

Ewing's Sarcoma of the Vulva: An Uncommon Tumor in an Uncommon Site

Introduction

Extraskelatal Ewing's sarcoma (EES) is an uncommon, aggressive, round cell tumor. It accounts to 16% among Ewing's sarcoma (ES). The most commonly involved sites are soft tissues of trunk or lower extremities, paravertebral tissues, chest wall, and retroperitoneum. EES presenting in the genitourinary tract is highly uncommon. There are very few cases of primary vulvar and vaginal ES which have been published to date. We report a rare case of ES of the vulva that presented with labial swelling.

Case Presentation

A 53-year-old postmenopausal female with no comorbidities presented with left labial swelling for 5 months. She was evaluated elsewhere and found to have a 3 cm × 3 cm left labial swelling. She underwent excision biopsy of the lesion and was referred to us for further management.

Question 1

Clinical differential diagnosis of such presentation in this age group?

Answer

1. Vulvar cysts (Bartholin's cyst)
2. Cutaneous adnexal tumors
3. Carcinoma of the vulva
4. Melanoma.

Histopathology showed small round blue cells arranged in diffuse sheets intervened by fibrous septae. The cells had minimal cytoplasm, vesicular nuclear chromatin, and inconspicuous nucleoli forming rosettes at places. Mitosis was brisk with areas of necrosis, suggestive of malignant round cell tumor of the left labia. Immunohistochemistry was positive for CD99 and Friend leukemia virus integration 1 (FLI-1) with focal synaptophysin positivity. Ki67 index was 20%. Features were suggestive of ES. Fluorescence in situ hybridisation (FISH) for ES breakpoint region 1 (EWSR1) gene rearrangement was done. Tumor cells were positive for EWSR1 gene translocation (t [22q12]) [Figure 1].

Question 2

Percentage of ES with EWS-FLI1?

Answer

t (11; 22) (q24; q12) leading to a chimeric transcript EWS-FLI1 is seen in 85% of cases. In 5%–10%, EWS gene is fused with other members of Erythroblast Transformation-Specific (ETS) genes like ETS-related gene (ERG), ETS variant transcription factor 1 (ETV1),

ETS variant transcription factor 4 (ETV4) and Fifth Ewing variant (FEV).^[1]

Contrast-enhanced computed tomography of the thorax, abdomen, and pelvis was done and did not show any residual disease, but was suggestive of postoperative changes in the left labia and subcentimetric retroperitoneal and pelvic nodes. Bone scan did not show any tracer uptake in the bones. Bone marrow aspiration and biopsy from the right iliac crest did not show any involvement by the tumor. A diagnosis of ES of Vulva pT1NoMo G3 Stage II was made.

Question 3

Incidence of ES of vulva?

Answer

EES of the female genital tract (FGT) is very rare. The most common sites in FGT were the ovaries followed by uterine body, cervix, vagina, and vulva.^[2] Less than 30 cases of ES of the vulva have been reported till date. To the best of our knowledge, we report the 5th case in the country.

The patient was started on VAC/IE (injection vincristine 1.5 mg/m², injection adriamycin 75 mg/m², injection cyclophosphamide 1.2 g/m² (D1)/injection ifosfamide 1.8 g/m², and injection etoposide 100 mg/m² (D1–D5) regimen). She has received four cycles of chemotherapy with resolution of iliac lymph nodes on contrast-enhanced computed tomography. She is planned for a total of 17 cycles of chemotherapy.

Discussion

ES is a highly malignant, small, round cell tumor which originates from primitive neuroectodermal cells first described by James Ewing in 1921.^[3] It is predominantly seen in males with a male-to-female ratio of 1.5:1.^[4] In general, 20%–30% of patients present with metastases at the time of their diagnosis.^[5]

Extraskelatal Ewing's sarcoma (EES) is uncommon. It accounts to 16% among ES.^[6] They usually occur in the soft tissue of trunk, lower extremities, paravertebral tissues, chest wall, and retroperitoneum. A few reported rare sites include larynx, nasal cavity, neck, lung, retroperitoneum, mediastinum, and genital tract. EES of the FGT is very rare, and the reported most common sites in FGT were the ovaries^[7] followed by the uterine body^[8] and less commonly the cervix,^[9] vagina, and vulva.^[2,10] EES usually occur in relatively young women; the mean age at the time of the initial diagnosis of previous cases is 27.6 years (median:

