

Squamous cell carcinoma arising from chronic osteomyelitis of the femur: A case report

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Abstract. Although chronic osteomyelitis (COM) affecting the extremities is a frequently occurring disease, the incidence of squamous cell carcinoma (SCC) arising from COM is rare. Consequently, understanding the diagnosis, treatment and prognosis of such a disorder remains limited. In the present study, a case of COM-associated SCC was demonstrated. A 65-year-old woman arrived to the Southern Medical University Nanfang Hospital (Guangzhou, China) with multiple sinus tracts and skin ulcers in the distal part of her left thigh, persisting for over 50 years following an open pierce injury by an ox horn. A local biopsy confirmed the diagnosis of COM-related SCC. Although limb amputation was recommended, the female patient declined initially. Instead, the female patient underwent focused debridement and wide resection of the tumor, followed by local implantation of calcium sulfate beads loaded with vancomycin and gentamycin, and application of a rail fixator. A total of 10 months later, the cancer recurred, affecting the osseous tissue. Subsequently, the patient underwent amputation of the thigh. At the one-year follow-up, the patient showed satisfactory recovery without signs of local recurrence. Despite its rarity, the severity of this disorder should not be underestimated. Personalized treatment strategies must be tailored to individual circumstances.

Introduction

Chronic osteomyelitis (COM) is characterized by a prolonged inflammatory process and is defined as an osseous infection, with or without involvement of the surrounding soft tissues. The etiology of COM is complex, often stemming from a contiguous focus, hematogenous spread, or vascular insufficiency (1). Despite significant advancements in medical technology, the incidence of COM continues to increase, even in developed countries (2). Despite various treatment strategies, reported rates of reinfection have been as high as 20-30% (3).

The persistent infection and high incidence of infection relapse notably increase the risk of malignant transformation, particularly in patients presenting with sinus tracts and skin ulcers. Hawkins first described such a malignant transformation among patients with COM in 1835 (4). However, due to its lower prevalence, this disorder still requires comprehensive understanding. The lower prevalence of this disorder underscores the importance of addressing its adverse consequences. According to a previous synthesis analysis, the overall incidences of local recurrence, distal metastasis and tumor-related death in COM-related squamous cell carcinoma (SCC) were over 10%, with all-cause death exceeding 30% (5). This highlights the necessity for a reevaluation of the significance of this disease. In the present study, a case report of SCC arising from COM of the femur was presented.

Case report

A 65-year-old woman arrived to the Southern Medical University Nanfang Hospital (Guangzhou, China) in November 2020, with a chief complaint of recurring pain and pus discharge in her left thigh for the past 50 years, following an open pierce injury caused by an ox horn. She did not receive immediate or standard therapy directly after the injury, leading to an infection. Over the past 5 decades, the 65-year-old female patient sporadically received antibiotics, resulting in fluctuating wound conditions. A total of 5 years prior to her visit to the Southern Medical University Nanfang Hospital (Guangzhou, China), the female patient was diagnosed with femoral COM at the Maoming Dianbai Hospital (Maoming, China) and underwent debridement. Unfortunately, the infection recurred

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6 months after the surgery, leading to worsening local pain, increased pus discharge and development of wound ulcers.

Upon initial examination, multiple sinus tracts were observed near local tissue breakdown in the distal medial part of the left thigh, with a cauliflower-like skin ulcer at the mouth of the sinus tracts (Fig. 1A). Additionally, X-rays (Fig. 1B and C) and magnetic resonance imaging (Fig. 1D) findings were consistent with signs of COM. Due to suspicion of malignant transformation of the skin ulcer, a biopsy was performed. The histopathological outcomes revealed that some nests of mild to moderate heterotypic squamous cells, microvascular hyperplasia, and moderate inflammatory cells and eosinophils infiltrations were discovered in the fibrous tissue, indicating well-differentiated SCC (Fig. 1E). Subsequently, the multiple discipline treatment (MDT) team, comprising specialists from oncology, imaging, infectious disease and pharmacy, recommended limb amputation based on comprehensive assessment of the 65-year-old female patient's condition. However, the female patient strongly insisted for a surgery with limb preservation. Consequently, the female patient underwent radical debridement with wide resection of the tumor, followed by placement of calcium sulfate (CS) beads with vancomycin and gentamycin. Given the potential risk of fracture post-resection, a rail fixator was also implanted. Histological analysis confirmed the diagnosis of COM, and intraoperative specimen culture indicated infection related to *Pseudomonas aeruginosa*.

