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A diagnostic challenge in an atypical variant of microcystic adnexal carcinoma mimicking ulcerative basal cell carcinoma: a case report and brief literature review

Nurul Indah Pratiwi[1], Khairuddin Djawad[1] ✉, Jonathan Kurnia Wijaya[1], Mahmud Ghaznawie[2], Siswanto Wahab[1], Airin Nurdin[1]

[1]Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [2]Department of Pathology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

Abstract

Microcystic adnexal carcinoma (MAC) is a rare adnexal tumor with eccrine and pillar differentiations with a localized and aggressive nature, often misdiagnosed as other dermatoses. The most common clinical manifestations of MAC are yellowish or skin-colored papules, nodules, and plaques. However, in some rare cases an atypical manifestation such as ulceration that resembles malignancies such as basal cell carcinoma (BCC) can also occur. Diagnosis of MAC mainly relies on the aid of histopathology. Due to potential infiltration to other structures such as in perineural invasion, wide surgical excision or Mohs micrographic surgery is the preferred surgical option. We report the case of a 75-year-old male patient with ulcerative lesion on the forehead that clinically resembled BCC in addition to typical dermoscopic findings of BCC. However, histopathology confirmed a diagnosis of MAC, prompting physicians to be more aware of this condition when encountering chronic ulcerative lesions. After wide excision and a 1-year follow-up, the patient exhibited no signs of recurrences and will continue long-term follow-up.

Keywords: microcystic adnexal carcinoma, basal cell carcinoma, ulcerative, atypical

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Introduction

Adnexal tumors are malignancies that occur on skin adnexal structures such as eccrine, sebaceous, apocrine, and follicular glands. Most cases of adnexal tumors are benign and rarely metastasize. The incidence of adnexal tumors is relatively rare, with many types, classifications, and variations. In general, adnexal tumors are characterized by solitary or multiple papules or nodules with minimal epidermal changes. The color of the lesion varies, ranging from skin-colored to bluish or pinkish. In addition, the presence of a central hair follicle orifice or punctum may also be visible (1, 2). Microcystic adnexal carcinoma (MAC) is a malignant adnexal tumor that was first described in 1982 by Goldstein et al. Initially, it was identified as a tumor with eccrine and pillar differentiation with an aggressive but localized nature that could infiltrate to the muscles, cartilage, blood vessels, nerves, and bones. Some synonyms for MAC include *sclerosing sweat duct carcinoma*, *sweat gland carcinoma with syringomatous features*, *aggressive trichofolliculoma*, *syringoid carcinoma*, and *malignant syringoma*. In general, MAC can be classified as a low-grade eccrine gland tumor (1–8).

Case report

A 75-year-old male patient visited the dermatology and venereology clinic and presented with a solitary ulceration on the forehead that had emerged 3 years prior. Initially, the lesion appeared as a black lump that gradually enlarged. Occasional pruritus caused the patient to scratch the lesion, resulting in slight excoriation, pain, and ulceration. The patient had a prior history of chronic sun exposure without any routine use of sunscreen. Otherwise, the patient was healthy and a family history of similar complaints was denied.

Physical examination found that the patient's vital signs were within normal limits, and dermatological examination revealed a solitary ulcer with a diameter of approximately 3 cm, crusting, and necrotic tissue surrounded by raised violaceous irregular borders (Fig. 1A). Dermoscopy revealed ulceration, scales, and blue-gray globules (Fig. 1B). Based on these findings, the patient was initially diagnosed with basal cell carcinoma (BCC).

Initially diagnosed as low-risk BCC, standard excision of the lesion was then performed with a 5 mm margin (Fig. 1C). Histopathological examination found proliferation of eccrine glands along with infiltrative hair follicle differentiation on the dermis and subcutaneous tissue that extended to the striated muscles. Formation of chain-like microcystic glands with collagen stroma cells could also be seen (Fig. 2A–C). In addition, there was also perineural invasion (Fig. 2D–E). The patient was then diagnosed with an atypical variant of MAC. After histopathological examination confirmed that the margin was free of tumor cells, the patient declined further operative reconstruction, and a 1-year follow up from secondary healing showed minimal scarring (Fig. 1D). Long-term follow-up was then scheduled to observe possible recurrences of the lesion.

