Marjolin’s ulcer in chronic osteomyelitis: seven cases and a review of the literature

Diagnostic et résultats du traitement : 7 cas

Ulcère de Marjolin sur ostéite chronique

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RÉSUMÉ

Les plaies et cicatrices instables en regard de foyers d’ostéite chronique peuvent se compliquer de dégénérescence maligne après une longue évolution.

Sept cas de carcinomes épidermoïdes sur lésions cutanées chroniques en rapport avec des infections osseuses sous-jacentes sont rapportés dans cette étude.

Les lésions sont survenues sur des infections osseuses chroniques avec 3 cas d’ostéite post-traumatique, 2 cas d’ostéomyélite hématoğène, un cas d’ostéite sur radionécrose et un cas de brûlure profonde compliquée d’ostéite. Ces lésions cutanées évoluaient depuis 43 ans en moyenne avant le diagnostic de dégénérescence maligne et se présentaient généralement sous la forme d’ulcérations bourgeonnantes et malodorantes. La variété anatomo-pathologique était un carcinome épidermoïde spino-cellulaire 5 fois et un carcinome épidermoïde verruqueux 2 fois. Dans tous les cas, un traitement conservateur avec excision large et couverture par lambeau a été tenté. Chez 4 patients, ce traitement a échoué et 3 patients ont été amputés. Un patient est décédé 2 ans après amputation, avec une récidive locale et une diffusion métastatique cérébrale.

Mots clés : Carcinome épidermoïde, ostéite chronique, ulcère de Marjolin.

ABSTRACT

Purpose of the study

Malignant degeneration of chronic wound inflammation is a rare complication that almost always develops late. Unstable wounds and scar tissue related to chronic osteitis can degenerate after a long period of chronic inflammation. We report seven cases.

Case reports

Seven patients presented squamous-cell carcinoma of the skin, which had developed on wounds related to deep bone infections. Three patients had chronic bone infections subsequent to posttraumatic osteitis, two after hematogenous osteomyelitis, one after osteitis that developed on a zone of radiation-induced necrosis, and one after a deep burn was complicated by osteitis. The skin lesions developed over a period of 43 years on average before the diagnosis of malignant degeneration was established. Most of the lesions presented as budding malodorous ulcers. The pathological diagnosis was spinocellular squamous-cell carcinoma in five cases and verrucous squamous-cell carcinoma in two. Conservative treatment with wide resection and flap cover was attempted in all seven patients.

Results

Treatment failed in four patients and three required amputation. One patient died 2 years after amputation with local recurrence and metastatic dissemination to the brain.
INTRODUCTION

The term “Marjolin ulcer” designates any malignant degeneration of a chronic inflammatory skin lesion, whatever the origin of the lesion and whatever type of cancer develops in the lesion. Marjolin’s (1) and Da Costa’s (2) original description corresponded to chronic ulcers of vascular origin and it was only in 1963, after the publication of Sedlin and Fleming’s (3) series, that this name was also applied to neoplastic transformations with onset on sites of chronic bone infection.

These ulcers are a malpighian epithelial keratinizing proliferation from keratinocytes of the epidermis or the oral, anal, or genital orifice malpighian mucous membranes. In the majority of cases, this is squamous-cell carcinoma. These malignant tumors with unlimited growth are susceptible to infiltration, destruction, and metastatic spread and compromise the vital prognosis if there is not early and adequate treatment [Grosshans (4)]. The unstable wounds and scar tissue around the chronic osteitis areas can become complicated by malignant degeneration after a long progression [Fitzgerald et al. (5)]. The physiopathological mechanism of this transformation is unknown. The chronic irritation of the skin or the exposure of the soft tissue to different growth factors undoubtedly plays an important role [Gebhart et al. (6)].

The diagnosis of Marjolin’s ulcer in chronic osteitis is difficult in practice, because although the degeneration of a chronic wound is well known by dermatologists, this notion does not easily come to mind in the orthopedics unit, particularly since this diagnosis is rare.

The incidence of this transformation is very difficult to evaluate, and is estimated between 0.2% and 1.7% of cases of chronic osteitis. These epitheliomas account for 0.05% of all squamous-cell carcinomas of the lower limbs [Sedlin and Fleming (3), Sankaran-Kutty et al. (7), Mabit et al. (8), Mc Grory et al. (9)].

