Case Report: iMDT Corner

A rare case report of a primary lung cancer comprising adenocarcinoma and atypical carcinoid tumor, with the carcinoid component harboring *EML4-ALK* rearrangement

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Background: The occurrence of pulmonary adenocarcinoma coexisting with atypical carcinoid tumors is a rare phenomenon. The presence of *EML4-ALK* fusion in an atypical carcinoid component of a histologically mixed tumor is even more uncommon. Due to their infrequency, the origin and pathogenesis of these mixed tumors remain largely unknown. The advances of therapy development in such patients are still limited and there is no standard treatment. We present a case of collision tumor in the lung consisting of atypical carcinoid and adenocarcinoma to better understand the clinical characteristics of this disease.

Case Description: We report an extremely rare case of *EML4-ALK* rearrangement in a pulmonary atypical carcinoid tumor that coexisting with adenocarcinoma. A 58-year-old woman, who was asymptomatic, underwent pulmonary lobectomy due to the detection of a gradually enlarging solitary pulmonary nodule in the right upper lung. Histological examination of the resected tumor revealed the presence of both atypical carcinoid (approximately 80%) and adenocarcinoma (approximately 20%) components. Metastases by the carcinoid component were observed in mediastinal lymph nodes (station 2R and 4R) and in the primary tumor. Anaplastic lymphoma kinase (*ALK*) rearrangement was detected in both the primary and metastatic lesions of the carcinoid tumor. Four cycles of chemotherapy with etoposide and carboplatin were dispensed after surgery.

Conclusions: This is the first reported case of coexisting pulmonary adenocarcinoma and atypical carcinoid tumor with an *ALK* fusion only detected in the carcinoid component. The presence of *ALK* rearrangement in pulmonary carcinoid tumor is very uncommon, and there is currently no standard treatment for advanced stages. Therefore, comprehensive molecular testing, including *ALK* rearrangement analysis, should be recommended for mixed tumors exhibiting features of atypical carcinoid. *ALK* inhibitors could represent a potential treatment strategy for selected patients.

Keywords: *ALK* rearrangement; pulmonary adenocarcinoma; pulmonary atypical carcinoid; case report

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Introduction

Combined pulmonary tumors are a unique type of primary lung neoplasm characterized by the simultaneous presence of two or more histologically distinct phenotypes. This usually arises from a common precursor cell differentiating or through phenotypical transformation of one component into the other(s) during their growth (1-3). Primary pulmonary atypical carcinoid is a subtype of lung neuroendocrine tumor and a rare component of combined pulmonary tumors. Atypical carcinoid is characterized by histological features such as 2–10 mitoses per 2 mm^2, with or without necrosis (4). In comparison to typical carcinoids, atypical carcinoids have a higher likelihood of local metastasis or recurrence and are associated with a poorer prognosis. An atypical carcinoid tumor with Ki67 proliferation index >3% is considered aggressive, significantly associated with post-operative recurrence (5).

The pathogenesis and origin of tumors combining carcinoid and adenocarcinoma components remain poorly understood due to their rarity. Anaplastic lymphoma kinase (*ALK*) is a tyrosine kinase receptor that belongs to insulin receptor superfamily, participates in regulating the signaling pathway of cell proliferation and oncogenesis. Echinoderm microtubule associated protein-like 4 (*EML4*) gene is a member of the echinoderm microtubule associated protein-like family. Abnormal fusion of parts of this gene with portions of the anaplastic lymphoma receptor tyrosine kinase gene, which generates *EML4-ALK* fusion transcripts, is one of the primary mutations associated with non-small cell lung cancer (NSCLC). *ALK* gene rearrangement present in approximately 5% of pulmonary adenocarcinomas (6). However, its occurrence in the atypical carcinoid component of histologically mixed tumors has not been previously reported. There is currently no established standard treatment for patients with advanced NSCLC harboring different phenotypes. Nonetheless, identifying actionable lung cancer-related genetic alterations is crucial as it forms the basis for determining targeted therapies and predicting treatment response.

In this study, we present a case of pulmonary atypical carcinoid coexisting with adenocarcinoma. Through fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS), we detected the presence of *EML4-ALK* gene fusion only in the atypical carcinoid component. We discuss the clinical significance of that alteration in this particular type of NSCLC. We present this article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-352/rc).

Highlight box

Key findings

- Hereby, it is presented an unusual case of mixed pulmonary adenocarcinoma and atypical carcinoid tumor with an anaplastic lymphoma kinase (*ALK*) fusion that was only detected in the atypical carcinoid component.

What is known and what is new?

- *ALK* rearrangements in carcinoid tumors are very rare and the coexistence of pulmonary atypical carcinoid tumors with adenocarcinoma also is an unusual malignancy.
- In this case, the *ALK* rearrangement was only detected in the carcinoid component, suggesting a polyclonal origin of this combined tumor, a unique finding that has not been previously reported.

What is the implication, and what should change now?

- Patients with mixed lung cancers and *ALK* rearrangement in only one component are exceedingly rare and currently there is no standard treatment for these patients in advanced stage. Yet, this case raises awareness for the existence of these mixed cancers, for the need of molecular testing of both components, and for the possibility of targeted treatment with ALK inhibitors.

