



Original article

Malignant transformation in chronic osteomyelitis[☆]



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ABSTRACT

Introduction: Carcinomatous degeneration is a rare and late complication developing decades after the diagnosis of chronic osteomyelitis.

Objectives: To present the results from a retrospective study of six cases of squamous cell carcinoma arising from chronic osteomyelitis.

Methods: Six cases of chronic osteomyelitis related to cutaneous squamous cell carcinoma were identified. The cause and characteristics of the osteomyelitis were analyzed, as well as time up to malignancy, the suspicion signs for malignancy, the localization and histological type of the cancer, and the type and result of the treatment.

Results: The mean time between osteomyelitis onset and the diagnosis of malignant degeneration was 49.17 years (range: 32–65). The carcinoma resulted from tibia osteomyelitis in five cases and from femur osteomyelitis in one. The pathological examination indicated cutaneous squamous cell carcinoma in all cases. All the patients were staged as NOM0, except for one, whose lombo-aortic lymph nodes were affected. The treatment consisted of amputation proximal to the tumor in all patients. No patient presented signs of local recurrence and only one had carcinoma metastasis.

Conclusion: Early diagnosis and proximal amputation are essential for prognosis and final results in carcinomatous degeneration secondary to chronic osteomyelitis.

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Transformação maligna na osteomielite crônica

RESUMO

Introdução: Degeração carcinomatosa é uma complicação rara e tardia que se desenvolve décadas após o diagnóstico de osteomielite crônica.

Objetivos: Apresentar os resultados de um estudo retrospectivo de seis casos de carcinoma espinho-celular em um contexto de osteomielite crônica.

Palavras-chave:

Osteomielite

Tumores malignos

Carcinoma de células escamosas

Transformação celular neoplásica

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Métodos: Identificamos seis casos de carcinoma espinocelular relacionados à osteomielite crônica. A causa e as características da osteomielite foram analisadas, bem como o tempo decorrido até transformação maligna, os sinais de suspeita de malignização, a localização e o tipo histológico do câncer e o tipo e os resultados do tratamento.

Resultados: O tempo médio entre a causa da osteomielite e o diagnóstico da transformação maligna foi de 49,17 anos (intervalo: 32 a 65). O câncer teve origem em osteomielites da tibia em cinco casos e em uma osteomielite do fêmur em um caso. A análise histológica demonstrou carcinoma espinocelular cutâneo em todos os casos. Todos os pacientes foram estadiados como N0M0, com exceção de um que apresentava atingimento dos gânglios linfáticos lomboaórticos. O tratamento foi a amputação proximal ao tumor em todos os pacientes. Nenhum dos pacientes apresentou sinais de recidiva local e apenas um desenvolveu metastização do carcinoma espinocelular.

Conclusão: O diagnóstico precoce e a amputação proximal ao tumor são fundamentais para o prognóstico e os resultados finais na transformação maligna secundária a osteomielite crônica.

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Introduction

Chronic osteomyelitis is a long-lasting and persistent bone infection caused by complex colonies of microorganisms involved in a matrix of proteins and polysaccharides, the biofilm, which protects them from the body's immune system and the action of antibiotics.^{1,2} This condition can have an hematogenous origin, by contiguity to a focus of infection or by direct inoculation.¹ Unlike hematogenous osteomyelitis, the incidence of osteomyelitis contiguous to a focus of infection originating from trauma, surgery, or implants has increased.³

Non-treatment of acute osteomyelitis, or treatment failure, associated with important lesions of the surrounding soft tissues, poor bone vascularization, systemic involvement, and multiple and resistant microorganisms leads to a chronic and refractory bone infection, whose constant inflammatory activity causes bone destruction and may favor the development of neoplasias.^{1,3} The incidence of malignant transformation in the setting of chronic osteomyelitis is very low in developed countries; nonetheless, it remains a major problem in countries with poor health care.¹

Parasitic infection and its effect on stem cell signaling is one of the oldest theories of cancer origin.^{4,5} Currently, it is accepted that the association of chronic infection and development of malignancies may be underestimated.⁵ Some authors acknowledge that over 25% of malignant neoplasms may originate from chronic inflammation and infectious agents. There is a considerable body of evidence for some of these associations, such as between *Salmonella typhi* and hepatobiliary carcinoma; *Opisthorchis viverrini* and *Clonorchis sinensis* and cholangiocarcinoma; *Schistosoma hematobium* and bladder cancer; and between hidradenitis suppurativa and cutaneous squamous cell carcinoma, among others.^{5,6}

