

CASE REPORT

Incidental early diagnosis of biphasic pulmonary blastoma in a patient with history of stage IV lung adenocarcinoma

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Introduction

Biphasic pulmonary blastoma is a rare lung malignancy with characteristic histology resembling 10- to 16-week gestational lung, containing both epithelial and mesenchymal components.¹ Since being first described in 1945, around only 200 cases have been reported.² Previously reported cases have been mostly limited to patients presenting at an advanced stage, and therefore the malignancy has been understood to have a poor prognosis.³ Here, we report a case of incidental early diagnosis and successful treatment of a biphasic pulmonary blastoma while undergoing surveillance after treatment for stage IV lung adenocarcinoma.

Case report

A 63-year-old female with a history of long-term tobacco use, COPD, and stable disease of stage 4 lung adenocarcinoma for three years after short-term nivolumab treatment, developed a pulmonary nodule in the right upper

Abstract

Biphasic pulmonary blastoma is a rare but lethal type of lung malignancy with characteristic histology of both epithelial and mesenchymal components. Previously reported cases have been limited to presentation at advanced stages, suggesting that the clinical course of the disease is usually aggressive. Here, we report a case of incidental diagnosis of biphasic pulmonary blastoma by imaging surveillance in a patient previously treated for adenocarcinoma of the lung. The patient was diagnosed with stage 1 disease and underwent successful resection. Next-generation sequencing (NGS) revealed a high mutation burden, a finding not previously reported in a patient with biphasic pulmonary blastoma.

lobe during the interval of her three-year surveillance for primary lung adenocarcinoma.

The patient was originally diagnosed with a stage IIIb adenocarcinoma nearly four years previously after initial presentation with left-sided neck lymphadenopathy. She had a left upper lobe mass with diffuse lymphadenopathies in the hilum and mediastinum visible on CT scan. She was treated with paclitaxel and carboplatin, but the disease progressed with brain metastasis and bulky lymphadenopathies over eight months. Her lung adenocarcinoma was restaged to stage IV. She received stereotactic radiation for brain metastasis and received nivolumab every three weeks, in total eight doses, until she refused further treatment. She underwent imaging surveillance every six months. Her scan revealed a partial response to immunotherapy with resolution of lymphadenopathy. Her primary lung cancer remained stable without any new nodules, progression, or metastasis for three years until a new nodule was found. The patient also

remained asymptomatic other than her chronic shortness of breath and cough due to her underlying COPD.

At her three-year surveillance, the newly developed right upper lobe nodule measured 1.5 cm × 0.8 cm (shown in Fig 1a). The patient missed her follow-up appointment, so PET-CT scan was delayed for two months. Following PET-CT scan, there were no other signs of increased metabolic activity other than the new nodule (as shown in Fig 2). At around the same time, the patient was seen at the emergency department due to exacerbation of her COPD symptoms. A CT pulmonary angiogram was carried out as part of her COPD exacerbation work-up at the emergency department visit. The study revealed an increase in the size of the mass to 2.8 cm × 2.1 cm, which was eight times larger in volume compared to that initially detected (shown in Fig 1b).

Histopathology from imaging-guided biopsy of the mass showed high grade neoplasm with malignant glandular and mesenchymal elements, consistent with biphasic pulmonary blastoma. Histologic characteristics were distinctly different from the patient's previously diagnosed adenocarcinoma. Immunohistochemistry stains revealed wild-type beta-catenin, diffuse p53 expression, positive AE1/AE3 in the glandular component, and negative TTF-1 and chromogranin. Her previous

adenocarcinoma exhibited a glandular pattern and TTF-1 expression was positive (Fig 3). Next-generation sequencing (NGS) revealed a genetic profile distinctly different from the primary lung adenocarcinoma. The secondary tumor expressed a high tumor burden with 23 mutations per megabase. Extensive mutations were found in NF1, FGFR3, MBN1, ATRX, KDMGA, PARK2, PBRM1, amplifications in MCL1, MDM4, NKX2 and PIK3CB with low expression of PD-L1 (Table 1). The primary adenocarcinoma was found to have a high PD-L1 expression in the primary tumor without high mutational burden.

