



## Case Report

# Rare capture: The detection of synchronous diffuse large B-cell lymphoma and lung adenocarcinoma diagnosed by effusion cytology

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## ABSTRACT

The diagnosis of two primary synchronous malignancies in a single pleural effusion cytology specimen is exceedingly rare. We describe, to the best of our knowledge, the first reported case of lung adenocarcinoma and suspected relapse of Diffuse Large B-Cell Lymphoma (DLBCL) diagnosed from a solitary effusion sample.

## 1. Introduction

Malignant pleural effusions are common complications in patients with primary lung cancer, breast cancer and lymphoma [1,2]. Synchronous malignancies (SM) occupying the same pleural space not only present an extraordinary phenomenon, but a dilemma which demands refinement of management and treatment. The definition of SM is diagnosing two or more different types of cancer within six months, which are distinct by histology and location [3]. The coexistence of two malignancies in the pleural fluid is extremely rare [4,5] and is sparsely reported in the literature. Here, we stress the utility and importance of the effusion cytology in unmasking a co-existing primary malignancy.

## 2. Case report

A 70-year-old female presented with progressively worsening shortness of breath, dyspnea on exertion and right sided pleuritic chest pain for two weeks duration. She had a history of right breast ER/PR positive HER-2 negative poorly differentiated ductal carcinoma status post wide local excision and adjuvant radiation therapy in 2021, Diffuse Large B-Cell Lymphoma (DLBCL) status post chemotherapy in 2018, right upper lobe pulmonary nodules status post wedge resection, with unknown pathology, in 2018, lung cancer status post left lower lobectomy, also with unknown pathology, in 2015 and chronic obstructive pulmonary disease (COPD). Physical examination significant for right basilar crackles and dullness to percussion of the right lung. Vital signs and routine laboratory

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tests were unremarkable. Chest x-ray (CXR) performed in the emergency department demonstrated a right pleural effusion (Fig. 1). A computed tomography (CT) angiogram of the chest confirmed moderately sized partially loculated right pleural effusion with associated right lower lobe compressive atelectasis as well as a new soft tissue nodularity noted along the right upper lobe wedge resection site (Fig. 2). Diagnostic and therapeutic thoracentesis was performed with removal of 900 cc of serosanguinous fluid. Post-thoracentesis chest x-ray demonstrated interval decrease of right sided effusion (Fig. 3). Analysis of pleural fluid was determined to be an exudative, lymphocytic predominant effusion (72% lymphocytes) (see Table 1). The fluid culture resulted negative.

Cytologic pleural fluid examination demonstrated small to medium sized lymphocytes, positive for cluster of differentiation (CD) 45. CD3 positive T-Cells are mixed with CD20 positive B-cells, more T-cells than B-cells. Flow cytometry reported monotypic B-cells (12% of cells), positive for lambda, CD19, CD20, CD23; negative CD10, CD5, CD38 consistent with a CD5, CD10 negative lymphoproliferative disorder. In 2018, the patient was diagnosed with DLBCL, with CD5<sup>-</sup>, CD10<sup>-</sup>, MUM1<sup>-</sup>, BCL 6<sup>+</sup> phenotype. Therefore, the lymphoma revealed in this pleural fluid specimen may well represent a relapse of DLBCL. Given the limitation of the tissue sample, with the cellblock sent to Foundation One for molecular study, no further immunophenotyping was able to be performed.

Further immunohistochemical stains (Fig. 6) were performed and revealed the malignant cells to be positive for Ber-EP4 and thyroid transcription factor- 1 (TTF-1), negative for CK7, CK20, PAX-8, CDX-2, Gata3; calretinin stain highlights the mesothelial cells. These findings were supportive of a diagnosis of metastatic adenocarcinoma of the lung. Hematopathology was consulted to rule out low grade lymphoproliferative disorder in the pleural fluid. After further review of the cell block, it was noted that there were small to medium sized lymphocytes (Fig. 7). Flow cytometry was performed revealing monotypic B-cells (12% of cells), positive for lambda, CD19, CD20, CD23 and negative for CD10, CD5, CD38. The findings were consistent with diagnosis of a lymphoproliferative disorder. The hematopathologist went on to note that since the patient had a history of DLBCL, the above findings may be consistent with a relapse of DLBCL. Fluid cytology was ultimately indicative of a synchronous primary metastatic disease.

