Epithelioid sarcoma

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Epithelioid sarcoma (ES) is a very rare sarcoma characterized by loss of INI1. Enzinger first described ES in 1970, but the histopathologic differential diagnosis of ES remains challenging. There are two ES subtypes, the classical type with spindle epithelioid to the central pseudogranulomatous cells, and the proximal type, which is predominantly composed of epithelioid and rhabdoid cells. ES symptoms and signs are not specific and depend on tumor localization. The only treatment for ES is radical excision with a microscope-radical margin. In general, the best treatment for ES in extremes is radical resection with a wide margin or amputation with or without lymph node dissection. Surgery may be followed by adjuvant chemotherapy and/or radiation therapy. Referral of patients with ES to a sarcoma center that offers hypofractionation RT trials and multidisciplinary clinical trials should be considered upfront. Neoadjuvant chemotherapy with ifosfamide and doxorubicin with or without radiation therapy must be used after a multidisciplinary team discussion. On 23 January 2020, the US Food and Drug Administration (FDA) first approved tazemetostat – an inhibitor of zeste homolog 2 enhancer – therapy for metastatic ES or locally advanced ES not eligible for radical resection.

Key words: sarcoma, epithelioid sarcoma, Enzinger, tazemetostat

Introduction

Epithelioid sarcoma is a very rare (less than 1% of all soft tissue sarcomas) high-grade soft tissue sarcoma (STS) with a known propensity for locoregional recurrence and dissemination [1]. In general, ES tumors are built by spindled and epithelioid cells that circumscribe areas of central hyalinization and necrosis. Although ESs are of mesenchymal origin, their mixed differentiation makes their histopathological differential diagnosis challenging. The incidence in the EU and the United States is less than 0.2 and 0.5 new cases per million inhabitants per year, respectively. Enzinger first described epithelioid sarcoma (ES) in 1970 as a rare tumor of the distal extremities with epithelioid cytomorphology on pathological examination [2, 3]. The 5- and 10-year survival rates for ES are approximately 68% and 61%, respectively. No survival advantage was found for any gender, race, or ethnic group [4]. In the course of the natural history of ES, local failure occurs in approximately 25%, lymph node involvement in 30% and distant metastases are found in more than 40% of patients [5]. However, ES is commonly initially diagnosed as a benign condition, thus delaying definitive treatment. ES can also be misdiagnosed as another subtype of sarcoma:

• clear cell sarcoma,
• fibrosarcoma,
• synovial sarcoma,
• peripheral nerve sheath tumor,
• spinal cell sarcoma,
• fibrous histiocytosarcoma or other fibrohistiocytic tumor,
• nodular tenosynovitis or fasciitis.
• squamous cell carcinoma,
• Dupuytren’s disease,
• necrotising granuloma,
• rheumatoid nodule [6, 7].

There are two typical ES morphologies:

• the classical type, which is a spindle-epithelioid to central pseudogranulomatous cells, and
• the proximal type, which is predominantly composed of epithelioid and rhabdoid cells.

Proximal ES is also known as the large cell subtype. The classic ES type is epidemiologically more common than the proximal type. Furthermore, the classic subtype is most commonly diagnosed in adolescents and young adults (10 to 40 years of age), while the proximal one in adults between 20 and 65 years of age. Classic ES is usually diagnosed in locations of the distal upper extremities with more than 50% developing in the hand and fingers. Proximal ESS develops more often in the hip, trunk, pelvis, pellencanal cavity, or inguinal and genital area. Proximal ES type is built of large cells with prominent nucleoli that resemble a poorly differentiated carcinoma and a frequent rhabdoid phenotype. In ES, periosteal bone invasion may also occur, as well as central necrosis of the tumor, its hemorrhage or ulceration [8].

