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Analysis of clinical and pathological characteristics of 10 cases of fetal lung adenocarcinoma

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Background: Fetal adenocarcinoma of the lung (FLAC) is a rare subtype of lung adenocarcinoma resembling the developing fetal lung at the pseudoglandular stage (8–16 weeks of gestation). This study investigates the clinicopathological features, along with key diagnostic and treatment considerations for FLAC.
Methods: Clinical data from 10 FLAC patients diagnosed at Linyi People's Hospital between January 2017 and December 2024 were retrospectively analyzed. Their clinicopathological characteristics were summarized in conjunction with relevant literature.
Results: The cohort comprised low-grade FLAC (L-FLAC, 6 cases) and high-grade FLAC (H-FLAC, 4 cases). Pathological examinations indicated higher frequencies of pleural invasion (3/4) and lymph node metastasis (1/4) in H-FLAC, which exhibited marked nuclear atypia and abundant mitoses, while L-FLAC demonstrated mild cellular atypia and morular structures. Immunohistochemistry revealed universal positivity for TTF-1. Napsin A expression was noted in both L-FLAC (3/3) and H-FLAC (2/4). In L-FLAC, β-catenin showed nuclear/cytoplasmic or nuclear expression in the vast majority of cases while H-FLAC displayed only membranous expression. Molecular testing detected an EGFR exon 19 deletion in one H-FLAC case and a KRAS G12C mutation in another. No recurrence was observed during follow-up, which ranged from 4 to 93 months.
Conclusion: FLAC exhibits distinctive morphological features and immunophenotypes, necessitating differential diagnosis from primary pulmonary tumors and metastatic malignancies. Surgical resection remains the primary therapeutic strategy. No disease recurrence was observed during follow-up from 4 to 93 months, although some patients had a shorter follow-up period of 4–6 months.

KEYWORDS
clinicopathological features, fetal adenocarcinoma, immunohistochemistry, lung, molecular genetics

Introduction

The fetal adenocarcinoma of the lung (FLAC), a rare subtype of pulmonary adenocarcinoma, was initially recognized by Kradin in 1982. The lesion earns its denomination due to morphologic resemblance to fetal lung during development [1]. It was later classified as a variant of invasive adenocarcinoma in the updated international

multidisciplinary classification established in 2011 by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS). This classification formally subdivided FLAC into two subtypes: low-grade fetal adenocarcinoma (L-FLAC) and high-grade fetal adenocarcinoma (H-FLAC) [2]. The 2015 World Health Organization (WHO) classification of lung tumors recognizes FLAC as an independent subtype of lung adenocarcinoma [3].

As a rare disease, the epidemiology of FLAC remains poorly understood. According to both domestic and international data, FLAC accounts for approximately 0.1%–0.5% of all lung tumors [4, 5]. Due to its rarity and the limited clinical recognition of this entity, the risk of clinical misdiagnosis is notably high.

This study systematically analyzed 10 cases of pulmonary fetal adenocarcinoma, summarizing their clinicopathological features along with key diagnostic and differential diagnostic considerations. This study aims to enhance clinicians' understanding of this disease and reduce the likelihood of clinical misdiagnosis.

Methods

Study population/participants

Clinicopathological data of patients diagnosed with lung adenocarcinoma at Linyi People's Hospital between 2017 and 2024 were collected. Based on the 2011 International Multidisciplinary Classification of Lung Adenocarcinoma established by the IASLC/ATS/ERS and the 2021 WHO Classification of Thoracic Tumors [2, 6], 10 patients diagnosed with FLAC who met the inclusion criteria were selected. All 10 FLAC cases underwent review and confirmation by two associate chief physicians or specialists with higher professional titles. Clinical data, including age, gender, symptoms, and physical signs, as well as imaging data (chest X-ray, chest CT, etc.), were collected concurrently for all confirmed FLAC patients. The study protocol received approval from the Ethics Committee of Linyi People's Hospital (Approval No.:202503-H-012), and informed consent was waived for all enrolled patients.

Morphological assessment

Surgical specimens were fixed in 10% neutral buffered formalin, routinely embedded in paraffin, and sectioned at a thickness of 4 μm. Specimens underwent staining with hematoxylin and eosin (HE). Diagnoses of L-FLAC and H-FLAC were established according to the essential and desirable diagnostic criteria outlined in the WHO classification of thoracic tumors. Essential criteria include an adenocarcinoma mimicking the pseudoglandular stage fetal lung airway epithelium; L-FLAC exhibits mild nuclear atypia and aberrant nuclear or cytoplasmic β-catenin expression, while H-FLAC displays severe nuclear atypia and often coexists with other adenocarcinoma patterns, with the high-grade component constituting over 50% of the tumor. Desirable criteria involve TTF-1 expression in L-FLAC and predominantly membranous β-catenin staining in H-FLAC [6].

