Proximal-type epithelioid sarcoma of the groin: Clinical experience and literature review

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ABSTRACT Background: Epithelioid sarcoma (ES) is a rare soft tissue tumor that mainly occurs

under the skin of the extremities. ES in the groin area may be easily misdiagnosed with undifferentiated pleomorphic sarcoma, leiomyosarcoma, rhabdomyosarcoma, and

other mesenchymal tumors. Herein, we reported a single case of a patient with

proximal-type epithelioid sarcoma of the groin, including its clinical and imaging

findings. We also discussed some previously reported similar cases. *Case Presentation*: Our ES patient was a 24-year-old male who developed a subcutaneous nodule in the

groin area 1 year before admission. After careful clinical and pathological examination,

the patient was diagnosed with ES. He received chemotherapy (doxorubicin,

ifosfamide plus cisplatin) and, later on, surgery. His symptoms improved, and he is still

being followed up. In addition, we conducted a review of the literature and compared

our data with 12 previously reported similar cases (including 17 patients with ES involving the groin). *Conclusion*: ES is a highly invasive tumor prone to metastasis and

postoperative recurrence. Surgery seems to be the most effective treatment for ES. The effectiveness of auxiliary and radiotherapy needs to be confirmed by a large

amount of data. A systematic understanding of the clinical and imaging features of ES

in the groin area may help clinical and imaging doctors to correctly diagnose the

► Case report

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INTRODUCTION

disease.

Epithelioid sarcoma (ES) is a rare mesenchymal tumor of uncertain origin and slow growth, whose incidence accounts for about 1% of soft tissue tumors. ES shares similar morphology and immunohistochemistry with some epithelioid tumors and thus may be easily misdiagnosed. This may further lead to insufficient treatment and early death ⁽¹⁾.

The etiology and pathogenesis of ES are still unclear, and there is no definite genetic basis. However, some studies suggested that the occurrence of ES might be related to the loss of SMARCB1/INI1 protein expression ^(2,3). ES can occur in any part of the body at any age but is more prominent in young adult men ⁽¹⁾. The morphological characteristics of ES usually manifest as single, hard bean-like nodules under the skin ⁽⁴⁾.

Clinically, ES is classified into classic or distal and proximal types ⁽⁵⁾. The distal type is more common and mainly occurs under the skin of the distal hand. It is also foot-related to tendons or aponeurosis. The proximal type occurs in the head and neck, trunk, pelvis, groin, perineum, external genitalia, and other parts and often manifests as nodules or masses involving the subcutaneous or deep soft tissues; when the lesion is large, hemorrhage and necrotic cystic change may also occur ⁽⁶⁾. The proximal-type ES can maintain a slow growth for a long time and can be easily mistaken for a benign lesion. Nonetheless, it is a highly malignant and aggressive tumor with poor therapeutic effect and susceptibility to recurrence and metastasis ⁽⁷⁾. Herein, we reported a single case of a patient with proximal-type epithelioid sarcoma of the groin, including its clinical and imaging findings. We also discussed some previous similar cases reports, which may be helpful in differentiating this type of malignancy from other tumors.

Case presentation

A 24-year-old male was admitted to our hospital with a left inguinal mass that appeared one year ago. The mass showed signs of significant enlargement and was accompanied by pain that lasted for the last two months. Physical examination revealed a hard closely attached to the skin in the mass corresponding area. The skin was still intact, and no ulceration was observed. Serum tumor markers showed a slight increase in neuron-specific enolase (NSE) value (28.280 ng/ml, reference value <16.3 ng/ ml); the values of other tumor markers, such as alpha -fetoprotein and carcinoembryonic antigen, were within the normal reference range. Based on the above clinical manifestations, physical examination, and laboratory examination results, the presence of a

malignant tumor was suspected. Consequently, a part of the tumor tissue was collected for immunopathological examination. Under the microscope, tumor cells appeared pleomorphic and with nodular arrangements, most of which are epithelioma-like cells. Immunohistochemical results showed that cytokeratin (CK), epithelial membrane antigen (EMA), Vimentin, CgA, inhibitor $bin\alpha$, Melan-A, and S100 were positive; Ki-67 was about 40% positive, and Syn was weakly positive (representative pathological and immunohistochemical images are shown in figure 1); all reagents were purchased from Fuzhou MXB Biotechnology Co., Ltd., China. The histopathological diagnosis was ES. To further assess the extent of tumor invasion and stage and to determine the treatment plan, the patient underwent a whole-body fluorine 18 labeled deoxyglucose positron emission tomography/ computed tomography (18F-FDG PET/CT) examination (Biograph mCT; Siemens; Germany); ¹⁸F-FDG PET/CT data are shown in figure 2. The results showed mass hypermetabolic regions in the coccyx and the left inguinal region. Moreover, bone destruction was seen in the coccyx. Considering that the patient developed distant metastases, he was treated with a chemotherapy regimen of doxorubicin, ifosfamide plus cisplatin. During chemotherapy, blood routine monitoring was conducted every two weeks. After receiving chemotherapy for eight months, the groin mass on the patient's left side was significantly reduced; thus, the doctor decided to surgically remove the mass.