Seven observations of Marjolin ulcer in chronic osteitis are reported in this study with the objective of evaluating their origin and the diagnostic and therapeutic problems encountered and comparing them to the data gathered from the literature.

MATERIAL AND METHODS

Seven cases of squamous-cell carcinoma on chronic cutaneous lesions related to underlying chronic bone infections were observed in our department between 1995 and 2003. In the present series, the inclusion criteria were the association of a chronic skin lesion related to a chronic bone infection and positive histology for squamous-cell carcinoma. The skin lesions had been evolving for several years before they became cancerous, which excluded the possibility of cancer preceding what was assumed to be causal disease.

The characteristics of the seven cases are summarized in table I and table II. All lesions were lodged in the lower limb (five in the tibia, one in the external malleolus, and one on the calcaneus) in six men and one woman, with a mean age of 66 years (range, 52-82 years). The chronic bone infection was posttraumatic in three cases, consecutive with hematogenic osteomyelitis in two, with radio-necrosis in one, and with a deep burn in one case. The cutaneous lesions had been evolving for several years before the cancerous condition was observed (mean: 43 years; median, 45 years; range, 19-68 years). All patients presented erosive ulceration and bleeding on contact (fig. 1 and fig. 2). This ulceration had developed in four out of seven patients from a chronic fistula (case no. 1, 2, 3 and 7). The warning sign for these skin lesions under prolonged treatment was the onset of pain (patients no. 1, 5, 6 and 7) or malodorous symptoms (patients no. 1, 4, 6 and 7). Adenopathies at the thigh root were found in two out of seven patients (Table I) and the histological analysis found malignant lymph node spread in one case (patient no. 2). On x-ray, six patients presented signs of bone invasion with the appearance of evolving osteolysis at the fistula and skin lesions (patients no. 1, 2, 3, 4, 6 and 7) (fig. 3a, fig. 3b and fig. 4a). Systematic biopsy of the lesions provided the diagnosis of malignant degeneration in six out of seven cases. In five patients, a single biopsy sufficed to make the diagnosis and for one patient (no. 7), the diagnosis was made after the second biopsy (the first one had found no signs of malignant degeneration). In one patient (no. 4), whose preoperative biopsy had contributed no information, chronic and fistulized osteomyelitis infectious lesions were resected, with excision passing near the limits of the ulcerated zone. The pathological examination of the excised specimen showed squamous-cell carcinoma, with the excision limits within the healthy zone, except at the bone level where there was superficial invasion requiring new surgery with repeated excision, with no interruption of the bone continuity and the cavity filled with a medial gastrocnemius flap cover associated with a soleus muscle flap cover.
The histological analysis of the excised specimens found five cases of differentiated and mature spinocellular squamous-cell carcinoma and two cases of differentiated and mature verrucous squamous-cell carcinoma.

Conservative treatment was undertaken for all patients; it was based on wide resection of the lesions, resection of infectious lesions (chronic osteitis lesions with soft tissue involvement), and the skin flap cover. After excision, definitive histological analysis of the resection specimen allowed evaluation of the quality of the operation in terms of cancer findings. When contaminated excision was found, after discussion with the multidisciplinary team and the patient, a new operation was indicated with renewed excision or amputation. In three patients (no. 1, 5 and 6), diaphyseal resection was required with stabilization using an external fixator, followed in two cases by a cancellous bone graft (fig. 4c and fig. 4d) (case no. 5 and 6) and in one case a second operation for amputation because of contaminated resection specimens. In five cases, a local posterior sural fasciocutaneous flap with a distal pedicle skin flap was used (in only two cases and associated with other flaps in three cases) and in one patient, a local soleus and medial gastrocnemius muscle flap. In one patient (no. 1), no flap cover was necessary.

