Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Primary Neuroendocrine Tumor of Vulva: A Case Report

Shaghayegh Kamian (MD)[1], Mitra Rafie Zadeh (MD)[2], Maliheh Arab (MD)[3], Masume Shafiei (MD)[1*]

[1]*Department of Radiation Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[2]*Department of Pathology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[3]*Department of Gynecology Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

ARTICLE INFO

Article type
Case report

Article history
Received: 22 Jun 2017
Revised: 26 Aug 2017
Accepted: 11 Sep 2017

Keywords
Neoplasms
Neuroendocrine tumor
Vulva

ABSTRACT

Vulvar cancer is a rare malignancy representing less than 1% of the cancers, which is diagnosed in women with a high incidence of local recurrence and distant metastasis and carries a poor prognosis. We presented a 51-year-old woman with a lesion in the vulva appeared for three months. The lesion was large, ulcerative, hemorrhagic, tender, and mobile with no lymphadenopathy. Excisional biopsy demonstrated a high-grade malignant neoplasm with lymphovascular invasion. Based on the immunohistochemistry test, the patient was diagnosed with neuroendocrine carcinoma with poorly differentiated tumor. In the diagnostic workup, there were two small lymph nodes on the left inguinal area. The patient was subjected to radical vulvectomy and bilateral illioinguinal lymphadenectomy. In addition, she was prescribed to undergo adjuvant chemotherapy for three cycles. Subsequently, she was given hyperfractionated radiotherapy in the pelvis and bilateral inguinals concurrently with chemotherapy. In the last follow-up visit in 32 months later, the patient was disease-free in the physical examination, and the laboratory tests and imaging findings were normal.

Please cite this paper as:
Kamian Sh, Rafie Zadeh M, Arab M, Shafiei M. Primary Neuroendocrine Tumor of Vulva: A Case Report. Rev Clin Med. 2018;5(1):19-22.

Introduction

Vulvar cancer is a rare malignancy accounting for less than 1% of the cancers diagnosed in women and more than 5% of the gynecologic neoplasms (1). A few cases of vulvar neuroendocrine tumor (NET also called Merkel cell carcinomas) have been reported (2). Histologically, this tumor is characterized by intradermal small cells with high mitotic index and frequent apoptosis.

The management of vulvar NET is dependent on the stage of the disease and is hampered by its rarity and lack of randomized trials. The prognosis of NET is variable; in this regard, this disease has an indolent course for some patients with localized disease. However, it can be aggressive and have a high tendency for locoregional recurrence and distant metastases in the advanced cases with a poor prognosis and a median survival of 9 months (2,3).

Herein, we reported a rare case of neuroendocrine tumor of vulva. There are only a few cases of this disease reported in the world. Given the lack of a standard therapeutic approach for this rare tumor, reporting the prognosis and treatment of this disease can facilitate the better management of the similar cases.

Case report

We presented an Iranian 51-year-old woman with the height of 155 cm and weight of 80 kg. She was a housewife. At the first visit, she was complaining of a lesion in the vulva having been appeared for three months. The physical examination revealed a 25*20 mm ulcerative lesion with

***Corresponding author:** Masoume Shafiei.*
Department of Radiation Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
***E-mail:** masumeshafiei@sbmu.ac.ir*
***Tel:** +989378361987*

well-defined margins extending from the left minor labia to the posterior fourchette. It was hemorrhagic, tender, and mobile. The uterus and adnexa were normal, and no lymphadenopathy was observed.

The excisional biopsy demonstrated a high-grade malignant neoplasm with lymphovascular invasion. In the pathologic examination, the sections showed ulceration in the skin tissue. The neoplastic infiltrative cells composed of nests and trabeculae were also observed. Furthermore, highly atypical cells with large vesicular nuclei and prominent acidophilic nucleoli, as well as high mitotic activity were detected. Different histopathologic diagnoses were malignant melanoma, Merkel cell carcinoma, poorly differentiated carcinoma, and metastatic carcinoma.

