Comprehensive review of fetal adenocarcinoma of the lung

Fetal adenocarcinoma of the lung (FLAC) is a rare tumor. It accounts for 0.1%-0.5% of all pulmonary neoplasms. Due to its rarity, much of the world literature regarding FLAC comes from case reports and case series. FLAC is an adenocarcinoma resembling developing fetal lung in its pseudoglandular stage (8-16 weeks of gestation). It is distinguishable from pulmonary blastoma (PB) because it lacks the mesenchymal component which is a hallmark finding in PB. Due to differences in histopathology and clinical course, FLAC has been further categorized into low-grade (L-FLAC) and high-grade (H-FLAC) forms. L-FLAC displays low nuclear atypia and prominent morule formation and has a pure pattern. H-FLAC typically presents with at least 50% fetal morphology, and is often associated with other conventional types of lung adenocarcinoma. FLAC expresses neuroendocrine markers and thyroid transcription factor 1 in most cases. L-FLAC has an aberrant nuclear/cytoplasmic expression of β-catenin and presents mutations in this gene. H-FLAC overexpresses p53. These tumors have a very low frequency of mutations in KRAS and EGFR; it is thought that they are different from a molecular point of view to conventional lung adenocarcinomas. Approximately 25%-40% of patients are asymptomatic at presentation; most of them are incidental findings on chest radiographs. H-FLAC is more common in elderly male patients, with a heavy smoking history. L-FLAC tends to occur in young females. Patients with L-FLAC are usually diagnosed with stage I-II disease, while patients with H-FLAC usually present with a more advanced-stage disease. Poor prognostic factors for FLAC are thoracic lymphadenopathy, metastases at diagnosis, and tumor recurrence; however, the 10-year survival for FLAC is estimated at 75%.

Keywords: lung cancer, fetal adenocarcinoma, outcomes, chemotherapy, radiotherapy, L-FLAC, H-FLAC, p53

Introduction

Fetal adenocarcinoma is a rare type of lung neoplasia. It accounts for 0.1%-0.5% of all pulmonary neoplasms. This tumor was first described by WG Barnard in 1945 and 1952, as a biphasic tumor of the lung comprising an epithelial component surrounded by mesenchymal stroma that resembled the fetal lung, hence naming it "embryoma of the lung." In 1961, Spencer introduced the term pulmonary blastoma (PB) after studying additional cases. Later on, several authors reported other epithelial lung tumors that shared histological characteristics of the epithelial component present in PB, but lacked the mesenchymal component. In 1984, Kodama et al introduced the phrase "well differentiated fetal adenocarcinoma of the lung" (FLAC) to categorize these tumors. Finally, in 1999 the World Health Organization (WHO) classified this tumor as a variant of lung adenocarcinoma and it is now known as FLAC. The

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biphasic tumor is now part of the sarcomatoid carcinomas category and termed PB. Today, FLAC is recognized as a very uncommon lung adenocarcinoma with different pathogenesis, clinical manifestations, histopathology, and prognosis than PB.\textsuperscript{9–11} Much of the world literature regarding FLAC comes from case reports and case series. This review will describe the histopathological findings of this tumor, the genomics, diagnosis, and clinical characteristics, treatment, and outcomes. Surgical resection is the standard treatment, although adjuvant therapy with radiotherapy and chemotherapy has been reported.

**Pathology**

FLAC is an adenocarcinoma resembling developing fetal lung in its pseudoglandular stage (8–16 weeks of gestation).\textsuperscript{12–14} The tumor is usually solitary, well demarcated, and peripherally located although endobronchial involvement has been described.\textsuperscript{12,15–17} FLAC comprises complex, branch forming tubular glands lined by glycogen-rich, non-ciliated columnar or cuboidal cells. The cells have clear cytoplasm; large vesicular nuclei are seen in addition to supranuclear or subnuclear vacuoles. The malignant glands are densely packed and situated within loose to moderate cellular fibroblastic stroma. There is a morphologic resemblance to early secretory endometrium.\textsuperscript{12,14,16–20} Due to differences in histopathology and clinical course, FLAC has been further categorized into low-grade (L-FLAC) and high-grade (H-FLAC) forms.\textsuperscript{11,14}

A study that screened 920 adenocarcinomas calculated the prevalence of FLAC to be 0.87%; among these 0.32% were L-FLAC and 0.54% were H-FLAC.\textsuperscript{18}

