

Demographic and histopathologic characteristics of Marjolin's ulcers in Razi Hospital, Tehran, Iran: A 5-year survey

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Background: Approximately 0.77% to 2% of cutaneous ulcers and post-burn scars will develop malignant degeneration. When squamous cell carcinoma (SCC) emerges in a chronic scar or ulcer, it often is referred to as Marjolin's ulcer (MU).

Methods: This cross-sectional study assessed demographic information and pathological features of MU in Razi Hospital during 2009 to 2014. We reviewed 5150 chronic scar/ulcer cases and found 30 MU cases.

Results: Patients had an average age of 59.2±19.9 years. Most cases were males. Among 30 cases of MU, well-differentiated SCC accounted for 43.3% of cases. Moderately-differentiated SCC comprised 13.3% of cases, whereas there was invasive SCC in 10% of MUs. Only 3.3% of patients showed poorly-differentiated SCC and 9 (30%) had undifferentiated SCC. The average latency between burn and malignancy was 32.4±18.5 years. In the majority (90%) of cases, the initial injury was a burn. The lower and upper limbs comprised 53.3% and 26.7% of cases, respectively. There was one case with a history of melanoma. Among the 4 measured concurrent risk factors for malignancy, sun exposure was the most prevalent.

Conclusion: Since there is a high possibility of SCC formation in burn lesions and other identical lesions, rapid follow-up and appropriate treatment in acute burn lesions is necessary.

Keywords: Marjolin's ulcer, ulcer, chronic burn scar, squamous cell carcinoma

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INTRODUCTION

Malignant transformation can occur in chronic burn scars and ulcers, unhealed ulcers, and frequently traumatized scars. This finding is most common in the lower extremities, specifically around synovial joints such as the knees ^{1,2}. Da Costa coined the term Marjolin's Ulcer (MU) in 1903 to describe malignant transformation of scars, specifically post-burn scars ³.

Approximately 2% of ulcers and post-burn scars will develop malignant transformation. Two percent of the total squamous cell carcinomas (SCCs) as well as 0.03% of basal cell carcinomas are formed

in post-burn scars ⁴.

Although the most common mechanism for basal cell carcinoma is contact burns, other histopathologic types of MU have a similar frequency in thermal burns, hot water scalding, and contact burns. However, there is a higher risk of MU regarding prolonged thermal burns ¹.

Post-burn scars follow mutagenic accumulation with regular mitotic activity in regeneration and healing. This is a key mechanism that eventually leads to stimulation of malignant transformation ². Other suggested mechanisms include chronic stimulation, frequent trauma, impaired immunologic reaction of scar tissue to tumor cells, toxin release

from scars, relative avascularity of scar tissue, and lymphatic obstruction of scar tissue which makes it inaccessible for the body's immune care⁵. Unstable depigmented scars are less capable of resisting against carcinogens⁶. Although proof of the genetics role remains to be determined, some disorders of gene p53 have been reported in these patients⁷.

In most cases, MU is an SCC (71%). MU cases are graded based on level of histopathologic differentiation. Grade I has more than 75% differentiated cells, whereas grade II has between 25% to 75%, and grade III consists of less than 25% of differentiated cells⁸.

Compared to similar skin carcinomas, MU tends to spread and invade more rapidly. It has been lethal in at least 21% of cases. The overall 5-year survival from MU is reported as 52%, with a 10-year survival of 34%, and 20-year survival of 23%⁸. However, with timely diagnosis, the patient may receive treatment and survive. Evaluation of clinical, epidemiological, and demographic information can assist with early diagnosis. This study intends to provide more information on MUs in patients from Razi Hospital, a referral center for skin diseases in Iran.

PARTICIPANTS AND METHODS

This case series study evaluated patients who presented to the Tumor Dermatology Clinic at Razi Hospital from 2009 to 2014. The Ethics Committee at Tehran University of Medical Sciences approved the study protocol. We reviewed 5150 files of patients with chronic scars/ulcers and enrolled 30 patients with pathologic diagnoses of MU.

