

The Radiologic and Pathologic Diagnosis of Biphasic Pulmonary Blastoma

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ABSTRACT

Pulmonary blastomas are rare malignancies, representing 0.25% to 0.5% of all primary lung neoplasms with often aggressive progression and poor prognosis. Clinical management of pulmonary blastomas depends on histologic subtype, staging, and presentation, and may consist of surgery, chemotherapy, and radiation. Biphasic pulmonary blastoma is a subtype of pulmonary blastoma that exhibits biphasic histology, with both epithelial and mesenchymal malignant elements. We report a case of biphasic pulmonary blastoma in a 33-year-old female with 1 pack per day history of smoking for approximately 16 years, who presented with left-sided pleuritic chest pain on deep inspiration without otherwise significant past medical history. Imaging evaluation using chest radiography, computed tomography, and magnetic resonance imaging identified a heterogeneous, well-circumscribed, left lower lobe mass with extensive necrosis and hemorrhage. No lymphadenopathy or distant metastasis was detected through imaging evaluation. Surgical resection of the tumor followed by histopathological analysis confirmed a biphasic pulmonary blastoma.

CASE REPORT

CASE REPORT

A 33-year-old female with 1 pack per day smoking history for 16 years, without otherwise significant medical history, presented with left side pleuritic chest pain on deep inspiration. Chest radiography on admission revealed a round 7 cm mass in the left lower lobe without evidence of cavitation or associated calcification (Figure 1). Subsequent contrast enhanced chest CT identified a 7.1 cm x 6.2 cm x 6.2 cm low density lesion within the left lower lobe, which splays the superior and basilar segmental bronchi. No cavitation or lesional calcification was noted (Figure 2, 3). Follow-up MRI showed a large thick-walled, heterogeneous, irregularly enhancing mass abutting the posterolateral pleura in the left lower lobe (Figure 4, 5), suggestive of a necrotic tumor. The possibility of a primary sarcoma versus a large necrotizing

carcinoma was raised. Due to uncertainty of endobronchial involvement, flexible bronchoscopy was performed, which showed erythematous mucosa in the left lower lobe bronchi but no endobronchial lesions. No abnormalities were seen in the right mainstem, lobar, or segmental bronchi. A nuclear ventilation-perfusion scan was performed to estimate split lung function, which demonstrated large photopenic area in the left lower lobe on both ventilation and perfusion scans (Figure 6).

Surgical resection was pursued. A preoperative radiograph re-demonstrated the known mass (Figure 7A). A serratus sparing left posterolateral thoracotomy was made through the sixth intercostal space, and the seventh rib was shingled posteriorly. The lung was isolated, which was adherent to the chest wall but easily separable. The left lower lobe lesion was visually confirmed. No tumor invasion into the chest wall was

noted. The left lower lobe bronchus was dissected. The lung mass was firm on palpation, approximated to the size of a softball. Grossly, the tumor was bi-lobed and appeared hemorrhagic (Figure 8). There was no frank purulence or clear evidence of infection. Culture swabs of the specimen were taken and sent to pathology for permanent section.

Carinal lymphadenectomy was performed, and several station 7 lymph nodes were sent for permanent section. The most medially accessible station 7 nodes as well as several station 5 lymph nodes were excised and sent for frozen and permanent section. A vascularized flap of parietal pleura, measuring approximately 3 cm by 10 cm, was harvested about the descending thoracic aorta. Post-operative radiograph demonstrated gross resection of the mass lesion with expected post-surgical changes (Figure 7B).

Pathologic evaluation of the mass was consistent with a 7 cm poorly differentiated, non-invasive mass with extensive internal necrosis and hemorrhage, containing immature glandular as well as stromal components, consistent with a biphasic pulmonary blastoma (Figure 9). Cytogenic analysis of the tumor revealed Trisomy 18 on all cells examined, with few cells displaying Trisomy 7 in addition to Trisomy 18. No lymph node tumor involvement was seen on histopathology.

Subsequently, the patient underwent an uneventful recovery. Follow-up 1-year radiographs revealed no evidence of recurrent or metastatic disease in the thorax (Figure 7C).

DISCUSSION

Etiology & Demographics:

Pulmonary blastomas are uncommon fast-growing lung neoplasms that account for approximately 0.25-0.5% of primary lung malignancies [1]. The pathogenesis of these tumors remains uncertain, but due to their resemblance to fetal lung tissue, it has been proposed that they originate from pluripotent pulmonary blastemas [2, 3]. They occur most often in infants and young children, however, adult cases have been reported [4-7]. Biphasic pulmonary blastoma is a histologically distinct subtype of pulmonary blastomas, which unlike the conventional type, occurs more frequently in adults with a peak in the fourth decade [7, 8]. While some studies have noted a male predominance in biphasic pulmonary blastomas (1.5 or 2 to 1 male to female ratio) [9, 10], others failed to report any difference [11, 12]. No definite causative agent has been determined. However, a strong association with smoking, like in the present case, has been suggested [11, 13]. Products of tobacco smoke, adducts of benzpyrene, have been detected in the tumor tissue [14]. Mutation in the p53 gene was found in 42% of the biphasic subtypes from a study involving 9 cases [15].