The exact mechanism of malignant transformation remains unknown. It is assumed that, in a multifactorial manner, the chronic inflammatory state behaves as a promoter in the complex process of carcinogenesis.^{1,6} Malignant

transformation begins in the skin or epithelium of the fistula and infiltrate the adjacent tissues, including bone.^{7,8} The prevalence of malignant transformation in the setting of chronic osteomyelitis ranges from 1.6% to 23%, and the most commonly affected bones are the tibia and femur. The most frequently observed malignant transformation is squamous cell carcinoma of the skin.^{1,5,9,10} The increase in fistulous drainage, as well as persistence, exophytic growth of an ulcer or mass can be warning signs for malignant transformation.^{1,11} All patients with ulcers and fistulas associated with chronic osteomyelitis should be frequently and carefully followed-up, and any characteristic alterations in a chronic wound should raise the suspicion of malignant transformation.^{8,12} Diagnosis is confirmed through biopsies, which should be performed early in multiple locations and depths, including ulcers, fistulas, and bone, in order to increase diagnostic accuracy and reduce the number of false negatives.^{10,12,13} When malignant transformation is diagnosed, it is essential to stage the neoplastic disease and to assess the presence of distant metastases through studies by computerized tomography, magnetic resonance imaging, and positron emission tomography.¹²

The definitive and most frequently used surgical treatment in these situations, considering that the majority of patients have advanced disease, is the proximal amputation of the neoplasia.^{7,10} Adjuvant chemoradiotherapy is indicated in metastatic disease and high-grade tumors.¹⁴ In selected patients without metastatic disease, limb-sparing extended tumor excision with limb salvage may be chosen.¹

The main prognostic factor is the staging of the neoplastic disease.^{8,10} In most cases, chronic osteomyelitis in squamous cell carcinomas is aggressive, with high levels of local recurrence and metastasis. Metastasis is observed early (in most cases, in the first 18 months after malignant transformation) and is mainly located in the lymph nodes.¹⁵ However, if the patient does not present metastatic disease during the first three years and the tumor lesion has been excised correctly, prognosis is favorable.¹⁵ Early diagnosis and aggressive treatment of the malignant transformation of



Fig. 1 – Patient LMM. (A) Radiography with signs of chronic osteomyelitis of the tibia; (B) Malignant transformation of ulcer into squamous cell carcinoma.

chronic osteomyelitis are critical to the prognosis and final results.¹ The most effective method of preventing the onset of these malignancies is appropriate and definitive treatment of chronic osteomyelitis, debridement, and antibiotic therapy.

Material and methods

A retrospective analysis of patients diagnosed with malignant transformation in chronic osteomyelitis was performed. The evaluation was made through the clinical records and consisted of an analysis of the etiology of chronic osteomyelitis and its characteristics, time elapsed until diagnosis of malignant transformation and reasons that led to its diagnosis, cancer location and histological type, and surgical treatment performed and its results.

Results

The authors present a series of six patients diagnosed with malignant transformation of chronic osteomyelitis (Table 1). All patients were male. It was observed that, in two thirds of the sample, chronic osteomyelitis originated from a trauma that had occurred at an early age, while the other third was associated with a hematogenous cause resulting from unspecified childhood infections. All traumatic causes of osteomyelitis were open fractures of the lower limb, with the exception of one patient whose trauma could not be ascertained. For all patients, the leg was the affected anatomical site, and the tibia was the most affected bone. In one patient, although osteomyelitis reached the leg bones, it had originated from an open fracture of the femur; patient developed a late chronic ulcer in the leg that later became malignant. In 83.33% of the patients, the cause of osteomyelitis occurred in childhood, while one patient had the initial trauma at 39 years of age. In all patients, the evolution from osteomyelitis

to malignancy occurred over decades, with a mean interval of 49.17 years (minimum of 32 and maximum of 65).

The persistent presence of a chronic ulcer was the red flag sign for all patients in this series. Other signs of suspected malignant transformation were also identified: in one patient, there was also an increase in the intensity of purulent fistulous drainage; in another, a recent increase in ulcer dimensions (Figs. 1–4). *Staphylococcus aureus* was detected in all microbiological analyses, *Pseudomonas aeruginosa* was present in two patients, and *Proteus mirabilis* in one patient. Pathological tibial fracture, which is one of the complications of chronic osteomyelitis, was also observed in two patients (Fig. 4).

Cutaneous squamous cell carcinoma was the type of neoplasia observed in all the patients in the sample. In 83.33% of the patients, no signs of metastasis were detected; in turn, one patient presented imaging data suggesting lumbar-aortic lymph node involvement. Although the initial staging corresponded to N0M0, a lytic lesion in the proximal portion of the contralateral femur was observed in one patient after five months, and later was diagnosed as a metastasis originating in squamous cell carcinoma.

