



## Giant Malignant Melanomas and their Clinical Implications: Review of Literature and Case Report

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### Abstract

**Background:** Cutaneous malignant melanoma is the sixth most commonly diagnosed cancer in the United States with an incidence that is increasing more quickly than any other type of cancer. Fortunately, the majority of the cases are diagnosed at early stage, conferring a better prognosis. However, there are rare giant destructive melanomas >10 cm that are described in the literature, most metastatic at time of presentation. Here we report the clinical case and genomics of the largest giant melanoma without evidence of metastatic disease described to date.

**Methods:** Literature search of Scopus and Pubmed from 1960-2016 was performed using the terms “giant, melanoma, cutaneous melanoma, and non-metastatic.” Cases were reviewed for location, tumor size, Breslow depth, presence of nodal and distant metastases, and surgical and medical treatments. In addition, we report the case of an 84-year-old female who presented with a giant melanoma of the shoulder without evidence of metastatic disease. We describe the clinical characteristics of the tumor and pathologic profile, including immunohistochemistry and genetic analysis.

**Results:** 18 cases of primary giant melanoma were identified in addition to our case. Female: 9. Male: 10. Age 1-88. Most common location was the trunk followed by the extremities. Average largest diameter was 13.3 cm with a range of 5-23 cm. Breslow thickness ranged from 0.45 to 100 mm. Four (21%) of patients were diagnosed with localized disease, four (21%) with loco-regional metastases and eight (42%) with distant metastases. Our patient’s tumor genetic analysis with Amplicon next generation sequencing for melanoma biomarkers was positive for NRAS Q61L but negative for BRAF, CTNNB1, GNA11, GNAQ, and KIT.

**Conclusion:** Giant malignant melanomas are extremely rare, particularly those without evidence of metastatic disease. While they represent a surgical challenge due to their locally destructive nature, wide local excision and sentinel node biopsy are still considered the standard of care and may be utilized in conjunction with chemotherapy, immunotherapy, or radiotherapy. Additional genetic analysis of particular phenotypes may help us to elucidate differences in behavior patterns of melanomas to better target therapy.

**Keywords:** Malignant melanoma; Giant melanoma; Melanoma metastases; Melanoma genetics

### Introduction

Since the mid 1950’s, the incidence of melanoma has increased more quickly than any other type of cancer [1], making cutaneous malignant melanoma the sixth most commonly diagnosed cancer in the United States [2]. Cutaneous melanomas are thought to arise either from the slow progression of a common nevus, first growing radially and then vertically to invade the vasculature and metastasize, or they arise rapidly into aggressive lesions without origin from nevus [3]. Fortunately, the majority of cutaneous melanoma is diagnosed early [4]. Lesions diagnosed later with increased thickness generally have worse prognosis, as Breslow thickness, or the depth of the lesions from the basement membrane of the epidermis to the deepest margin, remains the single most important predictor of long term survival. Other less predictive prognostic factors include ulceration, rate of mitosis, and nodal involvement [5]. Women generally have a higher rate of cutaneous melanoma [6] and these lesions are more frequently found in the lower extremities. Men present more often with lesions of the head, neck and trunk [7]. Truncal lesions are associated with the BRAF proto-oncogene [8].

