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Microcystic Adnexal Carcinoma and a Summary of Other Rare Malignant Adnexal Tumours

Arif Aslam, MBChB, MRCP

Address
St Helens and Knowsley Teaching Hospitals NHS Trust, Marshalls Cross Road, St Helens, WA9 3DA, UK
Email: a.aslam@doctors.org.uk

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Opinion statement

Microcystic adnexal carcinoma (MAC) is a rare, slow-growing, infiltrative malignant tumour most commonly found on the head and neck. It often presents as a solitary skin-coloured or yellow papule, plaque or nodule. Ultraviolet radiation, immunosuppression and ionising radiation are possible risk factors. Clinical and histological differential diagnoses include morpheaform basal cell carcinoma and desmoplastic trichoepithelioma. The diagnosis is usually made by skin biopsy, and the characteristic features are small keratin-filled cysts with nests and cords which resemble ductal structures. Immunohistochemistry can assist in differentiating MAC from other tumours. The local aggressive nature of the tumour and its potential to infiltrate beyond the assessed clinical margins warrant complete excision with margin control, and we recommend Mohs micrographic surgery. Wide local excision is widely performed but is associated with recurrence given its infiltrative nature and extensive subclinical extension. The role of radiotherapy in the management of MAC is unclear.

Introduction

Malignant adnexal skin tumours arising from sweat glands are rare. Microcystic adnexal carcinoma (MAC) is a rare malignant cutaneous tumour of the skin with pilar and eccrine differentiation first described as a clinical entity in 1982 [1]. Historical synonyms found in the literature include sclerosing sweat duct carcinoma, syringomatous carcinoma and malignant syringoma [2–7].

MAC is a locally aggressive, slow-growing and infiltrative tumour with a predilection for the head and neck and has the potential to invade the dermis, muscle, adipose tissue and nerves causing significant morbidity [3, 8].

MAC is clinically and histologically difficult to diagnose. It usually presents as a slow-growing indurated nodule, a plaque which can often be easily

confused with benign adnexal tumours such as trichoepithelioma, trichoadenoma or syringoma. Histologically, MAC is composed of keratin horn cysts, nests or cords of basaloid cells which are usually more prominent in the superficial dermis. Tumour strands and cystic dilated tubules are arranged in solid islands and embedded in the deeper desmoplastic stroma.

We suggest Mohs micrographic surgery as the treatment of choice for MAC.

Pathophysiology

Only a few hundred cases of MAC have been reported in the literature, and its rarity makes it difficult to establish its aetiology although ultraviolet radiation, immunosuppression and ionising radiation have been implicated [9–12].

Given that most tumours are located on the head and neck suggests ultraviolet radiation exposure may be the greatest risk factor for its development. This hypothesis is supported by a US case series in which 52% of tumours were located on the left (drivers side) side of the face in contrast with an Australian series where 56% were on the right side (drivers side) [9].

The risk of nonmelanoma skin cancer in the context of immunosuppression is well established and despite case reports of MAC associated with renal transplant and chronic lymphocytic leukaemia, the exact risk is unclear [10, 11].

Several case reports raise the possibility of ionising radiation as a risk factor for MAC [12].

Epidemiology

The largest reported series of patients with MAC—The Surveillance, Epidemiology and End Results (SEER) database analysis of 223 patients collected between 1973 and 2004—found an incidence rate of 6.5 per million Caucasian individuals with a slight female preponderance (57 versus 43%) [9] though it has also been reported in other ethnic groups. MAC commonly affects older patients, and in the SEER analysis, the average age was 68 years old although very rare paediatric and congenital case reports have also been published [13–16].

Clinical presentation

MAC usually presents as a solitary, asymptomatic, slow-growing, poorly defined yellow or skin-coloured papule or plaque most commonly found on the head and neck [9] (Fig. 1). It may resemble a morpheaform basal cell carcinoma, squamous cell carcinoma, scar, desmoplastic trichoepithelioma, trichoadenoma, metastatic breast carcinoma or syringoma. Additional reported sites of MAC include the scalp, trunk, extremities, breast, vulva, axilla, perineum, hands and feet [17].

A metastatic case has been reported in an adolescent [18•].

The average tumour size at presentation in one study was less than 2 cm in 80% of all patients although the clinical size is difficult to determine due to extensive subclinical involvement [19].

