Synchronous small cell neuroendocrine carcinoma of the cervix and immature ovarian teratoma: A case report and literature review

MINGYU XIE[1,2], YONGSEN LI[1], HUI CHEN[1], QINGPING JIANG[1] and HANZHEN XIONG[1]

[1]Department of Pathology, Guangdong Provincial Key Laboratory of Major Obstetric Disease, Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510150, P.R. China; [2]Department of Pathology, Zhanjiang Central Hospital, Guangdong Medical University, Zhanjiang, Guangdong 524045, P.R. China

Received January 17, 2023; Accepted December 15, 2023

DOI: 10.3892/ol.2024.14446

Abstract. The onset of two synchronous primary malignancies of the female genital tract is uncommon; therefore, the simultaneous occurrence of cervical small cell neuroendocrine carcinoma and ovarian immature teratoma is rare. The present study describes the case of a woman with cervical small cell neuroendocrine carcinoma complicated by ovarian immature teratoma. The clinical manifestations, and the histopathological and immunophenotypic features of the patient are recorded. Furthermore, all PubMed-indexed cases of synchronous primary malignancies in both the cervix and ovary have been briefly summarized.

Introduction

The co-occurrence of two or more primary malignancies of different tissue types in the female genital tract is rare, with an incidence of 0.6-5.4% worldwide (1,2). The majority of primary tumors of the female genital tract occur in the corpus uteri and ovaries; however, dual primary malignances of the ovary and cervix have rarely been reported, with the combination of cervical squamous cell carcinoma, ovarian endometrioid carcinoma and serous carcinoma being the most common. The current study describes the case of a woman with synchronous small cell neuroendocrine carcinoma of the cervix and ovarian immature teratoma. In addition, the clinicopathological features, histopathological characteristics, treatment and prognostic outcomes are recorded. Finally, 12 PubMed-indexed cases of synchronous primary malignancies in the cervix and ovary have been briefly reviewed.

Case report

The present study reports the case of a 29-year-old woman who presented with abnormal vaginal discharge for >1 month at The Third Affiliated Hospital of Guangzhou Medical University (Guangzhou, China) in November 2021. More than 1 year before the initial admission, a physical examination revealed that the patient was positive for human papillomavirus (HPV)18. After visiting a doctor, the patient underwent a cervical ThinPrep cytological test in November 2021, which showed atypical cells. In addition, gynecological examination revealed a ~2x1 cm vegetative polypoid lesion, originating from the endocervical canal. Additionally, a cystic mass (~5x3 cm) was palpated at the right adnexal site. Based on the results of a biopsy, the cervical neoplasm was pathologically diagnosed as small cell carcinoma of the cervix. The laboratory test results showed that the serum levels of α-fetoprotein (AFP) were 9.13 ng/ml (normal range, 0-7 ng/ml). Ultrasonography revealed a 37x26 mm irregular mixed echo mass inside the cervix (Fig. 1B and C). In addition, pelvic magnetic resonance imaging indicated that the cervical mass involved the posterior fornix, while a cystic lesion with hematocele in the right ovarian region was also identified (Fig. 1D and E). The surgical operation included abdominal radical hysterectomy, bilateral adnexectomy and pelvic lymphadenectomy.

Furthermore, macroscopic examination showed a protuberant mass (~3x2.5x1.5 cm) at the external orifice of the cervix. The cut surface was grayish-yellow, solid and soft, with clear boundaries. The right ovary was replaced by a ~6.5x5x4 cm cystic-solid mass. No obvious abnormality was observed in the uterine cavity and left fallopian tube (Fig. 1A).

Tissue specimens of the cervix and ovary were fixed in 10% buffered formalin for 8 h at room temperature and subjected to graded alcohol dehydration (70, 80, 95, 95, 100, and 100%), permeabilized with an environmentally friendly clarifier (xylene) and immersed in paraffin, all in a Leica fully automated dehydrator (Leica Microsystems, Inc.). The next day,

Correspondence to: Professor Hanzhen Xiong, Department of Pathology, Guangdong Provincial Key Laboratory of Major Obstetric Disease, Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, The Third Affiliated Hospital of Guangzhou Medical University, 63 Duobao Road, Liwan, Guangzhou, Guangdong 510150, P.R. China
E-mail: xionghanzhen@126.com

Key words: cervix, small cell neuroendocrine carcinoma, ovary, immature teratoma, synchronous primary malignancies

