation.[3,4] Infiltrative/morpheaform BCCs, by contrast, are aggressive uncommon histologic variants of BCC. Infiltrative/morpheaform BCC often presents as a white to yellow, poorly demarcated sclerotic plaque. Among subtypes of BCC, infiltrative/morpheaform BCC is second only to basosquamous carcinoma in risk for subclinical spread.[5] Microcystic adnexal carcinoma is an aggressive tumor first described by Goldstein et al[6] in 1982 and presents most often as a midfacial plaque with palpable borders in white patients aged 40 to 60 years. It is frequently misdiagnosed, resulting in incomplete excision and a high risk for recurrence.[7-9] Additionally, complete removal via Mohs micrographic surgery has shown that actual tumor size is a mean of 4 times larger than the clinically apparent tumor, emphasizing the failure of clinical margins to predict the tumor's full extent.[7]

Histologic evaluation with hematoxylin and eosin stain is the most useful tool in the diagnosis of tumors with basaloid cells in the dermis. Several authors have published criteria for distinguishing DTE and infiltrative/morpheaform BCC (Table 1).[2,10,11] Desmoplastic trichoepithelioma demonstrates a triad of thin epithelial strands, keratin cysts, and a sclerotic stroma without perineural growth.[2] Classic findings of infiltrative BCC include clumps of basaloid cells with minimal palisading in a loose stroma. Morpheaform BCC shows thin strands of basaloid cells in a sclerotic stroma, clefts between neoplastic cells and stroma, and frequent perineural infiltration.[2]

Histologic features shared by DTE and infiltrative/morpheaform BCC include aggregates of basaloid cells, sclerotic stroma, cystlike structures, and occasionally solar elastosis.[2,11] A case series examining the histologic differences of DTE and morpheaform BCC found a positive likelihood ratio greater than 10 for DTE if any of the following signs were present: symmetry; circumscription; a depression in the center; connection to the infundibula; infundibular, sebaceous, or follicular differentiation; granulomatous inflammation around ruptured cysts; calcification; absence of clefts between aggregations of cells and stroma; or absence of solar elastosis beneath the lesion.[11]

Characteristic histologic findings seen in sufficiently deep biopsies of MAC include a stratified appearance of superficial keratocysts; progressively smaller islands and strands of basaloid cells in deeper sections; and an infiltrative growth pattern with perineural infiltration, ductal differentiation, and a fibrous stroma.[12] Despite these common features, MAC can be difficult to diagnose by

Table 2.

Summary of Case Series Evaluating Positive Staining for DTE, Infiltrative/Morpheaform BCC, and MAC[a]

	Ber-EP4		Androgen Receptors		Cytokeratin 20				
	Hoang et al,[12] n	Krahl and Sellheyer,[14] n	Costache et al,[11] n	Katona et al,[15] n	Hoang et al,[12] n	Costache et al,[11] n	Katona et al,[15] n	Smith et al,[16] n	Abesamis-Cubillan et al,[17] n
DTE	4/8	12/16	0/19	2/15	1/8	19/19	15/15	0/4	14/14
Infiltrative/ morpheaform BCC	10/10	28/28	18/18	20/31	0/10	0/18	1/31	0/10	1/11
MAC	5/13	0/13	NA	NA	0/13	NA	NA	NA	0/8

Abbreviations: DTE, desmoplastic trichoepithelioma; BCC, basal cell carcinoma; MAC, microcystic adnexal carcinoma; NA, not applicable.
[a]Values for each case series represent number of cases indicative of DTE, infiltrative/morpheaform BCC, or MAC on histopathology.

hematoxylin and eosin staining alone. Ohtsuka and Nagamatsu[8] reported that 15 of 51 cases (29%) were initially misdiagnosed by histopathology. Chiller et al[7] reported that 13 of 48 cases of MAC (27%) were inaccurately characterized at initial biopsy. Leibovitch et al[13] found a misdiagnosis rate of 32.5%, and Snow et al[9] found that 9 of 13 cases of MAC (69%) were misdiagnosed preoperatively.

Definitive diagnosis of basaloid dermal neoplasms is clearly not always possible by routine histology. Advances in immunostaining techniques have led to better characterization of basaloid dermal tumors, potentially improving diagnostic accuracy. Numerous stains have been investigated over the last 10 years, including BCL2, Ber-EP4, androgen receptors (ARs), and CK20 (Table 2). Studies have found BCL2 to be an unreliable marker in distinguishing trichoepithelioma and BCC, and few studies have evaluated BCL2 in DTE and infiltrative/morpheaform BCC specifically.[11,18]

Ber-EP4 is a monoclonal antibody that recognizes glycopeptides found in most epithelial cells. It has been used to distinguish BCC from squamous cell carcinoma and to identify BCC in areas of inflammation during Mohs micrographic surgery.[19,20] More recently, Ber-EP4 has been investigated as a marker to differentiate DTE, infiltrative/morpheaform BCC, and MAC. However, 2 case series have yielded conflicting results, calling into question its value.[12,14]

Androgen receptors are transcription factors that have been explored as markers to distinguish DTE from infiltrative/morpheaform BCC. Costache et al[11] found AR positive in 0 of 19 cases of DTE and 18 of 18 cases of infiltrative/morpheaform BCC, suggesting usefulness in ruling out BCC. Katona et al,[15] on the other hand, found AR expression in 2 of 15 cases of DTE and 20 of 31 cases of infiltrative/morpheaform BCC. Thus, the validity of this immunostain also remains unclear.

Cytokeratin 20, a marker for Merkel cells, has shown the most promise in differentiating DTE, infiltrative/morpheaform BCC, and MAC. Desmoplastic trichoepithelioma typically retains Merkel cells within the superficial aspect of the lesion, whereas BCC lacks Merkel cells in tumor aggregates.[15] Three case series found CK20 universally positive in DTE and virtually absent in infiltrative/morpheaform BCC, demonstrating an excellent sensitivity and positive predictive value for DTE.[11,15,17] Additionally, all MAC evaluated stained negative for CK20.[12,17] Interestingly, of 161 tumors evaluated with CK20, only 2 lesions not diagnosed as DTE (both BCC) stained positive, suggesting its value in differentiating DTE from infiltrative/morpheaform BCC and MAC. Two smaller case series showing lower sensitivity in staining for DTE, however, leave the role of CK20 in delineating these tumors unclear.[12,16]

Our patient's presentation illustrates the diagnostic dilemma that sometimes arises when differentiating DTE, infiltrative/morpheaform BCC, and MAC. This difficulty stems from overlapping histologic features and immunostains with inconsistent results. Because of the aggressive nature of infiltrative/

morpheaform BCC and MAC, it is necessary to distinguish these tumors from DTE, an indolent tumor that may not require treatment. Margin-controlled excision is the treatment of choice for infiltrative/morpheaform BCC and MAC; differentiating them does not change the treatment plan.[5,7,9] Therefore, it is logical that if an adequately deep biopsy is performed and well-established histologic criteria fail to differentiate DTE from infiltrative/morpheaform BCC and MAC, a highly sensitive and specific immunostain that could rule out DTE (ie, rule in infiltrative/morpheaform BCC or MAC) would be ideal for determining the need for Mohs micrographic surgery. In tumors with basaloid cells in the dermis, CK20 appears to be the most sensitive and specific stain for DTE and potentially the most useful in directing the treatment plan. The tumor in our patient demonstrated negative staining for CK20, effectively ruling out DTE and supporting the decision to proceed with margin-controlled excision. Further studies are needed to clarify this approach and the validity of utilizing CK20 in the evaluation of unusual tumors with basaloid cells in the dermis.

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