

# A New Concept in the Management of Marjolin's Ulcers

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Marjolin's ulcers have a grave prognosis, especially when regional nodes are involved. Recent studies suggest such cancers are in an immunologically privileged sites due to the dense scar tissue. The prognosis has been shown to be much worse for tumors not having a round cell infiltrate prior to surgery, as in Marjolin's ulcers. The use of topical 5-fluorouracil (5-FU) induces a round cell infiltrate. Three case reports of large Marjolin's ulcers are presented which were first treated with topical 5-FU. Radical ablative surgery was avoided in these patients with a successful outcome.

**I**N 1828, JEAN NICOLAS MARJOLIN<sup>1</sup> described a villous lesion that developed in degenerating scar tissue. Although others had previously described cancers developing in burn scar,<sup>2</sup> Marjolin's name has been given to these malignancies.

The 25th edition of Dorland's Medical Dictionary<sup>3</sup> defines a Marjolin's ulcer as "an ulcer seated upon an old cicatrix; it may degenerate into a squamous cell carcinoma with a propensity for metastasis." Thus, such cancers may develop in varicose ulcers, areas of lupus, chronic osteomyelitis or in burn scars, and may be either squamous cell carcinomas or basal cell carcinomas.<sup>4-8</sup>

In reviewing the many articles written about Marjolin's ulcers, one is struck by the contradictions about these lesions. The lesions are slow to develop and metastasize, but they frequently have systemic metastases after surgery. While all authors describe these lesions as having a grave prognosis, Giblin et al.<sup>9</sup> reported only three deaths out of 21 patients, for a cure rate of 86%. Yet if regional lymph nodes are involved, surgery may offer less than 10% cure rates! Novick et al.<sup>10</sup> reported that 15 of 16 patients with metastasis died of their carcinoma. Treves and Pack<sup>2</sup> reported eight dead and only 12 living and free of disease. For prognosis, these authors stated: "Despite the slow progress, the absence of disturbing symptoms, and the lateness of regional metastasis, the prognosis is serious.

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The seriousness of the disease was emphasized by Bostwick et al.<sup>11</sup> in 1975 when they reported:

Six consecutive patients with large, indolent Marjolin's ulcers were seen in a four-year period. These six patients were each treated initially by a radical local excision of the epidermoid carcinoma, with an appropriate wound repair. All of them developed aggressive unresectable local disease with regional nodal metastases within six months after the local excision.<sup>11</sup>

The purpose of this paper is to report on three cases of Marjolin ulcer treated by a different and more conservative method.

## Case Reports

**Case 1.** This 57-year-old white woman was admitted to Hotel Dieu Hospital in January, 1968, with a biopsy-proven squamous cell carcinoma arising in a 10 × 15 cm stasis ulcer on the left lower leg (Fig. 1a). The patient was treated with twice daily local applications of 10% 5-fluorouracil (5-FU) cream. A large eschar developed (Fig. 1b). This eschar was (Fig. 1c) gradually debrided. After all biopsy specimens were negative, skin grafts were applied on May 13, 1968, and the ulcer rapidly healed (Fig. 1d).

The patient died four years later of a myocardial infarction, without evidence of the cancer. Inguinal node dissection was not performed.

**Case 2.** This 36-year-old black man was admitted to Charity Hospital in New Orleans, with a huge squamous cell carcinoma (Fig. 2a) involving both cheeks, the upper lip and nose. This cancer developed in an area of dense scarring caused by lupus that had plagued the patient for many years.

Topical administration of 5% 5-FU was initiated in June, 1976. After two weeks of topical therapy, 5-FU was injected into the lesion each week. While a visible reaction would occur with each injection, regression was very slow. Cautery was used to remove the bulk of the lesion.\* More topical 5-FU was applied to the base of the ulcers. Subsequently biopsy specimens demonstrated two areas of residual

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\* This patient was on the L.S.U. Plastic Surgery Service, George Hoffman, M.D., Chief.

disease which were then cauterized. Biologic dressings were applied followed by autografts after all biopsy specimens were negative. Because of a persistent palpable node on the left, a radical neck dissection was performed, and one node was cancerous. Subsequently, most of the depigmented facial skin has been replaced with skin grafts. The patient is still free from the carcinoma more than four years later (Fig. 2b, 2c, 2d).

