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Squamous Cell Carcinoma Complicating Chronic Osteomyelitis: A Retrospective Study

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Abstract: ***Background: Chronic osteomyelitis is often a recalcitrant entity and rarely may lead to malignant transformation. This study is aimed to retrospectively study cases of squamous cell carcinoma(SCC) arising from chronic osteomyelitis. Material and methods: Six cases of squamous cell carcinoma after chronic osteomyelitis were studied retrospectively. The location, disease duration and histopathological subtype of the tumor was studied. Results: The patients had an average age of 53 years (range 44 to 62 years), with a male predominance (5 men and 1 woman). The mean delay between the initial insult and the diagnosis of malignant transformation was 26 years (range 8 to 44 years). The carcinoma resulted from tibia osteomyelitis in four cases, femur in one case and ankle in one case. Histopathologically, four cases comprised of well differentiated SCC and poorly differentiated SCC was seen in two cases. Conclusion: Though a rare occurrence, squamous cell carcinoma complicating chronic osteomyelitis can lead to increase in mortality, thus treating orthopedic surgeon must be aware of this complication and undertake early intervention to prevent distant spread.***

1. Introduction

Chronic osteomyelitis is a persistent, difficult to treat and sometimes incapacitating infection of bone and bone marrow. Chronic osteomyelitis is considered a great challenge for the treating orthopedic surgeon. Apart from its chronic course and morbidity, it may rarely result in devastating complications like malignant transformation.Malignant transformation of chronic osteomyelitis has been known since the 19th century. In 1835, Hawkins was the first to document squamous cell carcinoma arising in patient with chronic osteomyelitis [1]. This malignant transformation is defined by a change in the clinical, radiological, bacteriological and histological symptomatology of the chronic osteomyelitis [2]. It is particularly seen after long bone infections and results most often in squamous cell carcinoma and rarely in a sarcoma or lymphoma.

It is a rare and late complication developing 20 to 40 years after chronic osteomyelitis. This may involve the surrounding skin, or result in formation of fistula or sinus tract. The pathophysiological mechanisms of this malignant transformation are unknown but the most widely accepted theory is focused on the chronic inflammatory state [3,4]. In these conditions, the immune system is dysregulated: Inflammatory mediators and cytokines expressed by the immune system modulate the genic expression of various proteins, including p53 [4]. Furthermore, avascular areas and lymphatic duct obliteration [3] are conditions that discourage antigen presentation. Polymicrobial infection sites are also characterized by horizontal gene transfer and consequent latent mutations that interfere with the immune response [5]. There is evidence that malignant transformation can follow a shift in bacterial flora. Gram-positive flora can be replaced by predominant gram-negative flora that produce endotoxins associated with cancer [5]. Biopsy is essential for appropriate diagnosis and treatment to these suspicious lesions. In this study, we report six casesof squamous cell carcinoma arising in patients with chronic osteomyelitis.

2. Material and Methods

The present study was carried out in Department of Orthopedics in a tertiary care hospital in North India. This was a retrospective study in which cases of squamous cell carcinoma arising in patients with chronic osteomyelitis were studied. All patients who were included in the study had histopathological confirmation of malignant transformation by skin biopsy. Lymph node status was noted. Radiographs of involved part, MRI and CT scan for staging was done.We analyzed the delay between initial insult and malignant transformation, clinical presentation, localization of tumour, histopathologicalsub type of carcinoma.

3. Results

The patients had an average age of 53 years (ranged from 44 to 62), with a male predominance (5 men, 1 woman). The presenting features were constant and severe pain, fistula adjacent to involved bone with discharge, growth near the involved bone, bleeding from site, loss of weight and decreased appetite. Clinically palpable lymphadenopathy was seen in 3 cases. The mean time between the occurrence of the initial injury and the diagnosis of malignant transformation was 26 years (ranged from 8 to 44 years).Tibia was the most common site of involvement (4 cases), followed by the femur (1 case) and the ankle (1 case). In three cases the osteomyelitis occurred after a fracture, of which one had an open fracture. The malignancy was confirmed with histopathological examination in all cases. Pathological examination showed 4 cases of a well-differentiated squamous cell carcinoma with bone invasion and 2 cases comprised of poorly differentiated squamous cell carcinoma.All 6 patients had plain radiograms and CT scan. In 2 patients magnetic resonance imaging (MRI) was performed as an additional imaging study to reveal bone lesions and soft tissue masses. Distant spread involving liver and skeleton was seen in 1 case. Microbiological sampling was positive in 5 cases. Most patients presented with mixed

infections. Staphylococcus was the most common organism isolated.

