

Large-cell neuroendocrine carcinoma of the uterine cervix complicating pregnancy

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Large-cell neuroendocrine cervical carcinoma is a rare and aggressive cancer that tends to spread and recur early despite intensive multimodal treatment. The optimal mode of therapy is still controversial and management during pregnancy is challenging because foetal well-being must also be considered. We report a patient with clinically stage IIB large-cell neuroendocrine cervical carcinoma who presented with a cervical polyp and vaginal bleeding at 18 weeks of pregnancy. The patient received concurrent chemotherapy and radiation after termination of pregnancy and remained in complete remission 21 months after completion of treatment.

Introduction

Neuroendocrine tumours of the uterine cervix are uncommon. They can be classified as typical carcinoid, atypical carcinoid, small-cell carcinoma, and large-cell neuroendocrine carcinoma. Most of the reported cases were small-cell carcinomas. Their aggressive behaviour and resistance to therapy have been well documented. Large-cell neuroendocrine carcinoma of the cervix is even more rare. Most reports in the published literature consist of descriptions of one or two cases only. The prognosis for these patients is poor despite multimodal treatment. Most die within 2 to 3 years of diagnosis. The optimal mode of therapy is yet to be established. Although there have been several published reports of small-cell carcinoma of the cervix occurring during pregnancy, our patient is the first with large-cell neuroendocrine carcinoma diagnosed during pregnancy to have achieved complete remission after radiation and chemotherapy.

Case report

A 30-year-old primigravida presented at 18 weeks of gestation with a 2-week history of unprovoked vaginal spotting. A speculum examination revealed a 5-cm cervical polyp that was removed for histological evaluation. A microscopic examination showed that the cervical polyp had been totally replaced by malignant cells and no normal residual cervical tissue was present. A histological examination showed anastomosing islands and trabeculae of carcinoma cells with abundant cytoplasm and distinct nucleoli. Peripheral nuclear pallisading was prominent (Fig). The mitotic count was high (up to 50 per 10 high-power fields). The neuroendocrine differentiation was confirmed by positive staining with synaptophysin and chromogranin. After counselling, the couple decided to terminate the pregnancy and start treatment as soon as possible. A complete abortion was achieved with vaginal and oral prostaglandin followed by surgical evacuation of the uterine contents. A physical examination found no peripheral lymphadenopathy or organomegaly and a pelvic examination done without anaesthesia found a bulky cervix without gross residual tumour. The vagina was not involved. The right parametrium was thickened but did not extend to the pelvic sidewall. The chest X-ray was normal and a baseline computed tomographic scan of the thorax/abdomen/pelvis showed no evidence of regional or distant metastases. The clinical diagnosis was consistent with stage IIB disease. Treatment was started 3 weeks after her first presentation. She was treated with external pelvic irradiation (whole pelvis 40 Gy in 20 fractions over 4 weeks, then additional parametrial irradiation 16 Gy in 8 fractions) and high-dose rate brachytherapy 7 Gy to point A, in 4 fractions over 2 weeks. Three cycles of chemotherapy with etoposide (100 mg/m²) and cisplatin (25 mg/m²) on days 1 to 3 were given every 3 weeks concurrently with radiotherapy, followed by three more cycles afterwards. She tolerated the treatment well and completed the whole course as scheduled, 5 months after the diagnosis, achieving a clinically complete remission of disease. One year after completion of the chemotherapy and radiation, a computed tomographic scan of the abdomen and pelvis revealed no evidence of recurrence or metastasis. Up to the time of writing this report (21 months after the completion of treatment), there has been no clinical evidence of relapse.

Key words

Carcinoma, large cell; Carcinoma, neuroendocrine; Pregnancy complications; Uterine cervical neoplasms

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孕婦子宮頸大細胞神經內分泌瘤

子宮頸大細胞神經內分泌瘤是一種罕見及侵略性相當高的癌症，即使施行積極多模式治療，腫瘤仍會擴散甚至復發。此病的最佳療法仍備受爭議。孕婦如有此腫瘤，由於要顧及胎兒，施行治療更見艱鉅。本文報告一名患有子宮頸大細胞神經內分泌瘤（臨床期數屬IIB）的孕婦，18星期時出現宮頸息肉及陰道出血。病人終止懷孕後，同時接受化療及放射治療。完成治療的21個月內腫瘤完全緩解。

