A Case of Recurrent Malignant Melanoma of the Left Foot with In-Transit Metastases

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ABSTRACT

We report a 73-year-old male with recurrent amelanotic malignant melanoma of the left foot with in-transit metastases to the left thigh. In-transit metastatic melanoma can often represent a diagnostic and therapeutic challenge for physicians. This patient was treated with talimogene laherparepvec injections (T-VEC; Imlygic) in the left inguinal and the left plantar region every two weeks for one year as oncolytic viral therapy for advanced non-operable malignant melanoma. He then received consistent follow-up including blood work and PET scans every four months, and he also required further lymph node surgical dissection. To date, our patient has survived 3 years and 11 months, which is 27 months longer than the estimated median survival of 1 year 8 months for patients diagnosed with in-transit metastatic melanoma.

KEYWORDS: melanoma, in-transit metastasis, oncology, surgery

INTRODUCTION

Melanoma is the deadliest form of skin cancer worldwide, with an overall incidence of approximately 21.8 per 100,000 Americans and increasing.[1] Metastatic melanoma is a relatively rare presentation at initial diagnosis, and it is associated with less than a 15% 5-year survival rate.[2] In-transit metastases are defined as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not located beyond the regional nodal basin.[3] In-transit melanoma – with an incidence of 4% for all melanoma patients – can present in a variety of pigmentations and textures and even masquerade as a rash.[3] As a result, the insidious presentation of in-transit metastasis represents a challenging diagnosis for even the most astute clinicians.[3] We present a case of a 73-year-old man diagnosed with in-transit metastasis for recurrent BRAF negative malignant melanoma of the left foot staged pT4bN2aMx (AJCC 7th edition TNM staging: pIIIC).

Methodology: A case report.

RESULTS

A 73-year-old man with type II diabetes controlled on metformin first presented to the Providence VA Medical Center Podiatry Clinic in March 2016 for routine diabetic foot care. The initial examination was notable for a 1 cm full-thickness ulcer with a granular base and swelling on his left foot's mid plantar region, most concerning for traumatic injury to the left foot with potential for foreign body insertion. The patient denied any fever, chills, nausea, vomiting, or night sweats. An MRI of the left foot ruled out a retained foreign body. Podiatry recommended proper diabetic foot care, including daily foot inspections and regular outpatient follow-up at three-month intervals.

Nine months later, the patient noticed increased discomfort across the left plantar region while walking barefoot. The podiatry service then performed an incisional biopsy of the plantar lesion which demonstrated superficial and deep mixed inflammatory infiltrate including plasma cells, lymphocytes, and eosinophils with CD3+ T-cells, CD20+ B-cells, and CD163+ histiocytes, suggestive of melanoma of the left plantar foot. Of note, Sox10 was negative for melanoma. A multi-disciplinary team approach discussed the options with the patient. These included offering the patient aggressive therapeutic modalities including wide local excision with possible skin graft and sentinel lymph node biopsy, as well as a potential need for chemotherapy. Given the graveness of malignant melanoma, the option of no further excision and focusing on palliative therapeutic modalities were also discussed. A wide local surgical excision to achieve a 2-centimeter margin with skin graft was undertaken with an associated sentinel lymph node biopsy. The sentinel lymph node biopsy was negative for metastatic disease. His post-operative course was complicated by wound infection and delayed wound healing which necessitated further skin grafting in consultation with plastic surgery.

Clinical follow-up was performed every three to six months with Dermatology, Oncology, and General Surgery in a multi-disciplinary fashion. This assessed for local recurrence as well as emergence of new lesions. Follow-up imaging included sequential PET scans which were obtained every four months. A follow-up PET scan seven months later revealed satellite disease recurrence on the plantar aspect of the left foot and metastases to the groin with associated left inguinal lymphadenopathy. Satellite disease is defined as

intra-lymphatic metastases less than two centimeters from the primary lesion.[4] A punch biopsy was positive for melanoma and left inguinal lymph node cytology via fine needle aspiration was also consistent with malignant melanoma. The patient then began talimogene laherparepvec injections (T-VEC; Imlygic) directly in the left inguinal region and the left plantar region every two weeks for a year as oncolytic viral therapy for advanced non-operable malignant melanoma. Follow-up imaging and biopsies approximately eight months later demonstrated no residual malignant melanoma on the left foot but were notable for a residual left medial inguinal lymph node positive for malignant melanoma. Surgical left inguinal lymph node dissection was completed. The T-VEC adjuvant therapy was completed four months after the lymph node dissection. A follow-up PET scan 14 months later identified a positive soft tissue deposit located anteromedial to the left knee, which was surgically removed. Corresponding surgical pathology was consistent with BRAF negative metastatic malignant melanoma (in-transit metastases), and the patient was started on cycles of monthly systemic immunotherapy of nivolumab (opdivo) 480 mg for twelve months.

