Diagnostic Pathology

CASE REPORT

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Two cases of mixed large cell neuroendocrine carcinoma and adenocarcinoma of the cervix: case report and review of the literature

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Abstract

Background Mixed adenoneuroendocrine carcinoma (MANEC) of the cervix is a rare malignant tumor with high malignancy and poor prognosis, of which large-cell neuroendocrine carcinoma and HPV-independent adenocarcinoma are particularly rare, which have been reported limitedly in the literature. Here, we present 2 cases of MANEC of the cervix and discuss important considerations for diagnosing cervical poorly differentiated carcinoma.

Case presentation we reported two cases of mixed large cell neuroendocrine carcinoma and adenocarcinoma of the cervix, one HPV-independent and one HPV-associated, both with vaginal bleeding. Magnetic resonance imaging showed a mass-like shadow in the cervix, with varying degrees of invasion into the vagina or the lower part of the uterine body. Histologically, the tumors showed two components: solid and glandular areas, with solid areas containing nests of tumor cells and focal necrosis. In the glandular area, one showed gastric-type glandular changes, while the other showed usual-type glands. The solid area expressed CgA (1/2), Syn (2/2), and the glandular area expressed p16 (1/2), Muc-6 (1/2), MSH2 (1/2).

Conclusion We made a diagnosis of mixed adenoneuroendocrine carcinoma (MANEC) of the cervix and performed a literature review to better supplement epidemiological data and assist in developing standardized treatment methods.

Keywords Cervix, Gastric-type cervical adenocarcinomas, Large cell neuroendocrine carcinoma

Introduction

Neuroendocrine cervical cancer (NECC) includes large-cell neuroendocrine carcinoma and small-cell neuroendocrine carcinoma, accounting for approximately 0.5–1.0% of all cervical cancers [1], of which LCNEC is particularly rare, accounting for only 12.5% of NECC [2], which is highly malignant with poor prognosis. Cervical adenocarcinoma can be divided into HPV-independent and HPV-associated, with the former accounting for only 10–15% of adenocarcinomas, predominantly of the gastric-type adenocarcinomas (GAS) [3].

On this basis, mixed adenoneuroendocrine carcinoma (MANEC) of the cervix is even more rare, with only 14 cases reported in the last two decades. The LCNECs in these cases often coexist with usual or intestinal-type adenocarcinoma and are HPV-positive. There is a lack of reports of LCNEC combined with GAS of HPV-independent types. Here, we report two cases of mixed LCNEC and adenocarcinoma of the

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cervix, one HPV-independent and one HPV-associated, from the perspectives of clinical features and pathological characteristics, which further enriches the case report database. Through a systematic review of related literature, we provide the first detailed discussion on the clinical characteristics and prognosis of cervical LCNEC combined with GAS, filling a gap in this pathological type. Additionally, we supplement a case of LCNEC combined with usual-type adenocarcinomas. This will further explore the clinical features of cervical MANEC, the relationship between HPV status and tumor staging, molecular mechanisms, treatment strategies, and prognosis, thereby aiding clinicians in proper clinical management of patients (Fig. 1).

Case presentation

We collected two cases of mixed LCNEC and adenocarcinoma of the cervix (Table 1).

Case 1

Female, 54 years old, was admitted to the hospital with prolonged menstrual cycle for six months and irregular vaginal bleeding for one month. Previous cervical biopsy results indicated a malignant tumor. HPV tests were negative, and CA125 level was 58.25 U/mL. MRI showed a cervical mass, with the largest slice measuring about 2.4 cm, invading the lower part of the uterine body and the vaginal fornix (Fig. 2A). The patient eventually underwent a radical hysterectomy. Macroscopic observation

