

Case report

Fertility sparing management of large cell neuroendocrine tumour of cervix: A case report & review of literature

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ABSTRACT

Large cell neuroendocrine cervical carcinoma (LCNEC) is a rare and aggressive cancer that tends to spread and recur early despite intensive multimodal treatment. Conventional treatment strategies for early stage neuroendocrine tumour (NET) include radical hysterectomy followed by adjuvant chemotherapy. There are only 2 reported cases of fertility sparing treatment for NET. We report on the first case of successful conception and delivery at term following radical trachelectomy for early stage LCNEC.

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1. Introduction

Neuroendocrine tumours (NET) were first described in 1972 by Albores-Saavedra. They are an aggressive subtype of cervical carcinomas with poor prognosis even at early stage. The natural history of NET is different to that of the more common squamous cell carcinoma (SCC) of the cervix with a propensity for early distant metastases and a high rate of both local and extra-pelvic recurrence (Yoseph et al., 2012). They are classified as either typical carcinoid, atypical carcinoid, small cell and large cell neuroendocrine carcinoma based on mitotic activity, nuclear atypia and geographic type of necrosis. Large cell neuroendocrine carcinoma (LCNEC) is similar to the small cell subtype in its biological behaviour and clinical prognosis.

A simple or radical trachelectomy with pelvic lymphadenectomy is usually offered to those women with early stage squamous or adenocarcinoma of the cervix (FIGO stage 1A2 and 1B1), who have no apparent lymph node involvement and who wish to preserve fertility. However due to the aggressive nature of neuroendocrine tumours, even early stage disease is conventionally treated in a multimodal fashion, including radical hysterectomy, pelvic lymphadenectomy and adjuvant chemotherapy (Gardner et al., 2011). We report a rare case of successful conception and childbirth following fertility-sparing radical trachelectomy for stage 1 LCNEC of the cervix (Fig. 1).

2. Case

A 27 year old nulliparous, Caucasian woman undergoing routine cervical screening was reported to have high-grade dyskaryosis with a glandular abnormality on her smear. Colposcopically directed punch biopsy identified high grade cervical intraepithelial neoplasia (CIN2) and thus a large loop excision of the transformation zone (LLETZ) was performed. Histology revealed a 4 mm wide by 2 mm deep LCNEC.

A staging computed tomography (CT) scan of the chest and abdomen and a magnetic resonance image (MRI) of the pelvis did not reveal evidence of residual disease, pelvic lymphadenopathy or distant spread; therefore the tumour was classified as FIGO stage 1A1. A positron-emission tomography (PET) scan did not reveal local disease but PET avid nodes were identified near the coeliac axis. Fine needle aspiration (FNA) of these nodes did not show metastatic spread.

Further treatment options were discussed with the patient, including no further treatment, radical hysterectomy and radical trachelectomy, both with bilateral pelvic lymphadenectomy and adjuvant chemotherapy. Because the patient wished to preserve her fertility, she decided to undergo radical trachelectomy. Prior to surgery, she also availed the option for egg retrieval and embryo storage.

A midline laparotomy was performed and the coeliac axis lymph nodes (identified on PET scan) were removed and sent for frozen section. The frozen section showed no metastatic disease. A radical abdominal trachelectomy with bilateral pelvic lymph node dissection and upper para aortic lymph node sampling was performed. A prophylactic cervical cerclage suture was also inserted.

The final histology report showed no evidence of residual NET or lymph node metastasis. Postoperatively, the patient was given 4 cycles

