# Epithelioid Sarcoma: An Unusual Presentation in the Distal Phalanx of the Toe

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## Abstract

**Epithelioid sarcoma is rare soft tissue sarcoma first described by Enzinger in 1970.**

**The classic variant often occurs in the deep or superficial soft tissue of the distal upper extremities of individuals between the ages of 10 and 35. Due to the tumor's benign clinical presentation, infrequent occurrence, and histological similarities with other disease processes, diagnosing epithelioid sarcoma in its early stages has become extremely difficult.**

**We report a rare case of epithelioid sarcoma of the toe with bone metastasis, as well as the clinical, pathological, and radiological difficulties in correctly diagnosing epithelioid sarcoma.**


Epithelioid sarcoma was first described by Enzinger[1] in 1970 as a rare sarcoma typically located in both deep and superficial soft tissue. The classic variant frequently occurs in the distal upper extremities in individuals between the ages of 10 and 35 years. Commonly, the tumor presents as a slow-growing, painless, and firm nodule that may become ulcerated. The benign clinical presentation and low occurrence rate make diagnosis of the lesion difficult during the early stages, as these symptoms are often confused with other diseases with similar presentations.[2,3]

Classically, the histologic appearance of epithelioid sarcoma demonstrates highly eosinophilic, pleomorphic epithelioid cells with a nodular pattern that may undergo central necrosis.[2] The similarities between the histologic presentation of epithelioid sarcoma and other benign and malignant diseases make diagnosis challenging, but advances in immunohistochemistry have facilitated the process and increased the frequency of proper diagnosis. The tumor cells are most frequently immunoreactive to cytokeratin antibodies AE1/AE3, epithelial membrane antigen (EMA), and vimentin.[2,4-6]

Radiologic studies may reveal a soft tissue mass with speckled pattern of calcification, followed by magnetic resonance imaging (MRI) to confirm the size and location. In addition, recent studies of fluoro-D-glucose (FDG) positron emission tomography (PET) imaging have shown possible benefits in determining metastasis of epithelioid sarcoma.[7,8]

This high-grade sarcoma is reported to have a local recurrence rate as high as 77% and a metastatic rate of up to 45%, with metastases most commonly found in the lung and regional lymph nodes, followed by the scalp and bone.[2,3] Due to the aggressive nature of the tumor, early detection and proper treatment are vital. The standard treatment of epithelioid sarcoma in most institutions follows the treatment recommendations of those given for other typical adult sarcomas. These recommendations include wide local excision followed by radiotherapy, with the option of multiagent chemotherapy, although there has been no published study indicating the benefits of adjuvant chemotherapy.[3,9,10]

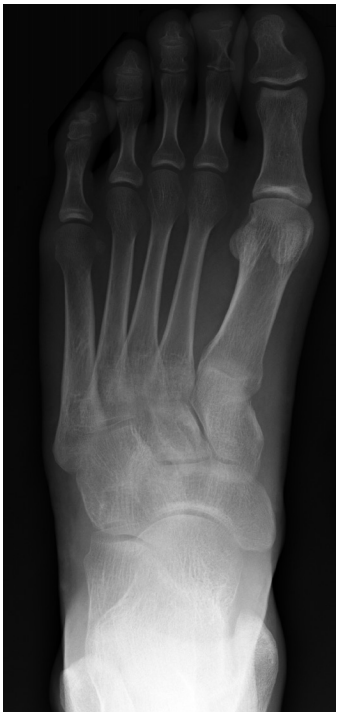

**Figure 1.** Plain radiograph taken during the patient's emergency department visit at the outside institution that shows partial destruction of the distal phalanx of the second toe.

Herein, we present a report of a rare case of epithelioid sarcoma of the toe with regional bone metastasis, emphasizing the difficulty that may be encountered in arriving at the correct diagnosis.

The patient provided written informed consent for print and electronic publication of the case report.

