Concurrent lung adenocarcinoma and bladder diffuse large B-cell lymphoma: a case report and literature review

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Abstract

Lung adenocarcinoma is one of the most common solid tumors, and diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of adult non-Hodgkin's lymphoma. Although extra-nodular lesions are frequently observed in patients with DLBCL, urinary bladder involvement is rare. We report the case of a 77-year-old woman with lung adenocarcinoma who was diagnosed with a second primary bladder DLBCL, 9 months after treatment with molecular targeted drugs. Simultaneous therapies for her lymphoma with lenalidomide and rituximab and a tyrosine kinase inhibitor therapy for her lung cancer were both effective. This result was consistent with previous reports suggesting that patients unable to tolerate intensive chemotherapy could benefit from targeted therapies. Current research into the use of lenalidomide for the treatment of lymphomas and solid tumors is promising in terms of exploring immunotherapy as an alternative option for patients with concurrent solid tumors and lymphomas who have poor tolerance to radiotherapy and chemotherapy.

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Introduction

Lung adenocarcinoma is the most common subtype of non-small cell lung cancer

(NSCLC), accounting for 83% of all lung cancers. It is considered as an advanced malignancy with a poor prognosis.[1] However, the recent identification of molecular targets has significantly improved the outcomes of patients with lung adenocarcinoma.[2,3] Mutations in the epidermal growth factor receptor gene (*EGFR*) are key drivers in NSCLC and are observed in up to 50% of lung adenocarcinomas.[2–5] Accordingly, EGFR tyrosine kinase inhibitors (TKIs) have been used in the treatment of NSCLC with *EGFR* mutations since 2000,[6] and have greatly improved the treatment response and long-term survival.[7–9]

Diffuse large B-cell lymphoma (DLBCL) is the most frequent histological subtype of adult non-Hodgkin's lymphoma (NHL),[10,11] and usually occurs as a primary B cell lymphoma or transforms from indolent lymphoma in rare cases. Although DLBCL can be cured by immunochemotherapy, its treatment remains challenging in older patients who more frequently present with a high international prognostic index (IPI) and are unable to tolerate standard chemotherapy. In addition to age and IPI, various other factors predict a poor response to immunochemotherapy, such as activated B cell (ABC) subtype,[12] double expression/double hit lymphoma,[13–15] and high-risk gene mutations, such as *TP53*.[16]

We present the case of an elderly female patient who developed DLBCL 9 months after a diagnosis of lung adenocarcinoma and during EGFR-TKI treatment. In addition to the TKIs for her lung adenocarcinoma, she received rituximab plus lenalidomide for the lymphoma.

Case Report

This study was approved by the Ethics Committee of the First Hospital of China Medical University (Approval no.: [2020] 2020-277-2). Written informed consent was signed by the patient. The study conformed to the CARE guidelines.[17]

A 77-year-old female patient was admitted to our hospital in April 2019 because of fatigue. A lung computed tomography scan revealed a mass lesion with a maximum diameter of 24 mm in the right upper lobe of the hilum (Figure 1a). Lung puncture biopsy was performed and histopathological analysis showed irregular distribution of heteromorphic cells with large nuclei and an imbalanced nuclear/cytoplasm ratio. Immunohistochemical assay results showed thyroid transcription factor-1 (+), carcinoembryonic antigen (+), p63 (scattered +), napsin-A (weak +), Ki-67 (30%), cytokeratin (CK)7 (+), and CK5/6 (±) (Figure 1b, 1c). A diagnosis of lung adenocarcinoma was confirmed based on the above results. Furthermore, deletion of *EGFR* exon 19 was demonstrated by quantitative real-time polymerase chain reaction with a panel of NSCLC-related driver mutations (including *ALK*, *ROS1*, *RET*, *MET*, *KRAS*, *NRAS*, *HER2*, and *PIK3CA*). She was accordingly treated with the first-generation EGFR-TKI icotinib orally.

