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CASE REPORT

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Therapy-related acute myeloid leukemia after chemotherapy in extensive disease-small cell lung cancer

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Key Clinical Message

We experienced therapy-related acute myeloid leukemia (t-AML) in a patient with extensive disease-small cell lung cancer (ED-SCLC). This case is rare and has educational message because ED-SCLC has a poor prognosis and often cannot survive until developing therapy related hematological malignancy. Furthermore this case had unique chromosomal abnormalities. With recent advances in chemotherapy and radiotherapy, the prognosis of lung cancer has improved, while t-AML has been increasing in frequency.

KEYWORDS

acute myeloid leukemia, etoposide, small cell lung cancer, topoisomerase II inhibitors, toxicity

1 | INTRODUCTION

Small cell lung cancer (SCLC) has a poor prognosis, and prognosis factor in patients with SCLC is the extent of disease at presentation. For patients with limited stage disease, median survivals range from 15 to 20 months, and the reported 5-year survival rate is 10%-13%. By contrast, for patients with extensive-stage disease, the median survival is 8-13 months, and the 5-year survival rate is 1%-2%.

Therapy-related acute myeloid leukemia (t-AML) is common in hematological malignancies and breast cancer.[1] With recent advances in chemotherapy and radiotherapy, the prognosis of lung cancer has improved, while t-AML has been increasing in frequency.[1] Since ED-SCLC has a poor prognosis, t-AML rarely develops in these patients. Alkylating agents and topoisomerase II inhibitors are the representative causative drugs, with each showing characteristic chromosomal abnormalities.[1–4] Here, we report the case of a patient who developed t-AML with atypical chromosomal abnormalities during treatment of ED-SCLC.

2 | CASE REPORT

A 75-year-old man with a 50 pack-year history of smoking was referred to our hospital because of cough and right pleural effusion on chest radiography. He had a history of diabetes mellitus and cerebral infarction. His medication included amlodipine, valsartan and vilanterol trifenatate, fluticasone furoate, and voglibose.

We made a diagnosis of SCLC with pleural effusion cytology. Positron emission tomography/computed tomography and enhanced brain magnetic resonance imaging revealed many pleural lesions and enlarged mediastinal lymph nodes (Figure 1). No other metastatic lesions were seen in December 2015. A clinical diagnosis of ED-SCLC (cT4N2M1a stage 4) was made based on these findings.

Carboplatin and etoposide combination therapy were selected as the first-line chemotherapy regimen; however, after six cycles, his disease was still active. The dose of carboplatin and etoposide was 330 mg (AUC = 5) and 165 mg

(100 mg/m^2). Chest computed tomography in August 2016 showed progressive disease.

