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Case report

A case of successful concurrent anti-cancer treatment in a patient who developed follicular lymphoma during treatment with afatinib for advanced lung adenocarcinoma

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ABSTRACT

The present report describes the case of a 64-year-old woman with advanced lung adenocarcinoma expressing mutant epidermal growth factor receptor (EGFR). The patient developed follicular lymphoma during treatment with the EGFR-tyrosine kinase inhibitor afatinib. Standard immunochemotherapy for follicular lymphoma was introduced in addition to continuing treatment with afatinib for lung cancer. Immunochemotherapy was effective and improved the patient's performance status while afatinib controlled the progression of lung cancer. Our case study suggests that it is safe to introduce standard immunochemotherapy for patients who develop malignant lymphoma while continuing treatment with tyrosine kinase inhibitors for lung adenocarcinoma expressing mutant EGFR.

1. Introduction

Molecular-targeted drugs such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and anaplastic lymphoma kinase (ALK) inhibitors have extended the life expectancy of patients with lung adenocarcinoma (LAD) [1–3]. Consequently, we often encounter patients with non-small cell lung cancer (NSCLC) who developed other synchronous or metachronous malignant tumors. A number of articles reported that patients with both NSCLC and other malignancies that have a good prognosis received surgery or radiotherapy for both or either malignant tumor. However, to the best of our knowledge, no study has reported that a patient with advanced stage in both NSCLC and another malignancy received the respective standard therapy for each malignant tumor concurrently.

Here, we report the case of a patient who, during treatment with the EGFR-TKI afatinib for LAD, developed malignant lymphoma and subsequently received R-CHOP therapy (cyclophosphamide, doxorubicin, vincristine and prednisone with rituximab) while continuing treatment with afatinib.

2. Case report

A 64-year-old woman was diagnosed with stage IVB (T4N3M1c) [4] LAD expressing mutant EGFR (exon 19 deletion) (Fig. 1-A). We administered afatinib (40 mg/day) as the first-line regimen. Three months after starting afatinib, the patient developed repeatedly grade 3 diarrhea (Common Terminology Criteria for Adverse Events version 4.0). Therefore, the afatinib dose was reduced to 20 mg/day until twenty-three months from starting afatinib, maintaining a partial response of the LAD (Fig. 1-B).

At the time of diagnosis of LAD, we detected abdominal lymphadenopathies by abdominal computed tomography (CT) imaging; however, we assessed them as metastases from the LAD (Fig. 1-C). During treatment with afatinib, abdominal lymphadenopathies and

Abbreviations: EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; ALK, anaplastic lymphoma kinase; LAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; R-CHOP, cyclophosphamide, doxorubicin, vincristine, predonisone with rituximab; CT, computed tomography; FL, follicular lymphoma

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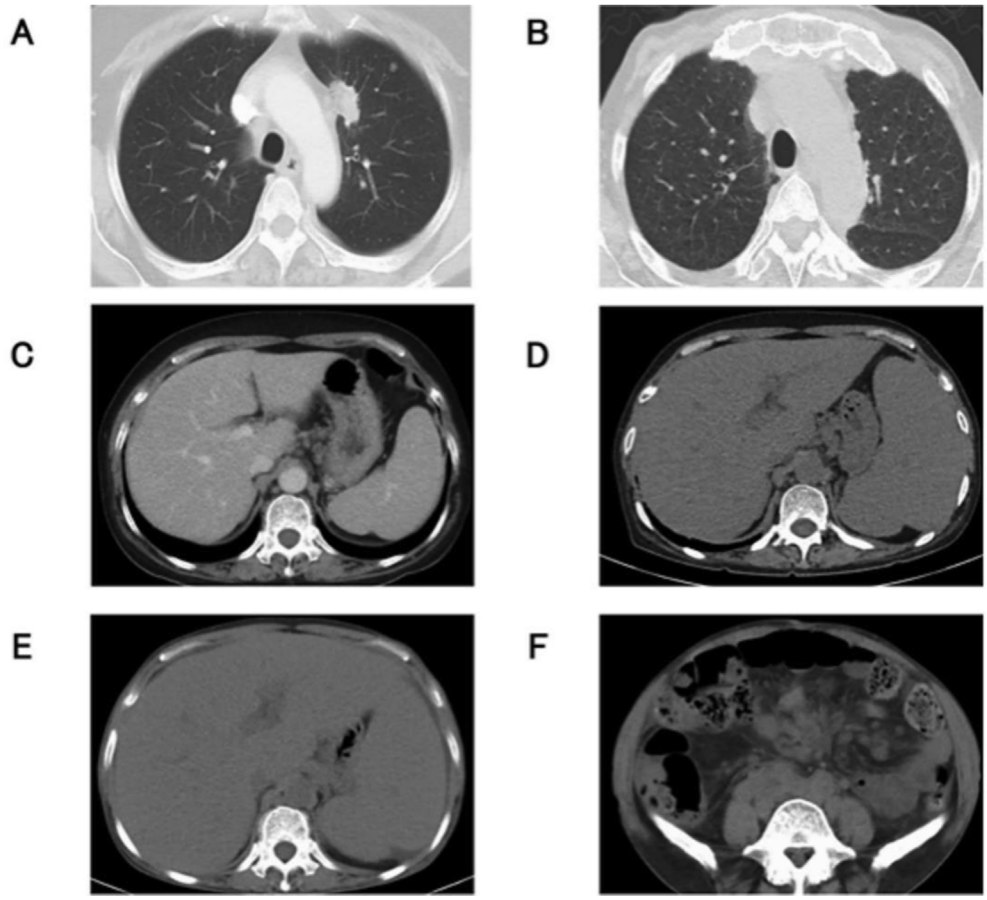