Nine months after initiation of icotinib treatment, the patient developed painless gross hematuria. Urinary bladder ultrasound revealed an 8.0×3.4 cm lesion. Positron emission tomography-computed tomography (PETCT) showed an irregular mass with soft tissue density in the left posterior wall of the urinary bladder, involving the left ureter, with a maximum standardized uptake value (SUV) of 30 (Figure 1d, 1e). Increased metabolic activity was also observed in multiple soft tissue nodules in the lower lobe of the left lung, and hilar and mediastinal lymph nodes, with a maximum SUV of 10.7 (Figure 1f). There was no significant change in the size of the primary lesion in the right lung. Cystoscopy of the bladder lesion was performed. Histopathological analysis demonstrated diffuse distribution of atypical large
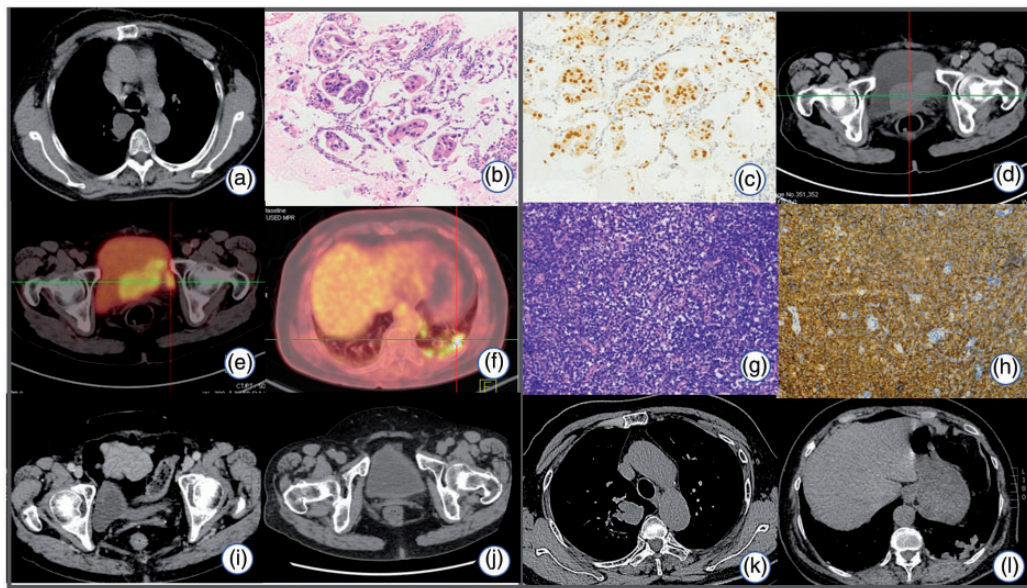
Figure 1. Lung adenocarcinoma and bladder diffuse large B-cell lymphoma (DLBCL) during treatment. (a) Lung computed tomography (CT) scan showed parahilar nodules in the upper lobe of the right lung with a maximum diameter of 24 mm before starting treatment. (b) Histopathological analysis of lung biopsy showed infiltration of heteromorphic cells (hematoxylin and eosin (H&E) staining, ×200). The nucleus was large and deeply stained and the nucleus/cytoplasm ratio was abnormal. (c) Histopathological analysis of lung biopsy showed positive expression of thyroid transcription factor-1. (d, e) Positron emission tomography (PET)-CT showed irregular soft tissue density mass in the left posterior wall of the bladder with left ureter involvement and a maximum standardized uptake value (SUV) of 30. (f) PET-CT showed a new nodule shadow in the left lower lung lobe with a maximum SUV of 10.7 after 9 months of treatment for lung adenocarcinoma. (g) Histopathological analysis of bladder biopsy showed diffuse distribution of atypical large lymphocytes (H&E staining, ×200) and positive expression of CD20 (h). (i ,j) CT scan of the urinary system showed disappearance of the occupying lesion in the bladder after treatment. However, heterogeneous enhancement of the bladder wall could still be seen. (k, l) Lung CT showed that both lesions in the left lung and right lung were larger than before treatment with icotinib and R2.