The post-operative radiograph revealed a rail fixator with local implantation of vancomycin and gentamycin loaded by CS beads in the distal femur (Fig. 2A). The wound exhibited satisfactory recovery before discharge. The patient was scheduled for follow-up appointments at intervals of 1, 2, 3, 6, 12, 18 and 24-months post-surgery. However, the compliance of the patient was suboptimal.

A total of 1-month post-surgery, partial biodegradation of the CS beads was observed on radiographs (Fig. 2B). Completed biodegradation of the beads accompanied by new bone formation occurred 4 months post-surgery (Fig. 2C). However, a subsequent X-ray image revealed an abnormal osteolysis signal at the surgical site, despite normal skin appearance at the 7-month follow-up (Fig. 2D, arrows). Considering the potential recurrence of COM with or without SCC, hospitalization was recommended to the female patient for further tests, which the patient declined. A total of 10 months post-surgery, the patient returned to the Southern Medical University Nanfang Hospital (Guangzhou, China) with complaints of recurrent pain accompanied by a draining sinus tract in the left thigh. An X-ray revealed a more typical sign of osteolysis with enlargement of the affected area (Fig. 2E, arrows). After counseling, the patient consented to undergo surgery to prevent pathological fracture.

Following admission, the patient underwent whole-body positron emission tomography/computed tomography scanning, demonstrating a high possibility of SCC recurrence in the left thigh, along with suspicious lesions indicating lymphatic metastasis in the inguinal region (Fig. 3A and B) and a draining sinus tract in the skin (Fig. 3C). Based on these findings, the MDT team once again recommended amputation due to the recurrence of SCC with a significant risk of metastasis, to which the patient consented. During the surgery,

the lesion was identified as bean curd-like necrosis with a foul odor, infiltrating the osseous tissue (Fig. 3D). Histological testing confirmed the presence of well-differentiated SCC. Subsequently, the patient underwent amputation of the middle thigh (Fig. 3E). Histological examination of the residual tissues revealed no evidence of tumor cells (Fig. 3F). The patient recovered well after the surgery, and no signs of recurrence were detected at the one-year follow-up assessment.

Discussion

COM is a common infectious disorder that can arise from contiguous focus, hematogenous spread and diabetic foot ulcers. The incidence of this disorder was even increased in developed countries, and one possible explanation is due to the increase in diabetes-related OM among the individuals over 60 years (2). However, the malignant transformation of SCC arising from COM is rare, with reported incidences ranging from 0.2-1.7% (6-8). Although SCC arising from COM was first documented by Hawkins in 1835 (4), the mechanisms underlying such malignant transformation from inflammation to tumor formation remain a topic of debate. One prevailing hypothesis suggests that COM may possess carcinogenic properties, implying that the long-term inflammation could facilitate malignant transformation, tumor development, invasion and metastasis. Additionally, mediators involved in COM pathogenesis may exert pleiotropic effects on tumor development (9), while inflammatory cytokines might influence the expression of tumor suppression genes (10,11). Moreover, factors such as heredity, exposure to toxins and immunologic factors (11-14) may also contribute to the pathogenesis of COM-related SCC. Therefore, a number of factors are considered to contribute to the development of SCC secondary to COM.

