Recalcitrant leg ulcers and the risk of cancerous degeneration

All forms of chronic leg ulcer have a risk of undergoing malignant transformation and squamous cell carcinoma is the most common type. Known as Marjolin's ulcers, they have a high metastatic potential and their prognosis is poor if they are not detected at an early stage. In this article the authors outline the pathophysiology of these ulcers as well as presenting features, detection and treatment methods. They conclude that healthcare professionals should monitor any chronic non-healing ulcers that do not respond to treatment very carefully and consider an early biopsy to assess for cancerous degeneration.

Stuart Enoch, Valentina Lefemine

KEY WORDS
Non-healing ulcers
Marjolin's ulcer
Repeat biopsy
Malignant transformation

Although uncommon, all forms of chronic leg ulcers have a risk of undergoing malignant transformation. This paper reviews the pathophysiology of squamous cell carcinoma (SCC) arising from leg ulcers, highlighting the need for an early diagnosis. The authors discuss the management options and emphasise the need to adapt a low threshold to biopsy chronic non-healing ulcers, and the need for vigilance and early investigation of possible metastasis.

SCC is the most common type of malignant degeneration of chronic ulcers. SCC may also arise *de novo*, presenting either as an ulcerated lesion

Stuart Enoch is Specialty Registrar in Burns and Plastic Surgery, North-West Regional Centre for Burns and Plastic Surgery, Wythenshawe Hospital, University Hospitals of Manchester and Valentina Lefemine is Specialty Registrar in General Surgery, All-Wales Specialist Training Programme, Royal Gwent Hospital, Newport

(*Figure 1*) or a simple nodular lesion. Marjolin's ulcer is the term used to describe the development of an SCC from long-standing, non-healing ulcers or scars. Due to the sometimes subtle nature of presentation, the diagnosis of SCC in ulcers can be challenging even to an experienced clinician. Biopsy of the wound for histology may be necessary to confirm the diagnosis, and the risk of rapid growth and metastatic spread of SCC demands urgent diagnosis and appropriate management to limit morbidity and even mortality.

The relationship between chronic leg ulcers and malignancy

SCC is the second most common cutaneous malignancy after basal cell carcinoma (BCC). It has a 2:1 male to female preponderance and tends to occur in older people (Du Vivier, 2002).

Most SCC arise either spontaneously, from pre-existing skin lesions such as actinic keratosis (in situ SCC), or from a pre-malignant area of Bowen's disease (intraepidermal carcinoma) (Britto et al, 1998). Various predisposing factors such as solar radiation, infection with human papilloma virus and exposure to cytotoxic drugs, chemical hydrocarbons, tar, and mineral oils have been identified for the development of spontaneous SCC (Lumley, 1997; Mork et al, 2001) (*Table 1*).

Figure 1. Squamous cell carcinoma presenting as extensive ulceration over the shin of an elderly woman.

Figure 2. Non-healing venous leg ulcer over the medial aspect of the lower leg in a 71-year patient. Biopsy revealed a Marjolin's ulcer (squamous cell carcinoma) with metastasis in the groin and para-aortic lymph nodes.

SCC also arises as a result of malignant transformation in chronic non-healing ulcers (*Figure 2*). Although Marjolin described the phenomenon of malignant degeneration from burn scars in 1827, the term 'Marjolin's ulcer' currently encompasses SCC arising from any form of long-standing chronic ulcers (Standkard et al, 1993) or scars (Browse, 2001), but specifically burn scars (Ozek et al, 2001). Some of the conditions that predispose to the development of SCC are listed in *Table 2*. Although malignant degeneration can take any form (Bowen's disease, BCC or SCC), SCC seems to be more frequent than BCC in chronic leg ulcers (Philips et al, 1991), however, there has been a rise in cases of BCC reported recently (Schwarze et al, 2000; Granel et al, 2001).

There appears to be a direct relationship between the duration of a chronic, non-healing ulcer and the chances of a malignant transformation. The longer the ulcer duration, the higher the chances for a malignant change (Smith et al, 2001). SCC arising from a chronic ulcer is usually slow-growing and less painful, although it may become painful if it invades deeper tissue/structures. Yang et al (1996) reported an incidence of 2.2 per 100 leg ulcers. In contrast, a Swedish epidemiological study estimated the relative risk of SCC arising from VLU to be about 5.8 for every 100 ulcers (Baldursson et al, 1995) but an accurate incidence of malignancy in leg ulcers is difficult to determine and this may be an overestimate (Voisard et al, 2001). The latency period of development of SCC from a chronic ulcer has not been established although it can vary from a few months to 50 years (Baldursson et al, 1999; Esther et al, 1999; Garzon et al, 2001).

