Understanding Marjolin's ulceration

KEY WORDS
- Malignancy
- Marjolin's ulcer
- Scar tissue
- Squamous cell carcinoma

Marjolin's ulcers are rare and aggressive malignant transformations seen in scar tissue and chronic wounds. The majority of the malignant transformations are due to squamous cell carcinoma. Here, Trudie Young gives an overview of the condition — its incidence, pathophysiology, clinical presentation and diagnosis as well as therapeutic management options and treatment plans required to ensure optimal care and good quality of life for patients with Marjolin's ulceration.

TRUDIE YOUNG
Director of Education and Training, Welsh Wound Innovation Centre, Ynysmaerdy, Wales

The term Marjolin's ulcer (MU) was named after the French physician Jean Nicolas Marjolin, who in 1828 first described chronic ulcers arising in scar tissue. However, Marjolin did not make the link to malignancy, this was made by an English surgeon Caesar Hawkins in 1833, who had identified skin cancer developing in burn scars (Dorr et al, 2019). Da Costa in 1923 is attributed as the first person to use the term MU in cases of burn injuries (Chalya et al, 2012).

Although used for many years to describe malignancies arising in burn scars, the term MU is now the umbrella label used for all malignant ulcers arising in chronic wounds and scar tissue, with burns still being the most prevalent wound type (Kirchberger et al, 2019). Therefore, MU is defined as a malignant degeneration in pre-existing scar tissue or chronic inflammatory skin lesions (Pekarek et al, 2011).

The malignancy in MU can take many forms, however, the most prevalent is squamous cell carcinoma (SCC) (Dorr et al, 2019). MU is a rare form of SCC and accounts for only 2% of all SCCs (Tobin et al, 2014; Bazalinski et al, 2017). The SCC found in MU is more aggressive in nature than primary SCC (Miller et al, 2004; Zieliński et al, 2010).

INCIDENCE AND LATENCY

The highest incidence of MU is found in burn scars, with 2% undergoing malignant transformation (Pekarek et al, 2011). The latency period, which is classed as time from having the original wound to the time the malignant changes happen and the wound becomes a MU, varies greatly from 7–75 years of age (Baldursson et al, 1995; Zieliński et al, 2010; Bozkurt et al, 2010; Pekarek et al, 2011). The mean age of development is 52 years, however, it is seen in a younger patient population (38 years) in developing countries (Chalya et al, 2012; Kirchberger et al, 2019). The most aggressive form of MU has a shorter latency period and a more progressive course (Tobin et al, 2014).

A study of MU in venous leg ulceration and mixed aetiology ulcers (n=145) found that wound area and duration of ulceration was not significant in the development of MU (Senet et al, 2012).

PATHOPHYSIOLOGY

The exact reason for malignant transformation in MU is unknown (Pekarek et al, 2011). However, several theories are suggested which include environmental, immunological and genetic influences (Iqbal et al, 2015; Dorr et al, 2019).

Chronic wounds are said to provide a breeding ground for cancer development (Dorr et al, 2019). Similarities are thought to exist between chronic wounds and malignancy with cell hyperproliferation and migration taking place in healing and the development of cancer, however, in healing it is said to be a self-limiting process (Dorr et al, 2019). Potentially mutations in the genes responsible for cell division and apoptosis can result in increased rates of cancer (Fairbairn et al, 2011).

The prolonged inflammatory state in chronic wounds produces repeated attempts at healing.

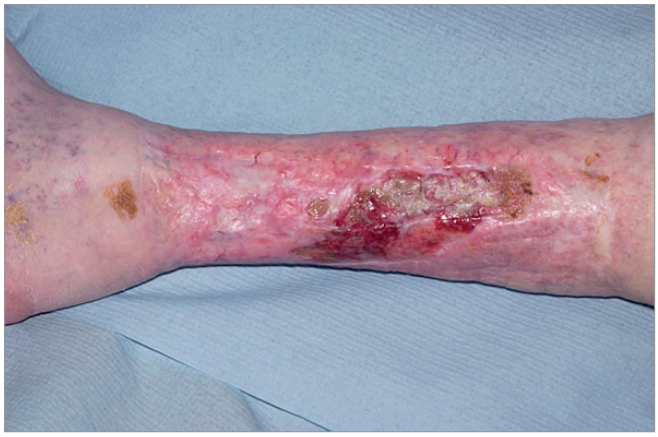

Figure 1. MUs can be found at any anatomical location on the body but is highest in lower extremities

Within the chronic wound bed there are cytokine imbalances that along with the mutagenic effect of toxins may increase the rate of cell mutation (Dorr et al, 2019).

