

Proliferative escalation and possible neuroendocrine carcinoma transformation in pulmonary metastases of a cervical neuroendocrine tumor: A case report

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Abstract. The present report describes a rare case of cervical adenocarcinoma with a coexisting neuroendocrine tumor (NET) G2 component that developed pulmonary metastases with proliferative escalation and possible transformation to neuroendocrine carcinoma (NEC). A 43-year-old woman with cervical adenocarcinoma (International Federation of Gynaecology and Obstetrics 2018 stage IB1) underwent radical hysterectomy, bilateral salpingectomy and pelvic lymph node dissection. The primary tumor had morphologic features of mixed adenocarcinoma and NET G2 [Ki-67, 3-30%; 5-8 mitoses/10 high-power fields (HPFs)], classified as postoperative pathological stage IB1 (pT1b1 N0 M0; American Joint Committee on Cancer 9th edition). After 2 years, chest computed tomography revealed multiple pulmonary nodules. Resection of a right middle lobe lesion revealed metastatic NET with increased proliferative activity (G3 based on gastrointestinal NET criteria; Ki-67 hotspot, 35%; >50 mitoses/10 HPFs). A left upper lobe lesion exhibited predominantly NET morphology, but focal areas exhibited high proliferative activity (Ki-67 hotspot, 93%; 50 mitoses per 10 HPFs) with features compatible with small cell carcinoma. The current case suggests a stepwise progression from NET toward

NEC, highlighting the importance of monitoring proliferative indices in cervical NETs, re-evaluating metastatic lesions histologically and considering multimodal treatment strategies.

Introduction

Neuroendocrine neoplasms (NENs) of the uterine cervix account for approximately 1-2% of all cervical cancers, wherein the vast majority are poorly differentiated neuroendocrine carcinomas (NECs), such as small cell NEC (SCNEC) and large cell NEC (LCNEC) (1). In contrast, well-differentiated NETs (G1-G2) and mixed tumors with NET and adenocarcinoma components are exceedingly rare, with reports limited to individual case descriptions or small case series.

NETs of the gastrointestinal tract reportedly exhibit increased proliferative activity during disease progression or metastasis, and in some cases, morphological transformation from NET to NEC-like features (2,3). However, in gynecologic oncology, systematic evidence on changes in proliferative activity in NETs remains scarce. This report describes a rare case of cervical adenocarcinoma with a coexisting NET G2 component, wherein postoperative bilateral pulmonary metastases demonstrated increased proliferative activity in the NET component alongside focal histological features suggesting NEC transformation. This represents an unusual example of a gynecologic NET exhibiting proliferative escalation in metastatic lesions during disease progression.

Case report

A 43-year-old woman presented at a respiratory clinic with a chronic cough. Chest computed tomography (CT) in March 2024 revealed 3 nodular lesions in the lung, each measuring 3-5 mm, located in the right middle, left upper, and left lower lobes (Fig. 1A-C).

The patient had a history of cervical cancer (FIGO 2018 stage IB1) diagnosed in March 2022, treated with radical hysterectomy, bilateral salpingectomy, and pelvic lymph

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Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; HPF, high-power field; NEN, neuroendocrine neoplasm; RFA, radiofrequency ablation

Key words: cervical neuroendocrine neoplasm, pulmonary metastases, Ki-67, neuroendocrine carcinoma

node dissection. Histopathological examination revealed a mixed tumor consisting of adenocarcinoma and NET (Fig. 2). Specifically, the transitional area had adenocarcinoma components proliferating in tubular, papillary, and cribriform patterns. Meanwhile, uniform cells with round nuclei formed solid nests, trabeculae, and rosettes, consistent with neuroendocrine morphology. The neuroendocrine component was positive for synaptophysin, chromogranin A, INSM1, p16, and CK7, while it was negative for CK20, TTF-1, PAX8, and YAP1. The tumor showed a p53 wild-type pattern with retained Rb expression. The Ki-67 index was approximately 30% in hotspots (overall range: 3-30%), and mitotic activity was 5-8 per 10 high-power fields (HPFs). Within the cervical tissue, the neuroendocrine component was confined to a well-differentiated NET, with no evidence of NEC. If classified using the gastrointestinal system criteria, the neuroendocrine component would correspond to NET G3, but the current classification of cervical NETs extends only up to G2. Thus, the tumor was considered a mixed adenocarcinoma and NET G2. According to the AJCC 9th edition, the postoperative pathological stage was stage IB1 (pT1b1 N0 M0) without distant metastasis.

