In-Transit Metastasis From Melanoma Presenting as Lymphangiectasis: A Case Report

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The estimated time to complete this activity is 1 hour.

GOAL

To understand in-transit metastasis (ITM) from melanoma to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Define risk factors for ITMs in patients with melanoma.
2. Discuss the influence of sentinel lymph node biopsy and nodal dissection on the development of recurrent ITM.
3. Differentiate between treatment options for ITMs based on benefits and disadvantages.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 148.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: August 2009.

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Malignant melanoma as a cause of inflammatory metastasis to the skin is a rare phenomenon referred to as in-transit metastasis (ITM). We report an unusual case of a patient who developed left leg lesions resembling lymphangiectasis. Punch biopsy results revealed atypical cells consistent with melanoma. The patient had a history of high-risk melanoma involving the left side of the lower extremity. This case highlights the need for a high index of suspicion for ITM in patients with a history of melanoma. Therapeutic options are discussed.

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Malignant melanoma as a cause of inflammatory metastasis to the skin is a rarely reported phenomenon. It is referred to as in-transit metastasis (ITM) and represents an unusual pattern of persistent or recurrent disease, usually presenting after wide local excision (WLE) and occasionally prior to any treatment. In a study of 1395 patients with primary melanoma who underwent a sentinel lymph node (SLN) biopsy and were followed for more than 3.9 years, 6.6% developed ITM.[1] In-transit metastasis often is a sign of disseminated disease and portends a poor prognosis.[2] Although the pathophysiology of ITM is not well understood, it likely is an intralymphatic manifestation of melanoma metastasis.[3-5] Dissemination of malignant cells to the skin is thought to occur through dermal lymphatic vessels.[6,7] The cutaneous site of metastasis often is in the area affected by prior surgery or radiation therapy.[6] We report a case of this unusual clinical manifestation of metastatic melanoma, initially diagnosed clinically as lymphangiectasis.

Case Report

A 44-year-old white man with a history of stage IIIC melanoma arising in the left foot was evaluated for the development of multiple tender papules on the left thigh and groin region of several weeks' duration. One month later, the lesions progressed to cover much of the surface of the left side of the lower extremity, with extension onto the lower abdomen, perineum, and left inguinal region.

The patient's medical history included malignant melanoma that involved the medial aspect of the left ankle and arose in a preexisting nevus. The patient reported bleeding at the site prior to biopsy. Biopsy of the lesion revealed malignant melanoma, with a Breslow thickness of 1.25 mm and pathologic evidence of ulceration. Immunohistochemical analysis indicated that the tumor was positive for melan-A and S100, and negative for cytokeratin.

The patient was treated with WLE and SLN biopsy. No evidence of residual tumor was identified in the WLE specimen. One SLN on the left aspect of the inguinal region and 3 non-SLNs were obtained; all showed no evidence of melanoma involvement. Initial disease staging was consistent with stage IIA (T2bN0M0), according to current American Joint Committee on Cancer (AJCC) staging criteria.[8] No further adjuvant therapy was undertaken at that time.

Six months after initial diagnosis and treatment, the patient developed a papule in the vicinity of the WLE. Results of a punch biopsy revealed malignant melanoma consistent with ITM. The patient underwent a repeat WLE and left inguinal SLN biopsy. A lymph node from the left aspect of both the inguinal and femoral regions were obtained and found to be involved with melanoma. Further, the femoral node demonstrated extracapsular spread of the disease. Completion lymphadenectomy yielded 7 additional femoral nodes and 18 left iliac and obturator nodes; all were uninvolved. This finding was confirmed by immunohistochemical analysis, with all nodes being negative for involvement after staining for human melanoma black–45 (HMB-45) and S100. Based on the apparent in-transit lesion at the vicinity of the original WLE site and concurrent locoregional nodal involvement, the patient's disease was upstaged to AJCC stage IIIC (T2bN3M0). No distant metastases were evident on staging studies at this time.

Because of the patient's high-recurrence risk, he enrolled in an adjuvant clinical trial. He received 3 cycles of biochemotherapy (cisplatin, dacarbazine, vinblastine sulfate, interferon alfa-2b, interleukin 2), which he tolerated well. He completed adjuvant therapy 3 months prior to presentation for his skin complaint and was seen in follow-up by his oncologist approximately 1 month prior to the presentation. The only notable finding on physical examination was lymphedema involving the left aspect of the lower extremity. Computed tomography showed no evidence of metastatic lesions.

The patient subsequently presented to his primary care physician with several inflamed lesions on the left thigh. The physician suspected a benign dermatitis and treated the patient with clobetasol propionate lotion 0.05% for 2 weeks. There was no improvement and the physician referred the patient to a dermatologist for further evaluation.

