

Malignancy in chronic osteomyelitis of the femur: a case report

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Abstract

Introduction Chronic osteomyelitis is a common disease, but malignancy is its rare and late complication. **The aim** is to present a clinical case of malignant transformation 34 years after the diagnosis of chronic osteomyelitis of the hip. **Materials and methods** The medical case history was studied and pathomorphological examination of the surgical material of patient D. with chronic osteomyelitis of the femur was conducted. **Results** Patient D., after a comminuted fracture of the left femur as a result of an accident, at the age of 25 years, developed chronic osteomyelitis, the surgical interventions did not lead to a long-term remission of the process. The course of the disease was complicated by malignancy and pathological fracture. The treatment ended with the amputation of the limb. The pathohistological examination revealed structural changes in bone tissue: necrosis, bone marrow fibrosis, bone microsequestration, inflammatory infiltrate with a high content of neutrophils that corresponded to the morphological signs of chronic osteomyelitis in the acute stage. Signs of pseudocarcinomatous hyperplasia, mass appearance of "horny pearls", invasion of the squamous epithelium of the bone tissue, squamous epithelial cells seemed to be highly differentiated. **Discussion** The pathomorphological picture of the surgical material was characterized as pseudocarcinomatous hyperplasia, the prolonged existence of which could cause the occurrence of squamous cell carcinoma of the femur. It is not clinically and histologically possible to establish when the reactive proliferation of the epidermis acquires fundamentally different biological properties of a malignant tumor. It is a serious problem in the timely diagnosis. **Conclusion** A thorough pathoanatomical assessment of the material from the affected areas (ulcers, fistulous tracts, bone marrow space) is necessary for the early detection of malignant neoplasms that may occur in osteomyelitis. The presence of long-term dynamics of pseudocarcinomatous hyperplasia requires vigilance in relation to the process of malignancy.

Keywords: chronic osteomyelitis, femur, pseudocarcinomatous hyperplasia, malignancy

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INTRODUCTION

Chronic osteomyelitis is one of the most severe post-traumatic complications that may develop after the treatment of long-bone fractures. Patients often undergo multiple surgical interventions and may remain uncured for decades. The disability rates of patients with chronic osteomyelitis are high and range from 50 to 90 % [1]. According to different authors, the femur is affected in 15 to 45 % of all cases of fractures [2, 3]. Patients with post-traumatic osteomyelitis of the femur account for up to 18.7 % among the disabled with purulent pathology of bones and joints, [4].

Malignant tumors that may develop in chronic osteomyelitis are a rare and late complication which has been poorly understood. The most common malignant neoplasm is squamous cell carcinoma, which develops decades after the diagnosis of chronic osteomyelitis. Previous studies have shown that the duration of the course of osteomyelitis is directly dependent on the number of detected cases of malignancy. The period of manifestation, according to different authors,

ranged from 24.5 to 49.2 years from the onset of the disease [5-8].

The causes of malignancy in chronic osteomyelitis are poorly understood, the exact mechanism of malignant transformation remains unknown. It is known that inflammation and/or infection contribute to the initiation of carcinogenesis. In case of chronic inflammation, the risk of tumor cell formation increases [9]. Malignant transformation begins in the skin or epithelium of the fistula and infiltrates adjacent tissues, including bones. An increase in discharge from the fistulous tract, as well as persistence, an exophytic form of ulcer growth or formation, may be precursors of malignant transformation [7, 10].

Early diagnosis and timely treatment of malignant transformation in chronic osteomyelitis are of decisive importance for the prognosis and final results of treatment.

We **aimed** to present a clinical case of malignant transformation 34 years after the diagnosis of chronic osteomyelitis of the femur.

MATERIAL AND METHODS

Medical records and pathomorphological examination of the surgical material of patient D was analyzed. The study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975, revised in 2013, approved by the ethical committee of the institution. The patient gave voluntary informed consent to the publication of the results of the study without disclosing his identity.