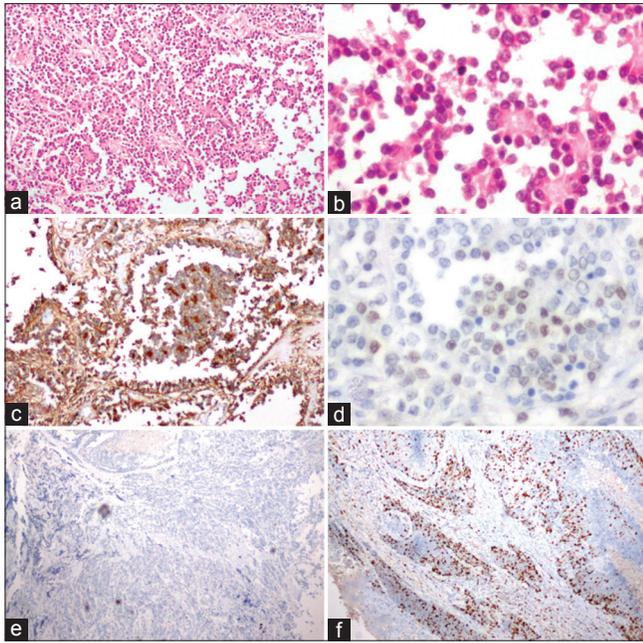


Figure 1: Histopathology of the resected specimen (a and b) low-power (H and E \times 100) and high-power view (H and E \times 400), respectively, showing sheets of small round blue cells forming rosettes at places; (c and d) immunohistochemistry showing neoplastic cells positive for CD99 and Friend leukemia virus integration 1, respectively; (e) immunohistochemistry showing neoplastic cells negative for leukocyte common antigen (f) Ki67 index of 20%

26, range: 10–52 years),^[11] but our patient was older than this.

The differential diagnosis of these tumors includes other small round blue cell tumors such as rhabdomyosarcoma, lymphoma, small-cell carcinoma (primary or metastatic), melanoma, cutaneous adnexal tumors, and Merkel cell carcinoma.

Demonstration of t(11;22) (q24;q12) chromosomal translocation (EWS-FLI1 gene rearrangement) is highly specific for ES/primitive neuroectodermal tumors since it is seen in more than 90% of the tumors.

The treatment of ES requires a multidisciplinary approach. It includes surgical resection with multiagent chemotherapy. Radiation therapy may be used to improve local control in cases of R1/R2 resection. The multiagent standard chemotherapy regimen typically includes doxorubicin, vincristine, and cyclophosphamide, alternating with ifosfamide and etoposide.^[12] Doxorubicin is replaced with actinomycin-D once the cumulative dose of 375 mg/m² is crossed.

EES has more aggressive behavior and a worse prognosis than their bony counterpart. Reported 5-year survival rate for skeletal ES is around 75% as compared to 38% in extraskeletal counterpart. However, there is favorable outcome for extraosseous ES arising in cutaneous and other superficial site.^[13,14] In the absence of metastatic disease, primary vulvar and vaginal ES neoplasms likely have a

more favorable prognosis. Hence, prognosis depends on tumor size, superficial location, early detection, metastasis, and complete surgical removal of the lesion.^[15] According to literature in metastatic cases, most patients either died of disease or were alive with disease during their last follow-up. In nonmetastatic lesions, there was survival benefit ranging from 18 to 51 months.^[16]

Conclusion

Early diagnosis and multimodality treatment are necessary for survival benefit. Because of fewer reported cases in literature, it is difficult to draw any conclusion about tumor behavior, epidemiology, or standard management. Hence, studies of more number of cases of primary vulvar ES with longer follow-up periods are needed to clarify the same.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Acknowledgment

Residents and faculty of Department of Pathology and Medical Oncology

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

**MC Suresh Babu¹, A Sreevalli¹,
Antony George Francis Thottian¹, MN Suma²,
D Lokanatha¹, Linu Abraham Jacob¹,
KN Lokesh¹, AH Rudresha¹, LK Rajeev¹,
Smitha Saldanha¹**

¹Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India, ²Department of Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Address for correspondence: Dr. A Sreevalli,
Department of Medical Oncology, Kidwai Memorial Institute of
Oncology, Bengaluru, Karnataka, India.
E-mail: svall88@gmail.com

