



## Original article

# Malignant transformation in chronic osteomyelitis<sup>☆</sup>



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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 lomboarctic 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 NOMO, 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.<sup>1,2</sup> This condition can have an hematogenous origin, by contiguity to a focus of infection or by direct inoculation.<sup>1</sup> Unlike hematogenous osteomyelitis, the incidence of osteomyelitis contiguous to a focus of infection originating from trauma, surgery, or implants has increased.<sup>3</sup>

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.<sup>1,3</sup> 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.<sup>1</sup>

Parasitic infection and its effect on stem cell signaling is one of the oldest theories of cancer origin.<sup>4,5</sup> Currently, it is accepted that the association of chronic infection and development of malignancies may be underestimated.<sup>5</sup> 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.<sup>5,6</sup>

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.<sup>1,6</sup> Malignant

transformation begins in the skin or epithelium of the fistula and infiltrate the adjacent tissues, including bone.<sup>7,8</sup> 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.<sup>1,5,9,10</sup> The increase in fistulous drainage, as well as persistence, exophytic growth of an ulcer or mass can be warning signs for malignant transformation.<sup>1,11</sup> 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.<sup>8,12</sup> 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.<sup>10,12,13</sup> 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.<sup>12</sup>

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.<sup>7,10</sup> Adjuvant chemoradiotherapy is indicated in metastatic disease and high-grade tumors.<sup>14</sup> In selected patients without metastatic disease, limb-sparing extended tumor excision with limb salvage may be chosen.<sup>1</sup>

The main prognostic factor is the staging of the neoplastic disease.<sup>8,10</sup> 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.<sup>15</sup> 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.<sup>15</sup> Early diagnosis and aggressive treatment of the malignant transformation of

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