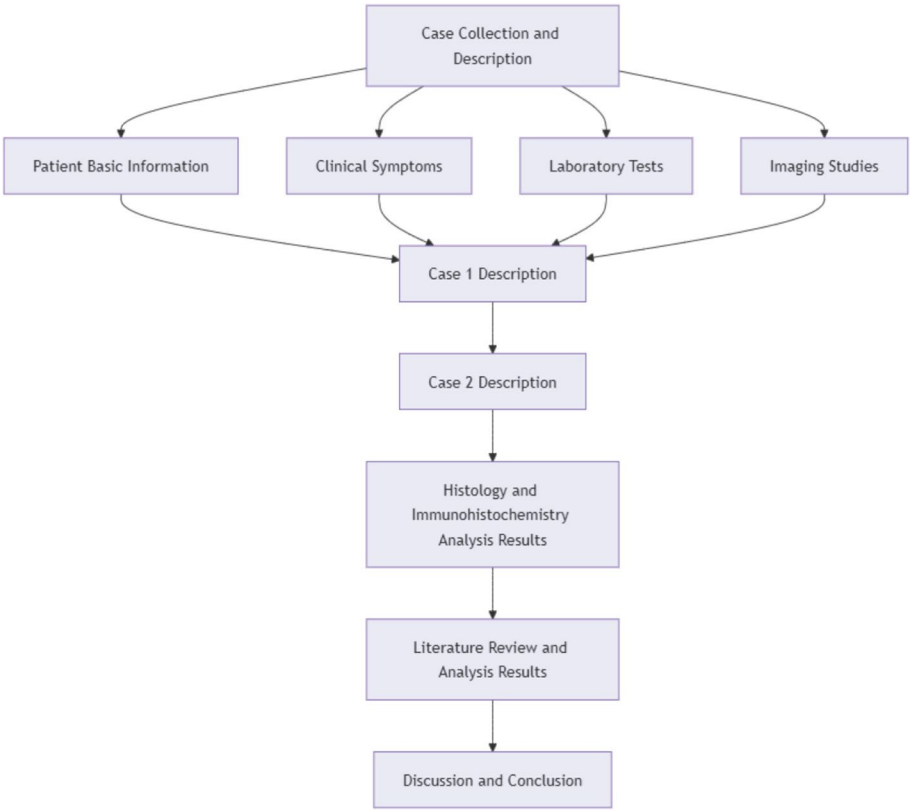

Fig. 1 Research roadmap

Table 1 Clinical characteristics

Case	Age	Clinical Symptoms	HPV	Tumor Markers	Tumor	FIGO Stage	Pathological Diagnosis	Surgery	Therapy	Distant Metastasis	Follow-up (months)
1	54	vaginal bleeding	−	CA125：58.25U/mL	rough region	IIA1	LCNEC（60%）+ HPV-unrelated gastric-type adenocarcinoma（40%）	RAH+BSO+PLND +PALND	8 cycles of post-operative chemotherapy+ 1 radiotherapy	bone	17
2	50	vaginal bleeding	18	SCC：3.96ng/mL	exogenous	IIIC1	LCNEC（50%）+HPV-related adenocarcinoma（50%）	RAH+BSO+PLND +PALND	4 cycles of pre-operative chemotherapy+ 2 cycles of postoperative	/	11

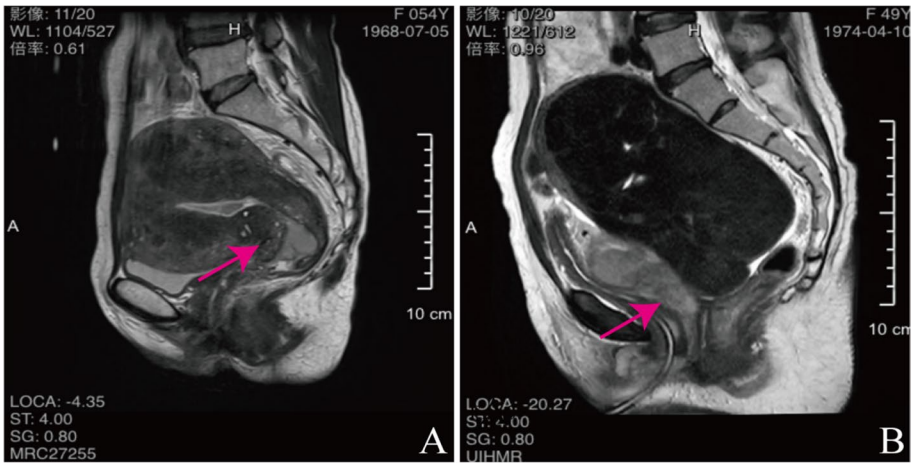

Fig. 2 Magnetic resonance imaging (MRI) **A** (case 1) cervical mass, with the largest diameter approximately 2.4cm, involving the lower part of the uterine body and the vaginal formix. **B** (case 2) a-mass like shadow is observerd at the lower edge of the cervix, measuring approximately 2×1.9×1/4cm

of the tumor: Severe cervical erosion, with an ulcer-like swelling about 3 cm seen from the cervical canal to the external os, with obvious contact bleeding. Microscopic examination: At low magnification the tumor consisted of solid area (40%) and glandular area (60%). Cells in the solid area were large, tightly arranged in nests, with abundant cytoplasm and large, vacuolated nucleus, prominent nucleoli, and visible mitotic figures (Fig. 3A). The glandular area showed gastric-type glands with high columnar cells, pale foamy cytoplasm, visible mucus, enlarged