Fig. 1. Computed tomography. (A) At the start of treatment with afatinib showing the primary lesion of the lung cancer. (B) At 32 months after the start of treatment showing the primary lesion that had decreased in size. (C) At the start of treatment showing intra-abdominal lymphadenopathy. (D) At 24 months after the start of treatment showing hepatosplenomegaly. (E, F) At 32 months after the start of treatment showing abdominal distension, hepatosplenomegaly, and intra-abdominal lymphadenopathy.

splenomegaly continued to increase on the CT image (Fig. 1-D). At the time of starting afatinib therapy, complete blood count showed normality of differential white blood count and only thrombocytopenia (white blood cells: 4500 [institutional normal range is 4000–8500]/μL; neutrophils 3290/μL, lymphocytes 790/μL, hemoglobin: 11.1 [11.0–15.0] g/dL and platelet: 7.5×10^4 [1.5–3.5 $\times$ 10^5]/μL).

Thirty-two months after starting afatinib treatment, the patient was admitted to the hospital due to acute abdominal distension. We detected hepatosplenomegaly, ascites, and intra-abdominal lymphadenopathies by abdominal CT (Fig. 1-E, F). The complete blood count revealed elevated white blood cell (24900/μL) and lymphocyte counts (21370/μL), including 87% of atypical lymphocytes that appeared small and cleaved typically (Fig. 2-A); Hemoglobin decreased to 9.3 g/dL, and thrombocyte count to 63000/μL. Immunohistochemistry of atypical lymphocytes in peripheral blood revealed that they were positive for CD10, CD19, CD20, CD79a, and BCL-2 (Fig. 2-B, C, D, E), and negative for CD3, CD4, CD5, and CD8 (not shown). On the basis of these findings, we suspected that lymphoid malignancy coexisted with LAD. Subsequent flow cytometry showed that the lymphoma cells were CD3-, CD4-, CD5-, CD8-, $CD10^+$, $CD19^+$, $CD20^+$, CD79a+, BCL-2+, and Ig-κ+. Similar findings were found in ascites and bone marrow. Fluorescence in situ hybridization of ascites revealed the translocation of IGH and BCL2 (Fig. 2-F). These pathological features were consistent with follicular lymphoma (FL). These findings, obtained by whole body contrast-enhanced CT, immunohistochemistry and flow cytometry of peripheral blood, ascites and bone marrow, and fluorescence in situ hybridization of ascites suggested that the follicular lymphoma infiltrated her bone marrow. Therefore, we assessed her clinical stage was stage IV of Ann Arbor classification [5] and high risk in FL international prognostic index-2 [6]. Retrospectively, we diagnosed this case as FL that was probably present before the diagnosis of LAD and developed slowly while on treatment with afatinib for LAD. At first, we could not ascertain whether intra-abdominal lymphadenopathies had resulted from LAD or lymphoma. We considered it reasonable to continue treatment with afatinib because the discontinuation of afatinib would have led to a rapid exacerbation of LAD. Furthermore, she developed FL with high tumor burden defined by GELF criteria [7]. Therefore, we decided to concurrently administer immunochemotherapy for FL.

