Case series

Proximal-type epithelioid sarcoma of vulva – Case series of a rare tumor

Biswajit Dash a, Bharat Rekhi b, T.S. Shylasree a,b, Amita Maheshwari a, Jyoti Bajpai c

a Department of Surgical Oncology, Gynecologic Oncology Division, Tata Memorial Centre, Homi Bhabha National Institute (HBNI) University, Mumbai, India
b Department of Pathology, Tata Memorial Centre, HBNI University, Mumbai, India
c Department of Medical Oncology, Tata Memorial Centre, HBNI University, Mumbai, India

ARTICLE INFO
Keywords:
Proximal-type
Epithelioid
Sarcoma
Vulva

ABSTRACT
Epithelioid sarcoma (ES) is rare and aggressive soft tissue neoplasm characterized by tumor cells showing epithelioid morphology and immunohistochemically, characteristic loss of INI1/SMARCB1 in most cases. The proximal-type ES usually involves the deeper soft tissues of the vulva or perineum is an extremely rare entity with diagnostic challenges. Surgery is the mainstay of treatment in localized diseases. Radiation and chemotherapy are used in the advanced and metastatic setting, however, their role in the adjuvant setting is uncertain. Anthracycline and gemcitabine-based chemotherapy are given in metastatic and recurrent tumors. We report 4 cases of ES treated over a period of 6 years at our center. All the cases initially presented at a local hospital with vulvar swelling with a benign mimic (3/4) or squamous cell carcinoma (1/4). The median age of diagnosis was 34 years (range: 17–80). The diagnosis was established with epithelioid morphology of tumor cells and immunohistochemically characteristic loss of INI1/SMARCB1 in all cases. 3 cases were treated with upfront surgery and two of them received adjuvant radiotherapy. One case received upfront palliative therapy due to lung metastasis at the time of presentation. On median follow-up of 24 months (2–63), 2 cases were disease-free. One case had a recurrence in the lungs and chest wall after a disease-free interval of 63 months. She underwent surgical excision of metastatic deposits, however developed second lung recurrence after 3 months and is being treated with Adriamycin-based chemotherapy. All patients are alive at the last follow-up.

1. Introduction

Epithelioid sarcoma (ES) is a rare and an aggressive soft tissue neoplasm, originally described by Enzinger in 1970 (Enzinger, 1970). Subsequently, proximal-type ES was described by Guillou et al. (1997). Till date, there are a limited number of reported cases of proximal-type ES of the vulva (Enzinger, 1970). The proximal-type ES usually involves the deeper soft tissues of the external genital tract, and the distal-type (conventional) involves the extremities, most frequently hand. An admixture of both the histomorphological patterns is referred to as "hybrid subtype" (Oda et al., 2020).

Given their rarity, the treatment guidelines for ES have been similar to other adult soft tissue sarcomas, with surgical excision in the case of localized disease. The role of radiation and systemic therapy in such cases is still evolving. We report four cases of proximal-type ES of the vulva managed at a single tertiary cancer center in India over a duration of 6 years.

2. Case presentation

2.1. Case 1

A 45-year-old parous lady was referred with a diagnosis of squamous carcinoma of the vulva. She had a history of vulvar swelling of 6 months duration. Her clinical examination revealed a 2 cm × 2 cm-sized nodular lesion in the left labia majora. The computed tomography (CT) scan did not reveal any locoregional or distant metastasis.

Histopathologic examination revealed a high-grade malignant tumor with a distinct epithelioid morphology. By immunohistochemistry (IHC), tumor cells were positive for pan-cytokeratin (AE1/AE3), CD 34, while negative for S-100P, p63, p40, and CK 7. There was a complete loss of integrase nuclear interactor 1(INI1)/SMARCB1 immunostaining within the tumor cells, confirming a diagnosis of proximal-type ES. (See Fig. 1).

She underwent radical excision of the lesion with clear resection margins. The diagnosis was further confirmed as proximal-type ES. Additionally, there were vascular emboli. She received adjuvant...
external beam radiotherapy (EBRT) to the vulva at a dose of 50 Gy in 25 fractions and is on follow-up.