Discussion

Epidemiology

A study in 2019 reported that the number of MAC cases globally was approximately 700 cases (9). Incidence varies between 1.6 and 6.5 cases per 10,000,000 population. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data in 2010 (10), MAC most often affects persons between

✉ Corresponding author: duddin@ymail.com

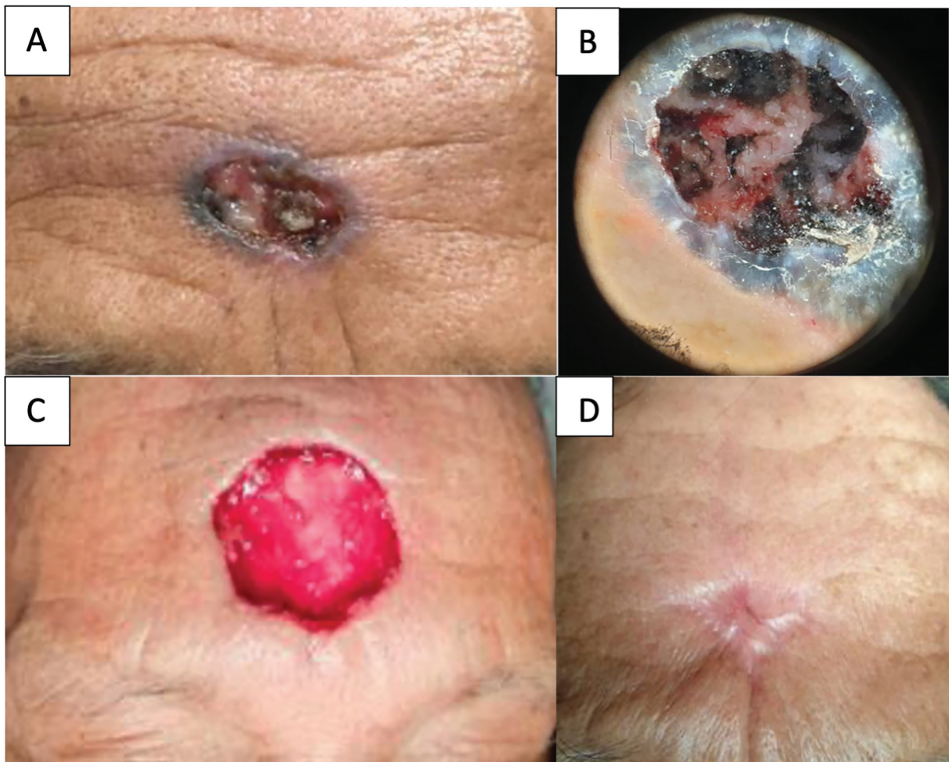

Figure 1 | (A) Initial lesion, (B) dermoscopy revealed ulceration, scales, and blue-gray globules, (C) resulting defect, (D) a 1-year follow-up showed minimal scarring.