Epithelioid sarcoma symptoms and signs are not specific and depend on tumor location, therefore include a lump or swelling in the area, with masses greater than 20 cm, slightly mobile tumors, painful on palpation and without skin changes, or ulcerated and indurated lesions, but also rectum bleeding, vaginal bleeding, epistaxis, hemoptysis, nausea, vomiting, abdominal pain, abdominal fullness, ptosis, headaches, neck swelling in the area, with masses greater than 20 cm, slightly mobile tumors, painful on palpation and without skin changes, or ulcerated and indurated lesions, but also rectum bleeding, vaginal bleeding, epistaxis, hemoptysis, nausea, vomiting, abdominal pain, abdominal fullness, ptosis, headaches, neck pain, eye pain and swelling, diarrhea or constipation, depression, anorexia, weight loss, or fever [2]. Regional spread of ES through lymphatic drainage and/or direct infiltration results in lymph node metastases, while distant metastases arise with hematogenous spread mainly in the lungs or liver [9]. Indolent tumor growth along with distal location may also lead to inappropriate primary diagnosis and subsequent surgical procedures prior to referral to the reference sarcoma clinic [10, 11]. Most often, at first, ES presents as a slowly growing, painless, and firm nodule, but the course of ES is unpredictable, including rapid progression with extensive lymph node or distant metastasis development. Furthermore, the natural history of ES is characterized by a high risk of multiple recurrences. ES tends to spread along the fascia and muscles, resulting in multifocality of the tumor [10, 12–14]. The 5-year risk of recurrence after radical treatment is high, up to 70% [5, 13, 15, 16]. The ES tends to have regional lymphatic spread by more than 20% [6, 17, 18]. Patients with proximal-type tumor, ES tumor diameter >5 cm, multifocal tumors, nodal involvement, ES tumor necrosis, vascular invasion, and high mitotic index have shorter 5-year disease-specific survival (DSS) [14].

Epithelioid sarcoma has a complex genome with a high mutational rate that is comparable to that of ovarian carcinoma. More than 90% of ES cases are characterized by the loss of function of integrase interactor 1 (INI1; SMARCB1/ hSNF5 – chromatin regulator, subfamily B, member 1 or malignant rhabdoid tumor suppressor) [11, 19]. The INI1 protein is a core component of the SwItch/ sugar non-fermentable (SWI/ SNF) chromatin remodeling complex that alters the structure of chromatin and facilitates transcription, replication, and DNA repair. INI1 is located on chromosome 22q11.2 [20]. Other key SWI/SNF complex subunits are BRG1 (SMARCA4), BRM (SNF2L2, SMARCA2), PBRM1 (HP1B, BAF180), and BAF155 (SMARCC1) that can all be lost in ES [21]. In ES, multiple mechanisms lead to inactivation of SMARCB1, including homozygous deletions, monallelic deletion, nonsense point mutations, epigenetic mechanisms, and microRNA down-regulation of mRNA [22]. INI1 signals regulate chromosomal stability by signaling through the p16INK4a-Rb-E2F pathway. At the same time, in tumors with the INI1 gene, zeste homolog 2 (EZH2) signaling is up-regulated [23]. As a result, EZH2 is recruited to Polycomb targets and trimethylation of histone 3 lysine 27 in these regions leads to repression of target genes [24]. The loss of INI1 expression is characteristic for both conventional ES and proximal ES [20].