After a disease-free interval (DFI) of 63 months, she presented with a painless swelling on the right-side chest wall measuring 10 cm × 7 cm. Fluorodeoxyglucose (FDG)-PET scan revealed a hypermetabolic mass (SUVmax 19.25), sparing her chest wall muscles. (See Fig. 2). Multiple hypermetabolic lung nodules were noted, the largest measuring 2 cm, suggestive of metastasis. A biopsy examination of the lesion confirmed tumor recurrence. Given a reasonable DFI, excision of the chest wall lesion, ipsilateral interpectoral nodes, and lung metastasectomy was performed. All the excised lesions on microscopic examination showed features of proximal-type ES, with free resection margins. There was no lymph node metastasis. Immunohistochemically, the tumor cells were positive for AE1/AE3 and CD34 and showed a complete loss of INI1, confirming a diagnosis of metastatic proximal-type ES. Three months later, the patient presented with bilateral lung nodules, the largest measuring 1.8 cm, along with another mass in the upper quadrant of her left breast, measuring 2.7 cm in the largest dimension. A biopsy examination of the breast mass revealed tumor metastasis. The patient is currently on single-agent adriamycin with palliative intent.

2.2. Case 2

A 27-year-old-lady, para 2, presented with a recurrent swelling in the perineal region of 4 months duration. She had undergone a surgical excision for a similar lesion at a local hospital 6 months ago, with a histopathological diagnosis of fibroma. On examination, there was an ulcer over the right labia majora measuring 3 cm × 2 cm with indurated margins and normal groins. Magnetic resonance imaging (MRI) showed a lobulated mass measuring 3 cm over the right labia majora, extending into the surrounding perineal fat with intermediate signal intensity on T1/T2-weighted imaging (WI), with heterogeneous post-contrast enhancement. There was a restriction in the diffusion-weighted imaging (DWI). There was no disease elsewhere on CT scan imaging. The patient underwent a right-sided radical hemi-vulvectomy with right groin-node dissection. Histopathologic examination and immunohistochemical staining results were consistent with a diagnosis of proximal-type ES. There were no lymphovascular emboli, perineural invasion, or regional lymph node metastasis. In view of a narrow inferior resection margin and base (distance of 1 mm and 6 mm from the inked surface, respectively), the patient received external beam radiation therapy (EBRT), with a dose of 40 Gy/16 cycles, followed by 15 Gy/6 cycles with a 10 cm × 10 cm field. The patient was disease-free at a 24-months follow-up

2.3. Case 3

A 37-year-old parous lady (P1) was referred to our center following an excisional biopsy of a painless 7 cm-sized lump on the vulva, at a local institution. A review of the excised vulvar lump showed a tumor comprising cells arranged in a nodular and diffuse pattern with “rhabdoid-like” morphology, variably myxoid stroma, and ulcerated overlying epithelium. By IHC, tumor cells showed positive immunostaining for AE1/AE3 and epithelial membrane antigen (EMA), while negative staining for desmin and S100P. INI1/SMARCB1 was completely lost in the tumor cells. A diagnosis of proximal-type ES was offered. Nearly 5% of tumor cells showed membranous staining for PDL-1 antibody. Surgical resection margins were free of tumor, however; the base was close to the tumor (less than 1 mm). PET-CECT was unremarkable, except it revealed two indeterminate, sub-centimeter-sized lung nodules in the left lung and indeterminate opacity in the right lung. The patient underwent a revised vulvar surgery with wide excision of the scar along with bilateral groin node dissection. There was no evidence of residual vulvar tumor and no metastatic groin nodes. A PET-CT scan after 4 weeks following surgical resection showed complete resolution of the lung lesions. The patient was disease-free during a follow-up of 12-months.