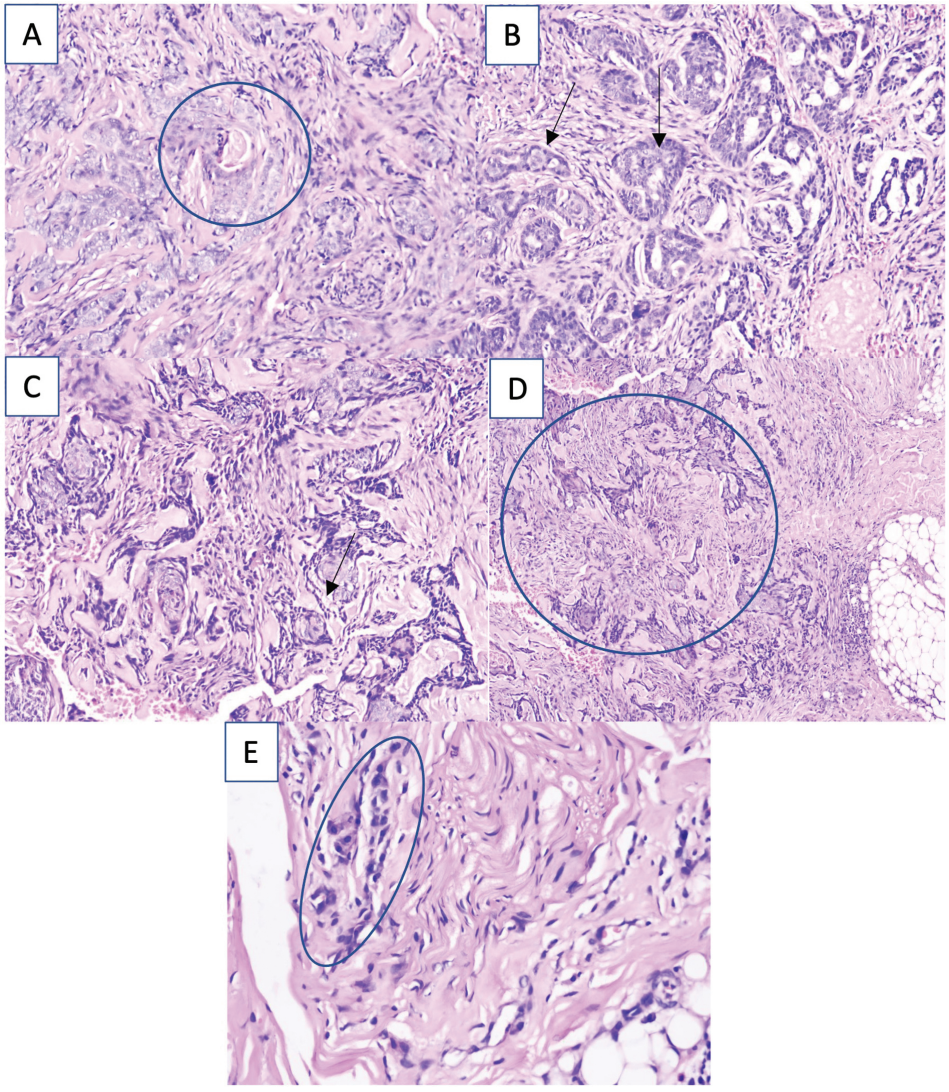

Figure 2 | (A) Histopathological examination showed hair follicle differentiation, (B) eccrine gland differentiation forming a microcystic structure, (C) a chain-like structure, (D, E) tumor perineural invasion.

the ages of 44 and 64, although it can also occur in other age groups (age range 11–90 years). Chiller et al. reported the median age of MAC incidence in females to be between 60 and 69 years, and between 50 and 59 years in males. Although some reports have stated that MAC has no sex preference, based on the latest SEER epidemiological data in 2019, MAC cases were dominated by females. In addition, the incidence of MAC in 2019 was 0.52 cases per 1,000,000 population, mostly occurring in white patients (83.3%), followed by Hispanics (5.9%), African-Americans (3.0%) and Asians (2.3%) (11). One of the challenges in the diagnosis of MAC is the overlap of histopathological examination results between benign and malignant cutaneous proliferations (4, 10).

Etiology and pathogenesis

Originally described as a tumor with pillar and eccrine differentiation, there have been other reports stating that MAC may originate from other structures, such as the apocrine glands. According to Requena et al., MAC is derived from the differentiation of apocrine, follicular, and sebaceous glands (12). In addition, with its predilection on the face and neck, it is hypothesized that chronic sun exposure may play a role in the pathogenesis of MAC (13). Furthermore, radiation exposure and immune suppression (e.g., organ transplantation and chronic lymphocytic leukemia) may also lead to the formation of MAC (5).

Studies reporting the incidence of MAC in patients with solid organ transplantation are still limited. One article reported a case of MAC on the glabella of a patient undergoing liver transplantation, and another case reported the occurrence of MAC in a kidney transplant patient (14). MAC after radiotherapy has also been reported, but this has not been conclusively proven (1, 15). A transcriptomic analysis reported that there are four genes that are upregulated in MAC; namely, *CACNA1S*, *MYLK3*, *RYR1*, and *ATP2A1*, which are all in the calcium signaling pathway and may be investigated further as both a diagnostic and therapeutic marker for MAC. One of the constraints of this study is the small sample size of only six patients (16).