Shortly after her diagnosis, the patient underwent right upper lobectomy and mediastinal lymph node dissection. Surgical margins and mediastinal lymph node dissection were negative for tumor involvement. The surgical pathology confirmed the biopsy pathological findings. The follow-up CT scan of her chest after recent surgery revealed only postsurgical changes. To date, the patient has remained clinically well at her follow-up appointments.

Discussion

To our knowledge, the case reported here represents an extremely rare clinical presentation of early stage biphasic

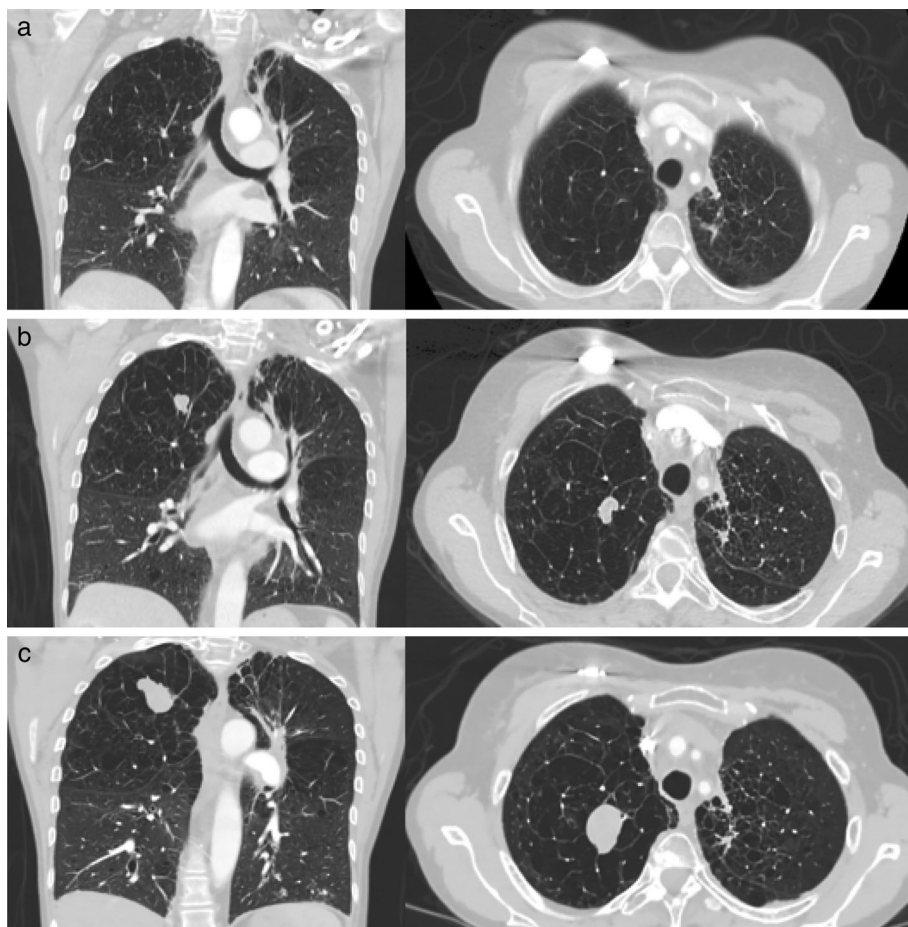


Figure 1 (a) Left (coronal), right (axial): computed tomography (CT) chest scan with contrast at 2.5 year surveillance for primary lung adenocarcinoma, with no detectable mass in the right upper lobe. (b) Left (coronal), right (axial): CT chest scan with contrast at three-year surveillance for primary adenocarcinoma, showed a new 1.5 × 0.8 cm pulmonary nodule in the right upper lobe. (c) Left (coronal), right (axial): two months after CT chest scan obtained at three-year surveillance as (b), three years and two months after diagnosis, CT pulmonary angiogram showed interval growth to 2.8 cm × 2.1 cm at the right upper lobe.

Figure 2 Left, right PET-CT scan obtained at initial diagnosis of pulmonary blastoma showed enhanced signal at the right upper lobe nodule with no other uptake.

