

Multiple Microcystic Adnexal Carcinomas

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GOAL

To understand microcystic adnexal carcinomas (MACs) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the distribution of MACs.
2. Describe the histology of MACs.
3. Identify treatment options for MACs.

CME Test on page 306.

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Microcystic adnexal carcinoma (MAC) is a relatively uncommon adnexal neoplasm that can demonstrate locally aggressive behavior; rare instances of metastatic lesions have been reported. We report a case of a 34-year-old black man with multiple primary MACs.

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Case Report

An otherwise healthy 34-year-old black man presented for evaluation of a progressive lesion on the left thigh that had been diagnosed as lichen simplex chronicus 15 years earlier. The patient stated that the lesion had been there for approximately 19 years and had gotten progressively but not rapidly larger. Results of a physical examination revealed a 3-cm indurated hyperpigmented plaque with prominent scale (Figure 1). There were approximately 21 other lesions (of varying age by patient report); the most prominent lesion was located on the right shoulder (Figure 2). Other clinically similar lesions, ranging from less than 1 cm to about 10 cm, were noted on the hands, arms, shoulders, back, abdomen, thighs, and lower legs in both sun-exposed and non-sun-exposed areas. There were no lesions on the face.

Biopsy results revealed a microcystic adnexal carcinoma (MAC). Subsequent workup, including computed tomography, revealed 3 small areas of



Figure 1. A 3-cm lesion on the left thigh.



Figure 2. A 2-cm indurated plaque on the right shoulder.

pleural thickening but no evidence of internal metastatic disease. The patient had no other significant medical history, and he reported no prior radiation therapy. He reported that none of his family members had a history of MAC. Eighteen months after the patient's lesions were first biopsied, no subsequent lesions had developed, and no substantial clinical progression of current lesions was noted; the patient remained in good health.

Histology—Punch biopsy specimens were obtained of lesions in the upper left lateral thigh, lower left inner leg, and left web space between the thumb and index finger. An excisional specimen was available for the lesion from the left thigh. Biopsies of all 3 lesions showed similar histology (Figure 3). Examination results from the specimens at low power revealed mild to moderate psoriasiform epidermal hyperplasia with acanthosis, hyperkeratosis, and basilar hyperpigmentation, changes similarly encountered in lichen simplex chronicus. Larger cystic structures were immediately subadjacent in the superficial dermis, with follicular differentiation and cyst formation. Admixed were ductal structures consisting of basaloid cells, with eccrine differentiation consisting of cells with a moderate amount of pale ill-defined eosinophilic cytoplasm and oval hyperchromatic nuclei. Cytologic pleomorphism was not encountered.

Overall, the tumors demonstrated a stratified appearance, with larger cystic structures in the superficial dermis being replaced by smaller cysts and cords and nests of cells in the deeper dermis (Figure 4). In all specimens, there was extension into the subcutis. Perineural invasion was identified focally. In the superficial dermis of some of the specimens, the follicular cystic structures showed evidence of rupture, with keratin debris in the

adjacent dermis and subsequent foreign body giant cell reaction. Results of immunoperoxidase tests on paraffin tissue showed the epithelial cells to be diffusely positive for cytokeratins (AE1/AE3) and carcinoembryonic antigen. Evaluations for the presence of estrogen and progesterone receptors both had negative results.

Comment

MAC is an uncommon adnexal malignancy with locally aggressive and infrequently metastatic behavior. Originally described by Goldstein et al,¹ this lesion has a propensity for the centrofrontal area. Clinically, this neoplasm usually presents with an indurated plaque or nodule averaging 2 cm. MAC has been reported as long-standing in some patients, with an inclination for recurrence despite extensive surgical therapy. The lesions are infiltrative, and perineural invasion is frequent.^{2,3} Locoregional metastasis is an infrequent occurrence,^{4,8} and widespread metastasis has been described in only one case.⁹

Although MACs can arise in virtually any age group, most MACs occur in older individuals, with a reported average age of incidence between 44 and 64 years and an overall range of 11 to 90 years.^{3,10} Although a slight female predominance has been noted in some case series, overall the sexes are equally affected.¹¹ A review of the cases of MAC in the slide files of our laboratory revealed a similar distribution, with an average age of 63 years and a 1:1 male-female ratio. Most of our cases also involved the face or neck, with this patient as the only case of MACs occurring elsewhere anatomically.

