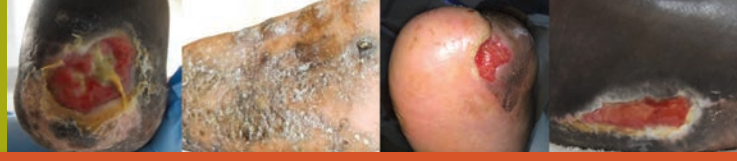

Ultra-rare Neoplasms as a Consequence of Non-Healing Chronic DFU's

Here's what you need to know about Marjolin's ulcers, myofibroblastomas, and desmoid tumors.

BY MICHAEL CORPUZ, DPM AND DAVID A. POUGATSCH, DPM

Healing stubborn and chronic diabetic foot ulcers (DFU) remains an arduous challenge for the podiatric physician. While attempting to heal chronic wounds can involve a fair share of complications, certain developments over its course can present, leading to rare formations of characteristic neoplastic lesions.

Marjolin's Ulcer

One such neoplasm is a Marjolin's ulcer, which is defined as a malignant degeneration arising within pre-existing scar tissue or chronic inflammatory skin lesions. Among the top causes for developing Marjolin's ulcers include burn scars, osteomyelitic wounds, and venous stasis/pressure ulcers. Though the exact etiologies are yet to be definitively determined, one prevailing theory of the direct cause of this malignancy centers on the blockage of the lymphatic system. Scar tissue obstructing lymphatic vessels can inhibit and delay delivery of tumor-specific antigen (TSA), allowing tumor cells to eventually penetrate and spread via the body's patent lymphatic vessels. With chronic DFUs, the irritation and inflammation sustained with repetitive micro-trauma via pressure and/or shear forces leads to increased development and turnover of normal tissue cells via mitosis. With such dramatic increase in activity comes uncontrolled proliferation of cells, resulting in an increased chance for mutations to occur, a situation that favors neoplastic processes.[6]

Yu and colleagues retrospectively reviewed 2,984 patients with chronic scar formations. Their study group was ultimately narrowed to 17 patients with diagnosed Marjolin's ulcers. They demonstrated that the rarity of this neoplastic lesion in those with pre-existing scars was slightly less than 1%. Additionally, they were able to directly correlate the duration of existing scars to a higher percentage of malignancy. Moreover, the recommendation was given, albeit anecdotal, to perform a biopsy of every wound that has not healed within three months.[9] Usually, the physician should re-think the treatment he is rendering if a wound has not reduced in area by 50% over four weeks. If this is done without improvement, the biopsy recommendation will almost become a necessity rather than an anecdote.

Intriguing case reports from a literature search demonstrate the clinical value in maintaining a high index of suspicion in treating chronic non-healing diabetic foot and venous leg ulcers. In one such paper, Stanford, et al., in 2012, described a 79-year-old female with a venous stasis wound for approximately 20 years. A biopsy was taken in 1999 that returned benign. Due to a high index of suspicion maintained by the clinician, another 4mm punch biopsy was procured in 2008 after the patient presented with a nodular and hypertrophic wound despite negative radiographs and bone scans. Histopathology results were consistent with invasive squamous cell carcinoma, and the patient was found to have metastasis to the left inguinal lymph node, necessitating an eventual above-knee amputation and lymph node dissection.[3]

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Perhaps the most crucial clinical

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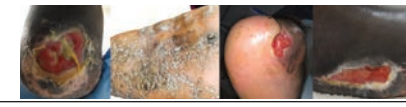

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pearl from the aforementioned studies is to maintain a high index of suspicion for these non-healing lesions. This, of course, implies the ulceration has still not closed despite exhausting all the common treatment modalities that apply to a particular wound (off-loading, surgical debridement, compression, etc.) and ensuring adequate vascularity to the site. It is important to remember that Marjolin's ulcers tend to be nodular and indurated, and located in high-flexion areas where previous scars are formed or where re-ulcerations commonly occur. Particular attention should also be paid to patients who are immunocompromised.

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Myofibroblastomas

A similar type of lesion that may result as a consequence of a non-healing diabetic wound is a myofibroblastoma. Sharing similar etiologic theories with Marjolin's ulcers, an investigative literature search on myofibroblastomas raises yet another controversial issue in the management of these soft-tissue neoplasms: one concerning the surgical treatment of such wounds and the debated need for a negative surgical margin post-resection.