Follow-up imaging was negative for melanoma until a PET CT and U/S of left thigh performed in December 2020 identified a 4 mm soft tissue deposit seen on nuclear imaging only, and an FNA was consistent with another in-transit deposit of disease. Given that this patient has survived well past the median survival of 20 months (now being 47 months), he underwent further surgical resection of the newly identified in-transit metastases.

Table 1. Summary of 2019 American Academy of Dermatology Malignant Melanoma Surveillance Guidelines[5,8-10,13]

Stage at initial diagnosis[a]	Time Frame	Recommended surveillance
Stage 0 (melanoma in situ)	Years 0–2	Physical exam and full skin exam at least every 6–12 months
	Years 2+	Annual physical examination and full skin exam
Stage IA–IIA	Years 0–5	Physical exam and full skin exam at least every 6–12 months
	Years 5+	Annual physical examination and full skin exam
Stage IIB or greater[b,c]	Year 0–2	Physical examination and full skin exam at least every 3–6 months Surveillance imaging recommended based on recurrence risk[5]
	Year 3–5	Physical examination and full skin exam at least every 6 months Surveillance imaging recommended based on recurrence risk[5]
	Year 5+	Annual physical examination and full skin exam

[a] Staging guidelines correspond with American Joint Committee on Cancer (AJCC) 7th Edition

[b] National Cancer Comprehensive Network (NCCN) guidelines include radiological surveillance for stage IIB or greater at the 3 and 12-month interval for up to 3–5 years.[5]

[c] Patients with in-transit metastases are classified as Stage IIIB or IIIC, corresponding to lymph node involvement.[6]

DISCUSSION

In-transit metastases represent one of the most significant diagnostic and therapeutic challenges in the long-term management of melanoma. The physical examination findings of patients with in-transit melanoma are often lacking, and therefore strict follow-up imaging (i.e., PET or CT scan) is critical to minimize the risk of missing an in-transit metastasis. Additionally, surveillance is recommended at intervals ranging from three–twelve months for up to five years (**Table 1**).[5] Imaging intervals depend on pathologic findings, adjuvant therapy, and clinical course. The identification of in-transit metastases might warrant a referral to a surgical oncologist for disease removal – a typically effective strategy if the recurrence is localized to a small number of sites (i.e., 1–3). However, given that in-transit metastases are rarely localized to a few locations, medical-surgical collaboration is often required.[6] Despite robust disease management and surveillance, in-transit metastases carry a poor prognosis with a 5-year survival rate of approximately 25%.[7] Systemic immunotherapy or chemotherapy is often ineffective, and surgical removal may also be unsuccessful depending on disease presentation and location.[6] These failures in the response of in-transit metastases have necessitated the development of novel regional pharmacologic therapies.[6]

In-transit metastases are a critical and often morbid component of malignant melanoma care. Initial work-up and management of the primary melanoma are vital. Suspicious skin lesions require a thorough work-up and/or referral to a dermatologist if needed. Current American Academy of Dermatology (AAD) guidelines recommend a narrow excisional/complete biopsy of a skin lesion with 1- to 3-mm margins, typically completed via elliptical excision (i.e., "fusiform"), punch excision, or deep shave (i.e., "saucerization") removal, for definitive diagnosis of cutaneous melanoma.[8] The deep shave removal is currently the most frequent diagnostic method utilized in the U.S. due to accessibility and cost.[8] Clinicians may consider sentinel lymph node biopsy if there is a high index of suspicion for metastatic spread.[8,9] While surveillance guidelines for malignant melanoma vary by society, surveillance frequency generally correlates to the tumor's staging and/or pathologic biopsy based on Breslow thickness.[10] Staging of melanoma is critical to directing how lesions and patients are to be followed. The AJCC Cancer Staging Manual[11] delineates the nature and degree of clinical or radiographic surveillance based

on the initial depth of melanotic lesions. These range from clinical and dermatology examinations for patients with Stage I/IIA lesions up to requirements for serial ultrasound imaging of the affected nodal field as well as PET/CT surveillance.[11,12] Initial clinical suspicion for possible risk of potential in-transit metastases included Stage III or greater, or evidence of ulceration at the time of the initial biopsy. A summary of current AAD surveillance guidelines for malignant melanoma are presented in **Table 1.**[8-10,13] After pathologic diagnosis of malignant melanoma, treatment generally involves surgical resection +/– adjuvant therapy. Pathology directly informs the likelihood of melanoma recurrence and systemic spread.[9,10]