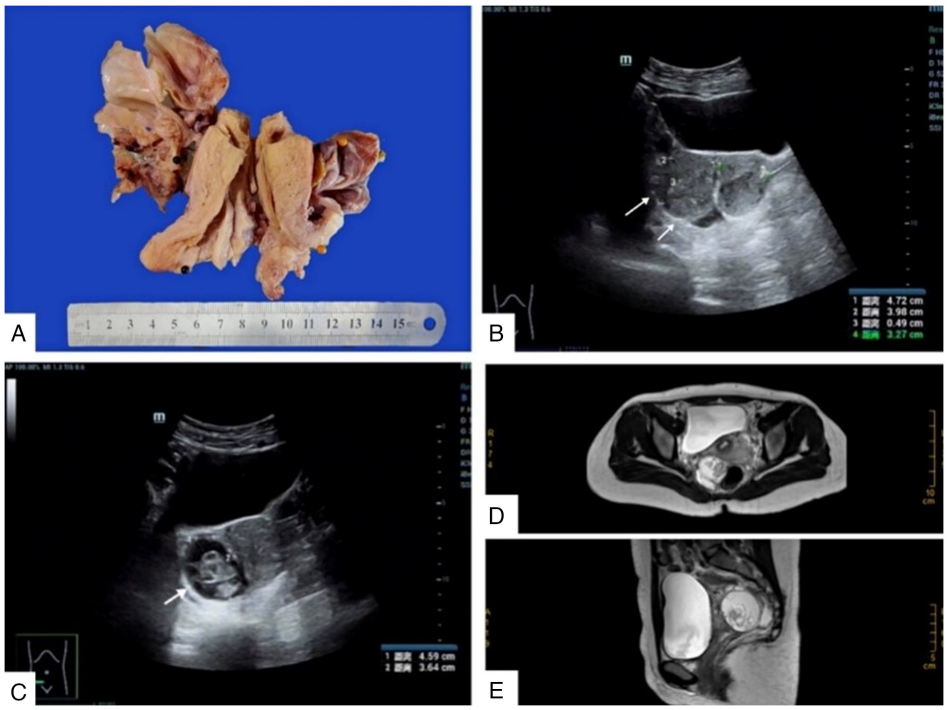

Figure 1. Gross view of the specimen and imaging data. (A) Gross view of the uterus and bilateral adnexa. Preoperative ultrasound images of the (B) cervical mass and (C) right ovarian area (the tumors are indicated by arrows). (D) Cross-section of magnetic resonance imaging scan images. (E) Sagittal plane of magnetic resonance imaging scan images.

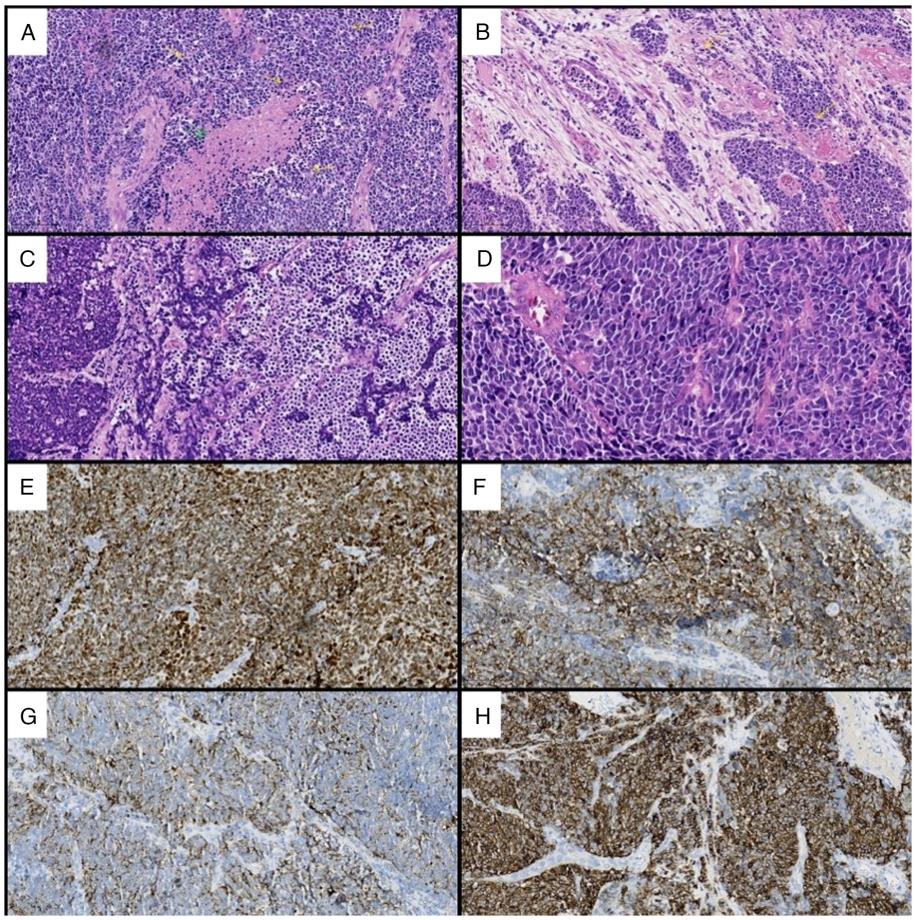

Figure 2. Cervical small cell carcinoma. (A) Tumor necrosis, (B) partial stroma with mucoid degeneration, (C) local tumor cells with clear cytoplasm (magnification, x200), and (D) tumor cells arranged in sheets and nests (magnification, x400) are shown. Immunohistochemical analysis revealed diffuse expression of (E) thyroid transcription factor-1 and the neuroendocrine-related markers (F) synaptophysin, (G) chromogranin A and (H) CD56 (magnification, x400). The green arrow indicates the necrotic area, while the yellow arrow indicates the mitotic figures.