Case presentation

A 58-year-old Chinese female, never-smoker, presented to her primary care physician at the Yushan County Hospital, complaining of a persistent cough. In March 2021, an initial chest computed tomography (CT) scan revealed a round, solid nodule measuring 6 mm in the peripheral region of the right upper lobe (*Figure 1A*). Follow-up chest CT after 6 months was recommended, but the

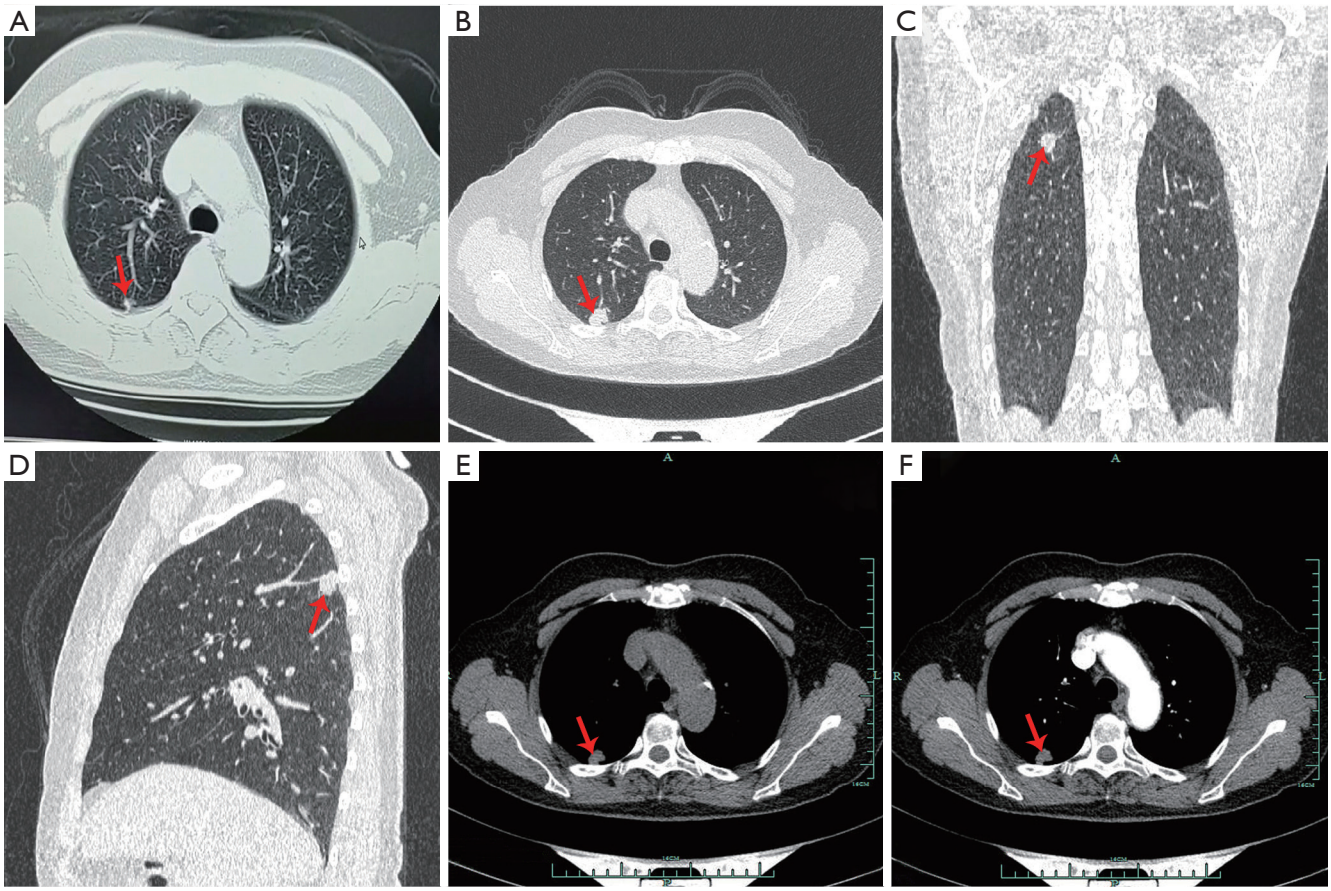

Figure 1 Preoperative chest CT scan images. (A) The CT scan shows a round 6 millimeter solid nodule located in the peripheral region of the right upper lobe (posterior segment); (B) the CT scan shows that the nodule has increased to 14 millimeter after 20 months; (C) coronal view of the nodule; (D) sagittal view of the nodule; (E) mediastinal window reveals the pulmonary nodule; (F) the enhanced CT scan shows mild to moderate enhancement of the nodule, and no enlargement of hilar or mediastinal lymph nodes. The red arrows in the image indicate the primary tumor. CT, computed tomography.

patient refused. Twenty months after the first CT scan, the patient underwent a new CT scan at a local clinic, which revealed significant enlargement of the pulmonary nodule. Subsequently, the patient was referred to Affiliated Hospital of Shaoxing University (The Shaoxing Municipal Hospital) for further evaluation. This patient had no family history of lung cancer.

The results of the physical examination were all in normal ranges. A contrast-enhanced chest CT examination was performed and showed a well-defined solid nodule with dimensions of 14 mm × 11 mm in the posterior segment of the right upper lobe. The average CT value of the nodule was approximately 11.7 Hounsfield Unit (HU). Mild-to-moderate enhancement was observed after contrast administration, and no enlargement of hilar or mediastinal lymph nodes was noted (*Figure 1B-1F*). At this time, the patient's serum tumor markers, cytokeratin 19 fragment (CYFRA21-1) and calcitonin were elevated (CYFRA21-1: 3.10 ng/mL; normal value: 0.00–2.08 ng/mL; calcitonin: 16.69 U/mL; normal value: 0.00–6.40 U/mL). Prior to surgery, the patient underwent additional systematic evaluations, including an abdominal CT scan, brain magnetic resonance imaging (MRI), and whole-body radionuclide bone scans. We performed 3-dimensional (3D) CT bronchography and angiography imaging, reconstructed using Mimics software (Materialise, Leuven, Belgium), to aid in surgical planning (*Figure 2*). Subsequently, the patient underwent a video-assisted thoracic surgery (VATS) right upper lobectomy.