2.4. Case 4

A 25-year-old nulliparous lady, presented at our center with a vulvar lump. Five months back, she underwent incision and drainage for a deep-seated abscess on her right labia majora at a local hospital. However, the tumor was progressively increasing along with discharge from the lesion. On examination, she was ECOG 3 and revealed a tender ulcer-proliferative lesion over the mons and labia majora measuring 8 cm × 5 cm, extending till the periurethral area. CECT scan revealed a heterogeneously enhancing lesion on her right vulva, involving the right lower anterior abdominal wall rectus muscle with infiltration of the right inguinal ligament medially. Additionally, there were large metastatic bilateral lung nodules.

Biopsy examination of the lesion showed a malignant epithelioid tumor comprising large, “rhabdoid-like” cells, tumor necrosis, focally myxoid stroma, and occasional intracytoplasmic vacuoles. Lymphovascular emboli were seen. Immunohistochemically, the tumor cells were positive for AE1/AE3, EMA, CD34(focal), while negative for S-100P. INI1/SMARCB1expression was lost in tumor cells. A final diagnosis was proximal-type ES of the vulva. The patient received palliative radiotherapy at a dose of 20 Gy in 5 fractions at the local site and is being currently planned for chemotherapy with single-agent adriamycin.

Fig. 1. (Case 1) Left: Gross appearance of a vulvectomy specimen showing a tumor with a grey-white cut surface, below the epidermis and unremarkable attached muscles. Right: Microscopic appearance(A-B). A. Tumour is composed of epithelioid to rhabdoid-like cells. H and E, x 400. B. Tumour cells with epithelioid appearance arranged in sheets and cords. H and E, x 200. C-E: Immunohistochemistry results. C. Tumour cells displaying positivity for pan-cytokeratin (AE1/AE3). Diaminobenzidine (DAB), x 400. D. CD34 positivity. DAB, x 400. E. Tumour cells showing loss of INI1/SMARCB1. Interspersed lymphocytes and endothelial cells retain nuclear positivity, acting as controls. DAB, x 400.
3. Discussion

Vulvar sarcomas comprise less than 5% of all the vulvar neoplasms, with leiomyosarcoma as the most frequent type. ES of the vulva is extremely rare and comprises approximately 1% of soft tissue sarcomas. To the best of our knowledge, 40 cases have been reported till date (Chung et al., 2021). The median age of such patients is 34 years (range 17 to 80), similar to other vulvar sarcomas, including the present study (median = 32 years) (Table 1) (Noh et al., 2021). The distal-type frequently occurs in the younger patients, most commonly in the extremities, and is relatively less aggressive than the proximal-type ES (Rekhi et al., 2008).

The usual presentation in these cases is a solitary painless lump that is invariably confused with a benign lesion, as was similarly noted in 2 out of 4 cases of our study. A biopsy examination is essential in differentiating ES from its diagnostic mimics. These tumors show partial or complete epithelioid morphology with multinodular sheets of polygonal/epithelioid cells, including pleomorphic nuclei, moderate to abundant eosinophilic cytoplasm, and intracytoplasmic rhabdoid inclusions, along with variable myxoid stroma. Tumour necrosis is identified. Lymphatic or vascular emboli may be seen, as noted in the present series.

Immunohistochemically, tumor cells show positivity for epithelial markers, such as AE1/AE3, and EMA, as noted in all 4 cases in our series, along with positive immunostaining for CD34 (mesenchymal marker), as noted in 2 cases. (Table 1). CD34 positivity helped in ruling out a carcinoma that was a close differential diagnosis (Rekhi et al., 2008).

Moreover, there were no glandular or papillary arrangements of tumor cells, indicative of adenocarcinoma, in any of our study cases. Additionally, negative p63, p40 immunoexpression, in the first case, was useful in ruling out a squamous cell carcinoma that was a diagnosis at the referring laboratory. Presently, demonstration of loss of INI1 protein or SMARCB1 (the gene that codes for INI1) is considered essential for the diagnosis of both, proximal and distal-type of ESs, and is seen in more than 90% of such cases (Oda et al., 2020; Hornick et al., 2009; Czarnecka et al., 2020). All 4 cases in our study displayed a complete loss of INI1/SMARCB1 immunostaining. INI1 loss is also seen in almost 60% of cases of malignant peripheral nerve sheath tumors (MPNST). However other IHC markers, such as diffuse S100P positivity is also seen in epithelioid MPNSTs, unlike ESs, which are useful in separating the two entities.