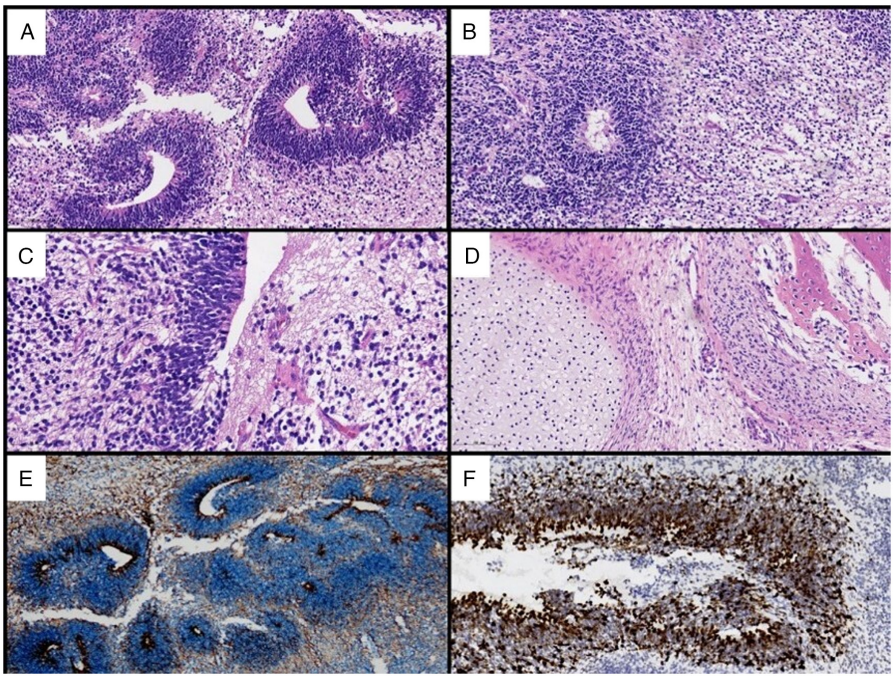

Figure 3. Ovarian immature teratoma. The ovarian tumor showed (A) abundant immature neuroectodermal tubules and (B) cell-rich glial tissue (magnification, x200), with (C) immature mesenchymal tissue (magnification, x400), including (D) immature cartilage and bone tissue (magnification, x200). Immunohistochemical analysis showed (E) glial fibrillary acid protein positivity in the lumen of the immature neuroectodermal tubules, while (F) the Ki-67 proliferation index was ~70% (magnification, x200).

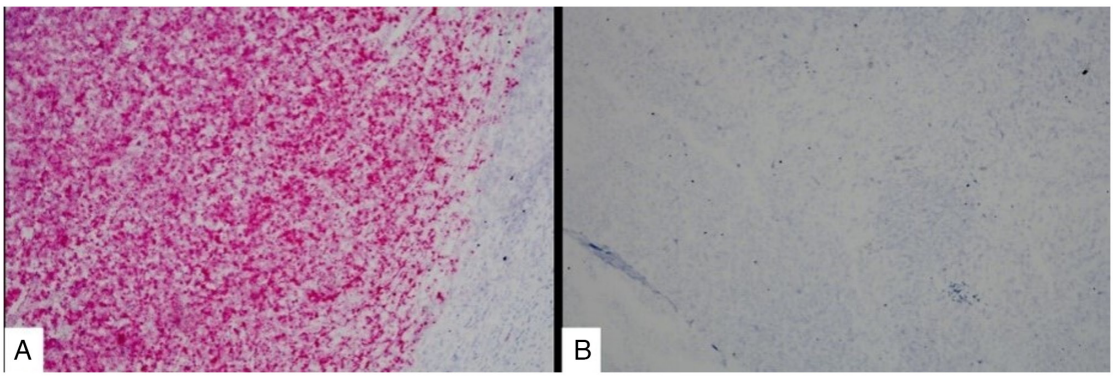

Figure 4. RNAscope HPV assay in the cervical and ovarian tumors. RNAscope HPV test showed (A) diffuse positivity in the small cell carcinoma area of the cervix and (B) negative staining in the ovarian immature teratoma area (magnification, x200). HPV, human papilloma virus.

after paraffin embedding, the tissue was cut into 3-μm sections and baked for 30 min before staining with hematoxylin (10 min at room temperature) and eosin (3 min at room temperature) in a Leica automated stainer (Leica Microsystems, Inc.). Microscopically, the sheets and nests of the cervical tumor cells were polygonal-ovoid with patchy areas of necrosis. The tumor cells were small to medium in size, with scanty cytoplasm, hyperchromatic nuclei, uniform and delicate nuclear chromatin, and mitotic figures (Fig. 2A-D). No neoplastic lesions of the squamous or glandular epithelium were observed. The right ovarian tumor showed a large number of immature neuroectodermal tubules and glial cell-rich tissue, rosette-like immature neuroectodermal tubules and mesenchymal-type tissue (cartilage and new bone tissue; Fig. 3A-D).

