Squamous-cell carcinoma and osteomyelitis: three cases and a review of the literature
À propos de 3 cas et revue de la littérature
Épithéliomas épidermoïdes et ostéomyélites chroniques
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RÉSUMÉ
Les ostéites chroniques associées aux carcinomes épidermoïdes représentent une pathologie qui reste rare mais classique. Nous rapportons 3 cas d’ostéite chronique du tibia compliquant un traumatisme ouvert de jambe. Au cours de leur surveillance, après modification des signes locaux secondaire à une période de latence de plusieurs dizaines d’années, des biopsies ont permis de faire le diagnostic de dégénérance carcinomatose. Le bilan d’extension loco-régional et général réalisé à la recherche d’éventuels autres foyers septiques et de métastases était négatif. Tous nos patients ont été traités par amputation avec de bons résultats précoces.
À partir de cette courte série, une revue de la littérature est réalisée permettant de dégager les principaux caractères épidémiologiques et diagnostiques, et d’insister sur les signes précoces d’alerte. La conduite à tenir n’est pas encore consensuelle, même si l’amputation, signe d’échec pour certains, est repoussée au-delà des limites du raisonnable.
Mots clés : Carcinome épidermoïde, ostéomyélite chronique, amputation.

ABSTRACT
Chronic osteitis and squamous-cell carcinoma is a rare but classically described association. We report three cases of chronic tibial osteitis which developed into an open leg wound. During the monitoring, after a latency period of several years, local signs developed: biopsy provided the diagnosis of degenerative carcinomatosis. The search for locoregional extension or metastatic dissemination was negative. All three patients underwent amputation with good results.
This small series, together with a review of the literature, enabled us to describe the principle epidemiological and diagnostic features, focusing on early signs. The appropriate management scheme remains to be determined, although amputation, which some may consider a failure, should not be postponed indefinitely.
Key words: Squamous cell carcinoma, chronic osteomyelitis, amputation.

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INTRODUCTION

The onset of squamous cell carcinoma is a classical complication in the course of chronic osteomyelitis [Devas (1), Giunti and Laus (2), McGrory et al. (3)]. This complication is very rare (only a few dozen cases have been described in the literature) and occurs late (after several years of latency). Many other histological types can be observed but squamous cell carcinoma dominates.

Progression is marked by a long history of chronic osteomyelitis with acute infectious flare-ups. The histopathogenesis remains unknown even though a chronic irritation associated with local inflammatory factors seems to be the source of the malignant transformation [Caron and Bonvalet (4)].

Through a study of three cases treated in our department, we propose to review the main characteristics of this complication, emphasizing the early signs that should bring to mind its appearance.

OBSERVATIONS

Three cases of malignant degeneration in chronic osteomyelitis have been observed in our department over the last 25 years. All three cases involved a serious injury to the leg complicated by osteomyelitis, finally treated by amputation.

Case no. 1

Mr. A., born in 1925, presented in 1945 with a Gustillo IIIB-type open fracture in the lower third of the tibia. In 1946–1947, osteitis appeared and was treated by a first Papineau-type operation with good initial results, but requiring retreatment around 1950. This osteitis was then contained through long-term antibiotic therapy associated with local care. In 2000, after hospitalization in the infectious diseases unit, effective antibiotic therapy was set up, but with recurrence of the infectious process as soon as treatment was stopped. This patient was treated in our department beginning in November 2001. At that time, he presented a deep cutaneous fistula that was unclean, malodorous, with major osteolysis progressing rapidly associated with periostium apposition extending to the upper metaphysis of the tibia (fig. 1a and fig. 1b). Leukocyte-marked scintigraphy found an infectious process located in the lower third of the tibia (fig. 2). Conservative treatment with necrosectomy and sequestrectomy (preserving tibial continuity) was provided. The pathological examination during surgery found infiltrating squamous-cell carcinoma. Locoregional CT-scan staging and then general staging were done. The leg was amputated to the upper third of the tibia with healthy margins. Postoperative monitoring showed good results and the patient is healthy after 3 years of follow-up.

