

Progressive Premalignant and Malignant Development (Metachronous Appearance) in Multiple Burn Scars (Marjolin's Ulcers) Report of a Rare Case and Review of the Literature

*Desenvolvimento Pré-Maligno e Maligno Progressivo (Metácrono) em Múltiplas Cicatrizes de Queimadura (Úlceras de Marjolin)
Relato de Caso e Revisão da Bibliografia*

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Abstract

The eponym Marjolin's ulcer is used to describe the malignant transformation of any skin ulcer or scar. A 35-year-old white woman sustained a thermal burn injury over her lower half of the body when she was 8 years old. After 16 years of the event and over 9 years, metachronous skin ulcers, pseudocarcinomatous hyperplasia and well differentiated squamous cell carcinomas occurred, mainly on both lower limbs. The clinical history, histologic aspects, histogenesis, follow-up data and therapeutic considerations are discussed along with a review of the relevant literature.

KEY WORDS: carcinoma, squamous cell carcinoma, burns, skin neoplasms, skin ulcers.

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Trabalho apresentado como Tema Livre no 15º Congresso AMRIGS e 4º Congresso Médico de Passo Fundo. (Passo Fundo - RS / maio 1998)

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Report of a Rare Case and Review of the Literature.

Resumo

O epônimo úlcera de Marjolin refere-se à transformação maligna de qualquer úlcera ou cicatriz da pele. Relata-se o caso de uma mulher, branca, de 35 anos de idade, que sofreu queimadura térmica na metade inferior do seu corpo quando estava com 8 anos de idade. Após 16 anos, e ao longo de 9 anos, apareceram em forma metácrona na pele de ambas as coxas, úlceras, lesões de hiperplasia pseudocarcinomatosa e carcinomas epidermóides. Discute-se a história clínica, a histopatologia e histogênese, o comportamento biológico, assim como o tratamento. A literatura mais relevante foi revisada.

PALAVRAS-CHAVE: carcinoma, carcinoma epidermóide; queimaduras; neoplasias da pele; úlceras da pele.

Introduction

Marjolin's ulcer is considered the malignant transformation of previously traumatized, chronically inflamed skin (1,2,3,4). Initial descriptions considered it in close association with thermal injury (1,2,3,4,5), and over the past years its occurrence in draining osteomyelitis and radiation-induced skin scars has also been described (6,7,8,9).

Tumors developing in burn scars are, overwhelmingly, squamous cell carcinoma (SCC) (1,2,3,4,5,6,7,8,9,10,11,12,13,14). Basal cell carcinoma (14,15) and malignant melanoma (1,16) were also reported. Premalignant conditions such as pseudocarcinomatous hyperplasia (PCH) have exceptionally been registered (7,9).

Multiple burn scars are considered as one of the major risk factors for malignant cells development. Most articles dealing with that subject established that oncogenesis occurs at the same time over the same damaged area, e.i. synchronous appearance. Progressive transformation (metachronous appearance) in several burn scars is an extremely rare condition and, to the best of our knowledge, has not yet been described.

The aim of the present paper is to report and discuss on such a case, considering histologic, histogenesis and treatment aspects as well as follow up data.

Case Report

A 35-year-old white woman was referred to the Hospital Universitário-FURG, a teaching hospital, in order to obtain a definitive solution to her skin lesions. The patient had a nine-year history of admissions to other hospitals (Fig.1 and Table 1). She was been

burned by flames when she was 8 years old, over the abdominal wall, back, pelvic area, and both lower limbs. All of them healed by second instance.

The patient was first admitted to the Hospital when she was 24 years because of a two-

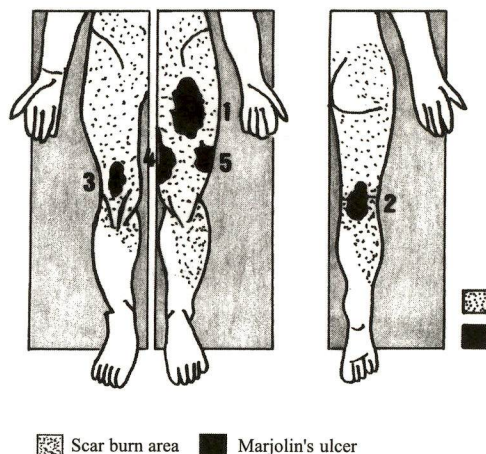


Figure 1: Right and left front views, and right back view.

Table 1: History of admissions to other hospitals.

Number	Year	Size/cm	H.D	Follow up
1	1987	12	SCC	exc.
2	1991	3	SCC	exc.
3	1991	2	PCH	exc.
4	1994	4	SCC	exc.
5	1994	5	PCH	exc.