Representative sections (4 μm) underwent immunohistochemical staining using a Roche BenchMark ULTRA IHC machine (Roche Diagnostics). Immunohistochemical staining was performed at 37˚C for 60 min with the following antibodies: Synaptophysin (cat. no. MAB-0742), chromogranin A (cat. no. MAB-0707), CD56 (cat. no. MAB-0743), thyroid transcription factor-1 (TTF-1; cat. no. MAB-0599), Ki-67 (cat. no. MAB-0672), P16 (cat. no. MAB-0673), glial fibrillary acid protein (GFAP; cat. no. MAB-0769), P53 (cat. no. MAB-0674), leukocyte common antigen (LCA; cat. no. Kit-0024), pan-cytokeratin (CK-pan; cat. no. MAB-0671), cytokeratin 5/6 (cat. no. MAB-0744), P40 (cat. no. RMA-1006), P63 (cat. no. MAB-0694), octamer-binding transcription factor 4 (OCT4; cat. no. MAB-0874) and spalt-like transcription factor 4 (cat. no. MAB-0691). The primary antibodies were all ready-to-use antibodies purchased from Fuzhou Maixin Biotechnology Development Co., Ltd., and were added manually without dilution. Subsequently, the sections were incubated with

Table I. Synchronous primary malignancies of the cervix and ovary in the female reproductive system (n=12).

First author, year	Age, years	Presentation	Site	Tumor histology	Therapy	Outcome	FU, months	(Refs.)
Huang, 2006	30	Abdominal fullness; chest tightness; dyspnea	Ovary and cervix	Ovarian endometrioid adenocarcinoma; cervical mucinous adenocarcinoma	CT	DOD	8	(9)
Phupong, 2007	50	Menorrhagia	Ovary, uterus and cervix	Ovarian mucinous adenocarcinoma; endometrial endometrioid adenocarcinoma; endocervical adenosquamous carcinoma	RT	DOD	3	(10)
Pekin, 2007	62	Spotting; vaginal bleeding	Ovary and cervix	Ovarian granulosa tumor; ovarian Brenner tumor; cervical squamous cell carcinoma	NM	NM	NM	(11)
Kilciksiz, 2007	43	Vaginal bleeding	Ovary, uterus and cervix	Ovarian serous carcinoma; endometrial endometrioid adenocarcinoma; cervical squamous cell carcinoma	CT and RT	DOD	4	(12)
Saglam, 2008	63	Postmenopausal bleeding; abdominal distention	Ovary, FT, uterus and cervix	Ovarian mucinous adenocarcinoma; FT papillary adenocarcinoma; endometrial endometrioid adenocarcinoma; endocervical adenocarcinoma	CT	NED	12	(13)
Hale, 2011	49	Fatigue; abdominal distention	Ovary, uterus and cervix	Ovarian mucinous, clear cell and endometrioid carcinoma; endometrial endometrioid adenocarcinoma; endocervical endometrioid adenocarcinoma	NM	NM	NM	(14)
Takatori, 2014	50	Metrorrhagia	Ovary, uterus and cervix	Ovarian serous adenocarcinoma; endometrial endometrioid adenocarcinoma; endocervical endometrioid adenocarcinoma	CT	NED	18	(15)
Chiofalo, 2016	38	Pelvic pain; vaginal bleeding	Ovary, uterus and cervix	Ovarian mucinous adenocarcinoma; endometrial endometrioid adenocarcinoma; endocervical mucinous adenocarcinoma	CT	NED	18	(16)
Abu-Zaid, 2017	55	Abdominal distention; abdominal pain; vaginal bleeding	Ovary, uterus and cervix	Ovarian clear-cell carcinoma; endometrial endometrioid adenocarcinoma; cervical poorly differentiated squamous cell carcinoma	None	DP	3	(17)
Wang *et al*, 2019	56	Vaginal bleeding uterus and cervix	Stomach, ovary,	Gastric adenocarcinoma; ovarian endometrioid adenocarcinoma; endometrial endometrioid adenocarcinoma; endocervical adenocarcinoma	None	Lost to FU after 1 year	12	(18)
Bacalbasa, 2020	53	Vaginal bleeding	Ovary and cervix	Ovarian serous carcinoma; endometrial endocervical adenocarcinoma	CT	NM	NM	(19)
Mishra, 2021	48	Progressive facial puffiness; intractable diarrhea	Ovary and cervix	Ovarian carcinoid tumor; cervical squamous cell carcinoma	None	NED	60	(20)
The present case	29	Abnormal vaginal discharge	Ovary and cervix	Ovarian immature teratoma; cervical small cell neuroendocrine carcinoma	CT	NED	3	-

