Original paper

Clinicopathological features of anaplastic lymphoma kinase-rearranged lung adenocarcinoma initially misdiagnosed with invasive mucinous adenocarcinoma – a retrospective study

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Anaplastic lymphoma kinase (ALK) rearranged lung adenocarcinoma is frequently characterised by prominent mucin secretion and a heterogeneous population of mucinous cells. These histological features may result in misdiagnosis as invasive mucinous adenocarcinoma.

We conducted a comprehensive analysis of 4 cases of ALK-rearranged lung adenocarcinoma, focusing on the clinicopathological features, genetic mutations, and clinical outcomes. Among these cases, 3 cases were initially diagnosed as invasive mucinous adenocarcinoma, while one case was identified as recurrent invasive mucinous adenocarcinoma. The cohort comprised 3 female and 1 male patient/s, with ages ranging from 47 to 63 years (mean age 54.8 years).

The tumour cells exhibited sieve-like tubular and solid signet ring structures, with evidence of intracytoplasmic and extracellular mucin secretion. Immunohistochemical analysis demonstrated diffuse expression of TTF-1, Napsin A, and ALK(D5F3) in tumour cells, while HNF4a, CK20, and MUC5AC were consistently negative. Next-generation sequencing analysis confirmed ALK rearrangements in 3 cases. Accurate identification of this specific subtype of lung adenocarcinoma is essential for administering appropriate treatment and reducing the risk of potential misdiagnosis.

Key words: anaplastic lymphoma kinase, mucinous, lung adenocarcinoma, immunohistochemistry, next-generation sequencing.

Introduction

Over the past 2 decades, extensive research has demonstrated a significant transition in the predominant pathological type from squamous cell carcinoma to adenocarcinoma. According to the current classification by the World Health Organisation, lung adenocarcinoma is categorised into invasive non-mucinous adenocarcinoma, invasive mucinous adenocarcinoma, colloid adenocarcinoma, foetal adenocarcinoma, and enteric-type adenocarcinoma [1]. As research into the pathogenesis of lung cancer advances, an increasing number of driver genes in non-small cell lung cancer have been identified, providing molecular targets for subsequent targeted therapies [2]. It has been established that the fusion gene formed by the combination of echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (ALK) serves as a driver mutation in lung cancer [3]. Clinical trials have demonstrated that patients harbouring ALK fusion mutations achieve significantly improved therapeutic outcomes and extended survival when treated with the corresponding targeted therapies [4]. Anaplastic lymphoma kinase-rearranged

Table I. List of primary antibodies used in the study

Antibody	Manufacturer	Species	Clone	Dilution
TTF-1	ZSGB-BIO	Mouse	8G7G3/1	Predilute
Napsin A	CELNOVTE	Mouse	C2C2	1 : 1
CK7	ZSGB-BIO	Mouse	UMAB161	1 : 200
P40	CELNOVTE	Mouse	C3B4	Predilute
HNF4a	Gene-Tech	Rabbit	EPR16885	Predilute
CK20	ZSGB-BIO	Rabbit	EP23	1 : 200
P53	ZSGB-BIO	Mouse	D0-7	1 : 500
CDX2	ZSGB-BIO	Rabbit	EP25	1 : 300
MUC5ac	ZSGB-BIO	Rabbit	EP362	1 : 200
ALK(D5F3)	Roche	Rabbit	D5F3	Predilute
EMA	ZSGB-BIO	Mouse	GP1.4	1 : 100
Ki-67	ZSGB-BIO	Mouse	UMAB107	1 : 400
PD-L1	DAKO	Mouse	22C3	1 : 50

lung adenocarcinomas account for approximately 5–6% of all lung adenocarcinomas and are predominantly observed in non-smokers or light smokers and younger individuals [3]. Histologically, ALK-rearranged lung adenocarcinomas exhibit characteristic features such as acinar, papillary, solid signet-ring cell patterns [5]. In certain cases, the presence of abundant mucin production may closely resemble invasive mucinous adenocarcinomas (IMA), thereby presenting significant diagnostic challenges in accurate diagnosis [6].

