THE CUTTING EDGE

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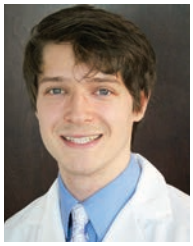
Peer-Reviewed

Malignant Transformation of Childhood Burn Wound with Metastasis: A Case Report

New CE Article



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Fellow members were given the opportunity to apply for a travel grant to attend an upcoming Fall Conference or Spring Meeting of their choice. Fellows were required to write a manuscript, and the four winning entries received a grant valued at up to $1800 (full week registration + $1000 to help cover travel expenses). Congratulations, Dominic, on your winning submission!

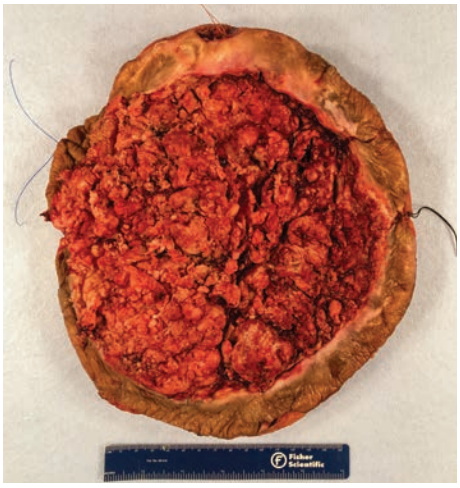
Abstract

Marjolin's ulcer is a rare and aggressive form of cutaneous squamous cell carcinoma (SCC) which forms through malignant transformation of chronically irritated previous injury, such as incompletely healed burns, ulcers, and other wounds. Although similar in microscopic morphology, Marjolin's ulcer is unique from other cutaneous SCCs in many other significant characteristics. The carcinoma often appears decades after the initial trauma, but once present it follows a rapid course of growth and metastasis. In the current case study, a male in his mid-30s with history of extensive burns as a child presented to the Emergency Department complaining of a large, open wound on his lower back. Biopsy of the primary lesion showed moderately to poorly differentiated squamous cell carcinoma, prompting wide local excision. Subsequent radiology and biopsy showed positive metastasis to the right ventricle of the heart, with concern for metastasis to the left lung and left axillary lymph nodes. The following article presents a rare and unique case, while advocating for complete submission of skin resection margins on large specimens even in the context of multiple negative intraoperative diagnoses.

Key words: Marjolin's ulcer, squamous cell carcinoma, burn scar, skin excision

Introduction and Brief Review of Literature

One of the rarest and most aggressive forms of squamous cell carcinoma (SCC) of the skin is found in malignant transformation of a site of previous trauma, a condition often nicknamed "Marjolin's ulcer" after a French physician who first described the condition in the early 19th century. However, this presentation represents only a small subsection of a much broader condition. While cutaneous SCC as a category is quite common, especially in older and light-skinned individuals, the predominant cause is exposure to ultraviolet (UV) light.[1] The high-energy UV light rays cause DNA damage and subsequent mutations in the well-known tumor suppressor TP53.



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AAPA American Association of Pathologists' Assistants

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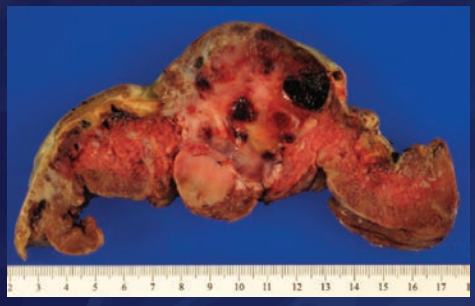

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Transformation

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In addition, the HRAS gene can undergo activating mutation—increasing cell division and survival—and Notch receptors can experience loss-of-function mutations, affecting the normal differentiation of squamous epithelium.[1] Lesions are generally well-defined and plaque-like, with ulceration present only in advanced cases. These common forms of SCC tend to be completely treatable by local excision and rarely metastasize to lymph nodes or other organs.

However, while still a cutaneous SCC, Marjolin's ulcer is distinct from standard cases in nearly every one of the characteristics described above. Neither age nor skin pigmentation are associated with risk or prognosis. Exposure to sunlight is generally irrelevant in cases of Marjolin's ulcer; instead, the cause is traumatic in nature, with malignancies most commonly forming at old burn scars but also on poorly-healed wounds of various sorts such as pressure, venous stasis, or diabetic ulcers.[2,3] According to available literature, from 1-2% of burn scars undergo malignant transformation but these represent <0.5% of all skin cancers.[4,5] Interestingly, rather than DNA damage due to UV rays, the pathophysiology of Marjolin's ulcer progresses through multiple diverse and simultaneous processes, many of which are still areas of active research. One significant mechanism involves the chronic irritation present in old, unhealed and possibly infected wounds—the epithelial cells are being damaged and regenerated at a much higher rate than usual, releasing high levels of necrotic toxins and providing exponentially more opportunities for mutations to arise.[4] Other studies have shown that chronic scar tissue lacks the usual immunological components of healthy dermis, including Langerhans cells and lymphatics, providing an uncontrolled site in which malignant cells can grow unchallenged. Finally, significant differences in gene expression have been noted between cells sampled from Marjolin's ulcer compared to other cutaneous SCC.[6] For example, heightened extracellular matrix turnover and epithelial-to-mesenchymal transformation have been traced to the drastically increased metastatic potential of these cells.