We recorded patients' demographic information that included age, gender, underlying cause of disorder, interval between injury and onset of the lesion, anatomical location of the lesion, history of sun exposure, radiotherapy, smoking, other skin cancers, and the pathologic features of MU. Due to the higher prevalence of SCC in histopathology, we analyzed these cases according to pathological reports. We evaluated the interval between primary injury and occurrence of MU, however 8 patients lacked this information. Primary lesions presumed to have formed during childhood (but not exactly remembered) were assigned the age of 10 years as the time of injury in order to obtain more precise

statistical analysis.

Data were entered in version 22 of IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) for analysis. We used mean, median, and standard deviation to describe quantitative data. Absolute frequency and relative frequency were used for qualitative data. The *t* and chi square tests were used to compare data between sub-groups. The level of statistical significance was 0.05.

RESULTS

We evaluated 30 patients with MU. Out of 30 patients, there were 20 (66.6%) males and 10 (33.3%) females. The average age of patients at the time of diagnosis was 59.2±19.9 years. Men received a diagnosis at 56.7±18.4 years whereas the average age at diagnosis for women was 64.2±22.7 years ($P>0.05$). The total interval between primary injury and occurrence of MU was 32.4±18.5 years. This interval was 34.4±19.9 years in 14 male patients and 16.3±28.8 years in 8 female patients ($P>0.05$).

The pathological grading system of SCC failed to report the differentiation level in 9 (30%) patients. We considered these cases to be undifferentiated.

There were 13 (43.3%) cases with well-differentiated SCC, 4 (13.3%) with moderately-differentiated SCC, 3 (10%) with invasive SCC, and one (3.3%) case had poorly-differentiated SCC. There were 9 patients diagnosed with SCC that did not have any known pathologic differentiation (lack of definite pathology) which we considered as undifferentiated. No statistically significant association existed between patient's age at the time of diagnosis, gender, interval between primary injury and occurrence of MU with pathological differentiation level ($P>0.05$). All 3 cases with invasive SCC were males (Figure 1).

We evaluated the underlying cause for MU and determined that 27 out of 30 (90%) cases had a history of burn injuries, 2 (6.7%) had trauma, and 1 (3.3%) resulted from a recurrent pilonidal cyst. We observed no association between underlying cause of MU and the patient's age, sex, or time period between primary lesion and MU occurrence ($P>0.05$).

The highest frequency of anatomical location was the lower limb in 16 (53.3%) cases, upper limb in 8 (26.7%) cases, head and neck in 4 (13.3%), and trunk in 2 (6.7%) cases. No significant association existed between location of malignancy, the