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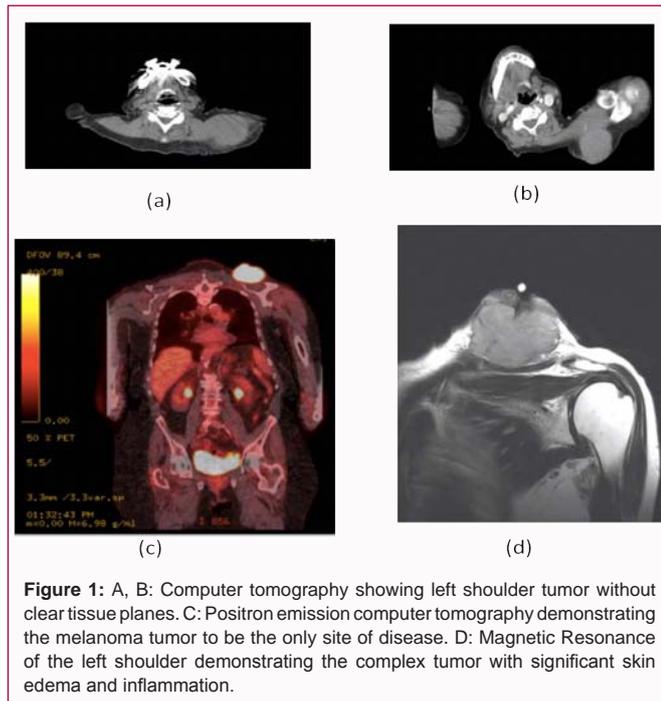
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**Figure 1:** A, B: Computer tomography showing left shoulder tumor without clear tissue planes. C: Positron emission computer tomography demonstrating the melanoma tumor to be the only site of disease. D: Magnetic Resonance of the left shoulder demonstrating the complex tumor with significant skin edema and inflammation.

While chemotherapeutic and immunologic agents are available for the treatment of systemic disease, surgical excision of early stage melanoma remains the standard of care for curative intent when disease is localized [3], with diameter of excision margin determined by Breslow depth [9]. This report describes the identification, staging, and treatment of a localized giant cutaneous melanoma, which is a rarely described phenomenon.

## Case Presentation

The patient is an 84-year-old Caucasian female nursing home resident with history significant for mild dementia and 20 pack-year tobacco uses. The patient presented with a left shoulder malodorous, fungating mass to a local community hospital where she was admitted for MRSA cellulitis requiring parenteral antibiotics. Computerized Axial Tomography (CT) scan showed a 6.2 cm solid enhancing mass posterior to the left trapezius muscle (Figure 1A and 1B). CT-guided biopsy initially was read as poorly differentiated malignancy favoring lymphoma, but pathology review at the University of Michigan was diagnostic of malignant melanoma. Immunohistochemistry was positive for S100, Cyclin D1, SOX 10, and MTF; rare cells were positive for HMB-45 and MART-1; negative for CD3, CD4, CD5, CD7, CD8, CD10, CD20, CD30, CD34, CD45, CD79A, CD138, PAX5, MPO, MUM1, ALK, BCL-2, BCL-6, Pancytokeratin, and P63. In situ hybridization was negative for EBER. Staging Positron Emission Tomography/CT showed 7.2 cm lesion with max SUV of 32.0 g/ml with no evidence of diffuse disease (Figure 1C). MRI of the left shoulder demonstrated muscular and soft tissue involvement but no osseous involvement (Figure 1D). MRI brain was also negative for metastatic disease.

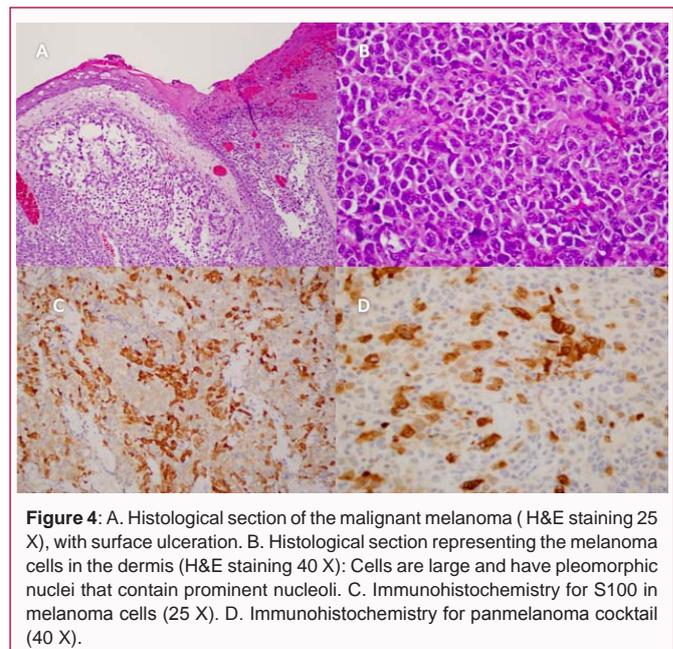
On exam, the tumor was noted to be ulcerated and exophytic with lobulations. It was actively bleeding and measured 20 x 20 cm with surrounding erythema (Figure 2A and 2B). Nodal involvement was clinically negative. Sentinel node biopsy was discussed but due to the patient's general condition, the patient's guardian declined. Ultrasound of the auxiliary and cervical nodes was negative for