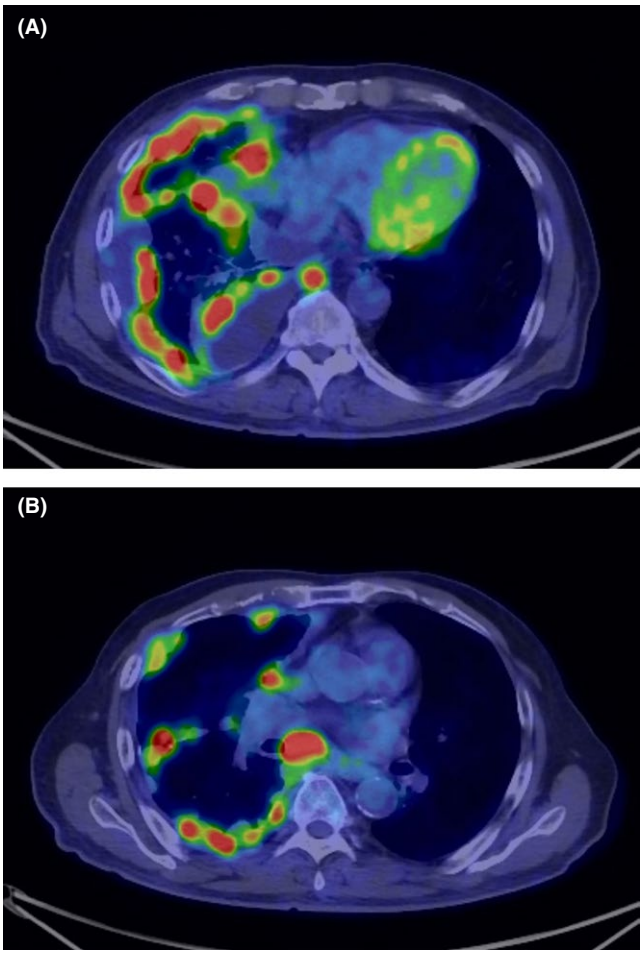

FIGURE 1 Positron emission tomography/computed tomography findings. Positron emission tomography/computed tomography revealed fluorodeoxyglucose accumulation in many pleural lesions (A) and enlarged mediastinal lymph nodes (B)

Amrubicin was selected as the second-line regimen in January 2017, but the disease continued to progress despite 11 cycles of amrubicin. We selected nogitecan as the third-line regimen in July 2017. After the first course, the patient's platelet count and haemoglobin level fell rapidly. Laboratory tests showed the following: white blood cells 4000/μL (myeloblasts 21.5%), hemoglobin 6.7 g/dL, and platelets 95,000/μL. In the bone marrow, 38.2% of the nucleated cells were myeloblasts that were positive for peroxidase staining, CD13, CD33, and human leukocyte antigen-D-related in flow cytometry (Figure 2). The total doses of the anticancer drugs administered were carboplatin 2150 mg, etoposide 2949 mg, amrubicin 1926 mg, and nogitecan 8.7 mg. We diagnosed the patient with t-AML according to the World Health Organization classification and AML with myelocytic maturation (AML M2) according to French-American-British classification.

The karyotype analysis revealed 47, XY, +8, inversion 16 (p13.1q22) in 14 of 20 cells (Figure 3). The chromosomal abnormalities of monosomy 7 and trisomy 8 were seen in his myeloblasts. The patient's performance status was 3 at the time of the t-AML diagnosis. Best supportive care was selected for his care, and he was treated with transfusions of red blood cells as palliative care. The patient died on day 17 after the t-AML diagnosis.

3 | DISCUSSION

This case highlights two important clinical issues. First, t-AML can occur during the treatment for ED-SCLC which has a poor prognosisand usually cannot survive until developing hematological malignancy (median survival of 8-13 months and <5% of patients surviving >2 years).[5] T-AML is common in hematological malignancies and breast cancer.[1] The

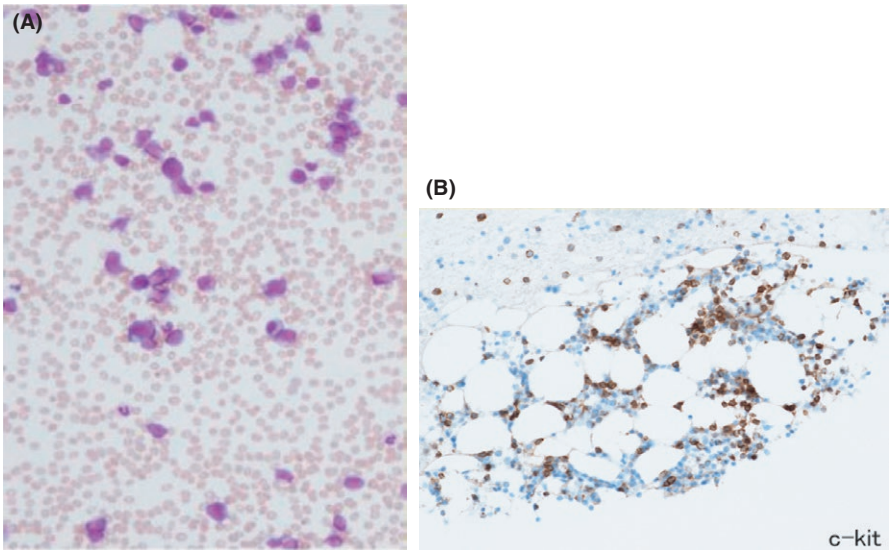

FIGURE 2 The bone marrow smear. Peroxidase positive blasts were counted at 38.2% (A) and approximately 20%-30% of the cells were c-kit positive (B)

