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Misdiagnosis of epithelioid sarcoma

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Abstract
A 17-year-old female with no notable past medical history presented with a mass on the plantar surface of her right foot, initially misdiagnosed and treated as a plantar wart. Following multiple failed excisional procedures, a biopsy confirmed epithelioid sarcoma, 9 years after its first appearance. This case emphasizes the critical importance of thorough diagnostic workups for reoccurring masses, particularly for rare malignancies such as an epithelioid sarcoma. Certain factors such as an atypical demographic presentation, improper patient advocacy, confirmation bias, and insufficient diagnostic methods appear to have played a role in the delay of this diagnosis. An early and accurate diagnosis is imperative in improving outcomes and preventing the complications associated with delayed treatment.

Keywords: Epithelioid sarcoma, mass, plantar wart, malignancies, biopsy

Introduction
An epithelioid sarcoma (ES) is a rare, slow growing, soft tissue cancer. Soft tissue sarcomas account for 1% of adult cancers and epithelioid sarcomas account for 1% of all soft tissue sarcomas in the United States. This cancer typically presents on the distal extremities such as the forearms, hands, legs or feet in teenagers and young adults. Proximal epithelioid sarcomas are far less common and are seen in the adult population. Due to the rarity of this disease is, the statistics regarding survival rate vary greatly. In general, the 5 year survival rate for ES is between 25 and 92%. The exact cause of ES is unknown but some researchers suggest it is linked to a mutation in the SMARCB1 gene [1]. SMARCB1/INI1 is part of the SWI/SNF chromatin remodeling complex and mutations in this gene have been linked to cancer formation including pediatric rhabdoid tumors [2]. Some risk factors for soft tissue sarcomas are radiation exposure, chronic lymphedema, chemical exposure, and family history of sarcomas. Diseases such as Neurofibromatosis, Li-Fraumeni Syndrome, and Retinoblastoma are known to have increased risk of sarcomas. Although there are various risk factors, many patients diagnosed with sarcomas have no known risk factors [3]. ES may not cause many signs or symptoms, especially in the early stages. As the tumor grows a lump will develop. Lumps may be painful, have ulcerations and increase in size [1]. Despite its slow growth and lack of symptoms, this tumor can lead to death. Unfortunately, it is often misdiagnosed because of its nonspecific symptoms and rarity. Reporting and studying each incidence of this disease is critical to saving the lives of patients with ES. An early diagnosis can mean the difference between a positive and poor prognosis for a patient. Improved knowledge of this disease allows physicians to develop stronger diagnostic and treatment plans for their patients.

Case Presentation
A 17 year old female with multiple excisional surgeries to the right foot presented with mass on the plantar surface of the right foot. The patient first noticed the mass 9 years prior to being diagnosed with epithelioid sarcoma and reported difficulty ambulating due to the presence of the mass. Patient endorses sharp pains on the plantar surface of her foot that are intermittent and resolve without medication. The mass had been previously diagnosed as a plantar wart by a podiatrist and performed multiple procedures to remove it, including cryotherapy, cantharidin administration and surgical excision were performed without success.

Parents endorsed asking for a biopsy during this time but the doctor dismissed this request. After the 3rd excisional procedure, a biopsy was taken and the diagnosis was confirmed to be an epithelioid sarcoma. Patient was then referred to orthopedic oncology. MRI confirmed 2x2 cm mass on the plantar aspect of the right foot and appears to abut the plantar fascial aponeurosis but does not appear to penetrate. After evaluation, of neoadjuvant radiation therapy was prescribed. A sentinel lymph node biopsy was taken from the right medial thigh along with radical resection of the right plantar foot sarcoma. The wound was packed with micronized dermis 15 and 4x8 cm dermal matrix allograft was applied. Intraoperative margins were determined to be negative however the final pathology suggested the deep margins may be positive. It was determined that a radiation boost to the deep and medial margin of the tumor bed to mitigate tumor recurrence.

Discussion

The initial evaluation is done by taking a detailed history of when the mass was first noticed, the rate at which it has been growing, and whether symptoms indicate distal neurovascular compromise. Physical examination should entail size, depth, fixation to adjacent structures, and any signs of edema or nerve impingement [5]. A delay in diagnosis of ES is common as patients tend to avoid medical care due to the painless nature of ES and assumptions of benignity.

The United Kingdom Department of Health published criteria for urgent evaluation of a soft tissue mass if >5 cm, painful, consistently increasing, recurrence post-excision [5]. In a prospective review of 365 patients, tumor depth was the most sensitive malignancy marker [5].

