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BRIEF REPORT

Mixed mucinous adenocarcinoma/large cell neuroendocrine carcinoma of the uterine cervix: case report and molecular characterization of a rare entity

Caterina Fattorini[1] · Bruno J. Rocca[1] · Andrea Giusti[1] · Marco Arganini[2] · Bruno Perotti[2] · Andrea Cavazzana[1] · Maria R. Ambrosio[1] · Marco Volante[3]

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Abstract

Mixed neuroendocrine-non-neuroendocrine carcinomas of the cervix are rare and generally aggressive diseases. They often present at an advanced stage with hematogenous or lymphatic metastases. The prognosis is poor, mostly influenced by the neuroendocrine component. Unfortunately, the rarity of the disease caused a lack of information about its pathogenesis and molecular landscape. The latest guidelines recommend a multimodal approach that usually includes radical surgery, platinum/etoposide-based chemotherapy, or chemoradiation. Here, we are presenting a case of metastatic mixed adenocarcinoma-large cell neuroendocrine carcinoma of the cervix in a 49-year-old female patient. The molecular characterization of the lesion highlighted the ubiquitous presence of human papillomavirus-18 DNA both in the adenocarcinomatous and the neuroendocrine components, suggesting a role for the virus in the pathogenesis. Moreover, a different set of mutations was detected in the two parts, thus ruling out a possible clonal evolution of the neuroendocrine component from the adenocarcinoma one. More studies are needed to clarify the molecular landscape of these rare lesions and identify putative targets for therapy.

Keywords MiNEN · Uterine NEN · Adenoneuroendocrine carcinoma · ERBB2 mutations · GNAS mutations · HPV

Introduction

According to the latest statistics from IARC (*International Agency for Research on Cancer)*, cervical cancer is the fourth most common cancer in women worldwide with 604,127 new cases in 2020 and 341,831 cervical cancer related deaths [10]. Human papillomavirus (HPV) is a well-known pathogen involved in the etiopathogenesis of these neoplasms.

Adenocarcinoma accounts for 5% of cervical malignancies, whereas neuroendocrine neoplasms (NEN) are uncommon, representing fewer than 1% of all gynecological malignant tumors. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) are even rarer [20].

A case of mixed mucinous adenocarcinoma-large cell neuroendocrine carcinoma of the uterine cervix is presented here. Our aim is to broaden knowledge about this rare entity, especially regarding its molecular characterization and potential therapeutic options, as data on epidemiology, pathogenesis, and molecular features are currently lacking.

Case report

In 2019, a 46-year-old female suffering from iron deficiency anemia was first diagnosed with uterine leiomyomatosis and subsequently scheduled for hysterectomy in the following months. However, due to the COVID-19 outbreak in early 2020, many elective surgeries were postponed to a later date, and so it was for the patient. Starting from late April 2020, she complained of cramping abdominal pain and was referred to Emergency Unit. Physical examination revealed a bulky abdominal mass in the periumbilical area and a peritoneal irritation in the left iliac fossa. A clinical diagnosis

✉ Maria R. Ambrosio
maradot@libero.it

[1] Pathology Unit, Azienda Sanitaria Toscana Nord Ovest, Via Cocchi 1, 56121 Pisa, Italy

[2] Surgery Unit, Ospedale Unico Versilia, Azienda Sanitaria Toscana Nord Ovest, 56121 Pisa, Italy

[3] Pathology Unit, Department of Oncology at San Luigi Hospital, University of Turin, Orbassano, Italy