Epithelioid sarcoma is characterized by the expression of carcinoma markers (e.g. cytokeratin and EMA) and sarcoma markers (e.g. vimentin), as well as CD34, while negative for: S-100, and CD31 [14]. Other alterations found in ES cells include activation of PI3K/AKT/mTOR, overexpression of EGFR, and activation of MET [11]. In an animal model, it was proven that smarcb1 deficiency with concordant TP53 mutation is sufficient to induce the development of ES [25]. In ES cells, it was shown that SMARCB1 negatively controls the expression of cyclin D1, E2F, and AURKA. As a result of the loss of SMARCB1 in these tumors, cyclin D1, E2F, and AURKA are upregulated and stimulate the cell cycle. In normal cells, SMARCB1/INI1 suppresses tumor progression by p16INK4a signaling to pRB (retinoblastoma), a tumor suppressor that negatively regulates cell cycle progression from G0/G1 to the S phase. At the same time, enhanced MYC activity and increased DNA replication are found in cells with SMARCB1 loss. Importantly, SMARCB1 interacts with the BRCA1, BARD1 and XPC proteins responsible for nucleotide excision repair. It also regulates chromosomal stability [26]. As a result, SMARCB1 loss results in the fast proliferation of cells and mutation accumulation. SMARCB1 also inhibits the signaling of the sonic hedgehog (SHH) pathway, and this pathway is important in the development of radio and chemo-resistance [27, 28]. Next-generation sequencing (NGS) may enable further insights into the pathogenesis of ES, allowing genetic classification and biomarker discovery. NGS may also be used to verify diagnoses [29, 30].

Radical treatment

The curative treatment of ES is radical excision with wide R0 margins. In general, the best treatment for ES in the extre-
mities is en bloc excision. In cases with large tumors, amputation must often be performed in order to obtain radical resection with tumor-free margins. Primary tumor resection may be accompanied by lymph node dissection. After MDT adjuvant chemotherapy and/or radiation therapy can also be used in high-risk patients [31–33]. MDT should consider neoadjuvant chemotherapy for ES patients based on prognostic stratification with Sarculator nomogram for STS (https://www.sarculator.com/) [32, 34, 35].

The proximal subtype of ES is more aggressive, has higher rates of recurrence and metastases, and generally worse prognosis and higher mortality compared to classical ES [36]. In ES treatment, a sophisticated and well-planned surgical reconstruction can be performed with microsurgery, including free flap reconstruction or tendon transfers. In general practice, most ESs are extracompartamental and infiltrate surrounding tissues, including the neurovascular plexus. Consequently, due to anatomical constraints, conservative surgery is not always possible in the case of locally advanced tumors. Furthermore, due to a common location in the distal part of the extremities, in cases of extensive infiltration of the soft tissues that limits the possibility of reconstruction, amputation can also be required [10, 12, 13]. In centrally located ES tumors, the complex anatomy surrounding the spine further complicates the treatment and often makes complete resection R0 extremely difficult or impossible [37]. If lymph node metastases occur, therapeutic lymph node dissection (LND) should be performed [6, 10, 38]. The high rate of nodal involvement may justify performing a sentinel node biopsy (SLNB) in selected cases of ES, but a low percentage of occult metastases was reported in this subtype of sarcoma. However, SLNB should be considered as a minimally invasive N disease staging procedure [17, 39–41].

Neoadjuvant chemotherapy and radiotherapy (RT) can be considered in patients with ES after multidisciplinary team evaluation (MDT) [42]. In fact, radiation therapy has been reported to reduce the risk of local recurrence, but not overall survival (OS) [43]. At this point in time, radical surgery with conventionally fractionated perioperative RT is considered the standard of care in ES [44], while patients should be referred to trials with RT hypofractionation and combined therapy clinical trials when available in a sarcoma center. There are no phase III data on the role of RT in recurrent and metastatic ES. If RT was not used in radical treatment, perioperative RT may be considered in recurrent ES. In the event of a local recurrence in the field, re-irradiation should be considered only in selected cases. Patients with a limited volume of local ES recurrence can be treated with perioperative or definitive brachytherapy in sarcoma centers [45]. Select ES patients with oligometastases may receive definitive radiation therapy [46, 47]. Patients with large recurrent ES tumors may receive multidisciplinary treatment with chemotherapy with RT with/without hyperthermia after MDT [48]. Palliative RT can be used for symptomatic ES metastases (palliative single fraction) [11].