Table 1

| Clinicopathological characteristics | Case 1 | Case 2 | Case 3 | Case 4 |
|-----------------------------------|--------|--------|--------|--------|
| Age                               | 45     | 27     | 37     | 25     |
| Parity                            | 2      | 2      | 1      | 0      |
| Site at presentation              | Labia Majora | Labia Majora | Labia Majora | Mons pubis, Anterior abdominal wall, Lungs |
| Mean size (cm)                    | 2x2    | 3x2    | 8x8    | 6x6    |
| Initial symptoms                  | Mass lesion | Mass lesion | Mass lesion | Mass lesion, Pain |
| Diagnosis at local institution    | Squamous cell carcinoma | Fibroma | Malignant tumor with rhabdoid morphology | Vulval abscess |
| Immunohistochemical results*      | AE1/AE3+, CD34-, S100P-, P63-, P40-, CK7-. Loss of INI1/SMARCB1 | AE1/AE3+, EMA-, CD34+, Focal+, CA125 +. Loss of INI1/SMARCB1 | AE1/AE3+, EMA+, Desmin-, S100P-, Loss of INI1/SMARCB1 | AE1/AE3 + . EMA + . CD34-F + . S100P-. Loss of INI1/SMARCB1 |
| Operability at presentation       | Operable | Operable | Operable | Inoperable (Distant metastasis) |
| Upfront treatment modality        | Radical local excision | Radical local excision | Radical local excision (revision surgery) | Palliative chemotherapy |
| Groin node dissection             | None   | Ipsilateral | Bilateral | --     |
| Adjuvant treatment                | RT     | RT     | None   | --     |
| Follow up period (months)         | 72     | 24     | 12     | 2      |
| Recurrence                        | Yes    | No     | No     | --     |
| Clinical outcome                  | Alive with disease | No evidence of disease | No evidence of disease | Alive with disease |

* "+" implies Positive staining result. "-" implies negative staining result, "NA" implies stain not applied.
Negative S100 P immunostaining also helped in ruling out a myoepithelial tumor, especially in cases 3 and 4, that displayed myxoid stroma (Meenakshi and McCluggage, 2009).

Pathologic factors associated with aggressive clinical course include larger tumor size and depth of invasion, hemorrhage, necrosis, high mitoses, necrosis, and vascular invasion. In cases of ES exceeding 5 cm in size, a significantly worse hazard ratio was reported, on multivariate analysis in SEER data (Johnson et al., 2020). Two cases in the present series had lymphovascular emboli and were associated with recurrences and metastasis. Lymph nodes and lungs are common sites of metastasis. Molecular cyto genetic characterization with complex translocations and recurrent genetic rearrangements involving chromosomes 8 and 22 commonly have been reported in proximal-type ES (Lualdi et al., 2004).

The only site of tumor recurrence in our series was the chest wall (case 1). The same case developed pulmonary metastasis after a DFI of 5 years.

Currently, complete surgical excision is the best treatment option in a localized ES. Three cases in our series presented with localized disease and underwent surgical resection. The role of prophylactic regional lymphadenectomy is unclear. Synovial sarcoma, clear cell sarcoma, angiosarcoma, and ES pose a relatively higher risk of lymph node metastasis. Therapeutic lymph node dissection is justified in the presence of lymph node metastasis (Czarnecka et al., 2020). None of our patients has lymph-node metastasis at the time of presentation or during recurrence. The role of sentinel lymph node dissection is uncertain, although it might be beneficial (Czarnecka et al., 2020). Nearly 50% of patients harboring proximal-type ES have been reported with lymph node recurrences (Table 2).

The role of adjuvant radiotherapy for improved oncological outcomes is unclear, even though it is commonly offered in cases of positive or close resection margins. (Czarnecka et al., 2020) Radiotherapy is considered in recurrent and palliative settings. Two of our study cases were offered adjuvant radiotherapy, due to close resection margins and a single case received palliative radiotherapy.