FT, fallopian tube; CT, chemotherapy; RT, radiotherapy; NM, not mentioned; DOD, died of disease; NED, no evidence of disease; DP, disease progression.

secondary antibodies from the MaxVision DAB Detection Kit (Polymer) (cat. no. Kit-0014; Fuzhou Maixin Biotechnology Development Co., Ltd.). After adding the prepared secondary antibody (100 μl, 1:100) and incubating for 15 min at room temperature, DAB was used as the color developer (8 min at 37˚C) and hematoxylin (37˚C for 8 min) was used for re-staining after color development. After being sealed with neutral gum, staining was detected under an Olympus light microscope (Olympus Corp.). Immunohistochemical staining showed that cell nuclei in the cervical tumor area were positive for TTF-1, and diffusely and strongly positive for the neuroendocrine markers synaptophysin, chromogranin A and CD56 (Fig. 2E-H). Consistently, cells were diffusely and strongly positive for CK-pan and P16, with a Ki-67 proliferation index of ~90% (data not shown). Furthermore, P53 was normally expressed (wild-type), whereas cells were negative for leukocyte common antigen, cytokeratin 5/6, P40, P63 and glial fibrillary acid protein (GFAP) (data not shown). Ovarian tumor cells were positive for GFAP, with a Ki-67 proliferation index of ~70% (Fig. 3E and F), and negative for OCT4, spalt-like transcription factor 4 and P16 (data not shown).

The RNAscope® 2.5 HD Assay was purchased from Advanced Cell Diagnostics, Inc. The experimental procedures were carried out in strict accordance with the manufacturer's instructions. Routinely, tissue samples were completely fixed in 10% formalin at room temperature for 16-24 h, embedded in paraffin, sectioned (3 μm), deparaffinized (using xylene for 10 min) and dehydrated (using absolute ethanol for 2 min). The sections were then treated continuously with Pre-Treatment 1-3 solution and rinsed with distilled water after each Pre-Treatment step. Sections without coverslips were then hybridized in HPV hybridization solution in a HybEZ Oven (Advanced Cell Diagnostics, Inc.) at 40˚C for 30 min. The hybridization probe signal was amplified by serial applications of Amp 1-6; the wash buffer steps were performed after each step. Signal intensity was demonstrated by applying DAB for 10 min at room temperature. Finally, sections were counterstained with hematoxylin, dehydrated in fractionated ethanol and xylene, and then mounted for observation under an Olympus light microscope. The HPV RNA signal was red in the nucleus or cytoplasm of the section, and the peripheral normal epithelium from the same patient served as an internal negative control. The RNAscope HPV assay showed diffuse positivity in the small cell carcinoma region of the cervix, thus suggesting the presence of E6/E7 mRNA in the cervical tumor region (Fig. 4A and B), which supported the association between HPV infection status and tumor onset at the transcriptional level. However, the ovarian immature teratoma region was negative for HPV RNA.

Therefore, the final pathological diagnosis was stage IIIC small cell carcinoma of the cervix, with metastasis of the cervical small cell carcinoma to the lymph nodes (data not shown), and stage IA immature teratoma (G3) of the right ovary. Based on the high clinical stage of the cervical small cell carcinoma and lymph node metastasis, the patient was treated postoperatively with a cisplatin plus etoposide regimen. The sixth cycle of chemotherapy was administered in June 2022 and the patient presented with bone marrow suppression. The patient survived disease-free until December 2023.