**RESULTS**

In three patients, this treatment resulted in complete resection with no recurrence at 2, 3 and 7 years of follow-up (patients no. 5, 6 and 7). In four cases, conservative treatment could not be provided or it failed: failure with resection in two patients (patients no. 1 and 3) and recurrence in two (patients no. 2 and 4), which required amputation in three cases. For these four patients with failure of conservative treatment, two have shown no recurrence after 4 and 10 years of follow-up (patients no. 1 and 3), one patient died (after local and general recurrence of cancer) 2 years after the amputation (patient no. 2), and another presented local recurrence but refused amputation (patient no. 4). Patient no. 2, who had local relapse 3 months after the amputation, had another surgery with inguinocrural gangliectomy. The pathological examination found lymph node metastatic invasion with capsular rupture of two out of three lymph nodes and invasion of the stump by multiple metastases.
secondary lesions. Treatment was completed by nine courses of chemotherapy (cisplatin and 5FU), associated with external radiotherapy of the limb. In all, three patients preserved their lower limb with no current recurrence, two patients underwent amputation and have presented no recurrence to date, one patient presented a local relapse and refused amputation, and one patient died 2 years after amputation, with local relapse and appearance of metastases to the brain (patient no. 2).

DISCUSSION

The age of our patients at diagnosis ranged from 52 to 82 years, for a mean age of 66 years, comparable to the data in the literature on this subject (depending on the series, mean age between 59 and 66 years, ranging from 22 to 86 years) [Gebhart et al. (6), Sankaran-Kutty et al. (7), Mc Grory et al. (9), Look et al. (10)]. This high mean age is explained by the long period of progression necessary for the development of degeneration of chronic wounds and fistulae.

All the patients in the series, who had chronic bone infection, presented unstable scar tissue on fistulae or chronic wounds, which is a classical risk factor for malignant degeneration [Look et al. (10), Arons et al. (11), Swanbeck et Hillstrom (12), Saglik et al. (13)]. In addition, chronic bone infection can itself be considered a risk factor for malignant degeneration in cases of Cierny-Mader type II osteitis [Cierny et al. (14)] in which the bone infection and unstable scar tissue are closely related.

Progression from initial lesions to diagnosis of carcinomatous degeneration is long, on the order of 30 years [Gebhart et al. (6), Sankaran-Kutty et al. (7), Mc Grory et al. (9), Look et al. (10), Arons et al. (11)]. In our series, the mean delay was 43 years, ranging from 19 to 68 years.

<table>
<thead>
<tr>
<th>Patient</th>
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<tr>
<td>Treatment</td>
<td>Diaphyseal resection + external fixator</td>
<td>Resection + posterior sural fasciocutaneous flap</td>
<td>Excision + filling + free flap of the latissimus dorsi + posterior sural fasciocutaneous flap</td>
<td>Bone excision + filling with soleus and medial gastrocnemial flap</td>
<td>Wide resection + posterior sural fasciocutaneous flap + external fixator. D+30: additional fasciocutaneous cover</td>
<td>Diaphyseal resection + posterior sural fasciocutaneous flap</td>
<td>Resection + posterior sural fasciocutaneous flap at 1 month</td>
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<td>Contaminated excision</td>
<td>Local recurrence</td>
<td>Contaminated excision</td>
<td>Local recurrence</td>
<td>Complete excision</td>
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<td>D+18: amputation to lower quarter of thigh</td>
<td>D+30: amputation to lower third of leg + chemotherapy</td>
<td>D+19: amputation to upper third of leg</td>
<td>At 10 months: repeated spongy bone material graft</td>
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<td>Progression</td>
<td>No recurrence at 10 years</td>
<td>Multiple recurrences beginning at 3 months</td>
<td>No recurrence at 3 years</td>
<td>Local tumor recurrence at 10 months</td>
<td>Removal of external fixator at 2 months</td>
<td>Tibia solid at 30 months</td>
<td>No recurrence at 2 years</td>
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<td>Death at 2 years</td>
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<td>Scarring at 4 months</td>
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<td>No tumor or septic recurrence at 3 years</td>
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<td>No recurrence at 7 years</td>
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In the literature, as in our series, Marjolin ulcers in chronic osteitis of the lower limb were clearly dominant [Sedlin and Fleming (3), Gebhart et al. (6), Sankaran-Kutty et al. (7), Mc Grory et al. (9)]. The frequency of ulcerating forms of chronic osteitis of the tibia explains this dominance. In their series, Mc Grory et al. (9) reported 50 cases of squamous-cell carcinoma that developed in chronic osteitis: 44 (88%) were located on the lower limbs (27 of which [54%] were on the tibia), three [6%] on the pelvic girdle, and three [6%] on the upper limbs.

