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*Original Article*

# Desmoplastic melanoma involving head and fingers: diagnostic challenges and clinical characteristics

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**Abstract:** Desmoplastic melanoma (DM) is considered a variant of melanoma, characterized by a paucicellular proliferation of malignant spindled melanocytes with an abundant collagenous or "desmoplastic" stroma and an intense inflammatory response. As DMs lack pigmentation, their appearances vary and can mimic many benign and malignant conditions, thus presenting a diagnostic challenge. Here, we are presenting one case involving the head and two cases involving fingers. One of our cases distinctively invade nerves and bones. We reviewed the literature for many similar cases. Most cases presented positive staining of S-100 and negative or focal positive staining of Melan-A and Melanoma. So far, the mechanisms of the rare entity have not been clearly recognized. Early accurate diagnosis and complete excision of this tumor is necessary. Some researchers considered BRAF-targeted therapy may be limited to a small number of patients with DM. Advanced DM may respond well to anti-PD-1 monotherapy.

**Keywords:** Desmoplastic melanoma (DM), malignant melanoma, diagnostic challenges, immunostaining, therapy

## Introduction

Desmoplastic melanoma (DM) is a relatively rare variant melanoma that was first described by Conley and his colleagues in 1971 DM is less than 4% of all primary cutaneous melanomas. Data from the Surveillance, Epidemiology and End Results (SEER) program from the National Cancer Institute (NCI) presented that the male/female ratio is approximately 2:1 and the mean age of patients is 66 years. The incidence has been steadily increasing over the past 15 years [1-4]. Nearly 3600 cases were identified in SEER database, up until now [5].

Unlike cutaneous pigmented melanoma, DM usually shows no or little pigment and is characterized by dense spindle-like shaped melanoma cells with abundant collagenous matrix. It can mimic many benign and malignant conditions, such as cutaneous scar, dermatofibroma, pleomorphic fibroma, neurofibroma, sclerosing melanocytic nevus, basal cell carcinoma, sclerosing spingdle cell squamous cell carcinoma, fibrosarcoma, myxofibrosarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor (MPNST). In addition, DM commonly is negative or only focally positive for Melan-A, gp100, tyrosinase, and MITF. DM is positive for S-100 and SOX-10 [1, 6, 7]. Of note, cutaneous scar is also positive for SOX-10 and MPNST is also positive for S-100 [8]. Therefore, immunostain expression should be interpreted with caution and in conjunction with an immunohistochemical panel, H&E staining, and growth pattern. Genetically, DM showed frequent mutations in the NF-1, TP53, NF-1, NF-2, NRAS, CDKN2A, and ARID2 genes but mutations in BRAF, GNAQ, GNA11 or KIT mutations are also absent [9-13].

The etiology of DM is still uncertain, but it seems to be associated with chronic ultraviolet exposure, as it frequently presents a firm amelanotic papule or nodule on a sun-damaged area. DM primarily presents in the head and neck area. Other sites can also be involved, including extremities, trunk, oral cavity, conjunctival, genital areas [1]. Recent studies indicated that distant recurrence rates and lymph node metastasis for DM were lower than what is seen for non-DM [4, 16-18], not in accor-

**Table 1.** Antibodies used for immunohistochemical staining

| Antibody | Clone number | Source | Dilution |
|---|---|---|---|
| CK (pan) | AE1/AE3 | MAB, Fuzhou, China | Ready to use |
| EMA | E29 | Dako | concentrated |
| Calponin | CALP | MAB, Fuzhou, China | Ready to use |
| S-100 | 4c4.9 | MAB, Fuzhou, China | Ready to use |
| NSE | E27 | MAB, Fuzhou, China | Ready to use |
| Langerin | 12D6 | MAB, Fuzhou, China | Ready to use |
| BCL-2 | MXD22 | MAB, Fuzhou, China | Ready to use |
| CD34 | QBEnd/10 | MAB, Fuzhou, China | Ready to use |
| CD31 | JC/70A | MAB, Fuzhou, China | Ready to use |
| CD99 | O13 | MAB, Fuzhou, China | Ready to use |
| actin | HHF35 | MAB, Fuzhou, China | Ready to use |
| desmin | D33 | Dako | concentrated |
| SMA | 1A4 | MAB, Fuzhou, China | Ready to use |
| Ki-67 | MIB-1 | Dako, Glostrup, Denmark | 1:100 |
| Melanoma | MX026 | MAB, Fuzhou, China | Ready to use |
| Melan-A | A103 | MAB, Fuzhou, China | Ready to use |
| P53 | MX008 | MAB, Fuzhou, China | Ready to use |

