Large Cell Neuroendocrine Carcinoma of Female Genital Tract: A Clinicopathological Study of Two Cases with Review of Literature

Umashankar Prakasam · A. K. Khader Hussain ·
P. P. Ansar · S. Ayyappan · Vikas Mahajan ·
Ganpathy Ramanan

Received: 12 July 2013 / Accepted: 4 November 2013 / Published online: 13 November 2013
© Indian Association of Surgical Oncology 2013

Introduction

Cervical cancer encompasses several histologic types, of which the most common is squamous cell (70 %) [1]. Adenocarcinoma and its variants account for about 25 % of cases, while other histologic subtypes are uncommon [2]. Neuroendocrine tumors represent only about 2 % of all female genital tract malignancies [3]. Among the various pathological variants the large cell type is considered extremely rare. Moreover these tumors are rarely seen arising from cervix and vagina. Literature search revealed only one such case arising from vagina and around 80 case reports of large cell neuroendocrine tumors originating from cervix. Here we report two cases of this rare malignancy arising each from cervix and vagina that were treated at our institution.

Case 1

A 68 year old female presented with intermittent lower abdominal pain of 2 months duration. USG revealed a cervical polyp and biopsy suggested poorly differentiated squamous cell carcinoma. Recto vaginal examination revealed a bulky cervix and no parametrial involvement.

On investigation, CT scan revealed a small lesion measuring 2 × 1.5 cm located in the right anterolateral wall of cervix. Metastatic workup was negative. A provisional diagnosis of

poorly differentiated squamous cell carcinoma of cervix (Stage IB₁) was made. Patient was offered the choices of both radiotherapy and surgery. Patient opted for surgery and a Type III radical hysterectomy and bilateral pelvic lymphadenectomy was done.

On histopathological examination, microscopy revealed sheets and nodular aggregates and trabeculae of atypical cells. These cells were large, round to oval in shape with pleomorphic nuclei and prominent nucleoli (Fig. 1).

The mitotic count was about 20–22/10hpf. The cytomorphological features were suggestive of a poorly differentiated carcinoma and hence an immunohistochemical analysis was done.

The tissue stained positive for Cytokeratin suggesting its epithelial origin. Also surprisingly, it stained positive for Synaptophysin and Chromogranin-A which was suggestive of neuroendocrine carcinoma. The routine markers of Squamous cell carcinoma such as CK 5/6 and P63 were negative. Ki67 index was high (60–70 %) suggesting the highly aggressive nature of the tumor.

Based on these findings a final pathological diagnosis of large cell neuroendocrine carcinoma of the cervix was made (Fig. 2).

Patient received concurrent chemoradiation as adjuvant therapy.

Four cycles of chemotherapy with Carboplatin and Etoposide were given with concurrent External Beam Radiotherapy of 50 Gy to pelvis in 25 fractions and 5 Gy of brachytherapy in 2 fractions.

On follow up after 3 months, patient was asymptomatic and her clinical examination was normal. PET scan done at 6 months did not reveal any local or distant recurrence. On her recent follow-up at 9 months the patient was alive and asymptomatic.

U. Prakasam (✉) · A. K. K. Hussain · P. P. Ansar · S. Ayyappan ·
V. Mahajan · G. Ramanan
Department of Surgical Oncology, Apollo Cancer Institute, 320,
Anna salai, Chennai 600035, India
e-mail: umashankar.prakasam@gmail.com

Fig. 1 Microscopic picture showing large cells with pleomorphic nuclei and prominent nucleoli

Case 2

A 68 year old lady presented with postmenopausal bleeding of 1 month duration. Her gynaecological examination revealed a reddish, fleshy tumor of about 1.5×1.5 cm size, arising from the anterior vaginal wall and was located very close to the external urethral meatus. On per vaginal examination, the tumor was firm and was involving the lower one-third of anterior vaginal wall (Fig. 3).

Biopsy revealed large cells with scanty cytoplasm and pleomorphic hyperchromatic nuclei.

On immunohistochemistry, the tissue stained positive for Cytokeratin, CEA, Synaptophysin, Chromogranin A and BerEP4 and was pathognomic of neuroendocrine carcinoma. The Ki67 index was very high (70–80 %).

A diagnosis of large cell neuroendocrine carcinoma of vagina was made. Metastatic workup was negative. While planning the treatment, the prospect of surgery and its morbidities were discussed. Since the tumor was in close proximity to external urethral meatus, the patient would probably need urethral excision for a three dimensional clearance and possibly require a permanent cystostomy. Alternately an anterior pelvic exenteration procedure may be required. These options were clearly discussed with the patient and the patient

Fig. 2 Immunohistochemical Staining (Synaptophysin)

Fig. 3 Picture showing tumor in close proximity to external urethral meatus

did not opt for surgery. Therefore it was decided to treat this patient with sequential chemoradiation.