These unique etiological characteristics contribute to Marjolin's ulcer having a particularly aggressive course, although the disease can be latent for decades following the initial trauma. In fact, the time elapsed between injury and presentation of malignancy has been reported to be as long as 74 years, with an average between 35-38 years.[2,5,7] Once carcinoma develops, there is high risk for deep and rapid local invasion, lymphatic spread and wide metastasis.[4] As with most conditions, early diagnosis and treatment leads to improved prognosis; however, this goal presents a particular challenge considering the long-term nature of the malignancy and the fact that such chronic lesions tend to be painless. Marjolin's ulcer generally presents as a large, irregular, ulcerated wound with an excavated center and fungating borders, and often produces a foul-smelling exudate. Wide excision of the primary lesion—including amputation of limbs—is the only treatment which has demonstrated efficacy to date. Systemic treatments such as chemotherapy have been used with patients suffering from widespread metastasis, but many such cases have a prognosis of only 2-3 years.[4] On the other hand, if the lesion can be completely excised with clear margins, patients recover well.

Patient History

A male in his mid-30s presented to the Emergency Department with a large, open lower back wound. The patient had a history of extensive burns to his back and lower extremities as a child, which he reported had healed by adulthood. Surgery had been performed on his left axilla to correct range of motion restriction due to severe scarring, with contracture release and skin grafting. However, some years following this operation, the patient noticed a small (less than 2 cm) wound on his left lower back, which progressively increased in size and depth, up to 30 cm in diameter. The patient had been avoiding healthcare due to insurance issues, but eventually presented to the emergency department following weight loss of 15 lb over the previous two months.

Hospital Course

Initial physical examination of the patient revealed a warm, pink area across the left back measuring approximately 30 x 30 cm, including a large eroding and fungating mass which released purulent discharge with a foul smell upon palpation. Samples were taken from six different locations around the periphery and center of the wound, all of which came back positive for invasive squamous cell carcinoma. The patient was then referred to surgery for wide excision of the mass. Although four frozen sections were sent intraoperatively—each of which was negative for carcinoma—the final specimen showed focally positive margins along one edge, prompting a full lateral re-excision six days later. Following the surgical course, concern for post-operative thrombosis called for a transthoracic echocardiogram, which showed an unexpected mass within the right ventricle. MRI was ordered, which confirmed an intramural right ventricular outflow tract mass measuring nearly 3 cm in greatest dimension, protruding into the right ventricle. Initial CT scans additionally showed a small (0.3 cm) but suspicious nodule within the left lung. Approximately six weeks after the initial surgery, the patient underwent transcatheter heart biopsy, which was diagnosed as metastatic squamous cell carcinoma. Cytologic evaluation of pleural fluid aspiration was negative for malignant cells, but follow-up CT scans showed an enlarged left axillary lymph node which had grown from 0.6 cm to 2 cm in four weeks, as well as noting that the pulmonary nodule mentioned earlier had more than doubled in size (to 0.7 cm) over the same time period. At the time of this writing, no further surgical treatment had been planned.

Pathology

The primary wide local excision received in the pathology gross room measured 24 cm in diameter, and the specimen was predominantly occupied by a centrally-ulcerated, tan to red, nodular, firm and friable mass which was raised a maximum of 2 cm above the skin surface **(Fig. 1).** On the deep aspect, the excision extended to the underlying muscular and fascial tissue, with a maximum depth of 4 cm. For the sake of consistency, the anatomic orientation markers were translated into clock-face designations, and the margins were inked such that the 12:00 to 6:00 (medial) edge, 6:00 to 12:00 (lateral) edge and deep aspect were represented in three different colors. After orientation and inking, the entire peripheral margin was circumferentially shaved and submitted en face **(Fig. 2**). The central area of the wound was sampled in relationship to all relevant points, including the attached muscle, fascia, unremarkable skin, greatest height of growth and point of deepest gross invasion.

Microscopic examination revealed invasive, moderately- to poorly-differentiated squamous cell carcinoma **(Fig. 3)** with an invasion depth of 3.6 cm into the deep subcutaneous tissue, resulting in an anatomic "Clark level" designation of V (out of maximum V) **(Fig. 4)**. Microscopy of the heart biopsy showed myocardium infiltrated by highly malignant neoplastic cells, with pleomorphism, high nuclear to cytoplasmic ratio, abundant eosinophilic cytoplasm, and hyperchromatic nuclei. The surrounding stroma was reactive and showed desmoplastic reaction typically seen surrounding neoplastic growth. Immunohistochemical stains of the heart biopsy were positive for AE1/AE3 (a cytokeratin combination characteristic of epithelial lineage) and negative for myogenin (which is expressed in muscular differentiation), strongly suggesting malignant squamous cell metastasis.[8,9] No

