

[ CASE REPORT ]

## Lymph Node Collision Tumor Consisting of Metastatic Pulmonary Adenocarcinoma and Diffuse Large B-cell Lymphoma

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### Abstract:

A 67-year-old man presented with a fever and general malaise. Computed tomography showed multiple nodules in the lungs and liver, associated with mediastinal and para-aortic lymphadenopathy. Bone marrow aspiration revealed diffuse large B-cell lymphoma (DLBCL). Renal and liver dysfunction and pancytopenia inhibited chemotherapy administration; the patient subsequently died of multiorgan failure. An autopsy revealed pulmonary adenocarcinoma with metastases to the lungs, liver, and adrenal glands; the DLBCL spread to the liver, spleen, and bone marrow. Adenocarcinoma and DLBCL collision was observed in the mediastinal and para-aortic lymph nodes. This was a rare case of collision metastasis occurring in the lymph node.

**Key words:** collision tumor, lung cancer, adenocarcinoma, malignant lymphoma, diffuse large B-cell lymphoma

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### Introduction

Collision tumors are rare entities defined by the presence of two tumors of independent origin within the same specimen. Collision tumors are distinguishable from tumors that contain two or more cell lines arising from a common source. One of the mechanisms by which collision tumors occur includes metastasis of two tumors arising in different organs to another common organ, most often the lymph nodes. Collision metastasis from lung cancer and malignant lymphoma is extremely rare, and only a few cases have been reported in the literature thus far (1-3). However, collision metastasis from pulmonary adenocarcinoma and malignant lymphoma to the same lymph node, to our knowledge, has never been reported.

We herein report an extremely rare case of lymph node collision metastasis from pulmonary adenocarcinoma and Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) of the elderly.

### Case Report

phoma (DLBCL) of the elderly.

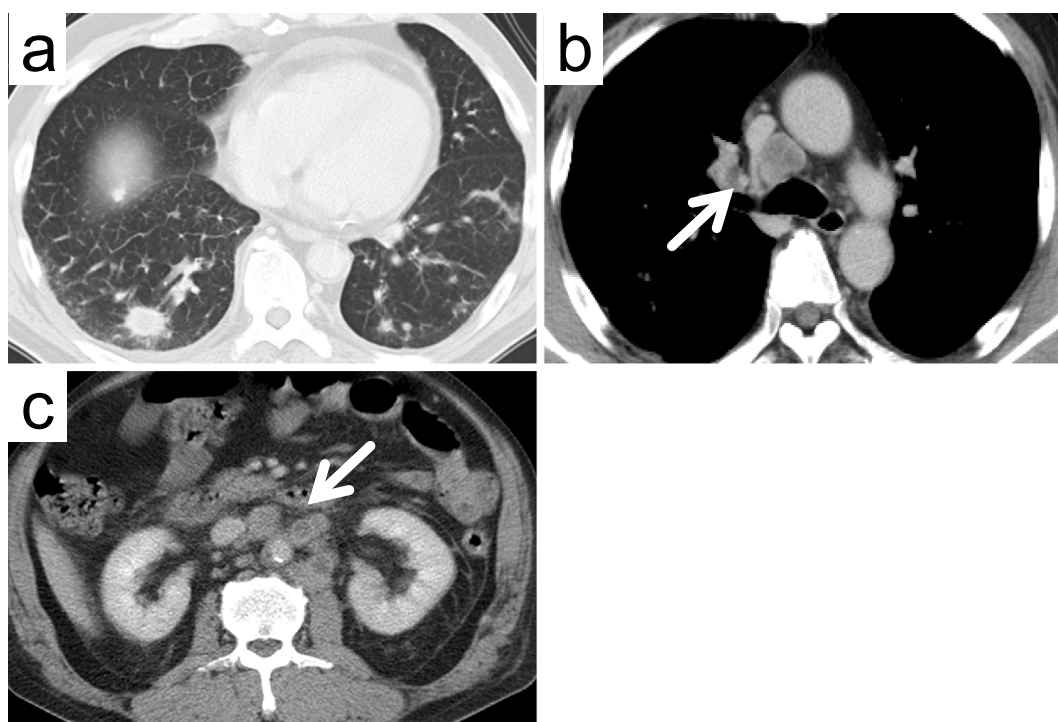
A 67-year-old man with a smoking history of 60 packs a year presented with a fever and general malaise. His medical history included hypertension, diabetes mellitus, and angina. In the emergency room, his body temperature was 38.9°C, blood pressure was 128/64 mmHg, pulse was 119 beats/min, respiratory rate was 20 breaths/min, and oxygen saturation was 94% on room air.