Immunohistochemical evaluation

Immunohistochemical staining utilized the EnVision two-step method for various markers: Thyroid transcription factor-1 (TTF-1, Clone 8G7G3/1, ZSGB-Bio, Beijing, China), Beta-catenin (β-catenin, Clone UMAB15, ZSGB-Bio, Beijing, China), Sal-Like Protein 4 (SALL4, Clone 6E3, ZSGB-Bio, Beijing, China), Glypican-3 (Glypican-3, Clone 1G12, ZSGB-Bio, Beijing, China), Napsin A (Clone OTI8A5, ZSGB-Bio, Beijing, China), P40 (Clone BC28, ZSGB-Bio, Beijing, China), Synapsin (Syn, Clone EP158, ZSGB-Bio, Beijing, China), Chromogranin A (CgA, Clone LK2H10, ZSGB-Bio, Beijing, China), P53 (Clone DO-7, ZSGB-Bio, Beijing, China), Alpha-fetoprotein (AFP, Clone OTI5D2, ZSGB-Bio, Beijing, China), Estrogen Receptor (ER, Clone SP1, Roche, Shanghai, China), Progesterone Receptor (PR, Clone 1E2, Roche, Shanghai, China), CK5/6 (Clone OTI1C7, ZSGB-Bio, Beijing, China), and Ki-67 (Clone MIB-1, ZSGB-Bio, Beijing, China).

Molecular testing

Main molecular detection methods employed included ARMS-PCR and next-generation sequencing (NGS). ARMS-PCR was performed on formalin-fixed paraffin-embedded (FFPE) tumor specimens using either a five-gene mutation detection kit or a three-gene detection kit (Amoy Diagnostics Co., Ltd, Xiamen, China). The five-gene kit detected single-nucleotide variants (SNVs) and small insertions/deletions (Indels) in EGFR, KRAS, BRAF, NRAS, and HER2, as well as hotspot mutations in PIK3CA and gene fusions involving ALK, ROS1, and RET. The three-gene kit was utilized for detecting EGFR hotspot mutations, ALK, and ROS1 fusions. NGS analyzed exons and rearrangement-prone intronic regions of 27 lung cancer-related genes to identify SNVs, small Indels, gene fusions, and copy number variations (CNVs). Sequencing and bioinformatics analyses followed standard pipelines.

Periodic-acid-schiff (PAS) staining

PAS staining reagents were obtained from Roche. PAS staining was conducted on formalin-fixed, paraffin-embedded tissue sections.

Statistical analysis

Considering the small sample size (n = 10) and the descriptive nature of this study, no inferential statistical tests were performed. Clinical and pathological data were summarized using descriptive statistics (frequencies, percentages, medians, and ranges where appropriate).

Results

Clinical features

A total of 10 patients with FLAC were enrolled in this study and categorized into the L-FLAC group (6 cases) and the H-FLAC group (4 cases) based on pathological features. In the L-FLAC group, there were 3 males and 3 females, with ages ranging from 33 to 66 years

TABLE 1 Clinical characteristics of patients with FLAC.

Patient	Sex (M/F)	Age (years)	Histological type	Smoking history (Y/N)	Location	Maximum diameter (cm)	Clinical symptoms	Clinical stage	CT examination	Lymph node metastasis (+/−)	Treatment	Follow-up (months)
1	M	33	L-FLAC	Y	Right middle lobe	2.8	Asymptomatic and detected on physical examination	IA	Solid nodule with clear margins and homogeneous density	-	Lobectomy with regional lymph node dissection	22, recurrence-free survival
2	F	64	L-FLAC	N	Right lower lobe	2.2	Asymptomatic and detected on physical examination	IA	Nodular hyperdense lesion with clear margins and lobulation	-	Lobectomy with regional lymph node dissection	38, recurrence-free survival
3	M	56	L-FLAC	N	Left upper lobe	6	Cough, sputum production, blood-streaked sputum	IIB	Mass-like soft tissue lesion with clear margins and lobulation	-	Lobectomy with regional lymph node dissection followed by chemotherapy	54, recurrence-free survival
4	F	47	L-FLAC	N	Right middle lobe	3	Cough, sputum production	IA	Mass-like soft tissue lesion with lobulated margins and homogeneous density	-	Lobectomy with mediastinal lymph node dissection	90, recurrence-free survival
5	M	59	L-FLAC	Y	Right upper lobe	1.5	Asymptomatic and detected on physical examination	IB	Irregular nodular lesion with lobulation and spiculation, showing enhancement on contrast-enhanced imaging	-	Lobectomy with regional lymph node dissection	6, recurrence-free survival
6	F	66	L-FLAC	N	Left upper lobe	0.9	Asymptomatic and detected on physical examination	IB	Solid nodule with spiculated margins	-	Lobectomy with regional lymph node dissection followed by chemotherapy	26, recurrence-free survival

(*Continued*)

