Malignant melanomas have a very high propensity to metastasize to the brain via hematogenous spread. In contrast, direct perineural extension of any skin malignancy to the cranial cavity is rare. Most such instances of perineural spread are due to squamous cell carcinoma. The cranial nerves most commonly affected are the facial nerve and branches of the trigeminal nerve.

Previously, Chang et al. published a series of 8 cases of head and neck melanomas with MR imaging evidence of perineural spread. Our case differs from these previously published cases in that the primary melanoma was an unusually subtle skin lesion that came to medical attention only 9 months after a partial resection of the relatively large intracranial mass, which was initially believed to represent an MPNST. Based on this instructive case, we discuss the challenging pathological differential diagnosis between desmoplastic melanoma and MPNST in the context of an intracranial mass associated with a cranial nerve, emphasizing the importance of obtaining a biopsy of any suspicious skin lesions.

**Case Report**

**Initial Presentation and Diagnosis.** This 65-year-old right-handed white male initially presented with a 6-month history of facial numbness in the left V3 distribution. The numbness progressed, and after 1 month, he noted the onset of episodic lancinating pain in the left V3 distribution; the pain had an electric shock–like character and was provoked by shaving or consuming hot beverages. He also developed intermittent diplopia that was worse with left lateral gaze. An MR imaging study obtained at that time demonstrated a homogeneously enhancing mass in the left Meckel cave consistent with either meningioma or schwannoma that measured 2.4 cm (AP diameter) × 1.0 cm (transverse diameter) × 1.4 cm (craniocaudal diameter) (Fig. 1 left). The patient was prescribed carbamazepine for his trigeminal neuropathic pain and serial MR imaging was planned. Two weeks later, the patient’s numbness had progressed significantly and he now had a complete left 6th cranial nerve palsy and masseter weakness. This sudden change prompted another MR imaging study; this second study demonstrated significant interval growth of the lesion, which now measured 3.5 cm (AP) × 1.2 cm (transverse) × 1.7 cm (craniocaudal) (Fig. 1 right).

**Initial Operation, Histopathological Findings, and Postoperative Course.** In light of the alarming rate of growth, surgery was undertaken. The patient underwent a left-sided pterional craniotomy and an extradural approach was used to mobilize the medial temporal dura off the lateral wall of the cavernous sinus, exposing the Meckel cave. The intraoperative frozen-section diagnosis was malignant spindle cell neoplasm. There were...
no clear planes between the tumor and the surrounding neurovascular structures, so a subtotal resection was performed. Examination of permanent microscopic sections demonstrated a highly cellular neoplasm composed of moderately to highly atypical spindle cells (Fig. 2). The mitotic index was high (9/10 high-power fields). A microscopic focus of tumor necrosis was identified. Immunohistochemical evaluation using a polyclonal antibody to SI100 protein (Ventana Medical Systems, Inc.) showed patchy immunopositivity for S100. The p53-immunolabeling index was high. The tumor contained entrapped, neurofilament-immunopositive ganglion cells and axons, consistent with involvement of the trigeminal ganglion by the tumor. Results of testing with CAM 5.2 (a cytokeratin antibody) and HMB-45 (an antibody that reacts positively against melanocytic tumors) as well as testing for EMA and the melanocyte MART-1/Melan-A were all negative. The MIB-1 proliferation index, evaluated using the Glasgow cell counting graticule, was high (37%). The immunohistochemical profile and histological features, as interpreted by a neuropathologist specializing in CNS tumors, were consistent with MPNST of intermediate grade (WHO Grade III). The patient did well following surgery, with stable cranial nerve deficits and no surgical complications. He underwent intensity-modulated radiation therapy with a dose of 45 Gy followed by a CyberKnife stereotactic radiotherapy boost for an additional 15 Gy.

Subsequent Operations, Histopathological Findings, and Postoperative Course. Approximately 9 months after the craniotomy, the patient presented to a dermatologist with concern about a textural change and erythema of the left upper lip for over 1 year. An excisional biopsy was performed on an ill-defined, shiny erythematous patch (1 × 2 cm) with 2 small 3- to 4-mm subtle brown macules within the patch (Fig. 3). The pathology was read by a dermatopathologist as desmoplastic melanoma with a junctional component, Clark Level V. The lesion was treated with wide local excision and reconstruction. Sentinel node biopsy performed during this procedure was negative. Microscopic sections of the wide skin excision demonstrated amelanotic, infiltrating spindle cells with markedly atypical, hyperchromatic nuclei within the dermis, extending into the subcutaneous fat (Fig. 4). There was desmoplasia (fibrosis) of the dermis, even outside the area of the biopsy scar. Perineural invasion (neurotropism) was identified, with tumor cells aggregating around and within intradermal nerve twigs (Fig. 4D). The tumor cells stained strongly positive for S100. The cytological features of the atypical spindle cells were very similar to those in the tumor removed from the Meckel cave, and the final unifying diagnosis was desmoplastic malignant melanoma with perineural spread to the Meckel cave. One month later, the patient developed expressive aphasia, and MR imaging demonstrated a new left temporal lobe/sylvian fissure mass (Fig. 5). This lesion was surgically debulked and the patient began palliative chemotherapy.