A multi-disciplinary approach to disease surveillance and regular follow-up is crucial in the long-term care of malignant melanoma. Given the critical component of the physical exam in patient surveillance, it is often best advised that one designated member from within the broader multi-disciplinary team be primarily responsible for overseeing long-term disease surveillance. Given the collaborative nature of these teams, all providers are equally suited to guide the patient through the treatment course; it is essential that patients consistently utilize a singular provider to monitor surveillance. Unlike in primary melanoma, secondary melanoma is more often discovered by a healthcare professional rather than patients.[9] One important consideration for provider selection is accessibility, wherein the patient needs to consistently schedule appointments with appropriate frequency (**Table 1**). Additionally, the surveilling provider should also communicate screening results with the rest of the treatment team; extensive collaboration among dermatologists, surgical oncologists, medical oncologists, and primary care physicians can improve the long-term outcomes of malignant melanoma.

The reported median survival time following the diagnosis of in-transit metastases is approximately 20 months.[14] Read et al. reported a median survival time of 19.9 months, whereas Mervic noted a significant discrepancy in sex, with men often presenting with a higher stage of melanoma and significantly shorter survival time from the diagnosis.[14,15] Given the often innocuous clinical findings of in-transit melanoma, much of this poor survival is often attributed to the difficulty in diagnosing the in-transit component. Following identification of in-transit metastases, the 5-year survival rate is reported to be 25%.[14] The current standard treatment for in-transit metastases includes wide local excision with up to 2 cm margins as well as potentially therapeutic nodal basin excisions. Systemic chemotherapy ranges from dacarbazine to PD-1 based immunotherapy. Specific considerations include the initial presentation, radiographic location, and patient choice.[6,10,14] Other treatment plans for in-transit metastases might include isolated limb infusion and isolated limb perfusion therapy.[16] Isolated limb perfusion therapy utilizes the placement of venotomy and arteriotomy catheter into major blood vessels localized near the tumor to regionally transmit chemotherapy and minimizing the systemic toxicity of chemotherapy.[16] Isolated limb infusion therapy, on the other hand, utilizes a percutaneous catheter thereby reducing time and cost of treatment duration.[16] Last, one recent innovation in immunotherapy is talimogene laherparepvec (T-VEC, Imlygic) – a genetically modified strain of HSV-1 – as injectable oncolytic viral therapy for non-operable malignant melanoma.[17,18] T-VEC therapy utilizes a combination of direct tumor cell lysis and upregulation of regional host immune response to eliminate regional metastases and reduce the need for potentially toxic systemic chemotherapy.[19] As a result, the utilization of novel oncolytic viral therapies such as T-VEC represent a potentially important breakthrough in cancer pharmacology.[19] Currently, T-VEC is approved by the U.S. Food and Drug Administration to treat non-operable Stage IIB–IV M1c melanoma located in a region where direct injection is possible.[20] Despite T-VEC's novel development, high financial cost (estimated to be $65,000) and low provider awareness might currently preclude more ubiquitous utilization.[21] Oncolytic viral therapy is currently being investigated as treatment in other cancers, including bladder cancer (adenovirus) and hepatocellular carcinoma (vaccinia virus).[22]

CONCLUSION

In-transit metastases represent a diagnostic and therapeutic challenge for oncologic care, particularly in melanoma. Concomitant follow-up imaging every four to twelve months and T-VEC adjuvant therapy may help reduce rates of metastatic recurrence. Although the median survival time following the diagnosis of in-transit metastases is less than two years[23], T-VEC and immunotherapy most likely prolonged the life in our patient with malignant melanoma. Extensive collaboration among primary care physicians, dermatologists, medical oncologists, and surgical oncologists can help prolong the survival of patients with in-transit metastases from recurrent malignant melanoma.

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