Cutaneous spindle cell carcinoma misdiagnosed as atypical fibroxanthoma based on immunohistochemical stains

Anastasia Benoit, MD,[a] Joshua Wisell, MD,[b] and Mariah Brown, MD[a]
Aurora, Colorado

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INTRODUCTION

Poorly differentiated spindle cell neoplasms pose a diagnostic challenge for dermatopathologists because of a lack of specific morphologic features on standard histopathology. Further characterization with immunohistochemical (IHC) studies is frequently required. We present a fatal case of spindle cell squamous cell carcinoma (SCC) misdiagnosed as atypical fibroxanthoma (AFX) based on a limited panel of IHC markers.

Abbreviations used:

AFX:	atypical fibroxanthoma
HMWK:	high molecular weight keratins
IHC:	immunohistochemical
MMS:	Mohs surgery
SCC:	squamous cell carcinoma

CASE REPORT

A 68-year-old white woman with a history of lung transplantation presented for evaluation of a 0.9 cm nodule on the right supraclavicular aspect of the chest. Shave biopsy results demonstrated a dense spindle cell proliferation on hematoxylin-eosin staining (Fig 1). IHC stains were negative for S100 and pan-cytokeratin (AE1/AE3) but positive for procollagen, leading to a final diagnosis of AFX (Fig 2). Surgical excision was delayed for 2 months because of an intervening hospitalization. When the patient presented for Mohs surgery (MMS), the lesion was 3.5 cm in diameter (Fig 3). Mohs frozen sections confirmed an extensive atypical spindle cell proliferation. Clear margins could not be obtained after 4 stages of MMS, and concern was raised for in-transit metastases, as the Mohs mapping showed noncontiguous tumor spread. Clinically, numerous subtle 1- to 2-mm subcutaneous papules were then noted on the chest immediately inferior to the excision site and extending up to 20 cm away. Surgery was suspended, and multiple biopsies of the chest papules and the Mohs tissue from the main bulk of the tumor were submitted for permanent histology. All samples were consistent with poorly differentiated SCC, spindle cell variant, based on more extensive IHC evaluation (p63+, cytokeratin $5/6^{+}$, $34betaE12^{+}$, $procollagen^{+}$, $AE1/AE3^{-}$; Fig 4). The patient was treated with radiation therapy, but unfortunately died of her disease within 6 months.

DISCUSSION

Spindle cell SCC is an uncommon variant of cutaneous SCC that typically arises on sun-damaged skin of elderly adults.[1] Solid organ transplant recipients appear to be at higher risk for this SCC subtype, which may behave aggressively and portend a poorer prognosis.[2] Histopathologic examination alone is frequently inadequate for diagnosing spindle cell SCC, as the pleomorphic spindle cells lack recognizable features of keratinization.[3] Distinction from other spindle cell tumors, mainly AFX and spindle cell melanoma, necessitates IHC studies. Furthermore, certain IHC markers for epithelial cells, especially the commonly used AE1/AE3 pan-cytokeratin IHC stain, may be negative in spindle cell SCC and other poorly differentiated SCCs.[3] Despite staining for multiple high and low molecular weight

From the Departments of Dermatology[a] and Pathology,[b] University of Colorado School of Medicine.
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Correspondence to: Mariah Brown, MD, 1665 Aurora Court, Mail Stop F703 Aurora, CO 80045. E-mail: Mariah.brown@ucdenver.edu.

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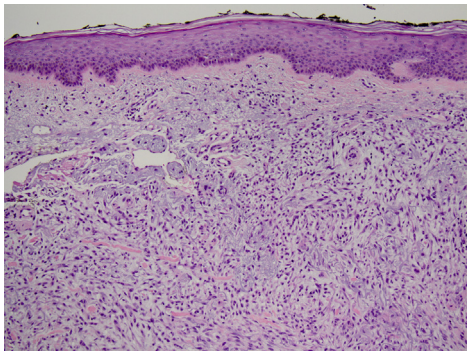

Fig 1. Invasive spindle cell proliferation with hematoxylin-eosin stain. (Original magnification: ×10.)