Individuals with immunosuppression, especially effecting lymphocyte activity and motility, may result in an impaired immune surveillance process that is unable to detect malignant transformations and provides the potential for the cancer to increase in aggressiveness and metastases (Kirchberger et al, 2019).

Chronic irritation to wounds and scar tissue due to repeated and long-term trauma may cause cell abnormalities leading to a malignant change (Bozkurt et al, 2010; Pekarek et al, 2011). Even though not mentioned specifically in the literature, long-standing venous ulcers, diabetic foot ulcers and pressure ulcers are subjected to repeated trauma from dressing changes.

It is suggested that, whenever possible, any wound should be closed by primary intention as leaving it to heal by secondary intention is providing the potential for chronic non-healing ulceration (Kirchberger et al, 2019). Although many chronic wounds are not suitable for primary closure. Another factor to consider is the loss of vascularity to areas of scar tissue (Tobin et al, 2014).

WOUND TYPES AND SITES

MU can be found at any anatomical location on the body but is highest in lower extremities *(Figure 1)* and rarely found on digits (Pekarek et al, 2011, Tobin et al, 2014).

Scar tissue, following burns and other traumatic injuries, are commonly known sites for MU (Iqbal et al, 2015, Kirchberger et al 2019, Dorr et al 2019). Common wound types that develop MU, include venous leg ulcers, pressure ulcers and diabetic foot ulcers (Berkwits et al, 1986; Senet et al, 2012; Bazalinski et al, 2017; Cavaliere et al, 2017; Dorr et al, 2019; Kirchberger et al, 2019).

MU have also been reported in lymphoedema ulcers, necrobiosis lipoidica diabeticorum, pilonidal sinus wounds, hidradinitis suppurativa (Tobin et al, 2014; Garcia-Marín et al, 2015; Iqbal et al, 2015).
Rarer sites include areas around stoma, leprosy ulcers, frostbite, snakebite, areas previously subjected to radiotherapy, osteomyelitis (Bozkurt et al, 2010; Garcia-Marín et al, 2015; Dorr et al, 2019; Kirchberger et al, 2019).

Bowens Disease is an intraepidermal cancer that may progress to SCC (Miller et al, 2004).

CLINICAL PRESENTATION

The clinical presentation is of a non-healing ulcer that is increasing in size and not responding to appropriate treatment within three months (Miller et al 2004, Chalya et al, 2012; Senet et al, 2012; Bazalinski et al, 2017; Dorr et al, 2019, Janowska et al, 2019).

The area may appear as an ulcer or an exophytic growth (grows outward beyond the surface epithelium it originates from), it may be verrucous or nodular in presentation (Miller at al, 2004; Bozkurt et al, 2010; Pekarek et al, 2011; Dorr et al, 2019).

Other common clinical signs include a raised, rolled, irregular or everted wound margin, contact bleeding, foul smelling exudate, excess, abnormal or translucent granulation tissue, pain (Miller et al, 2004; Pekarek et al, 2011; Chalya et al, 2012; Senet et al, 2012; Dorr et al, 2019; Janowska et al, 2019). However, pain may not be present in insensate individuals e.g. diabetic neuropathy, spinal cord injury (Berkwits et al, 1986).

DIAGNOSIS

The healthcare system may delay the diagnosis of MU especially if wound care centres have long waiting times (Miller et al, 2004).

The clinical diagnosis will depend on the history of the wound and its clinical presentation. However, a retrospective review undertaken in a specialist wound care centre found that of 76 biopsied chronic venous ulcers: 13 (17.1%) contained squamous or basal cell carcinoma or intra-epidermal carcinoma. The majority of these wounds (n=9) were previously identified as having no suspicious features other than they were

Box 1. General rules for proceeding if Marjolin's ulcer is suspected or diagnosed (adapted from Bazaliński et al, 2017)

- Excise and provide primary dressing for chronic, non-healing wounds
- Regularly inspect burn scars as well as chronic non-healing wounds, and inform patients at risk about the possible development of Marjolin's ulcer
- Prevent and treat infections of chronic wounds
- If suspicious-looking changes are present, always collect specimens from the centre and edges of the ulcer to perform histological examination
- Venous ulcers which do not heal during three-month conservative treatment should be qualified for specimens collection
- Pay attention to the condition of regional lymph nodes (the risk of metastases into regional lymph nodes is greater in Marjolin's ulcer than in typical skin cancer)
- During resection of Marjolin's ulcer maintain surgical margin of 2 cm in width and remove the tumour with fascia
- Regional lymph nodes that are clinically suspicious or have been verified by microscopy examination should be qualified for surgery
- Amputation of limbs should be applied only if infiltrations extend to bones, main vascular and nerve trunks and if poor functional effects are predicted
- Recommendations for chemotherapy and radiotherapy are defined case by case basis
- Following treatment, the patients should be systematically monitored by specialists.

non healing. There is potential for the absence of suspicious macroscopic features to hinder diagnosis outside of a specialist wound care centre (Miller et al, 2004).