Follow-up chest CT in June 2024 revealed that the pulmonary nodules increased in size compared to March 2024 (Fig. 1D and E). A right middle lobe lesion was partially resected for diagnostic purposes, yielding a small nodule measuring 5 mm in diameter. Histologically, solid nests of columnar to short spindle-shaped cells with oval nuclei were observed (Fig. 3). Central necrosis was present within the nests, with nuclear palisading at the periphery. More than 50 mitotic figures per 10 HPFs were counted. The Ki-67 index was 35% (hotspot). These features are consistent with G3 disease according to the gastrointestinal NET criteria. Immunohistochemically, the tumor cells were positive for CK7, p16, INSM1, and chromogranin A, but these were negative for CK20 and p40. These findings are morphologically and immunophenotypically consistent with metastatic NET originating from the uterine cervix. No areas lacking expression of neuroendocrine markers were identified within the specimen.

The patient was referred to our oncology department in August 2024 for further evaluation and treatment. Gastrointestinal endoscopy revealed no evidence of a primary tumor, with no abnormal uptake on octreotide scintigraphy. Treatment with everolimus was initiated in October 2024, and CT in December 2024 showed stable disease (Fig. 1F and G). However, in April 2025, the residual pulmonary lesions mildly increased in size, but with no new lesions (Fig. 1H and I). The patient declined continuation of everolimus, opting instead for a local treatment strategy.

Radiofrequency ablation (RFA) of a left lower lobe lesion was performed in May 2025, followed by partial resection due to its close proximity to the aorta in June 2025. Histopathological examination of the resected left upper lobe specimen revealed predominantly NET morphology with a focal area showing features suspicious for small cell carcinoma (Fig. 4). The tumor was composed of atypical cells proliferating in solid nests with rosette- and palisade-like arrangements, accompanied by foci of necrosis. The tumor cells had relatively abundant eosinophilic cytoplasm and enlarged, uniform, round to oval nuclei without marked nuclear atypia.

Immunohistochemical analysis demonstrated positivity for synaptophysin, chromogranin A, and INSM1, negativity for p40 and YAP1, partial positivity for TTF-1, a p53 wild-type pattern, and no loss of Rb expression. The Ki-67 index reached 93% in hotspots, while the mitotic count was approximately 50 per 10 HPFs. These findings supported a diagnosis of NEN. Although most of the lesion exhibited morphology consistent with NET, there were focal areas demonstrating a markedly high Ki-67 labeling index, partial TTF-1 positivity, increased chromatin, and a higher nuclear-to-cytoplasmic ratio, thus raising concern for small cell carcinoma. While these findings suggested a metastatic cervical origin, the unusual morphological overlap warranted further investigation for small cell carcinoma. Throughout the perioperative course and subsequent follow-up, regular tumor marker assessments showed no elevation of NSE or ProGRP. Postoperative chemotherapy with a platinum-etoposide regimen was recommended, but the patient declined. The patient has remained recurrence-free to date, with radiologic evaluation at 6 months after resection of the last tumor showing no evidence of recurrence under close follow-up.

Immunohistochemical analyses for the immunostaining images shown in the figures were performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections. The primary antibodies used for the immunostaining shown in Figs. 2 and 4 were as follows: synaptophysin (catalog no. 413831, clone 27G12; Nichirei Biosciences), chromogranin A (catalog no. M086901-2, clone DAK-A3; DAKO), p16 (catalog no. 550834, clone G175-405; BD Biosciences), YAP1 (catalog no. ab52771, clone EPR1674Y; Abcam), TTF-1 (catalog no. NCL-L-TTF-1, clone SPT24; NOVO), retinoblastoma protein (Rb; catalog no. 554136, clone G3-245; BD Biosciences), PAX8 (catalog no. ab53490, clone PAX8R1; abcam), and Ki-67 (catalog no. M7240, clone MIB-1; DAKO). Antibody dilutions were 1:1 for synaptophysin, 1:200 for chromogranin A, 1:20 for p16, 1:100 for YAP1, 1:100 for TTF-1, 1:400 for Rb, 1:20 for PAX8, and 1:2 for Ki-67. For the immunostaining shown in Fig. 3D, chromogranin A (catalog no. 412751; Nichirei) was used at a dilution of 1:1. Appropriate positive and negative controls were included in each staining run. Immunoreactivity was evaluated independently by experienced pathologists.