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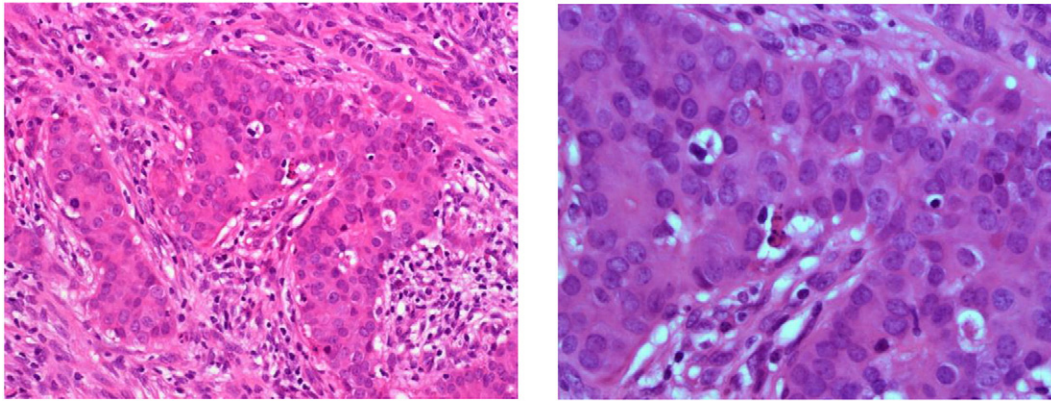


Fig. 1. (A) and (B): Large cell neuroendocrine carcinoma. Groups of cells with a typical nuclei and abundant cytoplasm are seen, some containing eosinophilic granules. The cells are arranged in an insular and trabecular pattern. Immunohistochemistry is diffusely positive with markers for chromogranin, CD56, synaptophysin and P16. There is a high proliferation index (80%).

of Cisplatin and Etoposide adjuvant chemotherapy. Follow-up 18 months after surgery with 3 monthly clinical assessments and yearly CT scans showed no recurrence and the patient had resumed a regular menstrual cycle.

She was subsequently seen in the antenatal clinic at early gestation. An ultrasound scan confirmed a viable singleton intrauterine pregnancy corresponding to 12 weeks. Since her risk of second trimester miscarriage was increased, she had regular hospital-based antenatal follow-up and delivered a 2.7 kg baby by elective caesarean section at 38 weeks' gestation. She remained recurrence free at the 6 month postnatal assessment with a normal cervical cytology result.

3. Discussion

LCNEC is rare, accounting for 0.087–0.6% of all cervical cancers and to date, only 70 cases have been reported in the literature (Wang et al., 2009). Historically, radical trachelectomy has been offered to only women with SCC or adenocarcinoma of the cervix achieving a pregnancy rate of 15–30%. There are only 2 reported cases in current literature on radical trachelectomy in management of small cell neuroendocrine cervical carcinoma (Hertel et al., 2006; Singh et al., 2015).

3.1. Presentation

The occurrence of LCNEC is associated with high-risk HPV subtypes 16/18 infection and to a lesser extent 31/33 subtypes. It can present in association with squamous cell carcinoma, cervical adenocarcinoma and CIN/CGIN. The majority of reported cases of LCNEC have presented with abnormal vaginal bleeding/discharge, or an abnormal cervical smear (Gilks et al., 1997). Rarely, they can present as carcinomatous meningitis or mimic vaginitis. Macroscopically, they are ill-defined or polypoidal exophytic masses with a brown-yellow-grey appearance.

3.2. Diagnosis

Cytopathologists are able to correctly identify LCNEC by the combined findings of a necrotic background, large cells with abundant cytoplasm, nuclei that are three to five times larger than the nuclei of small lymphocytes, rosette structures, naked nuclei, nuclear streaming, frequent mitoses, a coarse chromatin pattern and prominent nucleoli.

Histologically, they are seen as being composed of a relatively uniform, medium to large trabecular or insular arrangement of cells, containing eosinophilic cytoplasmic granules (Gilks et al., 1997). LCNEC have greater mitotic activity (>10 mitotic figures/10 high power fields) and typically show more extensive necrosis. Vascular invasion by tumour is common and extensive (Gilks et al., 1997). On immunohistochemical staining, the tumour shows diffuse positivity for cytokeratin

AE1/AE3 (Anti-Pan-cytokeratin) and neuroendocrine markers including chromogranin, synaptophysin and CD56; 50% of the tumours are positive for neuron specific enolase (Gilks et al., 1997). In addition, the tumour cells are focally positive for P63, a marker of cervical basal cells, which is diffusely positive in SCC of the cervix.

The histological differential diagnosis of LCNEC includes small cell carcinomas, poorly differentiated adenocarcinoma or squamous cell cancer of the cervix, and the rare primary or metastatic cervical melanoma (Gilks et al., 1997).

