CASE REPORT

Coexisting squamous cell carcinoma and high-grade neuroendocrine carcinoma, small cell type: a rare collision in cervix

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Accepted 1 May 2018

SUMMARY

Collision tumours of the uterine cervix are extremely uncommon with exact incidence not known. Unlike squamous cell carcinoma (SCC) and adenocarcinoma that are known to coexist, small cell neuroendocrine carcinoma (SCNEC) is rarely documented with other histological types in the cervix. We report such rare case of a collision tumour in cervix displaying dual histological component of SCNEC and SCC in a 36-year-old woman. The case is being presented because of its rarity and represents a unique and hitherto seldom-reported combination of two malignant tumours with distinct and often contrasting epidemiology, histology and prognosis coexisting in the same patient.

BACKGROUND

Cervical cancer is the third common malignancy afflicting women worldwide. Squamous cell carcinoma (SCC) along with adenocarcinoma together constitute over 98% of the cervical carcinomas diagnosed annually.¹ Neuroendocrine tumours in the cervix are, however, rare. In the new 2014 WHO classification, neuroendocrine tumours of the cervix are categorised into low-grade neuroendocrine tumours and high-grade neuroendocrine carcinoma. Among neuroendocrine carcinomas, small cell type (SCNEC) is the most common and accounts for about 1% of all cervical cancers.¹ Apart from pure neuroendocrine tumours, small cell component can be seen as a part of composite tumour whereby it arises as a divergent differentiation from adeno carcinoma or sqsquamous cell carcinoma (SCC). In contrast, in collision tumours, two independent neoplasms grow in close proximity and coexist simultaneously as one lesion.²⁻³ Collision tumours are unusual in the cervix and most of the reported combinations are of SCC and adenocarcinoma. Coexistence of SCNEC and SCC in the cervix is exceedingly rare and limited to isolated case reports.¹⁻⁴⁻⁵ We report a rare case of collision tumour in the uterine cervix of a 36-year-old patient clinically diagnosed with early stage cervical cancer.

CASE PRESENTATION

A 36-year-old multiparous woman presented to the outpatient department of the gynaecology unit with continuous bleeding per vaginum since 5 months. OnPer speculum examination, an exophytic

friable growth that bled on touch was visualised replacing the whole of the cervix. The vagina was healthy and appeared uninvolved. Vaginal examination confirmed the same findings. The uterus was anteverted and bulky and bilateral fornices were non-tender.

INVESTIGATIONS

A contrast-enhanced CT (CECT) of the abdomen and pelvis revealed a 6×5×5 cm mass arising from the uterine cervix. There was no involvement of the urinary bladder, ureter or rectum. An 8 mm left external iliac lymph node was present. There was no other significant lymphadenopathy or evidence of locoregional extension. Chest X-ray and CECT thorax did not reveal metastatic lesion.

With a presumptive diagnosis of carcinoma cervix, a cervical biopsy was performed which revealed a malignant tumour with cells arranged in sheets, exhibiting high nucleocytoplasmic ratio, nuclear moulding and foci of necrosis. The malignant cells were immunopositive for cytokeratin (dot-like paranuclear), synaptophysin, chromogranin and CD56 while negative for thyroid transcription factor-1 and had a 100% Ki67 labelling index, confirming a diagnosis of SCNEC.

TREATMENT

She underwent laparotomy with radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy and peritoneal wash. On gross inspection of the hysterectomy specimen, the growth was restricted to uterine cervix without any extension to uterine corpus, parametria or involvement of adnexa.