Intraoperative frozen section analysis revealed infiltrating

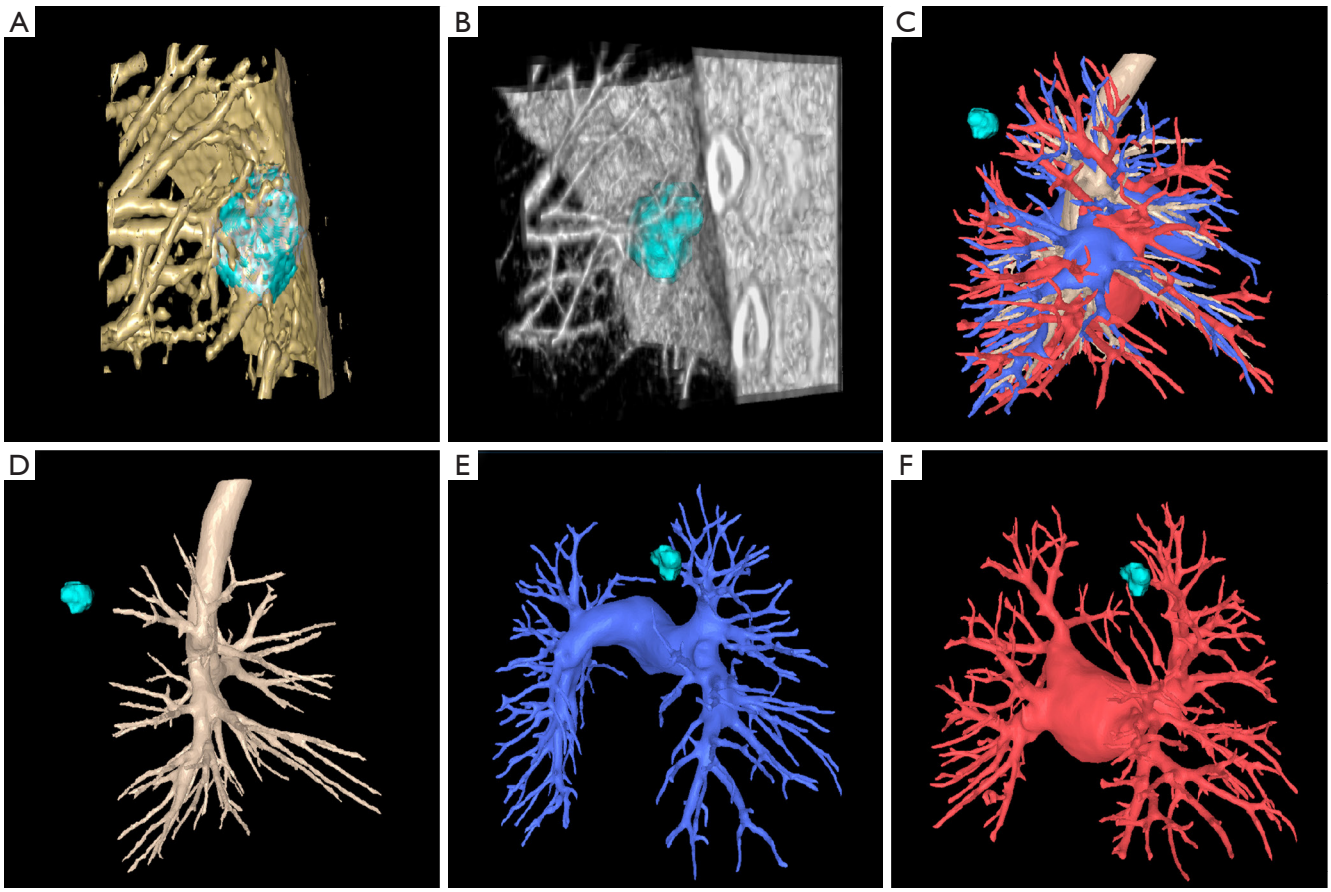

Figure 2 3D reconstruction of pulmonary nodule. (A) 3D reconstruction imaging shows the blood supply of the nodule; (B) maximum intensity projection of the nodule; (C) the reconstructed image shows the location of the nodules; (D) 3D reconstruction imaging shows the location relationship between the nodules and bronchus; (E) 3D reconstruction imaging shows the location relationship between the nodules and pulmonary arteries; (F) 3D reconstruction imaging shows the location relationship between the nodules and pulmonary veins. 3D, 3-dimensional.

carcinoma with a size of 1.41 cm × 1.11 cm. Immediate systematic lymph node dissection from station 2R (n=2), 4R (n=4), 7 (n=4), 9R (n=1), 10R (n=3), 11R (n=2), 12R (n=3), 13R (n=2), and 14R (n=1) was performed. Postoperative pathology results showed a mixed tumor consisting of atypical carcinoid and acinar adenocarcinoma, with approximately 80% of the tumor being composed of carcinoid component (*Figure 3A*,*3B*). The boundary between these tumor components was indistinct (*Figure 3C*). The carcinoid component displayed atypical cells with granular nuclear chromatin, 10 mitoses per 2 mm^2 (*Figure 3D*,*3E*) and foci of necrosis (*Figure 3F*). In addition, invasion of the visceral pleura and lymphatic vessels were identified (*Figure 3G*,*3H*). Metastatic disease was detected in mediastinal lymph nodes of stations 2R (both lymph nodes) and 4R (2 out of 4 lymph nodes) (*Figure 3I*). The final diagnosis was "combined pulmonary atypical carcinoid with adenocarcinoma", with a clinical IIIA stage (pT1bN2M0). Immunohistochemistry staining was positive for napsin A and thyroid transcription factor-1 (TTF-1) in the adenocarcinoma component. Chromogranin A (CgA), synaptophysin (Syn), and CD56 were positive in the primary carcinoid component and the lymph nodal metastases. The staining for p40 was negative in both components. The staining for ALK was positive in atypical carcinoid component and negative in adenocarcinoma component. The Ki-67 index was 10% (*Figures 4*,*5*). Programmed cell death 1 ligand 1 (PD-L1) IHC status showed tumor proportion score (TPS) <1%.