The immunoreactivity for human melanoma black 45, melan A, leukocyte common antigen, and cytokeratin 20 were negative, whereas stain 100, pan cytokeratin, choromogranin A, synaptophysin, and cytokeratin 7 were positive (Figures 1,2). The index of Ki-67 was 60% (Figure 3). It was consistent with poorly differentiated carcinoma with n

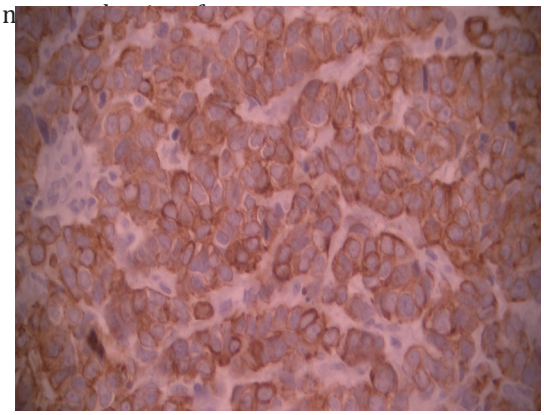

Figure 1. Immunohistochemistry staining for cytokeratin 7 showing strong cytoplasmic immunoreaction, diffuse, and strong intensity (˟400).

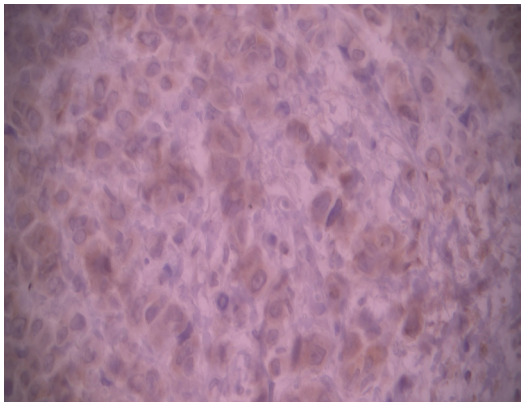

Figure 2. Immunohistochemistry staining for chromogranin showing weak positive finding, cytoplasmic immunoreaction, diffuse, and week intensity (˟400).

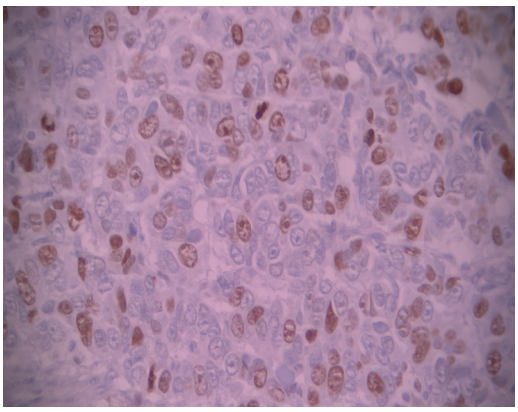

Figure 3. Immunohistochemistry staining for Ki67 showing positive nuclear immunoreaction, 60% distribution, and strong intensity (˟400).

Diagnostic workup, including whole body bone scan, mammography, as well as thoracic and abdominal computed tomography (CT) scans, revealed no other lesions. The pelvic CT scan showed two small lymph nodes (10 mm and 15 mm) in the left inguinal area. Surgical procedure, including radical vulvectomy and bilateral illioinguinal lymphadenectomy, was performed for the patient. Based on the histopathologic examination of the specimen, there was no tumoral residue, and all margins were free of tumor. However, 6 out of 27 lymph nodes were involved by the tumor.

The patient was referred for adjuvant treatment. She was admitted to the Radiation Oncology Department in Imam Hossein Hospital, Iran, in September 2014. The physical examination revealed lymphedema (3 plus) in both lower limbs. In addition, there was a soft, mobile, and non-tender mass measuring approximately 40 mm in the medial and upper part of the left thigh. The sonographic evaluation of this mass showed a large cystic lesion (about 50 mm in diameter and 70 cc volume) in the left inguinal region and a smaller cystic lesion next to it.

The sono-guided fluid aspiration showed fibrin clot in cytology. Therefore, the patient was referred to the lymphedema clinic and prescribed to undergo physiotherapy. Adjuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (area under curve=6) was started one month later. Chemotherapy continued for three cycles (every three weeks). Lymphedema was relieved, and the patient was treated with hyperfractionated radiotherapy (45 Gray in 30 fractions two times a day with at least 6 hours of interval) with three-dimensional conformal treatment planning for the pelvis and bilateral inguinals, which lasted for three weeks.

