Original Research Article

Epithelioid Sarcoma: An overview with emphasis on its differentiation from morphologic mimics

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Background: Epithelioid sarcoma (ES) is a malignant mesenchymal neoplasm that exhibits epithelioid cytomorphology and a predominantly epithelial phenotype. The principal types based on histopathological features and location; include the classic or conventional type (CES) and the proximal type (PES).

Aims: The aim of the study was to analyze our cases of ES regarding clinical, pathological and immunohistochemical features.

Materials and Methods: This is a retrospective study. Seven cases of ES were included in the study. Clinical and pathological details were retrieved from patient records. Details like site, size, histopathological type and IHC features of the tumors were studied.

Results: Out of seven, five were PES and two were CES. There were six males and one female; with age ranging from 12 to 68 years. Total five tumors involved extremities. One was noted at a rare site, paratesticular region. Three tumors were larger than 5 cm in greatest dimension. On immunohistochemistry (IHC), all the tumors were reactive for CK, EMA, Vimentin, Ca 125 and showed loss of nuclear expression of INI1. CD 34 was expressed in 6 out of 7 cases.

Conclusion: ES is a rare aggressive malignant tumor with dismal prognosis. It is often misdiagnosed because of nonspecific clinical features at presentation. Helpful clues in diagnosis are tumors in young males with epithelioid and/or spindle cell morphology, Rhabdoid cells and granuloma like central necrosis. Co-expression of epithelial and mesenchymal markers along with reactivity for CD34 and Ca 125 and loss on INI1 expression on IHC substantiate the diagnosis of ES.

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1. Introduction

Epithelioid sarcoma (ES) is a distinctive sarcoma showing epithelial differentiation and commonly affecting young patients.¹ It represents between 0.6 to 1% of all soft tissue sarcomas. There are two clinicopathological subtypes, the conventional or classic type (CES) affecting acral sites and the proximal type (PES) affecting mainly the truncal regions. Both the types affect patients over a wide age range.² ES is the most common soft tissue sarcoma in the hand and wrist.³ CES has cellular tumor nodules with central necrosis imparting a granulomatous appearance. PES has aggressive course and is characterized by sheets of large epithelioid tumor cells.¹⁻⁴ A variable number of rhabdoid cells may be seen in both types. ES is among the few sarcomas with a tendency to metastasize to lymph nodes and local recurrence.²,⁴,⁵ On immunohistochemistry (IHC), both CES and PES show immunoreactivity for vimentin, epithelial membrane antigen (EMA), CK8, CK19,Ca 125 and CD34 (in 50% cases).²,³,⁶,⁷ Loss of nuclear expression
of SMARC B1 protein/INI 1 has also been observed in both types of ES.\textsuperscript{2,6,8–13} Since ES is a rare sarcoma, literature shows many isolated case reports, very few being case series.\textsuperscript{9,14–18} We present clinicopathological and immunohistochemical profile of seven cases of ES; five PES and two CES, along with the review of literature.

2. Materials and methods

A retrospective study of seven cases of ES diagnosed between 2012-2021 was undertaken. Cases referred to us from outside for IHC were also included. Relevant clinical details like age, sex, location of tumor, whether single or multiple, size, duration, metastasis, treatment and follow-up information were retrieved from records. Diagnostic material included biopsy/resection specimens and paraffin blocks in cases referred from outside. Details of gross examination such as tumor size, circumscription, margins, areas of hemorrhage/necrosis were noted. Histopathological review with comprehensive IHC profile was undertaken in all 7 cases.

3. Results

There were seven cases of ES, five PES and two CES. There was strong male predilection with six males and one female. The age ranged from 12 to 68 years. 5 patients presented with nodule/palpable mass (cases 2,3,4,5 & 7). One patient (case 3) had ulceration of the overlying skin. One patient presented with scrotal mass (case 6) while case 1 was a known case of squamous cell carcinoma of tongue who presented with right cervical swelling clinically thought to be metastatic squamous cell carcinoma.

The sites involved were extremity in five cases (palm and wrist in case 3 and 4, forearm in case 2, arm in case 5 and leg in case 7), cervical region in one (case 1) and paratesticular region, a very rare site for ES, in one case (case 6).