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TABLE 1 Continued

Patient	Sex (M/F)	Age (years)	Histological type	Smoking history (Y/N)	Location	Maximum diameter (cm)	Clinical symptoms	Clinical stage	CT examination	Lymph node metastasis (+/−)	Treatment	Follow-up (months)
7	M	67	H-FLAC	Y	Left lower lobe	5.5	Cough, sputum production, blood-streaked sputum	IIB	Mass-like soft tissue lesion with clear margins	-	Lobectomy with regional lymph node dissection	93, recurrence-free survival
8	F	76	H-FLAC	N	Right middle lobe	2.5	Asymptomatic and detected on physical examination	IIB	Irregular nodular lesion with clear margins, lobulation, and spiculation	-	Lobectomy with regional lymph node dissection	4, recurrence-free survival
9	M	67	H-FLAC	Y	Right upper lobe	1.6	Cough, sputum production	IA	Irregular nodular lesion with lobulation, and spiculation, showing enhancement on contrast-enhanced imaging	-	Apical segmentectomy of the upper lobe with regional lymph node dissection	6, recurrence-free survival
10	F	51	H-FLAC	N	Left lower lobe	1.5	Asymptomatic and detected on physical examination	IIB	Solid nodule with clear margins	+	Lobectomy with regional lymph node dissection followed by chemotherapy	6, recurrence-free survival

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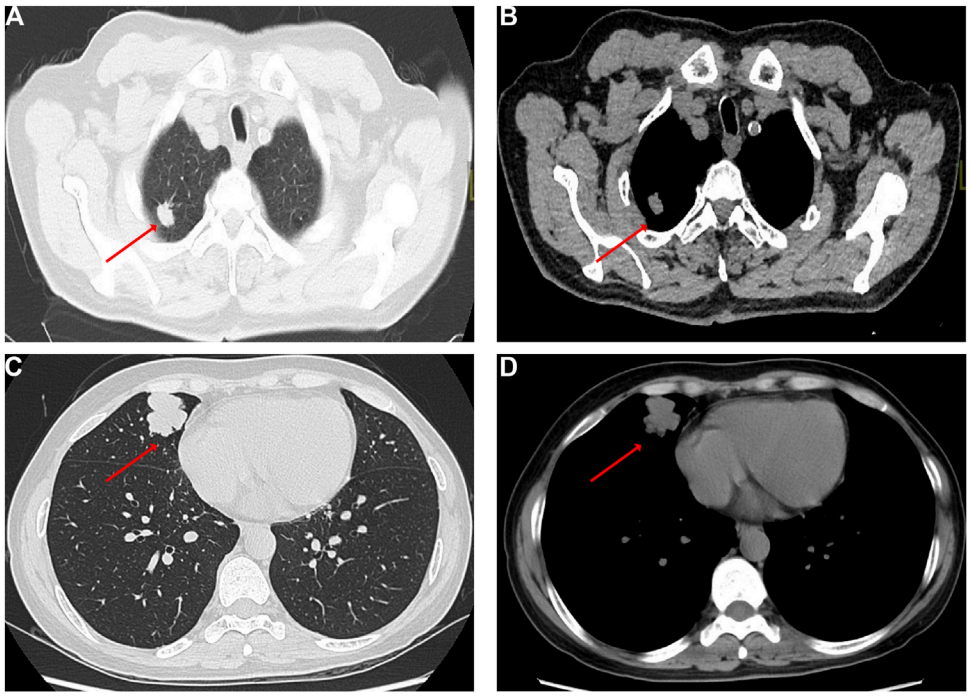


FIGURE 1
Imaging features of FLAC (indicated by arrows). **(A)** and **(B)** from one patient, **(C)** and **(D)** from another patient. **(A)** Lung window showing an irregular solid nodule in the right upper lobe with clear margins, lobulation, marginal spiculation, and bronchial truncation. **(B)** Mediastinal window showing marked enhancement of the nodule on contrast-enhanced imaging. **(C)** Lung window showing a mass-like soft-tissue density lesion in the right middle lobe with clear margins, a lobulated contour, and bronchial truncation. **(D)** Mediastinal window showing a soft-tissue density mass.

(median, 57.5 years). The maximum tumor diameter varied from 0.9 to 6.0 cm (mean, 2.7 cm). The H-FLAC group comprised 2 males and 2 females, with ages ranging from 51 to 76 years (median, 67 years). The maximum tumor diameter in this group ranged from 1.5 to 5.5 cm (mean, 2.8 cm). Six patients (60%) were asymptomatic, with tumors incidentally discovered during routine health check-ups; the remaining four patients (40%) presented with symptoms such as cough, sputum production, or blood-streaked sputum (Table 1).

Imaging features

All lesions were peripheral and appeared on imaging as solitary solid nodules or mass-like soft tissue densities with clear margins. Some cases exhibited lobulation and spiculation. Signs of air bronchogram were observed within the lesions, and bronchial truncation was noted in a subset of cases. Contrast-enhanced CT scans revealed variable degrees of enhancement (Figure 1).