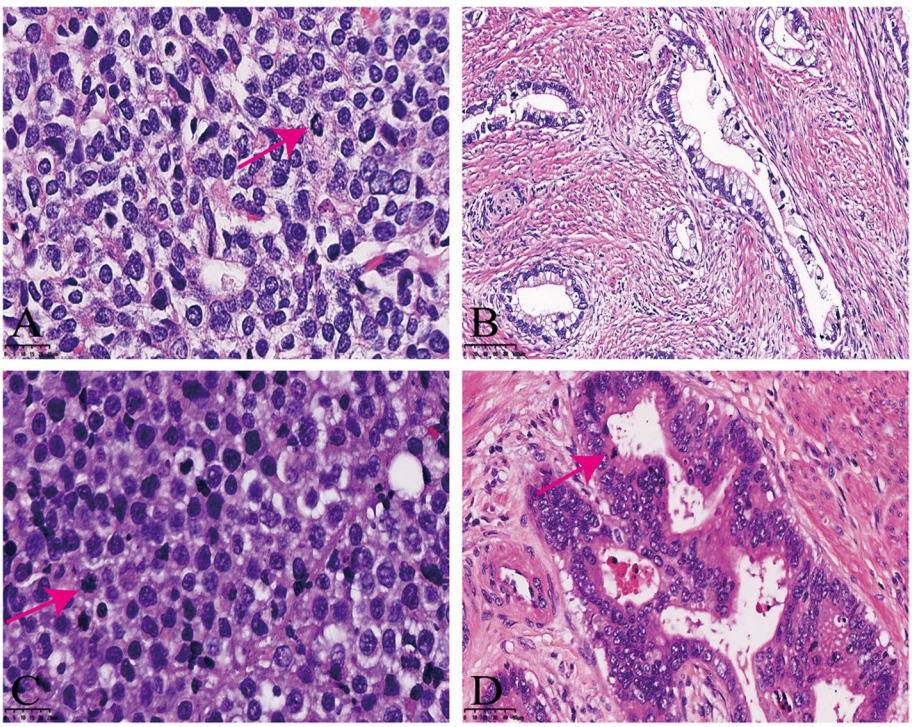

Fig. 3 Microscopic appearance of both components of the lesion in 2 cases: **A** (H&E, ×70, case1) Neuroendocrine cells are tightly arranged in nests, with abundant cytoplasm, prominent nucleoli, visible mitotic figures (red arrow) **B** (H&E, ×20, case 1) Adenocarcinoma cells contain foam cytoplasm, visible mucus; **C** (H&E, ×70, case2) Neuroendocrine cells are arranged in solid sheets; **D** (H&E, ×40, case2) The glandular ducts exhibit a pseudostratified arrangement, with visible mitotic figures at the apical (red arrow)

vacuolated nuclei located at the base, and frequent nucleoli (Fig. 3B). Tumor cells were diffusely distributed in the cervix and cervical canal, infiltrating downward to the upper third of the vagina and upward into the uterine myometrium, with metastatic adenocarcinoma in one ovary, and no metastasis in the lymph nodes. Immunohistochemistry: The solid area was strongly positive for CgA (Fig. 4A) and focally positive for Syn, while CD56 was negative. The glandular area was positive for CK-P, Muc-6 (Fig. 4B), and PAX-8, weakly positive for HNF1β. Notably, p16 was negative in both areas (Fig. 4C). Follow-up: The patient had received 8 cycles of chemotherapy and 1 cycle of radiotherapy in the 16 months since the surgery. The pelvic CT result in the 10th month after the 6th cycle of chemotherapy was abnormal, suggesting an abnormal signal in the left sacral promontory, and the bone image suggested an abnormal bone mineral density in the left sacral bone with active bone metabolism, which was considered to be metastatic. Additionally, the CA125 level has also abnormally increased.

Case 2

Female, 50 years old, was admitted to the hospital with vaginal bleeding and abdominal pain for 1 month. HPV 18 was positive, and SCC level was 3.96 ng/mL. MRI showed a mass at the lower margin of the cervix, approximately 2×1.9×1.4 cm, invading the upper third of the vagina (Fig. 2B). Cervical biopsy results suggested a poorly differentiated carcinoma with a tendency towards neuroendocrine carcinoma. After four cycles of chemotherapy, a radical hysterectomy was performed. Macroscopic observation of the tumor: A grayish-yellow, fragmented, exophytic mass in the cervix with a maximum diameter of 2 cm. Microscopic examination: At low magnification the tumor consisted of solid area (50%) and glandular area (50%). Cells in the solid area growed in nests with larger cells, rounded or polygonal nuclei, and marked heterogeneity (Fig. 3C). The glandular area had tall columnar cells, nuclei arranged in a pseudo-stratified manner, and the cytoplasm lacked mucus. Necrosis was visible within the lumens. Apical mitotic figures and basal apoptotic bodies were commonly observed (Fig. 3D). Tumor cells infiltrated about half of the cervical fibromuscular wall, and the adenocarcinoma component infiltrated the endometrium more than 1/2 of the myometrium. Two pelvic lymph nodes showed metastatic cancer, and the metastatic component was neuroendocrine carcinoma. Immunohistochemistry: The solid area was positive for Syn (Fig. 4D), CD56, SSTR2 and negative for CgA. The glandular area was positive for CK-P, MLH1, MSH2 (Fig. 4E), MSH6, PMS2, and negative for ER and PR. Both areas showed diffuse