Discussion
Desmoplastic melanoma is a rare subtype that accounts for approximately 1%–5% of melanomas and can be particularly difficult to accurately diagnose. Clinically, desmoplastic melanoma presents as a painless indurated plaque or occasionally as a small papule or nodule, often lacking pigmentation. It is a spindle cell neoplasm that is often amelanotic and highly infiltrative and has a penchant for microscopic perineural invasion (neurotropism). Since some melanomas consisting of spindle cells do not show significant desmoplasia (stromal fibrosis) microscopically but are otherwise similar to desmoplastic melanomas, desmoplasia may not be an essential feature of desmoplastic melanoma—despite the name. Although...
microscopic neurotropism is common in desmoplastic melanoma, symptomatic cranial neuropathy is rare and only affects 1.8% of patients with desmoplastic melanoma in the head and neck region. Due to the wide variety of histopathological appearances that metastatic melanoma can have, immunohistochemistry plays an important role in making the diagnosis. S100 is a calcium-binding protein that is commonly used as a marker for melanoma, nerve sheath tumors, and granular cell tumors. The sensitivity is reported to be 98.7% for spindle cell/desmoplastic melanomas. The specificity, however, is relatively limited in this context. Malignant PNST also stains positive for S100 in 50%–90% of cases; the staining pattern is characteristically patchy rather than diffuse. HMB-45, a marker for a premelanosomal glycoprotein, and MART-1/Melan-A, a cytoplasmic protein of melanosomal differentiation that is recognized by T cells, are highly specific and sensitive immunohistochemical markers of melanocytic neoplasms. However, these markers are only found in approximately 20% of spindle cell/desmoplastic melanomas, which makes their diagnostic value relatively limited for this subtype of melanoma. The results of staining for both of these markers are obviously negative in MPNSTs. Results of CAM 5.2 testing as well as testing for EMA are typically negative in both MPNST and malignant melanoma. The histological and immunohistochemical features of the intracranial tumor in this case were compatible with both the diagnosis of desmoplastic melanoma and the diagnosis of MPNST. A metastatic desmoplastic melanoma may be impossible to distinguish from an MPNST histologically and immunohistochemically, as these melanomas typically stain for S100 but not for any of the more specific melanoma markers, such as HMB-45 or MART-1/Melan-A. Even ultrastructurally, desmoplastic melanoma cells resemble Schwann cells more than melanocytes. A recent immunohistochemical study suggested that S100A1, a subtype of S100, may be somewhat helpful in the differential diagnosis: 73% of desmoplastic melanomas express S100A1 in more than one-half of the cells, whereas 84% of MPNSTs express no detectable S100A1 at all. Unfortunately, the polyclonal S100A1 antibody used in that study is no longer available from the manufacturer (catalog no. DAKS100A1/1, Dako). We attempted to replicate the previous results using a different S100A1 antibody (catalog no. HPA006462, Sigma-Aldrich), which should be specific to the A1 subtype of S100 based on a peptide sequence analysis of the immunogen. Immunolabeling indices for S100A1 were 1%, 2% (present case), and 90% in 3 cases of desmoplastic melanoma, 100% in a case of conventional melanoma, and 0%, 0.1%, and 10% in 3 cases of MPNST (unpublished data). These preliminary results suggest that the distinction between desmoplastic melanoma and MPNST cannot be solely based on immunohistochemistry for S100A1 using the Sigma-Aldrich antibody.
Melanotic schwannoma, a very rare tumor, could be ruled out because melanotic schwannomas are pigmented by definition and our tumor was not. However, some metastatic melanomas are pigmented. In those cases, attention must be paid to the cytological features and proliferative activity. Most melanotic schwannomas have relatively benign cytological features and few mitoses, whereas melanomas contain highly atypical cells and frequent mitoses. Psammoma bodies are often seen in melanotic schwannomas, particularly those associated with Carney complex, but are almost never seen in melanomas. A definitive distinction may not be possible in all cases, as some melanotic schwannomas contain atypical cells with prominent nucleoli, exhibit significant mitotic activity, and may even metastasize. Approximately 10% of melanotic schwannomas follow a malignant clinical course.

Overall, the evidence supports the idea that desmoplastic melanoma is a biologically distinct melanoma subtype characterized by Schwann cell differentiation, possibly reflecting the common embryological origin of both melanocytes and Schwann cells from the neural crest. Thus, the main difference between desmoplastic melanoma and MPNST may be the cell of origin, which is the melanocyte in desmoplastic melanoma and the Schwann cell in MPNST. In our case, the presence of a small component of conventional melanoma at the dermal-epidermal junction of the skin specimen (Fig. 4A) supports a melanocytic origin and classification as desmoplastic melanoma rather than MPNST.

In this patient, it is impossible to say with certainty whether the tumor in the Meckel cave is the result of hematogenous metastasis or perineural extension. However, the simplest explanation is that this represents perineural spread, given that the skin lesion is within the ipsilateral trigeminal distribution. The fact that neurotropism was seen on microscopic examination of the skin specimen (Fig. 4D) also favors perineural extension as the etiology of the intracranial tumor. This distinction may have been important in this case, as the shape and size of the radiation field would have included the path of the trigeminal nerve all the way from the skin lesion to the Meckel cave. Among 8 patients with head and neck melanomas with perineural extension identified by MR imaging, 5 had desmoplastic melanoma. In this previous study, 3 of the 5 patients were dead of disease at 2, 2, and 5 years after diagnosis, and 2 patients were alive with disease at 1 and 5 years after diagnosis. Controlled studies on the effectiveness of treatment of these lesions have not been published; most patients have been treated with surgery and radiotherapy. Some tumors may respond to stereotactic radiosurgery.

Conclusions

This case report demonstrates that an intracranial extension of cutaneous desmoplastic melanoma may be impossible to distinguish from an MPNST histologically and radiographically. As such, we recommend that a biopsy specimen should be obtained from any suspicious skin lesions, particularly those on the head or face, in patients in whom an intracranial MPNST is diagnosed. Furthermore, any aggressive or unusual lesions associated with cranial nerves warrant a thorough evaluation for potential primary lesions, including evaluation of the skin.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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