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of acute abdomen was posed. Abdominal ultrasound (US) showed a 170×50 mm large inhomogeneous mass of the left ovary. The lesion presented solid and cystic areas, the latter being frankly hemorrhagic, and was adherent to the sigmoid colon with no evidence of a cleavage plane. The right ovary was enlarged (70×50 mm) but homogeneous. Multiple intra-hepatic lesions of metastatic appearance emerged. Whole-body computed tomography (CT) scan, performed under urgency/emergency regimen, demonstrated that the left ovary was completely replaced by an 18×13×16 cm multiloculated cystic lesion, displacing the intestinal loops and adhering the aorta and the inferior vena cava. CT confirmed US detected right ovary enlargement with no evident lesions, as well as uterine leiomyomatosis and multiple hypodense nodules of secondary appearance within the liver parenchyma. Moreover, a hypoenhancing mass of 30 mm within the normally enhanced cervical stroma was also identified and a suspicious slight enlargement of pelvic and para-aortic lymph nodes was appreciated. Thereafter, the patient was hospitalized and underwent emergency/urgency surgery. Blood tests showed reduced hemoglobin levels (8.4 g/dL), while tumor markers CA 125, CA 19–9, and CEA were within reference range. Radical hysterectomy with bilateral salpingo-oophorectomy, removal of appendix, and nodulectomy of one of the suspect liver nodule was performed. Para-aortic/pelvic lymph node dissection was not performed in accordance with the current guidelines due to the metastatic nature of the disease. The specimen was sent for pathological examination to the Anatomic Pathology Department. Grossly, the left ovary was completely replaced by a 15-cm-diameter multiloculated cystic lesion with mucoid and hemorrhagic contents and necrotic areas. The right ovary was enlarged, and, on cut surface, a 7-cm-diameter whitish and solid mass with small cystic mucinous areas was identified. Macroscopic examination of the uterus, which measured 14×8×8 cm, identified two leiomyomas with a typical benign appearance, located at the uterine corpus and fundus and an enlarged-looking cervix, which was 4×3.5×3 cm. After cutting the specimen, a polypoid lesion of the uterine cervix was identified. The cervical lesion did not protrude through the cervical ostium, presented a fleshy whitish cut surface, and measured 3 cm in maximum diameter. The liver small resection showed a whitish intrahepatic solid lesion, measuring 1 cm in maximum diameter. Appendix was unremarkable. After formalin fixation, paraffin embedding, and section staining with hematoxylin and eosin (H&E), microscopy examination was carried out. The uterine cervix sections revealed the presence of two distinct malignant neoplastic components in contact with each other. The first one was glandular and presented a diffusely infiltrative growth pattern with confluent areas. The glands were characterized by atypical pseudostratified cylindrical cells with hyperchromatic nuclei and numerous mitoses. Most of the cells had intracytoplasmic mucin and displayed goblet cell intestinal differentiation (Fig. 1A and B). Interestingly, this glandular component seems to evolve from a tubulovillous adenoma to an invasive carcinoma by an in situ component. The other adjacent component comprised atypical cells of medium-large size, arranged in solid and nested patterns; scattered pseudorosettes were also visible (Fig. 1C and D). The cells had abundant eosinophilic cytoplasm, ovoid nuclei with dispersed and hyperchromatic chromatin, and inconspicuous nucleoli. Areas of necrosis were visible. The mitotic activity was brisk, ranging from 15 to 50 mitoses/2 mm^2 in the glandular component (mean value 25×2 mm^2), to 12 to 55 mitoses/2 mm^2 in the solid component (mean value 34×2 mm^2). Maximum depth of cervical stroma invasion was 15 mm with extent to deep one-third and Silva pattern of invasion "C." The resection margins also including the vaginal cuff, the low uterine segment, and the radial one were involved by invasive carcinoma. Lymphovascular spaces invasion was also identified. Ovaries showed both neoplastic components. No infiltration of the upper uterine segment, fallopian tubes, right and left parametrium, and appendix was observed. A metastatic localization was