Primary invasive mucinous adenocarcinoma is categorised as a non-terminal respiratory unit (non-TRU) subtype of adenocarcinoma [7]. It is histologically characterised by the presence of tall columnar tumour cells with basally located nuclei, intracellular mucus accumulation, and the presence of goblet cells [7, 8]. Notably, certain cases of IMA may demonstrate intracellular mucin depletion and moderate to severe cellular atypia, which some researchers have proposed as indicators of advanced malignant transformation [9]. *KRAS* mutations or *NRG1* fusions are frequently observed in IMA, and patient prognosis remains controversial, with no established targeted therapies currently available [7]. Considering that invasive non-mucinous adenocarcinomas harbouring ALK rearrangements may exhibit improved outcomes following treatment with tyrosine kinase inhibitors (TKI), it is crucial to distinguish these tumours from IMA. We reviewed 4 cases initially diagnosed as invasive mucinous adenocarcinoma or mixed mucinous and non-mucinous adenocarcinoma, which were subsequently identified as ALK-rearranged lung adenocarcinomas. The clinicopathological features, immunohistochemistry, and molecular genetic characteristics of these tumours are detailed and analysed in this study.

Material and methods

Patients and specimens

A retrospective review of our pathology database was conducted 2019–2024 to identify cases of lung IMA. Four cases were found to display morphological features distinct from those of classical IMA, exhibiting solid, papillary, and micropapillary architectural patterns. This study was conducted with the approval of an Institutional Review Board (IRB, approval no. ZJHIRB-016K). Each case included representative haematoxylin and eosin-stained glass slides for review, paraffin blocks, or unstained slides available for immunohistochemistry analysis, and 3 cases had paraffin blocks or unstained slides for molecular pathology studies. Patient clinical characteristics were obtained from their electronic medical records. The collected clinical information included age, sex, clinical presentation, lesion size and location, pathological stage, treatment details, and clinical follow-up information.

Immunohistochemistry

Immunohistochemistry was performed for clinical assessment in each case, where additional paraffin-embedded tissue blocks were available, supplementary staining was performed as part of this study. The antibodies utilised in this study are detailed in Table I. Two pathologists independently evaluated the immunohistochemical expression and intensity, reaching a consensus on scoring. A positive label "Positive (+)" was assigned when tumour cells exhibited nuclear, cytoplasmic, and/or membranous expression in at least 10% of the cell population. For programmed death ligand 1 (PD-L1) (22C3), the results were interpreted according to established guide-

Table II. Clinical findings of anaplastic lymphoma kinase-rearranged lung adenocarcinoma.

Case No.	Age (years)	Sex	Smoking	Symptom	Tumour marker assay	Tumour location	Tumour size [mm]	Staging	Treatment	Follow-up
1	47	F	(–)	Asymptomatic	NR	RML	16	pT1bN0Mx	Lobectomy	68m
2	58	M	(+)	Asymptomatic	NR	RLL	9	pT1aN0Mx	Lobectomy	57m
3	63	F	(–)	Asymptomatic	Carcinoembryonic antigen was elevated	LLL	28	rpT1cN1M1	Chemotherapy	14m
4	51	F	(–)	Asymptomatic	NR	LLL	15	pT1bN0Mx	Lobectomy	3m

F – female, LLL – left lower lobe, M – male, NR – normal range, RML – right middle lobe, RLL – right lower lobe

lines, and the tumour proportion score (TPS) was calculated: < 1% was considered negative, 1–49% indicated low expression, and > 50% denoted high expression.