**Case 3.** This 59-year-old white man was first seen on May 16, 1979, with a huge ulcer on his left heel (Figs. 3a and b). The patient was run over by a train 52 years before, resulting in a very high thigh amputation on the right and loss of the heel on the left foot. Pinch grafts were applied to the foot wound to help the indolent area heal over. The patient had frequent ulcers and was diagnosed as having osteomyelitis with a draining sinus for several years. Amputation was recommended, but the patient refused. Treatment with the topical administration of 5% 5-FU was initiated after biopsy specimens demonstrated the lesion to be a squamous cell carcinoma. The patient was malnourished and failed to react to a standard battery of skin tests used as a guide to the immunologic status of the patient. Protein supplements, vitamins, iron and zinc were "pushed." After two weeks of topical therapy, local injections of 5-FU were administered,



FIG. 1b. Photo showing dense eschar that developed after application of topical 5-FU for several weeks.



FIG. 1a. Photo of a Marjolin's ulcer arising in an area of varicose ulceration. Biopsy specimens demonstrated squamous cell carcinoma.

but these proved to be quite painful. Therefore, 500 mg 5-FU were administered intravenously in a 1000 cc saline solution every 24 hours, for four days at monthly intervals times two. The lesion regressed slowly, therefore, the bulk of the tumor was removed by cauterization. After biopsy specimens demonstrated no carcinoma in the soft tissue, skin grafts were applied. These covered much of the area, but drainage from the bone continued, and biopsy specimens again demonstrated carcinoma in the central area.

The patient finally agreed to a Syme amputation through the distal malleoli, with closure by the dorsal flap, on November 13, 1979. Approximately three inches of the original skin graft were left over the back of the ankle. The anterior flap was sutured to the graft over part of the original tumor bed (Fig. 3c). Wound healing was uneventful, and the patient was fitted with a prosthesis. By May, 1980, the patient had gained 20 lbs and all skin tests were positive except for mumps, which the patient has never had. While the patient did have palpable left inguinal lymph nodes, initially, biopsy specimens were never obtained and they are now clinically negative.

### Discussion

By definition, the malignancy of a Marjolin's ulcer arises in an area of dense scar. That such a scar is an "immunologically privileged site" is supported by the



FIG. 1c. Photo showing ulcer during period of gradual debridement of eschar.

observations of Casson et al.,<sup>12</sup> Castillo and Goldsmith,<sup>13,14</sup> Futrell and Myers,<sup>15</sup> and Boswick et al.<sup>11</sup>

Further credence to this concept of an immunologically privileged site is furnished by the work of Crawley, Dellon and Ryan.<sup>16</sup> After comparing the pattern of cellular infiltration in squamous cell skin cancers and the Marjolin's ulcers of patients who died and those who survived, these authors concluded:

In contrast, those patients who had little or no infiltration of small lymphocytes about the invading tumor developed either tumor recurrences or metastases. None with scar carcinoma, regardless of the degree of tumor differentiation, have had tumor recurrence or metastases (during follow-up periods of one to 21 years) when there has been a heavy infiltration of small lymphocytes. In contrast, the patients with well-differentiated squamous carcinomas arising in unscarred skin have had tumor recurrence

or metastases when there has been little or no infiltration of small lymphocytes.<sup>16</sup>

We believe that the use of topical 5-FU may be a method of producing such a round cell infiltration that does, in fact, change the immunologic balance in these patients. In previous publications,<sup>17-20</sup> we have described the use of 5-FU for skin cancer and shown how a round cell infiltration does develop at the site of a malignant or premalignant lesion after 12-14 days of topically applying 5-FU.<sup>18,19</sup> Studies from our department have shown that a type of sensitization does occur.<sup>21</sup> This is different from that evoked by D.N.C.B. or poison ivy, as the 5-FU ointment does not readily elicit a second reaction on normal skin, but will if premalignant or malignant changes are present at the site of application.<sup>22</sup> If, several months later, the 5-FU is administered to another lesion that drains to the same



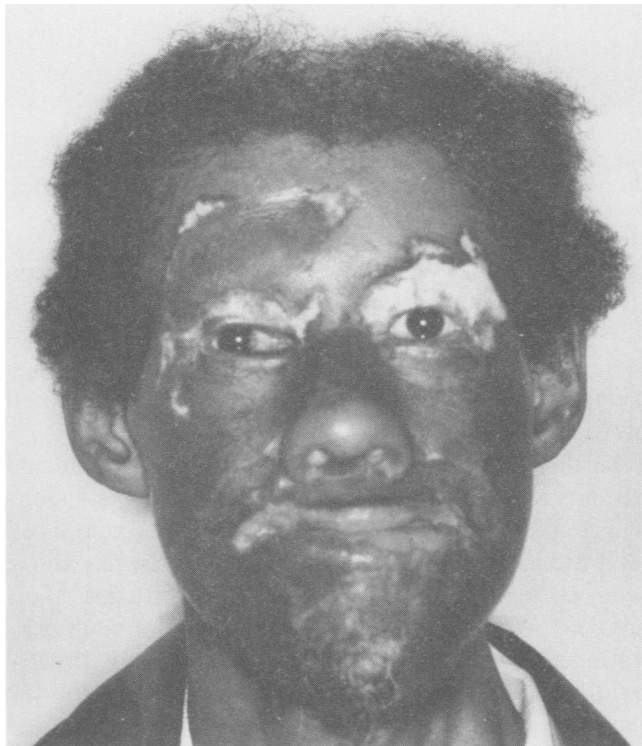
FIG. 1d. Photo showing healed split thickness skin grafts applied to ulcer after all biopsies were negative for cancer.