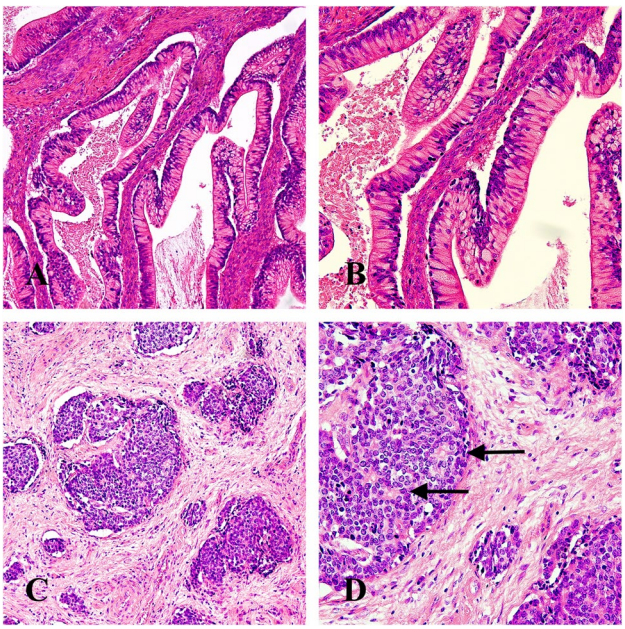

Fig. 1 Microscopic appearance of both components of the lesion: intestinal-type mucinous adenocarcinoma (**A** H&E stain, original magnification 10×; **B** H&E stain, original magnification 20×) and large cell neuroendocrine carcinoma (**C** H&E stain, original magnification 10×; **D** H&E stain, original magnification 20×). The adenocarcinomatous component displayed glandular architecture (**A**) and pseudostratified cylindrical cells (**B**); intracytoplasmic mucin and goblet cell intestinal differentiation can be readily appreciated. The neuroendocrine carcinoma component was arranged in solid sheets and nested patterns (**C**). At higher magnification (**D**), medium-large sized neoplastic cells with ovoid nuclei and inconspicuous nucleoli can be seen; two pseudorosettes are visible (arrows)

evident in the liver segment, exclusively composed by the more solid component. A detailed immunohistochemical study of both components was made (Fig. 2). The glandular neoplasm was positive for CK7, CEA, and CDX2, partially positive for PAX8, and negative for ER, PR, TTF1, synaptophysin, and CD56 and showed normal p53 and mismatch repair–related protein expression (MSH2, MSH6, PMS2, MLH1). Interestingly, neuroendocrine lineage specific markers chromogranin A, ISNM1, and hASH1 highlighted scattered endocrine cells within the glands of the adenocarcinoma component. The solid component was diffusely positive for synaptophysin, ISNM1, hASH1, CDX2, TTF1, CK7, and CEA and negative for chromogranin A, CD56, PAX8, ER, and PR. It also showed no abnormal pattern of nuclear expression for p53 and mismatch repair–related protein. Ki-67 proliferation index was 50% in the glandular component and 90% in the solid one. Both components showed diffuse block-type p16 positivity suggesting an HPV-related pathogenesis. Given this p16 diffuse positivity, the presence of HPV virus was subsequently investigated in all different involved tissues (cervix, ovaries and liver) using a multiplex real-time PCR based method (*Anyplex™ II HPV 28 Detection test, Seegene Inc.*). The analysis highlighted in all locations the presence of high risk HPV-18, confirming the HPV correlation of both neoplastic components.

Considering all these findings, a diagnosis of HPV-related MiNEN, namely, mixed neuroendocrine (large cell neuroendocrine carcinoma) and non-neuroendocrine (intestinal-type mucinous adenocarcinoma) neoplasm was made. At cervix level, most of the lesion consisted of adenocarcinoma (70% approximately) while only 30% of the mass was interested by the neuroendocrine neoplasm. In both ovaries, the neuroendocrine component took only a minor part (10%) of the mass. In contrast, the liver metastasis was entirely constituted by large cell neuroendocrine carcinoma (100%) (Fig. 3). Tumor staging was as follows: UICC TNM stage pT4 NX M1 [3] and FIGO stage IVB [2].

To identify a possible common origin of both components, a molecular characterization of both malignant components was performed using Myriapod® NGS 56G Onco panel CE IVD kit on Illumina® sequencing platform with Myriapod® NGS Data Analysis Software (version 5.0.2). For this purpose, either the adenocarcinoma and the neuroendocrine component were microdissected at uterine level. The adenocarcinoma carried a *GNAS* gene missense mutation (exon 8, c.602G > A, p.Arg201His) classified as Class 4/5 variant by ACMG/AMP (American College of Medical Genetics and Genomics/Association for