Characterization:

Following initial description by Barrett and Barnard in 1945 (originally termed embryoma of the lung) [16], pulmonary blastomas were subsequently classified into 3 subtypes histologically: pleuropulmonary blastomas, well-

differentiated fetal adenocarcinoma, and biphasic pulmonary blastomas. These subtypes contain an epithelial tissue component and/or a mesenchymal component. The designation of pleuropulmonary blastoma indicates the mesenchymal component is immature/malignant, whereas well differentiated fetal adenocarcinoma denotes malignancy of the mesenchymal component. In biphasic pulmonary blastomas, both components are immature and malignant [17]. Of those three, the biphasic subtype is the most common [18]. Based on the 2004 World Health Organization classification paradigm, well differentiated fetal adenocarcinoma is now considered a variant of adenocarcinoma of the lung. Pleuropulmonary blastoma is established as a distinct entity, and biphasic pulmonary blastoma represents a subtype of sarcomatoid carcinoma [12]. Many other malignancies have been associated with pulmonary blastomas, including cystic nephroma, Wilm's tumor, neuroblastoma, rhabdomyosarcoma, medulloblastoma and ovarian Sertoli-Leydig cell tumor [4].

Clinical & Imaging Findings:

There are no specific presenting signs or symptoms of biphasic pulmonary blastomas. Studies suggest symptoms are noted in about 60% of the cases, with the lesions for the rest of the cases found incidentally [10, 17]. When present, patients may experience fever, dyspnea, respiratory distress, cough, hemoptysis, chest pain, weight loss, anorexia, fatigue, or even neurologic symptoms [1, 10]. Currently, there is no specific serum marker for pulmonary blastomas [19].

On imaging, a usually solitary, well-demarcated, peripheral mass is often seen, which may be quite large, measuring more than 10 cm [11]. Some tumors may be large enough to completely opacify the hemithorax on chest radiography [20]. There is a possible slight upper lobar predisposition [10]. In the overwhelming majority of cases, the disease is unilateral, but bilateral disease has been reported. [8, 10] In some cases, pleural effusion may be seen [11, 17]. The tumor typically displaces, not infiltrates, the adjacent tissue [21]. Chest CT scans typically demonstrate a heterogeneous enhancing soft tissue mass with smooth or lobulated margins and probable areas of necrosis [4, 7, 22, 23]. A whirling soft tissue component within a low attenuating mass has been described, but is not always seen [24]. Cavitation is rare [11]. On MRI, the tumor manifests as a heterogeneous mass, typically hyperintense on both T1 and T2 weighted sequences [5]. At times, a multicystic appearance might be seen [20]. Koss et al., in reviewing 24 cases of biphasic pulmonary blastomas, found most cases to be solitary (83%), subpleural (67%), and well-circumscribed (67%). Intrabronchial component is sometimes seen (29%), and necrosis involving 25% or more of the tumor occurs half of the time [11].

On imaging, attention should be paid to regional lymph nodes. Local invasion to the esophagus, bronchial tree, and heart needs to be evaluated [17]. Direct involvement of the chest wall, ribs, and pleura, if present, is considered an indication of advanced disease [8]. Regional and distant metastases to the mediastinum, diaphragm, liver, and adrenal gland should be assessed.

Diagnosis:

The definitive diagnosis of PB is done by cytogenetic analysis of the tumor cells after surgical resection. The use of pre-operative histopathological sampling in diagnosing PB, by methods such as bronchoscopy, fine needle aspiration, CT-guided tumor biopsy, and other methods has been found to be of limited value. The histology of these tumors is diverse and misleading, with features resembling adenocarcinoma or other sarcoma of the lung. Tissue sampling from multiple areas is required to confirm the presence of both epithelial and mesenchymal malignant components and establish the diagnosis.

On the other hand, immune-histochemical analysis is supportive in reaching the diagnosis, due to the biphasic structure of the tumor. Epithelial components stain positive for Cytokeratin, CEA, epithelial membrane antigen (EMA), thyroid transcription factor-1 (TTF-1), and surface protein alpha. The stromal components stain positive for vimentin, desmin, muscle-specific actin, myoglobin, and S-100 [25].

Treatment & Prognosis:

The cornerstone of treatment for biphasic pulmonary blastoma is surgical resection by either lobectomy or pneumonectomy, taking into consideration the resection of any infiltrated organ, in particular the pleura and pericardium. The role of adjuvant therapy is not well cemented due to the still rarity of the condition and rapid advances in radiation and chemotherapeutic regimens. In cases of unresectable tumors, combination of chemotherapy and radiation has been used with at times favorable clinical response [13]. Some studies have suggested palliative radiotherapy in the case of brain metastases. A four-drug combination regimen consisting of cyclophosphamide, doxorubicin, vincristine, and dactinomycin has been noted to show some promise [26].

The prognosis of biphasic pulmonary blastoma is considered the poorest among all subtypes of pulmonary blastomas. The 5-year survival rate for BPB is documented at 16%-25%, and 10-year at 8% [11]. The median survival is documented at 26 months for patients who received lobectomy or minor resection versus 9 months in those who underwent pneumonectomy [9], likely reflecting the extent of disease at presentation. A large size of the tumor, metastasis at presentation, and tumor recurrence are poor prognostic factors [11]. Local recurrence is common after surgical resection (43%) [27]. Regional and distant metastases to the mediastinum, pleura, diaphragm, liver, adrenal gland, and heart are frequently reported [5, 8]. Recurrence tends to occur within the first year or not at all [9].

Differential Diagnosis:

The differential diagnosis of biphasic pulmonary blastoma is broad and includes other solitary lesions of the chest. In the setting of known primary malignancy, metastatic disease must be considered, in particular if multiple, multilobular, or bilateral disease is present. In the presence of smoking history,

as is common with biphasic pulmonary blastoma, bronchogenic carcinomas are much more common. The typical peripheral location of biphasic pulmonary blastoma makes it a likely mimic of large cell carcinoma or adenocarcinoma. Other primary pulmonary malignancies, such as sarcomatoid carcinomas (pleomorphic, spindle cell, giant cell, and carcinosarcoma) or pulmonary primitive neuroendocrine carcinomas, often cannot be confidently differentiated from biphasic pulmonary blastoma by imaging findings alone. Benign lesions of the chest should also be kept in mind. The presence of calcifications should raise suspicion for a granulomatous condition, pulmonary chondroma, sclerosing hemangiomas, or hamartoma. The presence of fat makes hamartoma a much more likely differential. The low density internal component of biphasic pulmonary blastoma may be mistaken for a complicated bronchogenic cyst, however, no complex enhancing component should be seen with bronchogenic cysts. Likewise, hematomas should not enhance.