Next-generation sequencing

DNA was extracted from the tumour regions of each unstained formalin-fixed paraffin-embedded section, guided by the corresponding haematoxylin and eosin-stained specimens, and using the DNeasy Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Sequencing libraries were constructed using a KAPA DNA Library kit (Kapa Biosystems, Wilmington, MA, USA). The coding and intronic regions of 18 genes, including *ALK*, *EGFR, MET*, *RET*, *ROS1*, *KRAS*, *NRAS*, *BCL2L11*, *TP53*, *NTRK1*, *NTRK2*, *NTRK3*, *ERBB2*, *BRAF*, *PIK3CA*, *AXL*, *PNET*, and *RB1*, were analysed using next-generation sequencing (NGS) technology. This analysis identified various genetic alterations, such as point mutations, insertion/deletion mutations, gene fusions, and copy number variations.

Results

Clinical findings

Table II summarises the clinical characteristics of our patient cohort. The patients included 3 female and 1 male, with ages ranging 47–63 years (mean age 54.8 years). One male patient had a history of smoking, while all 4 patients reported the absence of respiratory symptoms. Three patients were incidentally identified through routine physical examinations involving chest X-rays or computed tomography (CT) scans. One patient had a history of lung cancer diagnosed 4 years earlier. A follow-up CT examination was conducted due to persistently elevated carcinoembryonic antigen levels, revealing the presence of a new lesion. Three patients underwent lobectomy, and the patient with a history of lung cancer was confirmed through bronchial biopsy. The tumours ranged 9–28 cm in maximum diameter (mean diameter: 17 cm), presenting as irregular solid nodules. Specifically, one lesion was located in the right lower lobe, one in the right middle lobe, and 2 in the left lower lobe (Figure 1). According to pathological staging, 2 patients were classified as stage pT1b, 1 as stage pT1a, and 1 as stage pT1c. One patient received chemotherapy, while 3 patients underwent tumour resection alone, with no regional lymph node metastasis observed during surgery. Four patients underwent clinical follow-up, and no complications or disease progression were observed during the follow-up period, which ranged 3–68 months (median 35.5 months) post-diagnosis.

Histopathologic features

Macroscopically, the tumours were unencapsulated and exhibited invasive growth, with a greyish-white cut surface and no definite areas of necrosis. The tumours in the 3 surgical specimens demonstrated consistent pathological features, including acinar, cribriform, papillary, and micropapillary structures, along with extensive mucinous exudation within the alveolar cavities. The tumour cells display a glandular growth pattern characterised by tall columnar morphology, intracytoplasmic mucin accumulation, and mild cytological swelling, with nuclei positioned basally (Figure 2A). In certain regions, the tumour cells exhibit complex sieve-like and solid lamellar structures, featuring abundant eosinophilic cytoplasm, moderate cytological atypia, and prominent nucleoli (Figs. 2B, C). Locally within the tumour, numerous micropapillary cell clusters were observed in the alveolar spaces, floating in mucin pools (Figure. 2D). In focal areas of the tumour, irregular glandular cavities and papillary structures of non-mucinous adenocarcinoma were identified, with no evident mucous secretion (Figure 2E). Notably, the tumours demonstrated localised solid signet-ring cell masses without evidence of neoplastic necrosis in 4 cases. Bronchoscopic biopsy contained a relatively limited number of tumour cells, and it revealed solid tumour cells exhibiting signet ring morphology (Figure 2F) and minimal mucin exudation.

