CASE REPORT

Marjolin's ulcer: a rare entity with a call for early diagnosis

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SUMMARY

Marjolin's ulcer (MU) is an umbrella term covering squamous cell carcinoma (SCC), basal cell carcinoma and malignant melanoma that develop in chronic wounds, sinuses or scars. Cutaneous (non-MU) SCC is related to excessive sun-exposure, with Fitzpatrick skin types I and II being more susceptible. Radiation, genetic disorders (eg, Xeroderma pigmentosum) and immunosuppression, are other important risk factors often involved in the development of cutaneous malignancies and may also be involved in the development of MU. MU, first described by Jean-Nicholas Marjolin in 1828, is more aggressive than non-MU SCC, with a higher potential for early metastasis. A high index of suspicion and early histological diagnosis in chronic wounds and unstable scars with recent changes in characteristics offer the best prognosis with treatment. We present a case alongside a literature review contrasting the characteristics of MU and non-MU SCC, and suggest a management plan for early MU identification and prevention.

BACKGROUND

Marjolin's ulcer (MU) is a rare and aggressive cutaneous malignancy associated with chronic wounds, venous stasis ulcers, lupus vulgaris, pressure sores, osteomyelitis, anal fistulae, pilonidal abscesses and radiotherapy.[1–3] MUs were first described by Jean-Nicholas Marjolin, in 1828, as chronic ulcers arising from burn wounds; later, in 1903, Da Costa added the concept of malignancy to MUs.[4–6]

The most common histological findings in MUs are well-differentiated squamous cell carcinomas (SCC), which occur predominantly in burn wounds,[7] although basal cell carcinomas (BCC) and malignant melanomas (MM) have been reported.[8] Other malignancies are less likely as deeper tissues are usually undamaged and proliferate at a slower rate than the epidermis.[9] The incidence of MU varies, it is estimated that 1.7% of chronic wounds suffer malignant modification.[10]

Cutaneous (non-MU) SCCs are thought to have differing aetiologies and risk factors to MU SCC, which may explain some of their differing characteristics. We report a case of MU SCC and review the current literature contrasting the characteristics of non-MU and MU SCCs. In addition, a management plan for MU is suggested derived from our experiences.

CASE PRESENTATION

A 67-year-old woman suffered extensive flame burns to her chest and arms at the age of 6 years, and subsequently developed bilateral contractures in her axillae. This resulted in severe restricted movements in both arms. She presented with a scabbing and itching lesion in her right axilla, which developed over 3 months. The left axilla had a similar contracture but no abnormal growths. She was an ex-smoker with no other significant medical history.

A 50×33 mm raised crateriform, fungating lesion (figure 1A–C) was observed in the tight right axillary burn scar. Axillary lymph node examination was not possible due to the size of the lesion.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included: MU SCCs, other MU malignancies (BCC and MM), keratoacanthoma and necrotic abscesses.

TREATMENT

The patient underwent wide local resection and scar release under general anaesthesia, which led to an 18 cm defect in the mid-axillary line (figure 2). Normally, a flap cover is desirable for axillary contractures, however, the patient did not have adequate viable tissue for a local flap. She was not keen on receiving a free flap so a staged reconstruction was performed with an artificial dermal matrix (ADM) and negative-pressure wound therapy, followed by split skin grafts (SSG) as a second stage procedure.

OUTCOME AND FOLLOW-UP

The patient had an uneventful recovery.

Microscopic analysis of excised tissue revealed an invasive well-differentiated MU SCC (figure 3A, B) completely excised with a Breslow's thickness of 3.5 mm, Clark level IV and a deep margin of 0.2 mm. No perineural or vascular invasion was noted.

A subsequent computerised tomography scan showed no evidence of metastatic disease or axillary lymph node involvement. Therefore, lymph node dissection and radiotherapy were not undertaken.

The patient is planned for regular follow-up for 5 years.