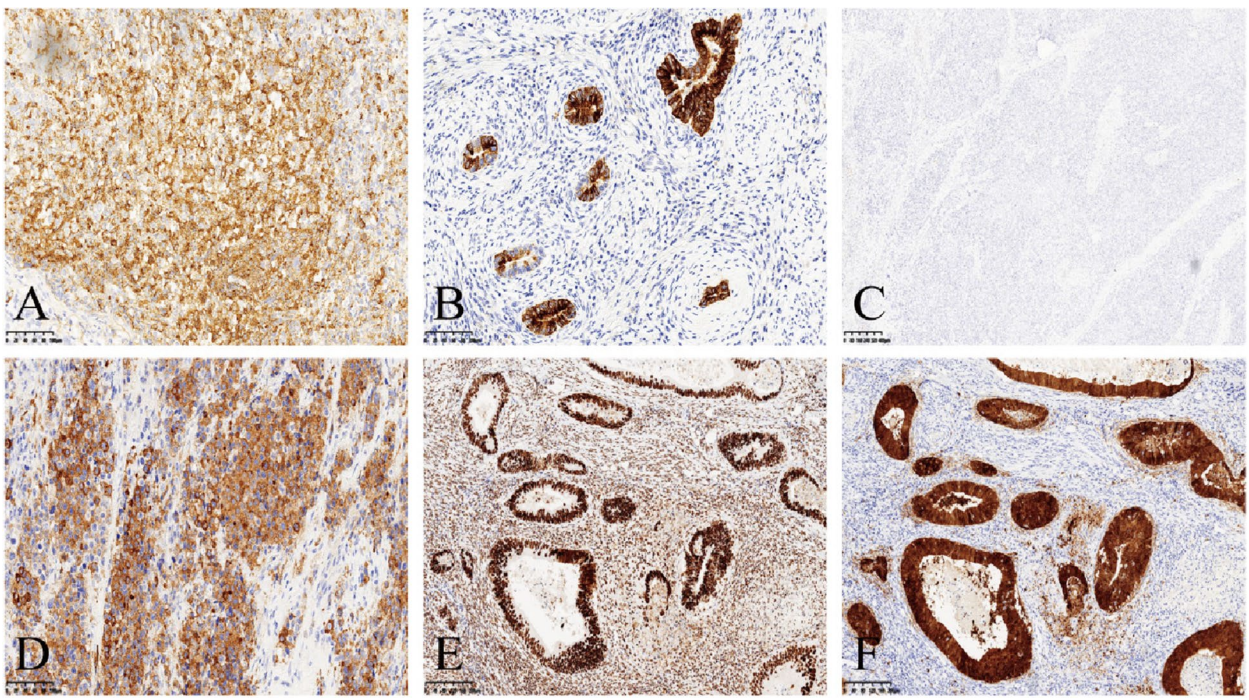

Fig. 4 Immunohistochemical study of the two components in 2 cases; **A** strongly positive for CgA in solid area (×20, case1); **B** Positive for MUC-6 in adenocarcinoma (×20, case1); **C** Negative for p16 (×4,case1); **D** Diffusely positive for Syn in solid area (×20, case2); **E** Positive for MSH2 in Adenocarcinoma (×20,case2); **F** Strongly positive for p16 (×20,case2)

strong positivity for p16 (Fig. 4F). The Ki-67 proliferative index was 50–80%. Follow-up: The patient had undergone 4 cycles of chemotherapy preoperatively, and only 1 cycle of chemotherapy has been administered in the 6 months since the operation. Pelvic CT result at 2 months postoperatively did not suggest significant abnormalities. During subsequent telephone follow-up, the patient informed us that due to financial difficulties, she had voluntarily chosen to discontinue further radiotherapy and chemotherapy. The patient reported no other physical discomforts. We deeply regret the patient's decision.

These two mixed cases of LCNEC and adenocarcinoma demonstrate the complexity of cervical MANEC and the potential therapeutic challenges. In Case 1, the significant elevation of CA125 levels may be associated with metastatic adenocarcinoma of the ovary, while the negative p16 result is inconsistent with the positive results usually observed in cervical adenocarcinoma, reflecting the particularity of GAS. Additionally, the observation of different metastatic components reveals differences in tumor biology and treatment response. In Case 1, the component metastasized to the ovary is adenocarcinoma, whereas in Case 2, the component metastasized to the lymph nodes is neuroendocrine carcinoma. Based on this, some adjustments to treatment strategies can be made. Case 1 can opt for chemotherapy drugs targeting adenocarcinoma, while Case 2 can opt for targeted therapy against neuroendocrine markers. Furthermore, we should also take into account the patient's economic situation to formulate more personalized treatment strategies for optimal long-term management.

Discussion

Cervical MANEC is a rare subtype of cancer, with only a few cases reported in the literature (Table 2).We have summarized the cases of cervical MANEC reported in the past 20 years, and only 14 cases were found (including 9 cases of LCNEC combined with adenocarcinoma [6, 7, 9, 12–15] and 5 cases of SCNEC combined with adenocarcinoma [4, 5, 8, 10, 11]). It can be noticed that both LCNEC and SCNEC lack specific age of onset and clinical symptoms. However, special attention should be given when vaginal bleeding occurs. Additionally, in the majority of cases, HPV16 and HPV18 are positive, though there are cases where no specifics of HPV are mentioned. This is consistent with previous studies confirming that the development of NECC is strongly associated with persistent infection with high-risk HPV types [16, 17]. The survival rate of MANEC is influenced by multiple factors. Studies have shown that the 5-year

Table 2 Literature reports on cervical neuroendocrine carcinoma mixed adenocarcinoma within the past 20 years [4–15]