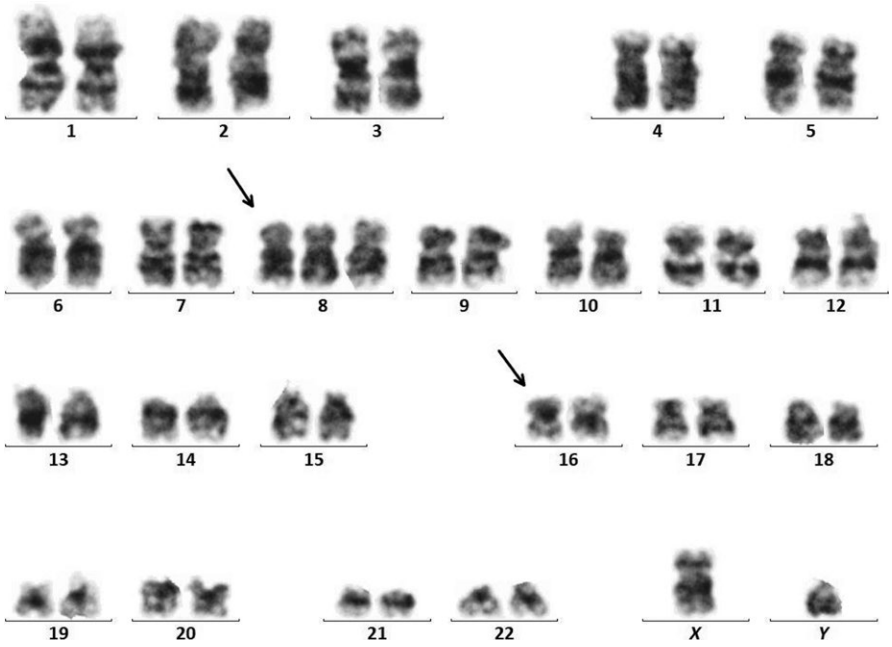

FIGURE 3 Chromosome analysis. The analysis of chromosome abnormalities revealed trisomy 8 and inversion 16 (p13.1q22) in the myeloblasts

onset of t-AML caused by topoisomerase II inhibitors is often delayed by 2-3 years, and at a total dose of 2000 mg/m^2 or more the incidence increases from 0.5% to 2.6%.[6] Since the median survival of ED-SCLC is 8-13 months, treatment-related leukaemia is not usually a problem as an adverse event. There is some published data of t-AML patients with SCLC, but there is no report of ED-SCLC. The patient, in this case, may have developed t-AML because his survival period was 21 months.

Second, t-AML in our case exhibited unique chromosomal abnormalities. Recently, t-AML was divided into two types according to clinical presentation, based on causative drugs and molecular cytogenetics: (a) t-AML caused by alkylating agents or radiotherapy, and (b) t-AML caused by topoisomerase II inhibitors.[7,8] T-AML caused by alkylating agents and radiotherapy usually develops 5-7 years after therapy and is characterized by monosomy.[3,4,7,9] On the other hand, t-AML caused by topoisomerase α inhibitors occurs typically 1-3 years after therapy and is characterised by the chromosomal abnormalities 11q23 and 21q22.[4,5] Because of the long-term administration of topoisomerase II inhibitors and the timing of the onset, t-AML in our case was classified as t-AML caused by topoisomerase II inhibitors. Although t-AML caused by topoisomerase II inhibitors usually exhibits 11q23 and 21q22, our case showed atypical monosomy 7 and trisomy 8 chromosomal abnormalities.

In conclusion, t-AML can develop even during the treatment of ED-SCLC, which has a poor prognosis. In the clinical setting, myelosuppression is a common adverse event during anticancer drug treatment. Therefore, when pancytopenia is encountered during anticancer drug treatment, peripheral blood smear samples should be checked and closely followed up, especially in patients who are exposed to many topoisomerase II inhibitors.

CONFLICT OF INTEREST

No conflicts of interest.

Consent: We obtained written consent from the patient in his life.

AUTHOR CONTRIBUTION

NU, KF, and YO: cared patient. KN and TM: supervised patient care. NU: drafted this manuscript. KF, YO, KN, and TM: revised this manuscript. All authors involved patient care, prepare, reviewed, and approved this manuscript.

ETHICAL APPROVAL

Our institution does not require ethical approval for case reports.

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