Under general anesthesia, the patient underwent enlarged resection of the left inguinal mass, left inguinal lymph node dissection (postoperative pathology confirmed with lymph node invasion), and left anterolateral thigh pedicled flap transfer repair. After surgery (1 day later), symptoms were relieved, and the patient was able to walk slowly. After surgical removal of the lump in the left groin, the patient was followed up for 17 months. Currently, the patient is still regularly receiving chemotherapy. Recently, he complained about the bulging feeling in the anus, so another CT scan (16 slices Spiral CT, GE Corporation, USA) was performed. CT data showed no tumor recurrence in the surgical area of the left groin, while the soft tissue mass in the tailbone area was larger than before the operation, as shown in figure 3.

Literature search for similar cases

PubMed, Embase, and Cochrane Library databases were searched for reports on Inguinal ES cases and case series published before March 31, 2021; only English articles were searched. The following keywords were used: "groin OR inguinal OR inguinal" AND "epithelioides sarcoma". Through the gradual elimination of duplicate literature, reviews, irrelevant publications, and articles that did not describe patients' clinical data, 12 full texts (including 17 patients) were obtained; a detailed screening flowchart of the literature is shown in figure 4. The detailed information of the patient's age and gender, the largest diameter of the mass, the lateral position (left or right), imaging findings, distant metastasis location and recurrence time, treatment decision, and follow-up time are presented in table 1.

According to the results of our literature search, only 21 cases of ES involving the inguinal area have been reported so far (8-19). Tateishi et al. included 4 cases of inguinal ES; however, since they reported no detailed clinical data of the patients, their study was excluded (20). We finally included and analyzed the clinical features of 18 cases of inguinal ES (including our case). The age range of the patients at the time of diagnosis was 10 to 64 years, the median age was 37.5 years, and the average age was about 36.7 years. There was no significant difference in the occurrence of ES in the groin area in terms of location and gender (both accounted for 50% of each, and most of the patients (14/18) were Asians) (figure 5). ES in the inguinal area was prone to metastasis (10/16) and postoperative recurrence (9/16), where the most common was lymph node metastasis (8/10), followed by bone metastasis (3/10) and other metastatic locations including lung, and abdominal wall. Out of 18 patients, 15 were timely followed-up. Kaplan-Meier survival curves were used to assess patient survival, and the average survival time of ES patients in the groin area was 120 months. Gender, type of treatment (whether combined with radiotherapy and chemotherapy after surgery), and whether metastasis occurred at the time of diagnosis resulted as factors that did not affect the average survival rate (*p* values < 0.05, as shown in figure 6).



Figure 1. Histopathological and immunohistochemical tumor staining. (A) Hematoxylin and eosin-stained sections of the tumor, the tumor cells are arranged in nodular shape, mainly epithelioid cells, Magnification, ×200; Immunohistochemical staining shows that the tumor cells were positive for CK (B, magnifification, ×40), EMA(C, magnifification, ×200) and vimentin (D, magnifification, ×100).



Figure 2. PET/CT examination of epithelioid sarcoma in the inguinal area. (A). The MIP (maximum intensity projection) figure showed a large mass of increased FDG uptake in the pelvic area, and SUVmax was 17.1(arrows). On axial PET (B, C) and fusion images (D,E), activity enhancement was located in the coccygeal vertebra (black arrow) and left inguinal region (white arrow). Axial CT showed bone destruction in the coccygeal vertebra (F, black arrow) and soft tissue mass shadows in the left inguinal region (G, white arrow).



Figure 3. Postoperative CT examination (A) showed that there was no obvious tumor recurrence at the operation site of the left groin area (arrows), but the soft tissue mass in the coccyx area was larger than before operation (pentagram arrow, B is preoperative).



Figure 5. Clinical distribution and characteristics of epithelioid sarcoma in the inguinal area. The occurrence of epithelioid sarcoma in the inguinal area is not significantly different between men and women, and on the left and right sides, and the proportion of Asians is higher than that of other places. It is prone to metastasis and recurrence, and the metastatic sites are mainly lymph nodes, followed by bones.