Discussion

Cervical NENs are rare, accounting for approximately 1-2% of all malignant cervical tumors, among which the vast majority are high-grade NECs (1). Low- to intermediate-grade (G1-G2) NETs are extremely uncommon, and cases with an admixed adenocarcinoma component are exceedingly rare. The 2020 WHO classification categorizes cervical NENs as either NET G1, NET G2, or NEC, but some reports have described tumors corresponding to NET G3 (4). At present, a formal category corresponding to NET G3 has not been established in the current classification of cervical neuroendocrine neoplasms. However, as described in this report, the existence of cervical NENs showing well-differentiated morphology despite a high Ki-67 proliferation index has been suggested in the literature, albeit mainly at the level of individual case reports. By analogy with pancreatic and gastrointestinal NET G3, such tumors of the cervix may exhibit biological behavior and treatment

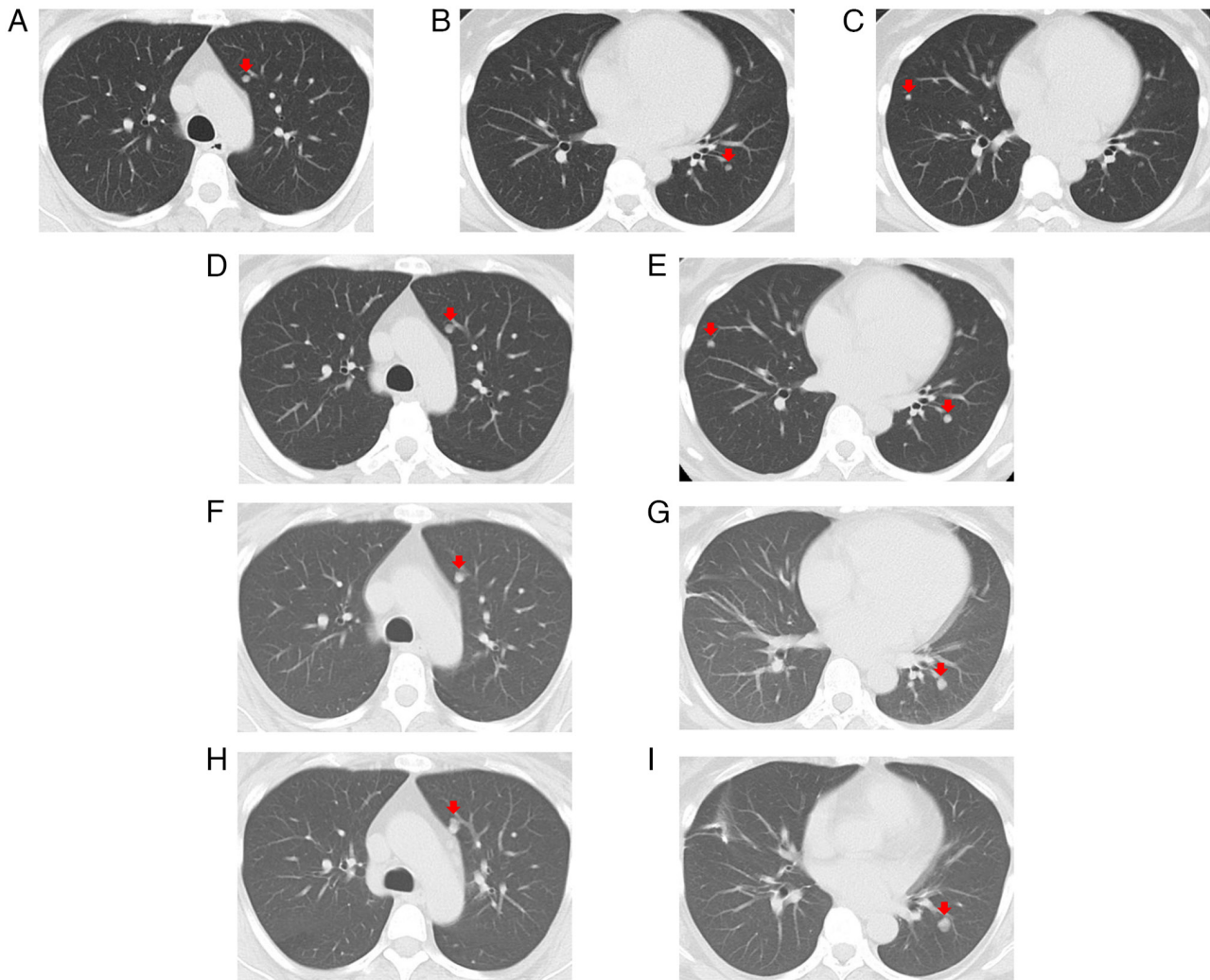


Figure 1. (A) Non-contrast chest CT scan obtained in March 2024 showing a small nodule in the left upper lobe. (B) Non-contrast chest CT scan obtained in March 2024 showing a small nodule in the left lower lobe. (C) Non-contrast chest CT scan obtained in March 2024 showing a small nodule in the right middle lobe. (D) Non-contrast chest CT scan obtained in June 2024 showing enlargement of the left upper lobe nodule. (E) Non-contrast chest CT scan obtained in June 2024 showing enlargement of the nodules in the right middle and left lower lobes. (F) Non-contrast chest CT scan obtained in December 2024 showing further enlargement of the left upper lobe nodule. (G) Non-contrast chest CT scan obtained in December 2024 showing further enlargement of the left lower lobe nodule. (H) Non-contrast chest CT scan obtained in April 2025 showing further enlargement of the left upper lobe nodule. (I) Non-contrast chest CT scan obtained in April 2025 showing further enlargement of the left lower lobe nodule. Overall, the nodules gradually increased in size over time. Red arrows indicate the tumor lesions.

