Epidemiology and predictors of recurrence of Marjolin's ulcer: experience from Mansoura University

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ABSTRACT

INTRODUCTION Marjolin's ulcer (MU) is an uncommon malignancy occurring on top of old scars. Once thought to be more common in Caucasians, is now detected increasingly in Africa.

METHODS This was a retrospective study of patients with MU attending a tertiary centre within Mansoura University (Egypt) from 2004 to 2015. An institutional-based registry of skin and soft-tissue malignancies in this period revealed 560 cases, from which there were 26 cases of MU.

RESULTS The most common underlying cause of MU was burns (92% of patients), followed by trauma. A predilection towards males was detected. The latent period was 4–70 (median, 25) years. Recurrence occurred in 12 cases, with multiple recurrences occurring in 5 cases. MU recurrence was noted as early as 3 months and as late as 25 years after surgery.

CONCLUSIONS Young patients with MU are at higher risk of recurrence and should be followed up closely. A thorough search for nodal metastasis (especially in those with high-grade tumours) should be done. Wide local excision and leaving wounds to heal by secondary intention seems to be a viable treatment option.

KEYWORDS

Marjolin's ulcer – Burn – Scar – Skin cancer – Carcinoma

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Marjolin's ulcer (MU) classically refers to squamous cell carcinoma (SCC) arising on top of a chronic burn scar.¹ The definition of MU is controversial because some authors include other types of malignancy (eg basal cell carcinoma, sarcoma) within this term, whereas other scholars include all carcinomas of scar tissue even if they have not been induced by a burn (eg venous ulcer, traumatic ulcer).²

MU is more aggressive than malignancies occurring in normal skin. Nodal and distant spread seems to be less common initially due to extensive fibrosis occluding surrounding vessels. After a critical size has been reached, and when the ulcer exceeds the boundary of the underlying scar, metastasis occurs rapidly.³

Most reports of MU have been from China, India, Turkey and Iran. No study recognising MU in Egypt and North Africa has been published. Here, 26 patients with MU from Egypt were studied.

Methods

We present a retrospective study of patients with MU attending a tertiary centre (Oncology Center Mansoura University) in Dakahlia – the fourth largest governorate in Egypt – from 2004 to 2015. An institutional-based registry of skin and

soft-tissue malignancies in this period revealed 560 cases, from which there were 26 cases of MU.

The data of these patients were analysed using SPSS v22 (IBM, Armonk, NY, USA). Continuous variables are presented as the mean when symmetrical, or the median and range if asymmetrical. Categorical variables are presented as proportions. Bivariate analyses were done using the Student's *t*-test, Mann–Whitney test and chi-square test. $p < 0.05$ was considered significant.

Results

Epidemiology of MU

A predilection towards males was detected (16 males vs 10 females). MU occurred in middle-aged and older persons (mean, 47 years) with the youngest case aged 24 years. The latent period varied from 4–70 (median, 25) years. No significant difference between the sexes with regard to the age at the diagnosis was noted.

The most common causative factor was burns (24 cases); trauma was the cause in 2 patients. MU affected mainly the lower limbs (20 patients), followed by the upper limb (5) and then the chest (1) (Fig 1). The most common site of MU in the lower limbs was the knee and popliteal fossa, which was

affected in 13 patients (Fig 2, 3), followed by the dorsum of the foot (Fig 4).

In all cases the pathology was SCC. MU tended to be differentiated. Grade-I SCC was encountered in 18 patients and grade II in the other 8 patients; no patients had high-grade carcinoma. Nodal metastasis was noted in 6 patients. There was a direct correlation between tumour grade and prevalence of nodal metastasis ($p=0.03$), whereas no relationship was detected for MU diameter and nodal metastasis. The largest diameter of MU ranged from 3–20cm. No patients presented with distant metastasis at the diagnosis.

Diagnosis

All patients were diagnosed by wedge biopsy. Ultrasound for regional nodal basins (inguinal or axillary) was done in 24 patients. Nodes deemed to be suspicious on radiography were detected in 7 patients. Other investigations (chest radiography; computed tomography or magnetic resonance imaging for the primary site) were done according to the clinical scenario.

Recurrence

Patients were followed up for ≥ 1 year after surgery (one patient with MU in the chest wall was followed up for 6

Figure 3 Marjolin's ulcer on the left popliteal fossa in an elderly female

Figure 1 Chest-wall Marjolin's ulcer on top of an old burn

Figure 2 Fungating Marjolin's ulcer on the right popliteal fossa in a young male

Figure 4 Marjolin's ulcer affecting the dorsum of the foot

months). Recurrence occurred in 12 patients, with multiple recurrences occurring in 5 patients (Fig 5). MU recurrence was noted as early as 3 months and as late as 25 years (for a patient who underwent primary surgery at another centre) after surgery. Recurrence was associated with distant metastasis in 3 patients (1 in the lungs; 2 in the lungs and liver).

