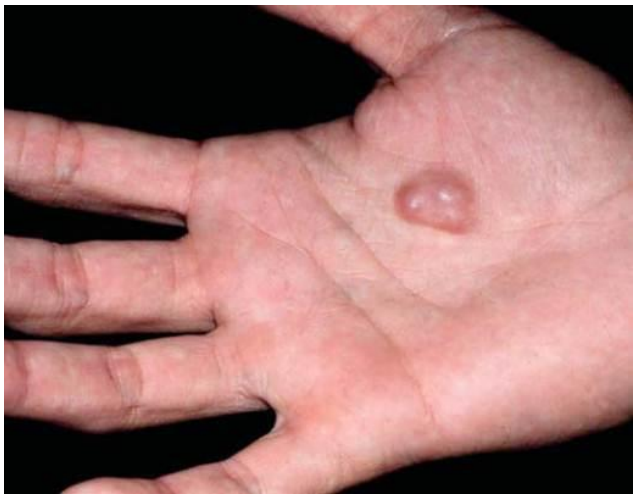
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Epitheloid Sarcoma

Introduction

Epithelioid Sarcoma (ES) is a rare soft tissue sarcoma in children and young adults (usually 20-39 year olds) involving the upper extremities 60% of the time. The name was given by Enzinger in 1970 to a group of soft tissue sarcomas that were confused with a variety of malignant and benign conditions, especially granulomatous process, synovial sarcoma and ulcerating squamous cell carcinoma. In 1997, a "proximal type variant" of epithelioid sarcoma was described arising in the deep parts of the pelvis, perineum, and proximal extremities. It consists of large epithelioid carcinoma–like and/or rhabdoid cells and has a more aggressive clinical course compared to tumours located distally.[10] This variant is also referred to as "large cell epithelioid sarcoma" due to presence of large rhabdoid cells.



[Picture Credit: Epitheloid Sarcoma Picture]

Epithelioid Sarcoma is a slow growing tumour with a high rate of recurrence and metastasis. Slow growth of the tumour, paucity of symptoms, benign appearance in early stage imaging studies, and indistinctive pathologic findings in some cases makes the diagnosis of epithelioid sarcoma challenging. The rarity of the disease also makes performing large controlled clinical trials to evaluate different treatment options almost impossible.

Epitheloid Sarcoma (ES)

Epithelioid Sarcoma is a rare, slow-growing type of soft tissue cancer. Most cases begin in the soft tissue under the skin of a finger, hand, forearm, lower leg or foot, though it can start in other areas of the body. It occurs more frequently in men. Typically, epithelioid sarcoma starts as a small firm growth or lump that's painless. It usually starts out as a single growth, but multiple growths may occur by the time a person seeks medical help. Sometimes this sarcoma appears as ulcers that don't heal, looking like open wounds over the growths.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Almost 40 years after Enzinger's first characterization of ES as a distinct clinicopathologic entity, ES is still of uncertain histogenesis (without a normal counterpart cell and a characteristic cytogenetic finding). However, it remains a distinct clinicopathologic entity with characteristic histomorphology, immunophenotype, and ultrastructure. The correct diagnosis of ES is essential because it can easily be misdiagnosed as another benign and less-aggressive malignant epithelioid lesions. Generally, the presence of large polygonal cells with prominent nucleoli and abundant necrosis on histology warrants the consideration of ES in the differential diagnosis. However, an immunohistochemical confirmation is a must for definitive diagnosis.

Rajeev, L.K., Asati, V., Babu, S., Babu, G. & Champaka, G. 2018.
"Epithelioid sarcoma first described by Enzinger (Cancer 26:1029-41, 1970) is a rare soft-tissue sarcoma typically presenting as a subcutaneous or deep dermal mass in distal portions of the extremities of adolescents and young adults. They are frequently mistaken for ulcers, abscesses, or infected warts that fail medical management. Patients often develop multiple local recurrences of long duration, with subsequent metastases in 30 to 50% of cases (Chase and Enzinger (Am J Surg Pathol 9:241-63, 1985))."

Incidence of Epitheloid Sarcoma (ES)
The South African National Cancer Registry does not provide any information on Epitheloid Srcoma.