SCC arising in chronic VLU has been shown to be more aggressive in nature and metastasise more frequently than those arising *de novo* and it is associated with a poor prognosis (Chong and Klein, 2005). Recurrent SCCs also tend to be more aggressive. On average, the

latent period between treatment of the primary tumour and diagnosis of metastasis has been estimated to be about 11 months (Joseph et al, 1992). SCCs commonly metastasise to the regional lymph nodes, lungs and liver. Although it can be as low as about 3% (Reynolds and Strayer, 2003), the rate of metastasis of lesions in high-risk areas such as the face or scalp could be as high as 30% (Garner and Rodney, 2000). In SCCs arising from chronic ulcers, scars and sinuses, the rate of metastasis is about 20% (Martin et al, 1970), with the lymph node being the most commonly involved site. In long-standing scars, the scarring process can cause the tissue surrounding the ulcer to become fibrotic and indurated, and can lead to destruction of adjacent subcutaneous/subdermal lymphatic channels. If these local lymphatic channels are destroyed, lymphatic spread may not be seen (Paredes, 1998).

Pathophysiology of SCC arising from chronic ulcers

Although the exact mechanism of malignant degeneration in chronic ulcers is not well established, several theories have been proposed. In a study of malignancies arising in burn scars, Arons et al (1966) proposed a two-step process by which normal cells are transformed into malignant cells:

- ‣‣ An initiation phase, when normal cells become dormant neoplastic cells
- ‣‣ A promotion phase that allows dormant cells to change into active tumoral cells, further stimulated by co-carcinogens (various toxins released from damaged tissue leading to mutation of cells and eventually a tumour) (Fleming et al, 1990).

The role of bacteria and infection in contributing to this process is

Table 1

Risk factors in the aetiology of squamous cell carcinoma

- ‣ Age >50 years
- ‣ Male sex
- ‣ Fair skin (i.e. burns easily, never or rarely tans)
- ‣ Living closer to the equator
- ‣ History of non-melanoma skin cancer
- ‣ Exposure to UV light (high cumulative dose)
- ‣ Exposure to chemical carcinogens (arsenic, tar chemical hydrocarbons and mineral oils)
- ‣ Exposure to ionising radiation
- ‣ Chronic immunosuppression
- ‣ Chronic scarring condition
- ‣ Genodermatoses
- ‣ Human papilloma virus (HPV) infection (specific subtypes)

Table 2

Conditions that predispose to the development of SCC

Chronic inflammatory and scarring conditions	Chronic infections	Genetic syndromes and dermatoses
Burn scar or thermal injury	Osteomyelitis	Dystrophic epidermolysis bullosa
Pressure ulcer	Chronic sinuses	Epidermodysplasia verruciformis
Pilonidal sinus	Acne conglobata	Xeroderma pigmentosum
Venous ulcer	Hidradenitis suppurativa	Oculocutaneous albinism
Chronic lymphoedema	Lupus vulgaris	Dyskeratosis congenita
Discoid lupus erythematosus	Lymphogranuloma venereum	Atopic eczema
Erosive oral lichen planus	Granuloma inguinale	Porokeratosis
Lichen sclerosis et atrophicus	Chronic deep fungal infection	Nevus sebaceous
Mutilating keratoderma	Chronic trophic ulcers as in leprosy	KID (keratitis, ichthyosis, deafness) syndrome
Necrobiosis lipoidica		

less clear. Hill et al (1990) proposed that chronic irritation leading to a continual circle of repeated damage and repair of the cells could be a contributing factor in the initiation of carcinogenesis. Trauma to the skin results in the implantation of epidermal cells into the dermis. The dermal tissue responds to this with a foreign body type reaction which, in turn, alters the normal regenerative process of the dermis. The dermis will fail to behave normally in response to further insults and the healing process will be altered leading to malignancy (Arons et al, 1966; Fleming et al, 1990). In support of this, Ozek et al (2001) also proposed the sequence of repeated ulceration and healing to be a mechanism for malignant transformation. A probable pathophysiology of SCCs arising from chronic ulcers is schematically illustrated in *Figure 3*.