SCC arising from COM shares several clinical characteristics with COM, such as a higher incidence in males and lower limbs, with trauma-induced infection being the most common cause (15). However, SCC also exhibits unique features. Notably, it often manifests after a prolonged period, with reported average durations of 27 years (5) or 31 years (16) before onset. Nevertheless, not all cases of malignant transformation take such a lengthy period. Khaladj *et al* (17) reported a case of SCC arising from foot osteomyelitis with a duration as short as three months. Additionally, SCC presents clinical signs and symptoms similar to those of COM, including sinus tracts, redness, pain and local swelling. Presently, specific indicators to monitor this transformation are lacking. However, patients with COM should remain vigilant for signs such as foul odor, exophytic or fungating masses, protracted wounds, aggravating pain and increased drainage, as these may indicate SCC development (5). Similarly, Corrigan *et al* (16) analyzed 106 literature-reported cases and suggested that SCC should be suspected in all patients with COM with skin changes, particularly those with sinus drainage persisting for more than three years. It should be noted that extended disease durations and aggravating clinical symptoms serve as clues for SCC development; however, definitive diagnosis relies on histological tests. In the present case report, the female patient had a notable prolonged history of COM with

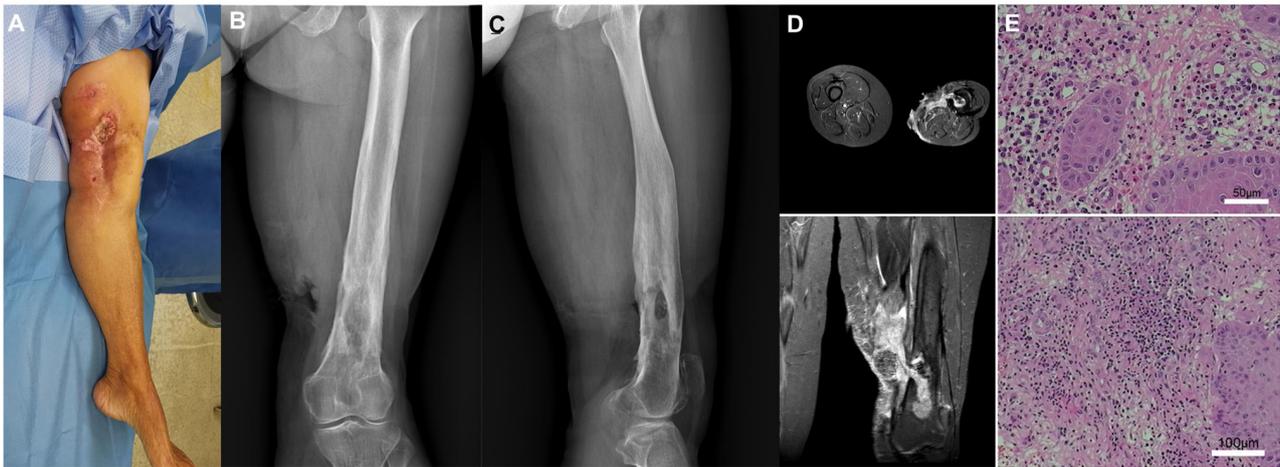


Figure 1. Physical examination, imaging tests and histology test of the reported patient (A) Physical examination showed sinus tracts in the distal medial part of the left thigh, with a cauliflower-like ulcer at the mouth of the sinus tracts. (B and C) X-ray images indicated osteolysis and osteosclerosis in the distal femur. (D) Magnetic resonance imaging revealed that infection affected both the intramedullary cavity and the surrounding soft tissue, classified as Cierny-Mader anatomy type III, localized infection. (E) Histology of biopsy confirms well-differentiated squamous cell carcinoma.