responsiveness distinct from those of morphologically defined neuroendocrine carcinoma (NEC). In particular, they may be less sensitive to platinum-based chemotherapy compared with classic NEC, although robust evidence to support this assumption is currently lacking. Currently, available data are insufficient to justify a distinct therapeutic strategy for these tumors, and therefore no change in clinical management can be recommended. Nevertheless, recognition of a potential NET G3-like subgroup among cervical NENs may have important clinical implications in the future, particularly with respect to treatment selection and clinical trial design. Further accumulation of cases and comprehensive clinicopathological and molecular analyses will be essential to clarify the biological and clinical significance of this entity.

The primary tumor in this case had Ki-67 labeling index of 30% at the hotspot, which corresponds to G3 according to the pancreatic NEN grading system. Cervical NENs are considered more prone to metastasis than squamous cell carcinomas (5,6).

In our patient, while the primary lesion had adenocarcinoma and NET components, nearly all the metastatic lesions were composed solely of NET. This observation raises the possibility that a NEN clone present within the primary tumor possessed superior metastatic potential compared with other tumor components and was therefore selectively able to disseminate and expand at metastatic sites. Furthermore, during the clinical course, the NET component had increased proliferative activity (as reflected by Ki-67 index and mitotic count), and the resected metastatic lesion ultimately contained foci that required differentiation from small cell carcinoma. In particular, the focal lesion exhibiting a Ki-67 index of 93% may represent a further selected subclone that acquired enhanced proliferative capacity during the metastatic process and/or under therapeutic pressure. These findings suggest the possibility that NEC may arise from preexisting NET and may provide a possible explanation for the phenomenon of grade progression of NET over the course of treatment. At the molecular level, the acquisition of TP53