Epitheloid Sarcoma has been shown to be the second most common soft tissue sarcoma in the hand and the sixth most common soft tissue sarcoma in the upper extremity. This tumour is more common in males (1.8:1) and affects the young adult population.

Signs and Symptoms of Epitheloid Sarcoma (ES)
Individuals who have Epithelioid Sarcoma usually notice a lump or mass somewhere in the soft tissue of their body. The mass can range in size from quite small to large. One can feel and sometimes see the tumour. Sores or ulcers may also appear over the mass or lump.

Epithelioid sarcoma can be present for months or even years before a person notices a mass. In most cases, Epithelioid Sarcoma does not spread. If it does spread, lymph nodes, the lungs and bones are the most common sites of metastases.

Diagnosis of Epitheloid Sarcoma (ES)
Epitheloid Sarcoma is often difficult to diagnose.

The following may assist in making a diagnosis:
Tests and procedures used in diagnosis of epithelioid include:

- Imaging**.** Magnetic Resonance Imaging (MRI) is typically the method of imaging because of the level of detail it provides. Sometimes other imaging tests, such as Computed Tomography (CT) or Positron Emission Tomography (PET), may be used.
- Biopsy**.** The doctor performs a biopsy using a long, thin needle to remove a sample of the suspected sarcoma or a larger lump for testing in a laboratory. Sometimes a biopsy sample is removed during

surgery. A pathologist analyses the sample to determine whether it is cancer, and if so, the type and whether it is aggressive.

There are no consistent or specific cytogenetic findings in ES, but several cases display chromosomal abnormalities in the 22q region. Additionally, inactivation of a tumour-suppressor gene *SMARCB1/INI1*, located at band 22q11, has been found in proximal, but not classic type, ES.

Ortoli JC, Mansouri S, Veron C, Servant JM, Marinho E, Aractingi S. 1998.
BACKGROUND: Epitheloid sarcoma is an uncommon malignant soft tissue tumor observed in the distal extremities of young men. We report a case of long standing ulceration of the sole which was found to be an epithelioid sarcoma.
CASE REPORT: A 78-year-old woman had an indolent ulceration of the left sole for several months. Physical examination disclosed a well demarcated 3-cm ulcerated lesion with a red center and flat edges. Skin sections confirmed the diagnosis of epithelioid sarcoma. Cells stained positively for anti-vimentin, anti-cytokeratin and anti-epithelial membrane antigen, but not for anti-S100 protein and anti-actin antibodies. Wide local excision was performed.
DISCUSSION: Epithelioid sarcoma is an uncommon malignant tumor which apparently differentiates from mesenchymatous cells. It is usually observed in the distal extremities in young males, predominantly the hands and forearms. The tumor presents a firm, flesh-colored indolent nodule. Ulceration usually develops and involves the subcutis and deeper soft tissue, particularly fascial planes, aponeuroses and tendon sheaths. Treatment is wide surgical excision with or without radiotherapy. The case reported here on the sole of the foot in a 78-year-old women is unusual. Clinicians should be aware that the initial biopsy may not be contributive and that repeated biopsies may be necessary for positive diagnosis.

Joseph, F., Sobanko, M.D., Lindsay Meijer, B.S. & Nigra, T.P. 2009.
Epithelioid sarcoma is a rare, highgrade, soft tissue tumor that has a known propensity for local recurrence, regional lymph node involvement, and distant metastases. We review the clinical and histological presentations of epithelioid sarcoma. Because epithelioid sarcoma presents innocuously, it is often mistaken as a benign process, which can result in insufficient treatment. Therefore, we emphasize the need for clinicians to consider this diagnosis when a slowgrowing tumor is found on the distal extremity of a young male as the malignancy inherently portends a poor prognosis. Prognostic factors, such as local recurrence, regional metastatic disease, and tumor width, are discussed along with current treatment modalities, which include radical excision, sentinel lymph node biopsy, and radiation.
Epithelioid sarcoma (ES) is a rare, high-grade malignancy that represents the most common primary soft tissue sarcoma of the hand. It was first described by Laskowski in 1961 as “sarcoma aponeuroticum” because of its involvement of aponeuroses and surrounding structures.[1] Less than a decade later, Enzinger coined the current term “epithelioid sarcoma” when recategorizing 62 previously misdiagnosed tumors.[2] Because of its epithelial and mesenchymal differentiation, this tumor was often mistaken for chronic inflammatory processes, necrotizing granulomas, and various fibrohistiocytic tumors.[3] These lesions were once documented clinically and histologically as malignant and nonmalignant conditions.[2] ES often presents in a banal fashion in young men, but its significance is great because of an inherent propensity for local recurrence in addition to regional lymph node involvement and distant metastases. Misdiagnosis of this tumor can lead to delayed and improper treatment, adversely affecting patient survival.