From our observations and the main series published, the following clinical signs of malignant degeneration of a chronic wound were highly suggestive [Sedlin et Fleming (3), Gebhart et al. (6), Sankaran-Kutty et al. (7), Mc Grory et al. (9), Look et al. (10), Saglik et al. (13), Fishman and Parker (15)]: hemorrhagic tendency, bleeding on contact, modification in size, aspect, budding, and malodorous smell generally accompanying a change in the features of discharge or an increase in pain.

The best warning sign was any change in the usual features of the ulcer, in principle well known by the patient and the usual caregiver. However, when the surgeon was consulted at the ulceration stage of chronic osteitis, the recent worsening was a notion that was difficult to assert.

There are no suggestive signs of cancerization on the imaging studies (x-rays, CT, MRI). The images of extended osteolysis can be related to the tumor extension but are also frequently found in cases of chronic bone infections (Fig. 3a, Fig. 3b and Fig. 4a). The changes caused by the infection disturb the interpretation of the imaging studies and limit their value in diagnosis and local staging of cancerous fistulae or chronic ulcerations [Cappello and Donick (16)].

Biopsy is essential for diagnosis. However, false-negative results occur with biopsy if it is done on the edges not affected by degeneration. One of our patients (no. 4) had a fragmented biopsy on the wound’s edges using a curette to take samples during consultation. The biopsied zone had no degeneration and only the complete histological examination of the excised specimen confirmed the diagnosis. The biopsy should include enough material and should be done on any suspected location on the wound for more accurate results [Sankaran-Kutty et al. (7), McGrory et al. (9), Look...
et al. (10), Dereure et al. (17)]. One should not hesitate to renew biopsies and even perform a wide biopsy with anesthesia if no sign of degeneration has been found on a suspect lesion. Indeed, within these chronic inflammatory lesions, it is sometimes difficult for the anatomical pathologist to make a formal diagnosis between pseudoeplitheliomatous hyperplasia and squamous-cell carcinoma [Dereure et al. (17), Wagner and Grande (18)].

The tumors developed on chronic osteomyelitis are generally squamous-cell carcinomas: they account for 94% of the cases in the series studied by McGrory et al. (9). The most frequent histological form is spinocellular squamous-cell carcinoma (five cases out of seven in our series). Two patients in our series suffered from verrucous squamous-cell carcinoma, still called cuniculatum carcinoma, which develops almost exclusively on the foot and has the misleading appearance of a wart [Soong and Hughes (19)]. We did not find these specificities in our observations. They may be more common in Marjolin ulcers that have developed on vascular ulcers.

In the dermatology and oncology literature, the treatment recommended is wide resection including a safety margin several centimeters wide, with the width depending on the size of the tumor and the extent to which it is likely to evolve [Ames and Hickey (20), Barr and Menard (21)]. Radiotherapy, chemotherapy, and immunotherapy are not effective in neoadjuvant treatment and are used instead in palliative situations in forms with metastatic spread [Ryan et al. (22), Ikic and Padovan (23), Edwards et al. (24), Lippman et al. (25), Kirsner and Garland (26), Kirsner et al. (27), Sadat-Ali and Geeranavar (28)].

For many authors, the treatment of choice for Marjolin ulcers in chronic bone infections remains amputation (in approximately 90% of cases) [Gebhart et al. (6), Sankaran-Kutty et al. (7), Mc Grory et al. (9), Saglik et al. (13), Cappello and Donick (16), Dereure et al. (17), Sadat-Ali and Geeranavar (28), Berkwits et al. (29), Fleming et al. (30), Lifeso et al. (31), Bartnicke et al. (32), Blidi et al. (33), Smidt et al. (34)]. In the literature, this has been...

Fig. 4. – Patient no. 6. a) CT view of the bone extension of squamous-cell carcinoma: tumor in contact with a bone modified by chronic infection. b) MRI showing the limits of the tumor but with poor specification of the bone extension. c) Conservative treatment: diaphyseal resection and cancellous bone graft. d) 30 months follow-up: union, no septic or tumor recurrence.
shown to be the surest way to treat both the cancer and the infection.