Presenting features of SCC

The SCCs which arise *de novo* may present in different ways. In the early stages, they may appear as simple ulcers or nodules, thus resembling benign and innocuous skin lesions, while in the advanced stages they can present as fungating and exophytic (mushroom-like) growths. Characteristically, however, the invasive SCC presents as a raised, firm papule or plaque, pink-to-flesh coloured, arising on sun-exposed skin, especially in the face (*Figure 4*) and hands. Surface changes may include scaling, ulceration, crusting, or the presence of a cutaneous horn. SCCs which present
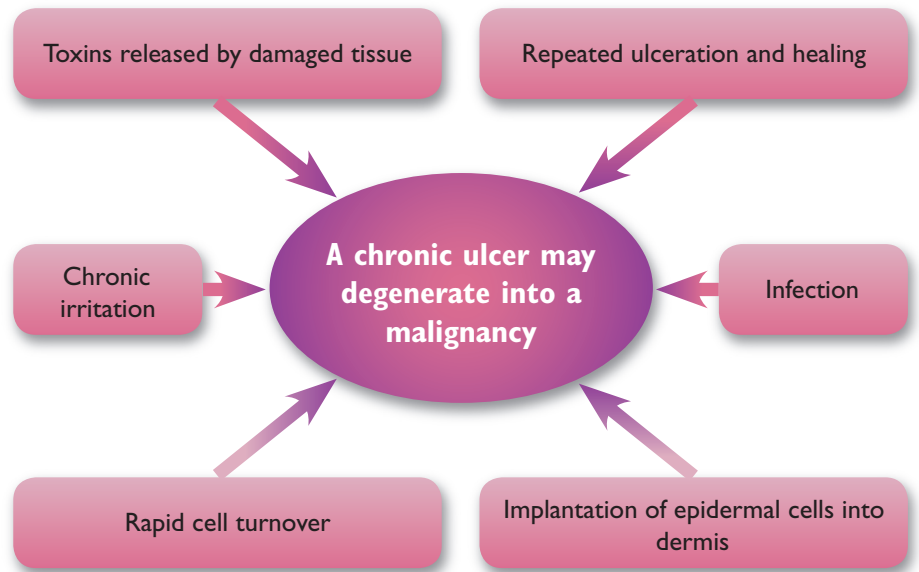

Figure 3. Pathophysiology of SCC arising from chronic ulcers.

as ulcers often have prominent, everted edges and a necrotic base. SCC may also manifest as a pink cutaneous nodule without overlying surface changes, although this type of presentation is rare. In addition, it may be challenging to diagnose early SCCs arising in sun-damaged skin in older people or over areas of previously healed scars.

It needs to be appreciated that none of the above features or characteristics may be present in the early stages of SCC or in those arising from long-standing leg ulcers. In such instances, SCC can appear as a new area of induration, elevation,

or ulceration at the site of a pre-existing scar or ulcer. The ulcer from which the SCC arises may show transient reduction in size if only part of a large ulcer has undergone malignant transformation, thus further complicating the clinical diagnosis.

Management and prognosis

Biopsy of the suspicious lesions for histopathology remains the gold standard for diagnosing malignancy. Excision biopsy is the preferred method, although it is not always feasible either due to the size or location of the lesion, or due to the lack of technical expertise to obtain appropriate wound closure. In such

Figure 4. Squamous cell carcinoma over the cheek of an elderly man.

Figure 5. Punch biopsy being obtained from the base of a non-healing venous ulcer.

instances, a full-thickness incisional or a 4–6mm punch biopsy (*Figure 5*) is an acceptable alternative (Reynolds and Strayer, 2003). If none of the above options are available, a shave biopsy of the lesion may be undertaken to obtain the diagnosis.

Once SCC is diagnosed, it has to be staged according to the American Joint Committee on Cancer guidelines (Greene et al, 2002), which use the tumour, node and metastasis (TNM) classification system (*Table 3*). Complete removal of the tumour is the principal aim of management. Various factors have to be taken into account when deciding on a management plan for SCC. These include the site and size of the lesion, whether the lesion is primary or recurrent, the presence or absence of metastasis, its histological grade, and the age and general health of the patient. Many medical and surgical treatment modalities exist for the management of SCC (*Table 4*).