L-FLAC displays low nuclear atypia and prominent morule formation (Figure 1A). The stroma is typically loose fibromyxoid tissue with spindle cells.\textsuperscript{12,14,18,21} L-FLAC is pure in pattern.\textsuperscript{12} In contrast, H-FLAC presents typically with at least 50% fetal morphology, and is often associated with other conventional types of lung adenocarcinoma (lepidic, papillary, acinar, micropapillary, and solid patterns). Although not recognized in the last WHO classification, a hepatoid pattern defined as a solid to trabecular growth of tumor cells with eosinophilic cytoplasm and clear cell component has also been described.\textsuperscript{14,18,22,23} According to WHO, H-FLAC diagnosis is rendered when the fetal histology is predominant. Additionally, these high-grade tumors have prominent nuclear atypia, prominent nucleoli, and frequent mitosis, in addition to lacking morule formation (Figure 1B).\textsuperscript{12,14,18,21,23} Currently, L-FLAC and H-FLAC are recognized by the WHO classification under the name of FLAC; nevertheless, some authors question whether H-FLAC is a distinct variant of lung cancer, which can present as a biphasic tumor or as pure fetal H-FLAC.\textsuperscript{18,23}

The histopathological and immunohistochemical characteristics of L-FLAC and H-FLAC are summarized in Table 1. These two categories of FLAC also show differences in their immunohistochemical profile. Both L-FLAC and H-FLAC show positivity for neuroendocrine markers

![Figure 1](https://www.dovepress.com/)

**Figure 1** Morphological characteristics of fetal lung adenocarcinomas.

**Notes:** (A) Histology and immunophenotype of L-FLAC, which consists of complex glandular structures lined with glycogen-rich columnar cells, with low nuclear atypia, and morule formation. (B) H-FLAC exhibits the absence of morules, broad areas of necrosis, and complex acinar glands that consist of columnar tumor cells with supranuclear or subnuclear cytoplasmic clearing, large vesicular nuclei, prominent nucleoli.

**Abbreviations:** L-FLAC, low-grade fetal adenocarcinoma of the lung; H-FLAC, high-grade fetal adenocarcinoma of the lung; APC, adenomatous polyposis coli; ER\(\beta\), estrogen receptor \(\beta\).
Lung adenocarcinoma. Interestingly, PB shares part of the immunohistochemical profile of both categories of FLAC, since it has aberrant nuclear/cytoplasmic β-catenin staining, more prominently in the epithelial compartment and also overexpresses p53, glypican 3, and SALL-4. Alfafetoprotein (AFP), glypican 3, and SALL-4 are also expressed in H-FLAC, with a more prominent expression profile in the non-fetal lung-like component compared to the fetal lung-like component.

### Genomics

Multiple molecular studies have reported very low rates of mutations in KRAS, EGFR, and PIK3CA in FLAC. A mutational analysis performed in a Chinese population identified an L858R point mutation in EGFR in a H-FLAC case and a T790M EGFR mutation in a L-FLAC case. The remaining cases had wild-type EGFR and harbored no other mutations in KRAS, PIK3CA, or BRAF. Another study identified an exon 19 deletion and the L858R point mutation of EGFR in one and two cases, respectively, of H-FLAC. E545A point mutation of PIK3CA was also detected in another H-FLAC case. No mutations on KRAS or BRAF were identified in this study. Morita et al reported one case of H-FLAC with an L858R mutation of EGFR and another showed a KRAS mutation in either codon 12 or 13. The remaining cases tested presented wild-type EGFR and KRAS. Conventional lung adenocarcinomas have a mutation frequency of 32%–64% for EGFR and 13% for KRAS. Given the high mutation frequency for these genes in lung adenocarcinoma in comparison to the low frequency seen in FLAC, several authors have suggested that these tumors may have distinctive molecular features and, because of this, the