The place of conservative treatment remains difficult to define and the question is whether amputation can be avoided by wide resection surgery that preserves the limb’s function while still treating the cancer effectively [Sankaran-Kutty et al. (7), Saglik et al. (13), Ueng et al. (35)]. The imperatives of cancer surgery in locomotor system tumors [Enneking (36), Campanacci (37)], and to warn the patient if a new therapeutic orientation is indicated for well-differentiated forms. On the other hand, a poorly differentiated and aggressive form can call for discussion of radical surgery, possibly associated with adjuvant treatment [Sadat-Ali and Geeranavar (28)]. One of the problems is the extension of the resection to include healthy margins. In this series, the margins were evaluated using Enneking’s criteria (Table II). Preoperative planning of the resection limits in cases of Marjolin ulcers in chronic bone infection is particularly difficult and the contribution of imaging (CT, MRI) is very limited [Cappello and Donick (16)]. Extemporaneous histological examination does not seem useful, and may even be dangerous, because it is difficult for the anatomical pathologist to make a definite diagnosis within inflammatory lesions that can closely resemble tumor [Dereure et al. (17), Wagner and Grande (18)]. It seems more reasonable to wait for the definitive examination of the resection specimen, which provides the basis for a multidisciplinary discussion with the anatomical pathologist, and to warn the patient if a new therapeutic orientation is decided upon. Gangliectomy is not indispensable in cases of amputation, but it is warranted if there is persistent adenopathy more than 3 months after amputation, according to Atlay et al. (40). For Sadat-Ali and Geeranavar (28), gangliectomy is indicated when the tumor is aggressive (invasive, poorly differentiated) before neoadjuvant radio-chemotherapy treatment.

Conservative surgical treatment of squamous-cell carcinoma in chronic bone infection presents three technical difficulties: performing wide resection of the lesions, resection of the infectious lesions (chronic osteitis lesions and soft tissue involvement), and the skin flap cover. This treatment is therefore based on wide resection and the principles of surgical treatment of bone infections in continuous bone, associating excision, filling of the resection cavity, and skin flap cover [Lortat-Jacob (41)]. When diaphyseal resection is necessary, stabilization is obtained using an external fixator and a bone graft is associated. Using flaps makes it possible to fill in the excision zone and cover it with skin. In our experience, in the lower half of the leg, the posterior sural fasciocutaneous flap with a distal pedicle is highly reliable and was used in five cases out of seven in this study. Of these five cases, three flaps provided complete cover with sparing per primam (patients no. 5, 6 and 7) and in two cases, amputation was performed later because of cancer recurrence (patients no. 2 and 3). This posterior sural fasciocutaneous flap with a distal pedicle can be used alone or associated with other flaps (patients no. 3, 5 and 7). The microanastomosed free flap of the latissimus dorsi is reserved for very extensive loss of substance.

Amputation remains a very important option in treating Marjolin ulcers, lesions that are rarely discovered at the initial stage with little progression. One must take into account the function that would be restored if the limb were saved after conservative surgery, with sometimes long aftereffects, and weigh this with the rapid return to function that a prosthesis on a stump in good condition after radical surgery would give. In addition, the patient should be informed that a complex conservative surgical program with resection, bone reconstruction, and grafted covering measures does not protect from recurrence that could require secondary amputation (four cases out of seven in our experience).

The overall prognosis for Marjolin ulcer is evaluated in the literature at 65%-75% for 3-year survival [Gebhart et al. (6), Mc Grory et al. (9), Saglik et al. (13), Fleming et al. (30), Grenier et al. (42)]. It is clearly better for well-differentiated squamous-cell carcinomas, the most frequent, than for other pathological types that are less well differentiated. For the same histological type, the only factor that we are sure will influence the prognosis is distant metastasis to the lymph nodes or the viscera, which lowers the 3-year survival rate to 35%-50% [Gebhart et al. (6), Mc Grory et al. (9), Fleming et al. (30)]. No study has demonstrated that survival is improved by adjuvant treatments at the palliative stage.

Preventing Marjolin ulcers from developing in chronic osteitis requires proper care of bone infections. Open bone graft techniques and wound closure by secondary intent should be abandoned in favor of therapeutic programs that immediately include skin covering. Enormous progress has been made in more than 20 years in the knowledge and use of local fasciocutaneous flaps of the lower limb. These are essential in the treatment of chronic osteitis, since they provide per primam wound healing with good-quality tissues and thus avoids chronic wounds with unstable, fragile, and crumby scar tissue, which can form the basis of the bed of squamous-cell carcinoma.

References