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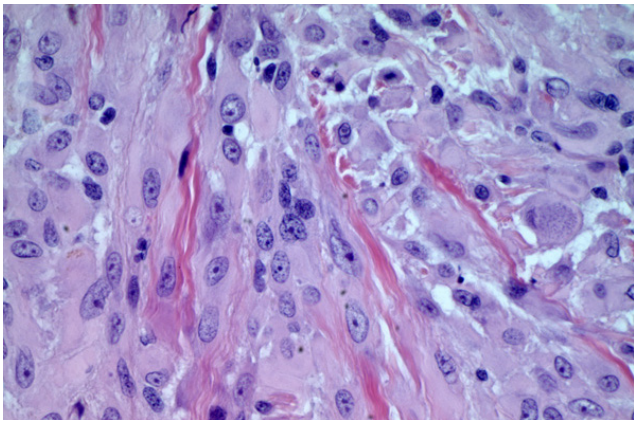

**Figure 2.** High power view demonstrating the pleomorphism of the tumor cells. Abundant eosinophilic cytoplasm is present. Several mitotic figures are noted. Intracytoplasmic bridges are absent, an important histologic difference between epithelioid sarcoma and squamous cell carcinoma.

## Case Report

A 22-year-old male presented to our institution with reports of pain in the left second toe for 7 months. The patient was initially evaluated 2 months following the onset of pain at the emergency room of an outside hospital. The pain was reported as constant and was exacerbated by prolonged rest. Following a plain radiograph of the left foot (Figure 1) and physical examination at the outside institution, the patient was thought to have a hammertoe deformity of the left second toe, with possible plantar fasciitis. Three months following the initial visit to the emergency department, an excision of the mass in the area of the suspected hammertoe deformity was performed and the specimen was submitted. The outside surgical pathology reports rendered a differential diagnosis between epithelioid sarcoma and squamous cell carcinoma (Figure 2). One month later, he was referred to our institution.

Initial physical examination at our institution was remarkable for a 4 mm healing surgical incision beginning at the base of the toenail of the second toe with an overlying sanguineous crust. The patient had limited range of motion of the toe at the proximal interphalangeal joint and full range of motion at the distal interphalangeal joint. There was point tenderness of both joints; however, no sensory deficits were noted, and brisk capillary refills were present. Proximal to the wound, there was no noted tenderness, and pulses were intact and equal bilaterally. There was no noted palpable lymphadenopathy in the inguinal, supraclavicular, and axillary regions. The patient denied recent weight loss, fevers, chills, fatigue, trauma, or any other past medical history.

Concurrently, the original histologic and immunohistochemical slides from the initial excision were reviewed at our institution. Furthermore, the immunohistochemical panel was repeated. The mass was positive for cytokeratin AE1/AE3, EMA (Figure 3A), vimentin