An initial laboratory examination showed a white blood cell count of 5,000 cells/ $\mu$ L (78% neutrophils), platelet count of 141,000 cells/ $\mu$ L, lactate dehydrogenase level of 297 U/L, and C-reactive protein level of 11.6 mg/dL. The serum levels of ferritin, carcinoembryonic antigen (CEA), cancer antigen (CA)19-9, cytokeratin 19 fragment (CY-FRA), soluble interleukin-2 receptor, and D-dimer were elevated at 6,790 ng/mL, 32.9 ng/mL, 3,457.6 U/mL, 14.3 ng/

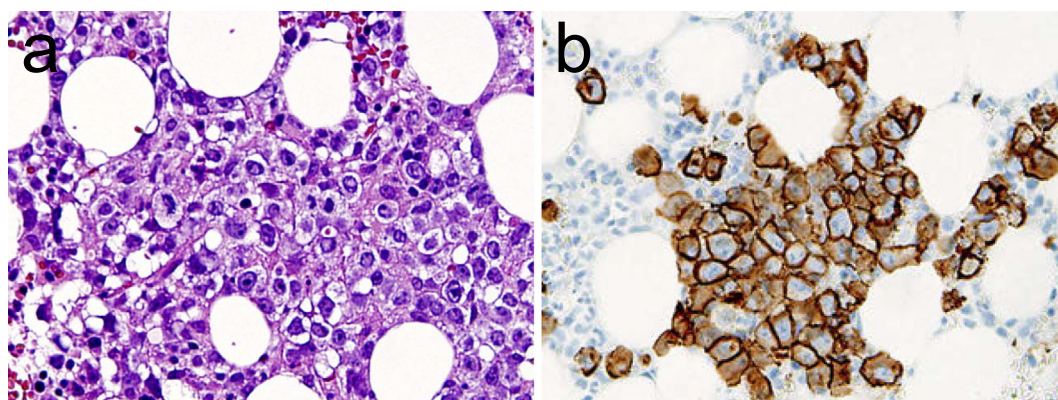
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**Figure 1.** A computed tomography image showing a nodule in the right lower lobe, miniscule nodules in the left lower lobe (a), right hilar and mediastinal lymphadenopathy (arrow) (b), and para-aortic lymphadenopathy (arrow) (c).