TEACHING POINT

Biphasic pulmonary blastoma is a malignant and rare lung neoplasm with a unique histology. It occurs most commonly in the 4th decade of life, and an association with cigarette smoking has been suggested. Approximately 60% of the patients present with non-specific symptoms. On imaging, a solitary, peripherally located, typically unilobar, heterogeneous mass is often seen, which can be quite large at presentation. Enhancing components and areas of necrosis are typical, and some studies report a swirling appearance of the internal soft tissue component. An associated pleural effusion is sometimes noted. Currently, there is no specific or diagnostic imaging finding for this entity. A poor prognosis has generally been reported, and surgical resection remains the preferred treatment.

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FIGURES

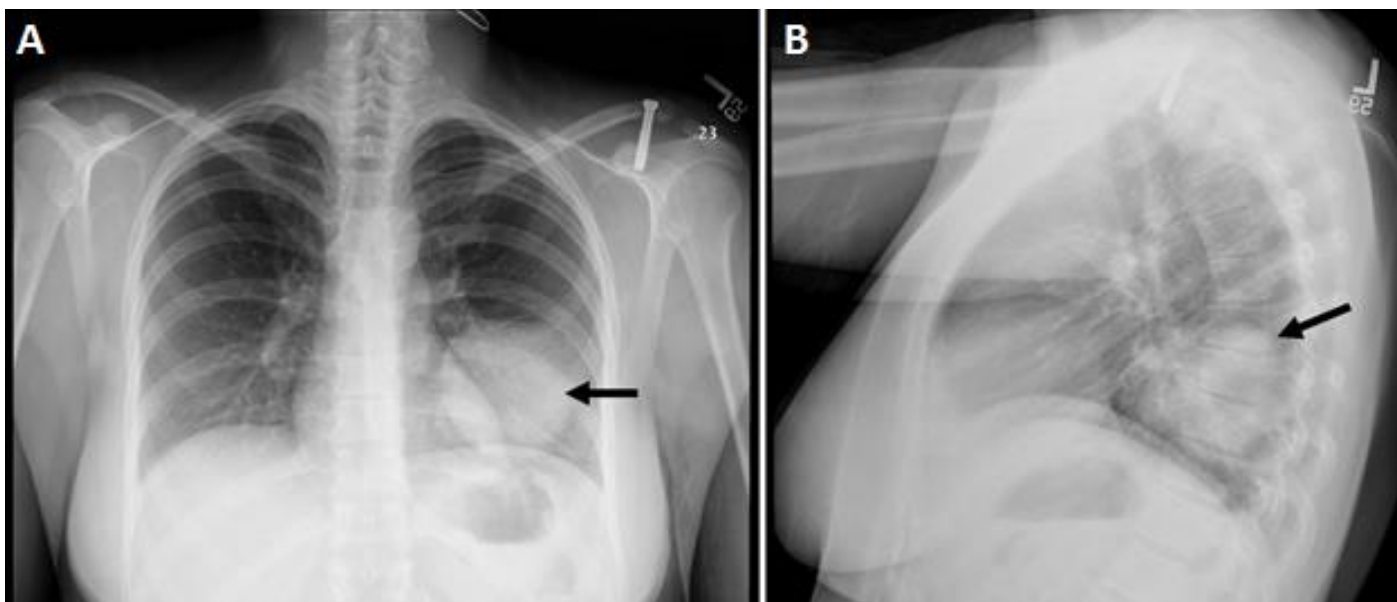


Figure 1: A 33-year-old female with biphasic pulmonary blastoma. Technique: Chest radiograph with anteroposterior view (A) and lateral view (B) Findings: There is a large, round, and well-circumscribed lesion projecting over the left lower lung zone on the frontal projection, which localizes to the lower lobe on the lateral projection (arrows). The left cardiac silhouette remains distinct. There is no evidence of hilar lymphadenopathy, erosive changes in the adjacent ribs, or presence of a pleural effusion.