In some cases, after MDT, perioperative chemotherapy can be considered [5, 13, 49, 50]. According to the current ESMO–EURACAN–GENTURIS Clinical Practice Guidelines, neoadjuvant treatment of operable localized STS of the extremities and the trunk wall is not yet standard treatment, although it can be proposed for fit patients with high-risk disease [51]. In patients with ES, MDT may advise perioperative chemotherapy for patients with large, high-grade tumors. After surgery with incomplete resection, as well as in cases of up-front metastases, chemotherapy is also considered [42, 52]. In studies by NIO-PIB, the Royal Marsden Hospital, Japan, and the French Sarcoma Group, doxorubicin with ifosfamide (AI) was the most commonly used [13, 49, 53, 54]. After neoadjuvant chemotherapy, objective and/or pathological responses are expected in 15% of cases [13, 49, 55]. Chemotherapy regimens used in radical and/or first-line treatment should be based on doxorubicin. In addition to the AI regimen and doxorubicin monotherapy, the use of CyVADIC (cyclofosfamide, vincristine, doxorubicin, and dacarbazine) and VAIA (vincristine, doxorubicin, ifosfamide, actinomycin-D) have also been reported [11, 50]. Most recently, ES patients were recruited into a trial of radiation therapy with or without combination chemotherapy or pazopanib prior to surgery to treat patients with newly diagnosed non-habadomysarcoma soft tissue sarcomas that can be removed by surgery. There are no reports on the association between perioperative chemotherapy and OS, DMFS, or LRFS [5, 42, 50, 52].

**Systemic therapies in advanced epithelioid sarcoma**

Epithelioid sarcoma metastasizes most frequently to the lungs or pleura [6, 12, 15, 56]. High-risk epithelioid sarcomas are patients with large tumors, high tumor grade, inadequate tumor resection, and metastatic disease, predicting a relatively poor clinical outcome [57]. There are no specific guidelines based on high-quality evidence on systemic therapy in advanced ES [58]. Patients treated at Royal Marsden Hospital benefit from significantly longer OS when treated with palliative chemotherapy versus BSC (mOS: 16.8 vs. 8.7 months, p = 0.044) [50]. Most available data on systemic ES therapy are reported as retrospective studies, case series, and case reports. Only a small number of patients with ES were treated in clinical trials. 27 ES patients were treated in EORTC trials 62012, 62043, 62072 and 62091. Among these cases, objective responses were reported for those treated with doxorubicin with ifosfamide (12.5 – 1/8), pazopanib (objective response rate [ORR] 100% – 2/2), or trabectedin (33.3% – 1/3), but without OR when treated with doxorubicin monotherapy. The median progression-free survival (PFS) for patients treated first-line was 4.04 months. The median OS of these patients was only 10.93 months [59]. The analysis of 74 patients with ES has shown that patients receiving first-line systemic therapy have ORR of 15%, disease control rate (DCR) of 20%, and a median duration of
In this case, the response CR was 4 years long [66]. Another ES complete remission (CR) of ES pulmonary metastases treated din [63, 65]. An interesting case report was published showing
famide, gemcitabine with cisplatin, dacarbazine, and trabectedin with gemcitabine 1250 mg/m² every 2 to 4 weeks) therapy. In this case, the response CR was 4 years long [66]. Another ES case achieved a partial response (PR) with a duration of 27.4 months [67].

Targeted therapies for ES are still in development. **Pazopanib** is the first tyrosine kinase inhibitor (TKI) approved for ES therapy [50, 61]. In a case series of 18 pazopanib patients treated, no ORRs were reported; 50% of the patients benefited with stable diseases (SD), but PFS was only 3 months. However, PR case reports on pazopanib treatment in patients with metastatic ES have also been published [68, 69]. In the pulled analysis of the EORTC trial, pazopanib was used in patients with ES in the second line and resulted in ORR 11.1% (1/9) and a median PFS of 2.73 months [59]. A case report on **sunitinib** therapy in ES was published. This patient achieved long-term stabilization of the disease (>32 months) after progression in two lines of chemotherapy [70]. Sunitinib in combination with nivolumab was found to improve PFS in patients with advanced epithelioid sarcoma [71].