Recommended imaging involves an MRI for a primary extremity or trunk lesion. Histologic examination of essential for diagnosis. It is recommended to obtain a specimen by core needle biopsy and to evaluate the specimen by a pathologist who specializes in soft tissue tumors [5].

Histology of ES reveals the presence of cytokeratin and epithelial membrane antigen, vimentin, and CD34. They are usually negative for INI-1, S100, CD31, neurofilament protein, carcinoembryonic antigen, and factor VIII-antigen [6]. The most widely used staging system is the tumor, node, metastasis (TNM) system [5].

ES usually presents as a slow-growing, painless, and multinodular distal upper-extremity swelling with lesions present in the dermis, subcutis, or the deeper fascia [7]. ES is usually less than 5 cm in the largest dimension, although the proximal variant of ES which is considered to be more aggressive, and tends to present in the pubic, genital, perineal and truncal areas can be as large as 20 cm [7]. It is aggressive in its local growth, with great potential to metastasize to regional lymph nodes, although it can also metastasize distantly to the scalp and lungs [7]. The differential diagnosis is vast, including fibromatosis, granulomatous diseases, nodular fasciitis, fibrohistiocytic lesions, tenosynovial giant cell tumors, metastatic carcinoma, melanoma, synovial sarcoma, vascular neoplasms, spindled squamous cell carcinoma, malignant peripheral nerve sheath tumor, and extrarenal rhabdoid tumor [7]. The majority of ES tumors completely lack integrase interactor-1 (INI1) expression, a finding seen in renal medullary carcinoma and extrarenal rhabdoid tumors, and to a lesser extent in epithelioid malignant peripheral nerve sheath tumors, pediatric myoepithelial carcinomas, and extra-skeletal myxoid chondrosarcomas [7-8].

If there is a primary ES tumor without metastasis, complete surgical resection can be curative, with added radiation therapy to reduce local recurrence as there is a risk of surgical resection in addition to late discovery of metastases [7]. Palliative measures including radiation therapy are options if the tumor is inoperable, if resections are incomplete, or if there is extensive metastatic disease [7]. Tazemetostat is an EZH2 inhibitor that was recently approved to treat advanced ES, with drug to drug interactions with moderate CYP3A inhibitors such as fluconazole, and no major renal or hepatic modifications necessary at this time [9].

Physicians may sometimes overlook symptoms for reasons such as the vague nature of early signs and preconceived notions based on patient demographics [10, 11]. Young patients, such as adolescents and adults, might not receive the attention they deserve when they exhibit atypical conditions for their age. The repeated surgeries undergone by the patient and the absence of an evaluation highlight a notable lapse in medical care [12]. Dismissal of symptoms can lead to delays in diagnosis, which can be detrimental to patient outcomes, particularly for aggressive cancers like epithelioid sarcoma (ES) [12, 13]. Early diagnosis and treatment are crucial in managing ES effectively. Patients should be encouraged to advocate for themselves, seeking second opinions if their concerns are not adequately addressed [10, 13].

Confirmation bias in the medical field occur when physicians focus on data that support their initial diagnosis while failing to seek out or consider contradictory evidence [4]. In this case, the physicians repeatedly treated the mass as a plantar wart. Despite multiple recurrences of the mass after removal, a biopsy was not performed even when the patient's family requested a biopsy be done. The unwavering belief that this patient had plantar wart caused a significant delay in diagnosis.

Healthcare providers should monitor persistent or recurring mass, regardless of the patient's age and demographics. Thoroughly reviewing patient history and conducting full physical examinations could ensure better outcomes [10]. MRI imaging and core needle biopsies aid in conclusive diagnosis when dealing with recurrent masses post-treatment in soft tissues [11]. Education and raising awareness through campaigns and ongoing medical education could aid in the early recognition of signs and symptoms of cancers such as ES, which could also lead to earlier referral and treatment processes [10, 11, 13].

Conclusion

Epithelioid sarcomas are a rare form of cancer with an insidious onset. In this case, there was a nine year delay in diagnosis due to several factors. Contributing factors include, inappropriate workup, lack of awareness for this disease and a failure to advocate for the patient. It is imperative that physicians become aware of biases they may have and how they could affect patient care. Confirmation bias is a common cause of inaccurate diagnosis of disease and in patients with cancer, this error can lead to metastasis and increased rate of patient mortality. Additionally, further education about this rare disease may lead to earlier diagnosis and treatment, thus improving patient prognosis.

Patient advocacy is a critical component in ensuring they receive the best medical care possible. Creating an environment where patients feel comfortable raising their concerns is one important component. The second component involves actively listening and ensuring appropriate steps are taken to address each concern.

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