Treatment of Epitheloid Sarcoma (ES)
Epitheloid Sarcoma may be treated by means of:

Surgery
The patient may have a wide resection with margins, to remove the tumour and some tissue around the tumour. If the doctor is concerned that the cancer has also spread to nearby lymph nodes, they may also be removed. Amputation of part of the affected limb may be necessary in severe cases.

Radiation Therapy
Patients may have radiation treatment before surgery to reduce the size of the tumour. After surgery, additional radiation therapy may be used to help kill any tumour cells left behind in the body.
Two types of radiation are sometimes used - regular radiation or proton radiation. Proton radiation has less side effects because it kills the tumour but does not hurt organs and healthy tissue.

Chemotherapy
If the tumour is large or has spread to other areas, the doctor may recommend chemotherapy or other types of drugs to help kill the cancer cells.

Tazemetostat, an orally available, first-in-class EZH2 inhibitor, may become a new treatment option for patients with Epitheloid Sarcoma, according to interim data from an ongoing phase 2 study presented by Epizyme at the European Society for Medical Oncology (ESMO) 2018 Congress in Munich, Germany.

The prognosis for patients with epithelioid sarcoma is poor, because a substantial number of patients present with extensive disease, lymph node metastases, and/or distant metastases. Treatment consists of radical surgical excision of the tumour and, if indicated, therapeutic lymph node dissection. In patients who have large tumours, isolated limb perfusion may be useful.

Accelerated Approval of New Drug by the United States Food and Drug Administration (FDA)
The U.S. Food and Drug Administration (FDA) granted accelerated approval to Tazverik (tazemetostat) for the treatment of adults and pediatric patients aged 16 years and older with metastatic (when cancer cells spread to other parts of the body) or locally advanced (when cancer has grown outside the organ it started in, but has not yet spread to distant parts of the body) epithelioid sarcoma not eligible for complete resection (surgically removing all of a tissue, structure, or organ). Epithelioid sarcoma is a rare sub-type of soft tissue sarcoma that often occurs in young adults.

“Epithelioid sarcoma accounts for less than one percent of all soft tissue sarcomas,” said Richard Pazdur, M.D., director of the FDA’s Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA’s Center for Drug Evaluation and Research. “Until today, there were no treatment options specifically for patients with epithelioid sarcoma. The approval of Tazverik provides a treatment option that specifically targets this disease. When we brought Tazverik’s application to the Oncologic Drugs Advisory Committee last month, the committee voted unanimously that the benefits of the drug outweighed the risks.”

Tazverik blocks activity of the EZH2 methyltransferase, which may help keep the cancer cells from growing. Most cases of epithelioid sarcoma begin in the soft tissue under the skin of an extremity, though it can start in other areas of the body. Surgical removal is considered the main treatment when the cancer is localized to one area of the body. Chemotherapy or radiation may also be given. However, there is a high likelihood for local and regional spread of the disease even with treatment and approximately 50% of patients have metastatic disease at the time of diagnosis. Metastatic disease is considered life-threatening to the patient.

Wollina, U., Schönlebe, J., Haroske, G., Unger, L., Kittner, T., Tchernev, G., Chokoeva, A.A. & Lotti, T. 2015.
"Epitheloid sarcoma is a rare malignant soft tissue sarcoma. We present a 36-year-old male patient with a primary tumour on his wrist and subcutaneous spread in a sporotrichoid pattern along the upper extremity. Early surgical treatment with micrographic control of all margins provides best long term outcome as long as a solitary lesion is present. In case of cutaneous and internal spread of the disease treatment options are only palliative. Early diagnosis, therefore, is most crucial."