Author	Year	Age	Race	Tumor	Clinical Symptoms	HPV	Immunohistochemistry	Pathological Diagnosis	FIGO Stage	Distant Metastasis	Follow-up (months)
Yohannis[4]	2024	40	Ethiopian	Exogenous	vaginal discharge postcoital bleeding	/	CK-P (+) CgA (+) Syn (+)	SCNEC+adenocarcinoma	IV	Abdominal wall thyroid gland	/
Ke Zhou[5]	2024	55	Chinese	/	vaginal bleeding	16,18	CD56 (+) Muc6 (+) Syn (−)	SCNEC+gastric-type adenocarcinoma (GAS)+ endometrioid adenocarcinoma	IB2	lung	24
Caterina[6]	2024	46	Korean	Not obvious	abdominal pain	16,18	CK-7 (+) P16 (+) CDX2 (+) Syn (+) MSH2 (+) ER (−) PR (−) CgA (−) CD56 (−)	LCNEC+mucinous adenocarcinoma	IVB	Dead	24
Kelly[7]	2023	44	American	rough region	dysmenorrhea	+	Syn (+) CgA (+) P16 (+) CK5/6 (−) P40 (−)	LCNEC+adenocarcinoma	IB1	No	96
Guralarasan[8]	2023	75	Indian	Exogenous	vaginal bleeding abdominal pain	/	CK-7 (+) P16 (+) NSE (+) Syn (+) CgA (−) P40 (−)	SCNEC+adenocarcinoma +CINIII	IB1	No	4
Ordulu[9]	2022	66	American	Exogenous	vaginal bleeding	16/18	Syn (+) CgA (+)	LCNEC+adenocarcinoma	IIIC	No	12
		49	American	Exogenous	Abnormal pap smear	16/18	Syn (+) CgA (−)	LCNEC+adenocarcinoma	IB1	Dead	58
		32	American	Exogenous	cervical mass on examination	16/18	Syn (+) CgA (+) CD56 (+)	LCNEC+Intestinal-type adenocarcinoma	IB2	/	/
Lee[10]	2021	51	Korean	Exogenous	vaginal bleeding vaginal discharge	/	CgA (+) Syn (+) CD56 (+) P16 (+)	SCNEC+adenocarcinoma	IIB	liver,lung omentum	11
Gizem[11]	2021	56	Turkey	solid tumor	vaginal bleeding abdominal pain	/	CgA (+) Syn (+) CD56 (+) P16 (+) P40 (−) TTF-1 (−)	SCNEC+adenocarcinoma	IIA	/	/
Hironao[12]	2013	36	Japanese	polyp	vaginal bleeding	18	CgA (+) P16 (+) Syn (−) CD56 (−)	LCNEC+ Intestinal-type Mucinous Adenocarcinoma	IB1	/	3
Hiroyuki[13]	2011	31	Japanese	Exogenous	/	18	CgA (+) P16 (+) CD56 (+) Muc2 (+) CEA (+)	LCNEC+intestinal variant invasive mucinous adenocarcinoma	IB1	No	/
Ma-Lee Ko[14]	2007	45	Tai Wan	Exogenous	vaginal bleeding	18	CgA (+) Syn (+) NSE (+)	LCNEC+adenocarcinoma	IB1	No	24
H.CETINER[15]	2006	47	Turks	Exogenous	vaginal bleeding	/	CK-P (+) CgA (+) NSE (+) CEA (+) EMA (+)	LCNEC+adenocarcinoma	IIA	No	6

survival rates for MANEC in gastrointestinal, pancreatic, and pulmonary locations are not satisfactory [18–20]. Grossi et al. found that the median survival period was only 12.3 months among 152 patients with lower gastrointestinal tract MANEC [18]. The rare cervical MANEC has limited survival data, primarily from small-scale case reports. The survival rates for patients in the early stages (such as IB1) are significantly higher than those in the late stages (such as IIIC and IV) [4, 7, 9]. In our reported cases, patient 1 began to show bone metastasis 17 months after diagnosis, and patient 2, after 11 months of diagnosis, did not undergo follow-up due to economic reasons, and the specific situation is unknown. Future clinical practices should place greater emphasis on long-term management of patients, especially those in the early stages.

In addition, by comparing cases of LCNEC and SCNEC, we have found some differences, including a greater variety of mass features in LCNEC, such as exophytic masses, rough areas, and polyps. This diversity of features may lead to clinical diagnostic complexity, as the atypical presentation of the mass may mask its potential aggressiveness. In cases of LCNEC, CD56 positivity is more common, while CgA positivity shows greater variability. In contrast, SCNEC cases frequently show CgA positivity, but CD56 positivity is less common. SCNEC cases often present with widespread disease stages and some cases exhibit distant metastasis at an early stage, leading to relatively poor prognosis [4]. In cases of LCNEC, although metastasis can also occur, some cases exhibit relatively better prognosis at early stages (such as IB1) [7]. Among the merged adenocarcinoma types, 9 cases of LCNEC are commonly combined with usual (5/9) and mucinous (4/9) types, which are HPV-associated, and there have been no reported cases of LCNEC combined with GAS, which is HPV-independent. We provide 2 cases of LCNEC, of which Case 1 is combined with GAS of HPV-independent types, which can fill the gap in the lack of case reports of this type, and case 2 combined with a usual type, which can further increase the diversity of cases of cervical MANCE to understand the clinical characteristics, pathological features, treatment strategies, and disease progression of LCNEC.