Case no. 2

Mr. D., born in 1928, was wounded in 1962 in the Algerian war. He presented a serious ballistic injury of the left leg with loss of bony and soft-tissue substance, classified Gustillo IIIB. He received emergency wound care and orthopedic treatment for his fracture followed early by iliac corticocancellous bone autograft and skin grafts. He was treated in our department beginning in 1983: given the persistent signs of deep suppuration, a curettage with skin graft was performed. During the following 10 years, the patient received local treatment, since surgery was contraindicated because of a consequential history (alcoholic cirrhosis complicated by recurring decompensation with the appearance of edema and ascites). At the beginning of 1994, a budding and bleeding nodule appeared in the upper part of the leg where skin had been lost (fig. 3). The biopsy done at this time provided the diagnosis of well-differentiated spinocellular carcinoma. Locoregional staging with MRI found multilobed mass syndrome extending from the tibial diaphysis to the skin level. General staging was negative. A radical transfemoral amputation of the left leg was performed with simple operative results. Mr D. died of a recurrence of decompensation from his cirrhosis in December 1994.

Fig. 1. – Case no. 1. a) Standard front and lateral x-rays of the leg in June 2000. b) Major osteolysis with rapid aggravation of the tibia in the same patient 1 year later.
Case no. 3

Mr. L., a mason born in 1945, fell from a ladder in a work accident in 1968. He presented an open Gustillo IIIB fracture of the leg, which was treated conservatively. Beginning in 1970, infectious phenomena with torpid progression appeared. The patient was treated in our department beginning in 1996. At this time, an 8-cm bony sequestrum in the area of a cutaneous fistula that had been treated locally for several years was found. We decided to treat the osteitis with a Papineau-type procedure in two sessions, with good initial results. However, signs of local infection (abscess) reappeared, which motivated a series of surgical cleanings of the skin and ablation of the necrotic zones, which were then covered by transfer of the medial gastrocnemius head.

In March 1999 during a fall, he presented a fracture of the changed and infected bone with recurrence of infectious discharge. We decided to resect a large fragment of infected and necrotized bone and placed an external fixator to compensate the bone defect using the elevator technique. However, a fistula with discharge persisted. Six months later, pain associated with an abscess and healing problems reappeared. Surgical cleaning was undertaken. The biopsies found a major inflammatory infiltrate with no formal sign of malignity. Corticotulle bandages were put in place. In June 2000, we observed a fulminating budding formation in the upper part of the wound (fig. 4). X-rays (fig. 5a and fig. 5b) showed osteolysis within the treated bone tissue. New biopsies diagnosed well-differentiated microinfiltrating squamous-cell carcinoma. A transfemoral amputation was decided on.
after negative staging. The results of the operation were good and the patient was in good health 4 years later.

**DISCUSSION**

The relations between chronic osteomyelitis and squamous-cell carcinoma have appeared in the literature for more than 150 years. Hawkins was the first to describe this clinical picture in 1835. In 1828, Marjolin reported on the malignant degeneration of a leg ulcer, and since then many authors have called these malignant transformations of chronic osteitis Marjolin ulcer. These malignant transformations have also been described in varicose ulcers, chronic bursitis, burns, anal fistulae, etc. [Arons et al. (5)]. The two largest series in the literature are the Mayo Clinic series (53 cases) [McGrory et al. (3)] and the Rizzoli Institute series (39 cases) [Giunti and Laus (2)], which has allowed some data analysis.

It is difficult to assess the frequency of this disease, estimated between 0.2% and 1.7% depending on the series [McGrory et al. (3), Gebhart et al. (6), Fitzgerald et al. (7)]. These squamous-cell carcinomas are only an infinitesimally small share (0.05%) of the squamous-cell carcinomas that develop in the lower limbs [Sedlin et Fleming (8)]. The male predominance is higher than 85%. Age at diagnosis is between 50 and 60 years (range, 22–80 years). The lesions are located in the lower limbs in 89% of cases, mainly in the legs (tibia: 61%, femur: 19%, foot: 8%, notably in the calcaneum). The upper limbs are involved in 7% of cases, and the axial skeleton in 4%. The etiology of chronic osteomyelitis is highly variable: hematogenic (50%), injury with open fractures (41%), neighboring cutaneous wound (3%), and unknown causes (6%). The proportion of cases of osteomyelitis of hematogenic origin is tending to decrease today, with more posttraumatic osteitis cases because of the axial skeleton in 4%. The etiology of chronic osteomyelitis is highly variable: hematogenic (50%), injury with open fractures (41%), neighboring cutaneous wound (3%), and unknown causes (6%). The proportion of cases of osteomyelitis of hematogenic origin is tending to decrease today, with more posttraumatic osteitis cases because of the increasing number of open fractures accompanying more and more violent accidents. The bacteria found comprise a highly polymorphic flora, frequently with Gram-positive cocci (Staphylococcus aureus and epidermidis, Streptococcus, Enterococcus, etc.), but also Gram-negative bacillus (Pseudomonas aeruginosa, etc.) and anaerobic bacteria (Bacteroids, etc.). Manale and Brower (9) noted that the carcinomatous transformation may go along with a modification in the flora: the Gram-positive bacteria initially present (staphylococci frequently found in the systematic samples taken in open fractures) may be replaced by mixed flora with a predominance of Gram-negative bacteria (Proteus, Pseudomonas, Klebsiella, etc.).