Jensen, D.B., Nielsen, N.H., Nielsen, P.L. & Krag, C. 1991.
"Epitheloid sarcoma (ES) is a malignant soft-tissue tumour which occurs particularly on the hand and forearm in young adults. The tumour grows slowly and metastasizes relatively late but has, nevertheless, a considerable mortality and morbidity because it is frequently erroneously diagnosed, both clinically and pathologically, either as a benign tumour or as a reactive inflammatory process. Two typical cases with diagnostic delays of 12 and 15 years, respectively, which required amputations through the upper arm or forearm are described. Even although ES is a rare tumour form, clinicians and pathologists should be aware of this possibility as, in the early stages, the tumour can frequently be treated effectively and radically by wide local excision without amputation."

Clinical Trials

Epithelioid sarcoma can be challenging to treat. In some situations, the doctor may recommend participating in a clinical trial.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

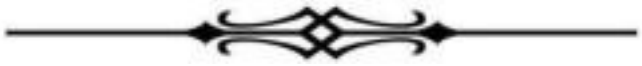
The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.



Sources and References Consulted and/or Utilised

Epitheloid Sarcoma
https://www.mayoclinic.org/diseases-conditions/epithelioid-sarcoma/cdc-20392420
http://sarcomahelp.org/epithelioid-sarcoma.html
https://www.archivesofpathology.org/doi/full/10.1043/1543-2165-133.5.814
https://www.frontiersin.org/articles/10.3389/fonc.2015.00186/full
http://www.pathologyoutlines.com/topic/softtissueepithelioidsarcoma.html
https://academic.oup.com/ajcp/article/131/2/222/1766026
https://www.cincinnatichildrens.org/health/e/epithelioid-sarcoma
https://www.mycancergenome.org/content/disease/epithelioid-sarcoma/
https://www.malacards.org/card/epithelioid_sarcoma
https://www.uptodate.com/contents/search?search=Epithelioid%20Sarcoma
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.22037
https://www.sciencedirect.com/topics/medicine-and-dentistry/epithelioid-sarcoma
https://www.cancertherapyadvisor.com/home/cancer-topics/sarcoma/tazemetostat-shows-promise-in-epithelioid-sarcoma/

Epitheloid Sarcoma Picture
https://www.orthobullets.com/pathology/8076/epithelioid-sarcoma

Jensen, D.B., Nielsen, N.H., Nielsen, P.L. & Krag, C. 1991. Epitheloid sarcoma – an overlooked diagnosis? *UgeskrLaeger*. 1991 Jun 24;153(26):1873-4.

Joseph, F., Sobanko, M.D., Lindsay Meijer, B.S. & Nigra, T.P. 2009. Epitheloid sarcoma: a review and update. *Journal of Clin and Aesth Dermatol.* Sobanko JF, Meijer L, Nigra TP. Epithelioid sarcoma: a review and update. *J Clin Aesthet Dermatol*. 2009;2(5):49–54.

Ortoli JC, Mansouri S, Veron C, Servant JM, Marinho E, Aractingi S. 1998. Epitheloid sarcoma manifesting as chronic plantar arch ulceration. *Ann Dermatol Venereol.* 1998 Mar;125(3):179-81.

Rajeev, L.K., Asati, V., Babu, S., Babu, G. & Champaka, G. 2018. Epitheloid sarcoma presenting as recurrent thumb ulcer: a lesson to learn. Indian *J Surg Oncol*. 2018 Jun;9(2):251-253. doi: 10.1007/s13193-018-0727-9. Epub 2018 Mar 20.

United States Food and Drug Administration
https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-option-specifically-patients-epithelioid-sarcoma-rare-soft-tissue

Wollina, U., Schönlebe, J., Haroske, G., Unger, L., Kittner, T., Tchernev, G., Chokoeva, A.A. & Lotti, T. 2015. Nodular epitheloid sarcoma of the upper limb. A case report and review of the literature. *J Biol Regul Homeost Agents*. 2015 Jan-Mar;29(1 Suppl):23-6.