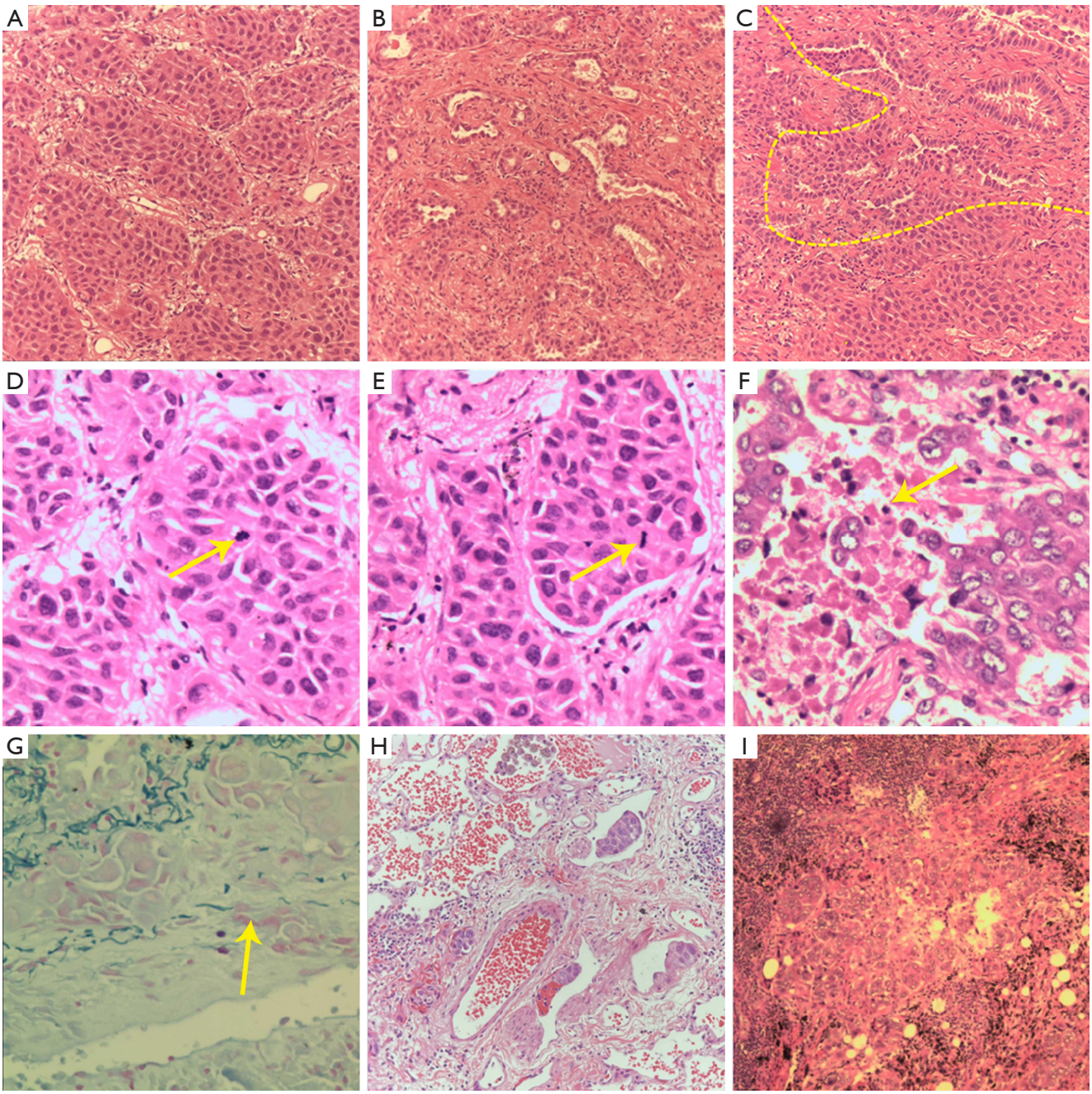

Figure 3 Histopathological image of the surgical specimen. (A) H&E of the atypical carcinoid tumor component, ×10; (B) H&E of the adenocarcinoma component, ×10; (C) H&E reveals indistinct boundary between the tumor components of atypical carcinoid and adenocarcinoma, ×10; (D) H&E reveals mitosis of the carcinoid cell, ×20; (E) H&E reveals mitosis of the carcinoid cell, ×20; (F) H&E reveals the carcinoid component with necrosis, ×20; (G) elastic fiber staining shows elastic fiber breakage, ×10; (H) H&E reveals lymphovascular invasion by the carcinoid component, ×10; (I) H&E reveals metastasis of carcinoid cells in lymph nodes, ×10. The yellow line indicates the boundary between two tumor components. The yellow arrows indicate the mitosis in (D)-(E), the necrosis in (F), the elastic fiber breakage in (G). H&E, hematoxylin and eosin.