lymphocytes with the following immunohistochemical features: CD20 (+), Bcl-2 (30% +), Bcl-6 (+), c-Myc (10% +), CD68 (−), multiple myeloma oncogene-1 (+), CD10 (−), Pax-5 (+), CD5 (−), CD3 (−), Ki-67 (80%), and Epstein–Barr encoding region *in situ* hybridization (−). DLBCL with ABC subtype was confirmed (Figure 1g, 1h). The prognosis was poor. Next-generation sequencing with a panel containing 82 DLBCL hotspot genes was carried out on the lymphoma tissue at Yuanqi Biomedical Technology Co. Ltd. (Shanghai, China). The results showed mutations of *TET2*, *TNFAIP3*, *SGK1*, *IGLL5*, and *CREBBP*. However, no mutations in the *EGFR* gene, including exon 18-G719X, exon 19-del, exon 20-T90M, or exon 21L858R were identified in the lymphoma tissue by Droplet Digital PCR (Yuanqi Biomedical Technology Co., Ltd., Shanghai, China).

The patient declined radiotherapy and chemotherapy for their bladder lesion. Rituximab plus lenalidomide (R2 regimen) was administered, with rituximab 600 mg on day 1 and lenalidomide 25 mg on days 1 to 14 every 21 days. This regimen was

used in combination with continued icotinib for treatment of the lung adenocarcinoma. After the first course of treatment, the patient's gross hematuria completely resolved. Consent for the use of TKIs and R2 was acquired from the patient before treatment. After six courses of treatment, CT scan of the urinary system showed that the lymphoma had achieved complete remission (Figure 1i, 1j). The treatment was well tolerated by the patient. However, a lung CT scan showed that the lung cancer had progressed (Figure 1k, 1l). In light of the potential development of resistance to icotinib, the small molecule multi-target TKI anlotinib was added to the icotinib treatment. The size of the lung cancer lesion reduced significantly over the following 6 months of combination therapy. To date, the patient had been followed for 24 months with clinical evidence of continued remission of the urinary bladder lymphoma. However, her response to the TKIs was poor and her lung cancer continued to progress to a more advanced stage.

Discussion

The occurrence of lymphomas as second tumors in patients with lung cancer is not rare. Although the exact cause of dual tumors is unknown, chemotherapy is considered to be a common cause of secondary lymphomas. However, evidence of secondary lymphomas after TKIs in the era of targeted therapy is uncommon.[18–20] Here we report a patient with a history of lung adenocarcinoma treated with TKIs who developed high-risk DLBCL with bladder involvement. Although DLBCL is curable with classical R-CHOP regimen,[21] the outcome in high-risk patients remains poor, especially in older, frail patients. The current patient was ineligible for standard therapy because of her age and poor disease condition. Although a driver EGFR mutation was detected as a potential target for

the treatment of her lung adenocarcinoma, the secondary lymphoma lacked indications for targeted drugs and was associated with several adverse factors for long-term survival, such as high IPI, extra-nodular disease, ABC subtype, dual expression of C-Myc and Bcl-2,[21–24] and TET2,[25] TNFAIP3,[26] and SGK1 mutations.[27]

The incidence of concurrent lung cancer and lymphoma has increased in recent years. Both lung cancer and NHL are associated with higher risks of secondary malignancies of 36.7%[28] and 10.95%,[29] respectively. A search of the National Cancer Institute's SEER database (www.seer.cancer.gov) identified 14,665 patients with concurrent malignancies from 1975 to 2016, including 2607 patients who developed lymphoma secondary to their lung cancer. Of these, 44.5% had lung adenocarcinoma, and chronic lymphocytic leukemia or small cell lymphoma was the most common subtype of lymphoma (25.5%) secondary to the lung carcinoma. As the second most common subtype, DLBCL accounted for 20.2% of concurrent lymphomas in patients with lung cancer. There were significant differences in survival times among patients with different types of lung cancer who developed secondary DLBCL: the median survival of patients with lung adenocarcinoma and secondary DLBCL was 11 months, which was slightly poorer than that in patients with small cell lung cancer (Table 1). However, the relevance of the biological origins of the two types of tumors remains unclear. Evidence from the current case suggested that the concurrent malignancies originated separately because they had different mutation spectra. No EGFR mutations were found in the DLBCL specimens and there have been few reports of lymphoma secondary to EGFR TKIs,[18,30] indicating that the two tumors were likely to have different origins. It was therefore necessary to choose a

Table 1. Effects of various factors on survival time in patients with lymphoma secondary to lung cancer (data from the SEER database (www.seer.cancer.gov)).