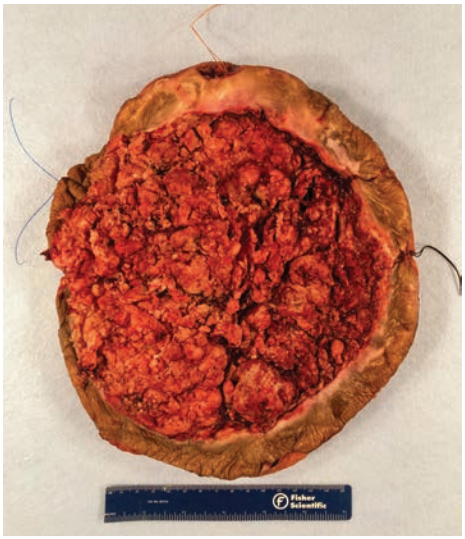

Fig. 1: Gross photograph of local skin excision specimen prior to sectioning.

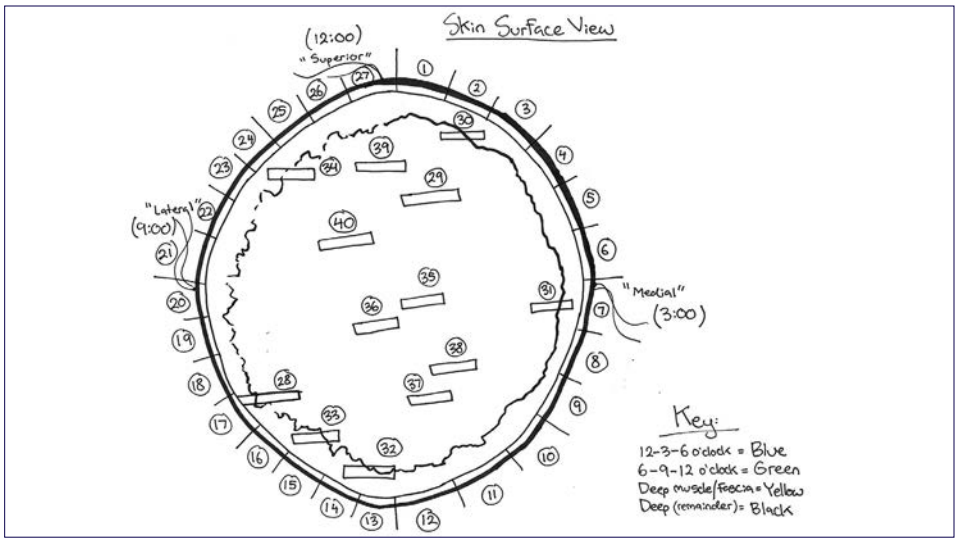

Fig. 2: Diagram used in pathology to demonstrate location and plane of sections.

lymph nodes had been biopsied at the time of this writing.

Discussion

The case discussed above is relevant across a broad range of healthcare disciplines. For the patient, education on this rare but aggressive complication of a decades-old wound could prompt a sooner hospital presentation and avoid the devastating diagnosis of top-stage cancer with widespread metastasis at such a young age. For example, had these risks been discussed more thoroughly with the patient following his previous skin graft operation, he may not have waited until the wound had grown from 2 cm to 30 cm before seeking medical attention. On the clinical side, heightened awareness of the risks associated with Marjolin's ulcer could lead to better follow-up, earlier detection and a much more optimistic prognosis. Finally, aside from the mere interest in such an unusual case presentation, the technical aspect of the grossing process in pathology deserves note because of its significant implications on diagnosis and subsequent treatment. This case provides an excellent example of the importance of shaving and submitting the entire peripheral margin, even on large skin resections and in the context of multiple negative intraoperative diagnoses. Had the pathologists' assistant only shaved representative segments of the margin, the positive foci would almost surely have been missed. Thankfully, proper grossing technique and careful examination by a dermatopathologist provided an accurate final diagnosis allowing for re-excision of the margin. Complete removal of the primary tumor was confirmed by shaving the new margin and submitting it entirely. ■

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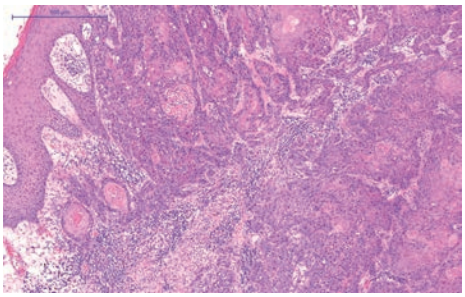

Fig. 3: Squamous cell carcinoma from border of mass.

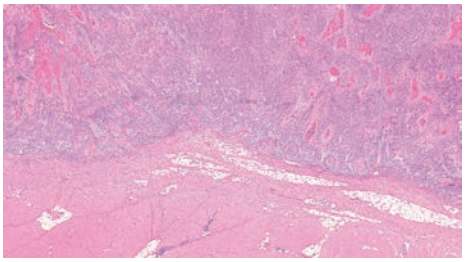

Fig. 4: Tumor invasion into deep subcutaneous tissue and skeletal muscle.

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