The surgical material (fragments of the cortical plate, free-lying spongy bone, the contents of the bone marrow cavity) were fixed in 10 % neutral formalin solution, partially decalcified in

a mixture of hydrochloric and formic acids. Then the samples were subjected to standard histological processing, dehydrated in alcohols of increasing concentrations, impregnated with a sealing mixture, and embedded in paraffin. Histological sections, 5-7 μm thick, were produced on a sledge microtome from Reichert (Austria), which were stained with hematoxylin and eosin. The study of micropreparations and microphotography was carried out using an AxioScope.A1 stereomicroscope with an AxioCam digital camera with Zen blue software (CarlZeissMicroImaging GmbH, Germany).

RESULTS

Patient D., aged 58, applied to the clinic for osteoarticular infection in 2019 with complaints of a sinus tract purulent discharge, pain in the left thigh, dysfunction of the left lower limb.

An. Morbi In 1987, he sustained an open comminuted fracture of the left femur in an accident. Skeletal traction was performed for a month. The wound healed. The fistulous tract opened one month later. It was debrided, intramedullary osteosynthesis and cerclage sutures were applied. One month after the operation his body temperature increased and was accompanied by pain. It required opening and drainage, removal of the intramedullary nail and cerclage wire. After two months, the fistulous tract reopened. He underwent surgery (osteonelectomy) five years after the injury. The effect was not achieved and conservative treatment followed. During the last 6 months, she suffered pain in the evening and at night in the lower third of the left thigh. Several surgical interventions were performed and samples of surgical material for pathomorphological examination were harvested. Morphological studies showed signs of osteomyelitis, without malignancy.

St. localis at admission He walked with a cane, limping on his left leg. The sinus tract passed on the border of the middle and lower third of the left thigh with purulent discharge, penetrated into the depths of the tissues. A soft tissue formation was seen at the level of the fistulous tract along the anterior surface (Fig. 1a), painful on palpation. Swelling of the left thigh was 5 cm and the left lower limb was shorted by 3 cm. He had rocking movements in the knee joint by extension of 180 degrees.

The radiographs of the left femur in standard projections showed a consolidated fracture of the distal left femur, heterogeneity, a bone defect along the lateral surface of the diaphysis with a pronounced periosteal reaction at this level and osteoporosis (Fig. 1b).

MSCT findings A cavity in the middle third of the medullary canal of the femur with an uneven internal contour was up to 9 cm long, and along its length there was a defect in the cortical plate along the anterior lateral surface. The density of the cortex at the level of the cavity was about 1100 HU. In the posterior sections of the cortex, a defect was filled with a porous substrate, $2 \times 2 \times 35$ cm in size (cancellous bone? implant?). In the central parts of the distal metadiaphysis, there was a linear avascular sequester, 0.65×7.5 cm in size (Fig. 1c).

Bacteriological study of the sinus discharge detected: *Pseudomonas aeruginosa* $5 \times 10 \times 4$ cfu/ml

The patient had surgery at the clinic for osteoarticular infection: revision of the fistulous tract in the left thigh, osteonelectomy (debridement), ultrasonic cavitation to extend the cortical wall defect for better visualization. There was an unpleasant odor in the medullary canal, pathological granulation tissue, sequesters, the inner cortical layer was affected by the osteomyelitis process. Osteonelectomy was performed with the collection of material for histological (cortex at the level of the cavity, the contents of the bone marrow canal) and microbiological examination. Avascular distal sequester, due to non-involvement in the inflammatory process, was not removed. After the operation, an intracanal cavity of a volume of 75 ml was obtained. The operation ended with treatment of the medullary canal with pulse lavage with lavasept solution and installation of two drains towards each other (Fig. 2). Bacteriological examination showed no growth of fungi and anaerobic flora, *Pseudomonas aeruginosa* was again identified. The patient received antibiotic therapy according to the sensitivity of the microorganism. On the 7th day after the operation, an unpleasant odor of the contents of the drainage appeared. The installation of a flow-through flushing system did not lead to the resolution of the process.