The patient subsequently underwent placement of a right indwelling pleural catheter (IPC) for management of recurrent and symptomatic pleural effusion (Fig. 4). Patient was discharged on hospital day three and was provided an outpatient oncology and pulmonary follow up. Upon follow up in the pulmonary clinic, a positron emission tomography (PET) scan was performed which demonstrated new sites of pathologic fludeoxyglucose (FDG) uptake suspicious for biologic tumor activity including diffuse heterogeneous uptake in thickened right pleura with a standard uptake value (SUV) up to 4.4, right paratracheal and supra hilar (SUV 4.1), right hilar (SUV 4.2), and subcarinal adenopathy (SUV 4.1) (Fig. 5). No other abnormal sites of FDG uptake noted. At the time of writing the patient continues to follow with the oncology and pulmonary team, respectively for medical management.

### 3. Discussion

We describe herein, and to the best of our knowledge, the first reported case of synchronous metastasis of lung adenocarcinoma and a recurrent DLBCL to the pleura. Pleural effusions may result from numerous plausible causes, the most common of which include congestive heart failure, cancer, and pneumonia and are classified as transudate or exudate based on the nature of the pleural fluid obtained by thoracentesis [1,2]. Malignant pleural effusions (MPE) are exudative effusions, accounting for 20% of pleural effusions,



Fig. 1. Chest Xray demonstrating right pleural effusion on presentation.

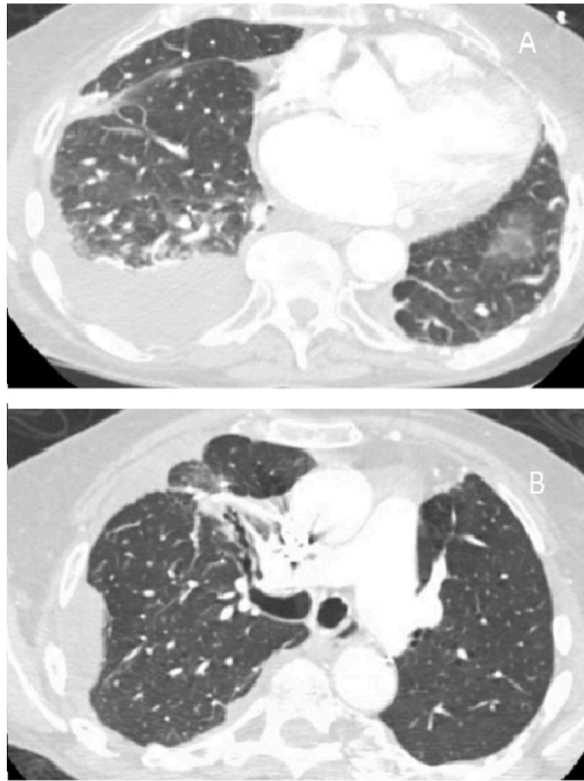


Fig. 2. Computed Tomography Angiogram of the chest revealing post right upper lobe wedge resection with increased soft tissue nodularity along the surgical sutures measuring up to  $1.4 \times 0.9$  cm (A) and moderate right pleural effusion (B).