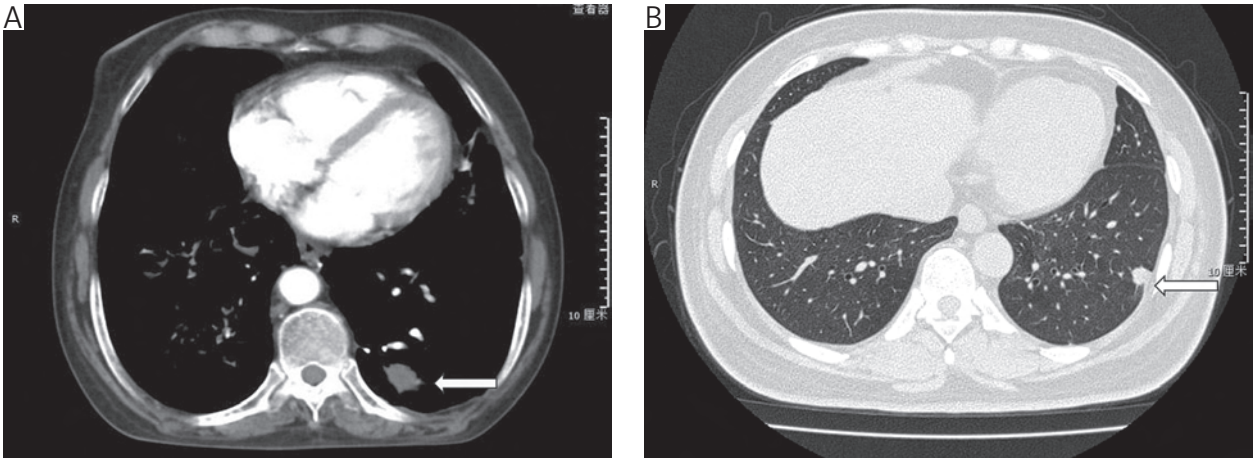

Figure 1. Computed tomography scan of anaplastic lymphoma kinase-rearranged lung adenocarcinoma. **A**) Computed tomography imaging revealed bronchiectasis with cystic dilatation in both lungs, with a nodular appearance observed in the lower lobe of the left lung, characterised by irregular margins (case 3). **B**) The nodule measuring approximately 11 mm in diameter is observed in the left lower lobe of the lung, characterised by relatively dense composition and well-defined margins (case 4)

Immunohistochemical findings

The immunohistochemical staining results are summarised in Table III. All tumour samples exhibited strong positivity for TTF-1, Napsin A, ALK(D5F3) (Figs. 3A–C), and CK7. EMA demonstrated a positive lateral margin in micropapillae characterised by polarity inversion (Figure 3D). In contrast, P40, HNF4a (Figure 3E), CK20, CDX2, and MUC5AC were consistently negative. The expression pattern of P53 was consistent with a wild-type profile, albeit with variable intensity (Figure 3F). Additionally, 4 cases were evaluated for PD-L1 expression; 3 patients exhibited a TPS of less than 1%, indicating negativity, while 1 patient had a TPS of approximately 20%. MIB-1 staining revealed a notable increase in proliferative activity, with nuclear positivity ranging 5–40% (mean 21.25%).

Next-generation sequencing

Next-generation sequencing analysis identified *ALK* gene rearrangements in 3 patients. Specifically, one case exhibited a PKDCC-ALK fusion (intergenic: 20), another case showed an unknown partner fused with ALK, and the third case demonstrated an EMAL4-ALK fusion (E6:A20) accompanied by MET amplification. Genetic testing was not feasible on bronchial biopsy samples due to an insufficient number of tumour cells. Notably, no mutations were detected in *EGFR*, *ROS1*, *RET*, *BRAF*, *KRAS*, *ERBB2*, or *TP53* mutations in any of the patients.

Discussion

Invasive mucinous adenocarcinoma of the lung may originate from the transformation of type II alveolar epithelial cells or Clara cells into bronchial ciliated columnar cells, which subsequently transform into mucinous columnar cells and ultimately develop atypical and malignant changes [10]. The incidence of IMA is relatively low, comprising approximately 5% of all lung adenocarcinomas. It predominantly occurs in non-smoking females and is typically located in the lower lobe of the lung [11]. Histologically, IMA can exhibit acinar, papillary, and micropapillary growth patterns, similar to non-mucinous adenocarcinoma [8]. The diagnosis of mixed invasive mucinous and non-mucinous adenocarcinoma should be considered if non-mucinous adenocarcinoma components constitute 10% or more of the tumour. Immunohistochemical analysis reveals that lung IMA expresses HNF4a and MUC5AC. In contrast, the expression levels of TTF-1 and Napsin A are markedly lower compared to non-mucinous adenocarcinoma, providing support for the hypothesis that IMA does not originate from TRU [12, 13]. *KRAS* is the most common driver mutation in IMA, rarely accompanied by *EGFR* or *TP53* mutations. *NRG1* fusion is identified in approximately 7–27% of cases, with fusion partners including *CD74*, *SLC3A2*, and *VAMP2* [14].