Submitted: 12-Feb-2020

Revised: 05-Apr-2020

Accepted: 01-May-2020

Published: 27-Jun-2020

References

1. Rekhi B, Chinnaswamy G, Vora T, Shah S, Rangarajan V. Primary Ewing sarcoma of vulva, confirmed with molecular cytogenetic analysis: A rare case report with diagnostic and treatment implications. *Indian J Pathol Microbiol* 2015;58:341-4.
2. Yang J, Guo Q, Yang Y, Zhang J, Lang J, Shi H. Primary vulvar

- Ewing sarcoma/primitive neuroectodermal tumor: A report of one case and review of the literature. *J Pediatr Adolesc Gynecol* 2012;25:e93-7.
3. Ewing J. Diffuse endothelioma of bone. *Pathol Soc* 1921;21:17-24.
 4. Yeshvanth SK, Ninan K, Bhandary SK, Lakshinarayana KP, Shetty JK, Makannavar JH. Rare case of extra skeletal Ewings sarcoma of the sinonasal tract. *J Cancer Res Ther* 2012;8:142-4.
 5. Cotterill SJ, Ahrens S, Paulussen M, Jürgens HF, Voûte PA, Gardner H, *et al.* Prognostic factors in Ewing's tumor of bone: Analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol* 2000;18:3108-14.
 6. Pradhan A, Grimer RJ, Spooner D, Peake D, Carter SR, Tillman RM, *et al.* Oncological outcomes of patients with Ewing's sarcoma: Is there a difference between skeletal and extra-skeletal Ewing's sarcoma? *J Bone Joint Surg Br* 2011;93:531-6.
 7. Kleinman GM, Young RH, Scully RE. Primary neuroectodermal tumors of the ovary. A report of 25 cases. *Am J Surg Pathol* 1993;17:764-78.
 8. Snijders-Keilholz A, Ewing P, Seynaeve C, Burger CW. Primitive neuroectodermal tumor of the cervix uteri: A case report-changing concepts in therapy. *Gynecol Oncol* 2005;98:516-9.
 9. Li B, Ouyang L, Han X, Zhou Y, Tong X, Zhang S, *et al.* Primary primitive neuroectodermal tumor of the cervix. *Oncol Targets Ther* 2013;6:707-11.
 10. Xiao C, Zhao J, Guo P, Wang D, Zhao D, Ren T, *et al.* Clinical analysis of primary primitive neuroectodermal tumors in the female genital tract. *Int J Gynecol Cancer* 2014;24:404-9.
 11. Che SM, Cao PL, Chen HW, Liu Z, Meng D. Primary Ewing's sarcoma of vulva: A case report and a review of the literature. *J Obstet Gynaecol Res* 2013;39:746-9.
 12. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, *et al.* Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med* 2003;348:694.
 13. Al-Tamimi H, Al-Hadi AA, Al-Khater AH, Al-Bozom I, Al-Sayed N. Extra skeletal neuroectodermal tumour of the vagina: A single case report and review. *Arch Gynecol Obstet* 2009;280:465-8.
 14. Tunitsky-Bitton E, Uy-Kroh MJ, Michener C, Tarr ME. Primary Ewing sarcoma presenting as a vulvar mass in an adolescent: Case report and review of literature. *J Pediatr Adolesc Gynecol* 2015;28:e179-83.
 15. Fong YE, López-Terrada D, Zhai QJ. Primary Ewing sarcoma/peripheral primitive neuroectodermal tumor of the vulva. *Hum Pathol* 2008;39:1535-9.
 16. McCluggage WG, Sumathi VP, Nucci MR, Hirsch M, Dal Cin P, Wells M, *et al.* Ewing family of tumours involving the vulva and vagina: Report of a series of four cases. *J Clin Pathol* 2007;60:674-80.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Access this article online	
Quick Response Code: 	Website: www.ijmpo.org
	DOI: 10.4103/ijmpo.ijmpo_57_20

How to cite this article: Babu MC, Sreevalli A, Thottian AG, Suma MN, Loknatha D, Jacob LA, *et al.* Ewing's sarcoma of the vulva: An uncommon tumor in an uncommon site. *Indian J Med Paediatr Oncol* 2020;41:397-9.