**Table 2.** Results of immunohistochemical staining

| Immunohistochemistry | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| S-100 | + | + | + |
| Melan-A (A103) | - | - | Focal + |
| Melanoma (HMB45) | - | - | Focal + |
| NSE | + | N | N |
| P53 | + | N | N |
| Ki67 | + | + | + |
| CK (pan) | - | N | - |
| EMA | - | N | - |
| Calponin | - | - | - |
| CD34 | - | - | - |
| CD31 | - | - | - |
| Desmin | - | - | - |
| SMA | Focal + | Focal + | N |
| Actin | Focal + | N | N |
| CD99 | - | N | - |
| Langerin | - | N | N |
| BCL-2 | - | N | N |

N, not performed.

dance with earlier studies. In contrast, the majority of studies indicated a high risk of local recurrence in DM. One of our presented cases developed local recurrence three times. In this study, we described three cases of DM with clinical, pathological, and immunohistochemical analysis.

## Materials and methods

Three cases of DM were obtained from the Department of Pathology of Ningbo Clinical Pathological Diagnosis center, China. One case was obtained from the Department of Pathology of Ninghai First Hospital, China. The tumors were reviewed by at least two pathologists (Y.S.Y and H.J.Z) with consensus on the diagnosis. The specimens were fixed in buffered formalin and processed routinely and paraffin sections were stained with hematoxylin-eosin (H&E). The use of these human tissue samples has been reviewed and approved by the Research Ethics Committee of Ningbo Clinical Pathological Diagnosis center.

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections by the labeled streptavidin-biotin peroxidase on an automated immunostaining module (Dako), according to the manufacturer's instructions. The tissue sections were immunostained with a panel antibody as listed in **Table 1**. Appropriate positive and negative controls were used for each antibody. Tumor reactivity for immunohistochemical antibodies was scored as follows: -, all tumor cells were negative; +, 5-25% of tumor cells were positive; ++, 26-50% of tumor cells were positive; and +++, > 50% of tumor cells were positive. Only tumor cells with distinct nuclear staining for S-100, Ki67, and P53 were recorded as positive; distinct cell membrane staining for CK (pan); distinct cytoplasm staining for Melan-A, Melanoma, SMA, Calponin, actin, desmin, and NSE; and distinct cell membrane and/or cytoplasm staining for EMA, CD99, BCL-2, Langerin, CD31, and CD34 were recorded as positive.

## Results

### *Clinical features*

The clinical features of all the cases were summarized in **Table 2**. In our case 1, a 76-year-old male with no significant medical history presented to a dermatology clinic due to a mass on the scalp of the right forehead region with pruritus, in March 2013. The mass was found ten