H.D.: histopathologic diagnosis; SCC: squamous cell carcinoma; PCH: pseudocarcinomatous hyperplasia; exc: excellent

year painful skin ulcer, 12 cm in diameter over the upper third, front face of the left thigh (Fig. 2). Elevated margins were biopsed and pathological report disclosed an invasive well differentiated SCC (Fig. 3). Lesion was surgically removed and margins were free of disease. Inguinal lymph nodes dissected showed no metastasis. Homologous skin graft was performed.

Six years later (patient was 30 years old), she returned with a 3 cm painful skin ulcer over the right popliteal region. Pathological report from surgical specimen revealed also an invasive well differentiated SCC, with surgical margins free of disease. Skin graft was also performed. Five months later, she returned because of a 2 cm painful cutaneous ulcer, over the front face of the right thigh. Microscopical examination from surgical removed specimen corresponded to a PCH (Fig. 4). Inguinal lymph nodes were not palpated.

Three years later (patient was 33 years old) she again returned with a 4 cm, skin ulcer over the lower third, inner face of the left thigh. An invasive well differentiated SCC was diagnosed, with margins free of disease. Three months later, a new 5 cm, painful skin ulcer appeared over the lower third, front face of the left thigh, corresponding to a pseudocarcinomatous hyperplasia.

Since that time (four years), follow-up does not reveal loco-regional spread, and the patient is free of some skin disease.

Discussion

Jean Nicolas Marjolin (1780-1850) was the first to recognize in 1829 a growing tumor in a post-traumatic scar ⁽¹⁷⁾. Guillerme Dupuytren is considered to be the first to describe in 1839 the malignant transformation of that type of lesion ⁽⁵⁾. Since then, a cluster of articles have been published mainly concerning on physical, therapeutic and pathologic aspects.

Marjolin's ulcer is defined as the malignant transformation of a chronic inflammatory cutaneous area or scar skin due to thermal ^(1,2,3,4,5) or electric burns ⁽¹⁰⁾. The eponym also

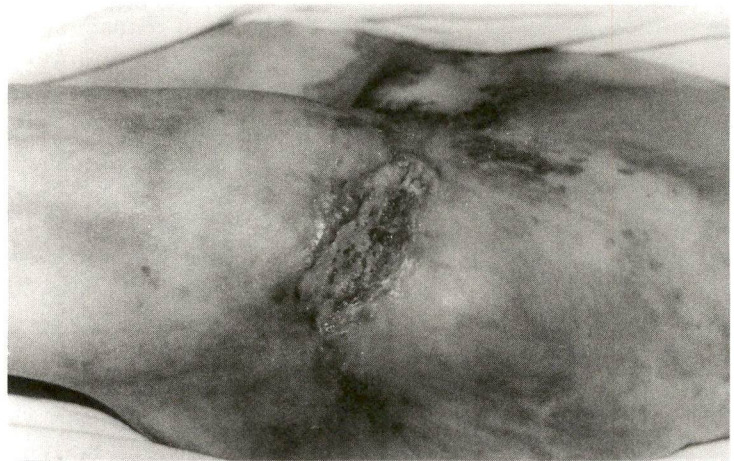


Figure 2: Marjolin's ulcer over front face of the thigh.



Figure 3: Invasive well differentiated squamous cell carcinoma (HE; 100x).

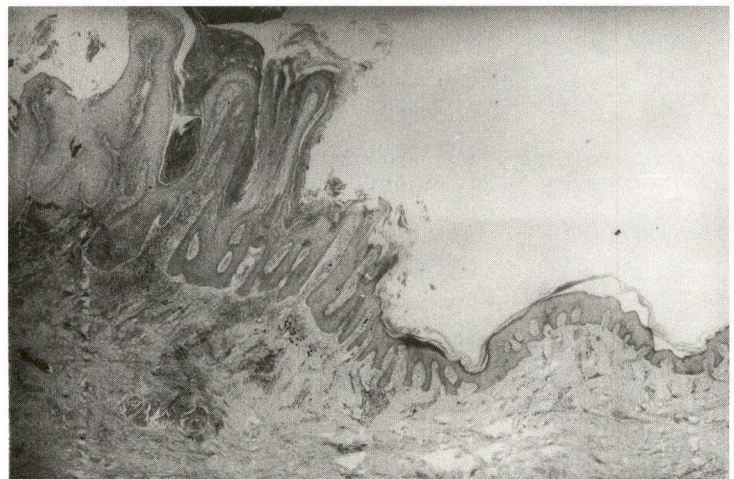


Figure 4: Pseudocarcinomatous hyperplasia (PCH) (HE 100x).

includes different kinds of chronic ulcers, induced by venous stasis ^(18,19), leprosy ⁽²⁰⁾, chronic pressure ^(21,22), intravenous cannula ⁽²³⁾, cold ⁽¹⁾, chronic osteomyelitis foci ^(6,7,8,9), systemic lupus erythematosus ⁽⁵⁾, vaccination areas ⁽²⁴⁾, urinary fistulas ⁽⁵⁾, dermatitis artefacta ⁽¹³⁾, grafted areas ^(11,24), and suppurative chronic adenitis ⁽²²⁾.