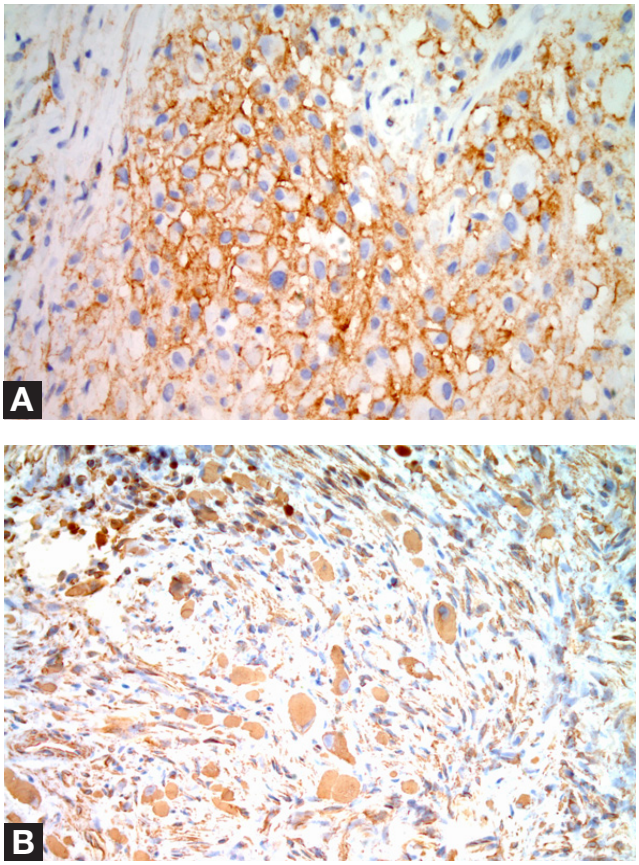


**Figure 3.** (A) Immunohistochemical staining for EMA demonstrates a membranous staining pattern around the neoplastic cells. (B) Immunohistochemical staining for vimentin demonstrates a cytoplasmic staining pattern of the neoplastic cells. Note the voluminous cytoplasm present.

(Figure 3B), and focally positive for smooth muscle actin. Further analysis demonstrated cells negative for CK5/6, p63, and CD34, effectively excluding a diagnosis of squamous cell carcinoma, and a diagnosis of epithelioid sarcoma was rendered.

Plain radiographs showed absence of the distal half of the second phalanx secondary to possible resection versus destruction with no other findings (Figure 4). PET-CT identified multiple lucent lesions in the left lower extremity with increased FDG activity (Figure 5), specifically in the left second mid-phalanx (Figure 6A), the left posterior calcaneus, the left lateral cuneiform, the left cuboid (Figure 6B), the base of the left third metatarsal, and the left anterior aspect of the left proximal tibia (Figure 6C). Additionally, focal avidity was noted in the soft tissue of the right dorsal foot overlying the second and fourth metatarsal bones, as well as intramuscular lesions in the lateral and posterior aspects of the left proximal leg. PET-CT was followed by MRI in order to further assess the disease process. MRI of the left lower extremity confirmed a destructive lesion involving the mid and distal phalanx of the second left toe (Figure 7A), a 1.0 x 1.0 cm lesion in the plantar aspect of the lateral cuneiform bone (Figure 7B),

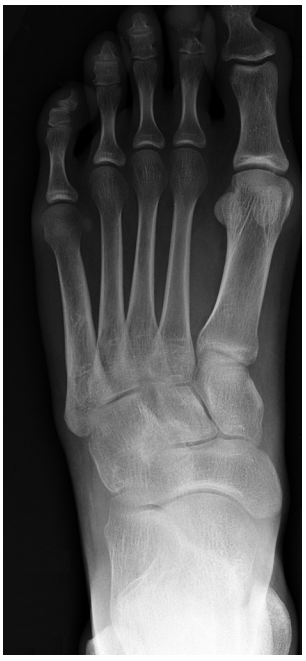

**Figure 4.** Plain radiograph taken 2 months after initial excision of the mass found in the toe, which demonstrates smooth and sharp bony edges of the distal half of the second distal phalanx secondary to resection.

**Figure 5.** Maximum intensity projection image of the lower extremity which demonstrates increased FDG activity at multiple sites of the left lower extremity.