The differential diagnosis of lung IMA includes metastatic mucinous adenocarcinomas originating from the digestive tract, breast, and ovary, which requires comprehensive evaluation integrating clinical history and imaging examination. Mutations in the *NKX2-1* gene are predominantly observed in primary lung IMA [15] and can serve as a valuable marker to differentiate it from metastatic mucinous adenocarcinoma. Additionally, it is important to differentiate colloid adenocarcinoma, which is histologically characterised by the presence of large amounts of mucus forming mucinous pools that replace alveolar structures, with clusters of mucin-producing tumour cells floating within these pools. According to Philipp,

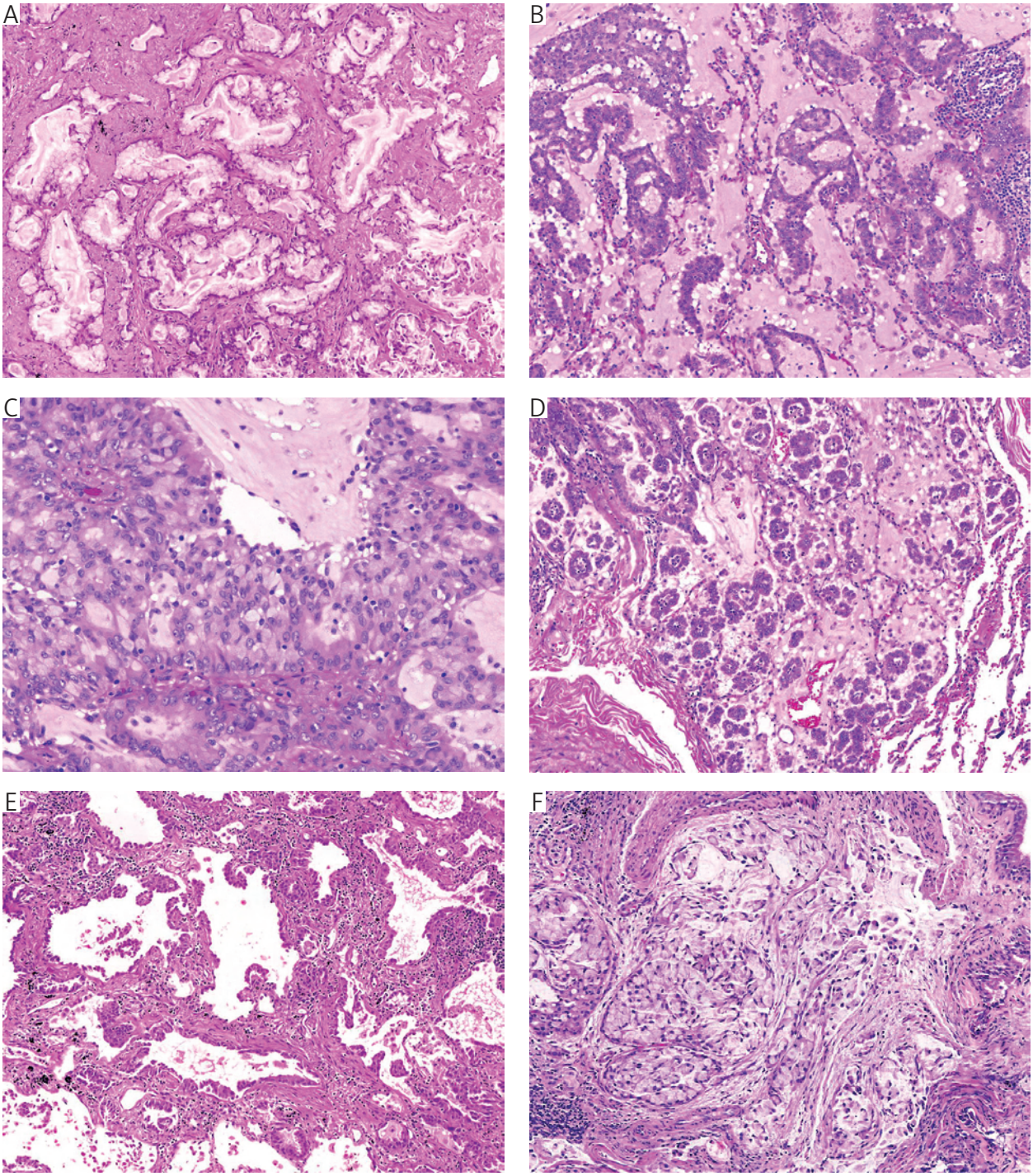

Figure 2. The histologic findings of anaplastic lymphoma kinase-rearranged lung adenocarcinoma. **A**) The tumour cells exhibited acinar. **B**) Ethmoid and solid architectures. **C**) Ethmoid and solid architectures with mild to moderate atypia, along with abundant intracytoplasmic and extracellular mucin. **D**) Distinct micropapillary structures were observed, floating within the alveolar spaces. **E**) In certain regions, the morphology was characteristic of non-mucinous adenocarcinoma, with focal papillary formations. **F**) Notably, the tumour cells formed solid lamellar and signet ring configurations

MYC gene amplification has be detectable in colloid adenocarcinoma, but it has not been observed in IMA [16]. Additionally, ALK-rearranged lung adenocarcinoma, characterised by abundant extracellular and intracellular mucin, is another type of tumour that must be differentiated from invasive mucinous adenocarcinoma [17]. Patients with ALK-rearranged lung adenocarcinoma tend to present at a younger age, are more prevalent among Asian male non-smokers, and often present at an advanced clinical stage [18].