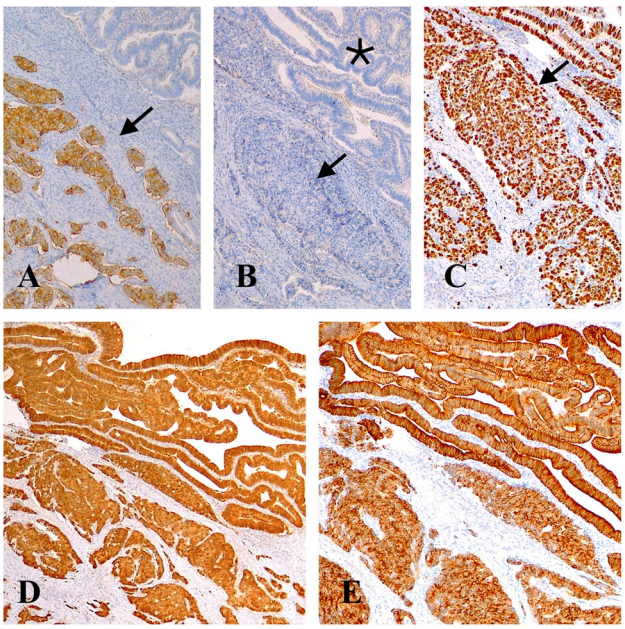

Fig. 2 Immunohistochemical study of the two components (original magnification 10×). **A** Synaptophysin stained positively the neuroendocrine carcinoma (black harrow) only. **B** Chromogranin A stained neither the neuroendocrine (black harrow) nor the glandular component (asterisk). **C** High-grade neuroendocrine neoplasms showed a very high proliferation index, as highlighted by Ki-67 stain (black harrow). **D** Diffuse block-type p16 positivity can be appreciated in both components suggesting an HPV-related pathogenesis. **E** The epithelial marker CK7 is diffusely positive in both components confirming the carcinomatous nature of both components

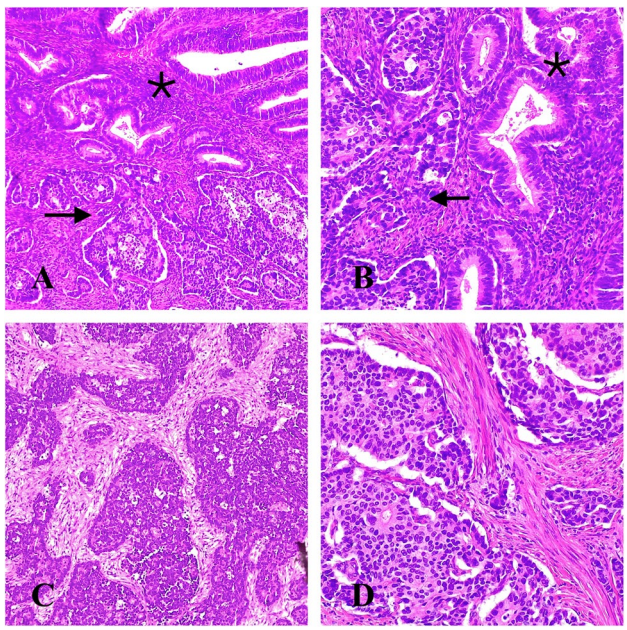

Fig. 3 Microscopic appearance of ovarian (**A** H&E stain, original magnification 10×; **B** H&E stain, original magnification 20×) and liver metastasis (**C** H&E stain, original magnification 10×, **D** H&E stain, original magnification 20×). In the ovary. the neoplasia showed a mixed phenotype: the adenocarcinomatous component (A–B: asterisks) is in continuity with the neuroendocrine carcinoma (A–B: arrows). On the contrary, at liver level, the tumor showed a homogeneous neuroendocrine component (**C-D**)

Molecular Pathology); the neuroendocrine part instead had a missense mutation of *ERBB2* gene (exon 17 c.2033G > A, p.Arg678Gln) of ACMG/AMP Class 4. Moreover, we tested the neuroendocrine metastasis of the liver. In addition to having the *ERBB2* gene mutation, a minority of tumor cells acquired further mutations: a Class 5 stop-gain *PTEN* gene mutation (exon 7, c.781C > T, p.Gln261*) and a Class 3 missense *TP53* gene mutation (exon 11, c.1118A > G, p.Lys373Arg).

