Metastatic Melanoma Arising 10 Years after Treatment of Primary Lesion: A Unique Case Representative of SOX-10’s Efficacy in Identifying Melanomas of Metastatic Origin

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Abstract
Metastatic melanoma has a five-year survival rate of 10% to 20%, with a median survival of about nine months. Clinical presentation and histopathology may vary, making diagnosis difficult. In this case, immunohistochemical markers can lend significant help in identifying metastatic melanoma. A variety of immunohistochemical markers that help characterize malignant melanoma of metastatic origin now exist. SOX10, a transcription factor involved in differentiation of neural crest cells to melanocytes, is suggested to be superior in sensitivity, specificity, staining intensity and ease of interpretation compared to other, previously commonly used markers. We describe a unique case of a 45-year old female who presented with metastatic melanoma appearing 10 years after the primary lesion was treated with Mohs and interferon therapy. Although the lesion appeared vascular in nature, both clinically and surgically, the positivity for the SOX10 marker and the clinical history helped hone the diagnosis of malignant melanoma of metastatic origin.

Introduction
Melanoma is the most common cancer in adults ages 25 to 29, and rates are increasing faster in women ages 15 to 29 compared to men of the same age. Risk factors include sun exposure, family and/or personal history, multiple nevi, skin type and immunosuppression.1 Due to its metastatic potential, melanoma causes more than 75% of skin cancer deaths. Ninety percent of all melanoma recurrences happen during the first five years following the primary diagnosis, with the greatest risk of recurrence in the first two years. Individuals with distant metastatic melanoma have a five-year survival rate of 10% to 20%, with a median survival of approximately nine months.2,3

Up to 45% of patients with metastatic melanoma develop cutaneous metastases, making melanoma among the most common malignancies that metastasize to the skin. Melanoma makes up 12% of cutaneous metastases in women and 32% of cutaneous metastases in men. For men and women combined, the percent of all primary melanoma patients with cutaneous metastases is 18%.4

Signs of cutaneous metastatic melanoma may consist of papules or nodules that vary in color from skin-toned, pink-red, blue, brown or black, and secondary ulceration or bleeding may be present.4 The location of melanoma metastasis is commonly the lower extremity, but may occur elsewhere. There are often multiple lesions located between the original cancer site and regional lymph nodes (likely from cancer cells in lymphatics). Some other, less common presentations include a hematoma-like lesion, pedunculated tumor, zosteriform distribution, miliary pattern, diffuse melanosis and inflammatory metastases.1

Diagnosis requires histopathologic examination. A classic histological feature is epithelioid cells with prominent nucleoli; however, metastatic melanoma mimics a wide variety of other tumors.4 Clinical presentation and histopathology may vary, making diagnosis difficult. Immunohistochemical markers can help identify metastatic melanoma. Common immunohistochemical markers used to diagnose metastatic melanoma include vimentin, S100, tyrosinase, Melan-A (MART-1), HMB45 and MITF.5,6

Case Report
A 45-year old female presented with an enlarging, right upper quadrant cutaneous nodule. Her past medical history included melanoma on the right triceps, treated in 2005 with Mohs and skin graft along with one year of interferon therapy. The lesion appeared approximately one month before presentation, with no inciting events prior to the appearance of the nodule. The patient had no
systemic symptoms, pain, pruritus, perilesional ecchymosis or bleeding.

The lesion was bullous, violaceous, and measured 5 cm x 5 cm x 3 cm (Figure 1, p. 41). A CT scan of the abdomen was performed and demonstrated a 5.8 cm x 6.2 cm lesion with well-defined and enhancing rims in the skin and subcutaneous fat of the upper right abdominal wall, appearing to minimally infiltrate the underlying rectus abdominis musculature without intraperitoneal communication (Figure 2, p. 41). After surgical excision, the lesion was found to have an abnormal-appearing capsule and was sent to pathology for further evaluation. The patient was discharged with outpatient follow-up instructions, but returned about three months after surgical excision due to a recurring, fast-growing mass at the previous surgical site (Figure 3, p. 41).