Figure 5 Axillary recurrence (for the third time) after wide excision and dissection of axillary nodes for a patient with a Marjolin's ulcer on the left forearm

Treatment

Surgery was the main treatment for a primary MU. Twenty-two patients underwent wide local excision with free margins ($>5\text{mm}$), and 4 patients underwent major amputation. A further 5 patients underwent major amputation for treatment of recurrence. The cause of amputation was: a non-functioning limb in 3 patients; encasement/infiltration of the neurovascular bundle in 3 patients; bone infiltration in 2 patients; unattainable negative margin in 1 patient. Lymphadenectomy (inguinal or axillary) was restricted to patients with regional lymph nodes showing malignancy upon ultrasound (7 patients). Radiotherapy was not used in any patient. Platinum-based chemotherapy was given to 3 patients. Reconstruction of a defect after surgery was done in 12 patients; 7 patients had a split-thickness skin graft; a pedicled flap was used in 2 patients (Fig 6); a free flap, full-thickness graft, and combined flap and graft were done in 1 patient each.

Predictors of recurrence

A young age at the diagnosis was an important predictor of recurrence ($p=0.006$) with a mean difference between the two groups of ≈ 15 years (Table 1). The second most important predictor of recurrence was nodal status, whereby all patients with malignancy in draining lymph nodes (6 patients) developed recurrence ($p=0.003$) (Fig 7). The third most important predictor was reconstruction of a defect after wide local excision, whereby recurrence was more common among patients who underwent reconstruction (flap or graft) than those with wounds left 'raw' ($p=0.052$) (Fig 8).

Table 1 Relationship between age at the diagnosis and recurrence

	Recurrence	N	Mean	Standard deviation	Standard error of the mean
Age at the diagnosis	No	14	54.21	15.187	4.059
	Yes	12	38.83	9.656	2.788

Figure 6 Reversed pedicled anterolateral thigh flap used to reconstruct the defect after excision of the Marjolin's ulcer seen in Figure 2

The diameter of MU was not a predictor of recurrence: diameter as large as 17cm was not associated with recurrence whereas that of 5cm was. Neither the grade nor the site of the primary MU was related to recurrence. The latent period did not correlate with the prevalence of recurrence. Procedures used for treatment (wide local excision or amputation) carried an identical risk of recurrence.

Discussion

In the present study, the most common underlying cause of MU was burns (92% of patients), followed by trauma. These

Figure 7 Relationship between recurrence and nodal status for patients with Marjolin's ulcer

Figure 8 Relationship between recurrence and reconstructive surgery for patients with Marjolin's ulcer

data are similar to those from Turkey and Western countries, whereas trauma is the most common cause of MU in sub-Saharan Africa.⁴

Several theories have been postulated as to how chronic ulcers develop into malignancy. Some scholars have suggested that chronic irritation causes cell atypia, and that continuous mitotic activity in regenerating tissue leads to DNA mutations, both of which precipitate malignant changes.⁴ Other researchers have suggested that scar tissue has an impaired immunological response to tumour cells.

In the present study, the male:female ratio for MU was 1.6:1, in comparison with 3:1 in other reports.⁵ Also, the pathology was primarily SCC, and no patients had high-grade carcinoma. In accordance with the literature,⁵ the lower limbs were affected in most cases.

Nodal metastasis occurred in 23% of patients, whereas distant metastasis was noted in ≈11% of patients (but not at the time of diagnosis). Ochenduszkiewicz and coworkers noted that the prevalence of metastasis from MU was 30%.⁶ Nodal metastasis was related to tumour grade rather than MU diameter.

Most studies have reported recurrence in 20–50% of patients.^{7,8} Recurrence is the major problem associated with MU; 46% of our patients suffered local recurrence and 19% suffered more than one recurrence. Three important predictors of recurrence were found in our study: (i) age at the diagnosis (the younger the age the greater was the risk of recurrence); (ii) nodal status (positive nodes were associated with recurrence); (iii) reconstruction with a flap or graft (those who underwent healing by primary/secondary intention without reconstruction carried a lower risk of recurrence). The relationship between reconstruction and an increased incidence of recurrence was reported first by Choi and colleagues, who concluded that reconstructive surgery with disturbed wound healing was accompanied by recurrence of carcinoma.⁸ Unfortunately, they did not make a comparison with patients who underwent excision without reconstruction.