	Number of people	Median survival (months)	Mean rank	Sum of rank	P
Stage					
I & II	307	16.5	299.34	91,897.00	<0.001*
III & IV	247	8	250.36	61,838.00	
Unknown	95	4.5	–	–	–
Age, years					
<60	57	12	336.88	19,202.00	0.616
≥60	592	9	323.86	191,723.00	
Chemotherapy					
Yes	400	15.5	368.46	147,384.00	<0.001*
No/unknown	249	4	255.18	63,541.00	
Sex					
Female	278	16	350.58	97,460.50	0.003*
Male	371	7.5	305.83	113,464.50	
Adenocarcinoma	309	11	236.49	$\chi^2 = 91.985$	<0.001*
Small-cell lung cancer	47	18	247.77		
Squamous cell carcinoma	200	7	374.89		

*Significant difference between the two groups (P < 0.05).

Table 2. Influences of different indexes on the survival time of lymphoma secondary to lung cancer (data from the SEER database (www.seer.cancer.gov)).

	Number of people	Median survival (months)	Mean rank	Sum of rank	P
Stage					
I & II	136	18	140.18	19,064.50	0.015*
III & IV	122	10	117.59	14,346.50	
Unknown	51	6			–
Age, years					
<60	24	15.5	152.94	3670.50	0.906
≥60	285	11	155.17	44,224.50	
Chemotherapy					
Yes	195	16	172.54	33,646.00	<0.001*
No/unknown	114	5	124.99	14,249.00	
Sex					
Female	153	16	162.43	24,852.00	0.147
Male	156	11	147.71	23,043.00	

*Significant difference between the two groups (P<0.05).

treatment regimen to take account of both types of tumor.

Chemotherapy has previously been the mostly widely used therapy for the treatment of lung cancer and lymphoma. However, although results from the SEER database showed that chemotherapy partly prolonged survival of these patients (Table 2), the overall outcome was poor. The database reported 309 patients with

DLBCL secondary to adenocarcinoma from 1975 to 2016, of whom 46 patients had received chemotherapy for lung cancer before the occurrence of their secondary DLBCL. The median survival was 6 months in these patients. Except for a small number of patients who died due to complications and tumor progression leading to respiratory and circulatory deterioration,[31,32] most patients in the reported studies were not followed-up long-term.

In the current case, intensive chemotherapy was not considered appropriate because of the patient's age, prior history of lung cancer, and comorbid lung cancer and DLBCL, and a chemo-free regimen of R2, consisting of rituximab and lenalidomide, was considered in light of promising results in patients with B-cell lymphomas.[33–36] The therapeutic effects of lenalidomide are especially notable, showing that it enhance the proliferation and function of T cells, repair synapses of effector T cells, increase antibody-dependent cytotoxicity mediated by natural killer cells, up-regulate costimulatory molecules on the surface of tumor cells, and inhibit angiogenesis,[37–41] all of which could be relevant to the treatment of solid tumors[42] including NSCLC.[32] R2 accordingly produced a rapid and durable response in the present patient with an early-stage urinary bladder cancer.

In summary, the current challenging case involved an elderly patient who developed urinary bladder DLBLC during targeted treatment of her lung cancer. Previous analysis has demonstrated poor outcomes of traditional chemotherapy, especially for elderly patients who cannot tolerate chemotherapy. The patient's lymphoma was well-controlled by the R2 regimen and she tolerated the treatment well. However, further follow-up is needed to determine the long-term therapeutic effect and survival. Chemo-free therapy with novel agents may thus provide an alternative treatment choice in patients in poor condition with concurrent lymphoma and lung cancer.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

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