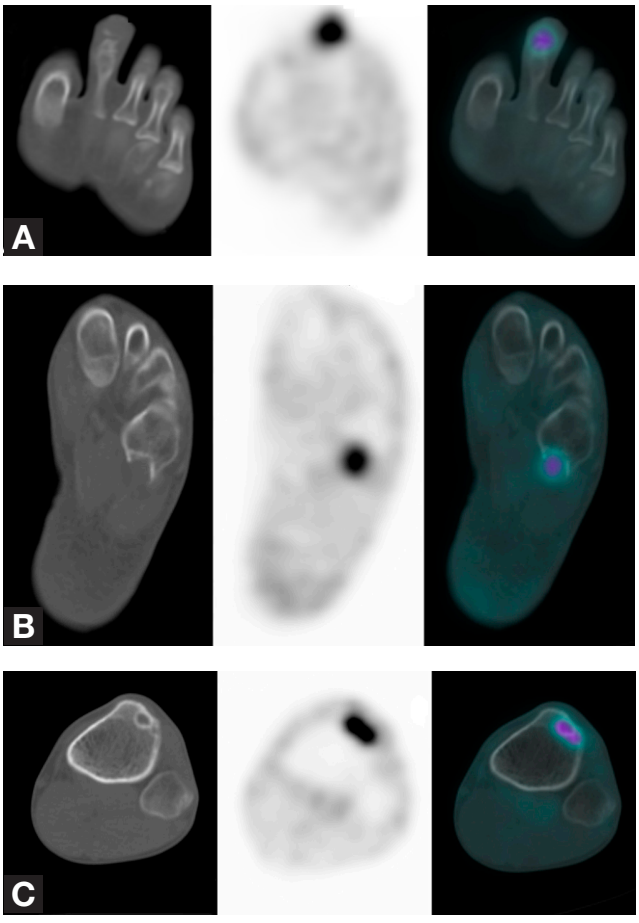


**Figure 6.** CT, PET, and PET/CT fusing images, from left to right, demonstrating multiple lytic lesions of the lower left extremity. Imaging shows intense uptake, with a standard uptake value in the range of 6.0 to 8.0, in (A) the second mid phalanx, (B) the cuboid, and (C) the anterior aspect of the left proximal tibia.

an 11.0 x 0.7 cm lesion in the proximal aspect of the cuboid bone, a 4.0 x 6.0 cm soft tissue lesion in the intraosseous muscle between the second and third distal metatarsals, and 2 lesions, the larger measuring 2.5 cm and the smaller measuring 1.9 cm, in the tibial tuberosity (Figure 7C).

Incisional biopsy of the left proximal tibia was indicated to confirm the presence of metastatic disease. Tissue was submitted for intraoperative consultation to ensure lesional material was present. Permanent sections revealed tumor cells with strong immunoreactivity for cytokeratin AE1/AE3, EMA, and vimentin; these cells were negative for CAM5.2. These findings were consistent with epithelioid sarcoma and histologically analogous to the previously biopsied lesions of the foot.

These findings were discussed with the patient and a decision was made for an amputation above the knee in order to render the patient with no evidence of disease. Gross pathology and histology of the amputation specimen confirmed the radiologic extent of disease. The surgical margins were free of tumor.

## Discussion

Epithelioid sarcoma is a rare high-grade sarcoma with an annual overall incidence of 0.041 per 100,000 persons.[11] Frequently, the tumor arises in the distal upper extremity (47%), typically in the hands and the forearms of individuals between the ages of 10 and 35 years. Other commonly affected sites include the distal lower extremities, proximal lower extremities, and proximal upper extremities, with percentages of 15%, 12%, and 10%, respectively. Though the distal lower extremity is the second most common primary site of epithelioid sarcoma, a primary lesion of the toe is a rare occurrence, with an incidence of less than 1%, as per reports by Enzinger and Chase.[2] A search of the English literature produced only 7 reported cases of epithelioid sarcoma with primary lesion located at the toe.[2,12-17]

To our knowledge, there has not been a reported case in the English literature demonstrating a primary lesion of the toe with both local invasion of bone, regional metastasis to the bone marrow, and intramuscular foci. Chase and Enzinger[2] reported the recurrence and metastasis rates to be 77% and 45%, respectively, with the most frequent sites of metastasis being the lung (51%), lymph nodes (34%), and the scalp (22%). Other sites of spread included bone, brain, and liver, with percentages of 13%, 13%, and 12%, respectively. Although their study of 11 cases showed a notable incidence of bone metastasis, it is difficult to discern whether these indi-