At first, we planned to perform R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab) as the first regimen for FL. However, we started CHOP alone to avoid infusion reaction in the first cycle, and subsequently added rituximab to CHOP from the second cycle.

After completing six-cycles of immunochemotherapy for FL, we evaluated the therapeutic effects on LAD and FL, respectively. The primary lesion of the LAD maintained reduced size but multiple small LAD metastases occurred in both lung fields (Fig. 3-A). A T790M mutation of the EGFR was detected by liquid biopsy, and therefore we administered osimertinib as a second line treatment. Treatment of the FL resulted in the disappearance of lymphoma cells in peripheral blood, reduction of hepatosplenomegaly, and shrinking of swollen intra-abdominal lymph nodes (Fig. 3-B), therefore we assessed that she achieved a partial response. Accordingly, the patient's performance status improved.

3. Discussion

The diagnosis of multiple primary malignancies is in accordance with the criteria developed by Warren and Gates [8]: each tumor must be malignant; each tumor must have its own unique pathological features; and metastasis or recurrence must be excluded. This case met these criteria. Previous literature reported the rate of patients with lung cancers and a second malignancy ranged from 0.9% to 26.3% [9–15]. Kim et al. [16] reviewed 1964 patient cases: of them, 47 patients (2.4%)

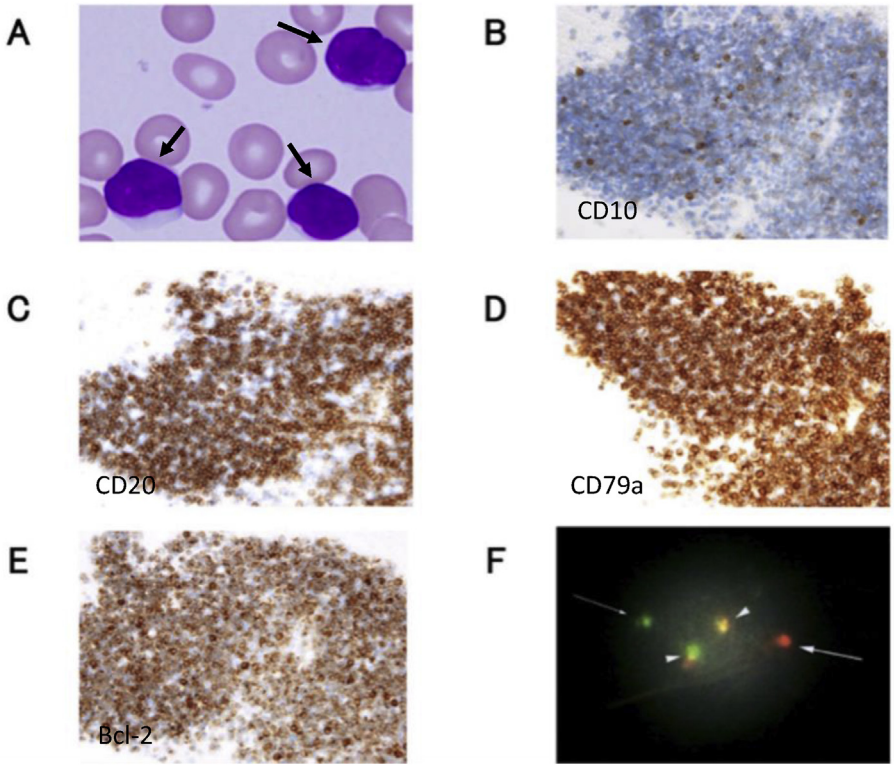

Fig. 2. (A) May Giemsa staining for peripheral blood cells showing atypical lymphocytes (high-power field). (B-E) Immunohistochemistry of cell blocks from peripheral blood cells; lymphoid cells showing diffuse positive results for (B) CD10, (C) CD20, (D) CD79a, and (E) Bcl-2 (high-power field). (F) Fluorescence in situ hybridization from ascites showing translocation of IGH and BCL2.