DISCUSSION

Currently, the term MU is applied to a variety of neoplasms of a heterogeneous nature. These include SCC, BCC and MM of varying differentiation and malignant potential, which can make meaningful comparisons difficult. Prognostic features such as size, depth, differentiation, clearance and presence of perineural and vascular invasion

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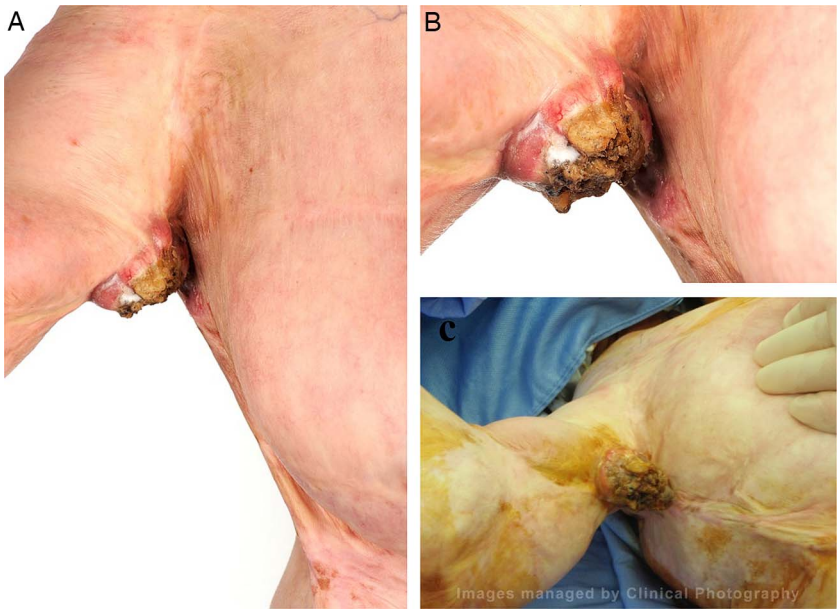

Figure 1 (A) Preoperative photo of MU in right axilla; (B) Close up of MU in right axilla; (C) MU and scar in right axilla. MU, Marjolin's ulcer.

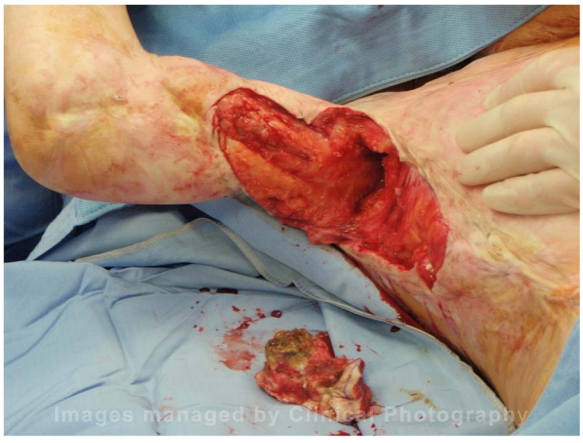

Figure 2 Removal of MU and release of scar in right axilla. MU, Marjolin's ulcer.

along with distant metastases, influence the type of treatment and follow-up regime.

Invasive and rapidly-growing MU SCCs are uncommon and their pathophysiology is incompletely understood. In non-MU SCC, UV-B radiation damages DNA and RNA, generating the following mutagenic photoproducts: pyrimidine–pyrimidine adducts and cyclopyrimidine dimers in the p53 tumour-suppressor gene, with UV-A further worsening the risk of this occurring by DNA damage through photo-oxidative-stress-mediated mechanisms.[11] Keratinocytes with one p53 mutation ('one hit') after exposure to UV radiation commonly undergo apoptosis, unlikely to result in malignancy. Keratinocytes with an existing p53 mutation may undergo a second mutation after exposure to UV radiation ('second hit') leading to uncontrolled proliferation, resulting in actinic keratosis, a prerequisite to SCC.[12]

The 'two hit' pathogenesis model may also occur in MU SCC but fails to explain its more aggressive nature. Other theories thought to be involved in the development of MU have been hypothesised, including those related to: tissue toxins released by the burn eschar as a result of poor vascularisation and autolysis of scar tissue.[9] Immunological and cocarcinogenic factors have also been put forward, along with local irritation and poor lymphatic regeneration due to obliteration by dense scar tissue.[9] Epidemiological data suggest burn scars increase tumour progression in existing cancerous cells rather than increasing the rate of cancer development in cells, although the nature of the evidence does not allow a cause and effect relationship to be established.[13] HLA-DR4 attributed to the development of cancer suggests that there may be a genetic influence to the development of MUs.[9]