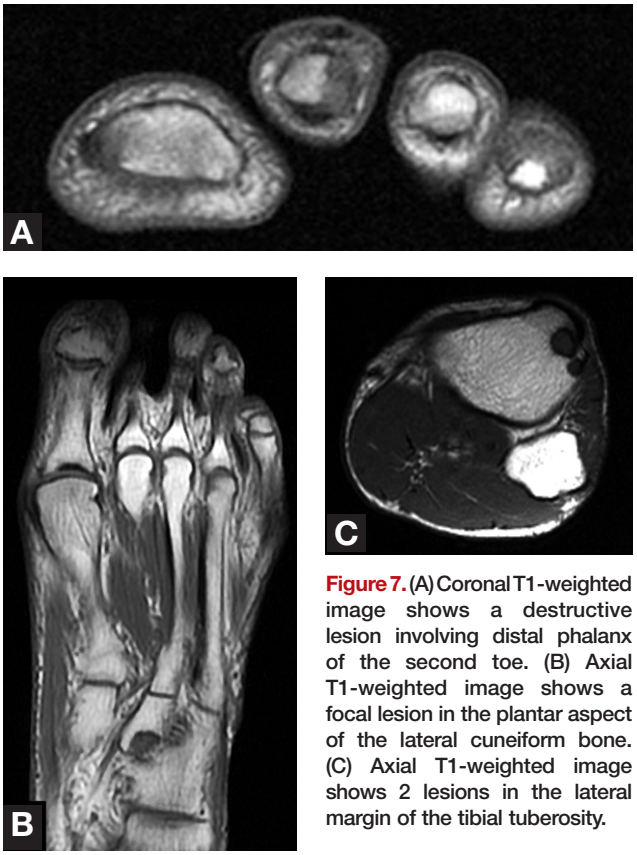


**Figure 7.** (A) Coronal T1-weighted image shows a destructive lesion involving distal phalanx of the second toe. (B) Axial T1-weighted image shows a focal lesion in the plantar aspect of the lateral cuneiform bone. (C) Axial T1-weighted image shows 2 lesions in the lateral margin of the tibial tuberosity.

viduals had true intraosseous metastasis of the bone or simply a local invasion of the tumor.[2] Our review of the English literature only identified 3 cases of true intraosseous metastasis, not including those of local recurrence or direct invasion of the bone.[15,18] It is also important to note that most soft tissue sarcomas spread hematologically, rarely metastasizing to bone or lymph nodes.[3] In a study conducted by Yoshikawa and colleagues,[19] bone metastasis was found in 27 individuals in 277 cases of soft tissue sarcomas, an incidence rate of 10%. Unlike the majority soft tissue sarcomas, epithelioid sarcoma displays an unusual tendency to spread via the lymphatic system and vascular system, thus explaining its ability to spread to areas such as the lymph nodes and the bone marrow, as well as the lungs and the brain.[2,10,20]

Misdiagnosis of epithelioid sarcoma is fairly common due to its insipid presentation and infrequent occurrence. Our patient presented with 2 months of constant pain of the second left toe that was exacerbated by prolonged rest. Initial assessment and radiographic findings at the outside institution led to a diagnosis of hammertoe deformity with possible plantar fasciitis. Enzinger and colleagues[2] report 148 cases of incorrect initial diagnosis of epithelioid sarcoma. The tumor was often confused with numerous other benign conditions, such as fibrous histiocytomas, fasciitis, reactive processes, synoviomas, and fibromas. In addition to the benign clinical presentation and infrequent occurrence, the uncommon primary location of the tumor prevents epithelioid sarcoma from being considered as a possible diagnosis.