4. Discussion

Neoplasms as a result of chronic insults were described as early as during the Roman Empire. Aulus Cornelius Celsius told of tumoralneoformations in correspondence to chronic wounds [6]. During the mid-19th century, Hawkins and Marjolin correlated these skin diseases with osteomyelitis [7]. In a Mayo Clinic study in which investigators analyzed about 4000 cases of chronic osteomyelitis, malignant lesions were noted in 23 % of the patients [8]. The incidence of skin lesions ranges between 0.2 % and 1.7 % of all patients affected by osteomyelitis [9,10]. Indeveloping countries, the percentages increase with delayed diagnosis and inadequate treatments [3].

Squamous cell carcinoma is the most common type of malignant tumor deriving from chronic osteomyelitis [11-13]. Squamous cell carcinoma is characterized by an intraepidermal proliferation of atypical keratinocytes [14], when associated with chronic osteomyelitis is usually of low grade malignancy [15].The duration of osteomyelitis appears to be the principal factor related to carcinogenesis onset, with a minimum latency period of 20 years or more [16]. Males are affected more often than women, with a predominance of 85 %, and patients' are typically aged between 50 and 60 years old [17]. The most frequently affected site is the tibia, followed by the femur. The upper limb is rarely affected. Accordingly in four out of six cases, a tibial localization was found

Clinical signs that should alert the clinician about malignant transformation include increased pain, blood, or foul release from the sinus; progressive bone destruction and erosion; and a growing mass in the area of the wound [18]. The presentation in our series was variable; we could observe an extension or an unusual persistence of skin ulceration, rapidly growing and disabling pain, discharge with an unpleasant odor, sometimes containing blood or systemic findings like history of weight loss [19,20]. When the neoplasm invades the bone, there is either osteolytic erosion or a pathological fracture. In our series, we observed osteolysis in all patients, which indicates the infiltrative stage of the disease. Diagnosis is confirmed by biopsy at all suspicious wound sites [21,22]. The malignant transformation most often results in squamous cell carcinoma and much more rarely in fibrosarcoma, osteosarcoma, reticulosarcoma, malignant fibrous histiocytoma or angiosarcoma [23-25]. It begins at the skin or epithelial structure of the fistulous route and then invades the bone. We observed only squamous cell carcinoma in our series, the most frequent type in the literature.Three of our patients had palpable lymph nodes at the initial assessment.The presence of satellite nodes is common but often indicates a simple inflammatory reaction.We observed one case of distant spread in our series. As reported in literature, the occurrence of metastasis is limited to 15% of cases, always occurring within five years of diagnosis [26].The prognosis is generally better for well differentiated squamous cell carcinoma than for other differentiated histological types. The existence of lymphatic node involvement or visceral metastasis lowers the 5-year survival rate to 35-50% [27].

Mankin *et al* [28] performed a study in 1982 to evaluate the hazards of 329 biopsies of primarily malignant musculoskeletal tumors, including bone and soft tissue. The results demonstrated troubling rates of errors in diagnosis and technique, resulting in complications and poor patient care. The same group of investigators replicated this study 10 years later and found similar results. A recent study in 2011 reported seven cases of chronic osteomyelitis related squamous cell carcinoma between 1993 and 2005 [29]. The patients had an average age of 55 years (ranged from 38 to 71 years), with a male predominance (6 men, 1 woman). The mean time between the occurrence of the skin lesions and the diagnosis of malignant degeneration was 25 years (ranged from 9 to 40 years). The carcinoma resulted from tibia osteomyelitis in 4 cases, femur in 2 cases and humerus in one case. The pathological examination showed five cases of a well differentiated squamous cell carcinoma with bone invasion, and two cases of invasive squamous cell carcinoma.

Malignant transformation after chronic osteomyelitis is a rare and late complication. It should be considered even years after the development of chronic osteomyelitis. The most suggestive signs are the persistence of a foul smelling fistula and the ulceration. The diagnosis can be made with histopathological examination and use of radiological imaging.Treatment depends on the stage of the disease: in the early stage, limb saving surgery can be performed, but in the advanced stages with bone invasion and large skin defects, amputation is necessary.

5. Conclusion

Malignant transformation in chronic osteomyelitis is a rare but devastating and potentially fatal sequelae. Orthopedic surgeons must be well aware of this complication.The aim of this retrospective study was to show the gravity of the disease and highlight the fact that this transformation can occur many years after the onset of osteomyelitis. To prevent local invasion and metastatic spread, early diagnosis and treatment must be instituted to avert associated mortality.

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