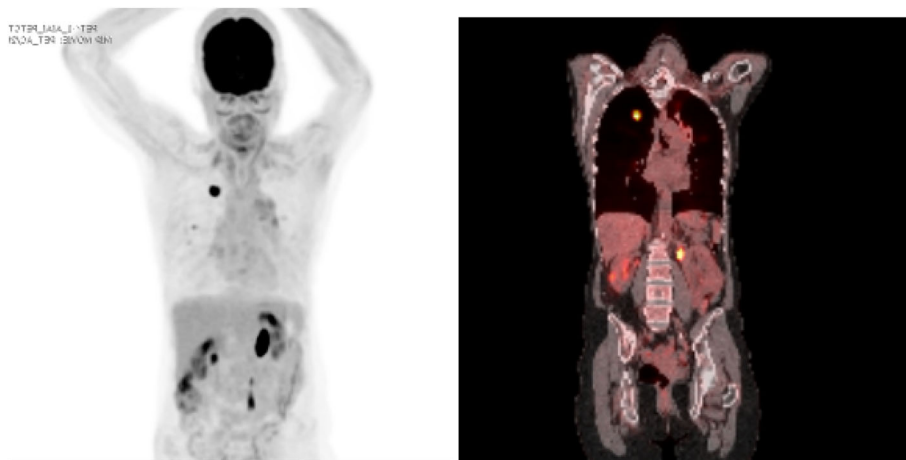
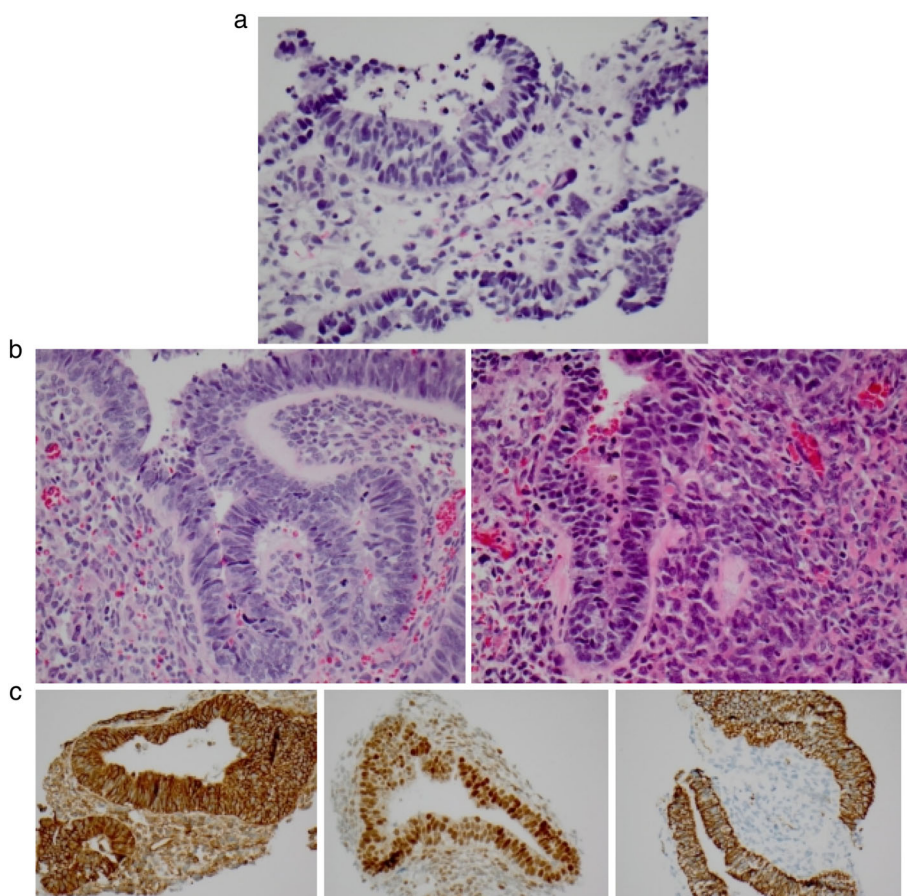