Almost all of these case reports focus on clinical presentation and immunohistochemical results, lacking detailed information at the molecular pathology. Only Ordulu et al. conducted research on molecular characteristics [9], discovering that ERBB2 was amplified in both components of one case of LCNEC with usual-type adenocarcinoma, and another case had mutations in KRAS and PIK3CA accompanied by MYC amplification. Additionally, in one case of LCNEC combined with intestinal type invasive adenocarcinoma, both MSH6 and MYC potentially underwent pathogenic mutations. This provides us with an insight: comprehensive analysis of disease-related molecular features can help integrate molecular pathology data with clinical data for analysis, uncovering potential molecular mechanisms and therapeutic targets. At the same time, more clinical data for cervical MANEC should be supplemented, including comprehensive records of HPV infection status, and strict postoperative follow-up should be conducted to record the disease progression and survival status of all cases, ensuring the integrity and accuracy of the clinical data.

Recent studies have shown that cervical LCNEC can be divided into two genetic subtypes: one is the SCLC type characterized by the co-mutation of TP53 and RB1, and the other is the non-SCLC type lacking co-mutations of TP53 and RB1 [21]. Non-SCLC cervical LCNEC is often HPV-positive, and TP53 and/or RB1 mutations often occur in HPV-negative LCNEC [22]. Compared with non-neuroendocrine cervical cancer, the expression of Yes-associated protein 1 (YAP1) is significantly increased in cervical NECC. YAP1 protein, known as an "oncogene," is an important component of the Hippo pathway responsible for multidrug resistance [23] and the unique YAP1 high molecular subtype of cervical LCNEC can promote tumor immune suppression, leading to its chemoresistance, which may be one of the important reasons for the high invasiveness of cervical LCNEC [24]. In addition, regarding the molecular characteristics of HPV-independent adenocarcinoma, Selenica et al. analyzed 68 cases of GAS by large-scale parallel sequencing and found that they mainly included the loss of p16 and the presence of gene mutations such as p53, PTEN, KRAS, and ARID1A, and genomic changes mainly involved the cell cycle and PI3K/AKT signaling pathway [25]. Some cases also suggest that HPV-independent adenocarcinoma is often associated with Peutz-Jeghers syndrome, and patients with STK11 germline mutations are more likely to have extensive lymphovascular invasion and lower survival rates [26, 27].

The typical pathological features are the main basis for diagnosing cervical LCNEC. LCNEC often presents as solid nests or island-like growth, accompanied by bleeding or geographic necrosis. The cells are large, with mostly round, significant pleomorphism, visible nucleoli and mitotic figures, abundant cytoplasm, weak acidophilia [28, 29]. When mixed with adenocarcinoma, the two components are often distributed in a mixed manner. Due to the poor differentiation of LCNEC, it is sometimes difficult to distinguish it from poorly differentiated squamous cell carcinoma and adenocarcinoma, often leading to misdiagnosis or missed diagnosis. Therefore, the positive immunohistochemistry of specific neuroendocrine

markers such as CgA, Syn, CD56 is an important basis for the diagnosis of cervical LCNEC. Studies have found that Insulinoma-associated protein-1 (INSM1) is a new neuroendocrine marker, but its sensitivity for diagnosing LCNEC is lower than SYN [30]. Considering the low degree of differentiation of LCNEC, the combined labeling of multiple markers is more meaningful for the diagnosis of LCNEC. When there is a mixed adenocarcinoma component, it is necessary to distinguish the type of adenocarcinoma. The 2020 version of the WHO classifies cervical adenocarcinoma into HPV-independent and HPV-associated types, with the former being predominantly gastric type [31]. In case 1, the tumor components showed negative results for p16, ER, PR, and positive results for CK7, MUC-6, HNF-1β, PAX-8, supporting the diagnosis of gastric type adenocarcinoma.

Cervical LCNEC often invades the mucosal epithelium and is associated with high-risk HPV infection. Cervical cytology screening is helpful for early diagnosis, but GAS is often unrelated to HPV infection, which is the particularity of case 1. With the introduction of HPV vaccines, the relative incidence of GAS may increase, and although primary screening plans based on HPV will not detect precursor lesions, nevertheless, early HPV vaccination is still essential [32]. As a rare malignant tumor of the cervix, the treatment of cervical LCNEC lacks standardization, and currently, radical surgery combined with radiotherapy and chemotherapy is the most common treatment method [33]. Studies have shown that the PD-1 inhibitor Nivolumab has shown some therapeutic effects in individual cases of recurrent and metastatic cervical small cell neuroendocrine carcinoma [34], so immunotherapy and targeted therapy can become a new treatment method for NECC patients, but the efficacy still needs further clinical research to confirm. Although multimodal treatment plans are used for this disease, the prognosis still falls short of expectations, with a 5-year survival rate of only 30–36% for patients. Therefore, early diagnosis, timely treatment after diagnosis is crucial for patients.