Treatment of deep burns with skin grafting is known to reduce the risk of malignant transformation. Also, non-healing ulcers should be excised and grafted. As a general rule, any ulcer persisting for >3 months should be biopsied.⁵

Wide local excision with free margins is the first-line treatment of MU. Amputation should be reserved for MU infiltrating bone or major vessels. Seeding of tumour cells into blood vessels and lymphatics may result in metastasis, so electrocautery during excision may help prevention of metastatic spread.^{4,9}

Although controversial, regional lymphadenectomy in clinically palpable/radiologically suspicious nodes or in pathologically proven high-grade cancers is undertaken by many scholars.¹⁰ Lymphatic 'mapping' and sentinel-node biopsy are not feasible in MUs occurring in areas of extensive scarring due to a low prevalence of detection.¹¹ In our study, 6 patients underwent inguinal block dissection (which revealed negative nodes in 1 patient) and 1 patient underwent axillary dissection based on clinical and radiological data.

Radiotherapy is indicated in patients with inoperable nodal metastasis, or with positive lymph nodes after node dissection plus any of the following (1) high-grade lesions, (2) tumours >10cm in diameter or (3) lesions arising in the head and neck.¹² None of our patients received radiotherapy, which may have contributed to the high prevalence of recurrence. Also, 2 cases received chemotherapy but with no evident benefit.

Prospective studies on a larger study group will be needed to: (i) clarify the relationship between reconstruction and recurrence; (ii) ascertain if the infection and disturbed wound healing associated with such reconstructive surgery are the initiators of recurrence.

Conclusions

Here, we showed that MU is an aggressive malignancy affecting Egyptians mainly after burns. Young patients with MU are at higher risk of recurrence and should be followed up closely. A thorough search for nodal metastasis (especially in those with high-grade tumours) should be done. Further studies are recommended to clarify the role and types of adjuvant therapy given to patients at high risk of recurrence. Wide local excision and leaving wounds to heal by secondary intention seems to be a viable treatment option.

References

1. Cruickshank AH, Gaskell E. Jean-Nicolas Marjolin: destined to be forgotten? *Med Hist* 1963; **7**: 383–384.
2. Yu N, Long X, Lujan-Hernandez JR *et al.* Marjolin's ulcer: a preventable malignancy arising from scars. *World J Surg Oncol* 2013; **11**: 313.
3. Aydogdu E, Yildirim S, Aköz T. Is surgery an effective and adequate treatment in advanced Marjolin's ulcer? *Burns* 2005; **31**: 421–431.
4. Asuguo M, Ugare G, Ebughe G *et al.* Marjolin's ulcer: the importance of surgical management of chronic cutaneous ulcers. *Int J Dermatol* 2007; **46**(suppl 2): 29–32.
5. Pekarek B, Buck S, Osher L. A comprehensive review on Marjolin's ulcers: diagnosis and treatment. *J Am Coll Cert Wound Spec* 2011; **3**: 60–64.
6. Ochenduszkiewicz U, Matkowski R, Szynglarewicz B, Kornafel J. Marjolin's ulcer: malignant neoplasm arising in scars. *Rep Pract Oncol Radiother* 2006; **11**: 135–138.
7. Chalya PL, Mabula JB, Rambau P *et al.* Marjolin's ulcers at a university teaching hospital in Northwestern Tanzania: a retrospective review of 56 cases. *World J Surg Oncol* 2012; **10**: 38.
8. Choi JY, Bae YC, Nam SB, Bae SH. Impact of disturbed wound healing after surgery on the prognosis of Marjolin's ulcer. *Arch Plast Surg* 2013; **40**: 198–202.
9. Kipikassa A, Guzman S. Marjolin's malignant ulcers in cicatricial tissue. *Acta Chirurgiae Plasticae* 1981; **23**: 224–234.
10. Copcu E. Marjolin's ulcer: a preventable complication of burns? *Plast Reconstr Surg* 2009; **124**: 156e–164e.
11. Motamedolshariati M, Rezaei E, Beiraghi-Toosi A *et al.* Sentinel node mapping in Marjolin's ulcers: is it feasible? 2015; **27**: 54–62.
12. Ozek C, Cankayah R, Bilkay U, Cagdas A. Marjolin's ulcers arising in burn scars. *J Burn Care Rehabil* 2001; **22**: 384–389.