There is a long period of latency between the diagnosis of osteomyelitis and the diagnosis of squamous-cell carcinoma: a mean 37 years (range, 10–70 years) [Sedlin and Fleming (8), Sankaran-Kutty et al. (10), Ziets et al. (11)]. Despite the rarity of this clinical entity, the history of the disease is quite stereotypical. A long history of infection is observed, alternating acute and chronic episodes of suppuration motivating multiple attempts at conservative treatment (curettage, lavage, placement of gentamicin sponges, bone grafts, skin grafts, etc.) followed by long periods of local treatment with repeated bandaging (frequently using anti-septic products that are potentially irritating: polyvidone iodine, hexamidine, eisin, boric acid, etc.). The succession of a long line of care givers in the patient’s treatment is also a cause of very late diagnosis, several months or even several years after the wound has become cancerous. The need for a “police interrogation” must be stressed so as to analyze the clinical history as accurately as possible, to study all the paraclinical data (radiographic, bacteriological, and pathological), and to identify all the treatments that have already been given. In 1953, Rowlands (12) described a triad associating increasing pain, purulent discharge, and hemorrhage. This triad is rarely observed. Any modification or exacerbation of local symptoms, notably after sNSeveral years of stable symptoms, should raise the suspicion of a malignant transformation. True warning signs do exist: recently appearing or increasing pain, ready bleeding, and appearance of an induration or a palpable mass. A foul-smelling odor can mean a change in the local flora, which can be confirmed by repeated bacteriological sampling. Other radiographic signs should attract attention: images of pathological fracture and lysis that progress rapidly. With only one of these signs, several surgical biopsies should be taken for a pathological examination that will provide a definite diagnosis. The biopsies must be taken widely and in tiers, in both superficial and deep tissues along the entire trajectory of the fistula in order to prevent false-negative results [Dereure et al. (13)].

The etiological factors are not perfectly known. Local and general factors can be distinguished. For Caron and Bonvalet (4), any chronic inflammatory cutaneous lesion can be the source of an squamous-cell carcinoma. In cases of chronic osteomyelitis, the inflammation is maintained by an irritation that can be exogenous (irritating products used during repeated bandaging or multiple surgeries that can accelerate degeneration) [Leis et al. (14)], but also endogenous (disability of foreign bodies — war wounds — and local infection that has not been eradicated with antibiotic therapy). This inflammation is the cause of high local concentrations of growth factors that can induce cellular events of malignant transformation. General factors such as a reduction in immune defenses (exogénosis, cirrhosis, diabetes, etc.) can also be blamed. A highly reactive epithelium can be found, which is hyperplastic with a great number of atypical mitotic cells. A continuum exists between the different stages of this transformation: simple hyperplasia with no cellular atypia, then the appearance of neoplastic atypias corresponding to in situ carcinoma before the invasive carcinoma stage after a more or less long period of time [Caron and Bonvalet (4)]. The pathological examination is difficult because tissue that is highly modified by chronic infection is observed, and these are polymorphic tumors [Giunti et Laus (2), McGrory et al. (3)]. In 94% of cases, well-differentiated spinocellular
squamous-cell carcinoma is most often found [Devas (1), McGrory et al. (3), Fitzgerald et al. (7), Sedlin and Fleming (8), Rowlands (12), Lifeso et al. (15), Hejna (16), Johnson and Kempson (17)]. Many other histological types have been described. Epithelioma cuniculatum is a slow-growing carcinoma and a locoregional malignancy that rarely progresses to lymph node invasion [Kao et al. (18)]. It consists of well-differentiated and keratinizing epithelial metastasis with no atypia, and it is malignant only when the epithelial layers are invaded [Grenier et al. (19)]. Pseudo-epitheliomatous hyperplasia presents as a nonkeratinizing tissue made up of epithelial bands with no neoplastic atypia [Warter et al. (20)]; this is a pseudocarcinomatous lesion but risks malignant transformation [Johnson and Kempson (17)]. Different series have also reported fibrosarcomas [McGrory et al. (3), Dereure et al. (13), Denham and Dingley (21), Akbarian et al. (22), Morris and Lucas (23)] or other sarcomas: osteosarcoma, reticulosarcoma [Lidgren (24)], angiosarcoma [Johnston and Miles (25)], rhabdomyosarcoma [Johnston and Miles (25)], and exceptionally a lymphoma [McGrory et al. (3)] or even myeloma [Baitz and Kyle (26)].