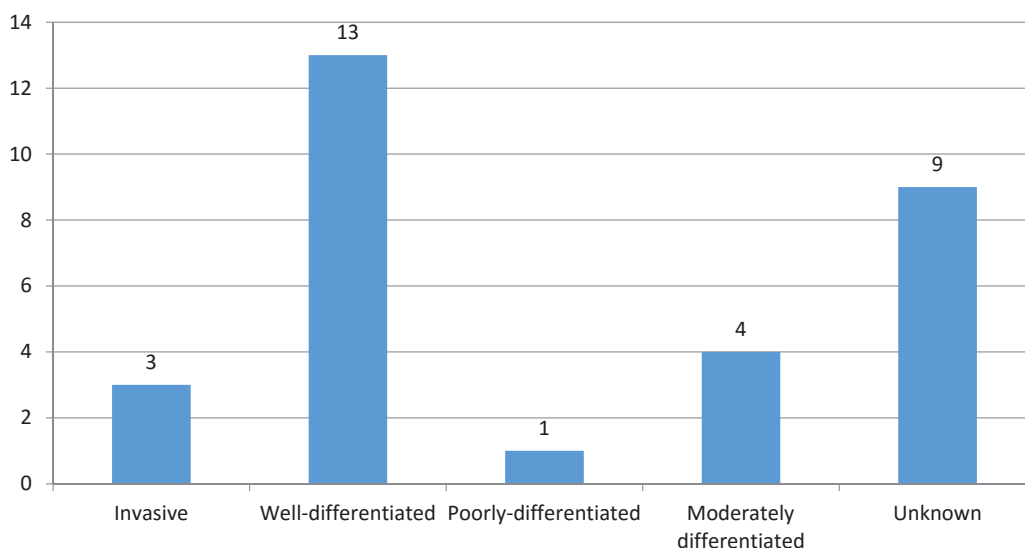


Figure 1. Pathological grading of squamous cell carcinoma based on degree of differentiation in patients with Marjolin's ulcer.

patient's sex or age, and the differentiation level in pathology ($P>0.05$).

We also assessed sun exposure, smoking, radiation exposure, and previous malignant skin diseases in the patient's medical records. There was a negative history of sun exposure in 20 (66.7%) and a positive history in 10 (33.3%) cases. There was a negative smoking history in 14 (46.6%) cases, positive in 5 (16.7%), and not mentioned in 11 (36.7%). Radiotherapy exposure was negative in 17 (56.7%) cases and not mentioned in 13 (43.3%). No positive history of radiation exposure was found. Only one (3.3%) case had a positive history

of prior skin cancer, negative history in 15 (50%) cases, and not mentioned in 14 cases. We assessed the relationship between these four factors and anatomical location, pathology, interval period between primary lesion and MU occurrence, and gender. There were no significant relations noted, except for prior skin cancer and anatomical location ($P=0.010$). Figure 2 shows the frequency of risk factors for occurrence of MU.

DISCUSSION

The current study patients had an average age

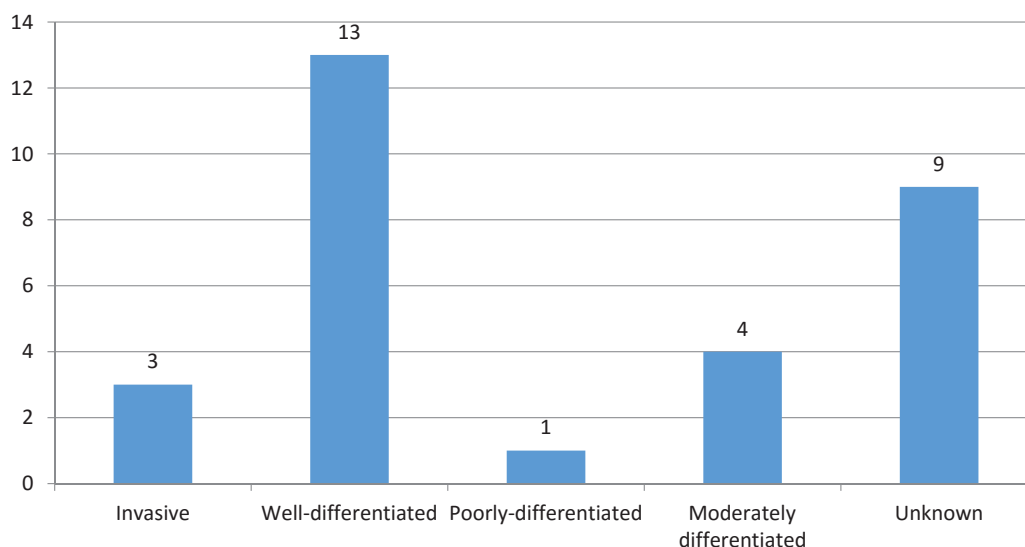


Figure 2. Frequency of risk factors in patients with Marjolin's ulcer.

of 59.2±19.9 years compared to 40.8 to 75 years in other studies of MU ^{2,9-11}.