Our patient presented to the dermatology clinic with multiple lesions on the left thigh and groin region. Physical examination revealed multiple, tender, initially nonpigmented, pink, well-marginated, infiltrating papules on the left thigh, accompanied by left leg edema and bruising. Clinical suspicion was high for lymphangiectasis because of the nonpigmented nature of the lesions, sudden onset of the eruption, and associated edema. Several punch biopsy specimens were obtained at this time. In the following several weeks, the lesions evolved into dark pink to red nodular lesions (Figure 1) extending onto the lower abdomen, perineum, and left inguinal region.

Histologic examination of several punch biopsy specimens showed an unremarkable epidermis, with many of the dermal and subcutaneous lymphatic channels occluded by neoplastic melanocytes (Figure 2). Tumor cells were positive for melan-A and S100. These findings were consistent with widespread ITM involving the left aspect of the lower extremity.

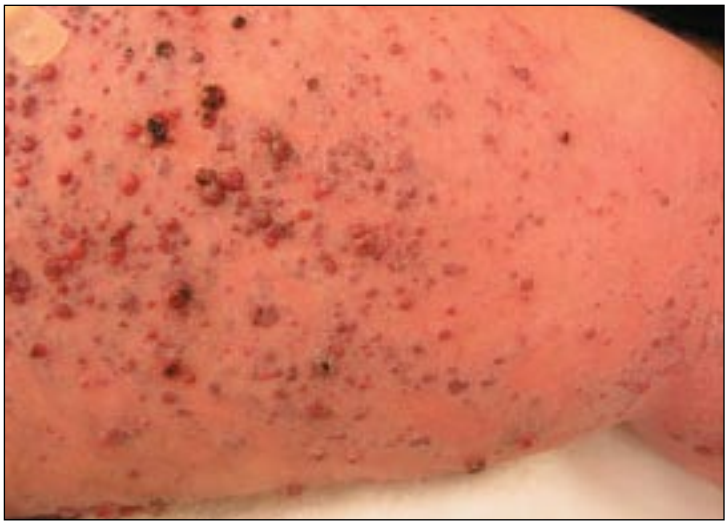

Figure 1. Medial aspect of the left distal thigh demonstrating well-marginated, infiltrating papules with generalized erythema and marked edema.

The patient was referred to his oncologist for further evaluation and treatment of stage IV cancer. Because these metastases extended further onto the abdomen and were not localized to the lower extremity, the patient was not a candidate for isolated limb perfusion (ILP) therapy. Thus the treatment of choice was systemic therapy.

Comment

In-transit metastasis can present as erythematous nodules or occasionally as macules ranging from 0.5 to 2 cm in diameter that may or may not be pigmented, accompanied by edema, warmth, and tenderness of the skin. Because of lymphatic blockage, these ITMs may extend retrogradely to the closest regional nodal basin with extensive disease.[8] Stage IIIB or stage IIIC melanoma is categorized depending on the absence or presence of regional nodal metastases, respectively.[9] Our patient's metastases extended onto the lower abdomen; therefore, his disease was classified as stage IV because of the extension beyond the regional nodal basin. Disease was limited to nodal and cutaneous lesions, and lactate dehydrogenase was within reference range, consistent with the M1a substage of metastatic disease. The AJCC specifies ITM as any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but not beyond the regional nodal basin. The AJCC distinguishes ITM from satellite lesions, which are within 2 cm of the primary lesion. In-transit metastasis and satellitosis are both intralymphatic extensions of the primary tumor. The tumor biology and prognosis are similar to those patients with multiple nodal metastases.[8,10] In a single study of 95 patients with ITM, the median survival time was 19 months, with only approximately 12% (11/95) surviving to 5 years.[11] At least one study reported 5-year survival rates ranging from 10% to 60%, depending on tumor burden.[1] Factors improving prognosis include presence of dermal-only metastases, sex (female), and lesions on the extremities versus the trunk or head and neck.[10]

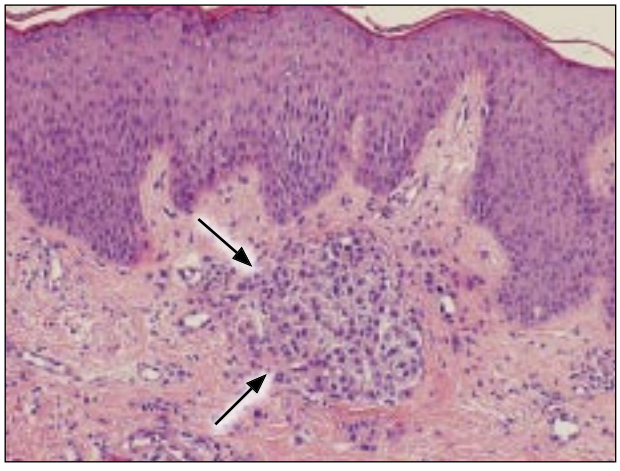

Figure 2. Unremarkable epidermis overlying a dermal lymphatic channel occluded by neoplastic melanocytes (arrows)(H&E, original magnification ×100).

