

Therapy-related acute myeloid leukemia with a rare complex karyotype following first-line therapy for small cell lung cancer: A case report

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Abstract. Therapy-related acute myeloid leukemia (t-AML) following chemotherapy in patients with small cell lung cancer (SCLC) is rare, and its clinical and genetic characteristics remain poorly elucidated. In the present study, a 53-year-old male patient with SCLC is reported. After diagnosis in June 2023, the patient received 9 cycles of etoposide and cisplatin (EP) chemotherapy, 7 cycles of EP plus durvalumab and 1 cycle of etoposide plus durvalumab sequentially. Hematological abnormalities developed 23 months after the initial chemotherapy. Bone marrow aspiration revealed 28% blasts, and flow cytometry identified 36.4% abnormal myeloid blasts. Chromosomal karyotype analysis displayed 46,XY,t(11;20)(p15; q11) [7]/46,idem,add(6)(p25)[13], consistent with a diagnosis of t-AML (M2). The present case represents t-AML with a rare karyotype and extreme latency following treatment for SCLC. The present case report enriches the available genetic spectrum of t-AML associated with SCLC, suggesting the necessity for long-term hematological monitoring in patients with SCLC and provides a reference for the clinical management of dual malignancies.

Introduction

Small cell lung cancer (SCLC) is an aggressive malignant tumor of neuroendocrine origin, accounting for 15-25% of all lung cancers. SCLC is characterized by rapid progression, early propensity for widespread metastasis and an unfavorable prognosis (1,2). The development of SCLC is associated with cigarette smoking, with an attributable risk as high as 85-90% (3). 60-70% of patients present with extensive-stage disease (ES-SCLC) at initial diagnosis, with a median overall survival of <1 year (4,5). Current standard treatment for SCLC

is dominated by systemic chemotherapy. For limited-stage disease, concurrent chemoradiotherapy is administered, while first-line therapy for ES-SCLC typically consists of etoposide combined with a platinum agent (cisplatin or carboplatin), namely the EP/CE regimen. The addition of immune checkpoint inhibitors (ICIs) such as atezolizumab or durvalumab to these regimens can notably improve progression-free survival and overall survival (6). However, the use of these cytotoxic agents is accompanied by severe long-term complications, among which therapy-related acute myeloid leukemia (t-AML) represents one of the most life-threatening (7). t-AML is a secondary malignant hematological neoplasm that arises following prior cytotoxic chemotherapy, radiotherapy or other antineoplastic treatments. The pathogenesis of t-AML is directly linked to DNA damage induced by chemotherapeutic agents in hematopoietic stem/progenitor cells (8). Compared with *de novo* AML, t-AML is characterized by an insidious onset, rapid progression, a high incidence of complex chromosomal karyotypes, lower remission rates and short survival, resulting in notably worse prognosis (9). The latency of t-AML arising post-chemotherapy in patients with solid malignancies typically spans 2-10 years, with wide variations in latency and cytogenetic features according to chemotherapeutic agent class (10). t-AML secondary to topoisomerase (TOP) II inhibitor therapy (such as etoposide) mostly manifests 2-3 years post-treatment and is defined by pathognomonic balanced chromosomal translocations. By contrast, alkylating agents (including cyclophosphamide, cisplatin and melphalan) are linked to a median latency of 5-7 years (11). These cases generally harbor complex karyotypes and are almost universally preceded by a well-characterized myelodysplastic syndrome (MDS) prodrome before leukemic progression (12,13).

Although t-AML is a well-recognized complication following chemotherapy for solid tumors, it is rare among patients with SCLC, and its clinicopathological and molecular characteristics remain poorly characterized. This may be partly attributed to the relatively short overall survival of patients with SCLC, which is often insufficient to reach the latency period required for t-AML development (9). However, with the prolonged survival of patients with SCLC due to recent therapeutic advances, the risk of late complications such as t-AML has emerged as a new challenge that clinicians must address.

Against this background, the present case report describes in detail a unique case of a 53-year-old male patient with

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SCLC who developed t-AML (AML-M2) with a short latency after treatment with etoposide, cisplatin and durvalumab. The leukemia was associated with a rare complex karyotype involving t(11;20)(p15;q11) and add(6)(p25).