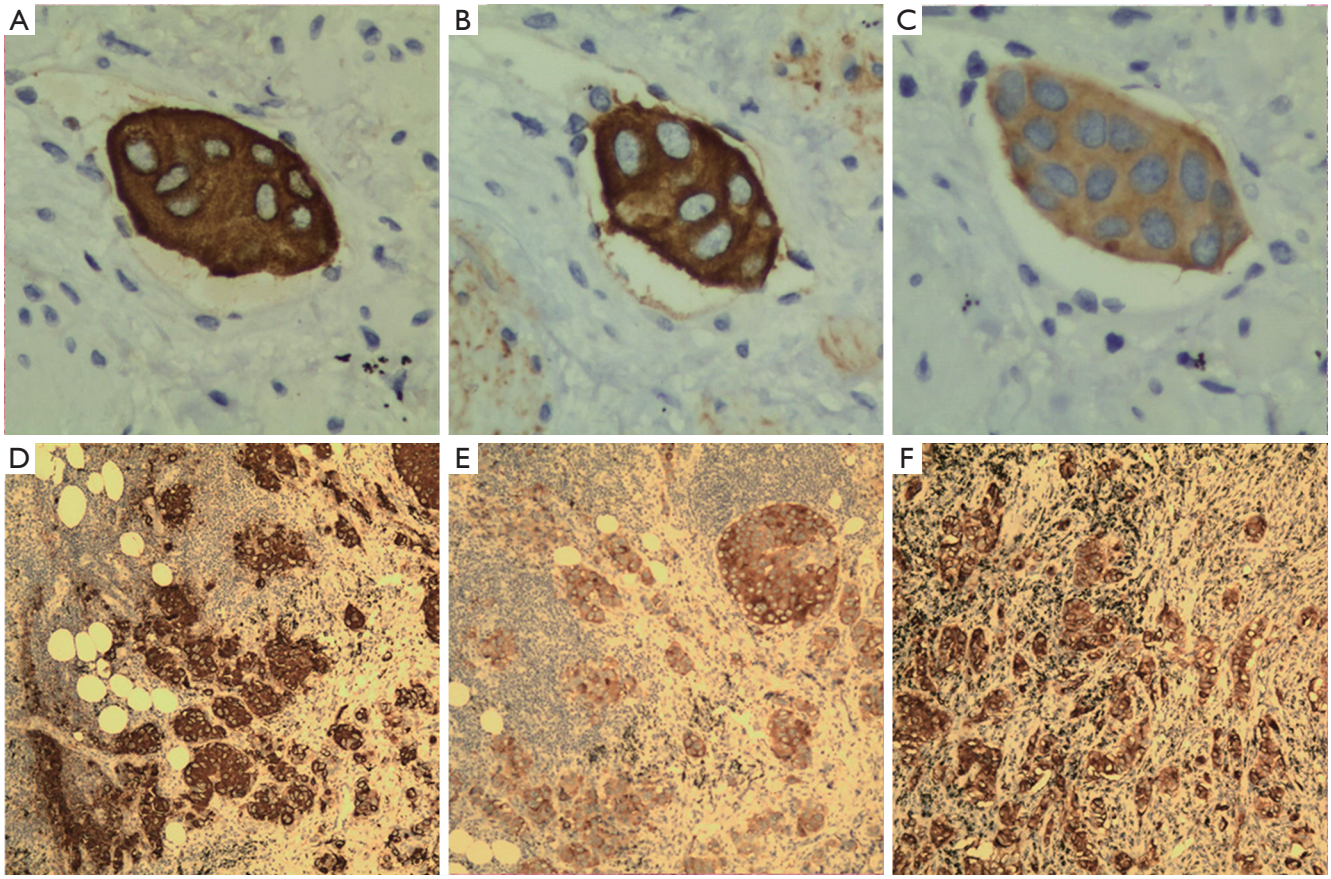

Figure 4 Immunohistochemical staining results of lymphovascular invasion and lymph node metastasis of carcinoid component. (A-C) The lymphovascular invasion of atypical carcinoid component stains positive for CgA (A), Syn (B), and CD56 (C). Magnification ×40. (D-F) The metastasis of carcinoid cells in lymph nodes stains positive for CgA (D), Syn (E), and CD56 (F). Magnification ×10. CgA, chromogranin A; Syn, synaptophysin; CD56, cluster of differentiation 56.

Further analysis using FISH (Vysis LSI ALK Dual Color Break Apart FISH Probes from Abbott) and NGS (Illumina Nextseq 500/550 second-generation sequencing platform) revealed *EML4-ALK* fusion in both the carcinoid component of the primary tumor and metastatic lymph nodes (*Figure 5H*,*5I*, *Figure 6*) with 21% of the cells carrying this rearrangement referred to the FISH analysis.

Four cycles of chemotherapy with etoposide and carboplatin were dispensed after surgery. Due to advanced stage, we recommended second-generation ALK-TKI targeted anti-tumor therapy, but the patient refused. Currently, no tumor recurrence has been observed after 1 year of follow-up.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

International multidisciplinary team (iMDT) discussion

Discussion among physicians from Affiliated Hospital of Shaoxing University

Neuroendocrine neoplasms of the lung are classified into typical carcinoid, atypical carcinoid, carcinoid/neuroendocrine tumors with elevated mitotic counts and/or Ki67 proliferative index, large cell neuroendocrine