Risk factors predicting locoregional recurrence after primary resection include primary tumor stage, anatomic location, SLN status, and prior nodal dissections.[2] The risk for developing ITM is directly related to the stage of the primary melanoma. The 2 most predictive factors in stage I and stage II melanomas are Breslow thickness and ulceration of the epidermis overlying the primary lesion, which are essentially the same as the factors that define prognosis associated with a primary melanoma.[12] In retrospective studies of patients with stage I and stage II disease, the incidence of ITM is between 2.3% and 12.0%.[1,3,8,13] In-transit metastasis occurs even more frequently if lymphatic invasion by the primary tumor is present. Risk for ITM also is influenced by the location of the primary melanoma and

the status of the primary lymph node. Patients with regional nodal involvement at presentation are at greater risk for ITM, with risk being proportionate to the number of nodes involved.[3,12] In a review of 1001 patients with cutaneous melanoma, the incidence of ITM markedly varied by anatomic site. It occurred most often when the primary lesion involved the lower extremity (19%) and was less common when the primary lesion involved the trunk (9%), upper extremity (8%), or head and neck (5%).[14] Patients with ITM or satellite metastases on the extremities have a better prognosis than those patients with lesions on the trunk or head and neck.[15]

The influence of SLN biopsy and nodal dissection on the development of recurrent ITM is controversial. It has been postulated that these interventions confine melanoma cells in lymphatic channels and give rise to ITM before it reaches regional nodes.[16] Subsequent studies failed to support this premise.[1,17] Sentinel lymph node status is one of the best predictors of local, in-transit, and distant recurrences in patients with melanoma. For example, one study of 1269 patients confirmed that SLN biopsy is more important than Breslow thickness, primary lesion ulceration site, anatomic location, sex, age, and Clark level in predicting ITM recurrence.[18] The rate of melanoma recurrence with a negative SLN biopsy result is approximately 8.9%.[19]

The influence of lymph node dissection (LND) on ITM incidence rate also has been questioned. Studies have revealed that the overall incidence of ITM is higher in patients after LND.[20,21] Other large studies showed no such increase.[17] A relationship between SLN biopsy, WLE plus SLN biopsy, and elective LND (ELND), and the increased incidence of ITM, could not be shown in a retrospective comparison of 4412 patients with stage I and stage II melanomas.[17] Elective LND, a procedure in which lymph nodes without evidence of cancer are removed, also has been debated. According to *The MD Anderson Surgical Oncology Handbook*, recent studies have demonstrated some survival advantage to certain patient groups undergoing ELND.[21] However, a randomized trial of 240 patients showed no benefit of ELND on the survival rate for patients with primary melanoma of the trunk greater than 1.5 mm in thickness, and only dissection of nodes positive for melanoma offered increased survival for these patients.[3] Elective LND is not widely recommended in the management of patients with melanoma and ITM, having been replaced by SLN biopsy.

Treatment options of ITM are classified as local, regional, or systemic (Table). The choice of therapy depends on the number of lesions, anatomic location, classification as dermal or subcutaneous, size, and presence or absence of extraregional metastasis.[2] Surgical resection of ITM is the preferred treatment in patients with a small number of lesions.[22] In a study of 648 patients undergoing surgical resection for locoregional metastases at first relapse, including ITM, 55% experienced a second locoregional relapse within 2 years and 82% by 5 years.[23] Most of these patients relapsed with more ITM. In a 39-month follow-up, approximately 33% of patients who had a second locoregional relapse and 77% of patients without further disease progression were still alive.[23]

The surgical principles for treatment of in-transit lesions differ from surgical excision of primary melanoma. It is sufficient to obtain histologically negative margins without the wider resection margin necessary for primary melanoma treatment.[8] In smaller in-transit lesions, negative margins usually can be accomplished with primary closure, with wound edges brought neatly together, avoiding the need for skin grafts and their attendant complications.