FIG. 2a. Photo showing biopsy-proven squamous cell carcinoma arising in an area of chronic scarring caused by lupus.

regional nodes as the first lesion, this round cell infiltration occurs within three to four days. This reaction can be felt by the patient as an awareness of the lesion, a tingling or itching.

We treated a patient with lesions of the forehead (Fig. 4a) in June, 1980. Then in October, a cheek lesion, which had previously been biopsied and diagnosed as actinic keratosis, was treated. The 5-FU was applied twice a day for three consecutive days. Little reaction was present on the morning of the third day when photos were taken (Fig. 4b), but by mid-day,



FIGS. 2b-d. Photos showing the patient four years after treatment of the cancer by topical and intralesional 5-FU and removal by cauterization. The raw base was skin grafted. Later, other areas of depigmented skin were removed prophylactically.



FIG. 3c. Photo of the stump after skin grafts and a later Syme amputation. Approximately three inches of skin graft over the site of the previous cancer can be seen on the posterior area of the stump.

the patient could feel the lesion, and examination showed the redness that had rapidly developed over a few hours (Fig. 4c). This is much like the lymphocytic infiltration that marks the turning of a benign melancytic lesion into a malignant one, as noted by Clark.<sup>23</sup>

Since 1967, we have used topical 5-FU for selected patients with oral carcinomas. Many of these lesions will decrease in size, and also have a marked round cell infiltrate. These cellular patterns are much like those seen in melanoma after successful perfusion therapy.<sup>24-26</sup> We have previously reported that such infiltration also occurs in basal cell skin cancers not directly treated with 5-FU, but located in an area having the same lymphatic drainage as other lesions being treated with topical 5-FU.<sup>26</sup>

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FIGS. 3a and b. Photos showing the huge squamous cell carcinomas arising in a scarred area treated by pinch grafts more than 50 years earlier.

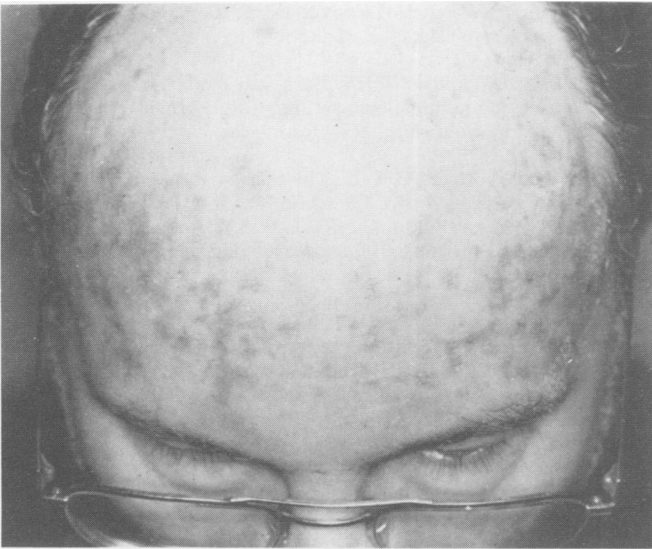


FIG. 4a. Photo showing the forehead lesions which were treated in June, 1980.

We also believe that when bone is involved, resection is necessary, as we have been unable to sterilize such wounds by topical 5-FU, local injections, or intravenous administration of 5-FU. It is reminiscent of



FIG. 4b. Photo showing the area of actinic keratosis in the nasal labial fold showing no reaction to topical 5-FU in the morning of the third day.