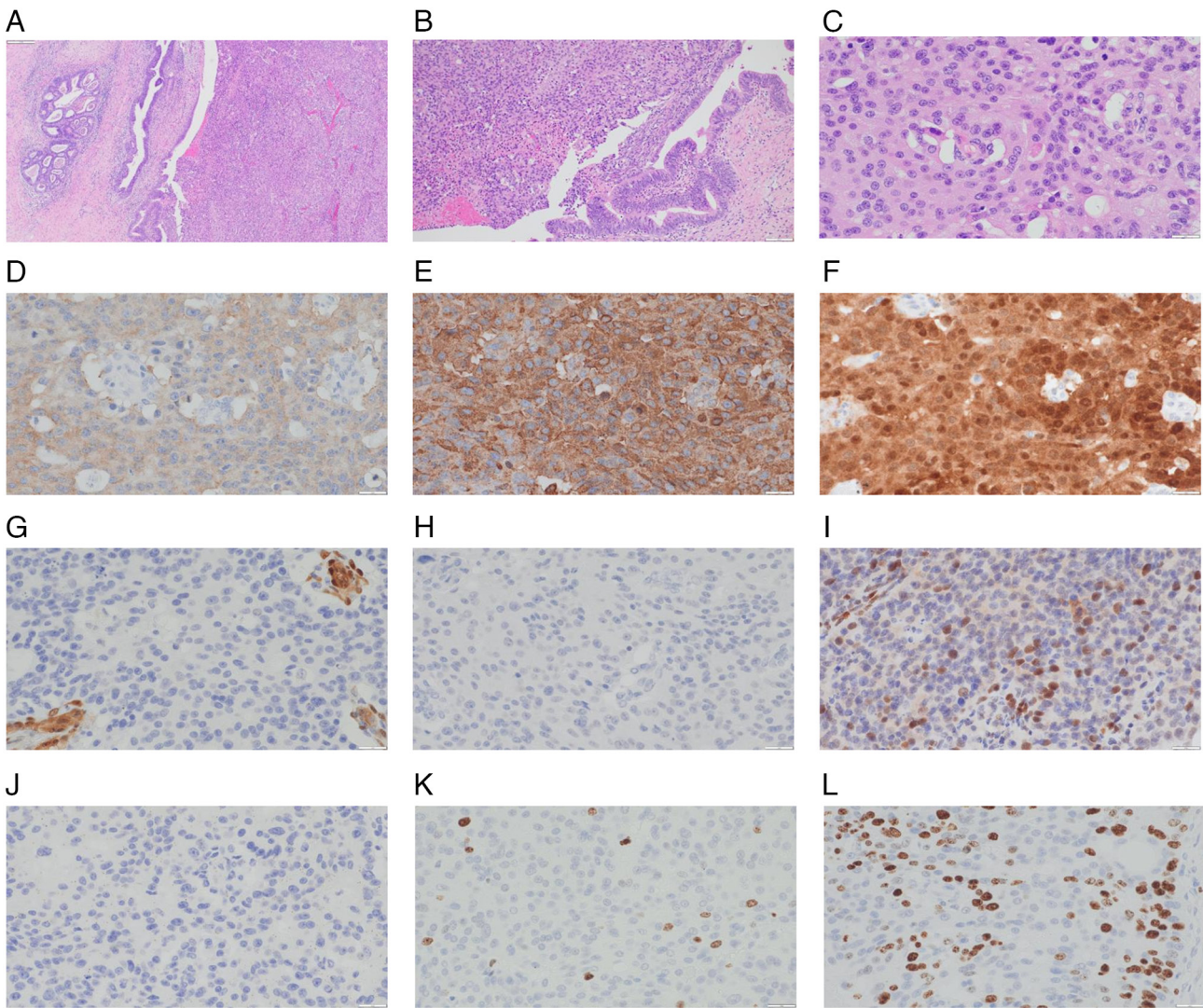


Figure 2. Histopathological and immunohistochemical findings of the cervical tumor. (A) H&E staining (ocular, x10; objective, x4; final magnification, x40) showing mixed histology. (B) H&E staining (ocular, x10; objective, x10; final magnification, x100) revealing coexistence of adenocarcinoma and neuroendocrine components. (C) H&E staining of the neuroendocrine component (ocular, x10; objective, x40; final magnification, x400). (D-L) Immunohistochemical analysis of the neuroendocrine component (ocular, x10; objective, x40; final magnification, x400) revealing the following: (D) Synaptophysin, positive; (E) chromogranin A, positive; (F) p16, positive; (G) yes-associated protein 1, negative; (H) thyroid transcription factor-1, negative; (I) retinoblastoma protein, wild-type expression; (J) paired box 8, negative; (K) Ki-67, low proliferative activity; and (L) Ki-67, hotspot with high proliferative activity.

and RB1 mutations is considered a key event in the progression toward NEC-like morphology, as reported in pancreatic and gastrointestinal NENs (3,7). However, beyond these alterations, there is a lack of large-scale molecular analyses in cervical NENs, and the precise mechanisms driving such transformation need to be further elucidated. Previous reports found that cervical NECs harbor non-silent TP53 and RB1 mutations at a much lower frequency compared to small cell carcinomas of the lung and bladder (8). Consistent with these observations, even the metastatic lesions showing markedly increased proliferative activity and NEC-like morphology demonstrated retained Rb expression and a wild-type p53 immunophenotype. These findings suggest that, at least in a subset of cervical neuroendocrine neoplasms, progression toward NEC-like features may occur through TP53/RB1-independent mechanisms. In the present case, as shown in Fig. 4H, focal TTF-1 positivity was identified in areas exhibiting morphological features suggestive of NEC. This spatial correlation between TTF-1 expression

and NEC-like morphology suggests that the tumor may have acquired a pulmonary neuroendocrine-like phenotype during disease progression, making a nonspecific or artifactual finding less likely. With respect to the pathological distinction between high-grade NET and NEC arising from NET, no single diagnostic parameter is sufficient. Rather, an integrated assessment of multiple pathological features is required, including the degree of cytologic atypia, the presence and pattern of necrosis, and the Ki-67 proliferation index. These features should be interpreted in conjunction with immunohistochemical findings, such as Rb expression status and p53 expression patterns. While the immunophenotype provides important supportive information, it should be regarded as an adjunct rather than an independent determinant of the final diagnosis. It should be noted that a limitation of the present study is that next-generation sequencing (NGS) was not performed on either the primary tumor or the metastatic lesions. As a result, specific acquired genetic alterations that may have driven the increased