Clinical manifestation

MAC may manifest clinically as hard, indurated plaques, with a major predilection on the face, particularly on the perioral, periocular, and central facial areas, as well as the neck (1, 4, 9, 17). Other clinical variants include solitary yellowish white papules or plaques with a diameter of 1 to 3 cm on the face or areas frequently exposed to sunlight (3, 9). Anatomically, MAC has most commonly been reported on the head and neck (75.1%), trunk (11.2%), shoulder and upper extremities (6.8%), lower extremities (4.0%), and other locations (3.0%) (11). Another study by King et al. in the United States found that out of a total of 67 MAC cases, 53 cases (79%) occurred on the face, followed by the trunk (9%), extremities (4%), and other areas (7%) (18). Although locally destructive, the mortality rate is relatively low, with no significant differences in the 10-year survival rate for patients with or without MAC (5).

A serial case study reported that MAC lesions had a diameter between 0.03 and 16 cm along with induration (4). The lesions are indolent and asymptomatic, and patients generally only sought medical care if the lesions enlarged or evolved. Its destructive but localized nature clinically resembles BCC and may lead to perineural invasion. When this occurs, patients may experience complaints of ulceration and paresthesia. In some rare cases, MAC can lead to lymph node metastasis (9). Similar to the case described in Kim et al. (9), the clinical findings for our patient were similar to ulcerative BCC, in which a solitary ulcer along with crusting and necrotic tissue surrounded by raised violaceous irregular borders forming a rolled border typical of BCC was found on the sun-exposed forehead area. Dermoscopic findings of ulceration, scales, and blue-gray globules are also common in BCC (9, 19).

Another article reports a case of chronic and indolent MAC of the upper lip that developed over 27 years in a 58-year-old white woman that presented with a yellow plaque with indistinct borders and telangiectasis (4). Although locally destructive, the mortality rate is relatively low, with no significant differences in the 10-year survival rate for patients with or without MAC (5).

Other uncommon clinical manifestations of MAC include fissures, atrophy, and scaling (4). Hinther et al. reported a case of MAC with poorly demarcated indurated nodules and plaques on the nasal and paranasal structures along with telangiectasis that resembled phymatous rosacea (6).

Histopathological and radiological findings

Histopathology aided in the diagnosis, with findings of basaloid follicular cells in the upper dermis with follicular differentiation and basaloid cells with ductal structures on the lower dermis (20). To obtain a valid biopsy result, the specimens taken must be deep enough to include the subcutaneous fat. Superficial biopsies may increase the risk of misdiagnosis with desmoplastic trichoepithelioma (3, 15). Therefore, the recommended biopsy techniques can be either an excisional biopsy or a punch biopsy (3).

The histopathological features of MAC may overlap with other tumors, making the diagnosis of MAC challenging (5). In general, the histopathological appearance of MAC is an infiltrative asymmetrical tumor (5). Microscopically, MAC findings can be divided into three zones. The upper dermis may contain tumor cells arranged as bands, threads, and horny keratinized cysts of various sizes and shapes. In the middle dermis, thread-like structures and ribbons may be visible. In the deep dermis, tadpole-shaped ductal structures and hyaline stroma nests can be found (13). Perineural invasion may occur with unclear borders (1, 5).

Extensive keratinocyte differentiation represents a follicular origin, whereas epithelial and ductal bands represent eccrine differentiation. These variations suggest that MAC originates from various keratinocyte adnexal structures (4). Staining with toluidine blue may be useful in detecting individual tumor cells or small tumor nests, as well as perineural involvement in frozen sections. In normal nerve fiber cells, toluidine blue staining will result in a blue color, whereas in nerves with tumor involvement a magenta or purplish-red color will be visible (4).