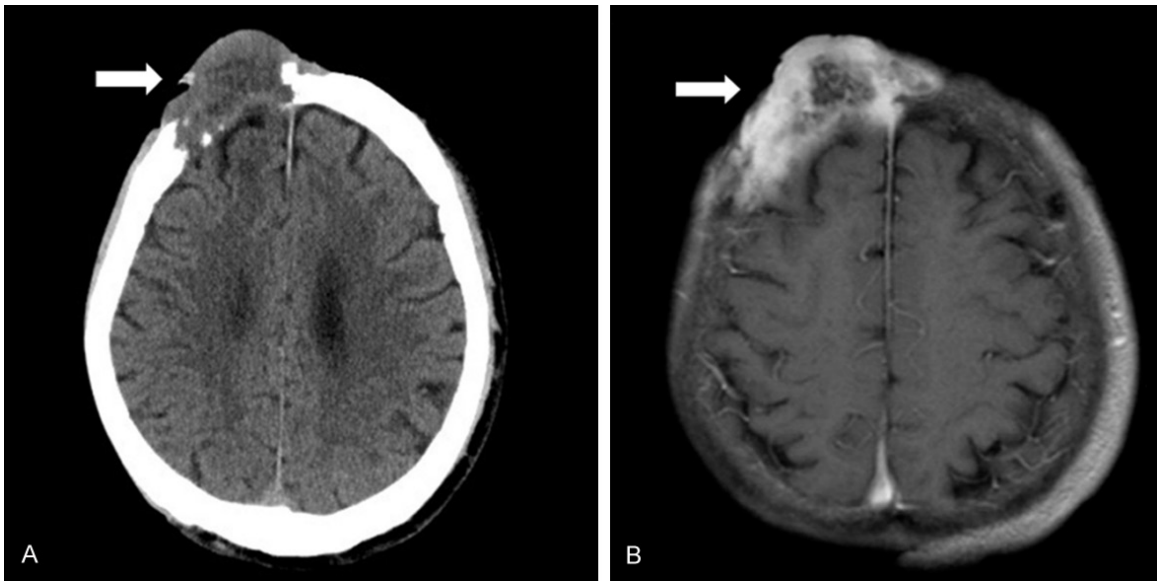


**Figure 1.** A, B. Computer tomography (CT) and magnetic resonance imaging (MRI) revealed a heterogeneous-density occupation in the head and destroyed the bone (arrows).

years ago and increased in size in the recent three years. He underwent excision of the scalp with the tumor. The skin area was 5.3×4.0 cm. The tumor was quasi-circular shaped with the size of 2.0×1.8×1.5 cm. The tumor was challenging given initial similarity to dermatofibrosarcoma protuberans.

The patient developed local recurrence two years after surgery. A re-excision of the recurrent tumor with skin grafting was performed again. One year later, the patient was hospitalized due to experiencing headaches for two months. Magnetic Resonance Imaging (MRI) revealed local destruction in the bone (**Figure 1**). The patient underwent tumorectomy again. After reevaluation of the original and current H&E slides with application of IHC analysis, the diagnosis of DM was finally rendered. The patient was diagnosed with high blood pressure eight years prior and achieved good control by regularly taking medicine. Chemotherapy and local radiation were never given. The patient was alive with headaches at the 3-year follow up.

In our case 2, a 65-year-old female complained of a mass on the dorsum of her left thumb with intermittent pain and skin burst. Physical examination revealed no other lesions. The mass appeared two years ago and originally presented as the size of a grain of rice and gradually enlarged to 2.0 cm. Then she received a local resection. The tumor was interpreted as desmoplastic melanoma by the referring pathologist. After surgery, the patient was not treated with additional chemotherapy or radiation therapy. She was free of disease at her 3-year follow up.

In our case 3, the patient was a 60-year-old female who presented with a mass on the left index finger with nail bed destruction. Subsequently, the patient received a complete excision of the mass and nail bed. The tumor was measured approximately 2×1 cm. The lesion was regarded as desmoplastic melanoma mixed with conventional melanoma, approximately 90% and 10% respectively. The postoperative adjunctive therapy was not administrated. There was no evidence of recurrence or metastasis 3 years after surgery.

In our case 4, a 71-year-old male went to the hand surgery of a local hospital because of a mass on the scalp of the right temporal region. Then, the patient underwent tumorectomy. The mass was originally considered as a spindle cell tumor and sent to consultation and finally diagnosed as desmoplastic melanoma by pathologists. Blood routine and the other laboratory examinations showed no abnormalities. After surgery, the patient did not receive the adjunctive therapy. He was free of disease until now.