Preliminary pathological findings of the original mass were consistent with invasive high-grade undifferentiated malignant neoplasm. Further immunohistochemical testing revealed that the tumor cells were positive for SOX10, vimentin, EMA, and Ki-67, and negative for Mart1, HMB-45, pan-cytokeratin, desmin, smooth muscle actin, CD31, CD34, ERG and tyrosinase (Figures 4, 5, p. 41). Given the clinical history, the morphologic and immunophenotypic findings were found consistent with malignant melanoma of metastatic origin. Further testing revealed positivity for BRAF VE1 and BRAF V600E, further confirming the diagnosis.

Discussion

Clinical presentation and histopathology of metastatic melanoma vary, making diagnosis difficult. In this instance, IHC markers provided significant assistance in identifying metastatic melanoma. In the past, the IHC marker of choice in detecting melanoma metastases in sentinel lymph nodes has been S100, as it has high sensitivity for melanocytes. Yet recognition of micrometastases and solitary melanoma tumor cells may be difficult at times due to presence of S100-positive dendritic cells. Other IHC markers suggested as useful (in combination) consist of SOX10, HMB-45, Melan-A/Mart-1, tyrosinase, Ki-67/Mib-1, MITF, and vimentin, among others.

Metastatic melanoma immunophenotype is typically different from that of primary tumors, with higher expression of Ki-67 and mutant p53 protein as well as loss of CD117 typically seen in metastatic cancers. This is in contrast with cutaneous primary lesions, which usually show lower expression of Ki-67 and p53 and positive CD117.5 Ki-67 (Mib-1) is a nuclear proliferation marker expressed in all phases of the cell cycle, but it is not cell-type specific.8 In a series of 202 nodular melanoma cases, Ki-67 was found to be a superior prognostic indicator compared to mitotic count.9

HMB-45, a premelanosome marker and marker of normal melanocyte maturation, has been found to stain positive in 58% to 95% of metastatic melanomas.3,10 Melan-A/Mart-1, two antibodies that stain the same epitope, stain melanocytic lesions.8 In contrast to S100, Melan-A is not expressed in dendritic cells in lymph nodes. Melan-A has a sensitivity of about 57% to 92% for metastatic melanoma.10 MITF (microphthalmia-associated transcription factor) is a nuclear melanocytic marker, and is positive in roughly 80% to 100% of melanomas; however, specificity is low, as it can be expressed in a variety of epithelial and mesenchymal neoplasms.8,10 Vimentin, a general marker for sarcomas, stains melanocytes as well as mesenchymal cells, endothelial cells, fibroblasts and others, but not keratinocytes or other epithelia.8

SOX10, a transcription factor involved in differentiation of neural crest cells to melanocytes, is suggested to be more sensitive and specific compared to S100 and others.10 Ordonez performed a review of material on IHC markers used in diagnosing melanoma and found that, in the limited number of studies published at that time, SOX10 was very sensitive (97% to 100%) for primary and metastatic melanomas. SOX10 has been found to be expressed in all subtypes of melanoma, including roughly 80% to 100% of desmoplastic melanomas.10 In addition to primary, desmoplastic and metastatic melanomas, SOX10 has proved a sensitive marker in spindled melanoma.8

Willis et al. compared the IHC profile of SOX10 to S100 protein, HMB-45 and Melan-A in 58 metastatic-melanoma-positive lymph nodes. A statistically significant increase in staining intensity was found with SOX10 compared to S100, HMB-45 and Melan-A, with P=0.000, 0.000 and 0.003, respectively.7 Vrotsos et al. performed immunohistochemical stains for S100 protein, SOX10 and KBA.24 on 50 metastatic-melanoma-proven lymph nodes. SOX10 stained 100% (50/50) of the cases. Also, there was no “background” staining of normal cellular components. This is in contrast to S100. Although 48/50 cases, or 96%, of metastatic melanoma cases were detected with S100, the authors reported instances of significant difficulty distinguishing cells of benign reticulum from single-cell metastatic melanoma due to S100-positive dendritic cells.11

Conclusion

There are a variety of immunohistochemical markers that help characterize malignant melanoma of metastatic origin. This case is a unique presentation of metastatic melanoma, in that it appeared 10 years after the primary lesion was treated with Mohs and interferon therapy. Even though the lesion appeared vascular in nature, both clinically and surgically, the positivity for the SOX10 marker and the clinical history helped hone the diagnosis of malignant melanoma of metastatic origin.

References