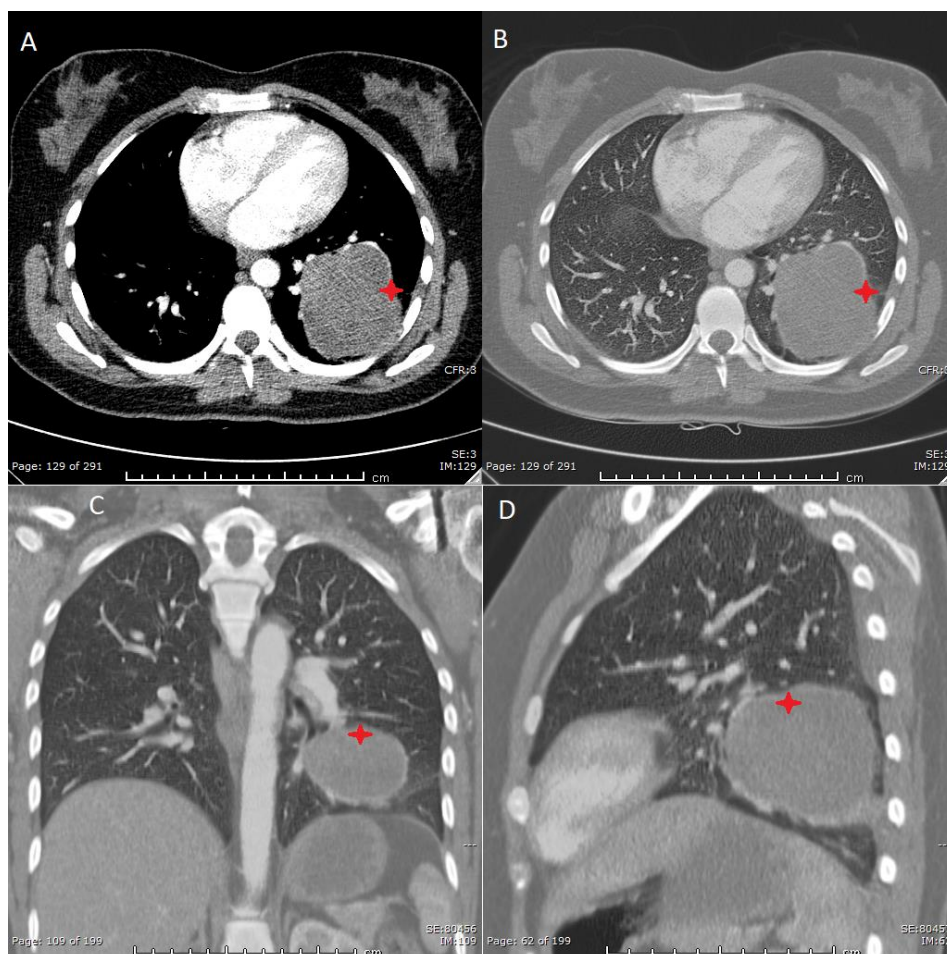


Figure 2 (left): A 33-year-old female with biphasic pulmonary blastoma.

Technique: Contrast-enhanced CT of the chest. Axial images at the level of the lower lung zone, with mediastinal window (A, level: 30, window: 300) and mediastinal/lung window (B, level: -300, window: 2000). Coronal (C) and sagittal (D) images with mediastinal/lung window (level: -300, window: 2000).

Findings: There is a 7 cm, solitary, low density, well-circumscribed, minimally heterogenous mass noted in the left lower lobe (asterisk). Subadjacent atelectasis of the lung is seen without infiltrative changes. Posteriorly, the mass abuts the pleural surface. There is no bony changes or clear evidence of chest wall invasion. No lymphadenopathy or additional pulmonary lesion is identified. Splying of the left lower lobe segmental bronchi is seen. The mass does not contact the more central hilar or mediastinal structures.

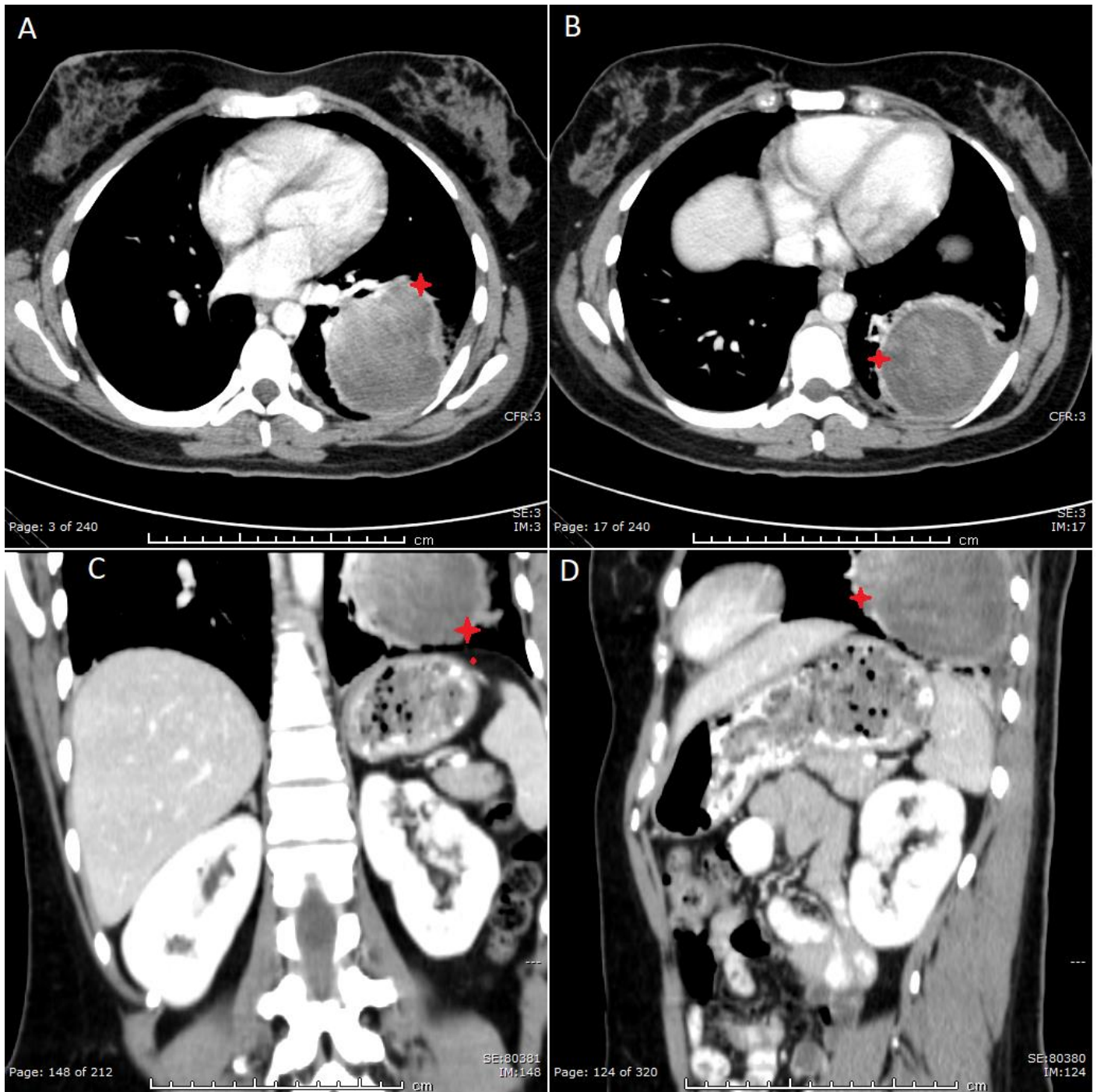


Figure 3: A 33-year-old female with biphasic pulmonary blastoma.