This study showed a 2:1 male to female ratio which proved a quantitative dominance of male cases over females. The same ratio was reported in studies by Ko *et al.* ¹², Chalya *et al.* ¹³, Tiftikcioglu *et al.* ¹⁴, and Tahir *et al.* ¹¹. A study by Fazeli *et al.* reported a 1.65:1 ratio ¹⁰, whereas Onesti *et al.* reported a 1.2:1 ratio ¹⁵ and Kasse *et al.* had a 1:1 ratio ⁹. In the current study, most cases (43.22%) were well-differentiated SCC which confirmed the results by Fazeli *et al.* that reported 38.6% of cases had SCC as the most common pathological type of MU ¹⁰. Onesti *et al.* also reported that most MU cases were SCC ¹⁵. Ko *et al.* observed that 100% of their cases had well-differentiated SCC ¹² and Chalya *et al.* reported that 91.1% of cases had SCC ¹³.

SCC is the most frequent pathologic report of MU. Most often, MU is considered the equivalent of SCC. Of note, Karasoy *et al.* have reported that 10.3% of SCC cases were attributed to MU ¹⁶. This finding showed the necessity for careful attention to MU for diagnosis and proper treatment.

MU has a long incubation period that usually lasts for decades ^{2,9,11,13-15}. Our study patients had an average incubation period of 32.4±18.5 years (34.4 years in men and 28.8 years in women). Most cases in the current study, as with the Fazeli *et al.* study ¹⁰, showed symptoms after more than 20 years. Only one case had an incubation period of less than one year (9 months) which we regarded as acute MU. In the study by Fazeli *et al.* ¹⁰, 7.2% of MU cases were diagnosed within one year. We reported that 3.3% of MU cases were diagnosed within one year.

The incubation period in our research was comparatively higher compared to previous studies which indicated a lack of patient awareness on health-related problems that delayed diagnosis and proper treatment. This lag period was shorter in developed countries with more health facilities.

Burns, particularly deep burns, have been considered the major part of primary lesions in most studies. Therefore, it seems feasible to call MU as a burn scar carcinoma. Hence, burn scars require special attention and treatment ^{9-11,13,14}.

The type of burn injury also influences MU. Cases damaged by thermal burns are more susceptible

to MU compared to those with hot water scalding, electrical, chemical, or contact burns ¹.

This study showed that 90% of MU cases reported a burn injury background. Fazeli *et al.* reported that 87.9% of MUs had a history of burn injury ¹⁰. This was perhaps due to the fact that patients with other types of damage (e.g., osteomyelitis) usually referred to general surgeons and other medical centers rather than dermatologists. This study was limited to the cases at Razi Hospital as the largest dermatologic center in Iran. We did not examine cases from other medical centers. This has shown the necessity for multi-center studies.

The lower limb area had the highest frequency of MU. Fazeli *et al.* reported that the most frequent anatomical locations for MU were the legs (49.4%) and scalp (15.6%) ¹⁰. Onesti *et al.* reported 100% of cases with affected lower limbs ¹⁵. Ko *et al.* ¹² reported that 81.5% of lower limb cases, whereas Chalya *et al.* ¹³ reported 42.9% of MU cases in the lower limbs.

Onesti *et al.* ¹⁵ evaluated 13 patients with MU, which included 3 melanoma cases. Our study included one case of melanoma.

The four examined factors of sun exposure, smoking, history of previous skin cancer, and radiation or radiotherapy exposure showed that sun exposure had the highest frequency which was mostly positive in upper limb lesions. Therefore, it could be concluded that the role of sunlight exposure in MU evolution was similar to excessive sunlight exposure that caused skin cancers such as SCC. However, more studies would be required to precisely recognize the role of sun exposure in malignant transformation of burn scars.

This was a retrospective study and different information was recorded by different individuals. Therefore, a lack of uniformity existed in the data sheets or descriptions. Many cases did not report the exact time of primary damage, which was attributed to lack of patient recall. Possibly some unreported MU cases have been diagnosed and treated as SCC and not covered in this study. Due to the rareness of MU, multicenter studies can achieve more precise, extensive data. Careful recording of the patients' description of their disease and timing is necessary. Regional lymph node evaluation, distant metastasis, and fatality rate of MU are important factors to be examined in future studies.

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