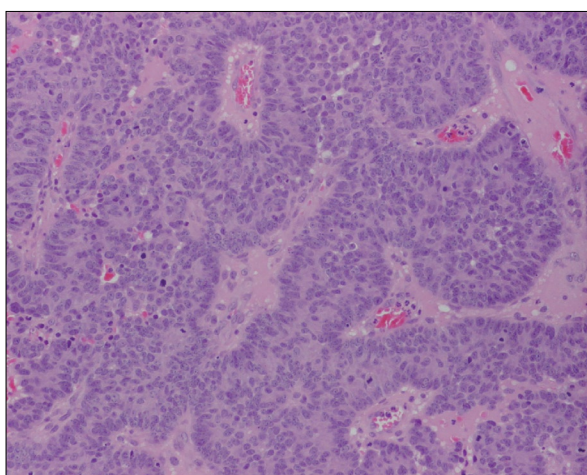


FIG. The tumour nests featured prominent peripheral nuclear palisading, which was a feature suggestive of neuroendocrine differentiation (x200)

Discussion

Tumours of the uterine cervix showing neuroendocrine differentiation are uncommon. These tumours account for only 1 to 2% of all uterine cervical cancers. Moreover, the terminologies are diverse, making comparison of the clinicopathological characteristics and treatment protocols difficult. In 1996, a common consensus was established at a workshop sponsored by the College of American Pathologists and the National Cancer Institute of the United States.¹ The four recommended categories are typical carcinoid tumour, atypical carcinoid tumour, small-cell carcinoma, and large-cell neuroendocrine carcinoma, based on features of cellular cytology, necrosis, and mitosis. This classification has also been adopted by the World Health Organization (WHO) Classification of Tumours.² Typical and atypical cervical carcinoid tumours are extremely rare. Small-cell carcinoma of the cervix is the most common category, and is associated with a poor prognosis since it is refractory to various modes of therapy.

Large-cell neuroendocrine carcinoma of the cervix is even more rare. Most reports in the literature consist of small case series (Table³⁻⁹). All presented with early stage disease and most received multi-modal treatment, yet the outcome was poor with early metastasis. About 50% of the patients died of the disease, typically within 2 to 3 years of diagnosis, confirming the aggressive nature of this tumour. Thus recognition and accurate diagnosis of this rare tumour are essential for formulating an effective treatment plan. Conventional treatment protocols

TABLE. Previously reported cases of large-cell neuroendocrine cervical carcinoma*

Reports	No. of cases	Age (years)	Stage	Treatment (No. of cases)	Outcome (No. of cases)
Gilks et al ³	2	36-38	IA2	RH (1)	NED 36 mo (1)
				RH with unknown adjuvant treatment (1)	LFU (1)
	9	21-36	IB	RH (1)	DOD 24 mo (1)
				RH + Chemo (6)	DOD 8-12 mo (3), NED 6-36 mo (3)
				RH + Chemo + RT (2)	DOD 18-24 mo (2)
	1	62	IIA	RH	DOD 6 mo
Krivak et al ⁴	1	25	IB1	RH+PLN+PALN+Chemo for metastasis 6 mo later	DOD 35 mo
	1	36	IIA	RT+Chemo	DOD 33 mo
Sato et al ⁵	5	27-51	IB	RH+RT+Chemo (5)	NED 12 mo (1)
					AWD with lung metastasis 151 mo (1)
					DOD 16-19 mo (3)
	1	42	IIA	RH+RT+Chemo	DOD 6 mo
Yun et al ⁶	1	31	IA1	RH	NED 10 mo
Cui et al ⁷	1	35	NA	Neoadjuvant Chemo+RH+PLN+PALN	NA
Dikmen et al ⁸	1	45	IIB	RH+PLN+RT+Chemo	NED unknown duration
Kawauchi et al ⁹	1	40	IB	TAHBSO+PLN	NED 9 mo

* AWD denotes alive with disease, Chemo chemotherapy, DOD died of disease, LFU lost to follow-up, mo months, NA not available, NED no evidence of disease, PALN para-aortic lymph node dissection, PLN pelvic lymph node dissection, RH radical hysterectomy, RT radiotherapy, and TAHBSO total abdominal hysterectomy with bilateral salpingo-oophorectomy

for squamous cell carcinoma of the cervix may not be appropriate for this aggressive cell type. One of the diagnostic pitfalls is that the neuroendocrine component may be overlooked; it has been shown that many cases are associated with adenocarcinoma, a tumour with a better prognosis. The correct interpretation depends on a high index of suspicion and appreciation of the features of neuroendocrine differentiation in the non-adenomatous component of the tumour. These features include uniform medium-to-large cells in a trabecular or insular pattern, eosinophilic granules in the cytoplasm and histochemical/immunohistochemical staining for neuroendocrine markers.³