In all the cases, the tumor was single, nodular with grey white cut surface punctuated by areas of hemorrhage and necrosis. PES accounted for five cases (cases 1,2,3,4 and 6) and CES for two cases (cases 5 and 7). Both the cases of CES and two cases of PES (cases 1 and 4) had tumor size less than 5 cm. Tumor was superficial in all cases. Ulceration of the overlying skin as well as invasion of the underlying bone was seen in a single case (case 3) of PES.

Slides of all the cases were reviewed by all three authors. On microscopy, CES had characteristic nodular arrangement of tumor cells with foci of central necrosis imparting a pseudogranulomatous appearance. Individual tumor cells were large, polygonal with hyperchromatic nuclei and abundant eosinophilic cytoplasm. These cells merged with plump spindle cells toward periphery of the nodules. Mitoses ranged from 10-28/10 high power fields (Figure 1).

PES was predominantly composed of large epithelioid tumor cells with marked nuclear atypia and intracytoplasmic hyaline eosinophilic inclusions resembling rhabdoid cells. Areas of hemorrhage and necrosis were common in both types but the granulomatous pattern seen in CES was not seen in PES. Both the types showed infiltration by chronic inflammatory cells. Hyalinization of stroma was observed in two cases of PES. The margins of both the tumor types were infiltrative. Number of rhabdoid cells was variable (Figure 4).

On IHC, both CES and PES were typically positive for cytokeratin (CK), epithelial membrane antigen (EMA), vimentin. CA 125 was expressed in all 7 cases and CD34 in 6 cases (except in case 4). Loss of nuclear expression of SMARC B1 protein/INI 1 was noted in all 7 cases (Figures 2 & 5). HMB45, S-100, smooth muscle actin (SMA), CD31 and desmin were negative in all (Figures 3 & 6).

Out of the 7 cases, 2 were treated with surgery and adjuvant chemotherapy (cases 3 & 6). Three cases were treated with chemotherapy (cases 1, 4 & 7) & were advised surgery &/or radiotherapy, but they refused further treatment. One patient died of disease within 5 months of diagnosis & treatment (case 6), two cases had metastasis, one involving lymph nodes and lung (case 3) and another involving lung (case 4). Follow up was not available in 4 cases as 2 cases were referred from outside for opinion (cases 2 & 5) and two were lost for follow up after 3 cycles of chemotherapy (cases 1 & 7). The clinical and pathological details of all 7 cases are summarized in Table 1.

![Fig. 1](image-url)
Table 1:

| S.No. | Age yrs | Sex | Location            | Size                  | Rhabdoid cells | Mitoses  | Type      | Metastasis | Treatment & Follow up                      |
|-------|---------|-----|---------------------|-----------------------|----------------|----------|-----------|------------|-------------------------------------------|
| 1*    | 68      | M   | Right cervical region | 4x3x2 cm nodule       | Present        | 36/10 hpf| Proximal  | Absent     | 3 cycles of chemotherapy. Refused further treatment. Lost for follow up |
| 2     | 22      | M   | Left forearm        | 7x6.2x4 cm mass       | Present        | 15/10 hpf| Proximal  | Absent     | Not available. Referred from outside      |
| 3     | 30      | M   | Right palm and wrist | 8.5x8 cm ulcer        | Present        | 30/10 hpf| Proximal  | 3/34 LNs Lungs | Surgery + Chemotherapy. Metastasis after 6 months |
| 4     | 55      | F   | Left palm           | 3.5x2.5x2.2 cm        | Present        | 24/10 hpf| Proximal  | Lung       | 3 cycles of chemotherapy. Advised radiation and surgery. Lost for follow up |
| 5     | 18      | M   | Right arm           | 2.1x1.2x1.2 cm        | Absent         | 8-10/10 hpf| Conventional | Absent     | Not available. Referred from outside      |
| 6     | 32      | M   | Paratesticular mass | 12x10x8.9 cm          | Present        | 5-10/10 hpf| Proximal  | Absent     | Surgery + Chemotherapy. Death within 5 months of diagnosis |
| 7     | 12      | M   | Right leg           | 4x4 cm                | Absent         | 20-22/10 hpf| Conventional | Absent     | 3 cycles of chemotherapy. Advised below knee amputation. Refused further treatment. Lost for follow up |
4. Discussion