Conclusion

Mixed LCNEC and adenocarcinoma of the cervix is a rare and poor-prognosis malignant tumor, with a lack of literature reports at present. The prognosis is mainly related to the behavior of the neuroendocrine component and the type of adenocarcinoma. The correlation between this tumor and HPV subtypes is clinically significant for diagnosis. Combining morphological observations with immunohistochemistry can achieve accurate diagnosis. Due to the rarity of such cases, more extensive clinical data are needed to supplement epidemiological studies and help develop standardized treatment methods.

Authors' contributions

Kang-Na Wei—study design, Integration of pathological results, manuscript writing. Xiao-Dan Fu—acquisition of pathological data. Min-Yuan Wang—acquisition of clinical data. Li-Xia Wang—critical review of the manuscript. All authors have read and approved the manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent for publication was obtained.

Competing interests

The authors declare no competing interests.

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References

1. Lee E, Ji YI Large cell neuroendocrine carcinoma of the cervix with sequential metastasis to different sites: a case report. Case reports in oncology. 2018;11:665–70.
2. Xu F, Yu Q, Wan D, Zhang Y. Cervical adenocarcinoma admixing with large cell neuroendocrine carcinoma: a rare case report. Asian J Surg. 2022;45:2932–3.
3. Yoshida H, Naka T, Kobayashi-Kato M, Kikkawa N, Tanase Y, Uno M, Ishikawa M, Kato T. Gastric-type cervical adenocarcinoma with squamous differentiation: buried in adenosquamous carcinomas? Virchows Archiv Int J Pathol. 2021;479:407–12.
4. Molla YD, Alemu HT, Selamawi AE, Tesema AY, Answar IO. Tadesse AK Adenocarcinoma admixed with neuroendocrine carcinoma of the cervix: a case report and review of literature. Case Rep Womens Health. 2024;12(41):e00594.
5. Cai H, Zhou K, Luo L. Mixed adenocarcinoma-neuroendocrine carcinoma of the cervix with pulmonary metastasis: a case report and literature review. Asian J Surg. 2024;24(24):S1015–9584.
6. Fattorini C, Rocca BJ, Giusti A, Arganini M, Perotti B, Cavazzana A, Ambrosio MR, Volante M. Mixed mucinous adenocarcinoma/large cell neuroendocrine carcinoma of the uterine cervix: case report and molecular characterization of a rare entity. Virchows Arch. 2024;484(1):141–6.
7. Lamiman K, Wilhelm AB, Eyzaguirre E, Richardson G. Diagnostic challenges and long-term outcomes of neuroendocrine carcinoma of the cervix: a case series. Int J Gynecol Pathol. 2024;43(2):149–57.
8. Gurubalan G, Parwaiz A, Ajit S, Kumar T, Kumari M, Bhadani P. Small cell neuroendocrine carcinoma with adenocarcinoma and high grade squamous intraepithelial neoplasia of the cervix. Autops Case Rep. 2023;13(13): e2023452.
9. Ordulu Z, Mino-Kenudson M, Young RH, Van de Vijver K, Zannoni GF, Félix A, Burandt E, Wong A, Nardi V, Oliva E. Morphologic and molecular heterogeneity of cervical neuroendocrine neoplasia: a report of 14 Cases. Am J Surg Pathol. 2022;46(12):1670–81.
10. Lee J, Park S, Woo HY, Kim HS. Clinicopathological characteristics of microscopic tubal intraepithelial metastases from adenocarcinoma and small cell neuroendocrine carcinoma of the uterine cervix. Vivo. 2021;35(4):2469–81.
11. Teoman G, Ersoz S. Mixed endocervical adenocarcinoma and high-grade neuroendocrine carcinoma of the cervix: a case report. Indian J Pathol Microbiol. 2021;64(1):174–6.
12. Yasuoka H, Tsujimoto M, Ueda M, Kodama R, Iwahashi Y, Inagaki M, Mabuchi Y, Ino K, Sanke T, Nakamura Y. Monoclonality of composite large-cell neuroendocrine carcinoma and invasive intestinal-type mucinous adenocarcinoma of the cervix: a case study. Int J Gynecol Pathol. 2013;32(4):416–20.