Discussion

Multiple primary malignant tumors have been defined by the International Association of Cancer Registries/International Agency for Research on Cancer as two or more malignant tumors with different histological characteristics that occur at different sites, including simultaneous and metachronous primary tumors (3). Metachronous tumors more commonly occur compared with simultaneous tumors, with a proportion of ~2.7 (3). In tumors of the female reproductive system, it is rare for two or more different types of primary malignancies to occur simultaneously. It is significant to identify the association between multiple primary tumors and metastasis, particularly in the case of morphologically similar tumors in different parts of the body. For dissimilar tumor subtypes in different sites of the body, the prognosis is associated with the clinical stage of each subtype (4). Although the cause of multiple primary tumors has not been elucidated, three common factors have been identified (5). The first is associated with host factors, including genetic susceptibility, immune status, hormone use and history of chemoradiotherapy. For example, Lynch syndrome is an autosomal dominant disease caused by genetic defects in one or more DNA mismatch repair enzymes, with MLH1, MSH2, MSH6 or PMS2 mutations detected in the majority of cases and EPCAM mutations in a few cases (6). The occurrence of malignant tumors can also be associated with somatic genetic abnormalities, including point mutations, loss of heterozygosity and microsatellite instability. The second category includes lifestyle factors, such as drinking and smoking history. The third category is associated with the effects of environmental factors. Notably, HPV infection is considered a significant cause of cervical cancer and precancerous lesions. A previous multicenter study (7) showed that high-risk HPV-DNA was detected in 94% of cervical adenocarcinoma *in situ*, 85% of adenosquamous carcinoma and 76% of adenocarcinoma cases. In addition, a previous study has demonstrated that cervical small cell carcinoma is associated with HPV18 infection (8). In the present case study, the female patient had no family history of gynecological cancer, estrogen use, and drinking or smoking habits; however, they were diagnosed with HPV18 infection. In addition, the RNAscope HPV assay showed that the area of the cervical small cell carcinoma was diffusely and strongly positive, whereas the area of the ovarian immature teratoma was negative for the presence of HPV RNA. The patient was subsequently diagnosed with synchronous primary tumors in the reproductive system.

Multiple primary malignancies of the female reproductive system are rare, whereas the simultaneous occurrence of primary malignant tumors of the cervix and ovary are even rarer. Table I summarizes all PubMed-indexed (https://pubmed.ncbi.nlm.nih.gov/) (9-20) cases of synchronous primary malignancies in both the cervix and ovary (n=12). However, to the best of our knowledge, the co-existence of cervical small cell carcinoma and ovarian immature teratoma has not been previously reported. For simultaneous primary tumors of two or more different tissue subtypes, adequate sampling, fine histomorphological evaluation and immunohistochemical analysis are required to achieve an accurate pathological diagnosis. High-grade small cell neuroendocrine carcinoma

of the cervix accounts for ~2% of global cervical cancer cases and is commonly accompanied by vaginal bleeding or cervical masses (21). In a few cases, some patients with neuroendocrine carcinoma have exhibited symptoms of hormonal changes, including adrenocorticotropic hormone, antidiuretic hormone, insulin, calcitonin, prolactin, parathyroid hormone-related protein, β-human chorionic gonadotropin and serotonin (21-24). More than half of the patients with small cell neuroendocrine carcinoma of the cervix are classified as having stage III or IV disease (8). The typical histopathological morphology is commonly mixed, including solid, nest or cord formation, with rosette- and acinar-like structures, varying from oval to fusiform, that are small to medium in size, with scant cytoplasm and nuclear molding. The nuclear chromatin is delicate, the nucleolus is not evident, and mitosis is active. Small cell carcinoma cells commonly express at least one neuroendocrine-related marker, including chromogranin A, which is the most specific, synaptophysin and CD56. P16 and TTF-1 are also expressed at different degrees. Notably, small cell carcinoma of the cervix is most commonly associated with HPV infection (HPV18).

Ovarian immature teratoma, which accounts for Σ2% of all global ovarian teratoma cases, more commonly occurs in premenopausal women and often manifests as an abdominal mass accompanied by slightly increased AFP serum levels (25). Histological features include embryonic manifestations, such as neuroectodermal components, including chrysanthemum-like neuroepithelium and tubules, cellular glial components and a few embryonic corpuscles (26). Other embryonic or immature tissues are also commonly involved, including the ectoderm, endoderm and mesenchymal tissue, such as cartilage and skeletal muscle tissue. Immunohistochemical analysis for Ki-67 and cyclin D1 is used to identify immature nerve tissue, while tumor cells are commonly positive for GFAP and OCT4 (27).

At the end of 2021, the National Comprehensive Cancer Network published the Clinical Practice Guide for Cervical Cancer (1st Edition), which included the relevant characteristics of cervical small cell neuroendocrine tumors, including their pathological features, imaging strategies and clinical treatments (28). For cases limited to the cervix and with a tumor diameter of ≤4 cm, surgeons can apply radical surgery plus pelvic lymph node dissection with para-aortic lymph node sampling, followed by adjuvant chemotherapy (cisplatin plus etoposide or carboplatin plus etoposide), or simultaneous radiotherapy and chemotherapy (29). Compared with cervical squamous cell carcinoma, cervical small cell carcinoma has been reported to exhibit higher lymphatic and distant metastasis rates, and to be characterized by poor prognosis and a lower 5-year overall survival rate (30).

The majority of ovarian immature teratomas originate from germ cells after the first meiosis (31,32). However, it has also been reported that some teratomas can occur prior to the first meiosis (26-27,33). Previous studies have also indicated that the majority of pure immature teratomas are diploid, and lack 12p abnormalities, which are commonly observed in mixed germ cell tumors (34,35). Notably, ovarian immature teratomas are prone to recurrence and metastasis; however, in the history of subsequent recurrence, they often change from immature to mature tissue. Currently, no consensus has been reached on the treatment of ovarian immature teratomas. Therefore, the decision to perform chemotherapy for patients with immature ovarian teratomas still needs to be carefully considered (36).