Pathological features

1. Gross examination: The maximum tumor diameter ranged from 0.9 to 6.0 cm (mean, 2.8 cm). Cut surfaces appeared gray-white or gray-yellow, with a soft consistency, no capsule, and relatively clear margins, growing adjacent to the visceral pleura. Gross necrosis was observed in one case. Among the 4 H-FLAC cases, 3 exhibited invasion of the visceral pleura; one patient had lymph node metastasis and demonstrated spread through air spaces. In the 6 L-FLAC cases, 2 showed invasion of the visceral pleura; no lymph node or vascular invasion was noted in these cases.
2. Microscopic examination: Histologically, tumor cells resembled fetal lung airway epithelium and displayed glandular (Figure 2A), papillary, cribriform, or sheet-like growth patterns. The neoplastic cells were non-ciliated columnar cells arranged in a pseudostratified fashion. The cytoplasm was clear or eosinophilic, rich in glycogen, and featured subnuclear or supranuclear vacuoles, resembling secretory endometrium (Figure 2B). In L-FLAC cases, nuclei were small, uniform, and exhibited mild atypia, with fine granular chromatin, inconspicuous nucleoli, and rare mitotic figures. Punctate necrosis and morule-like structures were present (Figures 2C,D; Table 2). All H-FLAC cases in our series met the WHO diagnostic criterion requiring high-grade fetal components to exceed 50% of the lesion. Among the four H-FLAC cases, two consisted purely of H-FLAC (100%). One case was composed of 60% H-FLAC and 40% conventional adenocarcinoma; the conventional component included lepidic (10%) and acinar (30%) patterns of the whole lesion. The remaining case contained 70% H-FLAC and 30% conventional adenocarcinoma, with the conventional component comprising papillary (20%), lepidic (5%), and acinar (5%) patterns of the whole lesion. The

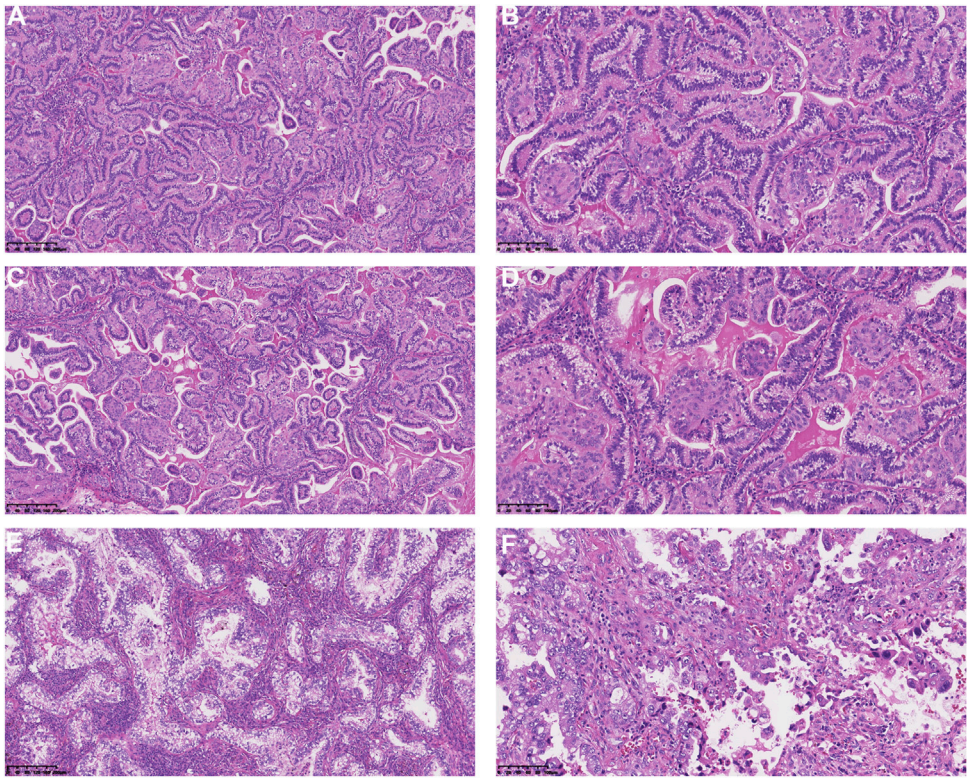


FIGURE 2
Microscopic histologic features of FLAC. **(A)** L-FLAC showing tumor cells arranged in complex glandular patterns (HE, × 100). **(B)** L-FLAC exhibiting mild nuclear atypia and resembling secretory endometrium (HE, × 200). **(C)** L-FLAC demonstrating morule-like structures along the luminal surface of the glands (HE, × 100). **(D)** L-FLAC demonstrating morule-like structures along the luminal surface of the glands (HE, × 200). **(E)** H-FLAC showing a glandular arrangement of tumor cells (HE, × 100). **(F)** H-FLAC demonstrating marked cellular atypia (HE, × 200).

tumor cells formed complex glandular structures (Figure 2E) with marked cellular atypia (Figure 2F). Morule-like structures were typically absent, mitotic figures were readily identified, and multifocal necrosis was observed (Table 2).