The role of adjuvant chemotherapy is uncertain. Anthracycline and gemcitabine-based regimens have shown some benefit in cases of unresectable or metastatic ES (Frezza et al., 2020). The response rates (27% and 22%, respectively) were found to be comparable in the largest multi-institutional retrospective case series (Frezza et al., 2018). Two of our study cases were planned for adriamycin-based chemotherapy in recurrent and unresectable cases in our series.

Tazemetostat (Tazverik™), is a first-in-class drug, an oral EZH2 (small molecule enhancer of zeste homolog 2) inhibitor that has shown clinical activity in advanced tumors displaying loss of INI1/SMARCB1, in an international phase 2 basket study (Gounder et al., 2020). It was granted accelerated FDA approval in January 2020 for use in patients ≥16 years with metastatic or locally advanced ES, who are not eligible for complete resection. The overall response rate was 15% and the time to response ranged from 2.4 months to 18 months. However, the cost of therapy is a major barrier to its use. Therapy with immune checkpoint inhibitors is investigational. Combining anthracycline-based chemotherapy and Tazemetostat are being currently evaluated for advanced cases of ES.

In conclusion, proximal-type ES of the vulva is an extremely rare and aggressive tumor affecting middle-aged women. A diagnosis is obtained by biopsy examination, along with the demonstration of loss of immunohistochemical expression of INI1. Surgery remains the treatment mainstay for localized disease. The role of adjuvant radiation and chemotherapy is limited. Lungs and lymph nodes are the most common site of metastasis. Anthracycline and gemcitabine-based chemotherapy regimens have shown some benefit in metastatic and recurrent tumors. Tazemetostat has been approved for use in specific settings. Inclusion of ES in rare tumor registries and mid to long-term oncological outcomes with newer drugs should be evaluated in the future.

### Table 2

| Clinical outcomes                  | Present series N = 4 | Compiled data (%) 1972-2018 (Noh J et al), N = 37 |
|-----------------------------------|----------------------|-----------------------------------------------------|
| No evidence of disease after treatment** | 2                    | 21 (57%)                                            |
| Recurred                          | 1                    | 14 (38%)                                            |
| Interval to recurrence (months)    | 1                    | Median 6.5 (Range 1–48)                             |
| Site of recurrence                | Lung and chest wall = 1 | Lung – 5 (36%)                                     |
|                                   |                      | Lymph node – 8 (57%)                               |
|                                   |                      | Local recurrence – 4 (20%)                          |
|                                   |                      | Others – 2 (14%)                                   |
| Died of disease                   | 0                    | 14 (38%)                                            |

* One patient is undergoing upfront palliative treatment.

### 4. Consent

Written informed consent has been obtained from all patients for publication of the case report along with the accompanying images.

### Funding

No outside funding was received.

### CRediT authorship contribution statement

Biswaijit Dash: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. Bharat Rekhi: Data curation, Methodology, Investigation, Writing – review & editing. Supervision. T.S. Shylasree: Conceptualization, Investigation, Supervision, Project administration, Writing – review & editing. Amita Maheshwari: Investigation, Writing – review & editing. Jyoti Bajpai: Investigation, Writing – review & editing.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.100921.

### References

Chung, H., Jang, T.-K., Kwon, S.Y., Ha, J., Shin, S.-J., 2021. A proximal type epithelioid sarcoma of the vulva with multiple distant metastases: A case report and review of the literature. Gynecol. Oncol. Reports. 37, 100035. https://doi.org/10.1016/j.gore.2021.100035.

Czarnecka, A.M., Sobczuk, P., Kostrzanowski, M., Spalek, M., Chojnacka, M., Suinmer-Cieckiewicz, A., Rutkowski, P., 2020. Epithelioid Sarcoma—From Genetics to Clinical Practice. Cancers (Basel). 12 (8), 2112. https://doi.org/10.3390/cancers12082112.

Enzinger, F.M., 1970. Epithelioid sarcoma. A sarcoma simulating a granuloma or a carcinoma. Cancer 26(5), 1029-1041.