The therapeutic choice for all patients was limb amputation surgery, notably amputation of the distal third of the thigh. In the patient with chronic osteomyelitis of the femur and invasion of the lumbar-aortic lymph nodes, disarticulation of the hip and the necessary lymphadenectomy would require a hemipelvectomy. However, due to the inherent risks of this surgery and the difficulty to achieve skin coverage, the authors decided against it, and thus a palliative amputation was performed through the distal third of the thigh. None of the patients developed local recurrence.

All patients in the sample, but one, died. However, the cause of death was related to the malignancy of osteomyelitis in only one patient, while in all others death was caused by other associated diseases. Survival after diagnosis of neoplasia was 3.8 years, with a minimum of eight months and a

Table 1 – Patient series.

Patient	Cause of the osteomyelitis	Affected bone	Age of the patient at osteomyelitis onset (years)	Time elapsed until neoplastic diagnosis (years)	Sign of suspected neoplastic lesion	Infectious agents	Type of neoplasia	Degree of metastasis in the initial staging	Treatment	Survival after the diagnosis of neoplasia (years)	Age (years) at the time of death and cause
JMB, ♂	Open femoral fracture	Femur + Tibia, fibula	7	65	Ulcer unresponsive to treatment and increased fistulous drainage	<i>Staphylococcus aureus</i> and <i>Proteus mirabilis</i>	Cutaneous squamous cell carcinoma	Lymph-aortic lymph nodes (N1M0)	Amputation of the distal third of the thigh	8	80 (stroke)
LMM, ♂	Hematogenic after unspecified infection	Tibia	6	57	Ulcer non-responsive to treatment	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i>	Cutaneous squamous cell carcinoma	No (N0M0)	Amputation of the distal third of the thigh	Currently alive	–
JLF, ♂	Hematogenic after unspecified infection	Tibia	7	62	Ulcer non-responsive to treatment and recent growth	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i>	Cutaneous squamous cell carcinoma	No (N0M0)	Amputation of the distal third of the thigh	2	71 (stroke)
AJS, ♂	Open fracture and leg slough	Tibia	6	43	Ulcer non-responsive to treatment	<i>Staphylococcus aureus</i>	Cutaneous squamous cell carcinoma	No (N0M0)	Amputation of the distal third of the thigh	7	56 (acute myocardial infarction)
SCL, ♂	Unspecified local trauma	Tibia	10	32	Ulcer non-responsive to treatment	<i>Staphylococcus aureus</i>	Cutaneous squamous cell carcinoma	No (N0M0)	Amputation of the distal third of the thigh	1	43 (chronic kidney disease)
AVS, ♂	Open tibial fracture	Tibia	39	36	Ulcer non-responsive to treatment	<i>Staphylococcus aureus</i>	Cutaneous squamous cell carcinoma	No (N0M0) The patient later developed metastasis	Amputation of the distal third of the thigh	0.5	75 (metastatic dissemination of squamous cell carcinoma)

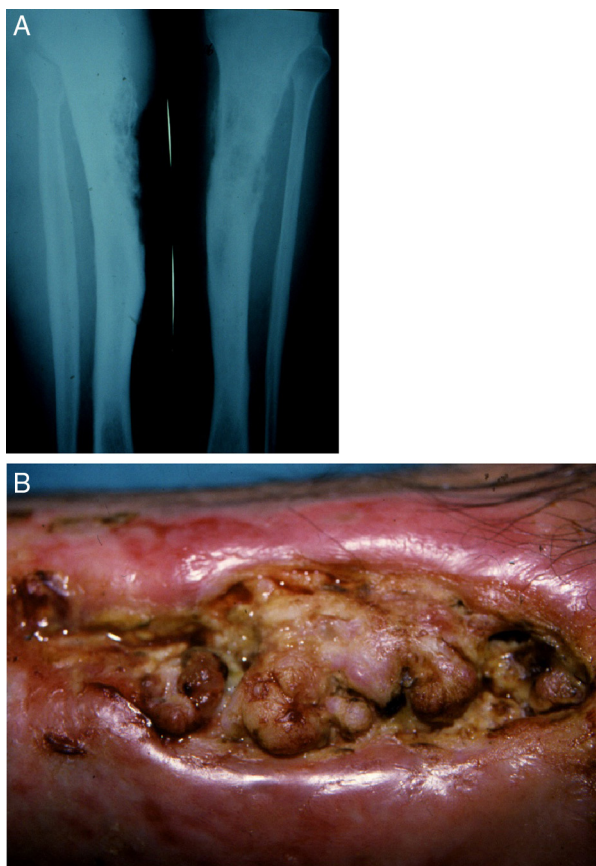


Fig. 2 – Patient JLF. (A) Radiography with signs of chronic osteomyelitis of the tibia; (B) Malignant transformation of ulcer into squamous cell carcinoma.

maximum of six years. The patient with concomitant chronic osteomyelitis of the femur presented infection of the amputation stump, which required surgical cleaning of the femur (Fig. 5).