Fig. 1 Patient D., aged 58, on admission: *a* photo; *b* radiographs of the femur capturing the knee joint in standard projections; *c* MSCT



Fig. 2 Postoperative wound

MSCT was repeated and revealed a cavity in the medullary canal of the lower third, up to 14 cm long, with a defect in the cortical plate along the outer surface. The contour of the cavity was clear, uneven. On the inner surface of the medullary canal formed small avascular sequestrs. There is a linear aseptic sequester up to 4.3 cm in the metaepiphysis. A revision of the

wound with osteonecrectomy was performed. Small crumbly sequestrs and aseptic sequestration were removed. The materials were taken for histological and bacteriological studies. On the 21st day after the operation, a purulent sac was opened. The patient was discharged and was followed up by an orthopedic traumatologist at the place of residence for the period of separation of avascular sequestrs.

Pathomorphological examination revealed the contents of the osteomyelitic cavity as granulation tissue of varying maturity with areas of fibrosis and an inflammatory infiltrate containing lymphocytes, histiocytes, neutrophils, and plasma cells (Fig. 3a). Randomly arranged complexes of squamous epithelial cells were detected (Fig. 3, b, c, d). Such complexes were characterized by changes in the size and shape of cells and their nuclei, the presence of polyploid forms, and rare pathological mitoses. Microscopy of spongy bone fragments between trabeculae revealed

granulation tissue of varying degrees of maturity, bone microsequestrs, and inflammatory infiltrate. Bone trabeculae contained empty osteocytic lacunae, bone matrix with stratifications of bone substance (Fig. 3e). There were extensive areas with necrotic trabeculae and foci of osteolysis, between which there were massive accumulations of squamous epithelium scales and an inflammatory infiltrate (Fig. 3f).

The patient was given slides and fragments of surgical material with recommendations to consult an oncologist.

The fistulous tract continued to function with serous-purulent discharge (Fig. 4), with an unpleasant fetid odor when the patient was hospitalized in 2020.

According to the patient, the oncologist did not confirm the malignant process. Conclusion: Based on the examination (CT, cytological and histological studies, PSA test), there are no convincing data for a malignant neoplasm of the left femur.

The next surgical intervention revealed small separately lying sequestrs, the inner cortical layer of the osteomyelitic cavity was covered with areas of granulation tissue and whitish soft tissue formations, which were taken for histological examination. However, the surgical treatment did not lead to remission of the osteomyelitic process. Under the conditions of the center's clinic, MSCT of the chest, abdominal cavity and small pelvis organs was

performed without and with contrast. The organs of the chest had no visible pathology. There was fatty infiltration of the liver and pancreas. PSA test was done, the result was negative.

Two months after treatment, a pathological fracture of the femoral diaphysis developed. Debridement and installation of an antimicrobial spacer with fixation with an orthopedic splint did not lead to remission (Fig. 5). The patient underwent osteonecrectomy twice of the resection type up to 7 cm with osteosynthesis with the Ilizarov apparatus. Consolidation was not achieved (Fig. 6).

The pathomorphological examination of the surgical material in 2020 detected signs of pseudocarcinomatous hyperplasia in the cavity of the medullary canal and invasive growth of epithelial bands (Fig. 7a), figures of mitotic division were rare (Fig. 7b), excessive keratinization was accompanied by the formation of "horn pearls" – rounded foci of hyperkeratosis with signs of incomplete keratinization in the center (Fig. 7 c, d). The inflammatory infiltrate of the lymphohistiocytic type contained neutrophils. A pronounced invasion of epithelial complexes, bone microsequestrs, and an inflammatory infiltrate were observed in spongy bone (Fig. 7e). Extensive areas of osteonecrosis were noted, with accumulations of squamous epithelium scales and an inflammatory infiltrate in the intertrabecular spaces (Fig. 7f).