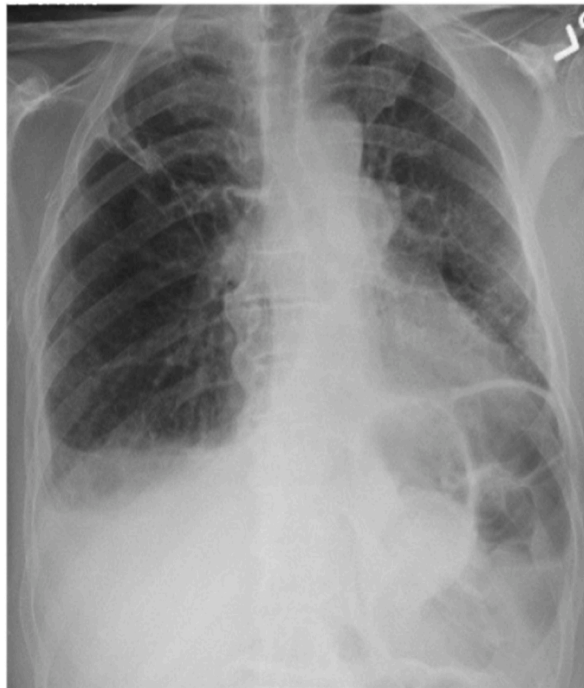
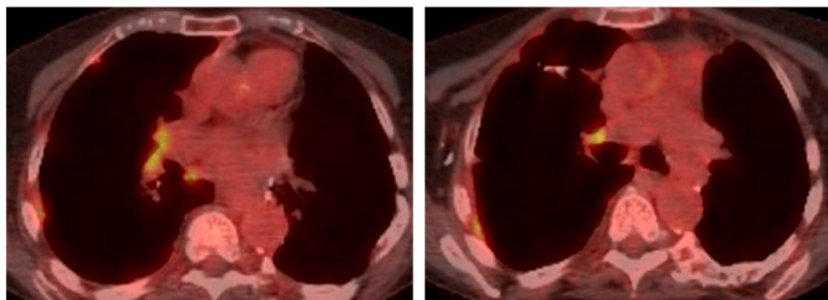


Fig. 3. Chest Xray demonstrating interval decrease in right pleural effusion post thoracentesis.

**Table 1**

Highlights of the pleural fluid and relevant serum results.

Pleural fluid results	
Cell count	1053 $\mu$ L
Lymphocytes	72%
Monocytes	4%
Segmented granulocytes	21%
Mesothelial cells	3%
Pleural Fluid pH	7.9
Protein	5.1 g/dL
Albumin	3.5 g/dL
Glucose	93 g/dL
Gram stain and culture	Negative for any growth, including fungus at four weeks.
Positive Immunohistochemical stains	1. Ber-EP4 2. TTF-1 3. Calretinin
Relevant serum studies	
Serum LDH	193 U/L
Serum Albumin	4.4 g/dL
Serum Protein	7.2 g/dL

**Fig. 4.** Chest Xray revealing of stable right pleural effusion and Interval right indwelling pleural catheter placement.**Fig. 5.** PET scan demonstrating pathologic FDG uptake suspicious for biologic tumor activity including diffuse heterogeneous uptake in thickened right pleura, right paratracheal and supra hilar, right hilar, and subcarinal adenopathy.

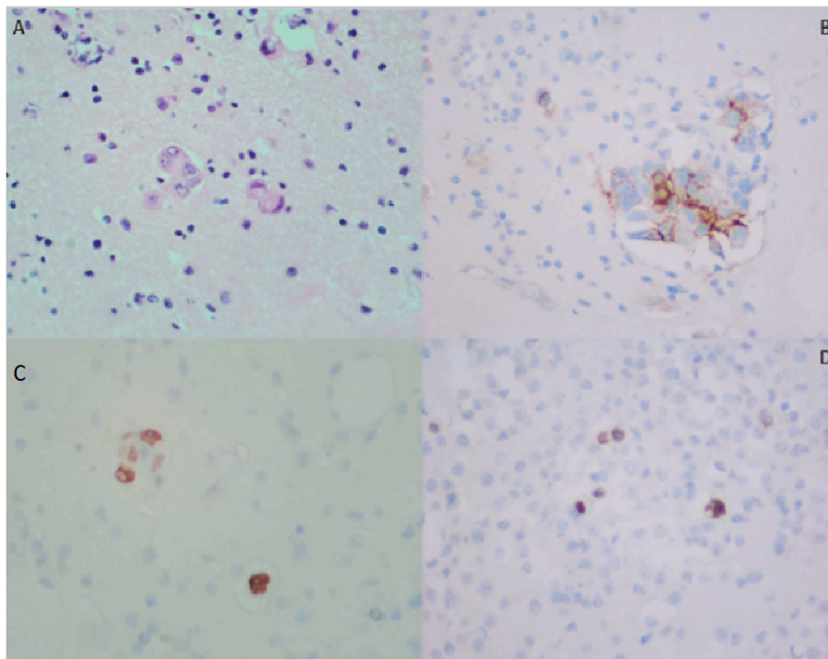


Fig. 6. Cell block of pleural fluid demonstrate the large metastatic adenocarcinoma cells admixture with many lymphocytes, H&E (A). The carcinoma cells are positive for BerEP4(B) and TTF-1 (C). Calretinin stains some scattered mesothelial cells (D).