Discussion

Studies in the English literature on malignant transformation in the setting of chronic osteomyelitis are scarce, consisting primarily of isolated clinical cases.¹ Only two articles were case series: one with six and another with seven patients.^{1,7,10} Therefore, this series is one of the first to analyze a series of patients diagnosed with malignant transformation in the context of chronic osteomyelitis.

The prevalence of males is in agreement with the literature.¹ In the present series, most cases of chronic osteomyelitis had trauma as their cause. Trauma remains the most frequent cause of osteomyelitis; open fractures of the long bones are associated with infection rates of 4–64% and infection recurrence rates of 20–30%.^{9,10,16,17} The tibia is the most commonly affected bone, followed by the femur, which is in line with the findings from other series.^{1,5,9,10}

Studies in this area demonstrated that the presence of chronic osteomyelitis with years or decades of evolution is the most important factor for malignant transformation; the interval from osteomyelitis diagnosis to malignancy ranges from 18 to 72 years.^{1,10,12} In all patients in this sample, an interval of decades was observed between osteomyelitis diagnosis and development of malignancy. The main sign of suspected malignant transformation was the persistence of an atonic ulcer that did not respond to treatment, followed by a recent enlargement of the ulcer and increased drainage. The most frequent symptoms that raise suspicion of malignant transformation are increased drainage, lack of lesion improvement



Fig. 3 – Patient AJS. (A) Radiography with signs of chronic osteomyelitis of the tibia and signs of lead remnants from the bullet that caused the original slough; (B) Malignant transformation of ulcer into squamous cell carcinoma.

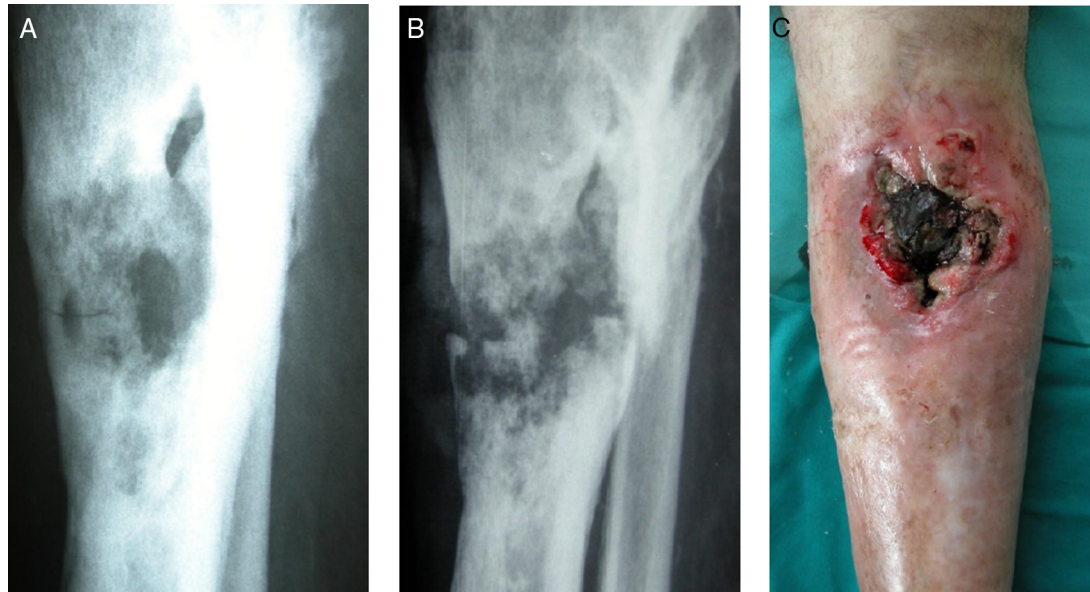


Fig. 4 – Patient AVS. (A) Radiography with signs of chronic tibial osteomyelitis, pathological fracture; (B) Non-consolidation after six weeks; (C) Malignant transformation of ulcer into squamous cell carcinoma.