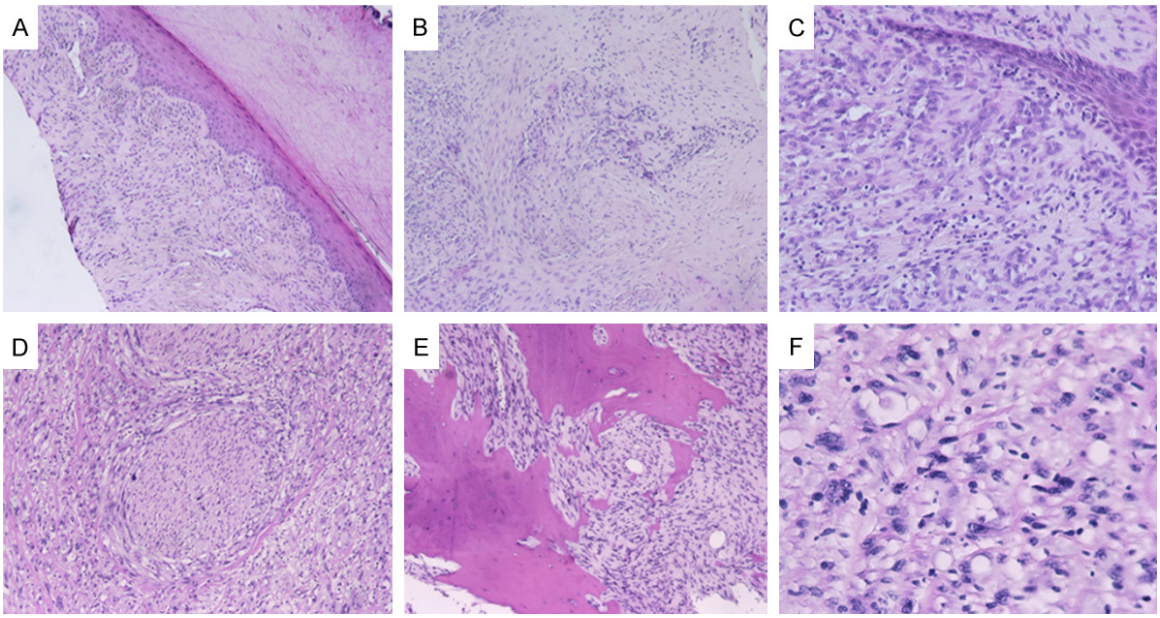


**Figure 2.** Microscopic features of DM. A-C. Irregular cells were predominantly composed of non-pigmented spindle-shaped malignant melanocytes (magnification, ×40), with abundant collagenous matrix, containing abundant lymphoid in flammmatory infiltrates (magnification, ×100). D, E. Tumor cells invaded nerve and bone in our case 1 (magnification, ×100). F. The irregular cells had a deceptively bland appearance with slightly pleomorphic and hyperchromatic nuclei, inconspicuous nucleoli and low mitotic activity (magnification, ×200).

*Pathological features*

Tumor size was approximately 2.0 cm in maximum diameter. On the cut section, the tumors were grayish-white to pink in color and firm. On low power, tumor cells were predominantly composed of non-pigmented spindle-shaped malignant melanocytes, with abundant collagenous matrix, containing abundant lymphoid inflammatory infiltrates (**Figure 2A-C**). Focal perineural involvement and bone destruction were found in our case 1 (**Figure 2D**, **2E**). Malignant cells had invaded the reticular dermis (Clark's level IV) in our three cases. Overall, in our three cases, the irregular cells had a deceptively bland appearance with slightly pleomorphic and hyperchromatic nuclei, inconspicuous nucleoli, and low mitotic activity (**Figure 2F**). However, in the third recurrence of in our case 1, tumor cells were characterized by pleomorphic and hyperchromatic nuclei with prominent nucleoli (**Figure 2D**).

*Immunohistochemical studies*

The results of immunostaining are shown in **Table 2** and **Figure 3**. Non-pigmented spindle cells in our three cases diffusely expressed S-100 with a distinct nuclear stain (**Figure 3A**). Irregular spindle cells displayed variable staining for Melan-A and Melanoma. Case 1 and case 2 were negative for Melan-A and Melanoma, but case 3 demonstrated focal positive for Melan-A and Melanoma and showed moderate intensity (**Figure 3B**, **3C**), coincide with most cases reported in previous literature. In addition, fibroblast cells were focal positive for SMA (**Figure 3D**). Immunostaining of CD31 was in vessels but not tumor cells (**Figure 3E**). The Ki67 proliferative index was approximately 10-15% (**Figure 3F**). Pleomorphic cells were negative for CK (pan), EMA, CD99 (**Figure 3G-I**).