Specialist wound care centres may use punch biopsies to diagnose MU. There is variation within the literature as when to undertake the biopsy from first presentation to a month (Miller et al, 2004; Garcia-Marín et al, 2015). When previous treatment is suboptimal, then a 3-month trial of gold-standard care can be tried before taking a biopsy. This may help to reduce the number of unnecessary biopsies and their associated complications (Miller et al, 2004).

It is suggested to take a biopsy of the wound border and the perilesional skin to diagnosis whether the ulcer is a MU or an inflammatory ulcer (Miller et al, 2004; Janowska et al, 2019).

The suggested number of biopsies taken from any one lesion varies with a minimum of six biopsies being the most samples recommended in the literature, and taken using a clock as guidance, so at the point of 2, 4, 6, 8, 10, and 12 o'clock (Bozkurt et al, 2010). Biopsy sites heal within a few weeks and do not delay healing (Senet et al, 2012).

A second diagnostic test is magnetic resonance imaging (MRI) to detect metastases and bony involvement (Pekarek et al, 2011; Bozkurt et al, 2010; Cavaliere et al, 2017).

METASTASES

Lung, breast and head and neck cancers have the most frequent cutaneous metastases (Janowska et al, 2019).

In MU the risk of malignant transformation is highest for burn scars (76.5%), chronic traumatic wounds (8.1%), venous leg ulcers (6.3%), fistulas arising due to chronic osteomyelitis (2.6%), the metastases are commonly found in the brain, liver, lung and kidney (Dorr et al, 2019).

The infiltrative form of MU presents with rapid formation of ulceration, worse prognosis and high probability of metastic spread (Chalya et al, 2012).
The metastases may spread to regional lymph nodes. Pressure ulcers in the sacral and iliac regions have extensive lymphatic drainage into the pelvis which explains their frequent local and distant metastases (Bazalinski et al 2017).

Cavaliere et al (2017) suggested that use of cautery during excision could potentially reduce the risk of metastic spread via the blood and lymphatic system.

TREATMENT

There is no definitive treatment for MUs, however, the most common treatment is local excision with adequate excision of the tumour margins followed by skin grafting or soft tissue flaps (Chalya et al, 2012; Cavaliere et al, 2017; Dorr et al 2019). If there is bone and/or joint involvement and osteomyelitis then amputation may be necessary (Miller et al, 2004; Pekarek et al, 2011; Garcia-Marín et al, 2015). Negative Pressure Wound Therapy (NPWT) has been used successfully as a post-surgical intervention in MU patients with and without an artificial dermal matrix (Iqbal et al, 2015; Cavaliere et al, 2017). Chemotherapy and radiotherapy may be required post-surgery or for patients with inoperable metastases (Tobin et al, 2014).

Local wound management may include dressings that are atraumatic on removal to prevent pain and bleeding and anti-microbial dressings to prevent and treat infections and reduce odour (Kirchberger et al, 2019).

It is thought that aggressive treatment reduces risk

of recurrence (Bozkurt et al 2010). The following is an example of aggressive treatment of MU in a male paraplegic with a MU in sacral and ischial pressure ulcers, which had been present for 10 years before malignant transformation. The surgical treatment involved the following: an abdomino/perineal resection and colostomy, radical excision of sacral and ischial pressure ulcer, debridement of left hemi pelvis, disarticulation and excision of left femoral head, femur, tibia and fibula, complete left lower limb myocutaneous fillet flap reconstruction pedicled on the femoral vessels. The lower leg was completely de-epithelialised and used to fill the pelvic cavity preventing herniation of abdominal viscera (Fairbairn et al, 2011). See *Box 1* for the general rules for interventions when MUs have been diagnosed.

FOLLOW UP

Regular follow up is recommended due to the risk of recurrence, with duration from 4 years to indefinitely proposed in the literature (Bozkurt et al, 2010; Chalya et al, 2012). Biopsy is also advocated at regular intervals for the life span of a chronic wound (Fairbairn et al, 2011).