The use of topical therapies such as fluorouracil (5-FU; an antimetabolite) (Nguyen and Ho, 2002), imiquimod (an immune response modifier) and photodynamic therapy are generally limited to premalignant lesions (actinic keratosis), SCC in situ and certain forms of BCC but is not recommended for treatment of invasive SCC (Hochman and Lang, 1999). Likewise, treatment with carbon dioxide laser, intralesional interferon or intra-arterial infusion of methotrexate remains largely experimental although Sheen et al (2003) reported a case where it had been successful in treating SCC of the toe.

Surgical excision is the preferred treatment for SCC and is considered the gold standard. In the early stages, SCC is amenable to simple excision with adequate margins and primary closure, or closure using a skin graft or a simple reconstructive procedure such as a local flap. When determining excision margins, various factors such as the type of tumour, its anatomical location and size, and whether it is primary or recurrent need to be considered. The operating surgeon

---

Table 3

TNM classification of SCC

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ
T1 Tumour less than 2cm in greatest diameter
T2 Tumour 2–5cm in greatest diameter
T3 Tumour greater than 5cm in greatest diameter
T4 Tumour with deep invasion into cartilage, muscle, or bone

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
NX Regional lymph node can not be assessed

M0 No distant metastasis
M1 Distant metastasis
MX Distant metastasis can not be assessed

Table 4

Some treatment options for SCC

Medical	Surgical
Topical chemotherapy	Cryotherapy
Topical immune response modifier	Electrodesiccation and curettage
Photodynamic therapy	Excision with adequate margins (and direct closure or skin grafting or reconstructive surgery)
Radiation therapy	
Systemic chemotherapy	
Intralesional interferon	Mohs micrographic surgery
	Carbon dioxide laser

---

should make a clinical decision on an individual basis taking all factors into account. Ulcerative lesions tend to invade more compared with exophytic lesions. Thus the greater the exophytic character of the lesion, the less invasion there is and a smaller margin is required (Stal and Spira, 1997). Likewise, tumours with well-defined margins require lesser margins compared with those with indistinct margins. Thus for clinically well-defined, low-risk tumours less than 2cm in diameter, surgical excision with a minimum 6mm margin (up to 10 mm) around the tumour border is appropriate and would be expected to completely remove the primary tumour mass in 95% of cases (Brodland and Zitelli, 1992).

In order to maintain the same degree of confidence of adequate excision in larger tumours, tumours extending into the subcutaneous tissue and those in high-risk locations, such as the ear, lip, scalp, eyelids and nose, a wider margin may be required. However, it needs to be appreciated that, paradoxically, it might be difficult to obtain wider margins in tumours in high-risk locations (such as around the eyes) which may mean that the use of Mohs micrographic surgery (MMS) would be appropriate. If the tumour is

extensive or advanced, a more radical approach may become necessary and, occasionally, amputation of the affected limb or digit may be indicated to prevent further spread of the disease.

MMS is a recognised treatment choice in the management of non-melanoma skin cancers (NMSC) and has similar cure rates, margin control and recurrence-free period compared with standard surgical excision. This modality of treatment is particularly useful in anatomical locations such as around the eyes where preservation of tissue becomes imperative. The other advantage of MMS over simple excision is the ability to examine all the surgical margins and to carefully map residual foci of invasive carcinoma. Rowe et al (1992) estimated the five-year cure rates for MMS to be about 90%, which was superior to the 76.7% obtained with standard surgical excision. Likewise, MMS can potentially salvage the affected digit as reported by Ashinoff et al (1997), who successfully treated SCC of the digits (without bony involvement) without compromising cure/recurrence rates. MMS, however, is time consuming since it requires the coordinated input of specialist surgeons and pathologists during the procedure. In the USA, MMS may be performed in the outpatient clinics under local anaesthesia (Hess and Schmult, 2006) but in the UK it is usually performed in operating theatres under controlled conditions.

<table>
<tr><td colspan="2">**Table 5**
Factors affecting the metastatic potential of SCC</td></tr>
<tr><td>**Tumour-related factors in high-risk SCC**</td><td>**Patient-related factors in high-risk SCC**</td></tr>
<tr><td>**Tumour location (i.e. lips, ears, nose)**
Tumour size greater than 2cm
Invasion to subcutaneous fat (or deeper)
Poorly differentiated tumour
Recurrent tumour
Perineural involvement</td><td>**Organ transplant recipient**
Haematologic malignancy (e.g. chronic lymphocytic leukaemia)
Chronic immuno-suppressive therapy
HIV infection or AIDS</td></tr>
</table>

Radiotherapy is considered to be a valid primary treatment option in patients with poor general medical health, very large tumours (which will require neo-adjuvant radiotherapy to debulk the tumour) or in difficult anatomical locations. Yaparpalvi et al (2003) have reported successfully treating a case of subungual SCC with osseous involvement with radiotherapy, thus preserving the affected digit. Radiotherapy can also be used in conjunction with surgery in recurrent or highly aggressive lesions and in metastatic cutaneous SCC to achieve loco-regional control (Veness et al, 2003). Systemic chemotherapy is usually reserved for patients with metastatic disease.