MUs have mutations in the Fas gene controlling apoptosis, which may result in uncontrolled proliferation in burn scars. Such mutations increase the risk of wounds healing through secondary intention in evolving into MUs.[9] This may be due to the

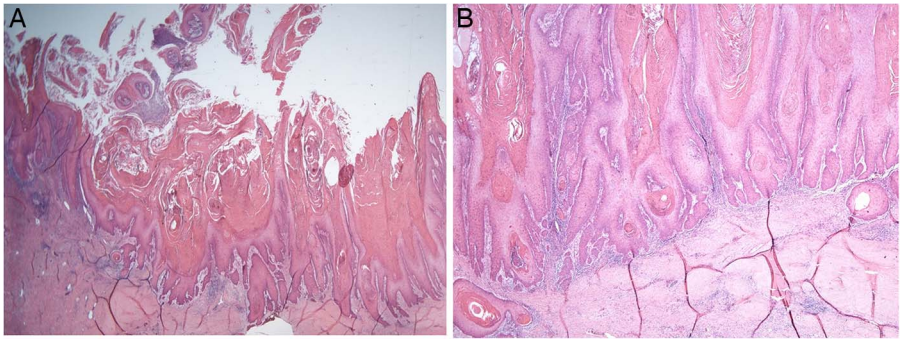

Figure 3 (A) Well-differentiated MU SCC ×10 magnification (H&E); (B) Well-differentiated MU SCC ×20 magnification (H&E). MU, Marjolin's ulcer; SCC, squamous cell carcinoma.

Table 1 Comparison between MU SCC and non-MU SCC[1 3 8 9 12 15–20]

Features	MU SCC	Non-MU SCC
Sex ratio (M:F)	3:1	1.1–1.7:1
Average age of presentation	52 years	66 years
Common sites for presentation	Lower extremities, scalp	Head and neck
Excision margins	2–4 cm	4–6 mm
Metastatic rates	27.5–40%	3–23%
5-year survival	43–58%	Poorly-differentiated 61.5% Well-differentiated 94.6%

MU, Marjolin's ulcer; SCC, squamous cell carcinoma.

greater risk of injury from normal activities to damaged skin that has lost its normal structures (dermis, vessels, elastin content). While theory is debated, there is a general consensus that irritation plays a role in the pathophysiology of MU SCC through the process of repeated ulceration and healing.[9]

A literature review revealed that the majority of patients (76.5%) developed MUs in old burn scars (n=443), our patient had thick unstable scars (figure 1C) following a burn injury, which put her at a high risk for MU SCC.[14] Table 1 summarises the differences between MU and non-MU SCCs; of note, the metastatic potential for poorly differentiated non-MU SCCs is considerably lower than the metastatic potential for MU SCC. Non-MU SCCs had a metastatic rate of 3–10% compared against MU-SCCs, which had a higher metastatic rate of 27.5–40%, indicating a need for early treatment given their more aggressive nature.[9] The current gold standard for MU diagnosis remains for the lesion to be biopsied.[7] Histological grading is the most important factor indicating prognosis, with evidence of lymph node metastases returning the poorest prognosis.[9 21]

In our case, the right axilla was the site of MU SCC, a site which suffered chronic irritation and rubbing in the flexure crease due to repeated activity. This process of repeated injury potentially propelled its malignant growth through inflammatory mechanisms.[22] Difficulty in examination of the heavily contracted area in our patient could explain the delayed diagnosis, with the malignancy likely being present before it was symptomatic. Relying on symptomatic presentation by patients themselves for the detection of malignancy may, therefore, be unreliable. The long-term effects on delayed diagnosis in our patient and other patients are not currently known and there is a need for longer follow-up studies. Compromised skin integrity is associated with the formation of MU SCC formation; patients often present during cycles of non-healing ulcers followed by skin rupturing, bleeding, itching and scratching, severe pain, discharge and a foul odour. Our patient presented in a similar clinical pattern with ulceration and pain. This suggests that the clinical presentation is predictable, yet MU is commonly misdiagnosed.