The initial plain radiographs of the patient's left lower extremity were reevaluated at our institution. Radiographic review revealed a deformity of the left second proximal phalanx with a questionable soft tissue mass and erosion of bone which was not noted in the report from the outside institution. The radiographic findings of epithelioid sarcoma are inconsistent, but a soft tissue mass with possible speckled calcifications may be demonstrated. Other infrequent findings include cortical thickening, cortical thinning, and localized demineralization. Positive findings are often followed by MRI in order to further assess the abnormalities.[2,21] F-18 FDG PET-CT of the patient identified multiple lytic lesions in the left lower distal extremity, demonstrating both local invasion and distant metastasis. Incisional biopsy performed on the most proximal lesion of the left proximal tibia confirmed the diagnosis of epithelioid sarcoma. A recent study published by Sakamoto and colleagues[8] discussed the potential usefulness of FDG-PET in epithelioid sarcoma. The researchers presented a case in which a CT scan detected enlarged lymph nodes, but results from MRI and a plain radiograph were nonspecific and unable to indentify any space occupying lesions. These imaging studies were followed by FDG-PET that showed multiple areas of increased uptake, which were confirmed at a later time to be epithelioid sarcoma.[8] This study displays the value of FDG-PET in assisting with early diagnosis and treatment of epithelioid sarcoma metastasis, a value reiterated by this case.

It is interesting to note the relatively high recurrence rate, as reported in earlier studies of epithelioid sarcoma following presumed wide excision of the tumor.[2,20] PET for oncologic screening has been a fairly recent advancement in medicine, with the first whole-body oncology image presented by Phelps and colleagues[22] in 1991. Most large studies of epithelioid sarcoma were made prior to the development of advanced imaging technology. Therefore, with future studies of epithelioid sarcoma, it may be necessary to reevaluate recurrence rates of this disease following the use of current advanced imaging.

Initially, the outside surgical pathology reports indicated a possible diagnosis of epithelioid sarcoma versus poorly differentiated squamous cell carcinoma. Microscopically, epithelioid sarcoma often demonstrates tumor cells that appear as highly eosinophilic epithelioid cells, which display a single or multi-nodular pattern with central necrosis; variants include ovoid or polygonal cells and plump spindle-shaped cells. The difficulty of executing a histological examination of epithelioid sarcoma lies in the disease's ability to mimic the appearance of other disease processes. Deep ulcerated lesions with large ovoid epithelioid cells may be confused with poorly differentiated squamous cell carcinoma, while small superficial lesions with nodular patterns

may be mistaken for a benign inflammatory process.[2,3] However, careful examination of the tumor cells will usually demonstrate a lack of intracellular bridges that are usually quite prominent in squamous cell carcinoma. Furthermore, the use of immunohistochemical studies has been of tremendous assistance in correctly diagnosing epithelioid sarcoma. A recent study of 106 cases by Chbani and colleagues[6] demonstrated tumor cells staining positively for vimentin, EMA, cytokeratin AE1/AE3, and CD34 in 100%, 98%, 96%, and 62% of the cases, respectively. Surgical pathology reports from the other institution noted positive cytokeratin AE1/AE3 and vimentin staining but were negative for CAM5.2 and EMA. The paraffin blocks of the same sample in our hands demonstrated positive vimentin, EMA, and cytokeratin AE1/AE3, but were negative for CD34. In order to differentiate epithelioid sarcoma from squamous cell carcinoma, immunophenotyping for CK5/6 and p63, which are often immunoreactive in squamous cell carcinoma but are negative in epithelioid sarcoma,[4] were sent and found to be nonreactive. A diagnosis of epithelioid sarcoma with superficial ulceration and focal bone involvement was ultimately made. Due to the difficulty in interpreting the immunohistochemical characteristics of epithelioid sarcoma, the importance of an experienced musculoskeletal pathologist cannot be overemphasized.

In conclusion, we present a unique case of epithelioid sarcoma with regional bone metastasis and the difficulties found with diagnosing this disease. To our knowledge, this is the first case of an epithelioid sarcoma with a primary lesion of the toe with true intraosseous metastasis. Due to the challenging and inconsistent presentation of the disease, proper diagnosis can only be achieved by undertaking a multidisciplinary approach that includes thorough patient history and physical exam, radiologic imaging studies, histologic findings, and immunohistochemical analysis.

## Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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