Frezza, A.M., Sigalotti, L., Del Savio, E., Baldazzi, D., Saraglia, M., Rigbi, A., et al., 2020. Epithelioid sarcoma: Molecular insights into proximal versus classic variant. J. Clin. Oncol. 2020 May 20;38(15_suppl):e23552–e23552.

Frezza, A.M., Jones, R.L., Lo Villu, S., Asano, N., Lucibello, F., Ben-Ami, E., Ratan, R., Tterycz, P., Boye, K., Ibrahimi, M., Palmerini, E., Freden, A., Vincenzi, B., Brunello, A., Denar, J.L.M.E., Benjamin, R.S., Blay, J.Y., Irot, J.M., Casali, P.G., Gelderblom, H., Grignani, G., Gronchi, A., Hall, K.S., Mir, O., Rutkowski, P., Wagner, A.J., Anurova, O., Collini, P., Dei Tos, A.P., Flucke, U., Hornick, J.L., Lobmairer, I., Philippe, T., Picci, P., Ranhere, D., Renne, S.L., Saraglia, M., Thway, K., Wagrodzi, M., Wang, W.-L., Yoshida, A., Mariani, L., Kawai, A., Stacchiotti, S., 2018. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma a multi-institutional case series. JAMA Oncol. 4 (9), e180219. https://doi.org/10.1001/jamaoncol.2018.0219.
Gounder, M., Schoffski, P., Jones, R.L., Agulnik, M., Cote, G.M., Villalobos, V.M., Attia, S., Clough, R., Chen, T.-W., Jahan, T., Loggers, E.T., Gupta, A., Italiano, A., Demetri, G.D., Ratan, R., Davis, I.E., Mir, O., Dileo, P., Van Tine, B.A., Pressey, J.G., Lingaraj, T., Rajarethinam, A., Sierra, L., Agarwal, S., Stacchiotti, S., 2020. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. Lancet Oncol. 21 (11), 1423–1432.

Guillou, L., Wadden, C., Coindre, J.-M., Krausz, T., Fletcher, C.D.M., 1997. ‘Proximal-type’ epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features: Clinicopathologic, immunohistochemical, and ultrastructural study of a series. Am. J. Surg. Pathol. 21 (2), 130–146.

Hornick, J.L., Dal Cin, P., Fletcher, C.D.M., 2009. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am. J. Surg. Pathol. 33 (4), 542–550.

Johnson, S., Renz, M., Wheeler, L., Diver, E., Litkouhi, B., Behbakht, K., Howitt, B., Karam, A., 2020. Vulvar sarcoma outcomes by histologic subtype: A Surveillance, Epidemiology, and End Results (SEER) database review. Int. J. Gynecol. Cancer 30 (8), 1118–1123.

Lualdi, E., Modena, P., Debicie-Rychter, M., Pedetour, F., Teixeira, M.R., Facchinetti, F., Degrada, G.P., Pilotti, S., Sozzi, G., 2004. Molecular cytogenetic characterization of proximal-type epithelioid sarcoma. Genes Chromosom. Cancer. 41 (3), 283–290.

Meenakshi, M., McCluggage, W.G., 2009. Myoepithelial neoplasms involving the vulva and vagina: report of 4 cases. Hum Pathol. 40 (12), 1747–1753.

Noh, J.J., Jeon, J.-E., Jung, H., Kim, H.S., Lee, Y.V., Choi, C.H., Lee, J.-W., 2021. Vulvar epithelioid sarcoma: A case report with literature review. Taiwan J. Obstet. Gynecol. 60 (1), 132–135.

Oda, Y., Dal Cin, P., Le Loarer, F., Nielsen, T.O., 2020. Epithelioid Sarcoma. Tumors of uncertain differentiation/Ewing sarcoma/Soft tissue and bone tumours. World Heal Organ, Classif. Tumors Editor board, Ed. 294–296.

Rekhi, B., Gorad, B.D., Chinoy, R.F., 2008. Clinicopathological features with outcomes of a series of conventional and proximal-type epithelioid sarcomas, diagnosed over a period of 10 years at a tertiary cancer hospital in India. Virchows Arch. 453 (2), 141–153.