Technique: Contrast-enhanced CT of the abdomen and pelvis with mediastinal window (level: 30, window: 300). Axial images at the level of the cardiac atria (A) and ventricles (B) as well as coronal (C) and sagittal (D) images through the mass.

Findings: On the abdominal images, there is partially seen and now better appreciated central heterogenous irregular areas of internal contrast enhancement within the lesion (asterisk), consistent with viable soft tissue component. The thick and mildly irregular peripheral component is now seen. The central soft tissue component measures 40 HU while the nonenhancing component measures 18 HU. Areas of atelectasis are again noted.

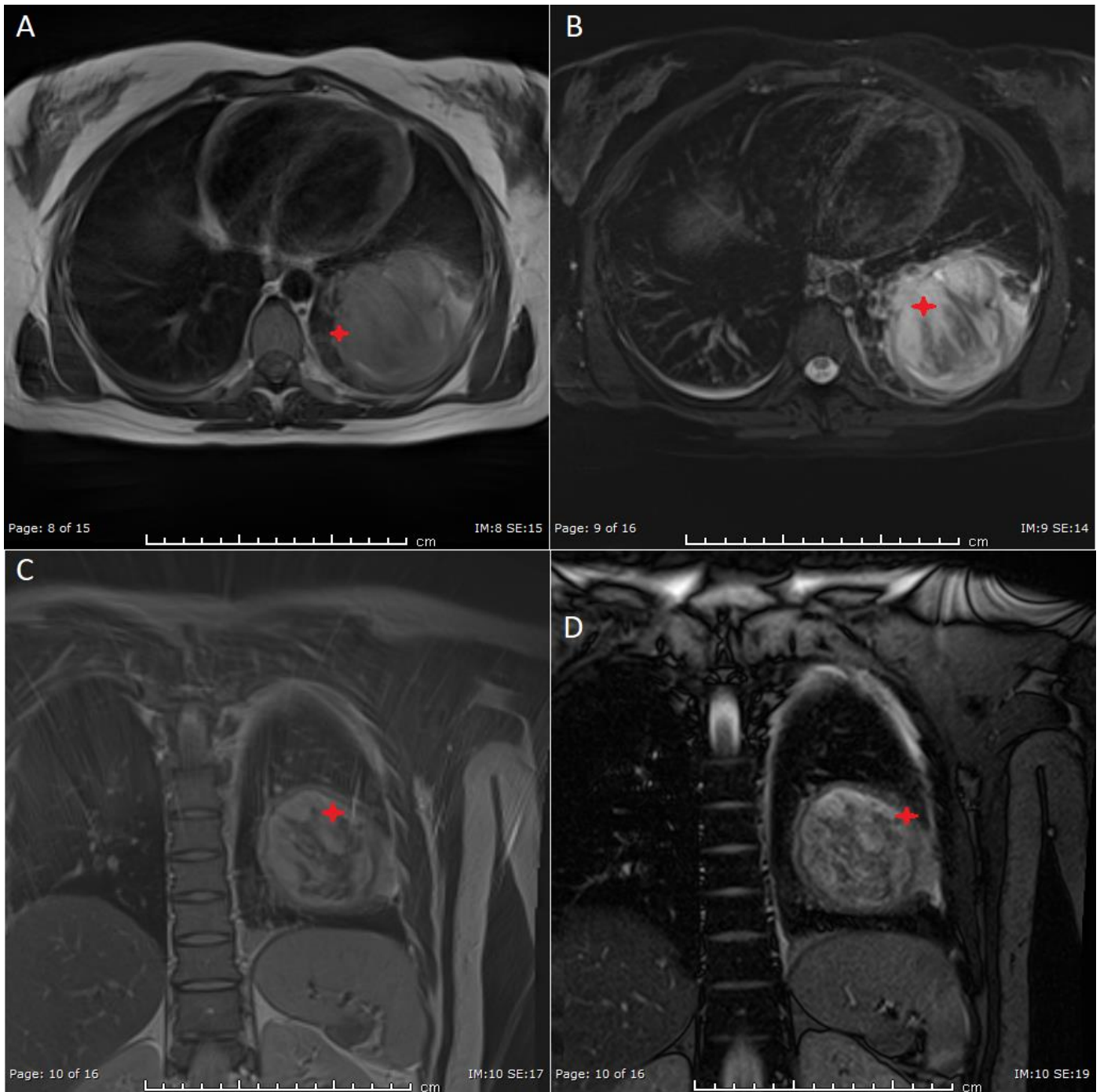


Figure 4: A 33-year-old female with biphasic pulmonary blastoma.

Technique: MRI axial view of the chest with fast spin echo T1 (A) and T2 (B) weighted images with coronal T2 (C) and coronal SSFP (D) images.

Findings: (A) The left lower lobe mass is noted to contain relative T1-hypointense areas of septations internally with otherwise relative T1-hyperintense central region, corresponding to the hypodense region on prior CT and consistent with increased protein content or hemorrhage. The soft tissue component of the mass (peripheral ring and internal septations) appear T1 hyperintense when compared to skeletal muscle. (B) On T2 images, the internal septations are better appreciated on the background of T2-hyperintense central region. A trace amount of pleural fluid is noted posteriorly. The heterogenous and complex nature of the lesion is also noted on the coronal images (C and D).