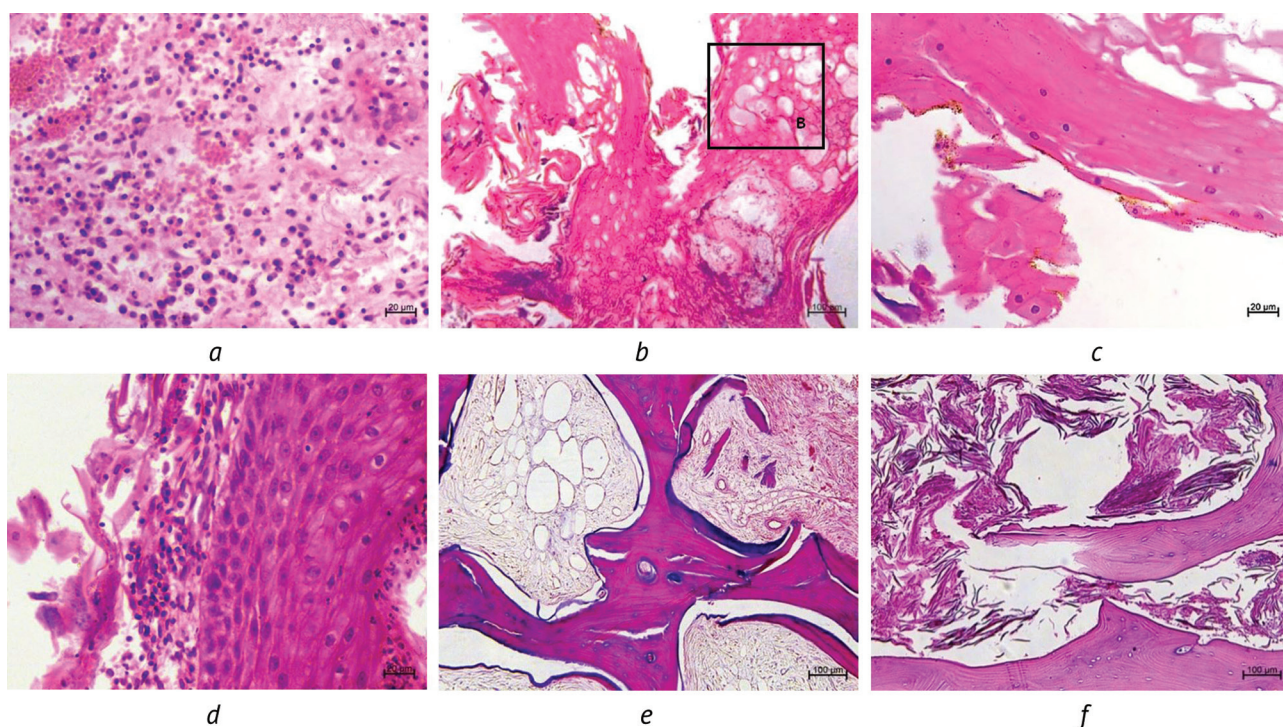


Fig. 3 Microphoto of the surgical material (2019): *a* fibrosis area with inflammatory infiltration and hemorrhage; *b* proliferation of squamous cell complexes with dyskeratosis, numerous cavities with the presence of horny scales; *c* area of squamous epithelium with a small number of keratocyte nuclei; *d* complexes of squamous epithelial cells; *e* osteonecrosis, bone microsequestrs, bone marrow fibrosis; *f* necrotic trabeculae, massive accumulations of squamous epithelium scales in the intertrabecular spaces. Paraffin sections, stained with hematoxylin and eosin. Magnification $\times 100$ (*b, e, f*), $\times 400$ (*a, c, d*)



Fig. 4 Fistulogram in two views capturing the knee joint



Fig. 5 Radiographs of the femur with a gap of the knee joint in two projections after debridement and installation of an antibacterial spacer

