

# Merkel Cell Carcinoma in a Vein Graft Donor Site

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## PRACTICE POINTS

- Malignancies (both primary and metastatic) can develop in graft donor sites including donor sites for split-thickness skin, full-thickness skin, tendon, bone, and vein grafts.
- Primary malignancies that develop in graft donor sites may be distinct from malignancies that develop in chronic wounds, as the former occur in healed surgical wounds and tend to occur sooner after injury (ie, weeks to months after graft harvesting versus years).
- Although the occurrence is rare, graft donor sites should be examined periodically for development of malignancies.

*The development of malignancies in graft donor sites is rare and may be caused by de novo malignancies as well as metastatic and iatrogenic spread. Malignancies in graft donor sites are distinguished from Marjolin ulcers by some investigators because they occur in healed surgical wounds rather than in chronic wounds or unstable scars and tend to occur sooner after injury. We present a unique case of Merkel cell carcinoma (MCC) developing in a vein graft donor site 18 years after vein harvesting.*

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## Case Report

A 70-year-old man with history of coronary artery disease presented with a growing lesion on the right leg of 1 year's duration. The lesion developed at a vein graft donor site for a coronary artery bypass that had been performed 18 years prior to presentation. The patient reported that the lesion was sensitive to touch. Physical examination revealed a 27-mm, firm,

violaceous plaque on the medial aspect of the right upper shin (Figure 1). Mild pitting edema also was noted on both lower legs but was more prominent on the right leg. A 6-mm punch biopsy was performed.

Histology showed diffuse infiltration of the dermis and subcutaneous fat by intermediate-sized atypical blue cells with scant cytoplasm (Figure 2). The tumor exhibited moderate cytologic atypia with occasional mitotic figures, and lymphovascular invasion was present. Staining for CD3 was negative within the tumor, but a few reactive lymphocytes were highlighted at the periphery. Staining for CD20 and CD30 was negative. Strong and diffuse staining for cytokeratin 20 and pan-cytokeratin was noted within the tumor with the distinctive perinuclear pattern characteristic of Merkel cell carcinoma (MCC). Staining for cytokeratin 7 was negative. Synaptophysin and chromogranin were strongly and diffusely positive within the tumor, consistent with a diagnosis of MCC.

The patient was found to have stage IIA (T2N0M0) MCC. Computed tomography completed for staging showed no evidence of metastasis. Wide local excision of the lesion was performed. Margins were negative, as was a right inguinal sentinel lymph node dissection. Because of the size of the tumor and the presence of lymphovascular invasion, radiation therapy at the primary tumor site was recommended. Local radiation treatment (200 cGy daily) was administered for a total dose of 5000 cGy over

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5 weeks. The patient currently is free of recurrence or metastases and is being followed by the oncology, surgery, and dermatology departments.

### Comment

Merkel cell carcinoma is a rare aggressive cutaneous malignancy. The exact pathogenesis is unknown, but immunosuppression and UV radiation, possibly through its immunosuppressive effects, appear to be contributing factors. More recently, the Merkel cell polyomavirus has been linked to MCC in approximately 80% of cases.<sup>1,2</sup>

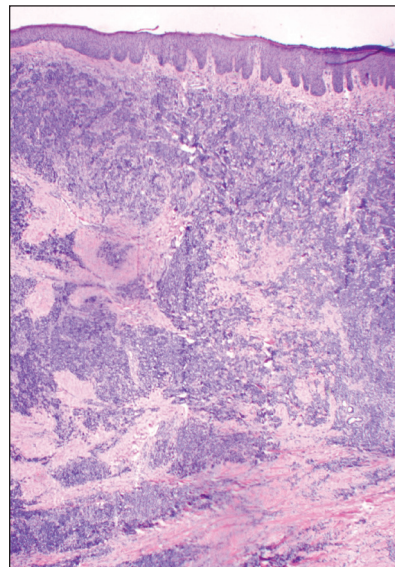
Merkel cell carcinoma is more common in individuals with fair skin, and the average age at diagnosis is 69 years.<sup>1</sup> Patients typically present with an asymptomatic, firm, erythematous or violaceous, dome-shaped nodule or a small indurated plaque, most commonly on sun-exposed areas of the head and neck followed by the upper and lower extremities including the hands, feet, ankles, and wrists. Fifteen percent to 20% of MCCs develop on the legs and feet.<sup>1</sup> Our patient presented with an MCC that developed on the right shin at a vein graft donor site.