By comprehensively analyzing the clinical course, pathological features, cytogenetic findings and immunophenotype of this case, the present case report aims to provide novel insights into the early recognition, molecular spectrum, underlying pathogenesis and clinical management of t-AML secondary to SCLC-directed therapy. The present case report also enriches the available clinical database and may help clinicians optimize long-term monitoring strategies for patients with SCLC.

Case report

A 53-year-old man with a 30-year smoking history (22.5 pack-years; 15 cigarettes per day on average) presented to The Second Affiliated Hospital of Dalian Medical University (Dalian, China) with recurrent cough for more than half a month. The patient had a medical history of coronary heart disease and hypertension, which were well-controlled with regular oral administration of valsartan and nifedipine tablets. A thorough oncological family history was obtained, covering all first-degree relatives and second-degree relatives; specific inquiry was made for both hematological malignancies and solid tumors, and none of the patient's family members had a confirmed diagnosis of any malignant neoplasm.

Upon admission, chest computed tomography (CT) revealed an irregular soft tissue mass (39x45 mm) in the right lower lobe of the lung, along with obstructive atelectasis and mediastinal lymphadenopathy. CT-guided lung biopsy revealed morphological features typical of small cell carcinoma. Immunohistochemistry showed positivity for AE1/AE3, thyroid transcription factor-1, CD56, synaptophysin, focal weak positivity for chromogranin A and negativity for P40 and neuroendocrine progenitor antigen, with a Ki-67 proliferation index that was 90% (Fig. 1). The patient was diagnosed with limited-stage SCLC.

Based on the diagnosis of SCLC, etoposide plus cisplatin was selected as the first-line chemotherapy regimen. The patient completed 4 cycles of EP regimen and 1 cycle of single-agent etoposide. The efficacy was evaluated as partial response. A month after completion of this course, follow-up chest CT detected new pulmonary nodules, indicating disease progression. The case was reclassified as extensive-stage SCLC with mediastinal lymph node and intrapulmonary metastases. The treatment regimen was adjusted to etoposide, cisplatin plus durvalumab and a total of 7 cycles were completed. Standard-dose chemotherapy was administered for the initial 2 cycles and the doses of etoposide and cisplatin were reduced thereafter due to impaired cardiac function. Stable disease (SD) was maintained throughout the entire treatment period. A total of 5 months after combination chemotherapy, the patient developed intermittent fever with a maximum temperature of 38°C, accompanied by elevated inflammatory markers. Chest CT revealed new pulmonary ground-glass opacities. Serial chest CT revealed dynamic evolution of lung lesions during chemotherapy (Fig. S1). Empirical anti-infective therapy was administered, leading to symptomatic improvement. Follow-up imaging 2 months later showed mild enlargement of

the original lesion, evaluated as SD (with lesion enlargement). Due to the risk of cumulative drug toxicity after multiple cycles of antitumor therapy, chemotherapy was discontinued for close observation following discussion with the patient's family. Following 2 months of treatment cessation, repeat evaluation confirmed persistent SD. The treatment was then switched to etoposide combined with durvalumab, and 1 cycle of maintenance therapy was completed.

Shortly after completion of maintenance therapy, routine blood tests revealed pancytopenia dominated by severe thrombocytopenia. Bone marrow aspiration was performed; fresh smears were fixed with methanol and stained with Giemsa working solution, and cell morphology was assessed under x1,000 oil immersion microscopy. Morphological analysis identified 28% bone marrow blasts, with morphological features consistent with acute myeloid leukemia (AML-M2; Fig. 2). Flow cytometry identified 36.4% aberrant myeloid blasts, confirming a myeloid lineage; granulocytes accounted for 47.94% and exhibited disordered maturation (Fig. 3). Integrating morphological and immunophenotypic profiles, the diagnosis of AML-M2 was established. Subsequently, cytogenetic karyotyping was conducted on bone marrow mononuclear cells via standard G-banding Giemsa staining, with 20 metaphases analyzed following International System for Human Cytogenomic Nomenclature guidelines (14).