**Figure 2:** A, B Exophytic, ulcerated, hemorrhagic left shoulder melanoma tumor measuring 20 x 20 cm in diameter.



**Figure 3:** A: Melanoma tumor with surrounding erythema. B: Excised specimen. C: Large surgical defect with exposure of osseous structures due to need of obtaining oncological negative deep margins.



**Figure 4:** A. Histological section of the malignant melanoma (H&E staining 25 X), with surface ulceration. B. Histological section representing the melanoma cells in the dermis (H&E staining 40 X): Cells are large and have pleomorphic nuclei that contain prominent nucleoli. C. Immunohistochemistry for S100 in melanoma cells (25 X). D. Immunohistochemistry for panmelanoma cocktail (40 X).

nodal involvement. She underwent en bloc resection of the tumor, skin, subcutaneous tissue and muscle down to the scapular bone protuberance with an additional 2 cm margin. (Figure 3A and 3B).

**Table 1:** Reported cases of giant malignant melanomas.

Case author	Sex (F= female, M= male), Age	Location	Size (cm)	Breslow thickness (mm)	Metastatic disease	Nodal diffusion	Therapy
Del Boz [13]	F, 29	Arm	20x15x7	70	Yes	Yes	Palliative debulking,
Grisham [16]	F, 45	Back	13 x NR	55	NR	Yes	WLE, AND INF
De Giorgi [15]	F, 45	Abdomen	16 x NR	0.45	NR	NR	NR
Kruijff [4]	F, 56	Back	8 x 6	48	Yes	Yes	WLE, AND
Kim et al	F, 56	Thumb	7x4x 3.5	> 4	No	Yes	Thumb amputation, INF, AND
Di Meo [25]	F, 60	Abdomen	18x15x6	40	No	Yes	WLE, AND, chemotherapy
Zeebregts et al.	F, 74	Thumb	7x5x5	NR	Yes	NR	Local perfusion of INF and anti-TNF, WLE, AND
Muller et al.	F, 84	Scalp	NR	5	NR	No	None
Harting et al.	M, 29	Back	25x22x7	54	Yes	Yes	WLE, AND chemotherapy
Eisen [17]	M, 47	Back	8 x 9	40	Yes	NR	WLE
Pai et al	M, 53	Eyelid	5x4.5x4	45	No	Yes	WLE
Panajotovic [12]	M, 57	Scalp	12x10	100	No	No	WLE
Tseng [14]	M, 63	Arm	23x21x6	75	Yes	Yes	WLE, AND
Ching [10]	M, 70	Scalp	14.5x 10.4	18	Yes	Yes	WLE, SND
Tseng [14]	M, 88	Arm	10x8x3	31	Yes	Yes	WLE, AND
Schneiderman et al.	M, premature newborn	Back	15x15x5	NR	NR	NR	None
Chong [10]	M, 60	Thigh	6 x 8.2	60	No	No	WLE, AND
Chong [10]	M, 60	Back	8 x7	24	No	No	WLE
Gishen et al., 2016	F, 84	Shoulder	20 x 20	70	No	No	WLE

**Table Key:** WLE: Wide Local Excision; AND: Axillary Node Dissection; SND: Sentinel Node Dissection; NR: Not Reported; INF: Interferon; anti-TNF: Anti Tumor Necrosis Factor

Tumor was lifted off of the left acromion and trapezius muscles, leaving a 22 cm by 25 cm defect (Figure 3C), requiring plastic surgery closure with bilaminar Integra and VAC dressing as an interim closure pending final surgical pathology. The patient tolerated the procedure well and returned ten days later for closure with split thickness skin graft.