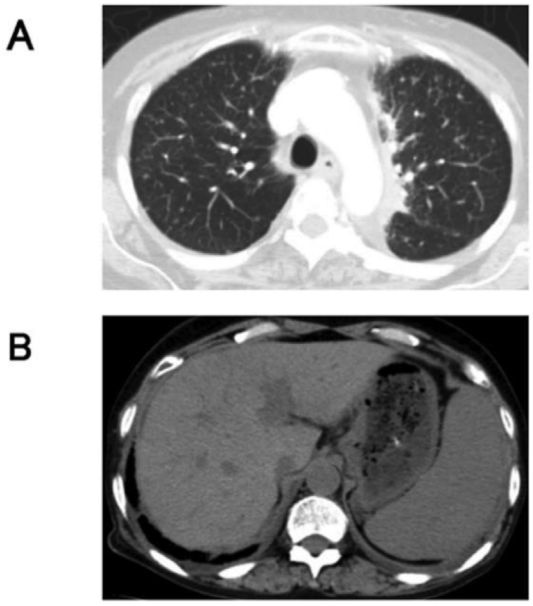

Fig. 3. Computed Tomography at the completion of the induction chemotherapy for follicular lymphoma. (A) Lung cancer: the primary lesion remained decreased in size, but multiple small lung metastases developed. (B) Follicular lymphoma: abdominal distension and hepatosplenomegaly improved.

had a history of lymphoma; 6 (13%) had Hodgkin lymphoma; and 41 (87%) had non-Hodgkin lymphoma. Histology of lung cancers revealed that 28 patients (60%) had adenocarcinoma, 17 (36%) squamous cell carcinoma, and 2 (4%) other lung cancers [16]. In double-primary malignant tumors, it is common to select surgery or radiotherapy when one or both treatments can be curative; however, when both cancers are in advanced stage, no clear guideline for treatment exists. In such cases, it is common to select therapeutic strategies specific for the treatment of each respective tumor according to the guideline considering type and progression of each tumor.

In this report, we describe a case of FL developing during treatment of an EGFR mutation-positive LAD. Generally, FL progresses slowly and even in high-risk groups, the three-year survival rate is 84% [6]. However, the median overall survival is 27.9 months in EGFR mutation-positive LAD [17]. Therefore, the prognosis of our patient was defined by the LAD. However, we assessed that it was also necessary to treat the FL, because of worsening of the patient's performance status due to high tumor burden. Therefore, we treated the patient concurrently for FL and LAD with R-CHOP and afatinib, respectively. We started the treatment for FL with CHOP alone to avoid infusion reaction in the first cycle because previous studies reported that bone marrow infiltration and higher circulating tumor lymphocyte counts were risk factors for infusion reaction [18,19], and patient's performance status was poor. After confirming safety, we subsequently added rituximab from the second cycle to the sixth cycle and continued with rituximab alone for three cycles. Her performance status having been improved, we discontinued rituximab as a maintenance regimen to prevent delayed side effects such as immunosuppression. Considering the poorer prognosis of LAD, we should have prioritized the treatment for LAD with cytotoxic chemotherapies when afatinib therapy failed.

Despite an extensive literature search, we could not find any report on concurrent introduction of anti-cancer agents to several advanced malignant tumors. In most cases, it would be difficult to introduce each respective cytotoxic chemotherapy for multiple cancers; however, in this case, the toxicities of the molecular-targeted drug and the cytotoxic chemotherapy did not overlap. Therefore, we could simultaneously administer both the standard treatments for LAD and FL. Prognosis of LAD, particularly of EGFR or ALK mutation-positive LAD has been remarkably improved by the development of molecular-targeted drugs. Opportunities to treat double-malignant tumors as described in this case will increase from now on.

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Conflicts of interest

T.H. has received lecture fees and research funding from Ono Pharmaceutical Co. Ltd. (Osaka, Japan), Lilly Japan Co. Ltd. (Hyogo, Japan), AstraZeneca Co. Ltd. (Osaka, Japan), Taiho Pharmaceutical Co. Ltd. (Tokyo, Japan), Chugai Pharmaceutical Co. Ltd. (Tokyo, Japan), MSD Oncology Co. Ltd. (Tokyo, Japan), and Merck Serono Co. Ltd. (Tokyo, Japan). The remaining authors (K.M., G.K., S.T., S.N., H.T., S.M., A.T., T.S., N.M., H.S., N.O., and H.K.) declare no conflicts of interest.

Ethics approval and consent to participate

The Osaka Habikino Medical Center's ethics committee approved this report (No. 841-1).

Patient consent for publication

Written informed consent is available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100862.

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