The use of immunohistochemical staining (IHC), although not diagnostic, may aid in diagnosis of MAC. Stains such as carcinoembryonic antigen (CEA) or epithelial membrane antigen (EMA) and CK20 can be performed to rule out the diagnosis of desmoplastic trichoepithelioma. Ber-EP4 stains are used to exclude morpheaform BCC if histopathological results are inconclusive (4, 13). Positive IHC stains in MAC include CK5/6, CK7, CK8/18, CK15, S100, and CD117 (1, 21, 22).

Radiological examination is generally not required, but magnetic resonance imaging can be used to define tumor borders, as well to evaluate potential metastasis (4). The use of optical coherence tomography (OCT) is a relatively new, non-invasive, and real-time investigation tool that can be performed prior to surgery

or to monitor treatment efficacy. The results of OCT in MAC are divided into two parts: superficial and sub-epidermal findings. In the superficial part, there is an irregular and uneven smooth surface without skin adnexa. In the subepidermal section, there is a regular structure that is round and large with both hyper- and hypo-refractive alterations resembling an onion, which is a keratin cyst (5).

Differential diagnosis

BCC is one of the most common misdiagnoses for MAC, mainly due to the similar clinical features and dermoscopic findings. However, our patient exhibited an atypical clinical manifestation of ulceration rather than dermal plaques or nodules, making the diagnosis more challenging. A similar case report from India reported a 58-year-old male patient with a 3 × 2 cm plaque on the right upper lip that extended to the vermilion area with a depression in the center of the plaque forming a crater-like structure. Dermoscopic examination revealed a white pink structureless area with crusts, scales, and bleeding spots. On the periphery, arborizing vessels and yellowish clumps with grayish-brown spots were found, features similar to BCC (8). One of the most characteristic dermoscopic findings in MAC is white clods of various sizes representing a keratinized cyst structure. Interestingly, although the appearance of arborizing vessels is commonly found in BCC, it can also be visible in MAC (8).

The rate of misdiagnosis of MAC may reach as high as 27%, and the disease is often reported as syringoma, morpheaform BCC, desmoplastic trichoepithelioma, cystic adenoid carcinoma, or squamous cell carcinoma (SCC). The superficial part of MAC lesions may show keratinized structures resembling SCC (1, 23).

Some features that are not histopathologically found in syringoma include asymmetry, single-celled thread structure features, and perineural and intramuscular invasion. Syringmatous carcinoma may be clinically indistinguishable from MAC, but histopathologically it can be distinguished by a more basaloid appearance and prominent dermal sclerosis (5).

Coexistence of other tumors may also occur, such as a case report of SCC with MAC. The patient was initially referred with an indurated plaque lesion in the vermilion area of the upper lip to the nasal vestibule area measuring 2.6 × 1.4 cm. She was initially diagnosed with BCC and underwent debulking and Mohs micrographic surgery (MMS), in which frozen sections showed atypical keratinocyte proliferation consistent with SCC. However, in the later stages of MMS, multifocal perineural invasion was found with basaloid tumor cells representing MAC. Analysis of the debulked permanent specimen revealed a large sclerotic epithelial tumor with indistinct borders and atypical keratinocytes from the epidermis to the superficial dermis (23).

Management and treatment

Because the patient in our case was initially diagnosed with low-risk BCC due to its size, a standard excision with a 5 mm margin was performed. According to consensus by the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC), a margin of 3 to 4 mm is sufficient for treatment (19).

The main goal of MAC treatment is complete removal of the tumor while preserving the patient's functional and cosmetic aspects (3, 24). Based on the *Journal of the American Medical Association* (JAMA) guideline in 2019, localized MAC can be treated with surgery such as MMS with frozen sections, permanent sections, and complete circumferential peripheral and deep margin assessment (CCPDMA) (3). Due to the invasive nature of MAC, defects produced by MMS can measure four times larger than the visible tumor (4).

An alternative to MMS is wide excision with a 2 cm margin through the deep fascia. Wide excision was reported to be the most common surgical technique for MAC according to SEER data in 2010 (87%), followed by MMS (10.8%) (10). However, the recurrence rate in excision is high, up to 47% in the first 3 years after excision (5), compared to MMS, which has a lower recurrence rate of 0 to 22% in the first 5 years post-surgery (25). On average, it takes about 2.6 stages of MMS to completely excise MAC. Another alternative is the slow Mohs technique, which uses a paraffin section, which is easier to examine histopathologically. However, this method is more time consuming (5).