Figure 3 (a) Left: H&E $\times 40$, right: IHC with TTF-1 $\times 40$, pulmonary nodule sample obtained by imaging-guided biopsy in 1/2019, mixed with glandular and stroma, negative TTF-1. **(b)** Left, right: H&E $\times 40$. Pulmonary nodule sample obtained after surgery, mixed glandular and stroma, similar pattern with embryonic lung at 10 to 16 weeks. **(c)** IHC $\times 40$, sample obtained by imaging-guided biopsy in 1/2019, left – IHC with beta-catenin, middle – IHC with p-53, right – cytokeratin.



pulmonary blastoma, with evidence of rapid growth prior to resection. The aggressive tumor growth observed here is consistent with the poor prognosis of most patients with this rare tumor. Many patients with advanced disease receive chemotherapy; however, the tumor usually relapses within one year. A case series study of 23 patients with

long-term follow-up reported that only nine patients out of 23 (39%) survived without cancer recurrence.⁴

This is also the first report in the literature of biphasic pulmonary blastoma presenting as a second primary lung malignancy. Despite the fact that lung cancer remains one of the deadliest types of cancer,⁵ the number of long-term

Table 1 Next-generation sequencing (NGS) results from pulmonary blastoma compared to primary adenocarcinoma

	Pulmonary blastoma	Primary adenocarcinoma
Tumor mutational burden	TMB-high (23Muts/Mb)	Could not be determined (low tumor purity)
Microsatellite status	MS-Stable	Could not be determined (low tumor purity)
	NF1 rearrangement intron 47	<i>KRAS</i> G12A
	FGFR3 amplification - equivocal	<i>TP53</i> R280*
	MEN1 splice site 670-1G > C	
	ATRX splice site 5698-2_5698-1AG > TA	
	KDM6A G1160V	
	MCL1 amplification - equivocal	
	MDM4 amplification - equivocal	
	NKX2-1 amplification - equivocal	
	PARK2 E207*	
	PBRM1 rearrangement exon 21	
	PIK3C2B amplification - equivocal	
	TBX3 Q722fs*170	
	TP53 T155I, E298*	
PD-L1 expression level (tumor proportion score)	0	80
Disease relevant genes with no reportable alterations	<i>EGFR, KRAS, ALK, BRAF, MET, RET, ERBB2, ROS1</i>	<i>EGFR, ALK, BRAF, MET, RET, ERBB2, ROS1</i>

*nonsense mutation.

survivors is increasing, probably because of more widespread screening and improved treatment such as in the case reported here. Because more patients are surviving lung cancer, studies are reporting an increasing number of diagnoses of second primary cancer and multiple primary lung cancer.⁶ Even though second primary cancer has been reported to have a better prognosis than first primary cancer,⁷ discussing prognosis or treatment plans with patients who have multiple primary cancers should be carefully assessed as reviewed previously.⁸ In our case, we believe the patient required continued monitoring and surveillance for both her primary and secondary cancer diagnoses, as patients have been known to have a poor prognosis with high recurrence and relapse, although, to date, the patient reported here had a good treatment response.

It is also notable that cancers with high mutational burden, such as the case reported here of pulmonary blastoma, have been thought to be a consequence of exposure to powerful carcinogens, such as tobacco exposure or mutagens such as ultraviolet light.⁸ Our patient's history of chronic inflammation secondary to COPD, long-term tobacco use, and prior exposures to chemotherapy, radiotherapy, immunotherapy or radiation exposure from surveillance could have conceivably played a role in the development of a second lung malignancy. Recently, high tumor mutational burden has been shown to be associated with better response to immune checkpoint inhibitors (ICIs) by causing increased immunogenicity.^{9,10} Whether the patient reported in our study, or other cases of biphasic pulmonary blastoma would respond to immune therapy

remains unknown, and therefore needs further study. Further genetic data from pooled cases of biphasic pulmonary blastoma are warranted to develop effective treatment approaches including the possible use of checkpoint inhibitors.

In conclusion, here we report an extremely rare case of incidental diagnosis and development of biphasic pulmonary blastoma. Our case demonstrated rapid growth of the tumor and interesting characteristics of genetic profile with high mutational burden that might explain the poor prognosis of tumor. Our case also implicates the need for additional genomic and clinical data to better understand the molecular pathways involved in tumor progression.

Disclosure

The authors declare that there are no conflicts of interest.

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