Complex clonal chromosomal aberrations were identified: 46,XY,t(11;20)(p15;q11)[7]/46,idem,add(6)(p25)[13]. Clonal translocation t(11;20)(p15;q11) was detected in all 20 cells, and an additional chromosomal abnormality add(6)(p25) was observed in 13 clones, indicating multiple clonal chromosomal aberrations (Fig. 4). Combining the long-term multi-agent antitumor treatment for SCLC, consisting of leukemogenic platinum alkylating agents, etoposide and ICIs, the well-defined temporal sequence between cytotoxic chemotherapy and leukemic onset, and the presence of typical complex clonal karyotypic aberrations pathognomonic for chemotherapy-associated secondary myeloid neoplasms, a definitive diagnosis of t-AML rather than sporadic *de novo* AML was established. The patient was recommended to receive combined chemotherapy with azacitidine + cytarabine + venetoclax, but the patient and his family opted for palliative care. The patient was discharged after supportive treatment such as blood transfusions and died 21 days following the diagnosis of t-AML. Fig. 5 illustrates the clinical timeline of disease progression from SCLC to t-AML in the present patient.

Discussion

As an aggressive subtype of lung cancer, SCLC is associated with a 5-year survival rate of only 3-5%, and the majority of patients succumb to the primary tumor due to rapid disease progression. Accordingly, second malignant neoplasms, particularly t-AML, remain rare with very few clinical reports, representing an uncommon event (15,16). In recent years, with the incorporation of programmed death-ligand 1 (PD-L1) inhibitors, the median overall survival of patients with ED-SCLC has improved from 10 months to 12-13 months, and the 2-year survival rate has increased from 10 to 22% (17). These improvements have allowed patients with SCLC to survive long enough to enter the risk window for therapy-related

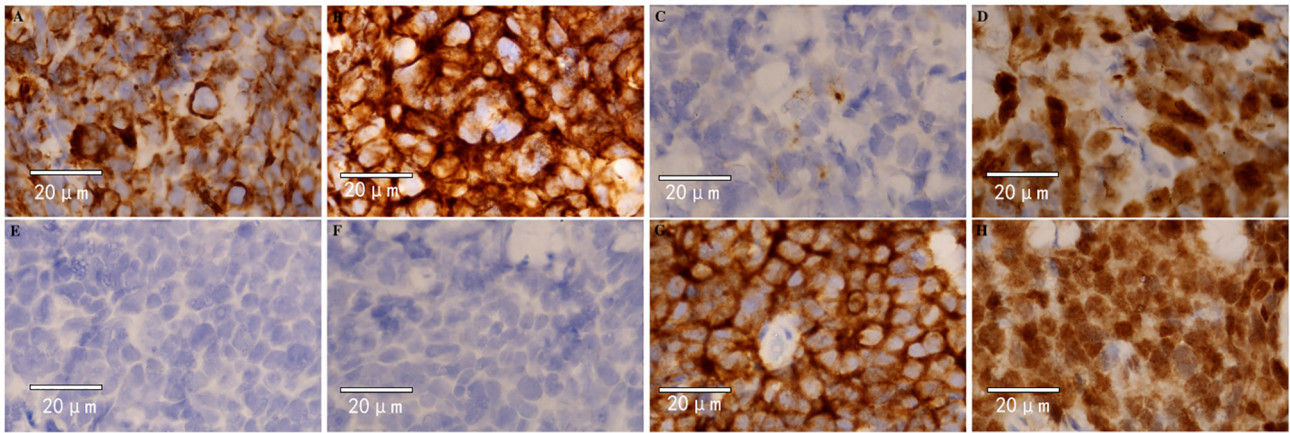


Figure 1. Immunohistochemical staining profiles of the tumor lesion. (A) AE1/AE3: Diffuse cytoplasmic positive staining. (B) CD56: Membranous positive staining. (C) Chromogranin A: Focal weak positivity. (D) Ki-67: High proliferation index (~90%). (E) Napsin A: Negative. (F) P40: Negative. (G) Synaptophysin: Positive. (H) Thyroid transcription factor-1: Nuclear positive staining. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded sections. Primary antibodies against AE1/AE3, CD56, Chromogranin A, Ki-67, Napsin A, P40, Synaptophysin and thyroid transcription factor-1 were used. Diaminobenzidine (DAB) was applied as the chromogen, and hematoxylin was used for nuclear counterstaining. Original magnification, x1,000. Scale bar, 20 µm.