After a regular post-surgical course, the patient was released on the fifth day; 3 + 2 cycles of adjuvant etoposide-cisplatinum-based chemotherapy were administered to the patient. After a few months, the patient complained of diffuse bone pains and was sent to radiologic investigations that showed disease progression. In May 2021, the patient unfortunately died.

Discussion

According to the last World Health Organization Classification [20], MiNENs are very rare tumors with manifestations similar to NEN, such as vaginal bleeding or spotting. In the female genital tract, this category of tumors occurs mostly in the uterine cervix [11]. Adenocarcinoma of usual HPV-associated type is the most common non-neuroendocrine component, whereas the neuroendocrine part is usually represented by neuroendocrine carcinomas [20].

Here, we present a case of mixed mucinous adenocarcinoma-large cell neuroendocrine carcinoma of the uterine cervix with ovary and liver metastases. The cervix lesion was missed by US, while CT only showed a suspicious area of hypoenhancing; but this is not surprising, as the more sensitive imaging tool for assessing cervical cancer is nuclear magnetic resonance (NMR) due to its superior soft tissue resolution. NMR is a second level exam, not applicable in emergency/urgency regimen as in our case. The rarity of cervix uteri MiNENs explains the lack of data on their epidemiology and pathogenesis. Similarly to cervical squamous cell carcinomas and adenocarcinomas, high-risk HPV DNA has been detected in the vast majority of high-grade neuroendocrine neoplasms of the cervix, especially HPV-16 and HPV-18 subtypes [1, 4]. In our case, both neoplastic components expressed p16 immunohistochemical marker and carried HPV-18 DNA suggesting a possible role of the virus also in MiNENs pathogenesis as a common ancestor.

Cervix, similarly to other epithelial sites, has a reserve of stem cell compartment capable of differentiating toward different epithelial subtypes, such as glandular or neuroendocrine cells. Given that, it is possible that HPV might promote stem cell transformation toward one or another cell line. Molecular analysis in our case showed that the glandular and neuroendocrine components have two different genotypes, since they carry different mutations: a *GNAS* gene missense mutation was detected in the former component while the neuroendocrine carcinoma carried a *ERBB2* gene missense mutation.

In our opinion, these data corroborate the fact that the neuroendocrine component did not develop from the adenocarcinomatous lesion or vice versa; on the contrary, they possibly evolved from a common precursor under the oncogenic effect of HPV integration and then progressed through different genetic pathways.

Prognosis of MiNENs of the cervix is invariably poor and is comparable to that of their pure neuroendocrine counterparts. Small cell or large cell neuroendocrine carcinomas of gynecological sites commonly present with distant metastases and have a diffuse hematogenous or lymphatic spread. In fact, in our case only the neuroendocrine component metastasized to the liver. Mortality is very high even at early stages: survival rates of neuroendocrine carcinoma of the cervix range between 25 and 35% [11]. Mean overall survival (OS) and recurrence-free survival (RFS) are, respectively, 40 months and 16 months [19]. The most important prognostic factors for patients with MiNEN of cervix overlapped those reported for pure neuroendocrine carcinomas at this site (tumor size, nodal status and FIGO stage) [17]. It is of utmost importance to early recognize this entity in order to set up a close follow-up to promptly detect any metastases and apply the most correct therapeutic protocol. Unfortunately, in this specific case, the diagnosis was delayed due to COVID-19 pandemic, and the disease became apparent at an advanced stage.

Due to the rarity of this type of cervix malignancy, no personalized treatment schedules are currently available neither for pure neuroendocrine carcinomas nor for MiNENs. Clinicians usually attempt multimodal approaches that build upon the treatments used for neuroendocrine carcinomas of the lung [19]. The latest guidelines for women with cervix neuroendocrine carcinomas drawn up by the Society of Gynecologic Oncology (SGO) recommend a multimodal approach with etoposide/platinum based neoadjuvant chemotherapy [9]. In our case, given the rapid onset of acute abdomen, the patient underwent emergency/urgency surgery with no time for pre-operatory pathological evaluation and neoadjuvant treatments. The use of targeted agents is rare and only few case reports on the subject are available: Lyons and colleagues administered trametinib, a *MEK* inhibitor, to a woman with recurrent neuroendocrine carcinoma of the cervix and *KRAS* mutation [13]; moreover in 2017 Sharabi and coworkers reported a good response to nivolumab in a patient with metastatic cervix neuroendocrine carcinoma refractory to chemotherapy [18].