The development of a cutaneous malignancy in a chronic wound (also known as a Marjolin ulcer) is a rare but well-recognized process. These malignancies occur in previously traumatized or chronically inflamed wounds and have been found to occur most commonly in chronic burn wounds, especially in ungrafted full-thickness burns. Squamous cell carcinomas (SCCs) are the most common malignancies to arise in chronic wounds, but basal cell carcinomas, adenocarcinomas, melanomas, malignant fibrous histiocytomas, adenoacanthomas, liposarcomas, and osteosarcomas also have been reported.<sup>3</sup> There also have been a few reports of MCC associated with Bowen disease that developed in burn wounds.<sup>4</sup> These malignancies generally occur years after injury (average, 35.5 years), but there have been reports of keratoacanthomas developing as early as 3 weeks after injury.<sup>5,6</sup>

In some reports, malignancies in skin graft donor sites are differentiated from Marjolin ulcers, as the former appear in healed surgical wounds rather than in chronic unstable wounds and tend to occur sooner (ie, in weeks to months after graft harvesting).<sup>7,8</sup> The development of these malignancies in graft donor sites is not as well recognized and has been reported in donor sites for split-thickness skin grafts (STSGs), full-thickness skin grafts, tendon grafts, and bone grafts. In addition to malignancies that arise de novo, some develop due to metastatic and iatrogenic spread. The majority of reported malignancies in tendon and bone graft donor sites have been due to metastasis or iatrogenic spread.<sup>9-14</sup>



**Figure 1.** Violaceous nodule on the medial aspect of the right upper shin within a scar.



**Figure 2.** Diffuse infiltration of the dermis and subcutaneous fat by intermediate-sized atypical blue cells with scant cytoplasm (H&E, original magnification  $\times 40$ ).

Iatrogenic implantation of tumor cells is a well-recognized phenomenon. Hussain et al<sup>10</sup> reported a case of implantation of SCC in an STSG donor site, most likely due to direct seeding from a hollow needle used to infiltrate local anesthetic in the tumor area and the STSG. In this case, metastasis could not be completely ruled out.<sup>10</sup> There also have been reports of osteosarcoma, ameloblastoma, scirrhous carcinoma of the breast, and malignant fibrous histiocytoma thought to be implanted at bone graft donor sites.<sup>14-17</sup> Iatrogenic spread of malignancies can occur through seeding from contaminated gloves or instruments such as hollow bore needles or trocar placement in laparoscopic surgery.<sup>11</sup> Airborne spread also may be possible, as viable melanoma cells have been detected in electrocautery plume in mice.<sup>13</sup>

Metastatic malignancies including metastases from SCC, adenocarcinoma, melanoma, malignant

fibrous histiocytoma, angiosarcoma, and osteosarcoma also have been reported to develop in graft donor sites.<sup>11,13,18,19</sup> Many malignancies thought to have developed from iatrogenic seeding may actually be from metastasis either by hematogenous or lymphatic spread. A possible contributing factor may be surgery-induced immunosuppression, which has been linked to increased tumor metastasis formation.<sup>20</sup> Surgery or trauma have been shown to have an effect on cellular components of the immune system, causing changes such as a shift in T lymphocytes toward immune-suppressive T lymphocytes and impaired function of natural killer cells, neutrophils, and macrophages.<sup>20</sup> The suppression of cell-mediated immunity has been shown to decrease over days to weeks in the postoperative period.<sup>21</sup> In addition to surgery- or trauma-induced immunosuppression, the risk for metastasis may increase due to increased vascular, including lymphatic, flow toward a skin graft donor site.<sup>13,16</sup> Furthermore, trauma predisposes areas to a hypercoagulable state with increased sludging as well as increased platelet counts and fibrinogen levels, which may lead to localization of metastatic lesions.<sup>22</sup> All of these factors could potentially work simultaneously to induce the development of metastasis in graft donor sites.