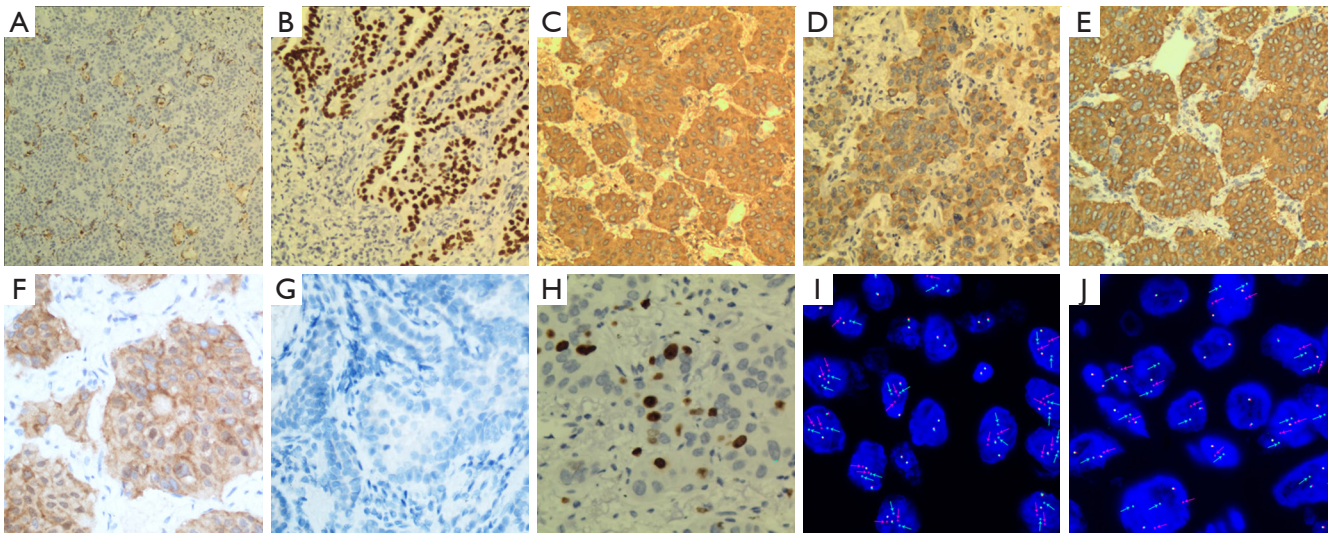

Figure 5 The results of immunohistochemistry and FISH. (A) The adenocarcinoma component stains partially positive for napsin A, ×10; (B) the adenocarcinoma component stains positive for TTF-1, ×10; (C) the atypical carcinoid component stains positive for CgA, ×10; (D) the atypical carcinoid component stains positive for Syn, ×10; (E) the atypical carcinoid component stains positive for CD56, ×10; (F) the atypical carcinoid component stains positive for ALK, ×40; (G) the adenocarcinoma component stains negative for ALK, ×40; (H) the Ki-67 index of the mixed tumor is approximately 10%, ×20; (I) FISH analysis reveals that the atypical carcinoid component from the primary tumour harbors *ALK* gene rearrangement (shown by the arrows), ×100; (J) FISH analysis of the metastatic lymph nodes reveals *ALK* gene rearrangement in tumor cells (shown by the arrows), ×100. FISH, fluorescence in situ hybridization; TTF-1, thyroid transcription factor-1; CgA, chromogranin A; Syn, synaptophysin; CD56, cluster of differentiation 56; *ALK*, anaplastic lymphoma kinase; Napsin A, novel aspartic proteinase A.

carcinoma, and small cell lung carcinoma (4). Atypical carcinoid is an intermediate grade malignancy with 2–10 mitoses/2 mm^2 and with or without focal necrosis (4). The coexistence of pulmonary adenocarcinoma and carcinoid tumors is extremely rare, with the first case reported in 1966 (7). Although most cases of combined tumors occur in patients with a smoking habit, our case involves a non-smoker. Cigarette smoking has become an independent risk factor for the development of synchronous multiple primary lung tumors by leading to cellular atypia and allele-specific imbalance in different areas of bronchial mucosa (7-9). The origin of lung carcinoids and adenocarcinomas differs, as carcinoids arise from pulmonary neuroendocrine cells whereas most adenocarcinomas originate from type II alveolar epithelial cells (10). The pathogenesis of mixed tumors remains unclear, but two theories have been proposed. The first theory suggests multiple clonal origins, where two independent tumor precursor cells coincidentally growing adjacent to each other (this is defined as collision or synchronous tumors) (10). Such pulmonary synchronous tumors expressing adenocarcinoma histology, but different molecular signatures comprising four or more alterations have been reported (11). The second theory, supported by evidence, proposes a monoclonal origin where the different components arise from a common precursor (known as mixed or composite tumors) (12).

It is important to distinguish collision tumors from composite tumors. While both consist of two morphologically and immunohistochemically distinct neoplasms coexisting within the same organ, composite tumors have actual cellular intermingling and common driver alteration(s) that results in divergent histology from a common source (1). A previous case report described a primary lung cancer composed of adenocarcinoma and atypical carcinoid tumor with a shared *BRAF* p.V600E mutation, supporting the monoclonal origin theory (13). However, in the present case study, the *ALK* fusion was only detected in the carcinoid component, and no genomic alterations detected in the adenocarcinoma component, suggesting a polyclonal origin. This discrepancy may be due to the inability to accurately detect the *ALK*-rearrangement