OUTCOME AND FOLLOW-UP

Microscopic evaluation of the growth in the cervix revealed two distinct tumour populations. Bulk of the tumour was small cell carcinoma mirroring the morphology and immunoprofile of the biopsy. However, there was also a distinct component of invasive SCC with adjoining foci of high-grade squamous intraepithelial lesion (figure 1). Both the components though present simultaneously had no areas of transition and showed presence of normal stroma in between. Immunohistochemistry for p40 confirmed the SCC which was conspicuously negative in the small cell carcinoma component (figure 2A,B). High-grade squamous intraepithelial

To cite: Kaushal S, Mathur SR, Kumar S. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223127

Figure 1 H&E: tumour with areas of small cell neuroendocrine carcinoma (SCNEC) (arrow) and squamous cell carcinoma (SCC) (arrowhead) (H&E, 100x) (A); typical features of SCC (H&E, 200x) (B); SCNEC area showing small round cells in nests and clusters (H&E, 200x) (C); tumour cells have scant cytoplasm, ovoid hyperchromatic nuclei and show moulding (H&E, 400x) (D).

lesion showed diffuse Ki67 in the surface epithelium (figure 2C). Synaptophysin, chromogranin and CD56 were negative in SCC areas unlike in SCNEC component (figure 3A–C). The cytokeratin immunostain revealed dot-like positivity in SCNEC component (figure 3D).

The lymph nodes were free of tumour. Peritoneal wash cytology was also reported negative for malignant cells. Her final diagnosis was stage IB2 cervical cancer with dual histological component, majority SCNEC with a minor component of SCC.

She was given postoperative chemoradiotherapy and is doing fine after 1 year of follow-up.

DISCUSSION

Collision and composite tumours are two distinct entities which need to be differentiated from each other.² Collision tumours show rare coexistence of two different origin tumours presenting as one lesion. Though both types exist in close proximity in collision tumours, they do not intermingle unlike composite tumours which originate from same pluripotent stem cell and show distinct areas of transition.^{2,3} Collision tumours have been described in various organs such as oesophagus, lung, breast and urinary bladder; however, their description in the cervix is exceptionally rare.³ The exact

Figure 2 Immunohistochemistry: strong p40 immunopositivity in squamous cell carcinoma areas (400x) (A); p40 immunonegativity in small cell neuroendocrine carcinoma component (arrow) (B) (100x); diffuse Ki67 in the surface epithelium, indicative of carcinoma in situ (400x) (C).

Figure 3 Immunohistochemistry: diffuse immunopositivity for synaptophysin (200x) (A), CD56 (200x) (B) and chromogranin (200x) (C) in the small cell neuroendocrine carcinoma (SCNEC) component and immunonegativity in the corresponding squamous cell carcinoma component; dot-like positivity for cytokeratin in SCNEC component (400x) (D).

incidence of collision tumours of the uterine cervix is not known due to rarity. There are numerous accounts of SCC and adenocarcinoma cervix coexisting in the same patient.^{5,6} Shi *et al* reported coexistence of SCC with an exceedingly rare variant of adenocarcinoma, adenoid cystic carcinoma, in three patients, both components showing presence of high-risk human papilloma virus (HPV) DNA and mRNA by in situ hybridisation.⁷ However, instances of SCNEC and SCC or adenocarcinoma coexisting in the same patient are much rarer (table 1). Toki *et al* reported a case of SCNEC coexisting with microinvasive SCC and adenocarcinoma in situ in the same patient. This was a 42-year-old woman who presented with complaints of abnormal vaginal discharge and indurative lesion on the posterior lip of the cervix. The patient died of progressive disease within 3 years of diagnosis.⁵ In the study by Ishida *et al*, two tumours had SCNEC coexisting with adenocarcinoma along SCC and cervical intraepithelial neoplasia, respectively. One case was of a 41-year-old woman who presented with early stage cervical cancer. She died of disease 2.5 years postsurgery. The other case was of a carcinoma in situ (CIN) in a 30-year-old woman, who also presented with early stage cervical cancer. She had no evidence of disease at 2.5 years follow-up.⁸ Rekhi *et al*, in a series of 50 neuroendocrine tumours of the cervix, reported seven cases of collision tumours of SCNEC with other tumours. The other component was SCC in four of the cases, adenocarcinoma in two and large cell neuroendocrine carcinoma in one of the tumours.⁴ The patients with SCC and SCNEC ranged in age from 45 to 60 years with a median age of 51 years. Two of them underwent multimodality treatment, surgery followed by radiotherapy and chemotherapy; however, one had progressive disease at 29 months follow-up and the other died of disease at 36 months postdiagnosis.⁴ Our patient is among the second youngest of all reported cases and presented with early stage cancer with distinct small cell carcinoma, CIN and invasive SCC components on histopathology.