A case report by Lopez et al. reported an 85-year-old female patient with a skin-colored papular lesion on the nasal tip. After several MMS procedures, she was initially suspected of having morpheaform BCC, and this was histopathologically confirmed as MAC. The patient went through 12 stages of MMS due to deep and multifocal infiltration, resulting in a large defect measuring 12 × 8 cm in size on the glabella, nose, and both sides of the cheek, causing significant morbidity (26).

Radiotherapy as monotherapy is generally not recommended, with the exception of inoperable and recurrent cases (3). Until recently, the use of chemotherapy was not the main therapeutic modality for MAC. One case report by Kim et al. reported the simultaneous use of chemotherapy and radiation therapy (chemoradiation) in a 72-year-old male patient with a confirmed history of MAC 12 years prior. The patient refused surgery and underwent chemoradiation therapy. After a 7-week treatment with a combination of carboplatin and paclitaxel, prophylactic radiotherapy was performed on several areas of lymphatic nodules to prevent the spread of tumor cells and, although it is toxic and not routinely used, the patient responded well to therapy. It should be noted, however, that in this case the PET/CT scan examination did not find any perineural, lymphovascular, or bone involvement (1).

Research is currently underway on the efficacy of using multitargeted tyrosinase receptor kinase (MTRK) therapy as well as a combination of targeted therapy with cetuximab and imitinib with conventional radiotherapy for cases of MAC that are resistant to surgery. Cetuximab functions as an antibody receptor that inhibits epidermal growth (3).

Follow-up and prognosis

Long-term patient follow-up is of paramount importance in MAC patients. The aim is to evaluate the possibility of metastasis and recurrencies. It is recommended that a period of up to 30 years post-surgery is needed. The JAMA guideline recommends an interval follow-up period between 6 and 12 months within the first 5 years. If recurrence occurs, MMS/CCPDMA with or without radiotherapy can be performed. Furthermore, if lymphatic spread occurs, the site of the primary tumor should be excised followed by excision of the affected lymphatic node. If metastases occur, confirmed through examinations such as PET/CT scan, multispecialty management with the oncology department is required (3). In our case, the patient is scheduled for routine follow-ups with a 6-month in-

terval over the next 5 years followed by routine annual check-ups.

Conclusions

MAC is a rare adnexal tumor with a high misdiagnosis rate. Adequate biopsy and histopathological findings are important to confirm the diagnosis. Although it has a relatively low mortality rate, MAC can cause significant morbidity due to resulting defects post-surgery (27).