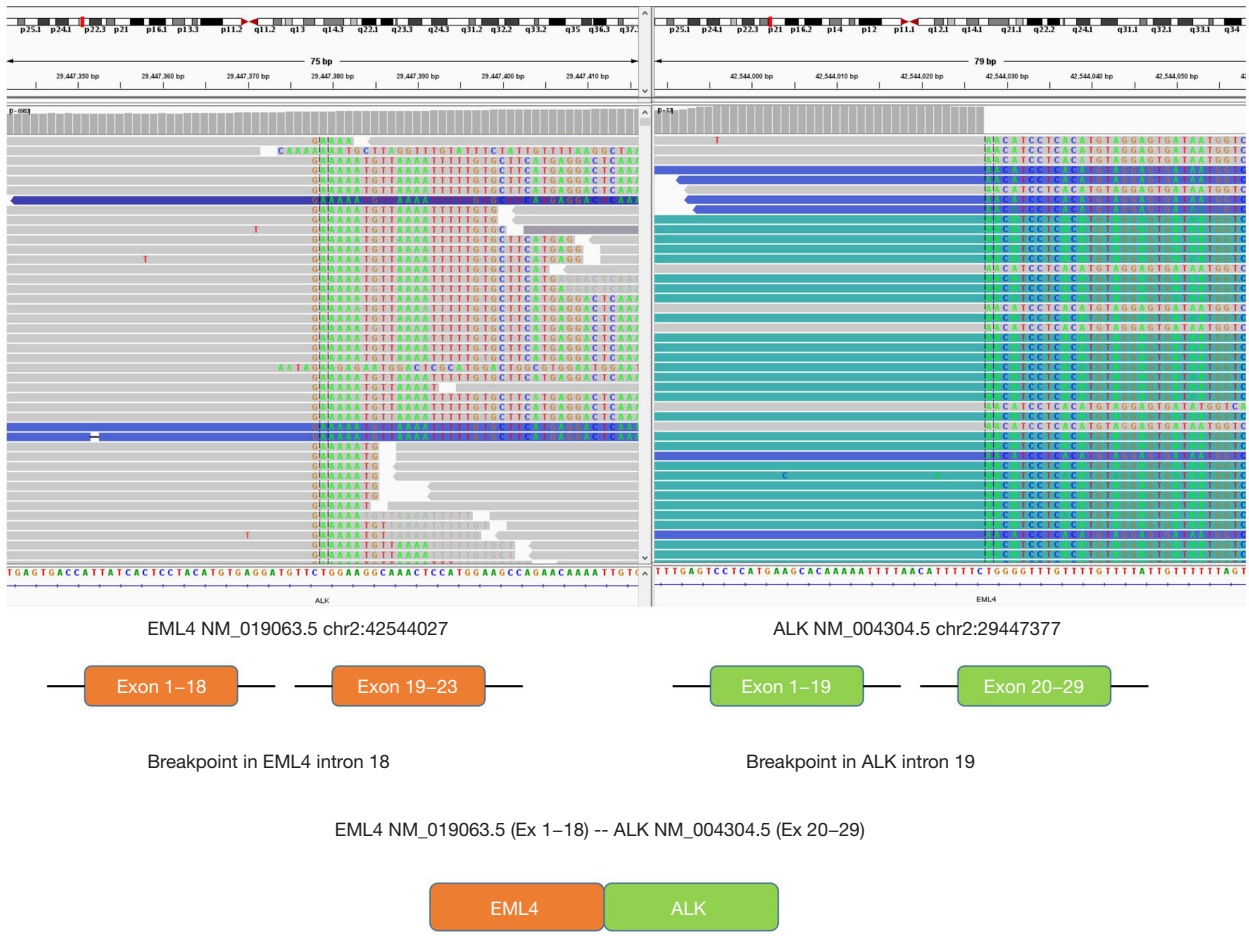

Figure 6 NGS showing the *EML4-ALK* fusion. NGS, next-generation sequencing; EML-4, echinoderm microtubule associated protein like 4; *ALK*, anaplastic lymphoma kinase.

in all adenocarcinomas.

In our case, as mentioned, the boundary between the two components, carcinoid and adenocarcinoma, was indistinct, and therefore we cannot exclude that under progression, the primary adenocarcinoma has transformed into carcinoid phenotype (11).

Diagnosing lung combined tumors before surgical resection is challenging due to the lack of specific imaging features. Accurate diagnosis often requires a complete surgical resection specimen to evaluate the relationship between the different tumor components. In this case, the initial CT imaging showed a small solitary pulmonary nodule, which increased in size during follow-up and was ultimately diagnosed as tumor combining atypical carcinoid and adenocarcinoma after surgical resection. The atypical carcinoids are tumors of intermediate grade of malignancy and histologically diagnosed as composed of neuroendocrine cells displaying 2–10 mitoses per 2 mm^2 with or without necrosis (4,14). The main distinguishing factors between typical and atypical histology are the number of mitoses and the presence or absence of necrosis (3,14,15). Atypical carcinoids are considered more invasive than typical carcinoids, with a higher likelihood of metastasis and worse prognosis. Steuer *et al.* reported that metastatic disease was present in 20% of patients at diagnosis (16). In this case, the presence of the atypical carcinoid component in the mediastinal lymph node metastasis confirms their aggressive nature. The prognosis of combined tumors depends on the behavior and progression of each individual tumor component (17). Targeted therapy has revolutionized the treatment of advanced NSCLC with driver gene alterations. The *EML4* gene is the most frequent *ALK* fusion partner

and *ALK*-rearrangement is detected in 3–7% of pulmonary adenocarcinomas. This subgroup has distinct clinical features: typically younger age at onset, never or mild smokers, males, and often diagnosed at an advanced stage (6,18,19). However, *ALK* fusion in pulmonary atypical carcinoids is extremely rare, and even rarer in mixed tumors (19,20). In this case, the *EML4-ALK* fusion gene was detected by NGS in the carcinoid component, both in the primary tumor and metastatic lymph nodes. This finding has not been previously reported in the literature.

The optimal treatment of patients with primary mixed tumors is not well-defined, and is mainly based on the more aggressive component and whether there are driving gene alterations. Our case provides new and interesting insight into the biology of this unclassified combined entity. Different from previous report, it seems to be more inclined towards polyclonal sources of two components, with clinical and therapeutic implications (13). Therefore, some clinical problems have also emerged, such as the following: Is adjuvant chemotherapy effective? What is the optimal plan for advanced disease? What is the most appropriate treatment method for combined tumors with *ALK* rearrangement? Which generation of *ALK* inhibitors should be considered the first choice? Available information suggests that chemotherapy has no remarkable response for metastatic carcinoid, due to its high resistance to this therapy (20,21). The advances of multimodality therapy development in mixed tumors are still limited and there is no standard treatment, especially for tumors with a dominant carcinoid component. Existing evidence suggests that second-generation ALK-TKI should be the first-line treatment due to its higher systemic and intracranial efficacy in patients with *ALK* rearrangement (19,20,22). There are currently no relevant data reports on the application of immunotherapy in such patients so far. Finally, we look forward to more research bringing good results to improve the prognosis of these patients.

In summary, the coexistence of pulmonary adenocarcinoma and atypical carcinoid tumor components is a rare occurrence. Knowledge of biological basis and optimal treatment approaches for combined tumors is still limited. Challenges remain in terms of adjuvant chemotherapy effectiveness, management of advanced disease, treatment options for combined tumors with *ALK* rearrangement, and the role of immunotherapy. Further research is needed to elucidate the prognosis of patients with these rare tumors.

Several issues regarding the diagnosis and treatment of this patient for further discussion

Is adjuvant chemotherapy effective for pulmonary atypical carcinoid tumor?

Dr. Paul Hofman: Systemic chemotherapy is used for atypical carcinoid tumors, although cytotoxic regimens have demonstrated limited effects with etoposide and platinum combination the most commonly used, however, temozolomide has shown most clinical benefit in certain cases.

Dr. Urbanska & Dr. Santoni-Rugiu: There is currently no data supporting adjuvant chemotherapy for low grade neuroendocrine tumors like carcinoid or atypical carcinoid. However, adjuvant alectinib may be considered for the rare cases of pulmonary atypical carcinoids with *ALK* fusions, as such approach has showed promising activity in adenocarcinomas (23). Though, the efficacy of alectinib in neuroendocrine phenotype may be lower. The acquisition of neuroendocrine phenotype may be one of the reasons for the resistance of ALK inhibitors.

Dr. Petros Christopoulos: The use of adjuvant chemotherapy for pulmonary carcinoid tumors is controversial in the literature guidelines due to the lack of high-quality prospective data. However, most experts as well as the guidelines from ENETS, NANETs, CommNETs and ESMO would consider adjuvant chemotherapy with platinum and etoposide for atypical carcinoid tumors with involvement of mediastinal lymph nodes, such as the case presented in this work (24-26).