Concurrent chemotherapy with cisplatin (75 mg/m^2) and etoposide (100 mg/m^2) was pre-

scribed at the beginning of radiation therapy (one cycle). The last cycle of chemotherapy with cisplatin (60 mg/m2) and etoposide (80 mg/m^2) was given one month after the end of chemoradiation (March, 2015).

We decided to continue chemotherapy; nonetheless, the patient could not tolerate it due to the sustained neutropenia and decreased performance status. The patient was followed up with physical examination and laboratory tests. In the last follow-up visit after 32 months (Sep 2014-May 2017), the patient was disease-free in the physical examination, and the laboratory tests (i.e., tumor markers and lactate dehydrogenase) and imaging demonstrated normal findings.

Discussion

Vulvar cancer is a rare malignancy representing less than 1% of the cancers diagnosed in women and less than 5% of gynecologic neoplasms (1-4). To the best of our knowledge, only 21 cases of this cancer have been reported in the literature (5). Neuroendocrine carcinoma is a malignant tumor that was first described by Toker (6-7). It is sometimes named as Merkel cell carcinoma. This rare tumor is observed most commonly on the sun-exposed areas, such as head and neck (50-85%), extremity, and trunk (6-14). This tumor has been reported in the genital tract, as well (1,6,8,11).

Vulvar neuroendocrine carcinoma is a very rare tumor; accordingly, the review of literature revealed a few reported cases in the world (6). These tumors are mostly observed among the Caucasian race (8) and in the 7-9th decades of life (6-8,11,12). However, it has been also reported to occur at younger ages (6,7). It is thought that ultraviolet ray has an etiologic role (6-8,11). Polyomavirus has been detected in these malignant cells in 43-85% of the cases (7,8,11). The other defined risk factors for this cancer are old age, immunosuppression, and European ancestry (7).

These tumors have aggressive behavior (6,7,9,14), high rate of lymph node involvement (48-100%) (4,6,8,10,14), and distant metastasis (15-100%) at the time of diagnosis (4,6,10,14). The cases reported in the literature show that the vulvar NET seems to have a more aggressive behavior and poorer prognosis than other sites 6, 8, 10. The common clinical presentation is a raised, purple to red, and firm nodule without any overlying skin ulceration that may be surrounded by small satellite tumors (6,7).

There are controversial ideas about the origin of this tumor. In the early reports, this mass was postulated to arise from the Merkel cells; however, the recent studies are in favor of the stem cell origin (7,14). In the light microscopy, sheets, nests, and hypochromatic nuclei are observed. Another histopathologic reported pattern is intradermal small cell with high mitotic index and frequent apoptosis (6-8,14).

The diagnosis cannot be only based on the light microscopic features. The final pathology can be distinguished with the aid of immunohistochemistry and/or electron microscopy. Other differential diagnoses are lymphoma, melanoma, and metastatic oat-cell carcinoma. Neuron-specific enolase and chromogranin are almost present. Other useful markers include cytokeratin 20, synaptophysin, epithelial membrane antigen, and neural cell adhesion molecule (6-8,10). Moreover, electron microscopy can facilitate diagnosis by detecting ultrastructural finding with dense membrane bound neurosecretory granules (4-8,10,14).

Systematic staging is usually recommended for the detection of distant metastasis and lymph node involvement due to the aggressive behavior of the tumor. In some recent studies, positron emission tomography-CT scan was shown to have a role in staging workup (6,8,13,14). The adoption of a multimodality approach is a reasonable measure for these rare tumors with the most important role for surgery (6,8).

There is no consensus on the appropriate treatment for the neuroendocrine carcinoma of vulva, and all available data are extrapolated from other sites (7). Surgery is the main therapeutic approach in this disease and could be perform by vulvectomy or hemivulvectomy with 3 cm margin with ipsilateral inguinal lymphadenectomy. If there is no enlarged lymph node in the physical examination, a sentinel lymph node biopsy could be performed. Surgery alone has a high recurrence rate (about 70-75%); however, adjuvant radiotherapy is generally recommended since it can decrease this risk. Fortunately, this tumor is radiosensitive (4-8,10,13,14).