En bloc prophylactic lymph node dissection is not indicated for SCC although it may be necessary in younger patients (<50 years of age) with large anaplastic tumours (Baldursson et al, 1999). However, if the loco-regional lymph nodes are found to be enlarged, they have to be sampled (by fine needle aspiration cytology or incision/excision biopsy) in order to obtain a definitive diagnosis of metastatic deposit. Regional lymph node spread is treated by surgical block dissection, radiotherapy or a combination of both. Factors affecting the metastatic potential of SCC are listed in *Table 5*. Perineural, lymphatic, and mucoperiosteal invasion are usually indicative of metastatic disease,

and thus a poor prognosis. Baldursson et al (1999), in a study of 25 patients with SCC complicating chronic leg ulcers, observed that the disease was fatal in 10 patients who had poorly differentiated tumours, and they died within a year of diagnosis (Baldursson et al, 1999). The tumour behaviour also correlates with the level of dermal invasion and the vertical tumour thickness. Friedman et al (1985) found that the tumours which recurred were >4mm thick and involved the reticular dermis. The thickness and level of invasion of cutaneous SCC appear to represent important prognostic factors and may be relevant indicators for wide field resection and/or elective lymph node dissection (Ames and Hickey, 1982).

The prognosis of SCC without metastasis is good with conventional treatment with a five-year survival rate of about 90%. Low-risk tumours are usually completely cured with appropriate surgical therapy, however, patients who develop one SCC have a 40% risk of developing additional SCCs within the following two years (Baldursson et al, 1999). In a retrospective review of 44 patients with SCC, Friedman et al (1985) observed that at five years only 14% of patients had recurrence or metastasis. However, the presence of lymph node metastasis, even with an operable tumour, brings the five-year survival rate down to 39% for people with SCC of the extremities (Ames and Hickey, 1982). If the tumour is inoperable, then the mean survival time is only 12.2 months (Josephe et al, 1992).

Discussion
In the past two decades, the treatment of ulcers in non-hospital settings has increased, and this must be encouraged. It has been estimated that more than 80% of all patients with leg ulcers are treated in the community by district, practice or specialist leg ulcer nurses, or by the patients' relatives (Walsh, 2002). Studies have shown community leg ulcer clinics to be cost-effective and with good overall healing

Key Points

▸▸ Squamous cell cancer can arise as a result of malignant transformation in chronic, non-healing ulcers.

▸▸ Malignant degeneration can occur without the ulcer manifesting any of the recognised features of malignancy.

▸▸ A policy of low threshold to biopsy for chronic, non-healing ulcers should be adopted and repeat biopsies may be necessary.

▸▸ The prognosis is good if the malignant degeneration in an ulcer is diagnosed and treated early.

▸▸ Delay in presentation or misdiagnosis can lead to systemic metastasis that could be life-threatening.

rates (Falanga and Eaglstein, 1986; Moffatt et al, 1992). However, the healthcare professionals (HCPs) in the community, and the patients and their relatives should be made aware of complications arising from chronic ulcers. Although the vast majority of leg ulcers seen in the community are of venous, arterial, diabetic or pressure aetiology, the possibility of malignant transformation in such ulcers should always be considered. It may arise without the characteristic features of malignant ulcers and, as such, any chronic ulcer that does not respond to appropriate wound care should be viewed with suspicion. In addition, SCC arises spontaneously and any unusual lesion should be monitored. Small, isolated skin lesions that raise the suspicion of a cutaneous malignancy may be treated conservatively for a maximum of 4–6 weeks with a topical anti-neoplastic agent such as fluorouracil. If the lesion persists after this period then it must be considered to be a skin cancer until proven otherwise (Stal and Spira, 1997).