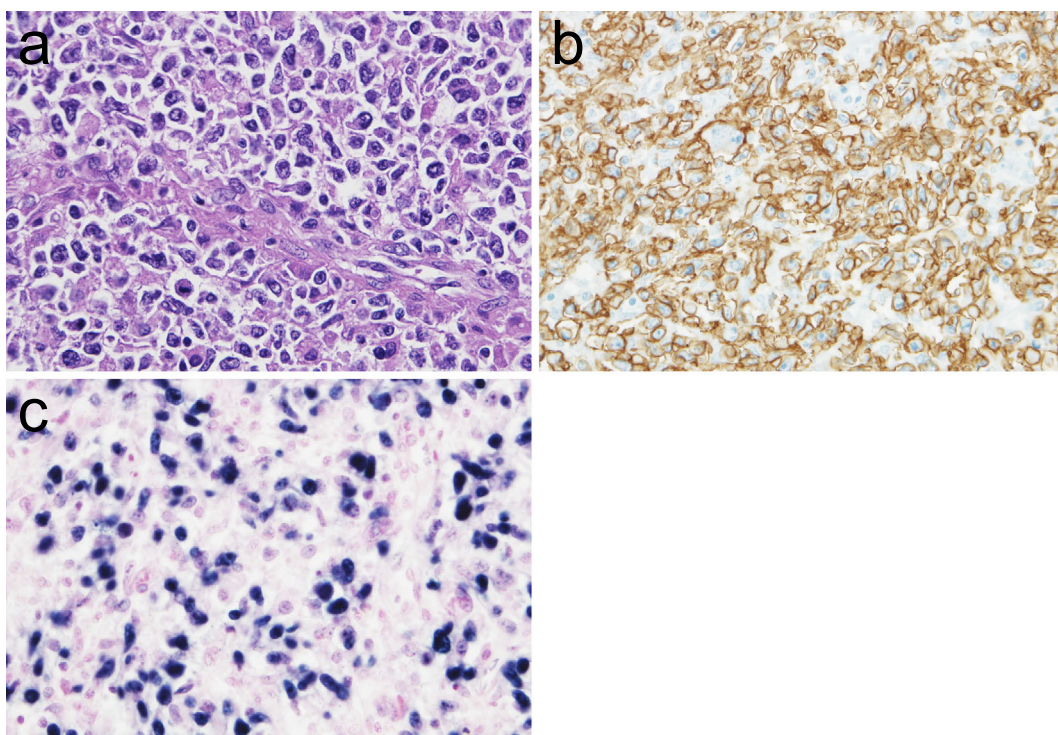
**Figure 2.** Histopathological findings of bone marrow aspiration. (a) Hematoxylin and Eosin staining, (b) CD20 staining. Bone marrow aspiration showed moderate-to-large atypical lymphocytes. Atypical lymphocytes showed positive staining for CD20, suggesting B-cell origin (b).

mL, 16,600 U/mL, and 4.7  $\mu$ g/mL, respectively. A chest radiograph revealed multiple nodules in both lungs. A computed tomography (CT) scan of the chest showed multiple nodules in both lungs, thickening of the interlobular septum, and enlargement of the right hilar, supraclavicular, and mediastinal lymph nodes (Fig. 1a and b). An enhanced CT scan of the abdomen showed multiple low-density areas in the liver, splenomegaly, enlargement of the adrenal glands, and swelling of the para-aortic lymph nodes (Fig. 1c). An examination of the upper gastrointestinal tract showed no abnormal findings. Bone marrow aspiration showed moderate-to-large atypical lymphocytes with positive staining for B-cell markers of CD20, suggesting DLBCL (Fig. 2).

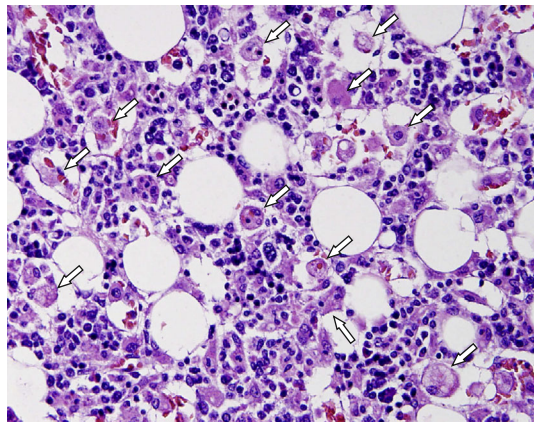
Chemotherapy could not be administered because of the rapid worsening of the renal and liver function as well as severe pancytopenia. His high fever, elevated levels of serum lactate dehydrogenase and ferritin, liver dysfunction, and severe pancytopenia suggested phagocytosis syndrome. The patient developed rapidly progressive multiorgan failure and eventually died on the 17th day after admission.

An autopsy revealed stage 4 extensive pulmonary adenocarcinoma with multiple metastases (T4N3M1). The lung cancer originated from the right lower lobe, and the size of the primary lesion was 2.3 $\times$ 1.5 cm. Metastases of the lung cancer were found in both lungs, the liver, both adrenal glands, as well as the lymph nodes of the bilateral hilar, me-





**Figure 3.** Histopathological findings of the autopsy specimens from para-aortic lymph node. (a) Hematoxylin and Eosin staining, (b) CD20 staining, and (c) Epstein-Barr virus (EBV) encoding region *in situ* hybridization (EBER ISH). Extensive large lymphocytes with an atypical nucleolus were seen, and immunohistochemistry of the lymphocytes revealed strong and diffuse positivity for B-cell markers (CD20). EBER ISH was positive in the atypical lymphocytes.