In our case series, one biopsy specimen exhibited predominantly signet-ring cell morphology. Given

Table III. Immunohistochemical results of anaplastic lymphoma kinase-rearranged lung adenocarcinoma

Case no.	TTF-1	Napsin A	CK7	P40	HNF4a	CK20	CDX2	P53	MUC5AC	EMA	ALK	MIB-1 (%)	PD-L1 (%)
1	+	+	+	–	–	–	–	WT	–	+	+	40	< 1
2	+	+	+	–	–	–	–	WT	–	+	+	20	< 1
3	+	+	+	–	–	–	ND	WT	ND	ND	+	5	< 1
4	+	+	+	–	–	–	–	WT	–	+	+	20	20

+ indicates positive
– indicates negative
ND – not done, WT – wild type

that the patient had undergone the left lower lobectomy at another institution 4 years prior, with a postoperative pathological diagnosis of IMA, we have preliminarily diagnosed it as a recurrence of IMA. Subsequent immunohistochemical analysis demonstrated that the tumour cells exhibited diffuse and strong positivity for ALK (D5F3), as well as positivity for TTF-1. Based on these findings, it is hypothesised that the prior surgical specimen may have represented ALK-rearranged lung adenocarcinoma with prominent mucin production. Regrettably, no archival tissue samples from the prior surgery were available for further confirmation. The other 3 surgical specimens displayed cribriform and tubular papillary structures, with minimal cellular pleomorphism but abundant extracellular mucus, mimicking IMA. These specimens also contained solid signet-ring cells, further complicating differential diagnosis from IMA. However, given the diffuse positive staining for TTF-1 and Napsin A, with the strong positive expression of ALK (D5F3), the findings are more consistent with the diagnosis of non-mucinous adenocarcinoma harbouring ALK rearrangement. Subsequent NGS testing confirmed ALK rearrangement in 3 cases, validating the consistency between ALK (D5F3) antibody detection and NGS results.