3. Immunophenotype: Immunohistochemical analysis of the 10 FLAC patients (Table 2) yielded the following results: TTF-1 was positive in all cases (Figure 3A). Napsin A was positive in three of the 3 L-FLAC cases (3/3) and in 2 of the 4 H-FLAC cases (2/4). SALL4 showed focal positivity in 2 of the 6 L-FLAC cases (2/6) and partial positivity in 2 of the 4 H-FLAC cases (2/4) (Figure 3B). Glypican-3 was focally positive in 1 of the 6 L-FLAC cases (1/6) and partially positive in 2 of the 4 H-FLAC cases (2/4) (Figure 3C). In the H-FLAC group, p53 staining patterns included wild-type in 1 case (1/4), overexpression in 1 case (1/4) (Figure 3D), and a null pattern in the remaining 2 cases (2/4). In the L-FLAC group, wild-type expression was observed in 5 cases (5/6), while the remaining case showed overexpression (1/6). β-catenin demonstrated nuclear/cytoplasmic positivity or nuclear positivity in L-FLAC in the vast majority of cases (Figure 3E) and membranous positivity in H-FLAC (Figure 3F). CgA and Syn were focally positive in L-FLAC (1/5 each) but negative in H-FLAC. The Ki-67 proliferation index ranged from 5% to 50% in L-FLAC and from 20% to 80% in H-FLAC. ER was positive or focally positive in 2 of 5 L-FLAC cases (2/5) and in 1 of 4 H-FLAC cases (1/4). All other tested markers, including p40, CK5/6, AFP, and PR, were negative in the examined cases.
4. Special staining: PAS staining was positive in the tumor cells of 5 cases, including 2 of the 3 L-FLAC cases (2/3) and 3 of the 4 H-FLAC cases (3/4) (Table 2).
5. Molecular testing results: Molecular testing was conducted in 5 cases, revealing genetic mutations in 2 patients (40% detection rate). One patient with H-FLAC harbored an EGFR gene mutation, specifically an exon 19 deletion. Another patient with H-FLAC had a KRAS gene mutation at codon G12C. The remaining three cases (all L-FLAC) showed no rearrangements or mutations in ALK, ROS1, BRAF, or other genes (Table 2).

Treatment and follow-up

All patients underwent lobectomy or segmentectomy along with lymph node dissection. Three patients received postoperative chemotherapy with pemetrexed plus platinum. The follow-up duration ranged from 4 to 93 months (mean, 34.5 months). During the follow-up period, all patients remained in good condition, with no evidence of recurrence or metastasis (Table 1).

TABLE 2 Histological, immunohistochemical and molecular features of FLAC.

Category	Parameter	Low-grade fetal adenocarcinoma of the lung (n = 6)	High-grade fetal adenocarcinoma of the lung (n = 4)
Major histological features	Nuclei	Small, uniform, mild atypia	Enlarged, pleomorphic, marked atypia
	Mitotic figures	Rare	Frequent
	Morular structures	Present	Usually absent
	Necrosis	Absent or punctate	Multifocal/confluent
	Proportion of fetal-type morphology	100% (pure)	At least 50%
Immunohistochemistry	TTF-1	6/6 (100%)positive	4/4 (100%)positive
	Napsin A	3/3 (100%)positive	2/4 (50%)positive
	p40	5/5 (100%)negative	4/4 (100%)negative
	CK5/6	2/2 (100%)negative	2/2 (100%)negative
	SALL 4	2/6 (33%)focally positive	2/4 (50%)partially positive
	Glypican-3	1/6 (17%)focally positive	2/4 (50%)partially positive
	P53	1/6 (17%)overexpression pattern,5/6 (83%) wild-type pattern	1/4 (25%)overexpression pattern,2/4 (50%)null pattern,1/4 (25%) wild-type pattern
	β-catenin	5/6 (83%)nuclear and/or cytoplasmic positive,1/6 (17%) membranous with focal nuclear positive	4/4 (100%)membranous positive
	CgA	1/5 (20%)Focally positive	4/4 (100%)negative
	Syn	1/5 (20%)Focally positive	4/4 (100%)negative
	Ki-67	5%–50%	20%–80%
	AFP	5/5 (100%)negative	4/4 (100%)negative
	ER	2/5 (40%)positive	1/4 (25%)focally positive
	PR	5/5 (100%)negative	4/4 (100%)negative
Special staining	PAS	2/3 (67%)positive	3/4 (75%)positive
Molecular testing		EGFR gene: No mutation detected; ALK fusion: Negative; ROS1 fusion: Negative	KRAS gene: G12C point mutation in exon 2
		TP53 gene: No tumor-associated somatic gene variants were detected	EGFR gene: deletion mutation in exon 19
		TP53 gene: No tumor-associated somatic gene variants were detected. Immune checkpoint inhibitor efficacy-related predictive genes: No variants in genes associated with the efficacy of immune checkpoint inhibitors were detected	

Abbreviations: TTF-1, thyroid transcription factor-1; p40, p40 protein; CK5/6, cytokeratin 5/6; SALL4, Sal-Like Protein 4; p53, tumor protein p53; CgA, chromogranin A; syn, Synapsin; Ki-67, Ki-67 proliferation marker; AFP, alpha-fetoprotein; ER, estrogen receptor; PR, progesterone receptor.