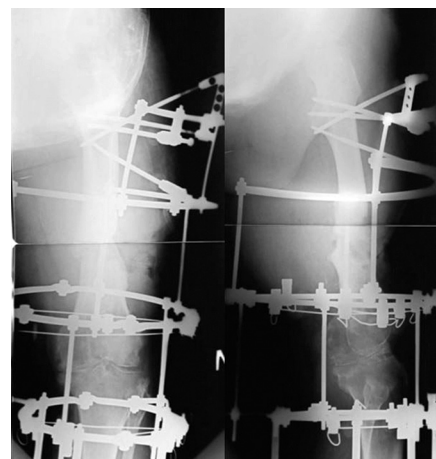
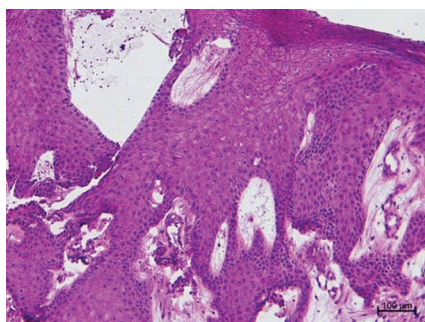
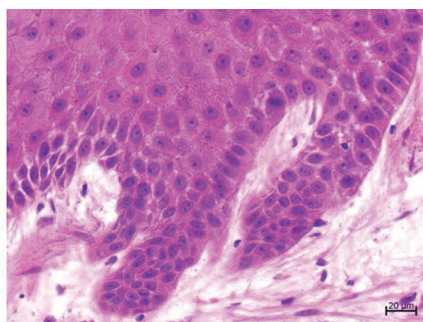


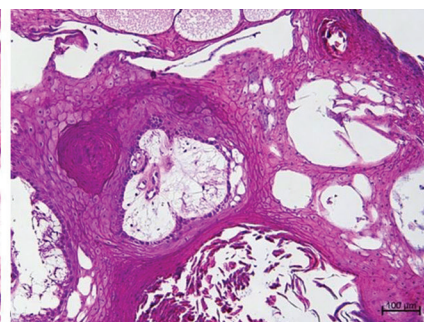
Fig. 6 Radiographs of the femur with adjacent joints in two projections after resection-type osteonecrectomy and osteosynthesis with the Ilizarov apparatus



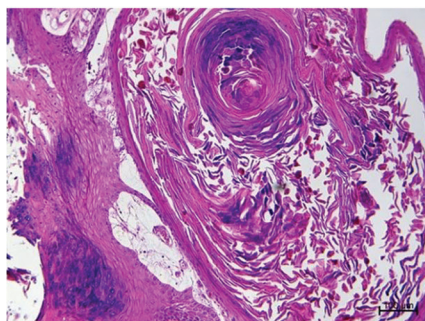
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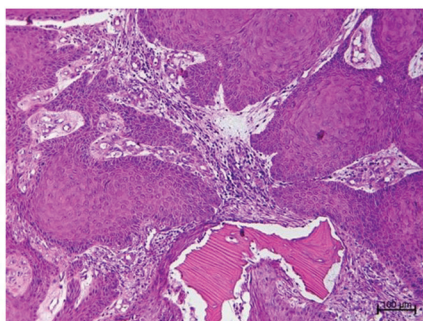
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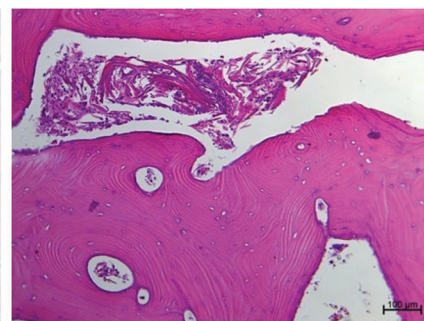
c



d



e



f

Fig. 7 Microphotos of the surgical material (2020): *a* pseudocarcinomatous hyperplasia, submerged growth of epithelial bands; *b* mitotic activity, moderate atypia of epithelial cells; *c* cribriform hyperplasia of squamous epithelium with an abundance of horny scales; *d* excessive keratinization, the formation of "horn pearls"; *e* extensive invasion of squamous epithelium in the bone tissue, bone microsequestrs and inflammatory infiltrate; *f* osteonecrosis, accumulation of squamous epithelium scales in the intertrabecular spaces, inflammatory infiltrate. Paraffin sections, stained with hematoxylin and eosin. Magnification $\times 100$ (*a, c, d, e, f*), $\times 400$ (*b*)

To confirm the diagnosis, we recommended that the patient re-apply to a specialized oncology clinic. In 2021, the limb was amputated at the level of 1/3 of the thigh

at the clinic of residence. We should note that gram-negative microflora was detected by all hospitalizations (*Pseudomonas aeruginosa*).