3.3. Staging

The staging of NET of the cervix follows that of traditional cervical cancer. Twenty percent of NETs present as stage IV disease compared with 4.3% of SCCs and the incidence of lymph node metastases varies between 40 and 60% (Gardner et al., 2011).

3.4. Management

Radiographic evaluation includes either a CT or PET CT scan. CT head is only warranted in the presence of lung metastases. In his fourteen year experience, Hoskins et al. found no cranial metastases on initial patient presentation (Hoskins et al., 2003).

Primary radical surgery followed by adjuvant chemotherapy is the preferred treatment modality for patients with early stage disease (Gardner et al., 2011). For tumours larger than 4 cm, a neoadjuvant approach with systemic platinum-based therapies followed by a localised treatment-based approach (including surgery) is suggested, provided the disease is limited to the cervix (Gardner et al., 2011).

4. Surgery

Studies have included radical hysterectomy with regional lymphadenectomy as a component of primary management (Gardner et al., 2011). In view of lymph node status as a prognostic indicator, Boruta et al. support pelvic and para-aortic nodal dissection in all early stage NEC patients (Boruta et al., 2001).

5. Chemotherapy

Most studies report long term survival only for those patients who have undergone surgical resection when performed in the context of a multimodality treatment approach with adjuvant chemotherapy (Gardner et al., 2011).

Postoperative chemotherapy with either Etoposide/Cisplatin (EP) or Vincristine, Adriamycin and Cyclophosphamide alternating with Cisplatin/Etoposide (VAC/PE) has been found to be associated with a

significant survival advantage in patients both with and without lymph node metastasis. Adjuvant radiotherapy in addition to chemotherapy has not been found to be beneficial. For advanced disease or for patients not suitable for surgery, combination chemotherapy (EP) with radiotherapy for local control should be considered (Gardner et al., 2011).

6. Prognosis

The presence of lymph node metastasis is the most important negative prognostic factor with advanced stage and larger tumour size being other poor prognostic variables (Boruta et al., 2001). Recurrences within the abdomen tend to occur in the liver, kidneys and adrenal glands while extra abdominal spread is mainly seen in the lungs, brain and supra-clavicular lymph nodes (Gardner et al., 2011).

Observed median survival for women with NET is 22 months versus 10 years for women with SCC. Age and FIGO stage-adjusted hazards of death are 1.84 times greater for neuroendocrine tumours than for SCC with hazard ratio of 2.18 for stage I/II and a ratio of 1.98 for stage III/IV.

7. Disease recurrence and treatment

Surveillance for disease recurrence is recommended at 3 monthly clinical reviews and annual CT scan of chest/abdomen & pelvis. CT Head is warranted only in the presence of neurologic symptoms or pulmonary metastases (Gardner et al., 2011). Treatment of disease recurrence after initial therapy may include multi-agent chemotherapy, with Etoposide appearing to have significant activity. Radiation to symptomatic metastasis is also a reasonable approach but may not afford a prolonged benefit. Surgery for recurrent LCNEC is controversial and has not been shown to improve long term survival.

Given the poor prognosis even with multimodality treatment, some novel treatment strategies have been proposed. Hormone therapy has been assessed for treating these tumours but only a very small proportion of recruited patients (3 out of 24) expressed estrogen (1 case) and progesterone (2 cases) receptors (Tangjitgamol et al., 2005). Kajiwaru et al. has proposed the use of somatostatin type 2A (SSTR2A) analogue Octreotide to treat neuroendocrine tumours because 3 out of 7 cases studied expressed SSTR2A receptors (Kajiwaru et al., 2009).

8. Conclusion

Well established data exists on clinical outcomes following radical trachelectomy for early stage non-neuroendocrine tumours of the cervix. The rarity of LCNEC precludes availability of such data for neuroendocrine tumours. Our experience with this case and the 3- year

recurrence-free survival with a successful pregnancy outcome would suggest that it is reasonable to offer fertility sparing surgery even for NET of the cervix. However, there is an ongoing need to collate data on both oncological and fertility outcomes in this rare cohort of patients.

Consent

Written informed consent has been obtained from the patient for publication of this case report and accompanying images.

Conflict of interest

The authors disclose no financial conflicts of interest.

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