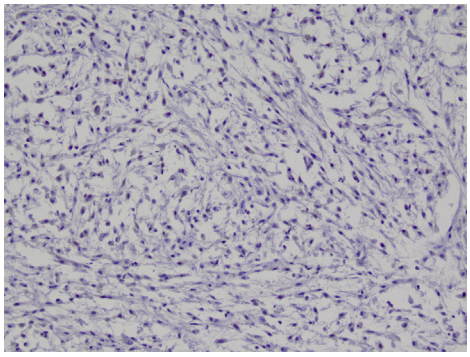

Fig 2. Negative IHC staining with pan-cytokeratin (AE1/AE3). (Original magnification: ×20.)

keratins, AE1/AE3 pan-cytokeratin stains may still be negative in some epithelial tumors.

Several case series support the use of high molecular weight keratins (HMWK) as more sensitive markers for spindle cell SCC than pan-cytokeratin alone. Morgan et al[4] found 100% sensitivity and specificity of 34betaE12 for spindle cell SCC, whereas Sigel et al[3] found 69% sensitivity of CK5/6. In addition to HMWK stains, p63 has been identified as reasonably sensitive and specific for spindle cell SCC, with sensitivity of 68% to 100% and specificity ranging from 80% to 100% in distinguishing spindle cell SCC from AFX.[1,5] Other IHC stains that have been useful in the diagnosis of cutaneous spindle cell SCC are p40, an isoform of p63, and MNF116, a low- and intermediate-weight cytokeratin stain.[6,7] In the case of our patient, the correct diagnosis was made based on labeling for markers specific for HMWK (CK5/6, 34betaE12) and p63, despite the absence of staining for AE1/AE3 pan-cytokeratin. Clinicians should be careful not to rely too heavily on a pan-cytokeratin stain when evaluating spindle cell neoplasms, and should consider the use of a more robust panel of epithelial markers.

Spindle cell SCC misdiagnosed as AFX may lead to delayed therapy and increased morbidity and mortality, especially in the immunocompromised organ transplant population. Clinicians should be aware that the AE1/AE3 pan-cytokeratin stain may frequently be negative in spindle cell SCC, while procollagen staining is often positive. As a result, the diagnosis of AFX, a much lower risk tumor, may be made rather than the correct diagnosis of spindle cell SCC. The routine addition of some combination of epithelial stains, such as p63, p40, MNF116, and HMWK stains (34betaE12 or cytokeratin 5/6) in addition to pan-cytokeratin, S100, and procollagen, to the panel of IHC markers may improve diagnostic confidence and patient outcomes when faced with difficult histologic analysis of cutaneous spindle cell proliferations.

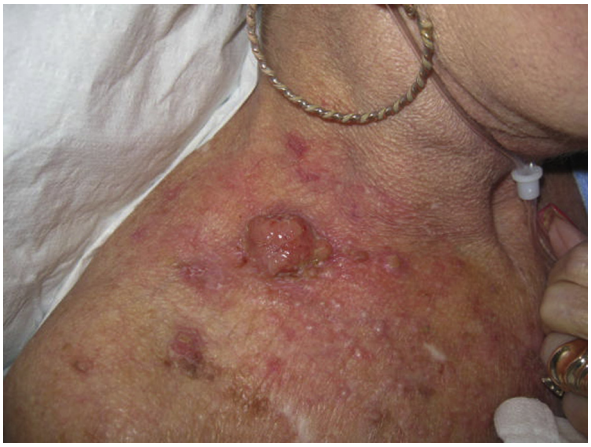

Fig 3. Clinical photograph of the tumor at the time of MMS. Note the small, skin-colored papules on the chest wall inferior to the tumor.

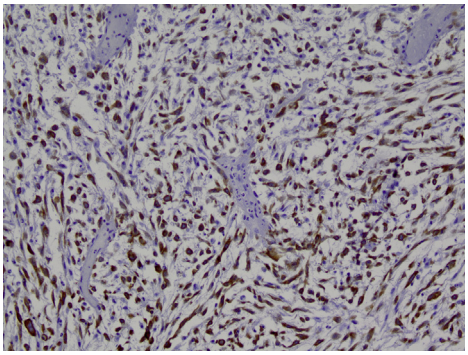

Fig 4. Positive IHC staining for HMWK (34betaE12). (Original magnification: ×20.)

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