References

1. Foreman RK, Duncan LM. Appendage tumors of the skin. In: Kong S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. Fitzpatrick's dermatology. 9th ed. New York: McGraw-Hill; 2019. p. 1820–56.
2. Shinohara R, Ansai S, Ogita A, Matsuda H, Saeki H, Tanaka M. Dermoscopic findings of microcystic adnexal carcinoma. Eur J Dermatol. 2015;25:516–8.
3. Worley B, Owen JL, Barker CA, Behshad R, Bichakjian CK, Bolotin D, et al. Evidence-based clinical practice guidelines for microcystic adnexal carcinoma: informed by a systematic review. JAMA Dermatol. 2019;155:1059–68.
4. Gordon S, Fischer C, Martin A, Rosman IS, Council ML. Microcystic adnexal carcinoma: a review of the literature. Dermatol Surg. 2017;43:1012–6.
5. Hamed NS, Khachemoune A. Microcystic adnexal carcinoma: a focused review and updates. J Dermatol Dermatol Surg. 2015;19:80–5.
6. Hinther K, Henni J, Asiniwasis RN. An atypical presentation of extensive centrofacial microcystic adnexal carcinoma responding to radiation: a case report and review of the literature. SAGE Open Med Case Rep. 2020;8:2050313X20953114.
7. Chen J, Yang S, Chen J, Liao T, Deng W, Li W. Microcystic adnexal carcinoma in a non-Caucasian patient: a case report and review of the literature. Oncol Lett. 2016;11:2471–4.
8. Gupta V, Kakkar A, Agarwal S, Sulaiman M, Ramam M. Dermoscopic pitfall: microcystic adnexal carcinoma mimicking basal cell carcinoma. Indian J Dermatol Venereol Leprol. 2020;86:202–5.
9. Kim DW, Lee G, Lam MB, Harris EJ, Lam AC, Thomas T, et al. Microcystic adnexal carcinoma of the face treated with definitive chemoradiation: a case report and review of the literature. Adv Radiat Oncol. 2020;5:301–10.
10. Yu JB, Blitzblau RC, Patel SC, Decker RH, Wilson LD. Surveillance, Epidemiology, and End Results (SEER) database analysis of microcystic adnexal carcinoma (sclerosing sweat duct carcinoma) of the skin. Am J Clin Oncol. 2010;33:125–7.
11. Amon G, Liszewski W, Maher IA. Epidemiology and survival of microcystic adnexal carcinoma by sex in the United States. Dermatol Surg. 2021;47:127–9.
12. Mamic M, Manojlovic L, Suton P, Luksic I. Microcystic adnexal carcinoma-diagnostic criteria and therapeutic methods: case report and review of the literature. Int J Oral Maxillofac Surg. 2018;47:1258–62.
13. Debata T, Pati P, Das S. Microcystic adnexal carcinoma of face a rare aggressive pathology. Oncol J India. 2017;1:16–8.
14. Stamey CR, Colegio OR, Book SE. Microcystic adnexal carcinoma of the glabella in a liver transplant recipient. JAAD Case Rep. 2020;10:126–9.
15. McKinley LH, Seastrom S, Hanly AJ, Miller RA. Microcystic adnexal carcinoma: review of a potential diagnostic pitfall and management. Cutis. 2014;93:162–5.
16. Yu S, Wang Y, Tang B, Liu X, Song L, Xu G, et al. Four calcium signaling pathway-related genes were upregulated in microcystic adnexal carcinoma: transcriptome analysis and immunohistochemical validation. World J Surg Oncol. 2022;20:142.
17. Cox D, Myers E. Microcystic adnexal carcinoma of the lower lip: a report of a case and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:198.
18. King BJ, Tolkachjov SN, Winchester DS, Baum CL, Brewer JD, Arpey CJ, et al. Demographics and outcomes of microcystic adnexal carcinoma. J Am Acad Dermatol. 2018;79:756–8.
19. Kura M, Aliporewala V, Bolde S, Bijwe S. Microcystic adnexal carcinoma. Indian J Dermatol Venereol Leprol. 2020;86:595–6.
20. Hoang MP, Dresser KA, Kapur P, High WA, Mahalingam M. Microcystic adnexal carcinoma: an immunohistochemical reappraisal. Mod Pathol. 2008;21:178–85.
21. Zhang L, Huang X, Zhou T, Cao H. Microcystic adnexal carcinoma: report of rare cases. Biosci Rep. 2020;40.
22. Ken KM, Moye MS, Vandergriff T, Nijhawan RI. Collision tumor of microcystic adnexal carcinoma and squamous cell carcinoma discovered on Mohs sections. JAAD Case Rep. 2020;6:479–81.
23. Al-Wassia RK, Al-Qathmi MS. Microcystic adnexal carcinoma of the scalp treated with surgical resection along with chemoradiation: a case report and review of the literature. Saudi J Biol Sci. 2021;28:7117–24.
24. Palamaras I, McKenna JD, Robson A, Barlow RJ. Microcystic adnexal carcinoma: a case series treated with Mohs micrographic surgery and identification of patients in whom paraffin sections may be preferable. Dermatol Surg. 2010;36:446–52.
25. Lopez M, Cole EL. Microcystic adnexal carcinoma: reconstruction of a large centrofacial defect. Plast Reconstr Surg Glob Open. 2014;2:e254.
26. Gerall CD, Sippel MR, Yracheta JL, Hogan FS. Microcystic adnexal carcinoma: a rare, commonly misdiagnosed malignancy. Mil Med. 2019;184:948–50.