DISCUSSION

Analysis of the literature showed that the duration of the osteomyelitic process is the main factor associated with the onset of carcinogenesis, with a minimum latent period of 20 years or more. Femur, tibia and foot bones are the most frequent localizations of purulent necrotic

process. Signs that should alert the attending physician to malignant transformation include increased pain, discharge from the fistula, progressive destruction and erosion of bones, a growing mass of the "tumor type" in the wound area [6, 7, 8, 11].

Jiang et al. (2020) analysed 167 cases and showed that squamous cell carcinoma in chronic osteomyelitis of the extremity most often occurred in patients with a history of post-traumatic osteomyelitis [12].

In the presented clinical case, a comminuted fracture of the left femur due to an accident at the age of 25 years resulted in a long-term chronic osteomyelitis that ended with a pathological fracture at the age of 59 and led to amputation of the limb. Noteworthy is the long-term relapse-free course of osteomyelitis for 34 years, the appearance of pain in the evening and at night in the thigh, the presence of gram-negative microflora, the presence of whitish soft tissue masses on the inner wall of the osteomyelitic cavity. During the last hospitalization, the patient was disturbed by severe pain in the projection of the purulent focus, that relieved with injections of tramadol solution twice a day.

The structural changes in the bone tissue detected by us – necrosis, bone marrow fibrosis, bone microsequestrs, inflammatory infiltrate with a high content of neutrophils – corresponded to the morphological signs of chronic osteomyelitis in the acute stage. The pathomorphological picture of the studied surgical material was characterized by the presence of pseudocarcinomatous hyperplasia, its prolonged persistence can cause the occurrence of squamous cell carcinoma of the femur.

It is not clinically and histologically possible to determine when reactive epidermal proliferation acquires fundamentally different biological properties of a malignant tumor [13], which is a serious problem in timely diagnosis.

Squamous cell carcinoma is characterized by intraepidermal proliferation of atypical keratinocytes; in chronic osteomyelitis, it usually has a low degree of malignancy [14]. Squamous cell carcinoma is known to be more common and more aggressive in

immunosuppressed patients. According to T. Kurihara, in chronic osteomyelitis, invasion of squamous cell carcinoma into the bone from soft tissues and the bone marrow cavity occurs in 77 % of cases [15].

In 2019, we revealed complexes of squamous invasive growth in the surgical material, in 2020 we noted the massive appearance of "horny pearls" and invasion of the squamous epithelium of the bone tissue, while the cells of the squamous epithelium seemed to be highly differentiated, in the intertrabecular spaces there was a massive accumulation of epithelial scales. Strengthening of signs of aggressiveness of invasive growth of squamous epithelium in the fistula cavity and the spread of the process into the bone tissue with the formation of "horn pearls" testified to the malignancy of the process.

In the presented clinical case, the development of squamous cell neoplasia occurred according to a highly differentiated type. A tumor from the epithelial tissue of a skin ulcer invaded the bone tissue along the bone marrow cavity.

The pathogenesis of malignancy is not well understood; the most widely accepted theory is focused on a chronic inflammatory condition [12, 16]. Microbial infection is characterized by horizontal gene transfer and subsequent latent mutations that disrupt the immune response. There is evidence that carcinomatous transformation may follow a change in the bacterial flora. The gram-positive flora can be replaced by a predominant gram-negative flora that produces endotoxins associated with carcinogenesis [17].

To prevent local invasion and metastatic spread, treatment should not be delayed. The most effective method of treatment in these cases is limb amputation; wide resection is indicated only in selected patients [18, 19, 20].

CONCLUSION

We present a rare case of malignancy in chronic osteomyelitis that was detected 34 years after primary infection treatment. The tumor invaded bone tissue along the bone marrow cavity from the skin ulcer epithelium. A thorough pathoanatomical assessment of the material from the affected

areas – ulcers, fistulous tract, bone marrow space – is necessary for the early detection of malignant neoplasms that occur in osteomyelitis. The presence of long-term dynamics of pseudocarcinomatous hyperplasia requires vigilance in relation to the process of malignancy.

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