There are much more controversies about adjuvant chemotherapy (6,8,13,14). Some authors recommend adjuvant chemotherapy, which could downstage tumor and treat distant metastasis (4,6,10,11), while others implement it for palliation (7). The most common used chemotherapeutic regimens are similar to the regimens used for the small cell carcinomas of the lung, such as cyclophosphamide, doxorubicin, vincristine (showing 75% overall response rate) cisplatin/carboplatin, and etoposide (with 70% overall response rate) (6-8,13).

Overall, these tumors are aggressive with a poor prognosis (4,6,8). Factors, such as the stage of disease, size of tumor, depths of invasion, histologic differentiation, and lymph node involvement, could influence the prognosis (6). Adjuvant treatment

can increase overall and disease-specific survival rates. Overall mortality of this diease is high with 2-, 3-, and 5-year overall survival rates of 50%, 17-31%, and 14%, respectively (6-9,11,13,14).

Conclusion

Vulvar cancer is a rare tumor in women. The most common pathology is squamous cell carcinomas. Neuroendocrine tumor is one of the rare pathology reports in the vulvar malignant masses. There is no standard treatment for this rare entity. Furthermore, this cancer has poor prognosis due to its propensity for distant metastasis. Our case had a primary ulcer in the vulva without distant metastasis. After the surgical resection of the mass and lymph node resection, we treated the patient with chemotherapy and chemoradiotherapy.

Although the patient experienced treatment side effects, especially in chemoradiation, all the adverse effects were resolved in the follow-up visits. After nearly 32 months, she was disease-free. Data collection on these rare cases can contribute to the treatment of the probable new cases in the future.

Acknowledgements

None.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Singh V, Singh H, Leong C, et al. Vaginal small cell carcinoma: case report and review of literature. New York Medical Journal, 2008, http://newyorkmedicaljournal.org/1/Articles/singh4-08.htm.
2. Halperin E, Wazer D, Perez C, Brady L. Perez and Brady's principles and practice of Radiation Oncology. Lippincott :Williams & Wilkins; 2013.
3. Bhalodia JN, Kapapura DV, Parekh MN. Primary small cell neuroendocrine carcinoma of vagina: a rare case report. Patholog Res Int. 2011;2011:306921.
4. Swann MH, Yoon J. Merkel cell carcinoma. Semin Oncol. 2007;34:51-56.
5. Butorac D, Djaković I, Kruljac I, et al. Vulvar Merkel Cell Carcinoma – Case Report. Endocr oncol metab. 2016;2:156-159.
6. Pawar R, Vijayalakshmy AR, Khan S, et al. Primary neuroendocrine carcinoma (Merkel's cell carcinoma) of the vulva mimicking as a Bartholin's gland abscess. Ann Saudi Med. 2005;25:161-164.
7. Sheikh ZA, Nair I, Vijaykumar DK, et al. Neuroendocrine tumor of vulva: a case report and review of literature. J Cancer Res Ther. 2010;6:365-366.
8. Iavazzo C, Terzi M, Arapantoni-Dadioti P, et al. Vulvar Merkel Carcinoma: A Case Report. Case Rep Med. 2011;2011:546972.
9. Bouhafa T, Kanab R, Bouayed N, et al. Small cell neuroendocrine carcinoma of the vulva. Gynecol Obstet Fertil. 2014;42:877-879.
10. Hierro I, Blanes A, Matilla A, et al. Merkel cell (neuroendocrine) carcinoma of the vulva. A case report with immunohistochemical and ultrastructural findings and review of the literature. Pathol Res Pract. 2000;196(7):503-509.
11. Jońska-Gmyrek J, Bobkiewicz P, Gmyrek L, et al. Merkel cell carcinoma of the vulva - case report and the literature review. Ginekol Pol. 2013;84:385-389.
12. Vigneswaran N, Müller S, Lense E, et al. Merkel cell carcinoma of the labial mucosa. An immunohistochemical and ultrastructural study with a review of the literature on oral Merkel cell carcinomas. Oral Surg Oral Med Oral Pathol. 1992;74:193-200.
13. Viola G, Visca P, Bucher S, et al. Merkel cell carcinoma. Clin Ter. 2006;157:553-559.
14. Husseinzadeh N, Wesseler T, Newman N, et al. Neuroendocrine (Merkel cell) carcinoma of the vulva. Gynecol Oncol. 1988;29:105-112.