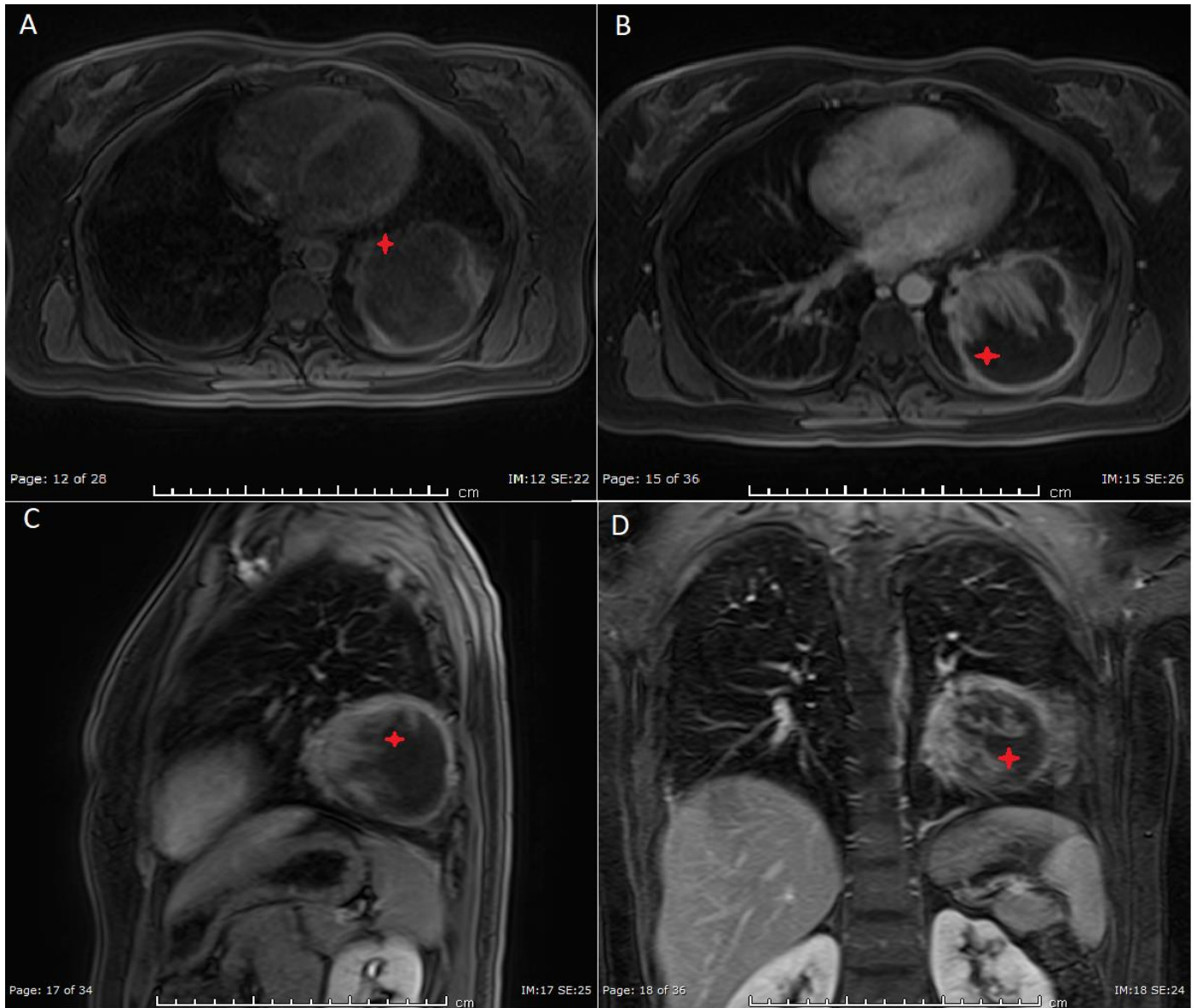


Figure 5: A 33-year-old female with biphasic pulmonary blastoma.

Technique: MR T1 weighted images of the chest with fat suppression prior to (A) and following (B) contrast administration in axial view as well as post-contrast images in sagittal (C) and coronal (D) views.

Findings: The left lower lobe mass appears well-circumscribed without infiltrative changes. The peripheral thick irregular rim and central areas of hair-like, curvilinear septations demonstrate avid enhancement: compare precontrast (A) and postcontrast (B) axial images.