It is an uncommon condition, accounting for 2 % of all SCC developed in old burn scars ⁽¹⁶⁾, and almost 3,9 % of all SCC of the extremities ⁽²⁴⁾. Most SCC are highly or well differentiated ^(9,12). Although SCC may occur anywhere on the skin and on mucosa membrane with squamous epithelium, SCC associated to Marjolin's ulcer affects mainly upper and lower limbs as well as head ^(1,25). Basal cell carcinoma ^(14,15), malignant melanoma ^{1,16} and mesenchymoma ⁽²⁶⁾ were also reported, accounting for less than 0,3 % of the cases. The former seems to be more prevalent in HIV-positive patients ^(14,27).

Oncogenesis still remains a controversial issue. The slow growing rate is one of the most conflicting problems. Scar fibrosis and thrombosis of blood and lymphatic vessels could explain that phenomenon. DNA damage and associated mutagenicity, aberrations in local immune networks and immunosuppressive effect on skin by affecting the normal surveillance function of antigen-presenting Langerhans cells in the epidermis responsible for T-lymphocyte activation, appear to have direct mutagenic effects, producing DNA adducts with subsequent oncogene activation ⁽⁷⁾. Moreover, incidence of SCC is significantly increased in immunosuppressed patients ⁽¹⁴⁾. At early stages, fibrosis would act as a blockade agent, preventing dermis invasion ⁽²⁸⁾.

The clinical aspect of Marjolin's disease discloses a well defined ulcer, with irregularly elevated margins and nodular surface. Average size is 5 cm in diameter ^(1,8,24), and polipous or cowliflor-like mass may also be observed ⁽²⁸⁾. Bleeding, foul odor and pain are the most conspicuous elements ⁽⁸⁾; even so, tenderness may be reduced in neuropathic plantar ulcers of leprosy ⁽²⁰⁾.

Interval between skin damage and tumor development varies from 3 months to 75 years, with an average of 36,8 years ⁽¹⁾. Taking into account clinical criteria, Mosborg et al. classified scar carcinomas in "acute type" when they occur within one to two years of injury, meanwhile the most common "chronic type" are those with an average latency of 35 years ⁽²⁵⁾. Most reports addressed a synchronous appearance of the tumor, and a synchronous bilateral case was even published ⁽²⁾. The sequence of events in our patient stresses a non-controversial cause-effect relationship. Pseudocarcinomatous hyperplasia is an irrefutable precursory lesion of SCC ^(7,9), and its metachronous appearance over spread burn scars areas during a long period of time is an absolutely exceptional case.

Possible complications of Marjolin's ulcer include sepsis ⁽¹⁰⁾, lymph nodes and distant metastasis ^(3,8,15,18,19,20,29). None occurred in our patient.

Due to low prevalence, there has been disagreement regarding its prognosis and methods of treatment. A well thought-out treatment plan is necessary to optimize care and assure patient survival. First, the importance of appropriate wound management with full-thickness skin graft and close observation must be pointed out ^(14,15,18). Obviously, early diagnosis of malignant lesion is imperative.

Conservative surgery is the logical treatment, with wide local excision. It is necessary to achieve adequate margins in order to avoid local recurrence. Sometimes limb amputation is required ^(2,3,8,19,28). Lymphadenectomy deserves mention ^(19,20,22,28). According to Barr et al. ⁽³⁾ prophylactic node dissection is not required in most patients. Hill et al. ⁽¹⁹⁾ advocates in favour only if the tumor is poorly differentiated. Also staging if nodes are involved remains controversial ⁽²⁰⁾.

Adjuvant radiation therapy may often improve the outcomes obtained with surgery alone ⁽²⁵⁾. The role for preoperative topical applications of 5-fluorouracil seems to show a great value in the treatment of Marjolin's ulcers. It would stimulate patient's own im-

munoreaction to the tumor, changing the cellular infiltrate from acute inflammatory cells to round cells, chiefly T-lymphocytes⁽³⁰⁾.

Prognosis depends mainly on immunological status, associated disease, histological type, and presence of regional and distant metastasis. Most authors stressed the aggressive nature of the scar carcinomas^(1,8,10,13,18,20,22,29). Surgical treatment alone for lower limbs tumors has resulted in a 87 % 5-year survival rate⁽³¹⁾. Local recurrence was less than 10 % and ranges from 6 to 11 months⁽⁸⁾. Regional metastasis developed in 44 %, and rate of metastasis at the time of diagnosis was 32 %⁽⁸⁾.

In summary, the particular characteristics of this case are exceptionally seen in Marjolin's ulcer, specially the metachronous appearance of carcinomas and pseudocarcinomatous hyperplasias on different locations.

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