The plan was to administer 6 cycles of chemotherapy with Cisplatin and Etoposide followed by pelvic EBRT.

After 2 cycles of chemotherapy, we noticed a complete clinical response. Unfortunately, this overwhelming response also encouraged the patient to default on further chemotherapy cycles and radiotherapy. The patient was lost to follow up. When the patient returned a year later, she had significantly enlarged bilateral inguinal lymph nodes and her performance score was poor. Interestingly there was no obvious recurrence at the primary site. Due to her poor general condition, she was started on oral salvage chemotherapy with Etoposide and patient was lost to follow up subsequently.

Discussion

Primary neuroendocrine tumors of the female genital tract are rare. Small cell neuroendocrine carcinoma, first described in 1957, is the most common neuroendocrine tumor. The less common large cell variant, although histologically distinct, shares the same natural history and is treated similarly. When found, they are often seen to be arising from ovary or uterus. These large cell neuroendocrine tumors originating from cervix or vagina is extremely rare. The natural history of large cell neuroendocrine carcinoma is significantly worse than that of the more common squamous cell cancer or adenocarcinoma [4]. Large cell neuroendocrine carcinomas are more likely to have lymph node metastases and lymphovascular space invasion, and their clinical course is marked by early hematogenous dissemination [5].

The mean age at diagnosis of the large cell variant is 34 years, but the range is wide (from 21 to 62) [6]. An

association with high-risk HPV infection (HPV18 more than HPV 16) has been described for both small cell and large cell neuroendocrine cancer [7]. There is usually no association with smoking unlike small cell neuroendocrine carcinoma of lung. Microscopically, the cells of the large cell variant of neuroendocrine carcinoma are distinguished by the presence of prominent nucleoli, vesicular nuclei with a more granular chromatin pattern, and variable amounts of cytoplasm. Neuroendocrine differentiation is demonstrated with pan-neuroendocrine markers such as chromogranin A, synaptophysin and neuron-specific enolase. Mitotic rates are high, and necrosis of individual tumor cells is common. Other large cell tumors that can arise in the cervix and may mimic large cell neuroendocrine carcinoma include embryonalrhabdomyosarcoma, lymphoma, and undifferentiated carcinoma arising from the lower uterine segment. These are usually excluded by immunohistochemical analysis. In addition, large cell neuroendocrine carcinoma must be differentiated from poorly differentiated squamous cell cancer with neuroendocrine features, as this was the case in our first patient where the initial biopsy suggested a diagnosis of a poorly differentiated squamous cell carcinoma.

A cervical mass can often be identified on examination, and the majority have bulky disease at the time of diagnosis [8]. Often, the presentation is that of a pelvic mass with bulky pelvic adenopathy or malignant ascites. Similar to small cell lung cancer, large cell neuroendocrine carcinoma have a particular propensity to spread to the liver, adrenals, bone, bone marrow, and the brain. Also in parallel to small cell lung cancer, large cell neuroendocrine carcinoma of the cervix can occasionally present with a paraneoplastic syndrome. Biopsy is required for definitive diagnosis. However, cytology, endocervical curettage, or cervical biopsy might not adequately differentiate these tumors from a squamous cell cancer or adenocarcinoma of the cervix. Hence larger samples such as hysterectomy are sometimes required to establish the diagnosis. Pap smear is usually inadequate as most of these tumors arise from submucosal region. Immunohistochemical staining for markers of neural and neuroendocrine differentiation are often needed for a definitive diagnosis.

Given the rarity of the condition, there are limited data to guide the treatment of large cell neuroendocrine carcinoma. Most published series contain few patients, and there are no prospective trials. In general, survival is poor with radical hysterectomy alone, but there is no consensus as to optimal management [9]. Treatment considerations have been largely extrapolated from the experience with small cell lung cancer [10]. Most clinicians favor the use of combined modality therapy (surgery followed by chemotherapy or combined chemoradiotherapy) for limited-stage potentially resectable disease, definitive chemoradiotherapy for locoregionally advanced unresectable but nonmetastatic disease, and palliative chemotherapy alone for those with metastatic disease, using

chemotherapy regimens that are typically used for small cell lung cancer. Some patients with early stage disease will not have metastases at presentation and are potentially curable with local therapies. However, given the propensity for early dissemination and patterns of treatment failure (with distant metastases predominating), and the sensitivity of large cell neuroendocrine cancers to platinum-based chemotherapy, systemic chemotherapy is considered a critical component of standard therapy for all stages of disease. There are no randomized trials comparing chemotherapy alone versus chemoradiotherapy, either as primary therapy, or in the adjuvant setting following radical hysterectomy. Despite the lack of data, most clinicians favor the use of combined chemotherapy and RT because of the strong evidence supporting concurrent chemoradiotherapy in other subtypes of cervical cancer. Adjuvant chemotherapy alone could be considered an option in patients who have undergone radical hysterectomy [11]. The role of surgery for large cell neuroendocrine carcinoma is not well studied. However, a role for surgery in patients with apparently early stage disease is supported by the fact that most series report long-term survival only for those patients who have undergone surgical resection in the context of multimodality treatment.