### Table 1: Histopathological, immunohistochemical, and genomic characteristics of L-FLAC and H-FLAC

<table>
<thead>
<tr>
<th>AFLAC</th>
<th>L-FLAC</th>
<th>H-FLAC</th>
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<tbody>
<tr>
<td>Prominent nuclear atypia, prominent nucleoli, and frequent mitosis</td>
<td>Low nuclear atypia and prominent morule formation</td>
<td>Prominent nuclear atypia, prominent nucleoli, and frequent mitosis</td>
</tr>
<tr>
<td>Absent morule formation</td>
<td>Pure pattern</td>
<td>Absent morule formation</td>
</tr>
<tr>
<td>50% Fetal morphology and often associated with other conventional types of lung adenocarcinoma</td>
<td>No p53 overexpression</td>
<td>Commonly nuclear p53 overexpression</td>
</tr>
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<td></td>
<td>Mutations in exon 3 of β-catenin. Mutations in these phosphorylation sites interfere with β-catenin degradation and cause it to accumulate in the nucleus and cytoplasm</td>
<td>No mutations in the β-catenin gene</td>
</tr>
<tr>
<td></td>
<td>Theoretical mutational inactivation of the APC or PTEN genes</td>
<td>p53 mutations</td>
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</tbody>
</table>

**Notes:** Diagnosis is rendered when the fetal histology is predominant. Lepidic, papillary, acinar, micropapillary, solid patterns, and hepatoid. Grade of positivity for neuroendocrine markers (chromogranin A and synaptophysin) for H-FLAC is dependent on the percentage of the fetal lung-like component present in the tumor. No mutation present in the β-catenin gene analyses but aberrant nuclear/cytoplasmic expression of β-catenin seen in immunohistochemistry. **Abbreviations:** FLAC, fetal adenocarcinoma of the lung; L-FLAC, low-grade FLAC; H-FLAC, high-grade FLAC; APC, adenomatous polyplosis coli; ERβ, estrogen receptor β; AFP, alfafetoprotein; GPC-3, glypican 3; TTF-1, thyroid transcription factor 1.
recognition of FLAC as a separate histopathological entity has been debated.\(^4\)\(^,\)\(^8\)\(^,\)\(^2\)\(^3\)

Other molecular markers have also been implicated in the tumorigenesis of FLAC. The Wnt signaling pathway is important during embryogenesis, but when altered can lead to tumor formation. The Wnt signal causes β-catenin to translocate to the nucleus, which activates target genes that form complexes with lymphoid enhancer factor/T-cell factor. In normal circumstances, a multi-protein complex (that includes the adenomatous polyposis coli [APC] tumor suppressor protein) degrades excess β-catenin, hence keeping its levels regulated. Mutational inactivation of APC or direct mutations on β-catenin that inhibit its degradation will cause nuclear accumulation of the protein. This will lead to the activation of oncogenic target genes such as c-myc and cyclin D1.\(^37\) Since the final step in the altered Wnt pathway is the nuclear accumulation of β-catenin, alterations in this pathway may be detected with direct gene analysis and with immunohistochemistry.\(^8\) Studies have indicated that various pathway may be detected with direct gene analysis and with immunohistochemistry.\(^8\) Studies have indicated that various

Immunohistochemical and molecular analyses of p53 and β-catenin have demonstrated that the epithelial and mesenchymal components of PB with morules are monoclonal.\(^2\)\(^9\)\(^,\)\(^3\)\(^0\) This finding has led to two different theories about the histogenesis of L-FLAC, H-FLAC, and PB. One theory states that when PB develops, if a β-catenin mutation occurs early in the process it will lead to L-FLAC, as a one-sided epithelial outgrowth with morule formation. If this mutation does not occur, PB with no morule formation with an abundant mesenchymal outgrowth with morule formation. If this mutation does not occur, PB with no morule formation with an abundant mesenchymal component will develop. This would suggest that these entities can be organized into a spectrum where PB with morules is placed between L-FLAC and PB without morules.\(^3\)\(^0\) In contrast, Nakatani et al suggest that L-FLAC and H-FLAC are histogenetically different tumors. They speculate that the formation of a biphasic pattern present in PB is a later event that arises from either L-FLAC or H-FLAC through the process of epithelial and mesenchymal transition. According to the extent of epithelial-mesenchymal transition, the proportion of the epithelial and mesenchymal components may vary.\(^2\)\(^6\) Further studies are warranted to solve this debate. Genomic characteristics of L-FLAC and H-FLAC are summarized in Table 1.
Diagnosis and clinical characteristics