The principle underlying risk factors for and etiologic influences of MAC are largely unknown. Several studies have noted that MACs are found predominantly on the left side of the face. The exact

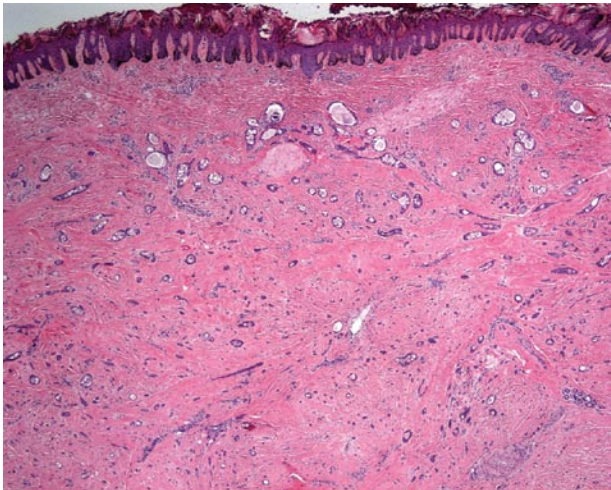


Figure 3. Photomicrograph of a lesion from the left thigh (H&E, original magnification $\times 40$).

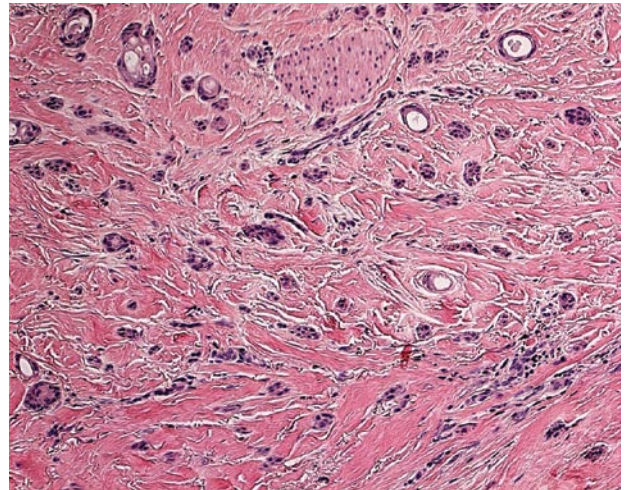


Figure 4. Higher power photomicrograph of the same lesion as Figure 3 (H&E, original magnification $\times 100$).

reason for this anatomic distribution is unclear, but it could be indicative of the fact that MAC has a tendency to develop in UV-exposed areas. A prior review has postulated that this distribution could be caused by sun exposure while driving; however, this theory has not been adequately tested because no comparisons have been made between incidence in the United States versus Australia or England where driving, and thereby sun exposure, occur on the right side.¹² Prior radiation exposure also has been implicated as a potential risk factor, and several cases have described MAC occurring in an area of previous radiation therapy.^{13,14} Similarly, a potential explanation for a portion of these lesions occurring on the face is that several patients with MAC have had prior radiation therapy for facial acne.^{10,15} There also is a report in the literature of MACs occurring in the axilla in patients who received radiation therapy for breast cancer.³ Additionally, immunodeficiency has been implicated as an etiologic influence,⁴ and there is one report of documenting a familial influence with occurrence in 2 sisters.¹⁰

MAC is a rare tumor, and the lack of physician familiarity with it and limited biopsy sampling can frequently lead to misdiagnosis. As described in the current case, MAC clinically can present as a plaquelike, nodular, or cystlike tumor existing for many years and occasionally for decades. The overlying skin may appear unaffected or have slight lichenification, and ulceration is extremely uncommon. Often, the tumor is biopsied numerous times during several years before a correct diagnosis is made.

As infrequent as MAC is, it is fleetingly rare in the black population. Only 3 case reports exist in the literature, and these lesions were all solitary.¹⁶⁻¹⁸ One

of the cases was similar to ours in that the lesion was very large and long-standing; the lesion was present on the scalp for at least 31 years. The other 2 reported cases involved the scalp and upper lip, and the lesions in both cases were smaller than 2 cm.¹⁶⁻¹⁸

The histologic similarities of MAC with other basaloid tumors, combined with its indistinct clinical appearance, can lead to misdiagnosis. MACs typically demonstrate histology results similar to our case. The Table lists both benign and malignant tumors that share histologic features with MAC. The histologic features that are most helpful in distinguishing MAC from these benign and malignant entities are a stratified histologic appearance with ductal differentiation and the presence of perineural involvement with deep dermal infiltration. Although a desmoplastic trichoepithelioma will commonly show similar 2-tier histology results, with the presence of superficial keratocysts and a deeper basaloid infiltrative cell population, the condition will not have deep dermal involvement, ductal differentiation, or perineural involvement. Perineural involvement also will not be demonstrated in syringoma or trichoadenoma. Although deep dermal involvement and perineural invasion can be seen in the 3 malignant entities included in the Table, the histology results of these conditions typically will not show a stratified appearance. Basal cell carcinoma, in addition, rarely demonstrates ductal differentiation in the morpheic or infiltrative form.¹¹