A clinical document on small cell neuroendocrine carcinoma issued by the SGO (Society of Gynecologic Oncologists) in 2011 recommended Radical hysterectomy with lymphadenectomy followed by chemotherapy (etoposide plus cisplatin) with or without RT, for early stage disease (I-IIA, <4 cm) and either combined chemotherapy and RT or neoadjuvant platinum-based chemotherapy followed by surgery if the disease remains localized (I-IIA, >4 cm) [12]. However the efficacy of these guidelines in the management of large cell variant is unknown. The role of lymph node dissection in patients with large cell neuroendocrine carcinoma is not defined. In clinically early stage disease, information about locoregional nodal status might help in planning radiotherapy if a radical hysterectomy is being planned as part of initial treatment. However, the value of surgical staging is not clear and routine lymph node dissection is often not undertaken if the initial treatment plan is for chemoradiation. Due to the early propensity for hematogenous spread despite locally negative resection margins and due to the limited prognosis, fertility-sparing surgery is not a recommended treatment option for young patients. Combination chemotherapy with Radiotherapy is used for locally advanced unresectable but non-metastatic disease. Post treatment surveillance after primary curative therapy for cervical cancer is uniformly recommended, although its effectiveness has not been well studied. In contrast to cervical squamous cell carcinoma and adenocarcinoma, the predominant site of failure for large cell neuroendocrine carcinoma is distant rather than pelvic and these recurrences occur earlier compared to other subtypes. Although therapy of recurrent disease is palliative and not

curative, survival and quality of life may be benefited by salvage chemotherapy. In our view, it is reasonable to consider CT or PET scan imaging every 3–6 months during the first 2 years of follow up or at any time there is suspicion of recurrence based on symptoms or physical exam findings, if the patient would be considered a candidate for additional therapy.

Conclusion

Large cell neuroendocrine tumors of the genital tract, especially vagina are very rare. Very few cases have been reported in the literature so far. There is currently no consensus to optimal management of these tumors due to their rarity. No prospective trials have been conducted yet to guide us with enough evidence to formulate treatment guidelines. Current treatment guidelines are based on the experience with small cell lung cancer. These tumors are highly sensitive to platinum and hence chemotherapy plays a crucial role in all stages of these tumors. Even though most oncologists prefer combined modality therapy, an ideal treatment strategy is yet to be determined.

References

1. Alfse GC, Thoresen SO, Kristensen GB, Skovlund E, Abeler VM (2000) Histopathologic subtyping of cervical adenocarcinoma reveals increasing incidence rates of endometrioid tumors in all age groups: a population based study with review of all nonsquamous cervical carcinomas in Norway from 1966 to 1970, 1976 to 1980, and 1986 to 1990. *Cancer* 89:1291–1299. doi:10.1002/1097-0142(20000915)89:6<1291::AID-CNCR14>3.0.CO;2-O
2. Albores-Saavedra J, Gersell D, Gilks CB et al (1997) Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. *Arch Pathol Lab Med* 121:34
3. Miller B, Dockter M, el Torky M, Photopulos G (1991) Small cell carcinoma of the cervix: a clinical and flow-cytometric study. *Gynecol Oncol* 42:27
4. McCusker ME, Coté TR, Clegg LX, Tavassoli FJ (2003) Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. *Gynecol Oncol* 88:333
5. Sheets EE, Berman ML, Hrountas CK et al (1988) Surgically treated, early-stage neuroendocrine small-cell cervical carcinoma. *Obstet Gynecol* 71:10
6. Gilks CB, Young RH, Gersell DJ, Clement PB (1997) Large cell neuroendocrine [corrected] carcinoma of the uterine cervix: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 21:905
7. Mannion C, Park WS, Man YG et al (1998) Endocrine tumors of the cervix: morphologic assessment, expression of human papillomavirus, and evaluation for loss of heterozygosity on 1p,3p, 11q, and 17p. *Cancer* 83:1391
8. Cohen JG, Kapp DS, Shin JY et al (2010) Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol* 203:347.e1
9. Viswanathan AN, Deavers MT, Jhingran A et al (2004) Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. *Gynecol Oncol* 93:27
10. Boruta DM II, Schorge JO, Duska LA et al (2001) Multimodality therapy in early-stage neuroendocrine carcinoma of the uterine cervix. *Gynecol Oncol* 81:82
11. Lee JM, Lee KB, Nam JH et al (2008) Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study. *Ann Oncol* 19:321
12. Gardner GJ, Reidy-Lagunes D, Gehrig PA (2011) Neuroendocrine tumors of the gynecologic tract: a society of gynecologic oncology (SGO) clinical document. *Gynecol Oncol* 122:190