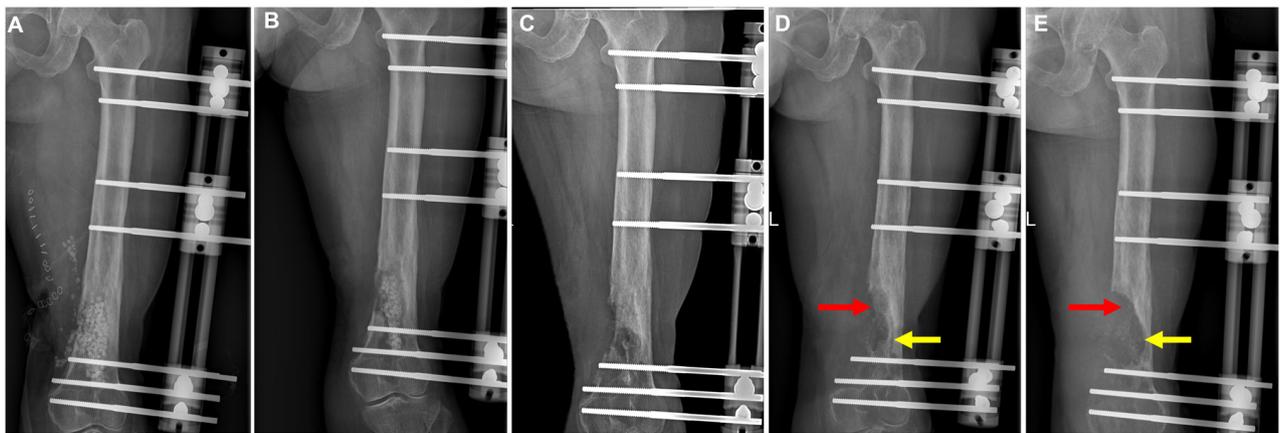


Figure 2. Postoperative follow-ups of X-ray images. (A) Immediate postoperative radiography showed implantation of the rail fixator with calcium sulfate containing antibiotics. (B and C) X-ray images at (B) 1 and (C) 4 months after the surgery revealed gradual biodegradation of the calcium sulfate beads with new bone formation. (D and E) X-ray images of the postoperative (D) 7 and (E) 10 months indicated abnormal osteolysis signals.

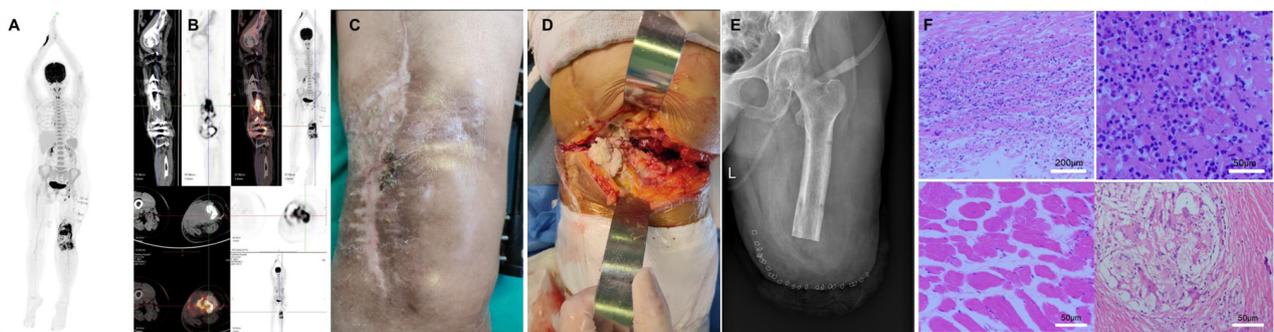


Figure 3. Whole-body positron emission tomography/computed tomography scanning before the second surgery suggested a high possibility of squamous cell carcinoma recurrence with lymphatic metastasis in (A and B) the inguinal region although the (C) skin recovered well. (D) A bean curd-like necrosis of the lesion with a foul odor was detected during surgery. (E) The female patient received left thigh amputation. (F) The residual tissues did not have tumor cells according to histology test.

sinus tracts and skin ulcers, coupled with inadequate standard treatment, which increased the female patient's risk of SCC development.

Based on previous systematic reviews, limb amputation remains the primary treatment modality for COM-related SCC (5,16), with both studies indicating that >80% of patients

with this condition undergo amputation. While amputation is a radical approach, it serves as a comprehensive strategy to eliminate both infection and tumor burden (18), leading to a faster and safer recovery, particularly in advanced or complex cases (19). In addition to amputation, wide tumor resection may be considered for patients without evidence of distal metastasis (18). Mohs micrographic surgery, characterized by serial sections to achieve absolute tumor resection, has been applied in COM-related SCC cases with satisfactory outcomes. However, due to the limited sample size of this patient group, future studies with large cohorts are warranted to more accurately evaluate the efficacy of Mohs micrographic surgery. Conservative therapy is generally not recommended as a routine management for SCC due to its malignant nature. However, it may be considered in patients with absolute contraindications to surgery (5). Currently, chemotherapy and radiotherapy are primarily employed in patients with local recurrence and distal metastasis. Nevertheless, the limited number of studies in this area results in a scarcity of robust evidence regarding their efficacy.