To our knowledge, no case reports of patients with multiple primary cutaneous lesions existed prior to the presentation of this patient. Martin et al¹⁹ describe an 8-year-old patient with multiple carcinomas on the lower extremities arising within systemized compound epithelial lesions; however, only

Tumors With Histologic Features Similar to Microcystic Adnexal Carcinoma

Benign Tumors

Syringoma

Desmoplastic trichoepithelioma

Trichoadenoma

Malignant Tumors

Basal cell carcinoma (infiltrative and morpheic types)

Squamous cell carcinoma (poorly differentiated)

Metastatic adenocarcinoma

one of these lesions was MAC, and the remainder showed divergent differentiation. Multiple primary lesions in our current case are manifested by the stratified histologic appearance of the tumor at the primary sites and are supported by the lack of metastatic disease elsewhere, which was demonstrated by extensive clinical examination and the absence of additional clinical symptoms or suspicious lesions on computed tomography.

Reports of metastasis in MACs also are infrequent and represent only 6 cases in the medical literature worldwide^{3-5,7-9}; 4 of these cases possibly do not describe true metastases^{3-5,7}—one in the axilla that arguably represented tumor extension.³ Two of the others showed metastatic disease in ipsilateral lymph nodes, with a primary lesion on the right posterior scalp⁴ and the upper forehead,⁷ respectively. The fourth case illustrated cutaneous metastases in transit, possibly representing recurrence and not metastasis.⁵

A recent report described a patient with lung metastases,⁸ and a single case exists in the literature of a patient with widely metastatic MAC of long-standing duration.⁶ For this reason, and despite its aggressive local behavior, MAC is considered to be a tumor with excellent overall prognosis. Of the more than 300 cases from the medical literature worldwide, only the group of aforementioned lesions demonstrated metastatic potential, which represents an incidence rate of only 2% (probably overrepresented because reported cases only are a fraction of cases in existence). The death rate of reported cases, 0.3%, is an overestimate for similar reasons.²¹

Because MAC demonstrates its greatest morbidity from local invasion and destruction with locoregional recurrence, the optimal therapeutic approach generally consists of Mohs micrographic surgery (MMS) or primary surgical excision (intraoperative frozen section).¹² Local recurrence following surgical excision, however, is not uncommon. In a comprehensive study using MMS, it was found that the extent of these lesions generally is 4-fold larger than the initially clinically evident lesion. Hence, intraoperative assessment of marginal status is paramount.¹²

In a study of 48 cases, 22 cases were treated with MMS, 23 cases were treated with simple excision, and 3 cases were untreated.¹² Only 2 of the cases treated with MMS recurred after a single procedure. In those cases treated with excision, 7 cases (30%) had to have at least one additional surgical procedure before excision was deemed complete, and 1 case experienced recurrence. The overall recurrence rate was similar between the 2 groups (1.98% per patient-year), but fewer procedures were required.¹² Although a small number of cases have been treated with adjuvant modalities, including radiation and chemotherapy, the effectiveness of this protocol, in addition to surgical excision, is most likely minimal.²²

Our case represents a therapeutic problem in that the number and size of the lesions would be a monumental task to undertake surgically. The indolent course of these lesions might require a conservative clinical approach, such as surgical therapy reserved for problematic or aesthetically displeasing lesions. Systemic therapy was proposed in this patient, possibly using currently known biologic adjunctive therapy such as tamoxifen citrate and trastuzumab. Given that this tumor tested negative for both estrogen and progesterone receptors, as well as HER2/neu, biologic therapy was not undertaken. In addition, the indolent nature and low proliferative rate of these neoplasms most likely would make them poorly responsive to radiation or chemotherapy.

A recent case report by Eisen and Zloty²¹ described a 58-year-old woman with a 12×12-cm MAC involving a large portion of the face. Similar to our case, this patient presented a difficult therapeutic problem because surgical intervention would involve substantial facial disfigurement. The authors opted, as we did, for close clinical surveillance; 2 years after initial diagnosis, the patient continued to do well, with no reported evidence of metastatic disease.²¹

Radiation therapy has been advocated for palliation in elderly or debilitated individuals; however, this therapy is less than ideal because these lesions generally are radioresistant, and recurrence following this therapy is not infrequent. In addition,

radiation has been implicated as a causative mechanism. Comparing treatment methods for a tumor for which no randomized prospective studies exist is difficult, but because the tumor can be locally aggressive, surgical therapy should be pursued if feasible.

Comment

Our case of multiple primary cutaneous MAC in a black patient appears to represent a unique presentation of MAC. Therapeutic options, particularly in a patient with multiple lesions, represent a difficult clinical problem; however, close clinical follow-up without surgical intervention, except for those cases in which MMS is feasible, remains a reasonable alternative.

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