The molecular profile of uterine cervix MiNEN is also poorly studied; to the best of our knowledge, there are no systematic studies on larger number of patients and only few reported cases in small series are available [6, 8, 12, 15, 16]. Our molecular analysis found that the adenocarcinomatous component of the neoplasm carried *GNAS* mutation,in fact *GNAS* mutations have been reported in numerous tumors of the gastrointestinal tract and also in endocervical mucinous adenocarcinoma [14]. Consequently *GNAS* mutations seem to accompany a differentiation toward a gastrointestinal glandular phenotype.

The neuroendocrine component, instead, showed a different molecular profile: *ERBB2* mutations were found in both the cervix lesion and the liver metastasis. Furthermore, the metastatic lesion acquired *PTEN* and *TP53* mutations. Mutations involving *PTEN* and *TP53* genes are known to affect cervix neuroendocrine carcinomas. In 2020 Eskander and colleagues [7] studied a large cohort of patients with high-grade cervical neuroendocrine carcinomas; they found that the most frequent altered genes were *PIK3CA*, *MYC, TP53*, and *PTEN* and that the main interested pathways were *PIK3CA/AKT/mTOR* and *RAS/MEK*. In a recent work, Ordulu and colleagues found a similar set of mutations in a series of 14 NEN of the cervix, also including *RB1* and *MSH6* genes mutations [16]. However, *ERBB2* mutations involving cervical neuroendocrine carcinomas are rarely reported in literature [5, 21]. It seems instead that *ERBB2* mutations mainly affect other histotypes. Zammataro and coworkers analyzed the genomic landscape of a cohort of adeno- and squamous carcinoma of the cervix and noted that 14% of patients harbored recurrent somatic mutations involving *ERBB2* gene [22]. They also studied *ERBB2* as a possible therapeutic target using pan-HER inhibitors in preclinical xenograft models obtaining promising results: tumors with *ERBB2* mutations were more sensitive to HER-inhibitors compared to wild-type tumors. These interesting findings suggest that cervical cancers harboring *ERBB2* mutations might benefit from available *HER2*-inhibitors, and this can include high-grade neuroendocrine carcinomas and MiNENs carrying the same category of mutations. To confirm these hypotheses more studies investigating the molecular landscape of these neoplasms and clinical trials are needed.

Conclusions

MiNEN of the cervix are rare and aggressive tumors that mimic the behavior of pure high-grade neuroendocrine neoplasms. Affected women frequently present at an advanced stage. It is therefore essential to promptly recognize this entity to set up an appropriate treatment and a close follow-up. Unfortunately, in this specific case, the patient received a delayed diagnosis when the disease was already metastatic mainly because of the ongoing COVID-19 pandemic.

Due to the rarity of the disease, there is a lack of data regarding its pathogenesis and molecular characteristics and the absence of specific therapeutic protocols. Molecular data in our case indicate that HPV was a key actor in the genesis of the disease that further developed following distinct genomic pathways, supporting the hypothesis that HPV would have caused the transformation of a common stem cell progenitor. Furthermore, the analysis of genetic mutations of the primitive and metastatic neuroendocrine component of the tumor allowed us to confirm the presence of known mutations involving cervix NEN, such as *TP53* and *PTEN* gene mutations, and also found *ERBB2* gene as a potential therapeutic target. Subsequent studies are needed to evaluate the presence of further possible targetable biomarkers that can be used for a personalized therapy of these rare neoplasms.

Author contribution CF, MV, and MRA—study design, acquisition of pathological data, manuscript writing. BJR, AG, AC—acquisition of pathological and molecular data. MA and BP—acquisition of clinical data, surgical procedures. MV and MRA—critical review of the manuscript. All authors have read and approved the manuscript.

Data availability All data and material are available.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Informed consent for publication was obtained from all authors.

Conflict of interest The authors declare no competing interests.

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