Neuroendocrine tumours of the cervix complicating pregnancy are rare. Several reports documenting cases of neuroendocrine small-cell carcinoma of the cervix complicating pregnancy have been published,¹⁰ however, we have not found any similar cases with large-cell neuroendocrine pathology in the literature.

Our patient presented at 18 weeks of pregnancy. In view of the early stage of foetal development and the aggressive nature of the disease, it was necessary to start treatment before the foetus could attain adequate maturity for survival. The choice was either termination of pregnancy followed by definitive treatment, or institution of definitive treatment disregarding foetal well-being. After counselling, with the pros and cons of each option explained, the couple chose the first option to avoid the possibility of irradiating the foetus, which might survive and be born alive.

The mainstay of treatment was concurrent chemotherapy and radiation. A radical hysterectomy was not performed because of the stage (IIB) of disease, and also because these tumours are highly aggressive and tend to metastasise early. In fact, despite radical hysterectomies being performed in almost all reported early stage cases, the prognosis was still poor, with early metastasis, even after adjuvant chemotherapy and/or irradiation. We believe that local control using pelvic irradiation together with concurrent and adjuvant systemic control using chemotherapy offered the patient the best chance of survival. The role of radical hysterectomy in the management of large-cell carcinoma of the cervix needs to be reconsidered. Upfront chemotherapy seems to be the cornerstone of treatment. Krivak et al⁴ also came to a similar conclusion, finding that chemotherapy is important due to the high rate of distant metastasis. For this reason, treatment options such as concurrent chemotherapy and radiation or neoadjuvant chemotherapy followed by radical hysterectomy should be further explored. The chemotherapeutic agents used in our patient as well as in most of the previous studies were etoposide and cisplatin. This is in contrast to using cisplatin

alone to manage squamous cell carcinoma of the cervix. The basis for this combination is the protocols used for the more common neuroendocrine tumours of the lung and small-cell cervical carcinomas. As the incidence and survival rates of large-cell neuroendocrine cervical cancers remain low, the best chemotherapeutic agents are yet to be identified.

Although our patient has had a satisfactory outcome with this treatment plan—disease-free survival of at least 21 months after completion of treatment—further reports and studies are required to confirm its effectiveness. Because a hysterectomy was not performed, there is some uncertainty about the lack of histological proof of residual tumour. No random cervical biopsies have been performed either because their role as a means of detecting residual disease in asymptomatic patients with normal recto-vaginal examinations is uncertain. Moreover, even if tumour cells are found in a cervical biopsy these may not be truly representative of residual disease because regression of disease after radiation may take a long time. Like other cervical cancers, the staging was based on clinical information and the parametrial involvement was not confirmed pathologically. Computed tomography is not able to detect parametrial involvement accurately.

The management and counselling would have been even more complicated if the patient had presented at a later gestation at which delivery would yield an extremely premature baby. The mode of delivery may also be controversial. Vaginal delivery may result in dissemination of neoplastic cells into lymphovascular channels, haemorrhage, cervical laceration and implantation of malignant cells in the episiotomy site, while abdominal delivery may delay the initiation of non-surgical treatment. Administration of chemotherapy to control the disease while waiting for foetal maturity, followed by definitive treatment, may be an alternative option. There have been isolated case reports of the use of cisplatin without teratogenic effects but the dosage may not be optimal.

In conclusion, recognition of this rare and aggressive tumour is important for planning effective treatment but the optimal mode of therapy remains controversial. Both failures and survivors have received multimodal therapy including surgery, multi-agent chemotherapy and radiotherapy. Each treatment and their different combinations need careful evaluation. Yet, the poor prognosis indicates that more reports and studies are needed to formulate the most appropriate therapy for these patients. Standard treatment protocols may not be established and multi-nation multi-centre randomised controlled trials may not be feasible due to the low prevalence of this tumour. Case reports and series are probably the only means of documenting and accumulating experience.

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