The diagnosis of ulcerative SCC (SCC arising de novo and presenting as an ulcer) may be considered easier to make and treat compared with SCC arising from chronic leg ulcers because they will have the classical everted edges and can be excised in full. There are certain recognised diagnostic features which suggest an ulcer to be SCC and these include everted wound edges, exophytic growth, irregular margins, necrotic base, excessive discharge, bleeding or overgranulation. However, it needs to be acknowledged that an SCC may present with none of the aforementioned features and the dogmatic reliance solely upon these features as an indication for biopsy and management should therefore be avoided.

Likewise, malignant degeneration in chronic ulcers may occur without the characteristic features. The majority of HCPs are familiar with the features of primary cutaneous malignancy but not with the subtle features of malignant degeneration in chronic ulcers. Thus the key to early detection lies in awareness of the heterogeneous association between chronic ulcers and malignancy.

Malignant transformation in chronic ulcers usually occurs from its edges. This is due to the fact that there is rapid turnover of cells along the wound edges, in an attempt towards re-epithelialisation. In long-standing ulcers, only one edge of the ulcer may undergo dysplastic changes, while the rest continue to improve and may even reduce in size. This may result in the deceptive appearance of a healing ulcer and the diagnosis of a malignancy may be missed or delayed, particularly in the absence of the classical features of malignancy. Any ulcer or part of an ulcer which breaks down recurrently after healing should be viewed with suspicion. Similarly, the appearance of unusual nodules in long-standing ulcers or any changes in the skin edge suggest a sinister pathology (Standkard et al, 1993; Browse, 2001). Biopsy should always be contemplated in such cases, even in the absence of typical features of malignancy.

The benefit of doing repeated biopsies in suspicious ulcers far outweighs the extremely low complication rate of the procedure. Pain can be controlled with simple analgesia and bleeding can be stopped using a calcium alginate dressing. Some authors have advocated a low threshold for biopsy, but opinion on this is divided. Falanga and Eaglstein (1986) have argued for biopsy of all ulcers at first presentation regardless of duration. Issues of costs and volume of work would make this an impractical policy in the majority of centres. In contrast, other authors have rejected the need for biopsy in the absence of features suggestive of malignancy (Harris et al, 1993).

More recent reports have recommended a period of 3–4 months (Hansson and Andersson, 1998; Ozek et al, 2001) without evidence of healing as an indication for biopsy but this time duration seems to be arbitrary. In practice, many chronic leg ulcers presenting to specialist clinics have duration greater than 12 months. For those ulcers which have been adequately managed and where no obvious factors exist that could impair the healing process (e.g. concurrent medical condition, recurrent infection, inappropriate treatment or non-compliance), biopsy may be indicated when they initially present to the clinic. Conversely, a conservative approach for a short duration (e.g. 3 months) may be adopted for ulcers which have been treated sub-optimally or where there are concurrent factors that impede healing. Biopsy could be performed at the follow-up consultation if evidence of healing is not apparent. This more pragmatic approach would minimise the number of unnecessary biopsies, the volume of work and cost. It is also important to acknowledge that, in addition to leg ulcers, malignant change can occur in any chronic ulcer such as a sacral pressure ulcer or a pilonidal sinus wound. HCPs should have a high index of suspicion in any non-healing ulcer receiving appropriate treatment and consider early biopsy.

When assessing patients with suspicious chronic leg ulcers, it is also essential to evaluate the regional lymph nodes. Although they may be palpable due to infection from the ulcers, the possibility of metastasis needs to be considered, as this has been shown to be the case in one-third of patients (Browse, 2001). Infection may lead to general malaise and pyrexia but symptoms such as cachexia, weight loss and loss of appetite should alert the HCP to the possibility of metastatic spread.

Conclusion

Marjolin's ulcers have high metastatic potential and their prognosis is poor if they are not detected at an early stage. Ulcers in unusual sites which do not respond to conventional treatment should be considered malignant until proven otherwise. Complete excision with appropriate margins is curative in the early stages, but a delay in diagnosis and treatment may lead to enlargement of tumour or invasion into the bone, which may necessitate amputation of the affected digit or limb. The authors advocate early biopsy for any chronic ulcer which fails to show signs of healing despite optimal treatment. **Wᴜᴋ**

References

Ames FC, Hickey RC (1982) Metastasis from squamous cell skin cancer of the extremities. *South Med J* **75(8)**: 920–3

Arons MS, Rodin AE, Lynch JB, Lewis SR, Blocker TG (1966) Scar tissue carcinoma. Part II: an experimental study with special reference to burn scar carcinoma. *Ann Surg* **163**: 445–60