Figure 6. Kaplan-Meier overall survival (OS) rate of epithelioid sarcoma in the inguinal area. (A). OS in all cases (N=15, 3 patients with no recorded follow-up time were excluded from the analysis), the mean survival time of patients is 120 months; (B).OS by gender; (C).OS by treatment; and (D). OS by stage.

| | Year/Nation | Sex/ Age | MD (cm)/ Side | History | | | | | |
|---|------------------|-------------|---------------------|---|-------------------|--|---|-----------|-----------------------|
| Study/ References | | | | | Methods | Imaging findings | Metastasis/ Recurrence | Treatment | Follow-up (months) |
| Mahajan et al. ⁽⁸⁾ | 2016/India | M/20 | -/L | Painless soft tissue mass | СТ | Low-density soft tissue mass surrounding the iliac vessels | lliac fossa LN | S+C | 24(0) |
| Irimura et al. | 2015/Japan | M/38 | 11/L | Left groin discomfort for 1 year | MR | T1WI is iso-signal, T2WI is uneven and high-signal, obviously enhanced | Lung | S+C | 54(0) |
| Kim <i>et al.</i> ⁽¹⁰⁾ | 2012/Korea | F/40 | 2.4/L | Groin mass | PET/CT | Soft tissue mass with radioactive uptake | 2 years recurrence | S | 42(0) |
| Rekhi <i>et al.</i> ⁽¹¹⁾ | 2016/India | M/46 | - | - | - | - | - | - | - |
| Fujiki <i>et al.</i> | 2015/Japan | F/64 | -/R | Painless soft tissue mass | - | - | None | S | 14(0) |
| Dainichi et al. ⁽¹³⁾ | 2008/Japan | F/37 | -/L | - | PET/CT | Soft tissue mass with radioactive uptake | - | - | - |
| Flucke et al. | 2010/ Germany | F/25 | 4.0/- | - | - | - | 1year recurrence | S | - |
| Rekhi et al. | 2016/India | F/58 | 5.0/R | Groin mass | MRI and PET/CT | T1WI is iso-signal, T2WI is uneven and high-signal, obvi- ously enhanced; high radioac- tivity uptake, SUVmax =25.13 | Abdominal Wall;3 years recurrence | S+R | 53(0) |
| | | F/33 | 3.2/R | Groin mass 1month | - | - | None | S+R | 7(0) |
| Khazeni <i>et</i> <i>al.</i> ⁽¹⁶⁾ | 2018/USA | F/33 | 3.6/R | Groin mass | СТ | Soft tissue masses with uneven density | Inguinal LN | S+C+R | 9(1) |
| Mannan et al. ⁽¹⁷⁾ | 2010/ Kuwait | M/47 | 14/R | Painless soft tissue swelling lasts for 1 year | CT/MRI | Low-density soft tissue mass: T1WI is iso-signal, T2WI is uneven and high- signal, obviously enhanced. | None | S | 14(0) |
| Hasegawa et al. ⁽¹⁸⁾ | 2001/Japan | M/43 | 4/- | Groin mass | - | - | 44months recurrence; LN ;Bone | S+C+R | 120(1) |
| | | M/47 | 3/- | Groin mass | - | - | 2 months recurrence; LN | S | 6(1) |
| | | F/26 | 2.5/- | Groin mass | - | - | 15months recurrence; LN | S | 18(0) |
| | | M/46 | 5.0/- | Groin mass | - | - | 93 months recurrence; LN; Bone | S+C+R | 226(0) |
| | | F/23 | 4.0/- | Groin mass | - | - | 144 months recurrence; LN | S | 188(1) |
| Kodet <i>et al.</i> | 1994/USA | M/10 | - | - | - | - | 23 months recurrence | S+C+R | 115(1) |
| | Present case | M/24 | 12/L | Groin mass 1year | PET/CT: | Soft tissue masses with uneven density; high radioac- tivity uptake, SUVmax=17.1 | Bone; Inguinal LN | S+C | 25(0) |

Table 1. The clinical features of epithelioid sarcoma in the inguinal area reported in the literature.

DISCUSSION

Primary tumors that occur in the groin area are relatively rare. We discovered that only 21 ES cases involving the groin area had been published so far (taking into consideration only English articles). Although ES in the groin area is uncommon, it is more aggressive than the classic ES that occurs in the distal extremities ⁽⁸⁾. Consistent with our data, the clinical history of most ES patients in the literature showed slow-growing painless nodules or masses in the groin. The masses can infiltrate the skin and form ulcers locally as the disease progresses. At present, the main causes leading to ES remain unclear. A previous study suggested that skin damage, history of trauma, or scar tissue formation after skin damage are important factors related to ES ⁽²¹⁾. Our patient showed a left inguinal nodule on admission, which was also why he did not timely receive radical surgery.