ES is a rare slow growing malignant soft tissue tumor accounting for less than 1% of adult soft tissue sarcomas and 4–8% of pediatric non-rhabdomyosarcomas.\textsuperscript{2,19} First described by Enzinger in 1970, it has a tendency to affect the flexor surfaces of fingers, hand, forearm followed by knee and lower leg of young adults.\textsuperscript{6,20,21} Proximal type arising in deep soft tissues of pelvis, perineum and genital tract and proximal extremities was described by Guillou.\textsuperscript{22} Rare sites of ES include orbital apex, scrotum, infraorbital region.\textsuperscript{23–26}

CES presents as a slowly growing indurated mass with a peculiar woody consistency and is often clinically mistaken for abscess, wart or other non-neoplastic process.\textsuperscript{3,6} It is deceptively circumscribed and always shows infiltration with small nests or single files of tumor cells at periphery, likely accounting for the high rate of recurrence. CES is composed of tumor nodules with central necrosis. On microscopy, in addition to epithelioid cells, many ESs also show spindle cells and this modulation from epithelioid to spindle cells is a characteristic finding.\textsuperscript{6} When tumor nodules grow along tendons and fuse, they produce a garland-like appearance.\textsuperscript{1,6} PES is more aggressive, tends to be located in axial areas and affects older people. ES composed predominantly of spindle cells is referred to as the fibroma like variant. Loss of cellular cohesion in tumor nodules with intrallesional hemorrhage results in pseudoagiosarcomatous pattern, referred by some as
Fig. 4: H & E images from a case of proximal epithelioid sarcoma (case 6) showing; a: A cellular tumor; b: nodules of tumor cells surrounded by myxoid stroma; c: large epithelioid cells with prominent nucleolus & abundant eosinophilic cytoplasm; d: large rhabdoid cells (black arrow) & increased mitosis (red arrows). [(a) to (d) x400]

Fig. 5: IHC images from a case of proximal epithelioid sarcoma (case 6) showing expression of a: CK; b: EMA; c: Vimentin; d: Ca125 & e: CD34; f: The tumor cells show loss of INI1 expression. The lymphocytes on the Left side of image serve as an internal control. [(a) to (f) x400]

Fig. 6: IHC images from a case of proximal epithelioid sarcoma (case 6). The tumor cells were negative for a: CD31; b: Desmin & c: S-100. [(a) to (c) x400]

The details of previously reported case series of ES are summarized in Table 2. Rekhi et al have reported 40 cases of ES, 26 CES and 14 PES with male to female ratio of 3.44:1. Thirty patients presented with painless swelling, 8 with ulceration and 2 with painful swelling. The average duration of symptoms was 17 months. Chbani et al have reported a series of 106 cases of ES, 70 CES and 36 PES with 66 males and 40 females. Average duration of symptoms was 12 months. Hasegawa et al reported 6 CES, 12 PES and 2 angiomatoid variants of ES in their series of 20 patients comprising of 12 males and 8 females. All the patients presented with palpable mass, two patients also had pain and one had deep ulcer. Li et al had 9 CES and 8 PES in their series of 17 cases affecting 9 males and 8 females. Thirteen patients presented with nodule, five with pain and one with an ulcer. We had total seven cases of ES, five PES and two CES affecting six males and one female. Of the 7 cases, 5 patients presented with nodule/palpable mass of which one had ulceration of the overlying skin. One patient presented with scrotal mass while one case presented with right neck swelling. The distinct male predominance and wide age range seen in other studies, was also observed in our study.

Rekhi et al had 30 out of total 40 cases located in extremities, 18 in upper extremity and 12 in lower extremity. Chbani et al had 76 out of total 106 cases affecting extremities, 59 affecting upper extremity and 17 lower extremity. Li et al also had 9 out of total 17 cases of ES affecting extremities. We had 5 out of 7 cases of ES involving the extremities. In the series by Rekhi et al, majority of the tumors were superficially located (33 out of 40) while Chbani et al reported more cases (66 out of 106) below the superficial fascia. In the present study, all the cases were located superficially.