## Discussion

Desmoplastic melanoma is a subtype of spindle cell melanoma with a particular clinical presentation and histologic features. It is characterized by spindled melanocytes, collagenous or "desmoplastic" stroma, and an intense inflammatory response [5, 9, 19, 20]. The diagnosis of DM is one of the major diagnostic challenges in dermatopathology, given it can imitate a number of other spindle cell tumors in the skin. In our case 1, the first differential diagnosis is malignant peripheral nerve sheath tumor (MPNST), owing to the similar histomorphology. They are both composed of a dermal

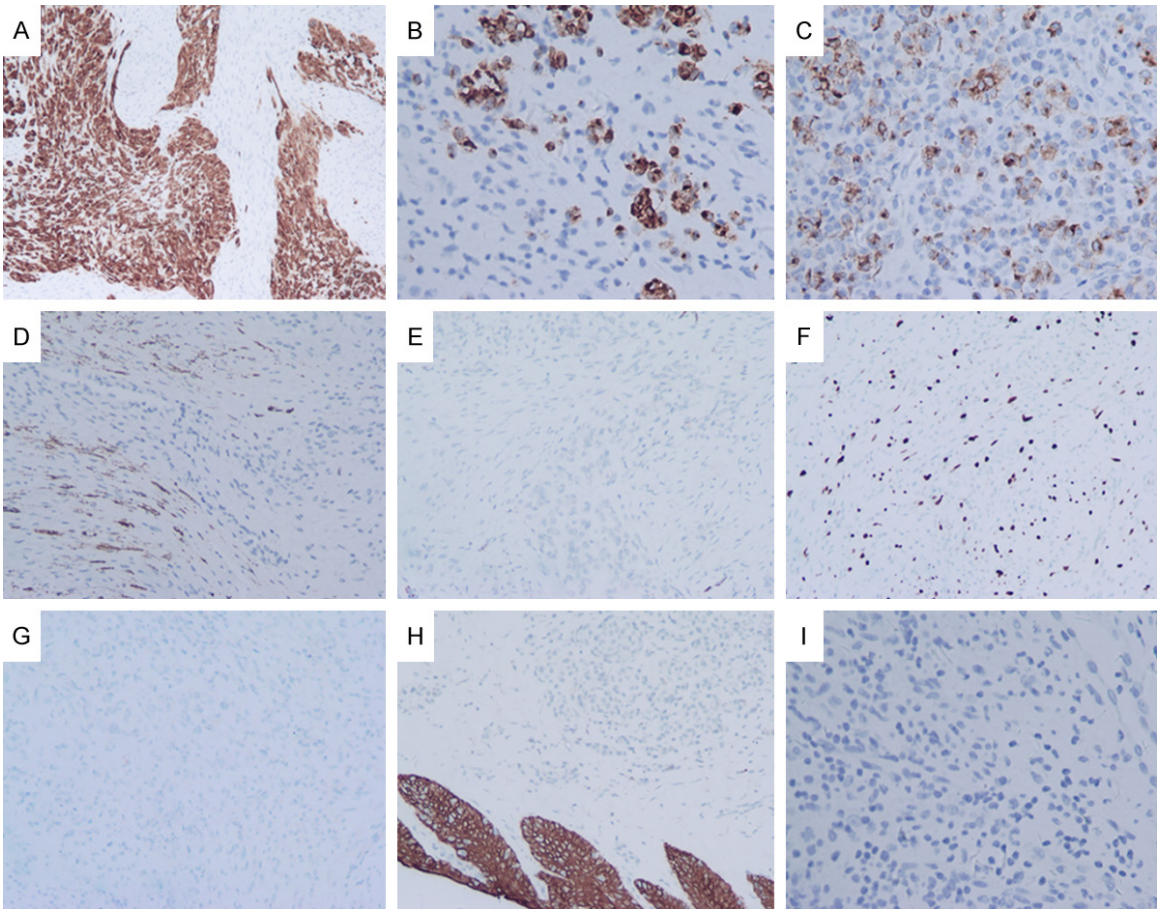


**Figure 3.** Immunohistochemical staining appearance. (A) Non-pigmented spindle cells in our three cases diffusely expressed S-100 with a distinct nuclear stain. (B, C) Irregular spindle cells demonstrated focal positive for Melan-A and Melanoma and showed moderate intensity in our case 3. (D) Fibroblast cells were focal positive for SMA and (E) immunostain of CD31 was in vessels but not tumor cells. (F) The Ki67 proliferative index was approximately 10-15%. (G-I) Pleomorphic cells were negative for CK (pan), EMA, CD99.

spindle cell population set within the desmoplasitic stroma and present a perineural invasion. The atypical spindle cells are positive for S-100 staining. However, the expression pattern is different. MPNST expresses strongly and homogenously for S-100, while S-100 expressions is confined in DM.