Yoon *et al*. conducted a comprehensive histological comparison between ALK-rearranged adenocarcinoma and KRAS-mutated mucinous adenocarcinoma, highlighting that ALK-rearranged adenocarcinoma exhibits characteristic tubular-papillary structures and apical rosettes [17]. Our cases also presented similar cytomorphological features, supporting the importance of detailed histological examination for differential diagnosis. Additionally, our study revealed that differences in immunohistochemical expression patterns could further distinguish these 2 types of tumours. Specifically, TTF-1 was expressed in all 4 tumour samples, while HNF4a and MUC5AC were not detected. Masato *et al*. further confirmed that ALK-rearranged lung adenocarcinoma may exhibit IMA morphology and is often associated with the absence of HNF4 expression [12]. The literature review revealed reports of invasive mucinous adenocarcinoma with rare ALK rearrangements, frequently characterised by strong positive TTF-1 expression in tumour cells [19]. We speculate that this might be due to confusion between IMA and invasive non-mucinous adenocarcinoma in ALK-rearranged cases. Yoshida *et al*. reported co-expression of TTF-1 and P63 in tumour cells of ALK-rearranged lung adenocarcinoma with signet-ring cell components [20]. In our study, none of the 4 cases demonstrated positive expression for P63, which may be attributable to the limited sample size.

Immunohistochemistry consistently shows expression of TTF-1 and Napsin A in ALK-rearranged cases. Several researchers have also documented one case where immunocytochemical staining was negative for TTF-1 but positive for Napsin A expression, which may be influenced by cytological specimens [21, 22]. Interestingly, Jokoji *et al*. reported that 7 cases of lung IMA were examined and found to be negative for ALK expression [23]. Previous studies reported 31 lung adenocarcinomas with ALK fusion were identified, showing negative HNF4a expression, but 3 cases were reclassified as IMA, leading to some controversy in the literature [12]. Anaplastic lymphoma kinase-rearranged lung adenocarcinomas are typically *EGFR* and *KRAS* wild-type, with TP53 mutations being the most common co-mutation [24]. Anaplastic lymphoma kinase rearrangement has been reported in only 1% of cases with *EGFR* mutations and 0.6% of cases with *KRAS* mutations [25].

In recent years, the continuous optimisation of ALK inhibitors and the introduction of novel therapeutic agents have enhanced treatment options and improved patient outcomes. Studies have demonstrated that patients with high expression levels of PD-L1 (> 50%) who receive first-line TKI treatment exhibit poorer progression-free survival [26]. However, this high expression is not significantly correlated with overall survival, thereby providing an additional predictor for the efficacy of TKI therapy. In our study, the PD-L1 test results were negative in 3 cases, while the TPS score for one case was approximately 20%. Most IMA patients lack effective targeted treatment options, advanced-stage patients