**Figure 4.** A bone marrow specimen obtained by an autopsy (Hematoxylin and Eosin staining) showed large atypical lymphocytes and histiocytes with phagocytosis (arrows).

diastinal, and para-aortic lesions. Immunohistochemistry of the lung cancer showed cytokeratin (CK)7 (+), CK20 (-), thyroid transcription factor-1 (-), napsin A (-), CEA (+), and CA19-9 (+). Based on the World Health Organization classification of tumors 4th edition, lung cancer was classified as invasive adenocarcinoma, acinar predominant (acinar 50%, papillary 40% and micropapillary 10%).

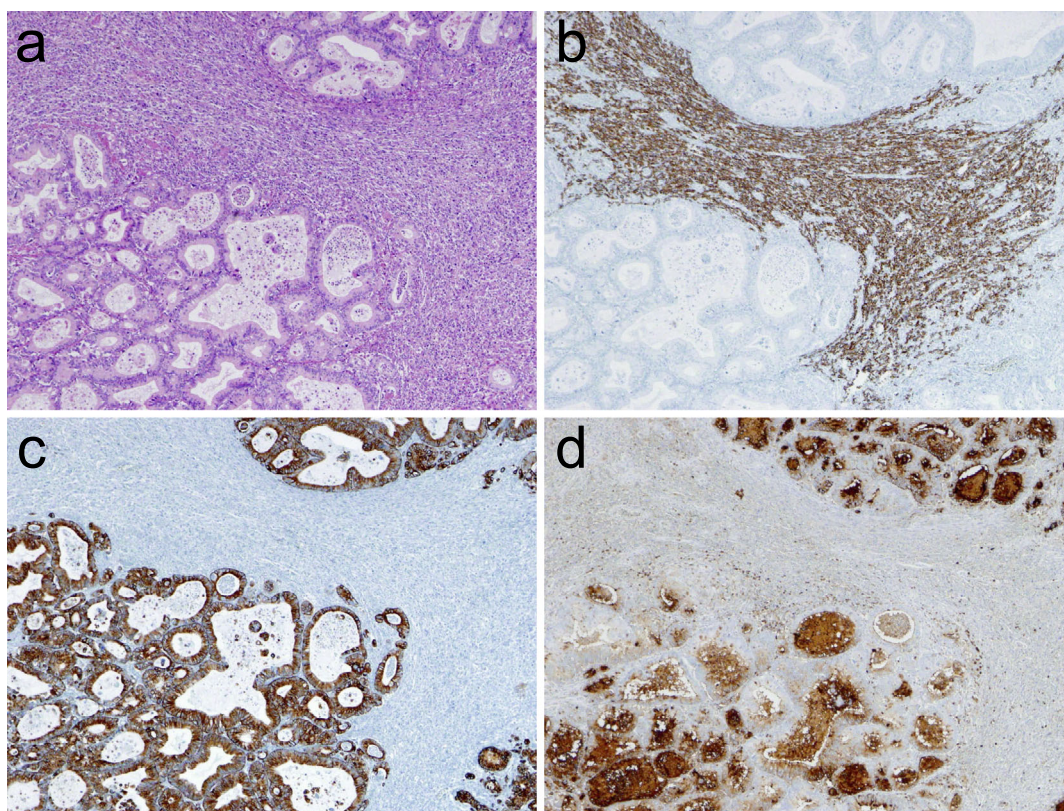
Autopsy specimens from the para-aortic lymph node revealed diffuse proliferation of large lymphoid cells with pleomorphic nuclei. The diagnosis of EBV-positive DLBCL