after three months of treatment, followed by increased or exophytic lesion, erythema, hemorrhage, lymphadenopathy and, less frequently, hyperkalemia, weight loss, anorexia, and hyperpigmentation of the surrounding skin.¹ In agreement with other studies, *S. aureus* was the most frequently detected microorganism.¹ The most frequently observed malignancy in chronic osteomyelitis is cutaneous squamous cell carcinoma, which was the only neoplastic histological type identified in the present study.^{1,5,9,10}

As mentioned in the introduction, squamous cell carcinomas in the context of chronic osteomyelitis are usually

aggressive and have high levels of local recurrence and early metastasis.¹⁵ Despite these data, in the present study, tumors showed no signals of metastatic disease at the moment of diagnosis in 83.3% ($n=5$) of patients. All six patients in the study by Alami et al.⁷ were staged as NOM0. In contrast, out of the seven patients in the study by Altay et al.,¹⁰ three were at the NOM0 stage; two, N1M0; one, N1M1; the other died prior to the staging. One of the patients in the present study, staged as NOM0, developed bone metastases within five months. These data point to the need for vigilance and assiduous monitoring of these cases, including those staged as

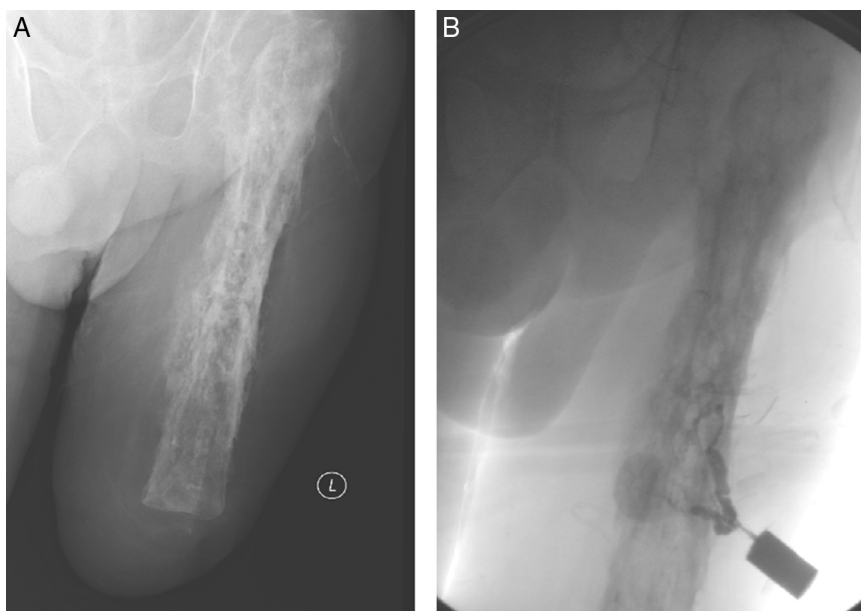


Fig. 5 – Patient JMB. (A) X-ray at six years after thigh amputation, with radiographic signs of femoral osteomyelitis; (B) Fistulography demonstrating fistula in posterior and upward direction, extending for about 6.5 cm in communication with the medullary canal of the femur.

NOMO, due to the precocity and rapidity of metastatic dissemination.

Amputation proximal to the lesion is a surgical treatment that resolves not only the neoplastic lesion but also the chronic osteomyelitis; it is the gold standard for malignant transformations of osteomyelitis. In all patients of this sample, an amputation was performed through the distal third of the thigh; no cases of local recurrence were observed. Mean survival after diagnosis of the neoplasia was only 3.8 years. This can be explained by the fact that four of the five patients died due to other associated diseases, not due to malignancy of osteomyelitis or to the surgical procedure performed (Table 1). Interestingly, the patient with the longest survival (eight years) was the one who underwent palliative amputation through the thigh and who presented concomitant chronic osteomyelitis of the femur as well as suspected lumbar-aortic lymph node involvement. The need for regional lymphadenectomy remains controversial, as the increase in lymph node size is often only reactive to inflammation.¹⁰ However, it is now thought that if the signs of lymphadenopathy persist six to 12 weeks after amputation, their surgical removal is required.^{10,11} In the aforementioned case, the lumbar-aortic adenopathies were probably reactive, rather than caused by metastatic disease, allowing the patient to survive for eight years after the diagnosis of squamous cell carcinoma.

Conclusion

Malignant transformation is a rare and late complication of chronic osteomyelitis, whose clinical signs of suspicion must be identified early. Early diagnosis by means of biopsies and aggressive treatment of these lesions are fundamental for the prognosis and final results.

Conflicts of interest

The authors declare no conflicts of interest.

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