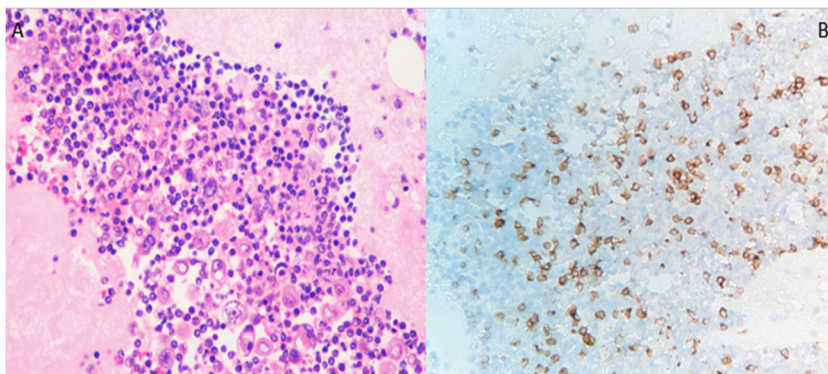


Fig. 7. Cell block of pleural fluid demonstrates large metastatic adenocarcinoma cells admixture with many atypical lymphocytes, H&E (A). The atypical lymphocytes are monotypic B-cells, (12% of cells) detected by flow cytometry. CD20 highlights the B-cells (B).

from which lung cancer is the commonest cause [1,2]. The malignant invasion of the pleura is via direct tumor inoculation, or by lymphatic or hematogenous seeding whereas the effusion filling is secondary to decreased lymphatic drainage [2,6].

Synchronous pleural effusions are particularly rare. There is some existing literature of synchronous malignancies being identified in the pleural fluid. Kai et al. reported the case of mantle cell lymphoma and lung adenocarcinoma detected in a pleural effusion [7], whereas Sur et al. were able to identify in the pleural fluid the same type of lung cancer but occurring with chronic lymphocytic leukemia [8]. Different scenario isolating both breast and colon malignant cells from the pleura, is also reported [9].

Some predisposing factors exist, putting patients at risk of synchronous malignancies including genetic alterations, smoking and autoimmunity [3,9]. The presence of one type of cancer increases the risk of developing a second type [9]. The frequency of synchronous lung cancer is up to 8%; some cases reported the coexistence of squamous carcinoma of the lung and bronchial lymphoma, while others reported adenocarcinoma of the lung and bronchial carcinoid concomitantly [3,10]. In the current era and with the advancement of the therapeutic modalities, there is an increase in survival rate, which increases the incidence of SM [9]. The presence of SM constitutes both diagnostic and therapeutic challenges [4], which sheds the light on the importance of the pathological expertise in the field.

In our case, we had a diagnosis in pleural fluid consistent with DBCL and adenocarcinoma of the lung. Each type of cancer must be staged separately, and therapeutic approach is also different which makes the situation more challenging. The prognosis for malignant pleural effusions on a whole is poor, with the average survival being 4 months [11] and the concurrent infiltration of the pleural space by synchronous malignancies renders the survival much worse.

#### 4. Conclusion

Malignant pleural effusions are an unfortunate common complication associated with malignancies. The presence of malignant pleural effusion increases the staging and indicates a worse prognosis. Synchronous malignant pleural effusions are a particularly rare finding and are associated with shorter life expectancy. This case highlights the challenges both pathologists and clinicians are facing in identifying the culprit disease and choosing the appropriate treatment. With the continuous progress of oncological targeted therapies and increased survival, could the prevalence of synchronous malignancies in a pleural effusion become the usual?

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#### Patient consent for publication

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#### Authors' contributions

All authors have made contributions to writing this case report. Phyllis Suen, Marc Assaad, Naureen Narula, and Danil Mishiyev have drafted the manuscript. Wei Xue helped with the histopathology description and gathering data. Michel Chalhoub is responsible for the editing and supervision.

#### Data availability

The authors declare that data supporting the findings of this study are available within the article.

#### Declaration of competing interest

The authors declare that there is no conflict of interest.

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