of the elderly was confirmed by immunostaining, which showed CD20 (+), CD79a (+), CD3 (-), CD5 (-), CD10 (-), CD15 (-), CD30 (-), CD56 (-), cyclin D1 (-), BCL-2 (-), and *in situ* hybridization showing EBV-encoded small RNA (Fig. 3). The DLBCL extended to the liver, spleen, bone marrow, and systemic lymph nodes and manifested as mediastinal, intraabdominal, and para-aortic lesions. Bone marrow specimens showed large atypical lymphocytes and histiocytes with phagocytosis (Fig. 4). Adenocarcinoma and DLBCL collision was observed in the mediastinal and para-aortic lymph nodes (Fig. 5). Immunohistochemistry showed that the cells observed in the center of the image were positive for CD20 but negative for cytokeratin 7 and CA19-9 (Fig. 5b-d), which is consistent with the diagnosis of DLBCL. In contrast, the cells in the upper and bottom regions of the image were positive for cytokeratin 7 and CA19-9 but negative for CD20 (Fig. 5b-d), thus confirming that the latter tumor was adenocarcinoma.

## Discussion

This report describes a case of lymph node collision metastases from pulmonary adenocarcinoma and DLBCL. The coexistence of pulmonary adenocarcinoma and malignant lymphoma is an extremely rare event. Thus far, only two cases of lung cancer and malignant lymphoma existing in the same node have been reported. These include one case of pulmonary squamous cell carcinoma and T-cell lym-





**Figure 5.** Histopathological findings of the collision tumor in the mediastinal lymph node. (a) Hematoxylin and Eosin staining, (b) CD20 staining, (c) cytokeratin 7 staining, and (d) cancer antigen (CA) 19-9 staining. In all panels, the diffuse large B-cell lymphoma metastasis is visible in the middle of the image. CD20 positivity can be observed, indicating B-cell origin. In the upper right and bottom left of the image can be seen a dysplastic cell with a large nucleus that is cytokeratin 7- and CA19-9-positive, indicating adenocarcinoma.

phoma (1), and one case of pulmonary adenocarcinoma and adult T-cell leukemia/lymphoma (2). There has been a case of a collision tumor of the lung comprising pulmonary adenocarcinoma and DLBCL (3). To our knowledge, however, collision metastasis of pulmonary adenocarcinoma and DLBCL in the same mediastinal and para-aortic lymph node has never been reported.

In the present case, the bone marrow specimen revealed characteristics of phagocytic syndrome. Furthermore, the multiorgan failure and pancytopenia progressed rapidly. This clinical course suggests that the DLBCL was the dominant cause of death. The natural clinical course of DLBCL is likely to be more rapid than that of pulmonary adenocarcinoma. The clinical events observed during the terminal stage and the results of the autopsy indicate that, from a systemic point of view, the pulmonary adenocarcinoma developed first, followed by the DLBCL. The predisposing factors for DLBCL and lung adenocarcinoma are diverse. In this case, a smoking history was presumed to be a major predisposing factor for the lung adenocarcinoma and latent EBV infection for the DLBCL. A previous animal model study reported the development of DLBCL in immunodeficient mice implanted with primary human non-small cell lung cancer (4). However, we cannot rule out the possibility that DLBCL oc-

curred first and was followed by the pulmonary adenocarcinoma. According to a study evaluating second primary tumors in 860 patients with non-small cell lung cancer, there were 16 cases of hematologic malignancy (leukemia, lymphoma, or myeloma), of which 15 lung cancer cases were diagnosed after the hematologic malignancy was detected (5). Because we could not access previous images of the patient, we could not confirm which tumor occurred first.

This case was not only rare but also valuable in terms of offering discussion points regarding the development of collision tumors. An autopsy revealed that the majority of the collision tumor comprised DLBCL rather than adenocarcinoma. One explanation for why the DLBCL occupied a larger area than the adenocarcinoma was that the DLBCL occurred before the adenocarcinoma in the mediastinal and para-aortic lymph nodes. This hypothesis is consistent with those described in a previous report wherein the coexisting adenocarcinoma occurred synchronously or after but never before the lymphoma of the intestinal tract (6). Another explanation is that the DLBCL spread at a much faster rate than the adenocarcinoma in the lymph nodes. This hypothesis allows for the possibility that the adenocarcinoma was followed by the DLBCL in the lymph nodes. A tissue cul-

ture study showed that the lymphocytes were the only cells attached to areas of mitosis, the only motile cells that attached to other cells for long periods of time, and were able to easily enter malignant cells (7). We believe the environment made it easier for the DLBCL to follow the adenocarcinoma rather than for the adenocarcinoma to follow the DLBCL in the lymph nodes.