Like proximal-type ES in other areas, the imaging features of ES in the inguinal area are usually not specific. ES in the inguinal area often appears as a slightly low-density soft tissue mass on CT; yet, the boundary is often unclear. Low-density cystic necrosis areas often appear when the mass is large, and calcifications are rarely seen. On magnetic resonance imaging (MRI), the masses often appear as signals equal to the surrounding muscles on the T1 weighted imaging (T1WI) sequence and unevenly high signals on the T2 weighted imaging (T2WI) sequence. MRI is more accurate than CT in showing the extent of tumor invasion. The lesions appear as an uneven enhancement on both contrast-enhanced CT and MRI scans. Tateishi *et al.* believed that such imaging findings accompanied by lymph node invasion are helpful for the recognition of this disease ⁽²⁰⁾.

PET/CT is also a reliable imaging method for positioning and qualitative diagnosis, which is of great value for detecting primary and metastatic lesions. It has an important role in tumor staging, determining a treatment plan, and evaluating the curative effect. The ES in the inguinal area reported in the literature showed high radioactivity uptake on ¹⁸F-FDG PET/CT, and the maximum standard uptake value (SUVmax) was as high as 25.13 (15), thus suggesting that the glucose metabolism of ES is relatively vigorous. In this case, PET/CT examination showed that in addition to the high metabolic radioactivity uptake in the left groin, the tailbone area also showed a soft tissue mass with high radioactivity distribution, and low-density bone destruction was seen on the CT bone window. However, our patient never complained about any discomfort in the relevant area on admission.

The most common malignant tumors in the groin area are metastatic tumors. Germ cell tumors (GCT) and mesenchymal tumors such as undifferentiated pleomorphic leiomvosarcoma. sarcoma. rhabdomyosarcoma, epithelioid tumors, and other mesenchymal tumors are usually rare ⁽²²⁾. In our case, in addition to the groin area, a large soft tissue mass was found in the tail bone, so metastases were considered. Laboratory examination of GCT showed elevated alpha-fetoprotein levels or human chorionic gonadotropin (β -HCG) in some patients. However, the imaging findings of the undifferentiated pleomorphic sarcoma, leiomyosarcoma, rhabdomyosarcoma, and other mesenchymal tumors are not specific, and all of them may present as irregular soft tissue mass shadows of equal or slightly lower density, prone to cystic degeneration and necrosis resulting in uneven mass density; calcification may also occur in some tumors (23). Therefore, it is relatively difficult to distinguish these tumors from ES. Chordoma that usually occurs in the sacrococcyx should be considered for the tumors occurring in the coccyx. Chordomas often occur at age 40-60 years, predominantly in males (its occurrence is 2-3 times higher than in females) ⁽²⁴⁾. CT findings show sacrococcygeal osteolytic or expansive bone destruction accompanied by a large soft tissue mass with uneven density, necrosis, cystic degeneration, and hemorrhage within the mass, often accompanied by calcification (25). Moreover, sacral giant cell tumor, neurogenic tumor, and chondrosarcoma should also be considered when

performing diagnosis. Giant cell tumor of bone usually presents as eccentric, expansive, soap-like bone destruction, with mild osteosclerosis and calcification: the osseous envelope is generally intact. without soft tissue mass ⁽²⁴⁾. Neurogenic neoplasms often present as well-defined soft tissue masses with mild sclerosis of surrounding bone, often without bone destruction. Chondrosarcoma is typically an obvious soft tissue mass with dot, arc, and arch annular calcification signs. Chondrosarcoma diagnosis is achieved by comparing the characteristic imaging manifestations of progressive enhancement like garlands in the internal spacings and peripheral regions after an enhanced scan (26). Our patient had two soft tissue masses in the left groin area and caudal vertebra, so the origin of the primary lesion was essential for differential diagnosis.

The diagnosis of proximal ES mainly relies on histopathological examination. ES cells, mainly epithelioid cells, are pleomorphic and have obvious atypia and large nucleoli. Moreover, the growth pattern of ES is mainly nodular and diffuse, and the diagnosis is confirmed by characteristic rhabdoid cells ⁽²⁷⁾. The CK and EMA proteins and vimentin in immunohistochemical staining are crucial for ES diagnosis and for distinguishing ES from other tumors, including synovial sarcoma, rhabdomyoid tumor, and granulomatous lesions ⁽¹⁾.

Extensive surgical resection is the main treatment for ES ⁽²⁸⁾. However, due to the recurrence of ES, adjuvant chemotherapy and local radiotherapy is often given after surgery ^(29, 30). For advanced or relapsed INI1-negative ES patients, a recent study showed that oral targeted drug tazemetostat could prolong the median survival rate of patients ^(31, 32).

CONCLUSIONS

Proximal-type ES is relatively rare, especially in the groin area. A clinical history of painless growth of a nodule or mass combined with radiographic findings of unevenly enhanced soft tissue density/ signal and high radioactivity uptake with lymph node infiltration may suspect ES. However, its final diagnosis depends on histopathological examination. Our case shows that ES should be considered a differential diagnosis of inguinal metastases and other mesenchymal tumors.

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