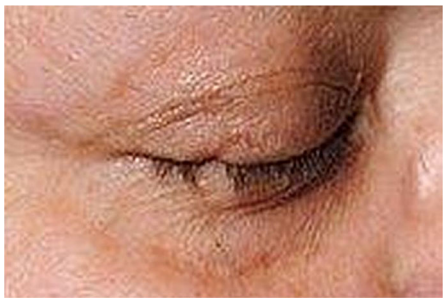

Fig. 1. A poorly defined scar-like papule on the right upper eyelid treated with Mohs micrographic surgery

Histopathology and immunohistochemistry

MAC is a deeply infiltrative asymmetrical tumour, and its key histological features are small keratin-filled cysts, islands of basaloid keratinocytes and ductal structures extending into the deeper dermis surrounded by desmoplastic stroma [2]. The neoplastic cells are often bland with little if any atypia and very few mitoses. The ductal features help differentiate MAC from other benign adnexal tumours such as desmoplastic trichoepithelioma and trichoadenoma which do not usually need treatment. Immunohistochemistry can be utilized to help differentiate between MAC and desmoplastic trichoepithelioma and morpheaform basal cell carcinoma. Among the most commonly employed markers are cytokeratin 7 (CK7), cytokeratin 15 (CK15), cytokeratin 19 (CK19), cytokeratin 20 (CK20), androgen receptor strains, carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA) and Ber-EP4 although no single marker is able to differentiate any of these entities.

BerEP4, a monoclonal antibody, recognizes two glycopolypeptides (34 and 39 kDa) found in most human epithelial cells differentiates with a high degree of reliability between basal cell carcinoma and squamous cell carcinoma. Several studies have supported its use in differentiating between MAC (BerEP4 negative) and BCC (BerEP4 positive) [20, 21].

A new follicular stem cell marker, pleckstrin homology-like domain family A, member 1 (PHLDA1) also known as T-cell death-associated gene 51 (TDAG 51) has recently been confirmed to be effective in differentiating between DTE and morpheaform basal cell carcinoma [22].

Diagnosis

A skin biopsy is usually sufficient to confirm the diagnosis of MAC, but a full thickness biopsy is required to avoid missing its deep infiltrative nature. Promising noninvasive imaging techniques such as reflectance confocal microscopy and optical coherence tomography have recently been reported to help detect MAC [23•, 24•].

Table 1 summarises the key clinical and histological features, immunohistochemistry and management of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheaform basal cell carcinoma.

Table 1. A summary of the clinical and histological features, immunohistochemistry and management of microcystic adnexal carcinoma, desmoplastic trichoepithelioma and morpheaform basal cell carcinoma

	Clinical features	Histological features	Immunohistochemistry	Management
Microcystic adnexal carcinoma (MAC)	Slow-growing solitary papule or plaque	Small keratin-filled cysts, islands of basaloid keratinocytes and ductal structures in the deeper dermis surrounded by desmoplastic stroma	BerEP4 negative CK15 positive	Mohs micrographic surgery
Desmoplastic trichoepithelioma (DTE)	Firm annular plaque or nodule with a central depression	Proliferation of basaloid cells arranged in small nests and strands in the superficial dermis	BerEP4 positive PHLDA1 positive CK15 positive	Observation
Morpheaform basal cell carcinoma	White or yellow depressed fibrotic scar which rarely bleeds or ulcerates	Angulated columns of neoplastic basaloid cells one to two cells thick in a dense collagenised stroma	BerEP4 positive PHLDA1 negative CK15 negative	Mohs micrographic surgery

Management

The rarity of this tumour, the pattern of growth and its recent description have resulted in only a small number of publications evaluating the best treatment option. Surgery is the most definitive treatment modality for MAC, and options include wide local excision with postoperative margin evaluation and Mohs micrographic surgery (MMS) which involves histological review of the complete tissue margin. We recommend MMS as the treatment of choice for MAC as the infiltrative nature and subclinical extension necessitate complete removal.

Wide local excision

Wide local excision is more readily available and has been successfully used for the management of MAC, but there are no consensus guidelines on the recommended surgical margins. The local recurrence rate for MAC in patients treated with a standard wide local excision reaches 60% in various series [8, 25], and re-excision will be required if postoperative histological assessment shows the tumour has not been removed with adequate margins. Standard histological techniques involve bread loaf sectioning of tissue where less than 1% of the entire margin is examined which could lead to undetected residual tumour.

Table 2. Key clinical and histological features of other rare malignant adnexal tumours