Table 1 Clinicopathological features of coexisting small cell carcinoma and squamous cell carcinoma cervix cases, published in English literature

Author (year)	Age	pTNM	Coexistent tumours	Treatment given	Follow-up (years)
Toki <i>et al</i> 1996 ⁵	42	NK	SCNEC+microinvasive SCC+AIS	HT	DOD (3)
Ishida <i>et al</i> 2004 ⁸	30	PT1a2N0M0	SCNEC+CIS + mucinous ADC	NK	NED (2.5)
	41	PT1bN0M0	SCNEC+SCC+ mucinous ADC	NK	DOD (2.5)
Rekhi <i>et al</i> 2013 ⁴	60	NK	SCNEC+SCC	NK	NK
	46	PT3bN0M0	LCNEC+SCC	NK	AWD (3 months)
	50	NK	SCNEC+SCC	HT	NK
	52	PT1b1N0M0	SCNEC+SCC	HT	DOD (3)
Present case, 2018	36	PT1b2N0M0	SCNEC+SCC	HT	NED (1.5)

ADC, adenocarcinoma; AIS, adenocarcinoma in situ; AWD, alive with disease; CIS, carcinoma in situ; DOD, died of disease; HT, hysterectomy; LCNEC, large cell neuroendocrine carcinoma; NED, no evidence of disease; NK, not known; SCC, squamous cell carcinoma; SCNEC, small cell neuroendocrine carcinoma.

SCNEC is extremely rare in the uterine cervix. While both SCC and adenocarcinoma have undisputed causal relation with HPV, the role of HPV in the pathogenesis of small cell carcinoma is less well established.^{8,9} Unlike SCCs and adenocarcinomas which are both preceded by well-characterised dysplastic lesions that can be diagnosed during screening by cervical cytology, SCNEC lacks any preceding in situ lesions.¹⁰

It is important to differentiate SCNEC from small cell variant of SCC as both have different therapeutic and prognostic implications. Use of immunohistochemistry (cytokeratin, p40 and neuroendocrine markers) serves as a valuable adjunct to differentiate the two entities. SCNEC carries a worse prognosis and is seen in younger patients as compared with SCC and adenocarcinoma.¹⁰ It tends to be detected at a later stage due to more infiltrative growth pattern resulting in a barrel-shaped cervix and is often diagnosed at an advanced stage with many patients already harbouring nodal/distant metastasis at diagnosis.¹¹

However, even in patients with early stage and node-negative disease, the survival of SCNEC is significantly worse as compared with stage-matched SCC and adenocarcinoma. Chen *et al* observed a 5-year survival of 35.7% for SCNEC compared with 60.5% and 69.7% for SCC and adenocarcinoma, respectively.¹² The rarity of SCNEC in the uterine cervical location has made it difficult to establish a standard therapeutic protocol. However, in view of its aggressive course, both the Society of Gynecologic Oncology and the Gynecologic Cancer Intergroup recommend multimodality therapeutic approach combining surgery and chemoradiation.¹³

Definite prognostic differences of collision tumours with SCNEC and pure SCNEC/SCC are not known. This case represents a unique, rare and hitherto seldom-reported case of two malignant tumours, SCNEC and SCC, with distinct and often contrasting epidemiology, histology and prognosis coexisting in the same patient.

Learning points

- Collision tumours are rare occurrence in the cervix and present with usual symptoms, hence difficult to diagnose clinically.
- A careful histopathological evaluation leads to accurate diagnosis.
- Awareness and recognition of more such cases is important to guide proper management protocols for patients presenting with uncommon histopathology combinations.

Contributors SKa: acquisition and interpretation of data, conception, design and drafting of the manuscript. SRM and SKu: acquisition and interpretation of data, critical review of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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