Two synchronous primary malignancies of the female genital tract is uncommon. Herein, a young female patient underwent radical surgery for cervical small cell carcinoma and ovarian immature teratoma. The etiology and mechanisms of synchronous primary malignancies remain controversial, and further research is needed to explain these simultaneous cancers.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MX and YL collected and collated the data, and wrote the manuscript. HC and QJ analyzed and interpreted the patient data. QJ and HX confirmed the authenticity of all the raw data. HX defined the overall conception and design of the article, and reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of any data and/or accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Tong SY, Lee YS, Park JS, Bae SN, Lee JM and Namkoong SE: Clinical analysis of synchronous primary neoplasms of the female reproductive tract. Eur J Obstet Gynecol Reprod Biol 136: 78-82, 2008.
2. Coyte A, Morrison DS and McLoone P: Second primary cancer risk-the impact of applying different definitions of multiple primaries: Results from a retrospective population-based cancer registry study. BMC Cancer 14: 272, 2014.
3. Meeks MW, Grace S, Chen Y, Petterchak J, Bolesta E, Zhou Y and Lai JP: Synchronous quadruple primary neoplasms: Colon adenocarcinoma, collision tumor of neuroendocrine tumor and schwann cell hamartoma and sessile serrated adenoma of the appendix. Anticancer Res 36: 4307-4311, 2016.
4. Saatli B, Yildirim N, Ozay AC, Koyuncuoglu M, Demirkan B and Saygili U: Synchronous tumors of the female genital tract: A 20-year experience in a single center. Ginekol Pol 85: 441-445, 2014.

5. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T and Omlin A: Multiple primary tumours: Challenges and approaches, a review. ESMO Open 2: e000172, 2017.
6. Biller LH, Syngal S and Yurgelun MB: Recent advances in Lynch syndrome. Fam Cancer 18: 211-219, 2019.
7. Tjalma WAA, Trinh XB, Rosenlund M, Makar AP, Kridelka F, Rosillon D, Van Dam PA, Collas De Souza S, Holl K, Simon P and Jenkins D: A cross-sectional, multicentre, epidemiological study on human papillomavirus (HPV) type distribution in adult women diagnosed with invasive cervical cancer in Belgium. Facts Views Vis Obgyn 7: 101-108, 2015.
8. Atienza-Amores M, Guerini-Rocco E, Soslow RA, Park KJ and Weigelt B: Small cell carcinoma of the gynecologic tract: A multifaceted spectrum of lesions. Gynecol Oncol 134: 410-418, 2014.
9. Huang YD, Hung YC, Yeh LS, Chiang IP, Zeng GC and Chang WC: Synchronous ovarian endometrioid adenocarcinoma and endocervical mucinous adenocarcinoma. Taiwan J Obstet Gynecol 45: 264-267, 2006.
10. Phupong V, Khemapech N and Triratanachat S: Triple synchronous primary cervical, endometrial and ovarian cancer with four different histologic patterns. Arch Gynecol Obstet 276: 655-658, 2007.
11. Pekin T, Yoruk P, Yildizhan R, Yildizhan B and Ramadan S: Three synchronized neoplasms of the female genital tract: An extraordinary presentation. Arch Gynecol Obstet 276: 541-545, 2007.
12. Kilciksiz S, Gokce T, Somali I, Uysal D, Baloglu A and Yigit S: A case with three different synchronous primaries of the female genital system and their treatment. J BUON 12: 291-293, 2007.
13. Saglam A, Bozdag G, Kuzey GM, Kucukali T and Ayhan A: Four synchronous female genital malignancies: The ovary, cervix, endometrium and fallopian tube. Arch Gynecol Obstet 277: 557-562, 2008.
14. Hale CS, Lee L and Mittal K: Triple synchronous primary gynecologic carcinomas: A case report and review of the literature. Int J Surg Pathol 19: 552-555, 2011.
15. Takatori E, Shoji T, Miura Y, Takeuchi S, Uesugi N and Sugiyama T: Triple simultaneous primary invasive gynecological malignancies: A case report. J Obstet Gynaecol Res 40: 627-631, 2014.
16. Chiofalo B, Di Giuseppe J, Alessandrini L, Perin T, Giorda G, Canzonieri V and Sopracordevole F: Triple synchronous invasive malignancies of the female genital tract in a patient with a history of leukemia: A case report and review of the literature. Pathol Res Pract 212: 573-577, 2016.
17. Abu-Zaid A, Alsabban M, Abuzaid M, Alomar O, Salem H and Al-Badawi IA: Triple synchronous primary neoplasms of the cervix, endometrium, and ovary: A rare case report and summary of all the english pubmed-indexed literature. Case Rep Obstet Gynecol 2017: 9705078, 2017.
18. Wang DD and Yang Q: Synchronous quadruple primary malignancies of the cervix, endometrium, ovary, and stomach in a single patient: A case report and review of literature. World J Clin Cases 7: 3364-3371, 2019.
19. Bacalbasa N, Balescu IC, Diaconu C, Dima S, Iliescu L, Vilcu M, Filipescu A, Halmaciu I, Cretoiu D and Brezean I: Synchronous cervical adenocarcinoma and ovarian serous adenocarcinoma-a case report and literature review. Medicina (Kaunas) 56: 152, 2020.
20. Mishra P, Sasmal PK, Jena SK, Senapati S and Patra S: Pure primary ovarian carcinoid tumor with carcinoid syndrome and cervical carcinoma: A rare concoction of dual primary malignancies. Indian J Pathol Microbiol 64: 563-567, 2021.
21. Kuriakose S, Umadevi N, Mathew S, Supriya N, Aravindan K, Smitha D and Amritha Malini G: Neuroendocrine carcinoma of the cervix presenting as intractable hyponatremic seizures due to paraneoplastic SIADH-a rare case report and brief review of the literature. Ecancermedicalscience 8: 450, 2014.
22. Wang M, Vasey Q, Varikatt W and Mclean M: Ectopic insulin secretion by a large-cell neuroendocrine carcinoma of the cervix. Clin Case Rep 9: 482-486, 2020.
23. Singh R, Bibbo M, Cunnane MF, Carlson JA and de Papp AE: Metastatic cervical carcinoma with ectopic calcitonin production presenting as a thyroid mass. Endocr Pract 8: 50-53, 2002.
24. Hausken J, Haave EM, Haugaa H, Løberg EM and Kongsgaard UE: A patient with solid gynecologic cancer causing lactic acidosis, severe hypercalcemia, and hypoglycemia. Clin Case Rep 7: 64-70, 2018.
25. Boussios S, Attygalle A, Hazell S, Moschetta M, McLachlan J, Okines A and Banerjee S: Malignant ovarian germ cell tumors in postmenopausal patients: The royal marsden experience and literature review. Anticancer Res 35: 6713-6722, 2015.
26. Parrington JM, West LF and Povey S: The origin of ovarian teratomas. J Med Genet 21: 4-12, 1984.
27. Snir OL, DeJoseph M, Wong S, Buza N and Hui P: Frequent homozygosity in both mature and immature ovarian teratomas: A shared genetic basis of tumorigenesis. Mod Pathol 30: 1467-1475, 2017.
28. Abu-Rustum NR, Yashar CM, Arend R, Barber E, Bradley K, Brooks R, Campos SM, Chino J, Chon HS, Crispens MA, *et al*: NCCN guidelines® insights: Cervical cancer, version 1.2024. J Natl Compr Canc Netw 21: 1224-1233, 2023.
29. Cohen JG, Kapp DS, Shin JY, Urban R, Sherman AE, Chen LM, Osann K and Chan JK: Small cell carcinoma of the cervix: Treatment and survival outcomes of 188 patients. Am J Obstet Gynecol 203: 341-347.e1-e6, 2010.
30. Li P, Ma J, Zhang X, Guo Y, Liu Y, Li X, Zhao D and Wang Z: Cervical small cell carcinoma frequently presented in multiple high risk HPV infection and often associated with other type of epithelial tumors. Diagn Pathol 13: 31, 2018.
31. Linder D, McCaw BK and Hecht F: Parthenogenic origin of benign ovarian teratomas. N Engl J Med 292: 63-66, 1975.
32. Nomura K, Ohama K, Okamoto E and Fujiwara A: Cytogenetic studies of multiple ovarian dermoid cysts in a single host. Nihon Sanka Fujinka Gakkai Zasshi 35: 1938-1944, 1983 (In Japanese).
33. Wang WC and Lai YC: Genetic analysis results of mature cystic teratomas of the ovary in Taiwan disagree with the previous origin theory of this tumor. Hum Pathol 52: 128-135, 2016.
34. Poulos C, Cheng L, Zhang S, Gersell DJ and Ulbright TM: Analysis of ovarian teratomas for isochromosome 12p: Evidence supporting a dual histogenetic pathway for teratomatous elements. Mod Pathol 19: 766-771, 2006.
35. Kraggerud SM, Hoei-Hansen CE, Alagaratnam S, Skotheim RI, Abeler VM, Rajpert-De Meyts E and Lothe RA: Molecular characteristics of malignant ovarian germ cell tumors and comparison with testicular counterparts: Implications for pathogenesis. Endocr Rev 34: 339-376, 2013.
36. Faure-Conter C and Pashankar F: Immature ovarian teratoma: When to give adjuvant therapy? J Pediatr Hematol Oncol 39: 487-489, 2017.