13. Hao H, Itoyama M, Tsubamoto H, Tsujimoto M, Hirota S. Large cell neuroendocrine carcinoma of the cervix associated with intestinal variant invasive mucinous adenocarcinoma. Pathol Int. 2011;61(1):55–7.
14. Ko ML, Jeng CJ, Huang SH, Shen J, Chen SC, Tzeng CR. Large cell neuroendocrine carcinoma of the uterine cervix associated with adenocarcinoma. Taiwan J Obstet Gynecol. 2007;46(1):68–70.
15. Cetiner H, Kir G, Akoz I, Gurbuz A, Karateke A. Large-cell neuroendocrine carcinoma of the cervix associated with cervical-type invasive adenocarcinoma: a report of case and discussion of histogenesis. Int J Gynecol Cancer. 2006;16(1):438–42.
16. Caruso G, Sassu CM, Tomao F, Di Donato V, Perniola G, Fischetti M, Benedetti Panici P. Palaia I the puzzle of gynecologic neuroendocrine carcinomas: state of the art and future directions. Crit Rev Oncol Hematol. 2021;162:103344.
17. Salvo G, Gonzalez Martin A, Gonzales NR, Frumovitz M. Updates and management algorithm for neuroendocrine tumors of the uterine cervix. Int J Gynecol Cancer. 2019;29(6):986–95.
18. Paspala A, Machairas N, Prodromidou A, Spartalis E, Ioannidis A, Kostakis ID, Papaconstantinou D, Nikiteas N. Management of MANEC of the colon and rectum: a comprehensive review of the literature. Mol Clin Oncol. 2018;9(2):219–22.
19. Li X, Li D, Sun X, Lv G. Mixed adenoneuroendocrine carcinoma (MANEC) of the ampulla of Vater in a Chinese patient: a case report. J Int Med Res. 2020;48(8): 300060520947918.
20. Sakai Y, Yamasaki T, Kusakabe Y, Kasai D, Kotani Y, Nishimura Y, Itoh T. Large-cell neuroendocrine carcinoma of lung with epidermal growth factor receptor (EGFR) gene mutation and co-expression of adenocarcinoma markers: a case report and review of the literature. Multidiscip Respir Med. 2013;18(81):47.
21. Uccella S, La Rosa S, Metovic J, Marchiori D, Scoazec JY, Volante M, Mete O, Papotti M. Genomics of High-Grade Neuroendocrine neoplasms: well-differentiated neuroendocrine tumor with high-Grade features (G3 NET) and neuroendocrine carcinomas (NEC) of various anatomic sites. Endocr Pathol. 2021;32(1):192–210.
22. Saghaeiannejad Esfahani H, Vela CM, Chauhan A. Prevalence of TP-53/Rb-1 Co-mutation in large cell neuroendocrine carcinoma. Front Onco. 2021;31:653153.
23. Huang J, Wei W, Kang F, Tan S, Li Y, Lu X, Wang N. ANXA3, associated with YAP1 regulation, participates in the proliferation and chemoresistance of cervical cancer cells. Genes Genom. 2023;45(12):1575–86.
24. He C, Lv X, Huang C, Angeletti PC, Hua G, Dong J, Zhou J, Wang Z, Ma B, Chen X, Lambert PF, Rueda BR, Davis JS, Wang CA. Human papillomavirus-independent cervical Cancer animal model reveals unconventional mechanisms of cervical carcinogenesis. Cell Rep. 2019;26(10):2636–e26505.
25. Lu S, Shi J, Zhang X, Kong F, Liu L, Dong X, Wang K. Shen D Comprehensive genomic profiling and prognostic analysis of cervical gastric-type mucinous adenocarcinoma. Virchows Arch. 2021;479(5):893–903.
26. Kotaka S, Kanno K, Yanai S, Omori M, Andou M. Peutz-Jeghers syndrome complicated by gastric-type cervical mucinous carcinoma and primary peritoneal carcinoma. J Obstet Gynaecol Res. 2021;47(10):3732–6.
27. Neyaz A, Husain N, Deodhar M, Khurana R, Shukla S, Arora A. Synchronous cervical minimal deviation adenocarcinoma, gastric type adenocarcinoma and lobular endocervical glandular hyperplasia along with STIL in Peutz-Jeghers Syndrome: eliciting oncogenesis pathways. Turk Patoloji Derg. 2019;35(3):247–53 English.
28. Murakami R, Kou I, Date K, Nakayama H. Advanced composite of large cell neuroendocrine carcinoma and squamous cell carcinoma: a case report of uterine cervical cancer in a virgin woman. Case Rep Obstet Gynecol. 2013;2013:921384.
29. Sarfraz H, Syal S, Sarfraz S, Fuentes Rojas S. Janjua E Large Cell Neuroendocrine Cervical Carcinoma: A Case Report. Cureus. 2020;12(1):e6544.
30. Ting CH, Wang TY, Wu PS. Insulinoma-associated protein 1 expression and its diagnostic significance in female genital tract neuroendocrine carcinomas. Int J Gynecol Pathol. 2021;40(5):452–9.
31. Herrington CSKK-R, Kong CS,Longacre TA et al. Tumours of the uterine cervix. In: WHO classification of tumors editorial board, eds. World Health Organization classification of tumours: female genital tumours. 5th ed. Lyon, France: International Agency for Research on Cancer; 2020:335–389.
32. Jenkins D, Molijn A, Kazem S, Pirog EC, Alemany L, de Sanjosé S, Dinjens W. Quint W molecular and pathological basis of HPV-negative cervical adenocarcinoma seen in a global study. Int J Cancer. 2020;147(9):2526–36.
33. Xie S, Song L, Yang F, Tang C, Yang S, He J, Pan X. Enhanced efficacy of adjuvant chemotherapy and radiotherapy in selected cases of surgically resected neuroendocrine carcinoma of the uterine cervix: a retrospective cohort study. Med (Baltim). 2017;96(11):e6361.
34. Paterniti TA, Dorr K, Ullah A, White J, Williams H, Ghamande S. Complete response to combination Nivolumab and Ipilimumab in recurrent neuroendocrine carcinoma of the Cervix. Obstet Gynecol. 2021;138(5):813–6.

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