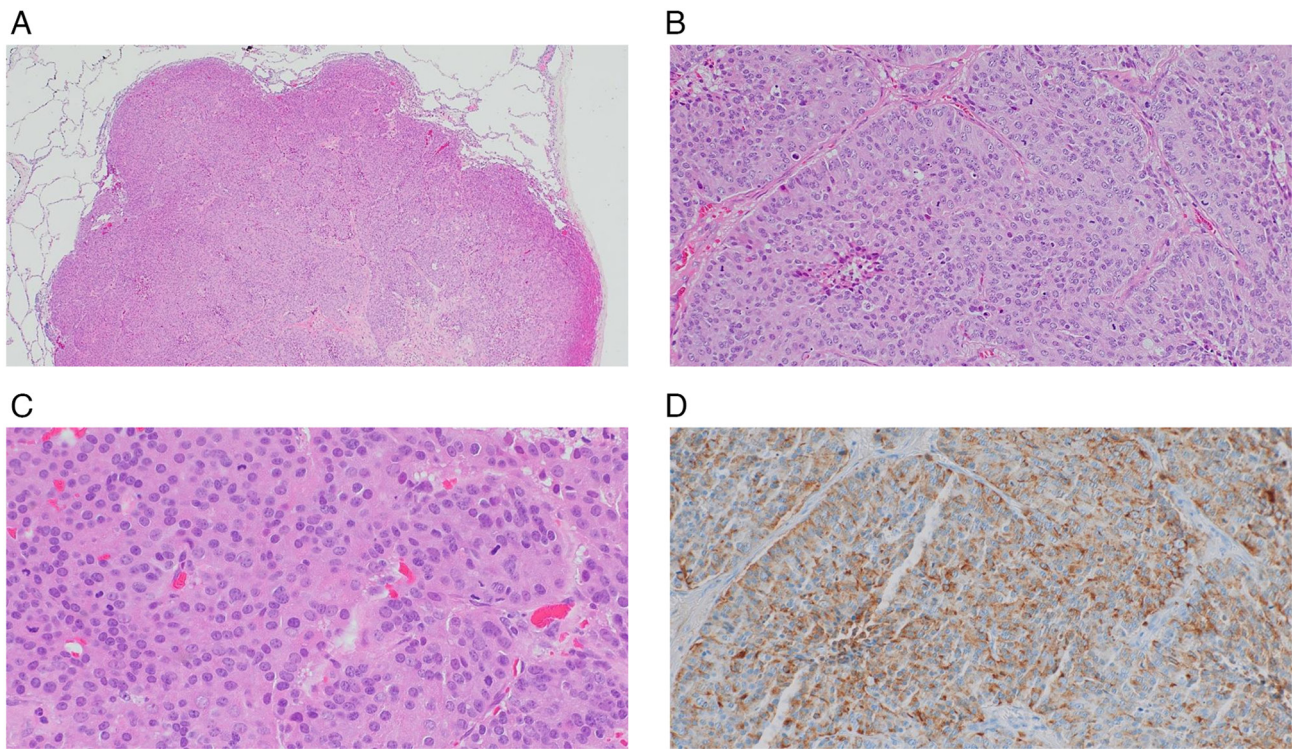


Figure 3. Histopathological and immunohistochemical findings of the right middle lobe lung tumor. (A-C) H&E staining of the resected specimen showing exclusively neuroendocrine tumor components. (A) Ocular, x10; objective, x4; final magnification, x40. (B) Ocular, x10; objective, x10; final magnification, x100. (C) Ocular, x10; objective, x40; final magnification, x400. (D) Chromogranin A immunostaining (ocular, x10; objective, x40; final magnification, x400) demonstrating positive expression in tumor cells.

proliferative activity or the emergence of NEC-like features could not be identified, and any discussion of molecular drivers of transformation in this case remains speculative. Thus, future studies need to clarify the mechanisms underlying the morphological transformation from cervical NET to NEC. In addition, diffuse p16 positivity was observed in both the primary and metastatic lesions, including the NEC-like components, suggesting possible involvement of high-risk HPV infection. Although previous analytical studies have reported an association between cervical neuroendocrine neoplasms and high-risk HPV infection (9), HPV PCR testing was not performed for the individual tumor components in the present case; therefore, a common origin from a single HPV-transformed progenitor cell could not be definitively demonstrated.

Several reports have described metastatic gastrointestinal NETs undergoing grade progression and acquiring NEC-like morphology (2,3). In contrast, cases of primary cervical NET with direct documentation of sequential changes in metastatic lesions (e.g., increased proliferative capacity and morphological transformation toward NEC) are extremely rare. Given that the present report describes a single case, it is difficult to draw robust conclusions regarding the frequency or generalizability of this evolutionary pattern. Nevertheless, careful documentation and reporting of such cases may incrementally contribute to a better collective understanding of the biological behavior of cervical neuroendocrine neoplasms. From a future research perspective, further studies are needed to validate the evolutionary model suggested by this case. In particular, accumulation of additional cases with detailed longitudinal pathological evaluation of both primary and metastatic lesions

will be essential to determine the frequency and reproducibility of grade progression from NET to NEC in cervical neuroendocrine neoplasms. Comprehensive molecular profiling, ideally using next-generation sequencing of paired primary and metastatic samples, may help identify genetic alterations associated with increased proliferative activity and morphological transformation. In addition, prospective collection of fresh or appropriately preserved tumor tissue may enable functional studies, such as patient-derived organoid or other experimental models, to further elucidate tumor evolution and therapeutic vulnerabilities. Although such approaches were beyond the scope of the present case report, they represent important directions for future investigation.