A thorough understanding of these rare lesions begins with a review of fibroblasts and their role in wound healing at the cellular level. Recall that healing in soft-tissue occurs in four unique but overlapping stages: hemostasis, inflammation, proliferation, and remodeling. The proliferative phase heavily involves fibroblasts, and it is widely hypothesized that it is their organization and action that will ultimately determine how well a wound heals. Through a still largely unknown mechanism, fibroblasts and myofibroblasts, the latter a specific differentiation of the former, generate and spread an appropriate force across an extracellular matrix to contract a wound. This, in turn, reduces healing time as progressively less granulation tissue is needed to replace the deficit.[1,7]

Desmoid tumors, also referred to as aggressive fibromatosis, are usually of abdominal origin and are infrequent, slow-growing, usually benign lesions.

Under normal cell physiologic conditions, these fibroblasts and myofibroblasts undergo programmed cell death once their function has been served. It is hypothesized that failed apoptosis can be responsible for an overproliferation and eventual neoplasm of these cells. The nomenclature also varies; neoplasms consisting of fibroblasts are generally known as desmoid tumors, whereas neoplasms of the more differentiated myofibroblasts are termed myofibroblastomas.[1,7]

Desmoid Tumors

Desmoid tumors, also referred to as aggressive fibromatosis, are usually of abdominal origin and are infrequent, slow-growing, usually benign lesions. Similarly, myofibroblastomas are a particularly ultra-rare manifestation in the lower extremity and are primarily seen in mammary tissue. Together, they comprise only 0.03% of all neoplasms. With less than 3% of these appearing in soft-tissue, and only approximately 33% of those manifesting in either the upper and lower extremities, this amounts to an approximately 0.021% incidence rate in an extremity, either upper or lower. Needless to say, lower extremity manifestations of these neoplasms are extremely rare.[3]

A quandary that arises with surgical management of

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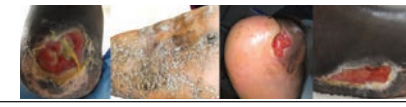

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these lesions concerns the need for wide excision and the requirement of a negative margin. MacGill, in 2011, detailed a case that involved complete excision of a painful dorsal desmoid fibromatosis that eventually yielded positive margins. However, even without obtaining clear margins, there was no evidence of recurrence 28 months after surgical intervention.[3]

A quandary that arises with surgical management of these lesions concerns the need for wide excision and the requirement of a negative margin.

Melis, et al. explored this predicament in-depth with their 2008 meta-analysis study, questioning how crucial a negative surgical margin is in the management of desmoid tumors. The study highlights literature that explains there is no statistically significant difference in recurrence rates between positive and negative margin excisions. The authors also shed light on an important consideration in the clinical management of these soft-tissue lesions, wondering whether adjuvant therapy (i.e., radiation) would be indicated on a lesion that yields microscopically positive margins post-excision. Nevertheless, their overarching conclusion stresses that microscopically negative margins should not be chased at the cost of disfigurement or an extensive procedure leading to loss of function or eventual loss of limb.[4]

Though occurrence of a Marjolin's ulcer or myofibroblastoma from a chronic non-healing wound in our diabetic patient population is indeed a diagnosis that is made after normal treatment has yielded unfruitful results, clinicians must maintain a high level of suspicion and continuously be aware of the potential for malignancy. Like several pathologies in the field of podiatric medicine and surgery, a great deal of this topic remains unknown and indeed warrants further investigation. **PM**

References

[1] Desmouliere A, Redard M, Darby I, Gabbiani G (1995) Apoptosis mediates the decrease in cellularity dduring the transition between granulation tissue and scar. Am J Pathology 146(1): 56–66.

[2] Karakousis CP, Mayordomo J, Zografos GC, et al. (1993): Desmoid tumors of the trunk and extremity. Cancer 72: 1637.

[3] MacGill A (2011). Extra-abdominal Desmoid Fibromatosis in the Foot: A case study. J Am Podiatr Med Assoc 101(1):70-74.

[4] Melis M, et al. (2008). Multimodality Management of Desmoid Tumors: How Important Is a Negative Surgical Margin? Journ Surg Oncol 98:594-602.

[5] Nuyttens JJ, Rust PF, Thomas CR JR, et al.: Surgery versus radiation therapy for patients with aggressive fibroma- tosis or desmoid tumors: a comparative review of 22 articles. Cancer 88: 1517, 2000.

[6] Pekarek B, et al (2011). "A Comprehensive Review of Marjolin's Ulcer: Diagnosis and Treatment." JACCWS; 3, 60-64.

[7] Ryan GB, Cliff WJ, Gabbiani G, Irle C, Montandon D, Statkov PR, Majno G (1974) Myofibroblasts in human granulation tissue. Hum Pathol 5(1): 55–67.

[8] Stanford, R, et al. (2012). "Marjolin's Ulcer of the Leg Secondary to Nonhealing Chronic Venous Stasis Ulcer." JFAS; 51, 475-478.

[9] Yu X, et al. (2013). "Marjolin's ulcer: a preventable malignancy arising from scars." World Jour of Surg Onc; 11:313, 1-7.

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