Another local treatment option for a small number of ITMs is intralesional injections with BCG vaccine, dinitrochlorobenzene, or interferon alfa-2b. In one study, 20 of 27 patients had an objective response to intratumoral BCG injections.[26] A pooled analysis of 15 noncontrolled trials of intralesional BCG therapy revealed complete and partial responses of 19% and 26%, respectively.[27] On occasion, BCG injections have been associated with dissemination of bacille Calmette-Guérin infection and skin ulceration and necrosis.[8] In a small trial comparing intralesional BCG injections and dinitrochlorobenzene, a similar response rate was reported.[28] Intralesional injections with interferon alfa-2b also have been studied in ITM. In one study of 51 patients, a 47% (24/51) objective response rate was demonstrated. Interestingly, several patients had substantial regression of the noninjected lesions, which suggests an activation of the host immune response against the melanoma.[40]

External beam radiation therapy may be used in the management of surgically unresectable melanoma and as a local adjuvant therapy, providing palliative benefit and local control.[8] However, both the relative radioresistance of melanoma[22] and the dermatologic side effects of radiotherapy, such as poor wound healing, limit its utility in ITM therapy.[24] Radiation therapy also is not associated with a survival benefit. A retrospective review of 89 patients with axillary node metastases who underwent adjuvant radiation therapy demonstrated an 87% five-year regional control rate compared

Treatment of In-Transit Metastases

Therapy	Benefits	Disadvantages
Local		
Surgical resection[8,22,23]	Long-term, relapse-free survival in patients with locoregional disease only	Often fails to control regional disease; only effective for a single or few ITM; no effect on latent disease
CO_2 laser ablation[2]	Good short-term control with ≤4 treatments	Only in the management of small nodules (<1.5 cm); high incidence of recurrence at laser sites; no effect on latent disease
External beam radiation[8,22,24,25]	Noninvasive; treats latent disease in radiation field	Radioresistance of melanomas; dermatologic effects of radiation, including poor wound healing
Intralesional injections with BCG, DNCB, and interferon alfa-2b[8,26-28]	Regression of noninjected lesions, possibly due to host immune response; simple to administer	Systemic complications, including dissemination of BCG infection and allergic reactions
Electrochemotherapy: intralesional injection with EP and bleomycin sulfate[29]	EP permeabilizes tumor cell membrane, potentially increasing bleomycin sulfate efficacy	Limited success (36% complete regression with this therapy vs bleomycin sulfate alone)
Regional		
Isolated limb infusion[4,15,30]	Well tolerated; may markedly reduce tumor burden in some patients; 46% complete remission; 40%–68% response rate	Often short duration of remission; little pharmacologic advantage over systemic chemotherapy; not widely available; no proven effect on survival
Isolated limb perfusion[31-39]	Can be curative; minimal systemic toxicity; high response rates (up to 100%); best loco-regional control option for inoperable disease	Limb toxicity; damage to blood vessels, nerves, muscles; no proven effect on survival; costly and technically demanding; not widely available
Systemic		
Chemotherapy[22,30]	Improved response with multiagent therapy; overall response rates of 10%–20% and duration of ≈2–4 mo	Most response is only partial and transient; systemic toxicity; no proven survival benefit
Immunotherapy[23]	Some prolonged remissions with high-dose interleukin 2; possible cures in some cases	Substantial toxicity; not appropriate for many patients; most patients derive no benefit; not widely available

Abbreviations: ITM, in-transit metastasis; DNCB, dinitrochlorobenzene; BCG, bacille Calmette-Guérin; EP, electroporation.

with the 50% to 70% local control achieved with surgery alone.[25] Similar results were demonstrated in a subsequent study of 40 patients with inguinal or pelvic lymph node metastases.[24]

Carbon dioxide laser ablation is used for the management of small nodules (<1.5 cm). Because of the high incidence of recurrence at treated sites and minimal effect on latent disease, this therapy is considered inferior to ILP; however, it probably is useful for palliation of patients who cannot receive more aggressive therapies.[2]

Isolated limb infusion and ILP are among the more effective regional therapies for ITM. Isolated limb infusion, a less invasive procedure, involves percutaneous placement of venous and arterial catheters and the infusion of chemotherapeutic agents, such as melphalan, cisplatin, or dacarbazine, into the affected extremity. Unlike ILP, it does not require an oxygenator; additionally, operating time is shorter and complication rates are lower (approximately 1%).[15] Response rates vary from 40% to 68%, and the duration of remission tends to be short.[4,30] One study administered intra-arterial cisplatin and dacarbazine to 30 patients with regionally advanced melanoma refractory to standard therapy. An objective response was documented in 11 of 30 patients (37%), including 3 complete (10%) responses.[4] This technique is well-tolerated, even in frail and elderly patients. However, it is limited by short duration of remission, lack of wide availability, and lack of apparent advantage over systemic chemotherapy.