Currently, there is no established standard treatment for cervical NENs, although in cases of NEC, adjuvant chemotherapy with platinum agents and etoposide is often administered alongside surgery and/or radiotherapy (1). In gastroenteropancreatic NET G3, sensitivity to platinum-based chemotherapy with etoposide has been reported to be lower than that observed in NEC (10,11). Based on this consideration, everolimus was selected and initiated in the present case. Everolimus was administered for approximately 6 months for the treatment of pulmonary metastases, during which no new lesions appeared. Considering that the pulmonary metastatic tumors were initially regarded as neuroendocrine tumors, that no new metastatic lesions developed over a six-month period, and that the patient did not wish to undergo intravenous cytotoxic chemotherapy, we considered that reducing the overall tumor burden through local interventions might contribute to prolongation of disease control and potentially improve prognosis. This enabled local surgical

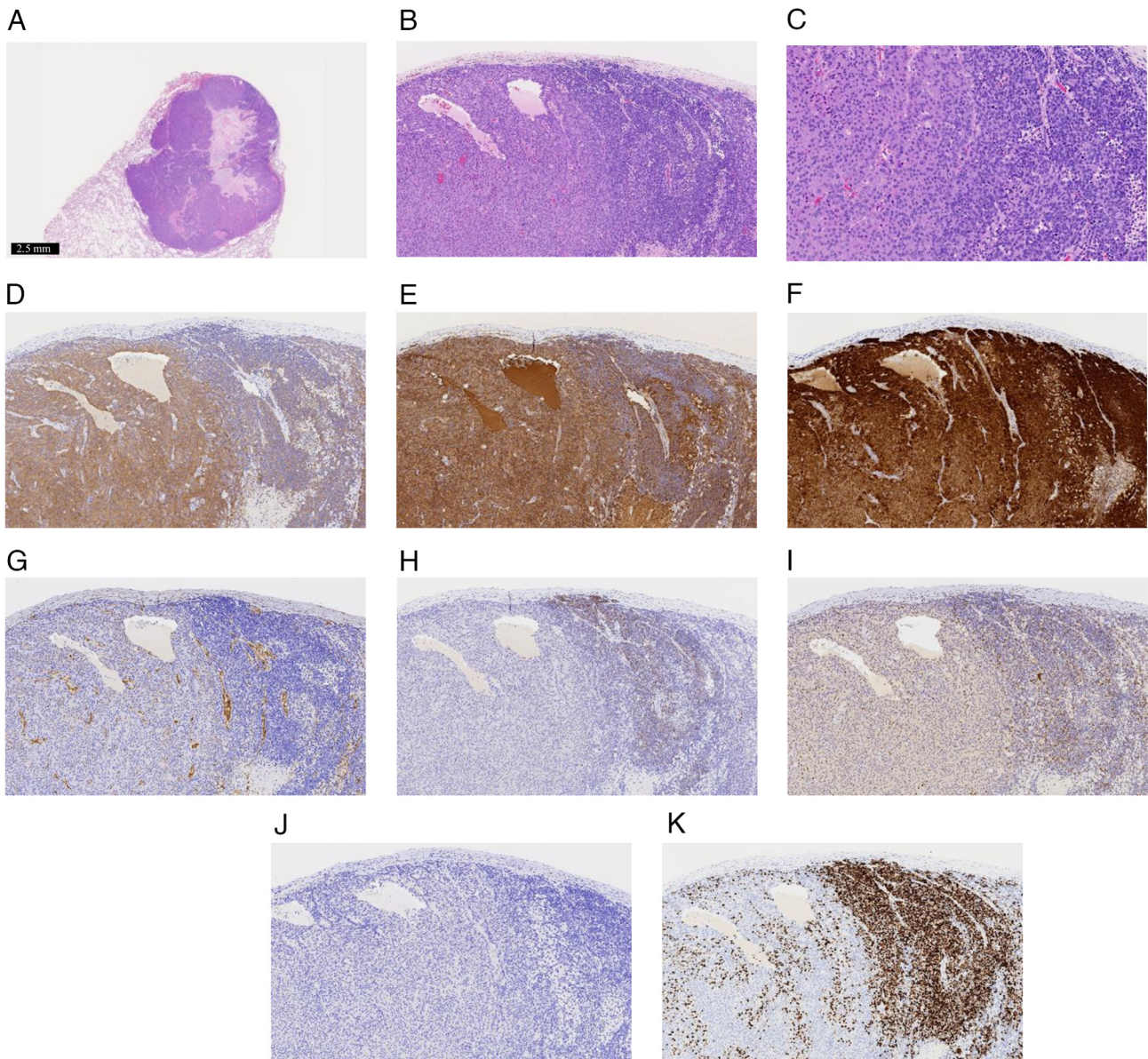


Figure 4. Histopathological and immunohistochemical findings of the left upper lobe lung tumor. (A) Low-power view of H&E staining (scale bar, 2.5 mm). (B) H&E staining (ocular, x10; objective, x10; final magnification, x100). (C) H&E staining (ocular, x10; objective, x20; final magnification, x200). (A-C) The tumor consisted predominantly of NET components but with areas of increased chromatin and a higher nuclear-to-cytoplasmic ratio, suggesting the presence of NEC components. (D-K) Immunohistochemical analysis (ocular, x10; objective, x10; final magnification, x100) revealed the following: (D) Synaptophysin, positive in NET areas but weaker in suspected NEC areas; (E) chromogranin A, positive; (F) p16, positive; (G) yes-associated protein 1, negative; (H) thyroid transcription factor-1, negative in NET areas but focally positive in suspected NEC areas; (I) retinoblastoma protein, wild-type expression; (J) paired box 8, negative; and (K) Ki-67, high proliferative index in suspected NEC areas. NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

resection and histopathological examination, which revealed areas requiring differential diagnosis from small cell carcinoma, strongly suggesting progression from NET to NEC. Marked spatial heterogeneity of the Ki-67 proliferation index may reduce the representativeness of small biopsy specimens and complicate prognostic assessment and evaluation of treatment response. From a prognostic and therapeutic standpoint, when substantial intrapatient heterogeneity is present, it is reasonable to consider that the clinical behavior of the disease is driven by the most aggressive tumor component. Accordingly, particularly when high-Ki-67 areas are associated with aggressive growth patterns or morphological features suggestive of progression toward NEC, treatment decisions should be guided by the highest-grade lesion. In the present case, NEC-like morphology was identified

in the additionally resected pulmonary tumor tissue; therefore, adjuvant chemotherapy was recommended postoperatively. However, as the patient declined further systemic therapy, close clinical follow-up was subsequently adopted.