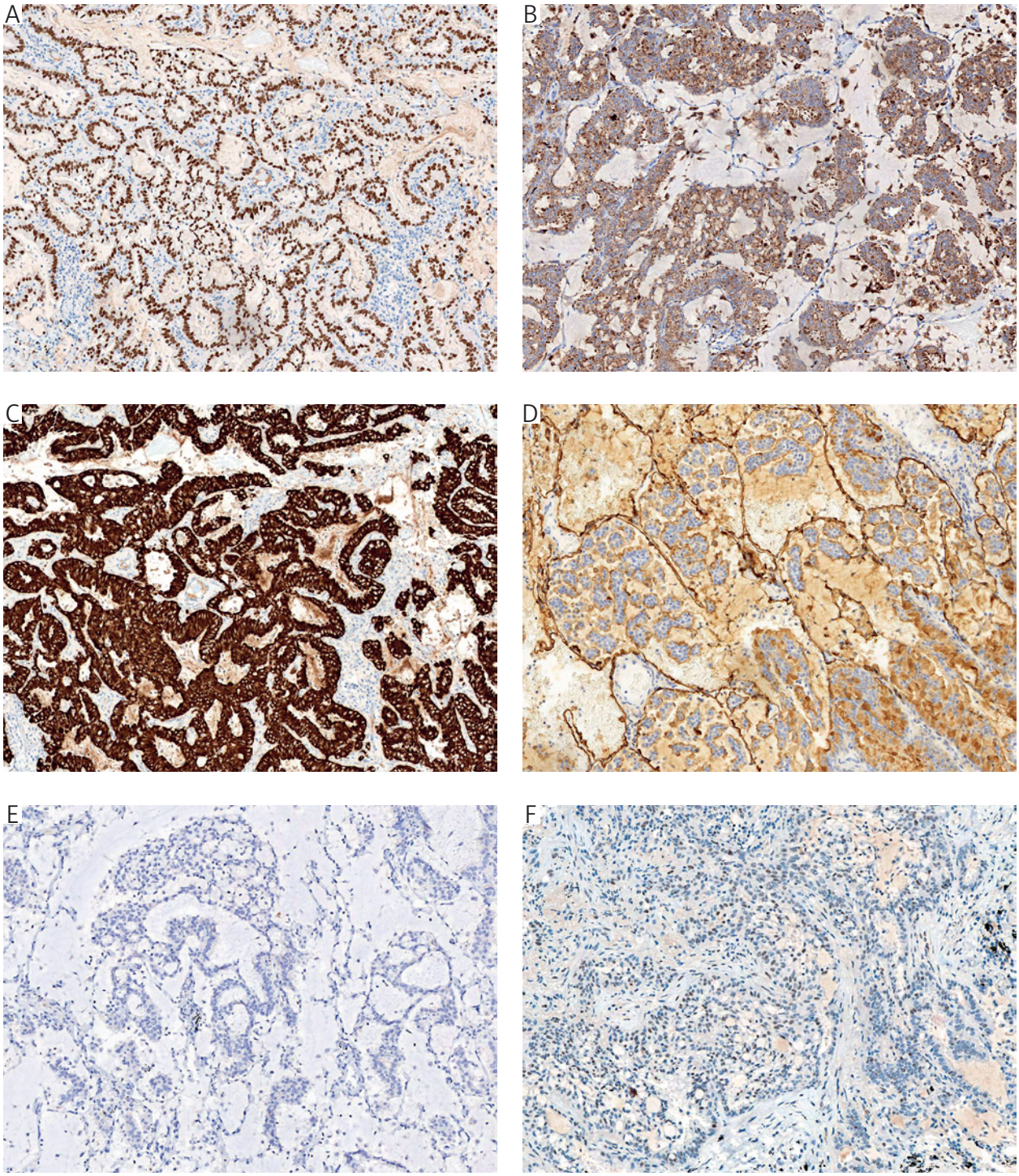

Figure 3. Representative immunohistochemistry findings of anaplastic lymphoma kinase (ALK) rearranged lung adenocarcinoma. **A, B, C**) TTF-1, Napsin A, and ALK (D5F3) exhibited strong and uniform positivity in the tumour cells. **D**) The micropapillary cells demonstrated positive expression of EMA. **E**) HNF4a was entirely negative. F) P53 displayed a wild-type expression pattern

typically receive conventional platinum-based chemotherapy. However, studies have indicated that this approach does not significantly improve overall survival. Additionally, the expression rate of PD-L1 in IMA is approximately 6%, suggesting that further investigation into the efficacy of immunotherapy is warranted [27].

Conclusions

Anaplastic lymphoma kinase-rearranged lung adenocarcinoma exhibits notable morphological similarities to lung invasive mucinous adenocarcinoma. However, significant differences are observed in immunohistochemical expression, with ALK-rearranged ad-

enocarcinomas predominantly demonstrating positive expression of TTF-1, Napsin A, and ALK(D5F3), while lacking expression of HNF4a and MUC5AC. These 2 tumour types exhibit distinct differences in their tissue origins and genetic alterations, which have critical implications for definitive pathological diagnosis, clinical management strategies, and patient outcomes.

Disclosures

1. The study received approval from the Zhejiang Hospital Ethical Review Committee (Approval number: ZJHIRB-016K).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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