Ashinoff R (1997) Mohs micrographic surgery. In: Aston JS, Beasley RW, Thorne CNM (eds) *Grabb and Smith's Plastic Surgery 5th edn.* Lippincott-Raven Publishers, Philadelphia: 121–5

Baldursson BT, Hedblad MA, Beitner H, Lindelof B (1999) Squamous cell carcinoma complicating chronic venous leg ulceration: a study of the histopathology, course and survival in 25 patients. *Br J Dermatol* **140(6)**: 1148–52

Baldursson B, Sigurgeirsson B, Lindelof B (1995) Venous leg ulcers and squamous cell carcinoma: a large-scale epidemiological study. *Br J Dermatol* **133(4)**: 571–4

Britto JA, Fenton L, Fenton OM (1998) The skin, skin tumours and plastic surgery In: Bernard KG, Young AE (eds) *The New Aird's Companion in Surgical Studies 2nd edn.* Churchill Livingstone Publications, London: 191–2

Brodland DG, Zitelli JA (1992) Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol* **27**: 241–8

Browse NL (2001) The skin. In: Browse NL (ed) *An Introduction to the Symptoms and Signs of Surgical Disease 3rd edn.* Arnold Publications, London: 66–9

Chong AJ, Klein MB (2005) Marjolin's ulcer. *N Engl J Med* **352(1)**: e9

Du Vivier A (2002) Non-melanoma skin cancer. In: Du Vivier A (ed) *Atlas of Clinical Dermatology 3rd edn.* Churchill Livingstone Publications, London: 178–83

Ellison DA, Hayes L, Lane C, Tracey A, McCollum CN (2002) Evaluating the cost and efficacy of leg ulcer care provided in two large UK health authorities. *J Wound Care* **11 (2)**: 47–51

Esther RJ, Lamps L, Schwartz HS (1999) Related Articles, Marjolin ulcers: secondary carcinomas in chronic wounds. *J South Orthop Assoc* **8(3)**: 181–7

Falanga V, Eaglstein WH (1986) A therapeutic approach to venous ulcers. *J Am Acad Dermatol* **14(5Pt1)**: 777–84

Fleming MD, Hunt JL, Purdue GF, Sandstad J (1990) Marjolin's ulcer: A review and re-evaluation of a difficult problem. *J Burn Care Rehabil* **11**: 460–9

Friedman HI, Cooper PH, Wanebo HJ (1985) Prognostic and therapeutic use of microstaging of cutaneous squamous cell carcinoma of the trunk and extremities. *Cancer* **56(5)**: 1099–105

Garner KL, Rodney WM (2000) Basal and squamous cell carcinoma. *Prim Care* **27(2)**: 447–58

Garzon R, Burgos EB, Garzon FL, Cippitelli L, de Cabalier ED, Cabalier LR (2001) Marjolin ulcer. *Rev Fac Cien Med Univ Nac Cordoba* **58(1)**: 93–7

Granel F, Barbaud A, Schmutz JL (2001) Basal and squamous cell carcinoma associated with chronic venous leg ulcer. *Int J Dermatol* **40**: 539

Greene FL, Page DL, Fleming ID et al (2002) *AJCC Cancer Staging Handbook. Part VI (23): Carcinoma of the Skin. 6th edn* Springer-Verlag Publishers, New York

Grey JE, Enoch S, Harding KG (2006) Venous and arterial leg ulcers. *Br Med J* **332(7537)**: 347–50

Hansson C, Andersson E (1998) Malignant skin lesions on the legs and feet at a dermatological leg ulcer clinic during five years. *Acta Derm Venereol* **78(2)**: 147–8

Harris B, Eaglstein WH, Falanga V (1993) Basal cell carcinoma arising in venous ulcers and mimicking granulation tissue. *J Dermatol Surg Oncol* **19(2)**: 150–2

Hess SD, Schmult CD (2006) *Squamous Cell Carcinoma* (Topic 401). Emedicine. www.emedicine.com. www.emedicine.com/derm/topic401.htm. Last accessed September 2007

Hill BB, Sloan DA, Lee EY, McGrath PC, Kenady DE (1996) Marjolin's ulcer of the foot caused by non-burn trauma. *South Med J* **89**: 707–10

Hochman M, Lang P (1999) Skin cancer of the head and neck. *Med Clin North Am* **83**: 261–82