We propose two hypotheses for the mechanism of collision tumors. One explanation is the seed-and-soil theory. The occurrence of a tumor alters the surrounding microenvironment, thereby allowing for the development of a second tumor in the same location. In a case report of a collision tumor consisting of gastric adenocarcinoma and metastatic lymphoma in the stomach, Yanagawa et al. suggested that gastric adenocarcinoma may produce chemokines and induce lymphocyte migration (8). In a recent review of metastasis, the authors showed that rich vascularity was partially responsible for the secondary tumor metastasizing and growing (9). Another explanation is that the synchronous development of lung adenocarcinoma and DLBCL in the same lymph nodes was a random coincidence, and the lesions did not have any specific association.

Over the last decade, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and other endoscopic procedures have demonstrated an increasingly important role in the diagnosis of mediastinal tumors (10). In this case, the increase in CEA and CA19-9 levels suggested the presence of an adenocarcinoma. Pulmonary adenocarcinoma was confirmed on the basis of the autopsy findings. Therefore, even if EBUS-TBNA had been performed, we cannot guarantee that adenocarcinoma specimens would have been obtained. The existence of a collision tumor in the mediastinal lymph node emphasizes the importance of obtaining several biopsy specimens during EBUS-TBNA.

In conclusion, we report a rare case of a collision tumor comprising metastatic pulmonary adenocarcinoma and DLBCL.

**The authors state that they have no Conflict of Interest (COI).**

## References

1. Kawashima O, Sakata S, Kamiyoshihara M, Maeshima A, Ishikawa S, Morishita Y. Primary pulmonary collision tumor including squamous cell carcinoma and T-cell lymphoma. *Lung Cancer* **23**: 67-70, 1999.
2. Miyahara H, Itou H, Sekine A, et al. A case of adult T-cell leukemia/lymphoma with primary lung cancer. *Nihon Kokyuki Gakkai Zasshi (J Jpn Respir Soc)* **47**: 342-346, 2009 (in Japanese, Abstract in English).
3. Du C, Gao F, Wen E, Liu X, Du L, Luo F. Successful treatment of coexistence of diffused large B cell lymphoma and lung adenocarcinoma, a case report. *Int J Gerontol* **10**: 242-244, 2016.
4. John T, Yanagawa N, Kohler D, et al. Characterization of lymphomas developing in immunodeficient mice implanted with primary human non-small cell lung cancer. *J Thorac Oncol* **7**: 1101-1108, 2012.
5. Duchateau CSJ, Stokkel MPM. Second primary tumors involving non-small cell lung cancer: prevalence and its influence on survival. *Chest* **127**: 1152-1158, 2005.
6. Cornes JS. Multiple primary cancers: primary malignant lymphomas and carcinomas of the intestinal tract in the same patient. *J Clin Pathol* **13**: 483-489, 1960.
7. Pulvertaft RJV. Cellular associations in normal and abnormal lymphocytes. *J R Soc Med* **52**: 315-322, 1959.
8. Yanagawa N, Ogata S, Fukushima N, Maeda K, Tamura G. Synchronous double malignant tumors consisting of stomach and Hodgkin's lymphoma with collision between gastric adenocarcinoma and Hodgkin's lymphoma in the stomach. *Case Rep Gastroenterol* **6**: 797-802, 2012.
9. Campbell LV, Gilbert E, Chamberlain CR, Watne AL. Metastases of cancer to cancer. *Cancer* **22**: 635-643, 1968.
10. Dziedzic D, Peryt A, Szolkowska M, Langfort R, Orlowski T. Evaluation of the diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration for metastatic mediastinal tumors. *Endosc Ultrasound* **5**: 173-177, 2016.

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