We found that SCCs and keratoacanthomas, which may be a variant of SCC, are among the only primary malignancies that have been reported to develop in skin graft donor sites.<sup>6-8</sup> Malignancies in these donor sites appear to develop sooner than those found in chronic wounds and are reported to develop within weeks to several months postoperatively, even in as few as 2 weeks.<sup>6,8</sup> Tamir et al<sup>6</sup> reported 2 keratoacanthomas that developed simultaneously in a burn scar and STSG donor site. The investigators believed it could be a sign of reduced immune surveillance in the 2 affected areas.<sup>6</sup> It has been hypothesized that one cause of local immune suppression in Marjolin ulcers could be due to poor lymphatic regeneration in scar tissue, which would prevent delivery of antigens and stimulated lymphocytes.<sup>23</sup> Haik et al<sup>7</sup> considered this possibility when discussing a case of SCC that developed at the site of an STSG. The authors did not feel it applied, however, as the donor site had only undergone a single skin harvesting procedure.<sup>7</sup> Ponnuvelu et al<sup>8</sup> felt that inflammation was the underlying etiology behind the 2 cases they reported of SCCs that developed in STSG donor sites. The inflammation associated with tumors has many of the same processes involved in wound healing (eg, cellular proliferation, angiogenesis). Ponnuvelu et al<sup>8</sup> hypothesized that the local inflammation caused by graft harvesting produced an ideal environment for early carcinogenesis. Although in chronic wounds it is believed that continual repair and regeneration in

recurrent ulceration contributes to neoplastic initiation, it is thought that even a single injury may lead to malignant change, which may be because prior actinic damage or another cause has made the area more susceptible to these changes.<sup>24,25</sup> Surgery-induced immunosuppression also may play a role in development of primary malignancies in graft donor sites.

There have been a few reports of SCCs and basal cell carcinomas occurring in other surgical scars that healed without complications.<sup>24,26-28</sup> Similar to the malignancies in graft donor sites, some authors differentiate malignancies that occur in surgical scars that heal without complications from Marjolin ulcers, as they do not occur in chronically irritated wounds. These malignancies have been reported in scars from sternotomies, an infertility procedure, hair transplantation, thyroidectomy, colostomy, cleft lip repair, inguinal hernia repair, and paraumbilical laparoscopic port site. The time between surgery and diagnosis of malignancy ranged from 9 months to 67 years.<sup>24,26-28</sup> The development of malignancies in these surgical scars may be due to local immunosuppression, possibly from decreased lymphatic flow; additionally, the inflammation in wound healing may provide the ideal environment for carcinogenesis. Trauma in areas already susceptible to malignant change could be a contributing factor.

## Conclusion

Our patient developed an MCC in a vein graft donor site 18 years after vein harvesting. It was likely a primary tumor, as vein harvesting was done for coronary artery bypass graft. There was no evidence of any other lesions on physical examination or computed tomography, making it doubtful that an MCC serving as a primary lesion for seeding or metastasis was present. If such a lesion had been present at that time, it would likely have spread well before the time of presentation to our clinic due to the fast doubling time and high rate of metastasis characteristic of MCCs, further lessening the possibility of metastasis or implantation.

The extended length of time from procedure to lesion development in our patient is much longer than for other reported malignancies in graft donor sites, but the reported time for malignancies in other postsurgical scars is more varied. Regardless of whether the MCC in our patient is classified as a Marjolin ulcer, the pathogenesis is unclear. It is thought that a single injury could lead to malignant change in predisposed skin. Our patient's legs did not have any evidence of prior actinic damage; however, it is likely that he had local immune suppression, which may have made him more susceptible to these changes. It is unlikely that surgery-induced

immunosuppression played a role in our patient, as specific cellular components of the immune system only appear to be affected over days to weeks in the postoperative period. Although poor lymphatic regeneration in scar tissue leading to decreased immune surveillance is not generally thought to contribute to malignancies in most surgical scars, our patient underwent vein harvesting. Chronic edema commonly occurs after vein harvesting and is believed to be due to trauma to the lymphatics. Local immune suppression also may have led to increased susceptibility to infection by the MCC polyomavirus, which has been found to be associated with many MCCs. In addition, the area may have been more susceptible to carcinogenesis due to changes from inflammation from wound healing. We suspect together these factors contributed to the development of our patient's MCC. Although rare, graft donor sites should be examined periodically for the development of malignancy.

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