This case highlights three important clinical implications. First, even in cases diagnosed as NET, tumors with a high Ki-67 proliferation index warrant close follow-up because of the potential for morphological transition toward NEC. In particular, for cervical neuroendocrine tumors with an initial Ki-67 index greater than 20%, closer radiologic surveillance should be considered, even in patients with low-stage disease who have undergone apparently curative resection. The present case suggests that tumors with high proliferative activity may harbor an increased risk of early recurrence or progression that

may not be adequately captured by standard follow-up protocols. Second, the pathological re-evaluation of metastatic lesions is crucial in guiding therapeutic decision-making. When the primary tumor demonstrates mixed histology, the emergence of new lesions during follow-up should prompt histopathological confirmation whenever feasible. In such situations, repeat biopsy is preferable to radiologic surveillance alone, as reassessment of tumor histology and grade may reveal phenotypic evolution with direct implications for treatment selection. Third, given the rarity, biological heterogeneity, and potential for rapid progression of cervical neuroendocrine tumors, multidisciplinary management is essential. We believe that such cases should be routinely discussed in a multidisciplinary tumor board involving gynecologic oncologists, pathologists, radiologists, and medical oncologists with expertise in neuroendocrine neoplasms. A multidisciplinary treatment strategy that integrates systemic therapy and local interventions may help optimize patient management and improve prognosis. Another limitation of this study relates to radiologic assessment. All metastatic lesions were small and did not meet RECIST criteria for measurable target lesions; therefore, radiologic evaluation was qualitative rather than quantitative. In addition, 18F-FDG PET/CT was not performed, precluding assessment of metabolic activity and correlation between SUVmax and pathological features such as the Ki-67 proliferation index or NEC-like morphology. Although such radiologic-pathologic correlations may strengthen the link between imaging phenotype and biological aggressiveness, these data were not available in the present case. Future studies incorporating standardized quantitative imaging and metabolic evaluation are warranted. Taken together, clinical decision-making in gynecologic oncology should consider not only the initial histologic classification but also proliferative activity, histologic heterogeneity, and dynamic changes over time, including the potential progression from NET to NEC-like morphology that has been described in the gastrointestinal field.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NH conceptualized the manuscript. Data acquisition and interpretation were performed by NH, HK, RS, YK, YY, MO, SO, YN, TU, RM, MH, AY and MT. The original draft was written by NH, while the final manuscript was written, reviewed and edited by NH and MT. NH and MT confirm the authenticity of all the raw data. All authors agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. The patient was informed that all identifying information would be removed to ensure anonymity.

Competing interests

MT received honoraria from Chugai Pharmaceutical, AstraZeneca K.K., Bristol-Myers Squibb Company, Novartis Pharma K.K. and Ono Pharmaceutical. The other authors declare that they have no competing interests.

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