Discussion

FLAC is a relatively rare subtype of lung adenocarcinoma, accounting for only 0.1%–0.5% of all lung tumors [4]. In domestic reports, the prevalence of FLAC ranges from approximately 0.32%–0.54% [7, 8]. The tumor derives its name from its striking histological similarity to fetal lung epithelium at the embryonic stage (8–16 weeks of gestation). Initially described by Kradin in 1982, FLAC was later classified as a distinct subtype of invasive lung adenocarcinoma in the IASLC/ATS/ERS classification of 2011 [2]. The 2015 World Health Organization (WHO) classification of lung tumors recognizes FLAC as an independent subtype of lung adenocarcinoma [3].

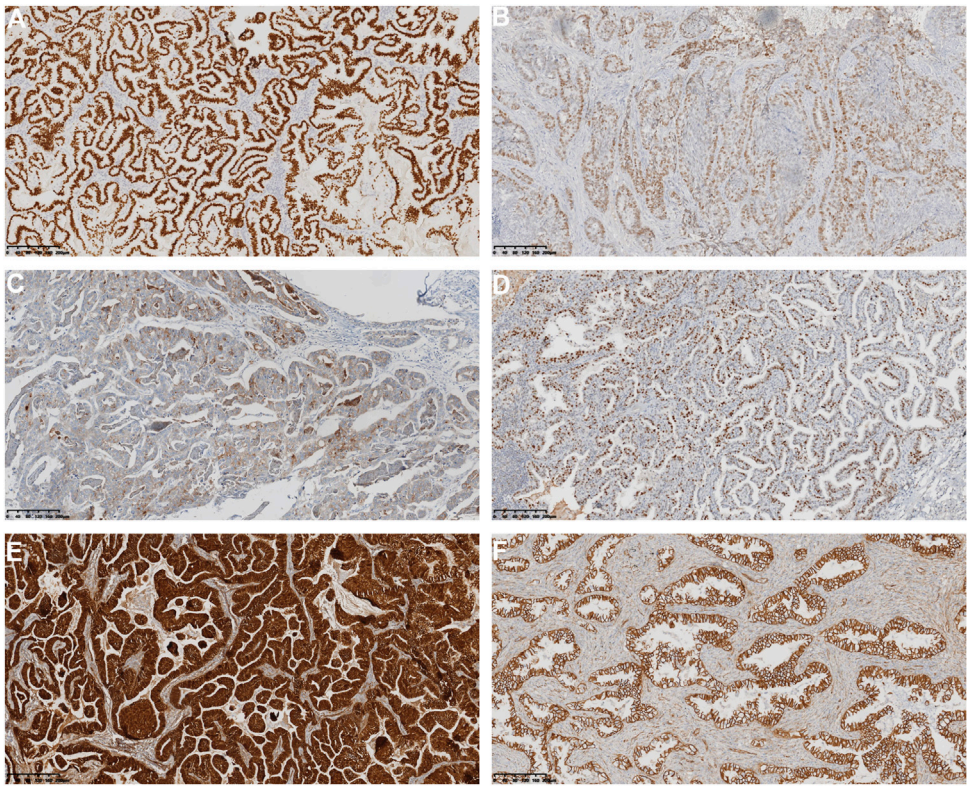


FIGURE 3
Immunohistochemical features of FLAC. **(A)** Positive expression of TTF-1 in tumor cells (EnVision method, × 100). **(B)** Positive expression of SALL4 in tumor cells (EnVision method, × 100). **(C)** Positive expression of Glypican-3 in tumor cells (EnVision method, × 100). **(D)** Positive expression of p53 in tumor cells (EnVision method, × 100). **(E)** L-FLAC showing nuclear/cytoplasmic positivity for β-catenin (EnVision method, × 100). **(F)** H-FLAC showing membranous positivity for β-catenin (EnVision method, × 100).

FLAC can arise at any age. Literature indicates that L-FLAC is more common in younger patients, while H-FLAC predominantly affects elderly smokers [7, 9]. Among the 10 patients in this study, the 6 cases of L-FLAC exhibited a male-to-female ratio of 1:1, a mean age of 57.5 years, and 2 patients had a history of smoking. Early-stage disease (stage I) constituted 83.3% (5/6) of L-FLAC cases. The 4 H-FLAC cases also had a male-to-female ratio of 1:1, a mean age of 67 years, with 2 patients having a smoking history. Stage IIB disease accounted for 75% (3/4) of H-FLAC cases.