	Common sites	Clinical features	Histological features
Adenoid cystic carcinoma	Face, head and neck Can occur at other sites (salivary gland, breast, lung and external auditory canal)	Slow-growing skin-coloured nodule Associated with an increased risk of haematological malignancy following diagnosis	Poorly circumscribed tumour composed of basaloid cells with a glandular, cystic, cribriform and tubular arrangement embedded in a loose fibrous and sometimes mucinous stroma
Apocrine carcinoma	Axilla, anogenital region, scalp, eyelid and nipple	Highly variable but slow-growing erythematous plaque or nodule	Tumour cells are characterized by hyperchromatic nuclei, nuclear pleomorphism, mitotic figures and a lack of decapitation secretion
Cylindrocarcinoma	Most commonly on the scalp	Rapidly growing bleeding ulcerated preexisting lesion	There is usually a benign component with transition to areas with features of malignancy
Digital papillary adenocarcinoma	Fingers and toes	Solitary nodule located on the volar aspect of upper extremity digits; most often found in Caucasian men in their 50s to 70s and can be present weeks to years before being diagnosed	Solid cystic multinodular tumour located in the dermis or subcutis with papillary projections into the cystic space. It has tubuloalveolar and ductal patterns with papillary projections and a stroma with both fibrous septae and hyaline collagen
Endocrine mucin-producing sweat gland carcinoma	Eyelid (most commonly lower eyelid)	Slow-growing cyst or swelling	Well-circumscribed, typically multinodular tumours with solid or partially cystic nodules with areas of papillary architecture
Hidroadenocarcinoma	Most frequently head and neck	Solitary nodule or plaque with telangiectasia and ulceration	There are two different cell types: eosinophilic cytoplasm laiden darker fusiform/spindle cells and larger clear cells exhibiting atypical mitotic figures and nuclear pleomorphism
Porocarcinoma	Most frequently on the lower legs	Solitary plaque or nodule which evolves slowly leading to bleeding and ulceration. Often mistaken for a pyogenic granuloma or squamous cell carcinoma	Ulcerated tumour with connection to the epidermis consisting of lobules and anastomosing trabeculae with a pushing border
Primary cutaneous mucinous carcinoma	Most commonly on the face particularly the eyelids and scalp of elderly females	Slow-growing indolent erythematous nodule	Nests and strands of epithelial cells separated by thin fibrous septae surrounded by abundant mucin

Table 2. (Continued)

	Common sites	Clinical features	Histological features
Primary cutaneous signet ring cell carcinoma	Occurs almost exclusively on the eyelids or axilla with a male predominance	Presents with eyelid inflammation and oedema often misdiagnosed as ptosis or blepharoconjunctivitis. In the axilla, it presents as subcutaneous nodule	Polygonal cells with a histiocytoid appearance, granular eosinophilic cytoplasm with prominent nucleoli forming signet ring cells
Spiroadenocarcinoma	Can occur anywhere on the body	A previously undiagnosed lesion on the trunk or extremities which rapidly enlarges, changes colour, ulcerates or becomes painful	By definition, the diagnosis requires identification of a benign spiradenoma within or adjacent to the malignant tumour. There is abrupt transition from the benign component to a high-grade carcinoma or a low-grade tumour with similar architectural features to a benign spiroadenoma
Squamoid eccrine ductal carcinoma	Incredibly rare. Predilection for the head and neck in the elderly	Ill-defined nodule or plaque	Deeply infiltrative involving the dermis with areas of squamous and ductal differentiation

Mohs micrographic surgery

MMS involves horizontal en-face sections of the entire outer surface of the excised tissue, thereby examining 100% of the peripheral and deep margins. Several case series have been published on the successful treatment of MAC with MMS [26–30].

The Australian MMS database contains the largest reported prospective series of MAC managed with MMS [19]. Of 44 cases treated between 1993 and 2005, 20 completed a follow-up period of 5 years. The 5-year recurrence rate was 5% which is much lower than the wide local excision technique and is similar to other previously published series. This study found perineural invasion to be very common in recurrent tumours emphasising the importance of complete excision using MMS. This same group reported the 5-year follow-up data of five periocular cases from the 44 of which three were followed up for 5 years, and there was no recurrence [30]. A recent 10-year case series review of periocular MAC also demonstrated extensive perineural invasion in at least half of all cases highlighting that MMS is the required treatment for periocular MAC to maximize the possibility of tumour clearance [33••].

Several retrospective studies have found recurrence rates after MMS to be between 0 and 12% [28, 29, 31].

The role of adjuvant radiotherapy

Despite the isolated case reports on the success of radiation therapy, its role in the management of MAC is uncertain and there is insufficient evidence to

support its routine use. Further studies are required to determine its efficacy, safety and optimum treatment regime. A retrospective study on the use of adjuvant radiation therapy after surgical intervention in 14 patients of which 11 had positive surgical margins who were followed up for a median of 5 years showed 13 out 14 patients achieved local control suggesting that radiation therapy after conventional surgery could match success rates in those treated with MMS [32].

Follow-up

There are no universal guidelines on the follow-up of the patients with MAC, but given the potential for recurrence, we recommend long-term follow-up. All patients should undergo a full skin and lymph node examination every six to 12 months.

Other malignant adnexal tumours

Malignant adnexal tumours are a heterogeneous group of rare tumours that are diagnostically challenging with similar names and no consensus regarding their classification and nomenclature.

Table 2 summarises the key clinical and histological features of other rare malignant adnexal tumours.

Compliance with Ethical Standards

Conflict of Interest
The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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