Chbani et al had 80 cases presenting as single nodule and 17 cases presenting with multiple nodules. In all our cases, tumor presented as single nodule. Size of the tumor was variable in all the studies, ranging from 1 – 30 cm. Rekhi et al observed size less than 5 cm in 16 out of 26 cases of CES and more than 5 cm in 10 out of 14 cases of PES. In our study, 4 cases (cases 1,4,5 & 7) had tumor less than 5 cm and in 3 cases (cases 2,3 & 6) had tumor was more than 5cm.

CES is reported nearly twice as often as PES. This has been reported in majority of the case series also. However, we had five PES and two CES, similar to the observation by Hasegawa et al, who had 12 PES and six CES. This could be due to the smaller sample size in both the studies.

Rekhi et al reported rhabdoid cells in all 14 cases of PES. Chbani et al observed rhabdoid cells in 15 cases of PES and 12 cases of CES while Hasegawa et al observed them in 10 cases of PES, 3 cases of CES and 1 angiomatoid...
ES. In our study, rhabdoid cells were seen in all 5 cases of PES.

Most of the studies have shown that ES has characteristic co-expression of epithelial markers like CK, EMA and mesenchymal markers like Vimentin, CD 34 (in approximately 50% cases). Interestingly Ca 125, initially supposed to be ovarian surface epithelial marker; has been consistently reported in cases of ES, irrespective of subtype. Loss of nuclear expression of SMARCB1 protein/ INI 1 has also been uniformly observed in both types of ES.

Cyogenetic analysis shows frequent inactivation of SMARCB1/INI1 tumor suppressor gene in both types of ES. The same gene is involved in the development of malignant rhabdoid tumor (MRT) affecting children. Features that differentiate ES from MRT include i) presence of epithelioid, spindle and rhabdoid cells in ES as against monomorphic rhabdoid cells in MRT, ii) SMARCB1/INI1 deletions are observed in ES while in MRT, there are frequent point mutations, iii) CD34 expressed in 50% of ES is consistently negative in MRT. INI1 expression is retained in most of the epithelioid neoplasms that might be confused with ES like epithelioid vascular tumors, epithelioid mesothelioma and metastatic poorly differentiated carcinoma. Epithelioid malignant peripheral nerve sheath tumors (EMPNST), however, show loss of INI1 expression in 50% cases. Also, EMPNSTs may be positive for CK, EMA and S-100 protein (80% cases). Negative CD34 expression may be helpful in differentiation.

Rekhi et al have reported recurrence in 24 out of 40 cases, while Hasegawa et al reported recurrence in 13 out of 20 cases. Metastases were reported in 12 out of 40 cases by Rekhi et al, 43 out of 106 by Chbani et al, 15 out of 20 cases by Hasegawa et al and 10 out of 20 cases by Li et al. Lymph node was the commonest site of metastasis in both types. Location of tumors in the subcutis or deep soft tissues without any connection with the overlying epidermis or adnexa, no histologic features of squamous or glandular differentiation, reactivity for CD34 in 50% of cases and loss of INI1 favor ES over undifferentiated carcinoma. EA shows positive staining for CD31, FLI-1, vWF and INI1 which are all negative in ES.

The mainstay of treatment is surgery with adjuvant chemotherapy and radiotherapy and local recurrence as high as 70%, often as multiple nodules, is the major cause of treatment failure. Adverse prognostic factors in both CES and PES include male sex, older age, axial or proximal extremity location, involvement of deep soft tissue, tumor size more than 5 cm, tumor multifocality, high mitotic activity, nodal involvement and extensive necrosis.

5. Conclusion

ES is a rare aggressive malignant tumor with dismal prognosis. It is often misdiagnosed because of nonspecific clinical features at presentation. Helpful clues in diagnosis are tumours at young age especially in males with epithelioid and/or spindle cell morphology. Rhabdoid cells and granuloma like central necrosis. Co-expression of epithelial and mesenchymal markers along with reactivity for CD34 and Ca 125 and loss on INI1 expression on IHC substantiate the diagnosis of ES. Radical surgery with adjuvant chemotherapy and radiotherapy and regular follow up is necessary as these tumors frequently recur and metastasize.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

7. Source of Funding

None.

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