Cutaneous scars may be mistaken for DM because scars have been reported positive for SOX-10 [8, 21]. The distinction between scars and DM requires accurate interpretation of SOX-10 immunostain in conjunction with H&E staining. Christopher and John compared SOX-10 staining patterns in 35 scars versus 12 DM to ensure which morphologic features can distinguish the two entities [8]. They found SOX-10 positive cells in scars may look mildly atypical and the nuclei are predominantly monomorphic and small. Nuclear atypia, tissue disorganization, and infiltrative growth can distinguish AM from scars. Prudent use of immunostains and awareness of a potential SOX-10 positive stain in scar tissue should prevent the misdiagnosis and overtreatment of DM. Of note, DM can morphologically mimic synovial sarcoma. TLE1 was widely regarded as a sensitive biomarker for synovial sarcoma, so it can seem to distinguish the DM from synovial sarcoma. However, Travis et al. identified that TLE1 was positive in a significant proportion of melanomas [22]. Therefore, S-100, Melan-A, SOX-10, and TLE1 expression should be interpreted with caution and in conjunction with an immunohistochemical panel, H&E staining and growth pattern.

Desmoplastic melanoma is known to carry a high mutational burden. Lise Boussemart and his collegues reported a panel of 12 desmoplastic melanomas from 1,240 melanoma ca-

ses. They have revealed a median tumor mutational burden (TMB) of 77 mutations in DM. TP53 was the most frequently mutated gene. Neurofibromin genes (NF1 and NF2) were also altered. Other frequently mutated gene included NRAS, CDKN2A, and ARID2 [9]. They presented TMB and UV signature showed significant promise as an approach to identify patients who are likely to benefit from PD-1 targeted immunotherapy. Interestingly, desmoplastic melanomas were not found or low detection of BRAF V600E mutations in recent studies [4, 11, 23, 24], in contrast to non-DM. Thus, the use of BRAF-targeted therapy may be limited to a small number of patients with DM. GNAQ, GNA11, or KIT mutations are also absent in desmoplastic melanomas [10-12].

Treatment of localized DM consists of wide local excision utilizing margins that take into account both thickness and histologic subtype, as used for a non-DM [25, 26]. Adjuvant radiation therapy may be considered to improve local disease control in DM patients, particularly because the higher local recurrence reported for DM. Guadagnolo et al. reported that 24% of patients who had surgery alone and only 7% of patients who had surgery and radiation developed a local recurrence [27]. Jamie and his colleagues analyzed 2082 patients who were treated with a wide local excision (WLE) and 308 who were treated with a wide local excision and adjuvant radiation therapy (WLE+RT). This retrospective study demonstrated significantly improved overall survival (OS) in early-stage DM patients treated with WLE+RT compared to WLE alone [28]. Studies suggest that patients with metastatic DM may respond well to immune checkpoint inhibitors. George et al. revealed overall response rates of about 15% for ipilimumab, 30% to 40% for anti-PD-1 monotherapy, and 50% to 60% for ipilimumab with nivolumabin advanced melanoma [29-31]. A recent retrospective study showed that all patients with advanced DM were treated with anti-PD-1 and anti-PD-L1 agents and that the objective response and complete response rates were 70% and 32% of cases [31].

In addition, desmoplastic melanomas are normally resistant to nanoparticle-based chemotherapy due to dense stoma and limited particle permeability inside the tumor. Chen and Song et al. showed the hydralazine (HDZ)- an antihypertension vasodilator- would promote nanoparticle penetration in desmoplastic melanomas by reducing tumor stroma and fibroblasts and ameliorating the hypoxia status [32]. Obvious immune microenvironment changes were observed after HDZ-liposome treatment, which means HDZ-liposome may also be applied to enhance the efficiency of immunotherapy including the checkpoint inhibitors.

In conclusion, DM is considered a relatively rare variant of malignant melanoma, which mainly consisted of spindle shaped melanoma cells with abundant collagenous matrix, with a high potential recurrence. The mechanisms of DM have not been clearly recognized and further study is required. So far, wide local excision is necessary therapy for patients with DM. Adjuvant radiation therapy is also required. Moreover, some researchers considered BRAF-targeted therapy may be limited to a small number of patients. Advanced DM may respond well to anti-PD-1 monotherapy.

## Disclosure of conflict of interest

None.

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