Treatment of squamous-cell carcinomas that complicate the progression of chronic osteomyelitis should aim for two objectives so as to prevent recurrence: treat the tumor and the infection. Only surgery is effective and there is little place for other treatments such as radiotherapy or cryotherapy (cyclical application of liquid nitrogen), which are reserved for patients who are not eligible for surgery. Staging is done once the definite diagnosis is established. Staging is first local using MRI, which evaluates bone and soft tissue invasion by the infectious and tumoral processes. It defines the level of resection or amputation. Leukocyte-marked scintigraphy looks for other septic locations. Regional staging looks for adenopathies that need to be biopsied to differentiate metastatic lymph node invasion of a reactionary adenopathy, which is banal in this chronic septic context. The rest of staging is completed by a chest x-ray and abdominal ultrasound (or spiral CT of the thoracoabdominal region) looking for distant metastases.

Therefore, treatment is most often radical amputation surgery, treating both the tumoral and infectious processes. However, conservative surgical alternatives have been suggested [Ueng et al. (27), Weiland et al. (28)]. They associate bone and soft tissue reconstruction in one or several operations. These are heavy and long procedures reserved for selected patients (no regional extension, good general health) [Ueng et al. (27)] and are associated with fairly high failure and complication rates [Weiland et al. (28)]. The functional results are sometimes disappointing. Resection of the tumor and the osteitis must be wide to prevent possible local recurrence [Atkins et al. (29), Saglik et al. (30)]. In case reconstruction fails or the problem recurs, amputation can be performed [Weiland et al. (28), Atkins et al. (29)]. An extemporaneous pathological examination of the edges of the resection can be useful for locations close to the pelvic girdle or on the axial skeleton. For these locations that require delicate reconstruction, some authors use cryotherapy [Gebhart et al. (6)] to widen the resection margins after surgical excision. Others prefer adjuvant radiotherapy. If there is lymph node invasion, amputation may itself be insufficient because it does not cure the tumoral disease requiring lymph node removal, which is not systematic when there is no documented invasion. The lymph node areas must be carefully monitored. Persistence of adenopathies more than 3 months after surgery calls for excision. Adjuvant radiotherapy is therefore recommended by some authors [Fitzgerald et al. (7), Mabit et al. (31)].

The frequency of local recurrence is not insignificant (15% in the Mayo Clinic series) [McGrory et al. (3)] and is highly dependent on the quality of the initial treatment, hence the importance of a rigorous staging and oncologic enquiry. A total of 15%–30% of metastases are found [Fitzgerald et al. (7)], despite the reputation for a low incidence of malignity in squamous-cell carcinomas complicating chronic osteomyelitis. They show up 18 months to 3 years after surgery [Sedlin and Fleming (8)] and are most often located in the liver or the lungs. When sarcomatous degeneration is found, the metastasis rate increases to 60% of cases. Regular clinical and radiological monitoring is therefore necessary. The prognosis is rather good for the tumoral disease, and the patient can be considered as cured when there is no local recurrence or metastases 3 years after surgery. The prognosis is more reserved for localized squamous-cell carcinomas in the limbs, with only 31% 5-year survival [Lifeso and Bull (32)]. Nevertheless, 39% of patients die of an intercurrent pathology and 17% of another neoplasia (ENT, digestive system, etc.) [McGrory et al. (3), Fitzgerald et al. (7)], with frequent onset in these high-risk patients.

CONCLUSION

Squamous-cell carcinoma remains exceptional as a complication of chronic posttraumatic osteomyelitis, with a very late onset in the progression of the disease. It most often affects men around 60 years of age with a long history of chronic osteitis of the leg. It is our duty to not misjudge this complication by suspecting it when local signs are modified. This requires preforming multiple biopsies. Surgical treatment is most often amputation. The chances for cure in our series, as in the literature, are better if we remain attentive to this late complication. This diagnosis, although rare, should be suggested.

References

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