FLAC typically presents with non-specific clinical manifestations. In this study, only 4 of the 10 patients showed symptoms such as cough and sputum production, likely attributed to tumor location and growth rate [10, 11]. Imaging findings generally reveal a peripheral solid pulmonary mass, which may exhibit lobulation, spiculation, air bronchogram signs, bronchial truncation, and pleural traction in some cases, with contrast enhancement noted on enhanced scans [12]. However, these features are non-specific, complicating the distinction of FLAC from other lung tumors.

The diagnosis and grading of FLAC rely on pathological evaluation. Its core histological feature is the formation of glandular structures that resemble fetal lung airway epithelium, composed of non-ciliated columnar cells arranged in a pseudostratified manner, with cytoplasm rich in glycogen. Significant differences in cellular morphology, necrosis extent, and characteristic structures between L-FLAC and H-FLAC provide critical clues for grading diagnosis [4, 8]. Due to the heterogeneity of lung adenocarcinoma, the fifth edition of the WHO Classification of Thoracic Tumors specifies that a diagnosis of H-FLAC requires at least 50% of the tumor tissue to exhibit H-FLAC morphology to avoid misdiagnosing conventional adenocarcinoma with only minor fetal-like structures as H-FLAC [6]. All H-FLAC cases in our series met this WHO diagnostic criterion, with high-grade fetal components exceeding 50% of the lesion.

The immunophenotype of H-FLAC is characterized by positivity for TTF-1 and Napsin A, frequent overexpression or a null pattern of p53, and predominantly membranous β-catenin expression. Together with its molecular features, this suggests that H-FLAC should be regarded as a high-grade special subtype within the conventional lung adenocarcinoma spectrum rather than an entirely independent entity. This classification is further supported by the observation that H-FLAC often contains conventional adenocarcinoma components, such as lepidic, micropapillary, or solid patterns [13]. In contrast, L-FLAC exhibits a higher detection rate of CTNNB1 gene mutations, particularly activating mutations in exon 3, which are recognized as a characteristic molecular alteration of this subtype [4, 14]. Such mutations lead to impaired degradation of β-catenin, resulting in cytoplasmic accumulation and nuclear translocation, which

produces a distinct nuclear/cytoplasmic immunohistochemical expression pattern. This also aberrantly activates the Wnt/β-catenin signaling pathway, driving the formation of characteristic morphological features of L-FLAC, such as morules [14]. As noted in previous reports, the nuclear/cytoplasmic expression pattern of β-catenin, combined with CTNNB1 mutation testing, aids in distinguishing L-FLAC, H-FLAC, and morphologically similar conventional adenocarcinomas. In our study, among the six L-FLAC cases, five showed nuclear and/or cytoplasmic β-catenin positivity, and one exhibited membranous staining with focal nuclear positivity. By contrast, all four H-FLAC cases demonstrated membranous β-catenin positivity. Although gene sequencing was not performed in this study, the β-catenin immunohistochemical findings align with the subtype-specific staining patterns previously described for L-FLAC and H-FLAC, further corroborating the documented differences in molecular pathways between these two tumor subtypes.

Concerning neuroendocrine differentiation, earlier studies indicated that approximately 80% of H-FLAC and a subset of L-FLAC express neuroendocrine markers [8, 15]. However, the results of the present study deviate from this observation, as all H-FLAC cases were negative for neuroendocrine markers. Conversely, focal positivity for CgA and Syn was noted in a subset of L-FLAC cases, consistent with findings reported by Bai et al. [16]. Regarding other markers, literature suggests that H-FLAC may express AFP, Glypican-3, and SALL4 [3, 17]. However, no AFP expression was detected in any of the cases within this group, and this negative finding may be attributed to the small sample size and tumor heterogeneity. SALL4 demonstrated focal or partial positivity in a subset of both L-FLAC and H-FLAC, indicating expression heterogeneity. A comprehensive diagnostic immunohistochemical panel for FLAC should include core markers such as TTF-1, β-catenin, p53, neuroendocrine markers (Syn, CgA), and oncofetal markers (AFP, SALL4, Glypican-3). This approach simultaneously facilitates diagnostic differentiation between L-FLAC and H-FLAC subtypes, identifies therapeutically relevant targets, and provides prognostic information. Additionally, future large-sample studies integrating multi-omics approaches are necessary to enhance the refinement of diagnostic criteria, molecular subtyping, and the relationship of FLAC with the conventional adenocarcinoma lineage.