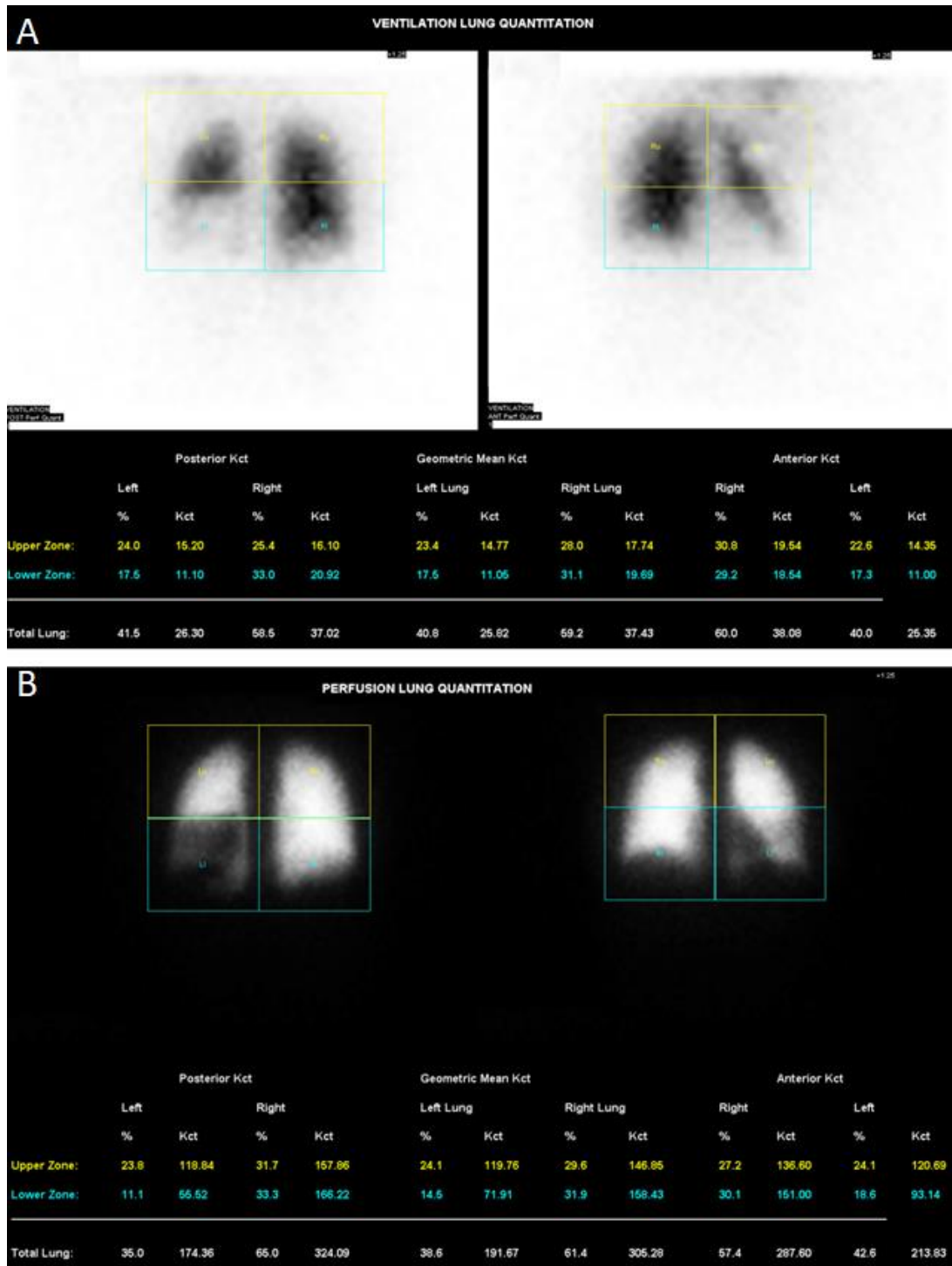


Figure 6: A 33-year-old female with biphasic pulmonary blastoma.

Technique: Ventilation-perfusion scan using ¹³³Xe INH and ^{99m}Tc macroaggregated albumin IV.

Findings: Nuclear ventilation-perfusion scan of the lungs for pre-operative lung function evaluation demonstrates large photopenic defect in the left lower lobe on both ventilation (A) and perfusion (B), corresponding to the known lesion. The split function was estimated at approximately 40-60 left to right split.



Figure 7: A 33-year-old female with biphasic pulmonary blastoma. Technique: Portable AP radiographs of the chest (A and B) with normal PA frontal (C) and lateral (D) radiographs of the chest.

Findings: Pre-operative frontal radiograph of the patient demonstrates the known large left lower lobe mass (A). Portable frontal radiograph of the chest after left lower lobectomy demonstrates expected postsurgical changes with two chest tubes in place on the left (B). The lesion is no longer seen. Follow-up radiographs 1 year after surgery demonstrate changes of prior left lower lobectomy without evidence of recurrence (C and D).



Figure 8 (left): A 33-year-old female with biphasic pulmonary blastoma. Technique: Gross surgical specimen of the resected tumor. Findings: The opened gross specimen demonstrates a well-circumscribed tumor, measuring approximately 7 cm. The peripheral aspect of the mass is solid. Internally, areas of soft tissue as well as hemorrhage (arrows) are seen.