Approximately 25%–40% of patients present with asymptomatic disease; therefore, most of the cases are diagnosed through incidental findings on chest radiographs. Symptoms are related to bronchial irritation: chest pain is usually the main complaint, cough, hemoptysis, and dyspnea have also been reported. Pleural effusion is uncommon. On chest radiographs, FLAC is seen as a peripherally located well-demarcated lesion ranging from 2 to 12 cm with peripherally placed radiopacities. On computed tomography, these tumors show a heterogeneous appearance with enhancing whorls of soft tissue and non-enhancing areas of necrosis. Metastases to the same or opposite lung, or to the mediastinal compartment may also be apparent. Patients with H-FLAC may present with elevated serum levels of AFP. From a pathologic point of view, FLAC is difficult to diagnose preoperatively. Usually the diagnosis is made on postoperative specimens or at autopsy. Metastases to the ovary, eye, and skin have been described.

L-FLAC and H-FLAC also show different clinical characteristics. H-FLAC is more common in elderly male patients, around the sixth to seventh decade of life, with a heavy smoking history (93% smoking rate). On the other hand, L-FLAC tends to occur in young females at the third to fourth decade of life. Patients with L-FLAC usually present with stage I–II disease, while patients with H-FLAC usually present with a more advanced-stage disease (stage III–IV) (Table 2).

Table 2 Clinical characteristics in L-FLAC and H-FLAC

<table>
<thead>
<tr>
<th>L-FLAC</th>
<th>H-FLAC</th>
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<tr>
<td>Young females at the third to fourth decade of life</td>
<td>Elderly male patients, sixth to seventh decade of life</td>
</tr>
<tr>
<td>Present with stage I–II disease</td>
<td>Heavy smoking history</td>
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<tr>
<td>Present with an advanced-stage disease (III–IV)</td>
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Treatment

Due to the fact that PB and FLAC were categorized as two separate entities, studies that evaluate the treatment of this entity in an independent manner are limited. Surgical resection is the standard treatment for PB and FLAC. Radiotherapy and chemotherapy have been used as adjuvant therapy, although in some reports they have shown limited effect. A case study reports a patient with T3N0 disease who underwent treatment with three cycles of etoposide–cisplatin protocol. The patient showed a 12% tumor reduction evaluated through computed tomography. Another patient with a T4N0M0-stage disease treated with neoadjuvant chemotherapy (mitomycin, ifosfamide, and cisplatin) showed a downstage prior to tumor resection. Kyung et al reported the case of a patient with locally advanced disease that was treated with concurrent chemotherapy with docetaxel; the patient had a partial response. The combination of surgery, adjuvant radiotherapy, and chemotherapy based on cisplatin and etoposide has been suggested. A Swiss study used treatment with cisplatin, VP-16, uromitexan, ifosfamide, and 64 Gy or mediastinal radiotherapy on a T3N2M0 patient and reported a 33-month survival. (A summary of the therapeutic approach can be found in Table 3.)

Outcomes

Poor prognostic factors for FLAC include thoracic lymphadenopathy, metastasis at diagnosis, and tumor recurrence. Size of the tumor has been debated. Koss et al showed that the median survival for patients with FLAC was not reached at 10 years while that of PB was of ~1 year. Larsen and Sorensen showed a median survival for FLAC of 34 months and for PB of 11 months. Several studies have shown 10-year survival for FLAC of 75% and for PB of 15%. The prognostic studies performed by Kodama et al and Koss et al showed differences in outcomes and survival within all of the FLAC cases. Nakatani et al suggested that the grade of malignancy and the tumor stage explained the differences in prognosis seen in these two studies, and further stated that even though it is not known whether the prognosis of H-FLAC is worse than the stage-matched conventional adenocarcinoma, L-FLAC probably has a better prognosis than the stage-matched conventional pulmonary adenocarcinoma.

Table 3 Therapeutic approach for patients with FLAC

<table>
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<th>Treatment</th>
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<tr>
<td>Standard: surgical resection</td>
<td>Radiotherapy and chemotherapy used as adjuvant therapy have shown limited effect</td>
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<th>Poor prognostic factors</th>
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<tr>
<td>Thoracic lymphadenopathy</td>
<td>Metastases at diagnosis</td>
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<tr>
<td>Tumor recurrence</td>
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Abbreviation: FLAC, fetal adenocarcinoma of the lung.
Disclosure
The authors report no conflicts of interest in this work.

References