Although amputation is the primary treatment for SCC arising from COM, its clinical efficacy remains suboptimal, with local recurrence, distal metastasis and tumor-related death rates exceeding 10% (5), demonstrating a less-than-ideal prognosis. In the present reported case study, despite recommendations from the MDT specialists for limb amputation, the patient initially declined due to a strong preference for limb preservation. Consequently, radical debridement with wide tumor resection was performed. Unfortunately, the tumor recurred shortly after surgery, ultimately leading to limb amputation. The specific risk factors contributing to local recurrence and distal metastasis remain unclear. However, according to a synthesis analysis of 176 reported cases by Jiang *et al* (5), patients with regional lymphadenopathy at diagnosis and those with moderately to poorly differentiated types of SCC may be at a higher risk of local recurrence. In the present reported case, the female patient experienced a satisfactory recovery one year after undergoing amputation surgery.

In addition to the present case, numerous previous studies also reported clinical characteristics and treatment efficacy of patients with SCC arising from COM. In a retrospective study of eight cases, Li *et al* (20) indicated that the mean duration from COM to SCC occurrence was 28 years, with the tibia as the most frequent affected site. Furthermore, amputation was performed in seven cases, with no recurrence and metastasis during the follow-up time. Quite similar to the present case study, Luchs *et al* (21) also reported a patient with a 50-year history of femoral COM, and they used an *en bloc* tumor resection combined a Van Ness rotational repair. However, they did not track the treatment efficacy. In a recent systematic review, Bryce-Alberti *et al* (22) summarized the treatment approach and oncological outcomes of SCC arising from extremity COM. It was also discovered that such a disorder mostly occurred following trauma, with the tibia, foot and femur as the top sites. Meanwhile, it was indicated that bone invasion was common (83%), and most patients received limb amputation (90%), which appeared to be related to a higher survival rate compared with limb salvage strategies. These findings were supported by the present case report. In the present study, a

wide resection of the tumor together with local antibiotics and a rail fixator as the primary limb salvage strategy was initially utilized, but unfortunately due to its well-differentiated type it resulted to a failure. The present case study once again suggested that limb preservation surgery should be conducted cautiously for patients with COM-related SCC.

There are several limitations to the present study. First, it was presented as a single case report, leading to a limited level of evidence. Second, the patient was only followed-up for 1 year after the final amputation surgery, which may be insufficient to fully evaluate the efficacy and prognosis of SCC. Third, while limb amputation remains the primary treatment for SCC, the attempt at limb salvage using wide tumor resection was unsuccessful. The potential effectiveness of alternative limb preservation strategies, such as Mohs micrographic surgery or segmental infected bone and soft tissue resection, remains unclear in these patients. Nonetheless, the present case study offers valuable insights into COM-associated SCC, which may enhance understanding of this disorder. In conclusion, while SCC arising from COM is rare, it is crucial for patients with COM, particularly those with prolonged disease duration, to remain vigilant for signs of potential malignant transformation, including aggravating symptoms, foul odor, exophytic or fungating masses, protracted wounds, worsening pain and increasing drainage. Once the diagnosis of SCC has been established, caution must be exercised when considering limb preservation strategies, as the risks of local recurrence and distal metastasis are high. Currently, limb amputation remains the primary treatment strategy for SCC arising from COM. It is important to note that modern prosthetics do not notably impact the patient's quality of life. Nonetheless, ongoing research may lead to the development of novel limb preservation strategies in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YJH and BY conceptualized the present study and confirm the authenticity of all the raw data. NJ, YSY and QRL conducted the investigation. NJ and YSY curated the data. YSY wrote and prepared the original draft. NJ, YJH and BY wrote,

reviewed and edited the manuscript. YJH and BY supervised the project. BY was the project administrator. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written, retrospective informed consent for publication following detailed explanation of the purpose of the manuscript and understanding that no identifiable information was going to be released.

Competing interests

The authors declare that they have no competing interests.

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