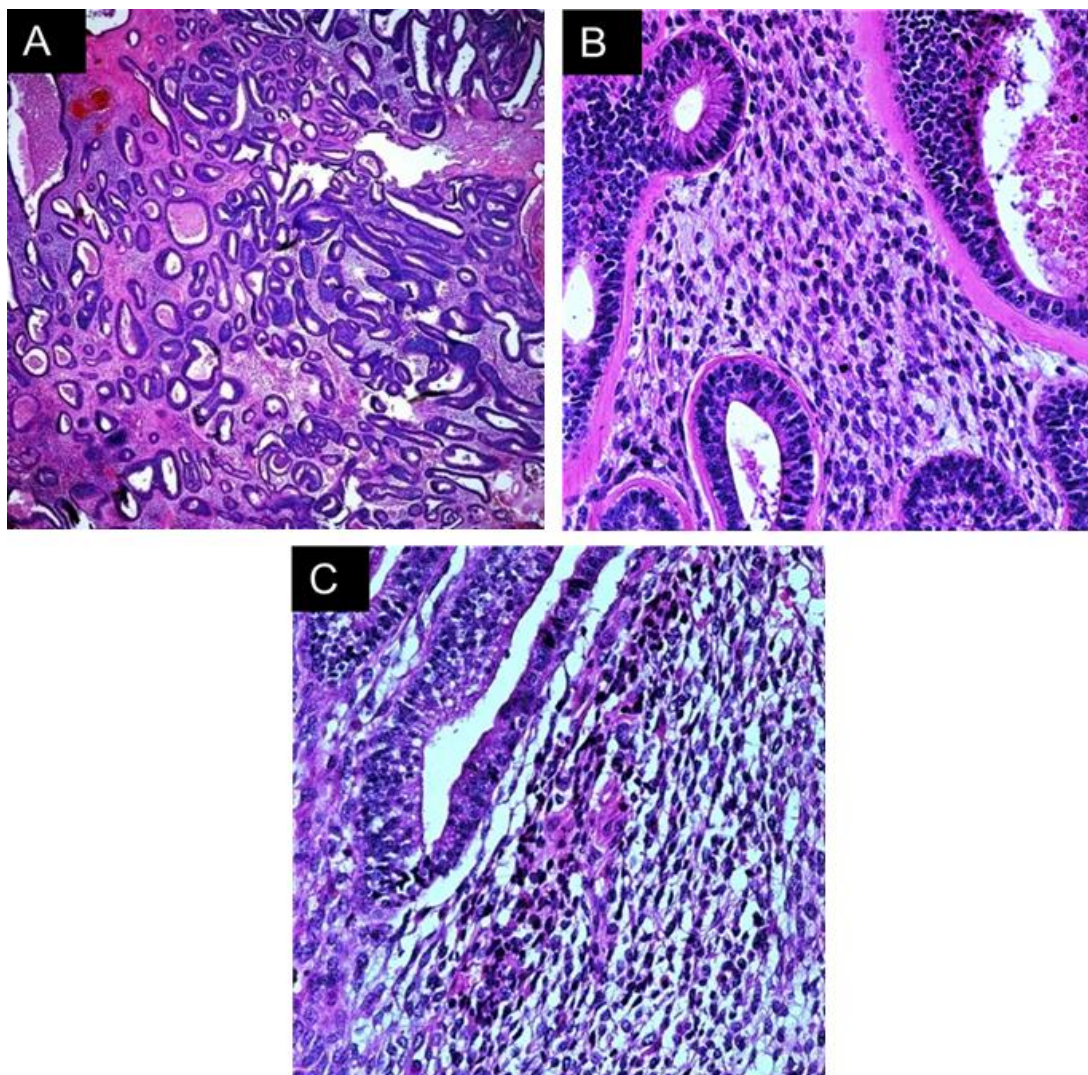


Figure 9: A 33-year-old female with biphasic pulmonary blastoma. Technique: Low power field (A, original magnification x 100) and high power field (B and C, original magnification x 400) microscopic images with hematoxylin and eosin stains from the tumor Findings: (A), (B), and (C) shows the tumor to be biphasic with malignant, but primitive, glandular and stromal elements.

Etiology	Uncertain, possibly originate from pluripotent pulmonary blastemas
Incidence	Rare, accounting for 0.25-0.5% of primary malignant lung malignancies
Gender ratio	Equal or male predominant
Age predilection	Adults with a peak in the fourth decade
Risk factors	Strong association with smoking with some cases demonstrating p53 mutation
Treatment	Surgical resection
Prognosis	Poor, with 5-year survival rate at 16-25% and 10-year at 8%
Findings on imaging	Usually presents as a solitary, large, well-circumscribed, peripheral lung mass mostly unilateral not infiltrative to adjacent tissues. Appears heterogenous with enhancing components. Necrosis is common.

Table 1: Summary table for Pulmonary Blastoma.

	CXR	CECT	MRI
Biphasic Pulmonary Blastoma	- well-demarcated, peripheral solitary mass	-Heterogeneous enhancing soft tissue mass with smooth or lobulated margins and probable areas of necrosis	- Heterogeneous mass, typically hyperintense on both T1 and T2 weighted sequences. A multicystic appearance might be seen
Pulmonary Carcinosarcoma	-Pulmonary mass or nodule - In case of endobronchial carcinosarcoma, opacification with post-obstructive changes (atelectasis- pneumonia-consolidation) may be shown.	-Well-circumscribed tumors. Heterogenous enhancement with areas of low attenuation represent necrosis or cavitation. Calcification may be observed	-Heterogenous mass with variable signal intensity on both T1 and T2 weighted sequence. Internal regions of high signal intensity consistent with cystic components
Mucoepidermoid Carcinoma	-Pulmonary mass or nodule - In case of endobronchial MEC, opacification with post-obstructive changes (atelectasis- pneumonia-consolidation) may be shown.	-Well defined endobronchial mass or peripheral nodule with 50% chance of calcification. Variable levels of contrast enhancement depending on tumor grade.	-Heterogeneous mass with changeable signal intensities based on the tumor grade. Low grade tumors demonstrate low signal intensity on T1 and high signal intensity on T2. High grade tumors demonstrate low to intermediate signal intensity on both T1 and T2
Pulmonary Hamartoma	-Sharply demarcated pulmonary mass or nodule with characteristic calcifications.	-Smooth margin tumor. Fat-containing lesion with focal calcifications -In case of endobronchial hamartoma, post-obstructive changes (pneumonia- atelectasis-consolidation) may be shown.	-Heterogenous mass with intermediate signal intensity on T1, high signal intensity on T2

Table 2: Differential diagnosis table for Pulmonary Blastoma.

Diagnosis	Epithelial Component	Mesenchymal Component	Population
Biphasic pulmonary blastoma	Immature	Immature	Adults, middle age to elderly
Pleuropulmonary blastoma	N/A	Immature	Children
Well-differentiated fetal adenocarcinoma	Immature	N/A	Adult, females in their 40s

Table 3: Differential diagnosis table for Pulmonary Blastoma based on microscopic morphology.

ABBREVIATIONS

CT = Computer Tomography
MRI = Magnetic Resonance Imaging

KEYWORDS

Pulmonary Blastoma; Biphasic Pulmonary Blastoma; Pulmonary Neoplasm; Magnetic Resonance Imaging; Computed Tomography

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