Dr. Robert A. Ramirez: The short answer is No. There have been no large studies indicating benefit and several large series indicating detrimental effects. This recommendation was recently adopted by the NCCN guidelines and also has been adopted by NANETS and CommNETs.

Dr. Toyoaki Hida: Atypical carcinoid is relatively resistant to chemotherapy and radiotherapy, and there is no proven optimal therapy for metastatic unresectable carcinoids tumors.

In the case of carcinoid with molecular targets, the corresponding molecularly targeted drugs could also be effective.

What is the most appropriate treatment of method for collision tumors with ALK rearrangement, in particular for those with mediastinal lymph node metastasis?

Dr. Paul Hofman: Probably ALK-tyrosine kinase inhibitors

(such as alectinib) after chemotherapy (or IO-CHEMO according to the TPS of PD-L1?).

Dr. Urbanska & Dr. Santoni-Rugiu: For metastatic disease the targeted therapy with ALK-TKI might be a good option as previously published in several case reports (15,20,21). For stage III large cell neuroendocrine tumor efficacy of alectinib was reported (27). Taking into consideration a significant risk for recurrence in patients with mediastinal lymph nodes involvement and poor response to chemotherapy, targeted therapy with ALK-TKI represents a reasonable option despite the evidence is limited to several case reports. Since carcinoid tumors with *ALK*-rearrangements are extremely rare, phase III studies are hardly expected to be performed in patients with this phenotype.

Dr. Petros Christopoulos: For tumors involving the mediastinal lymph nodes, adjuvant treatment should generally be offered in order to reduce the risk of relapse. For carcinoid tumors, the chemotherapy of choice is platinum-etoposide. In the particular case of an oncogenic *EML-ALK* fusion, additional treatment with alectinib for at least 2 years is expected to further reduce the risk of relapse, based on the results of the ALINA trial (23). Although no adjuvant chemotherapy was used with alectinib in ALINA, adjuvant chemotherapy before adjuvant alectinib would probably convey an independent and additive benefit based on the experience from adjuvant osimertinib in the ADAURA trial, as discussed in the literature (28,29). For the adjuvant therapy of non-carcinoid NSCLC, most experts would prefer vinorelbine as the platinum partner, however etoposide, as used in the case presented here, is also active and thus covers the entire spectrum of collision carcinoid tumors (30).

Dr. Robert A. Ramirez: Given the presence of an ALK rearrangement it is completely reasonable to consider an ALK inhibitor. That said we don't have data on how this would work in a pulmonary carcinoid tumor, however, if we extrapolate from NSCLC it would be beneficial.

Dr. Toyoaki Hida: Surgical resection, and adjuvant ALK inhibitor in stage III lung cancer.

How to accurately distinguish the various components of mixed tumors in pathology and their impact on subsequent treatment?

Dr. Paul Hofman: Ideally microdissection of the different components and made an NGS in each of the selected tissues.

Dr. Urbanska & Dr. Santoni-Rugiu: An accurate distinction of different components in mixed tumors requires a thorough histological, immunohistochemical, and molecular characterization of each component. Particularly in this reported case, in which one component is described as atypical carcinoid, the histological evaluation should clearly show the WHO's histological criteria for such diagnosis *vs.* large cell neuroendocrine carcinoma (LCNEC), which is much more commonly involved in mixed NSCLCs than atypical carcinoid. Thereafter, an immunohistochemical differentiation of the components is necessary, and in a case like the present one can be utilized to better appreciate which components metastasize. Finally, the genomic landscape of the components should be characterized separately and compared. In the present case, this approach would help define the entire therapy-relevant molecular signature of each component, including assessment and subtyping of *ALK*-fusions (variants) and co-alterations. This might contribute to support the classification of the tumor as mixed/combined, to reveal potential druggable targets, and to better predict the response to the targeted treatment.

The impact on subsequent treatment depends on the dominating component, either in terms of percentage of tumor tissue or known biological behavior—clinical aggressiveness. In this case, the presence of *ALK*-rearrangement in the carcinoid component represents the possibility of targeted therapy, but experience with ALK-TKIs in this type of lung tumors is limited to only case reports.

Dr. Petros Christopoulos: In order to accurately distinguish the various components of mixed tumors in pathology, thorough analysis of surgical specimens is necessary. If only small biopsies are analyzed, minor histologic components can be missed, as also underlined in the current WHO classification (12). Besides, for optimal decisions about subsequent treatment, molecular workup of the tumors is also essential and would ideally comprise both quantification of the PD-L1 expression by immunohistochemistry and screening for actionable mutations using DNA/RNA-based NGS, which is more accurate than other methods (31,32).

Dr. Robert A. Ramirez: It takes an expert thoracic pathologist. Another aspect that was not discussed as if the patient underwent a Dotatate positron emission tomography (PET)/CT. This could potentially pick up disease not seen on conventional imaging such as CT or fluorodeoxyglucose (FDG) PET.

Dr. Toyoaki Hida: Comprehensive analyses of various components of mixed tumor are necessary (i.e.,

immunohistochemistry; genetic analysis; whole genome sequencing, if possible). Targeted therapy can be considered if molecular targets are present in the tumor.

Conclusions

The coexistence of pulmonary atypical carcinoid tumor with adenocarcinoma is rare. The presented case suggests a polyclonal origin of the combined tumors, as *ALK* rearrangement was only detected in the atypical carcinoid component. This finding is unique and has not been previously reported. Pulmonary carcinoid with *ALK* rearrangement is also extremely rare, and there is currently no standard treatment for patients with advanced disease. However, based on this case, it is recommendable to perform molecular testing, including *ALK* rearrangement, in mixed tumors with atypical carcinoid and adenocarcinoma components. *ALK*-inhibitors could potentially be an effective treatment strategy for some patients with this rare combination of tumors and *ALK* rearrangement. Further research is needed to better understand the optimal treatment approaches and improve the prognosis for patients with these complex tumor entities.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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