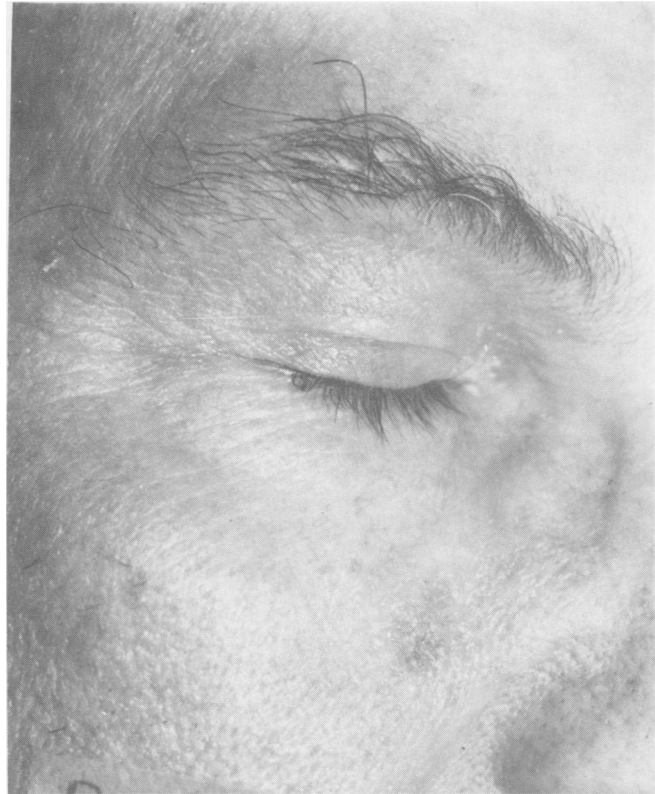


FIG. 4c. Photo showing the reaction present four hours after photograph 4b—itching, erythema and swelling were present.

treating chronic osteomyelitis with antibiotics. The dead bone should be removed to achieve a cure.

#### Summary and Conclusions

Three cases of extensive squamous cell carcinomas arising in a varicose ulcer, scarring of lupus, and chronic scar and osteomyelitis are presented as cases of Marjolin's ulcer. Topical administration 5-FU was the initial treatment for the lesions. In one patient this cleared the cancer, and skin grafts allowed the ulcer to heal. After sensitization in the second patient, the bulk of the tumor was removed by cautery and the base was successfully skin grafted. Radical surgery with its necessary reconstruction was avoided. In the third case the patient appeared to have his tumor arrested, and a much less radical amputation gave him a serviceable weight-bearing stump.

The use of topical 5-FU induces a round cell infiltrate that may change the immunologic balance in what has been described as an "immunologically privileged site."

In addition to the general supportive measures for correction of anemia, malnutrition and vitamin and mineral deficiencies, we recommend using topical 5-FU as the initial treatment for extensive squamous

cell carcinoma of the skin such as Marjolin's ulcer. If such treatment will clear the lesion, as happened in Case 1, the skin defect may be repaired. If the malignancy involves the underlying bone, the bone must be resected, but this can be done after much of the original tumor has been greatly decreased in size. Regional lymph node dissection is performed only when clinically positive lymph nodes are present. As stated previously,<sup>26</sup> we believe that 5-FU causes some type of immune reaction or sensitization of the tumor, and should be used before surgery.

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### DISCUSSION

DR. JOHN C. McDONALD (Shreveport, Louisiana): Dr. Ryan and his colleagues suggest that the success of this program depends upon the unique characteristics of the tumor. The hypothesis suggests that the burn scar, due to its paucity of lymphatic channels, represents an immunologically privileged site, and when low-grade malignant transformation occurs within this site, the host is unaware of its presence until it attains too large a bulk for autogenous control, or it metastasizes to regional nodes at a time when the host has not developed an immune state.

Indeed, there is evidence to support such a hypothesis, the best of which was performed in a laboratory model by Dr. William Futrell, whose work is referenced in the manuscript. A correlate of this hypothesis is that local 5-FU either combines with the tumor, or induces the tumor, to produce more antigenic material, which creates a state of immunity to aid in the control of the lesion.

The experience of others suggests that scar cancers which engender round cell infiltrates have a better prognosis than those which do not, and this current experience supports this general hypothesis.

Drs. Ryan, Litwin, and Krementz have diligently studied the value of topically applied 5-fluorouracil in the treatment of integument tu-

mors for numbers of years. This body of work is scholarly, and among the best in the field, and I recommend it to you.

I should point out that the evidence supporting this hypothesis is circumstantial, and the phenomenon can be explained by a number of alternative mechanisms, one of which might be that the burn scar simply acts as a mechanical barrier, allowing the tumor to grow to substantial size without metastasizing. Nevertheless, the paper is important, in that it proposes a hypothesis which can be tested, and it offers an additional example of the successful treatment of a malignancy with a multimodal approach, thus supporting the thesis that some tumors can be treated from a biologic point of view, rather than in a purely anatomic way.

DR. JAMES D. HARDY (Jackson, Mississippi): I'm somewhat apprehensive about discussing this paper, on two counts. First, Dr. Ryan and his colleagues have given us such a comprehensive survey of this problem that my one case may seem a little thin. Second, I fear I may be accused of attempted one-upmanship in relating the following experiences.

But when I arrived in Philadelphia from the Army in 1946, all set to begin surgical training and do hernias, Dr. I. S. Ravdin looked