MU may be prevented with early surveillance of high-risk patients (Iqbal et al, 2015).

PATIENT EDUCATION

Patient education is recommended post burn and traumatic scar injury to alert the individual to the potential for malignant transformation and to encourage early presentation should any malignancy arise (Bazalinski et al, 2017). This is especially relevant in developing countries when late presentation is said to be due to poverty, inexperience, poor referral systems in relatively wealthy healthcare systems devoid of meaningful health insurance (Chalya et al, 2012).

CONCLUSION

MU is a rare and aggressive malignant transformation seen in scar tissue and chronic wounds. The majority of the malignant transformations are due to SCC. They may have overt or covert clinical signs, the latter delaying presentation and detection. The exact pathophysiological changes are unknown but are thought to have genetic, environmental and immunological components. There is often a latency period of many years before the malignant transformation takes place.

The treatment usually requires surgical excision followed by a skin graft or flap with or without adjunctive chemo and radiotherapy. The aggressive nature of MU involves development of metastases that ultimately lead to death. Due to the severity of the disease, clinicians should have a high index of suspicion and a low threshold for taking a biopsy to diagnose the condition, especially in chronic wounds that remain non-healing despite optimal care (Miller, 2004; Tobin 2014).

Patient education and long-term follow up have the potential to reduce recurrence of MU. WUK

REFERENCES

Baldursson B, Sigurgeirsson B, Lindelof B (1995) Venous leg ulcers and squamous cell carcinoma: A large-scale epidemiological study. *British Journal of Dermatology* 133(4): 571–74

Bazaliński D, Przybek-Mita J, Barańska B, Więch P (2017) Marjolin's ulcer in chronic wounds– review of available literature. *Contemp Oncol (Pozn)* 21(3): 197–202

Berkwits L, Yarkony GM, Lewis V (1986) Marjolin's ulcer complicating a pressure ulcer: Case report and literature review. *Arch Phys Med Rehabil* 67(11): 831–3

Bozkurt M, Kapi E, Kuvat SV, Ozekinci S (2010). Current concepts in the management of Marjolin's ulcers: Outcomes from a standardized treatment protocol in 16 cases. *J Burn Care Res* 31(5): 776–80

Cavaliere, R, Mercado, D.M., & Mani, M. (2018). Squamous cell carcinoma from Marjolin's ulcer of the foot in a diabetic patient: Case study. *J Foot Ankle Surg* 57, 838–43

Chalya PL, Mabula JB, Rambau P et al (2012) Marjolin's ulcers at a university teaching hospital in NorthWestern Tanzania: A retrospective review of 56 cases. *World Journal of Surgical Oncology* 10: 38

Dörr S, Lucke-Paulig L, Vollmer C, Lobmann R (2019) Malignant transformation in diabetic foot ulcers - case reports and review of the literatures. *Geriatrics* 4(4): 62

Fairbairn NG, Hamilton SA (2011) Management of Marjolin's ulcer in a chronic pressure sore secondary to paraplegia: A radical surgical solution. *Int Wound J* 8(5): 533–36

Garcia-Marín JA, de Alcala Martinez-Gomez D et al (2016). Marjolin's ulcer. A 10-year experience in a diabetic foot unit. *Cirugía y Cirujanos* 84(4): 340–43

Iqbal FM, Sinha Y, Jaffe W (2015) Marjolin's ulcer: A rare entity with a call for early diagnosis. *BMJ Case Rep* bcr2014208176

Janowska A, Dini V, Oranges T et al (2019) Atypical ulcers: Diagnosis and management. *Clin Interv Aging* 14: 2137–43

Kirchberger MC, Erfurt-Berge C (2019) Management of malignant wounds. *Zeitschrift für Gerontologie und Geriatrie*. doi: https://doi.org/10.1007/s00391-019-01629-w

Pekarek B, Buck S, Osher L (2011) A comprehensive review on Marjolin's ulcers: Diagnosis and treatment. J Am Col Certif Wound Spec 3(3): 60–64

Senet P, Combemale P, Debure C et al (2012) Malignancy and chronic leg ulcers. The value of systematic wound biopsies: A prospective, multicentre, cross-sectional study. *Arch Dermatol* 148(6): 704–708

Tobin C, Sanger JR (2014) Marjolin's ulcers: A case series and literature review. *Wounds* 26(9): 248–54

Zieliński T, Lewandowska M (2010) Marjolin's ulcer – a malignant lesion arising in chronic wounds and scars. Analysis of 8 cases. *Przegl Dermatol* 97: 38–42