Another therapy that has shown some benefit in case series is another TKI, anlotinib, in combination with PD-1 inhibitors [72]. Some data on **dasatinib** activity in ES are also available. In an open-label single-arm SARC0009 study 2/7 patients achieved objective tumor responses according to Choi's criteria. The mPFS was 7.9 months and the PFS rate at 6 months was 57%. However, the OS was poor with a 2-year OS rate of 21% [73]. Another study investigates ipilimumab in combination with dasatinib in patients with refractory and/or unresectable GIST or other STS, including epithelioid sarcoma [74].

As ES sarcoma was reported to have a relatively high mutation rate, it is a candidate for **immune checkpoint inhibitor** therapies [75]. ES patient were recruited in a KEYNOTE-051 study of pembrolizumab in patients with PD-L1 positive, advanced, refractory, or refractory solid tumors, but no subgroup ORR was reported until now [76]. Case reports of the efficacy of pembrolizumab in advanced ES in adults have also been published. Pembrolizumab was used in the second line of palliative therapy, after chemotherapy with doxorubicin-ifosfamide [77]. In the study of nivolumab, a 24-year-old male ES metastatic lung patient had PR after 4 immunotherapy cycles, but the response was not durable as the patient progressed after the next 4 cycles [78]. An interesting case of long-term response to camrelizumab was recently published. This patient had high expression of PD-L1 and a high number of tumor-infiltrating lymphocytes in the tumor [79]. Currently, patients with ES are enrolled in a study of nivolumab and ipilimumab in children and young adults with INI1 negative cancers and tigolimumab and atezolizumab for the treatment of SMARCB1 or SMARCA4 deficient tumors.

On 23 January 2020, the US Food and Drug Administration (FDA) approved the first EZH2 methyltransferase inhibitor – **tazemetostat** – for the treatment of patients with locally advanced and metastatic epithelioid sarcoma not eligible for complete resection in patients older than 16 years. In a phase I trial (NCT02601937) for patients with tazemetostat ES, they achieved SD and continued treatment for >20 months [80]. Later, FDA approval was granted based on the results of a phase 2 trial (NCT02601950). In the analyzed ES cohort (cohort 5), 62 patients were treated, 24 in the first line and 38 in the second
Epithelioid sarcoma is built by pleomorphic epithelioid cells and the proximal subtype is more aggressive than the classical subtype, as it has higher recurrence and metastasis rates, and shorter overall survival. ES occurs more frequently in adolescents and young adults with a slight predominance of men. Loss of expression of SWI/SNF chromatin-remodeling complex proteins plays an important role in ES development. At initial diagnosis, the tumor stage should be evaluated not only with clinical and radiological examination, but also with imaging focused on regional lymph nodes and the chest. During the follow-up, patients should be examined regularly with clinical and radiological examination, but also with imaging focused on regional lymph nodes and the chest. Radiation therapy should be considered after MDT to decrease the local recurrence rate. Currently hypofractionated preoperative RT may be advised [87, 88]. Referral to a sarcoma center for hypofractionated radiotherapy with hyperthermia may be considered in patients with marginally resectable or unresectable ES and in patients who are not eligible for chemotherapy [89]. Adjuvant radiation therapy is recommended in cases with positive margins (R1/R2 resections). Local recurrences are common in ES and most often develop within six months after radical treatment. Up to 75% of cases with local recurrence also develop distant metastases [9]. However, most patients have an advanced stage at first diagnosis with lymph node and/or lung metastases. Chemotherapy may provide palliation in patients with metastatic and unresectable epithelioid sarcoma, but responses are short and there is still an unmet need for more effective novel targeted therapies. Immunotherapy may be an alternative option for patients with metastatic ES. Most recently, tazemetostat showed activity in advanced ES with loss of SMARCB1. Tazemetostat therapy is a new treatment option for patients with ES approved by the FDA [90, 91].

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