Surgical pathology noted invasive malignant melanoma, unclassifiable type; Clark Level 5 and Breslow Depth of 70 mm surgical margins were negative. No radial growth, microsatellitosis, or associated melanotic nevus was identified. Vascular invasion, tumor-infiltrating lymphocytes, and vertical growth phase were present. Cytology was predominantly epithelioid. Immunohistochemistry with melanocytic markers revealed expression of SOX 10 of 80%, MiTF of 70%, S100 of 40%, pan-melanoma cocktail of 10%, and MART-1 of less than 1% (Figure 3). Results indicate that a significant number of melanoma cells lost MART-1 expression during tumor progression. Pathology demonstrated a very high mitotic rate with 12 mitosis/mm<sup>2</sup> on HE staining and 18 PHH3 positive cells/mm<sup>2</sup> on two colors IHC with PHH3 and MART-1. (Figure 4A, 4B and 4C). Genetic analysis with Amplicon next generation sequencing for melanoma biomarkers was positive for NRAS Q61L but negative for BRAF, CTNNB1, GNA11, GNAQ, and KIT.

The patient was evaluated by medical oncology but was not a candidate for adjuvant immunotherapy with interferon given her old age, dementia, and general performance status. While new immunotherapy agents such as the PD-1 inhibitors Keytruda (pembrolizumab) and Opdivo (nivolumab) are promising, their side effect profiles render them better suited for treatment of recurrence. The patient was advised to follow up with routine surveillance. She was with no clinical evidence of recurrence at 6 months follow up. Patient has since deceased of unknown cause.

## Literature Review

Eighteen previous cases of primary giant melanoma from 1960 to June 2016 were identified in addition to our case. Analysis of all 19 cases revealed 9 females and 10 males, with median age of 57, ranging from 1-88 years old. The most common location was the trunk, followed by the extremities. The average largest diameter was 13.3 cm (5-23 cm). Breslow thickness ranged from 0.45 to 100 mm. Four (21%) of patients were diagnosed with localized disease, 4 (21%) with loco-regional disease, and 8 (42%) with distant metastases. The majority of patient underwent wide local excision and auxiliary node dissection. Two patients receive systemic adjuvant treatment with chemotherapy.

## Discussion

While melanoma is the sixth most common cause of cancer in the United States, giant primary melanomas, defined as lesions of at least 10cm diameter [10], are rare. Of the previous 18 cases reported, the majority is associated with significant local regional metastatic disease [10]. Interestingly, there was no evidence of nodal or systemic disease in our case. In an earlier literature review by Ching et al. [11] that identified nine cases of giant melanoma, only one case reported no regional lymphadenopathy and no evidence of metastatic disease.

Previously documented cases of giant primary melanoma report lesions occurring on the scalp [12], arm [13,14], abdomen [15], and back [4,16,17]. Our patient's tumor location on the shoulder presented a unique challenge in terms of surgical reconstruction; a conservative approach with Integra grafting and VAC dressing was chosen to await for final pathology results prior to skin grafting. Per the treatment guidelines published by the National Comprehensive Cancer Network for those melanomas with Breslow depth of 4 mm

and greater, the principal treatment of wide local excision remains valid for giant melanomas [18]. These tumors necessitate a minimum of recommended 2 cm excision margin, with no survival benefit noted with a greater than two-centimeter margin in melanomas with thickness greater than 4 millimeters because the risk of death is more likely from metastatic disease than from recurrence [19]. In the case presented in this report the lesion was successfully excised with eventual skin graft reconstruction.