Joseph MG, Zuleta WP, Kennedy PJ (1992) Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. *Aust NZ Surg* **62(9)**: 697–701

Lumley JSP (1997) The skin. In: Lumley JSP (ed) *Hamilton Bailey's Physical Signs: Demonstrations of Physical Signs in Clinical Surgery 18th edn.* Butterworth-Heinemann Publications, Oxford: 140–1

Margolis DJ, Bilker W, Santanna J, Baumgarten M (2002) Venous leg ulcer: incidence and prevalence in the elderly. *J Am Acad Dermatol* **46(3)**: 381–6

Martin H, Strong E, Spiro RH (1970) Radiation-induced skin cancer of the head and neck. *Cancer* **25(1)**: 61–71

Moffatt CJ, Franks PJ, Oldroyd M, et al (1992) Community clinics for leg ulcers and impact on healing. *Br Med J* **305 (6866)**: 1389–92

Moffatt CJ, O'Hare L (1995) Venous leg ulceration: treatment by high compression bandaging. *Ostomy Wound Manage* **41(4)**: 16–25

Mork J, Lie AK, Glattre E et al (2001) Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* **344(15)**: 1125 –31

Nguyen TH, Ho DQ (2002) Nonmelanoma skin cancer. *Curr Treat Options Oncol* **3(3)**: 193–203

Ozek C, Cankayali R, Bilkay U et al (2001) Marjolin's ulcers arising in burn scars. *J Burn Care Rehabil* **22(6)**: 384–9

Ozek C, Celik N, Bilkay U, Akalin T, Erdem O, Cagdas A (2001) Marjolin's ulcer of the scalp: report of five cases and review of the literature. *J Burn Care Rehabil* **22**: 65–9

Paredes F (1998) Marjolin ulcer. *Acta Med Port* **11(2)**: 185–7

Philips TJ, Salman SM, Rogers GS (1991) Non-healing leg ulcers: A manifestation of basal cell carcinoma. *J Am Acad Dermatol* **25(1pt 1)**: 47–9

Reynolds PL, Strayer SM (2003) Treatment of skin malignancies. *J Family Practice* **52(6)**: 456–64

Rowe DE, Carroll RJ, Day CL Jr (1992) Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol* **26(6)**: 976–90

Schwarze HP, Loche F, Gorguet MC, Kuchta J, Bazex J (2000) Basal cell carcinoma associated with chronic venous leg ulcer. *Int J Dermatol* **39**: 75–80

Sheen YS, Sheen MC, Sheu HM, Yang SF, Wang YW (2003) Squamous cell carcinoma of the big toe successfully treated by intra-arterial infusion with methotrexate. *Dermatol Surg* **29(9)**: 982–3

Smith J, Mello LF, Nogueira Neto NC et al (2001) Malignancy in chronic ulcers and scars of the leg (Marjolin's ulcer: a study of 21 patients). *Skeletal Radiol* **30(6)**: 331–7

Stal S and Spira M (1997) Basal and squamous cell carcinoma of the skin. In: Aston JS, Beasley RW, Thorne CNM eds. *Grabb and Smith's Plastic Surgery 5th edn.* Lippincott-Raven Publishers. Philadelphia: 117–19

Standkard C, Cruse C, Wells K, Karl R (1993) Chronic pressure ulcer carcinomas. *Ann Plast Surg* **30**: 274–7

Veness MJ, Palme CE, Smith M, Cakir B, Morgan GJ, Kalnins I (2003) Cutaneous head and neck squamous cell carcinoma metastasis to cervical lymph nodes (non parotid): a better outcome with surgery and adjuvant radiotherapy. *Laryngoscope* **113(10)**: 1827–33

Voisard JJ, Lazareth I, Baviera E, Priollet P (2001) Leg ulcers and cancer: 6 case reports. *J Mal Vasc* **26(2)**: 85–91

Walsh R (2002) Improving diagnosis of malignant leg ulcers in the community. *Br J Nurs* **11(9)**: 604–13

Yang D, Morrison BD, Vandongen YK, Singh A, Stacey MC (1996) Malignancy in chronic leg ulcers. *Med J Aust* **164(12)**: 718–20

Yaparpalvi R, Mahadevia PS, Gorla GR, Beirler JJ (2003) Radiation therapy for the salvage of unresectable subungual squamous cell carcinoma. *Dermatol Surg* **29(3)**: 294–6