Fetal adenocarcinoma of the lung (FLAC) harbors a molecular landscape distinct from that of classic-type lung adenocarcinoma. EGFR and KRAS gene mutations are well-established driver events in conventional lung adenocarcinoma but are relatively rare in L-FLAC [12]. Ma et al. analyzed the correlation between driver gene alterations and pathological subtypes in 3,012 primary lung adenocarcinomas, revealing that EGFR mutations predominate in invasive non-mucinous adenocarcinoma, while KRAS mutations are the primary alteration in invasive mucinous adenocarcinoma [18]. Li Sun et al. found that TP53 was the predominant mutated gene in all FLAC patients as well as patients with H-FLAC, whereas CTNNB1 mutations were most frequent in L-FLAC [19]. Some studies have detected KRAS and EGFR mutations in H-FLAC [5, 20], indicating potential molecular genetic heterogeneity among different grades of FLAC. In this study, molecular testing was performed on 5 patients (3 with L-FLAC and 2 with H-FLAC). Driver gene mutations were detected in two patients, both of whom had H-FLAC. One pure H-FLAC case exhibited an EGFR exon 19 deletion. This relatively rare molecular alteration aligns with prior case reports and supports genomic heterogeneity among H-FLACs. The other case, consisting of 60% H-FLAC and 40% conventional adenocarcinoma, harbored a KRAS G12C mutation. Since DNA was extracted from the bulk FFPE tissue block without microdissection to separately enrich the two histological components, we could not determine whether the KRAS G12C mutation arose from the high-grade fetal adenocarcinoma compartment or the classic-type lung adenocarcinoma compartment, and both possibilities remain. This represents a limitation of the present study. Future investigations may utilize microdissection to isolate distinct tumor components and clarify the clonal origin of such mutations. Notably, the EGFR and KRAS mutations identified herein may serve as potential therapeutic targets. Nevertheless, treatment response was not assessed in this cohort, and additional studies with larger patient cohorts are warranted for further validation of their clinical relevance.

Due to the absence of specific clinical manifestations and imaging findings, FLAC must be differentiated from several other entities both clinically and pathologically, including pulmonary adenosquamous carcinoma, acinar adenocarcinoma, pulmonary blastoma, and metastatic endometrial adenocarcinoma of the lung. (1) Conventional adenocarcinoma: Tumor cells may exhibit lepidic, acinar, or papillary growth patterns, lacking embryonic glandular epithelium and morule-like structures. (2) Pulmonary adenosquamous carcinoma: Composed of both adenocarcinoma and squamous cell carcinoma, the squamous component demonstrates intercellular bridges, keratinization, or keratin pearls, while FLAC comprises only an adenocarcinoma component. (3) Pulmonary blastoma: This tumor consists of malignant primitive epithelium and malignant mesenchyme. The primitive epithelial component is arranged in tubular structures lined by simple cuboidal cells, with mesenchyme comprising immature mesenchymal cells. The primitive epithelial component is distributed within the mesenchymal tissue, contrasting with FLAC, where the stromal component is benign, aiding in differentiation. Immunophenotypically, the epithelial component in pulmonary blastoma is positive for CK and epithelial membrane antigen (EMA), whereas the mesenchymal component is positive for vimentin. (4) Metastatic endometrial adenocarcinoma of the lung: Such cases often present with corresponding gynecological symptoms and a history of endometrial carcinoma, with imaging possibly revealing uterine or ovarian masses. The immunophenotype typically exhibits positivity for ER, PR, and vimentin, while TTF-1, Napsin A, and SP-B are generally negative. In contrast, FLAC is frequently positive for TTF-1.

No specific treatment exists for FLAC, and complete surgical resection remains the first-line treatment, followed by adjuvant chemotherapy or radiotherapy. In this study, all patients underwent lobectomy or segmentectomy with lymph node dissection. Three patients received postoperative chemotherapy with pemetrexed plus platinum. The follow-up duration ranged from 4 to 93 months, with a mean of 34.5 months. Throughout this

follow-up period, all patients remained alive and well, with no evidence of tumor recurrence or metastasis.

Conclusion

In summary, FLAC exhibits distinct clinicopathological, immunophenotypic, and molecular characteristics. Given its extremely low incidence, recognition and comprehensive understanding of this rare tumor remain insufficient, leading to frequent missed diagnoses and misdiagnoses in clinical practice. Therefore, enhancing clinical awareness of FLAC is essential to improve diagnostic accuracy.

Limitations

Several limitations of the present study should be acknowledged. As a single-center retrospective investigation with a relatively small sample size and incomplete molecular profiling due to the rarity of FLAC, rigorous statistical analysis was restricted, which may limit the generalizability of our findings. Additionally, PD-L1 immunohistochemical staining was not performed in this cohort, as long-term preservation of FFPE specimens may compromise the reliability of staining results. Despite these shortcomings, our study provides valuable supplementary evidence for clarifying the differential diagnosis, clinical management, and prognostic features of both L-FLAC and H-FLAC. Future large-scale, multicenter prospective studies with comprehensive molecular and biomarker assessments are warranted to validate our findings and deepen the understanding of this rare pulmonary malignancy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Linyi People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because this was a retrospective analysis of de-identified data, the requirement for written informed consent was waived by the ethics committee.

Author contributions

All authors listed contributed significantly to the design of the investigation. Conceptualization: YQ and NZ; Data collection: YQ and QJ; Investigation: WL, QJ, and YW; Methodology: XS and NZ; Supervision: NZ; Validation: YQ and WL; Writing – Original Draft Preparation: YQ; Writing – Review and Editing: WL and NZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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