Isolated limb perfusion works by separating the blood flow of the affected limb from the rest of the body and circulating a high dose of a chemotherapeutic agent through the limb for a short time.[31] It is performed in the operating room under general anesthesia. Treatment duration is approximately 60 to 90 minutes. One catheter is placed into the artery, which feeds blood into the limb, and another is placed into the vein, which drains it. A tourniquet is tied around the limb to ensure that blood from the limb does not enter the general circulation. The blood exits the limb through catheters, is heated and oxygenated by extracorporeal heart-lung machines, and then is recirculated back into the limb. Concentrated chemotherapy drugs are put into the limb at the start of the session; by the end of the procedure, the drugs are completely washed out of the limb, and the limb's circulation is returned to normal.

In ITM that is not amenable to surgical therapy, ILP provides the best locoregional control.[21,31,32] However, there have not been randomized trials comparing the 2 modalities. Isolated limb perfusion of an extremity using melphalan can yield complete responses in more than 50% of treated patients, with overall response rates of approximately 80%.[32]

Although earlier reports indicated improved response rates when using tumor necrosis factor α (TNF-α) in addition to melphalan, more recent studies have not demonstrated a substantial enhancement of short-term response rates over melphalan alone. The combination of TNF-α and melphalan was associated with a higher complication rate[33] with or without interferon γ.[34] Two studies of patients failing ILP with melphalan alone showed that retreatment with TNF-α had benefit.[35,36] Reperfusion was associated with an overall 94% response rate and a 65% complete response rate. Of the patients who failed an initial ILP with melphalan alone, the overall response rate was 90% after the reperfusion with TNF-α and melphalan. In patients who failed an initial ILP with agents other than melphalan, the complete response rate was 100% after ILP with TNF-α and melphalan.[35,36]

Despite impressive local response rates to this therapy, no effect on survival was evident in a large prospective trial comparing surgery plus adjuvant ILP with surgery alone.[37] Survival benefit would not necessarily be expected because the presence of ITM strongly correlates with distant metastasis development. Isolated limb perfusion would not be predicted to alter development at sites not subject to the treatment. Nevertheless, a palliative benefit of local disease control can justify the procedure.

Isolated limb perfusion has limited systemic toxicity but is associated with undesirable local sequelae.[30] Adverse effects include limb toxicity and damage to blood vessels, nerves, and muscles. One concerning retrospective review of ILP in 54 patients with ITM reported that 26 of 59 perfusion procedures (44%) resulted in serious toxic effects associated with persistent range of motion abnormalities or sensory deficits in the perfused limb.[37] Regional toxicity after hyperthermic ILP with TNF-α and melphalan was substantially increased compared with ILP with melphalan alone.[38] The procedure also is costly, technically demanding, and not widely available.

Systemic chemotherapy and immunotherapy usually are reserved for patients with recurrent ITM who are not candidates for either local or regional therapy. Presently, only 2 agents (dacarbazine, interleukin 2) are approved and widely used in the United States for the treatment of unresectable stage III and stage IV melanomas. Overall response rates with dacarbazine or interleukin 2 are similar and range from 10% to 20%.[25] A pooled analysis of 270 patients treated with high-dose interleukin 2 resulted in an overall objective response rate of

16%.[39] Best clinical responses were observed in patients with metastatic disease involving soft tissues and lymph nodes. The overall median survival time in these patients was 11.4 months. A small number of treated patients (approximately 6%) experienced complete responses, some durable and representing cures. Disease limited to the skin and subcutaneous and nodal tissues (M1a according to the AJCC) was a predictor of response, which included patients with isolated ITM.[39] The severe toxicity and overall low rate of benefit limits the use of interleukin 2 for this indication.

High response rates (up to 64%) have been noted with multiagent therapy, including cisplatin, dacarbazine, vinblastine sulfate, interferon alfa-2b, and interleukin 2.[30] However, no significant prolongation of median overall survival has been demonstrated, and combination therapy has been associated with more severe adverse side effects. These therapies remain experimental.

The index case demonstrates the importance of a high level of suspicion for ITM in patients with a history of melanoma. In-transit metastasis initially may mimic other inflammatory skin conditions, such as lymphangitis, lymphangiectasis, pyogenic granulomas, folliculitis, cellulitis, and panniculitis. The development of ITM portends a guarded prognosis. Treatment options must be tailored to the patient and are admittedly suboptimal, affecting local control without impacting overall survival. Further advances in the treatment of ITM await the development of more effective systemic therapies for melanoma.

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