The mean patient age for the diagnosis of MU is reported to be 52.1 years, and the mean latency interval for MU-SCCs is reported to be 32 years.[8 22] Our patient presented later in life (aged 67 years) with a long latency period of 61 years, a factor shown to be associated with a higher mortality rate.[21] Yu *et al*[7] reported a negative correlation between age of patients at injury and the length of the latency period ($r=-0.8$, $p<0.01$), which is congruent with our case. The latency periods for the purpose of surveillance need to be further investigated. The patient had symptoms for 3 months; experience with patients in multiple centres have shown that MU SCCs can be preventable with early wound surveillance and evaluation of any changes through histological analysis of biopsies.[7 14 23 24] Therefore, if patients are educated on the pre-ulcerative symptoms of burning and itching, which are followed by blisters,[7] there may be scope for earlier self-recognition and presentation to a medical professional.

The standard treatment of MUs involves a wide local excision, although resection margins are debated. The literature suggests a 2–4 cm free resection margin;[1 13] in our case, we performed an excision biopsy with a 1 cm margin initially, followed by wide local excision by a further 2 cm margin, and contracture release along with staged reconstruction using ADM and SSG. Adjuvant radiotherapy is controversial; radiotherapy is thought to inhibit fibroblast proliferation and angiogenesis, reducing excessive collagen production, however, the literature reports highly variable results.[22] In our patient, clinical and radiological assessment did not reveal lymph node involvement; consequently, lymph node dissection and radiotherapy treatment were not undertaken.

In contrast, a surgical resection margin of 4–5 mm for well-defined non-MU SCCs is recommended as this gives a peripheral clearance rate of approximately 95%. A resection margin of greater than 6 mm is recommended for poorly-differentiated non-MU SCCs.[25] Larger resection margins often result in poorer cosmesis, particularly for MU SCCs on the face. Larger margins can be avoided with Mohs micrographic surgery, however, it is not available at all hospitals.[14] While aesthetics always need to be considered, this should be outweighed by adequate margins to prevent cancer recurrence. Local recurrence in MU SCC after excision occurs in 16% of cases, with males being at greater risk.[8] Lymph node metastasis ranges from 27.5–40% with systemic recurrence occurring in the lungs, brain and liver.[8 14]

In conclusion, the term MU applies to a heterogeneous group of malignancies of a more aggressive nature compared to their non-MU counterparts. A common observable pattern would

Learning points

- There should be a high index of suspicion for recent changes in longstanding chronic unstable scars, ulcers and sinuses, as early diagnosis through clinical suspicion and biopsy can result in early appropriate treatment leading to a more favourable prognosis.
- Marjolin's ulcer (MU) squamous cell carcinoma (SCCs) are more aggressive, have higher recurrence rates, higher metastatic rates and higher mortality rates compared to non-MU SCCs, and should therefore be thought of as a differential in any chronic wound, especially when related to burn injuries.
- Further research needs to be undertaken on the pathophysiological development of MU SCC to innovate new preventative and curative strategies.
- Currently, there is no consensus on the education and surveillance of high-risk patients, the use of adjuvant radiotherapy or the length and frequency of follow-up for recurrence in patients with MU SCC.
- The term 'Marjolin's ulcer' should be used with further qualification, as it encompasses various heterogeneous cutaneous malignancies.

involve an unstable scar or chronic wound that has been present for many years and is presented to a medical professional with recent changes in characteristics. We recommend the term MU be used with further qualification, such as MU with '-SCC', '-BCC', '-MM' differentiation status. MU SCCs are more aggressive, have a higher recurrence rate, higher metastatic rate and poorer survival compared to non-MU SCCs. We recommend excision of chronic unstable areas and sinuses with subsequent flap or graft cover on the defect to reduce the likelihood of MU development. If this is not possible, we recommend close surveillance, as early diagnosis and biopsy of a non-healing lesion in a chronic scar, with appropriate follow-up treatment, offers the most favourable outcomes. Further research to understand the differences between non-MU SCC and MU SCC is needed to comprehend the more aggressive nature of MU SCCs. A follow-up regime for MU SCC is not agreed on, although lifelong follow-up is recommended and commonly implemented. Additional work is needed to determine the regularity of follow-up, with a particular focus to determine the time frame where patients are most vulnerable to recurrence following surgical excision. A 5 year follow-up, as for MM, may be a reasonable starting point.

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