While radiation has not been used historically as a primary treatment for melanoma due to radio-resistance, radiation therapy should be considered for giant melanomas. Radiation therapy has been shown to help palliate approximately 50 percent of patients with unrespectable, recurrent, or metastatic disease. Radiotherapy may be used after complete excision, after lymphadenectomy, or to prevent local recurrence, although evidence is limited [20].

Based on literature review, the likelihood of regional and metastatic disease is exceptionally high with giant melanomas. Only three known cases of giant melanoma with no evidence of metastasis have previously been reported [10,12]. This case report is the 4<sup>th</sup> case in the medical literature. Chong et al. [10] reported 2 cases of giant melanoma without metastasis. The two lesions described by Chong measured 6.0×8.2 cm and 8×7 cm, respectively. Additionally, a scalp melanoma measuring 12 x 10 cm without metastatic disease has been described [12]. The lesion described in this case report measured 20 x 20 cm, making this tumor the largest known giant melanoma without metastatic disease. The occurrence of such lesions might suggest a less aggressive variant of the disease.

As the relationship between melanoma and the expression of genetic markers is better understood, the current four subtype histopathologic classification schemata is challenged, particularly because genetic profile may prove more predictive of tumor behavior than histology. For example, desmoplastic melanoma presents with more advanced Breslow depth but fewer regional metastatic lesions. The more recently classified primary dermal melanoma, which by definition is confined to the dermis, shows better survival rates when compared with nodular melanoma of equal thickness [10]. The surgical pathology of the lesion presented in our case study demonstrated an invasive malignant melanoma of unclassifiable type, Clark Level 5 up to the skeletal muscle with Breslow depth of 70 mm. Ulceration and vascular invasion were both present, which is remarkable in light of the fact that despite vascular invasion no metastatic lesions were noted wither clinically or radiographically.

The tumor's slow growth over the course of ten years with sudden rapid expansion over the course of several months prior to excision with no proven metastatic disease demonstrates the need for continued research to elucidate what determines the growth phase, rate, directionality and metastatic potential of giant melanomas. The complexity of diagnosing and treating malignant melanoma in part is due to the fact that melanoma has more gene mutations per cell than any other type of cancer. In order to more accurately diagnose and treat the disease, we need to better understand the complex genomic profiles, signaling pathways, and immune checkpoints that drive tumor progression and cause some lesions to advance quickly and metastasize while others grow slowly to an impressive size. Aside from the four main subtypes of melanoma, as many as seventeen rare variants have been described. Nevoid melanomas are often mistaken for benign dermal nevi but do have a metastatic potential. Desmoplastic melanoma, which appear scar-like, have a significant

amount of mucin and most often appear poorly circumscribed with an impressive vertical growth phase [21]. Solitary dermal melanoma is a variety of tumor confined to the dermis. Regardless of subtype, hematoxylin and eosin staining remains the gold standard of diagnosis. However, pathologists often measure antibodies directed against S-100, MART-1/Melan-A, and HMB45 [22,23]. They utilize reverse transcriptase polymerase chain reaction (RT-PCR) to uncover melanoma-specific tumor markers such as tyrosinase messenger RNA [24]. Specifically, additional research is required to elucidate the underlying genetic profiles that drive the local growth of giant melanomas, and to better treat these tumors when their size prevents surgical resection. Genetic profiling with comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH) can guide therapy for giant melanomas that prove unrespectable. In the presence of mutated BRAF, combination therapy with BRAF and MEK inhibitors is standard of care. First line treatment options include Dabrafenib/trametinib or Vemurafenib/cobimetinib, or monotherapy with either Vemurafenib or Dabrafenib. The choice of therapy is based on the individual patient. In the absence of a BRAF mutation, immunotherapy with anti-PD1 agents Pembrolizumab or Nivolumab as monotherapy or in combination is a category 2A recommendation [19].

## Conclusion

In conclusion, giant malignant melanomas are extremely rare and represent a surgical challenge due to their destructive nature. Even though they have significant metastatic potential, a subset of these tumors could have a more indolent clinical course. Genetic analysis may prove a valuable clinical tool to predict phenotype and to provide more individualized treatment options.

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