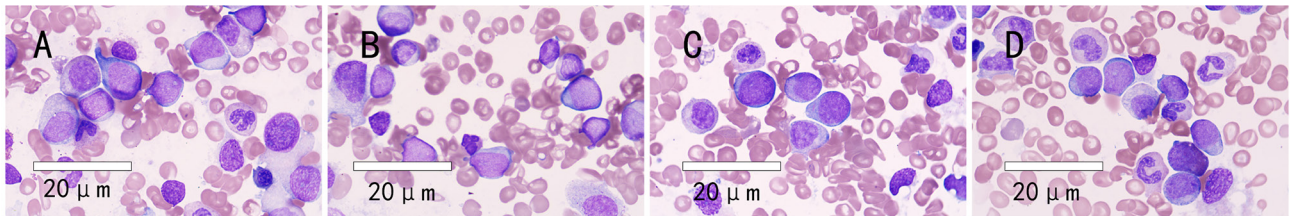


Figure 2. Bone marrow morphology. Under oil immersion microscopy, numerous abnormal myeloblasts with variable sizes, distinct nucleoli, moderate amounts of grayish-blue cytoplasm were observed, consistent with the morphological features of acute myeloid leukemia. (A) Clusters of abnormal myeloblasts with prominent nucleoli and moderate greyish-blue cytoplasm. (B) Abnormal myeloblasts showing irregular nuclear contours and varying cell sizes. (C) Individual and small-grouped myeloblasts with high nuclear-cytoplasmic ratio. (D) Numerous circulating abnormal myeloblasts. May-Grünwald-Giemsa staining; original magnification, x1,000. Scale bar, 20 µm.

secondary malignancies such as t-AML. In the present case, the patient developed t-AML just 23 months after the initial diagnosis of SCLC. The superimposition of two highly aggressive malignancies created a complex clinical scenario, underscoring the urgent need for clinicians to recognize and monitor this potentially fatal long-term complication.

One of the key features of the present case is its complex cytogenetic karyotype: 46,XY,t(11;20)(p15;q11)[7]/46,idem,add(6)(p25)[13]. Karyotype analysis revealed the clonal abnormality t(11;20)(p15;q11) accompanied by add(6)(p25), which was detected in all 20 metaphase spreads, suggesting it is a leukemogenic driving karyotype. The t(11;20)(p15;q11) translocation is a rare but non-random chromosomal aberration, rare in AML with only sporadic case reports in *de novo* AML, and to the best of our knowledge, has not been documented in t-AML (18-20). Molecular genetic studies have indicated that the t(11;20)(p15;q11) translocation results in the fusion of the nucleoporin 98 and 96 precursor (NUP98) gene (located at 11p15) and the TOP1 gene (located at 20q11) (21,22).

NUP98 is a component of the nuclear pore complex, involved in nucleocytoplasmic transport and gene transcription regulation (23). TOP1, serves as a core regulator of DNA metabolism, acting both as a key target for chemotherapeutic agents and a key partner in the formation of oncogenic fusion

genes via chromosomal translocations (24). The NUP98/TOP1 fusion protein is regarded as an oncogenic driver; it can aberrantly recruit transcriptional complexes, alter the expression of target genes (such as the HOXA gene cluster), thereby disrupting normal hematopoietic differentiation and promoting leukemogenesis (25). The add(6)(p25) aberration indicates the addition of an unknown origin segment to the distal short arm of chromosome 6, a non-balanced abnormality leading to changes in gene dosage. Notably, this region harbors tumor suppressor genes such as FOXO4 and cyclin-dependent kinase inhibitor 2A, whose amplification or breakage may further exacerbate the malignant proliferation of hematopoietic cells (25). More importantly, this abnormality represents a secondary event occurring on the basis of t(11;20), resulting in the coexistence of a major clone and a subclone. This depicts the clonal evolution of leukemia: Following the formation of an initial malignant clone driven by NUP98-TOP1, a new genetic hit [add(6p)] occurs in its progeny, generating a subclone with enhanced proliferative advantage and ultimately leading to the full-blown manifestation of the disease (26). Such complex karyotypes and clonal evolution serve as key biological underpinnings for the unfavorable prognosis of t-AML.

As a TOP II α inhibitor, etoposide induces DNA double-strand breaks by stabilizing enzyme-DNA complexes

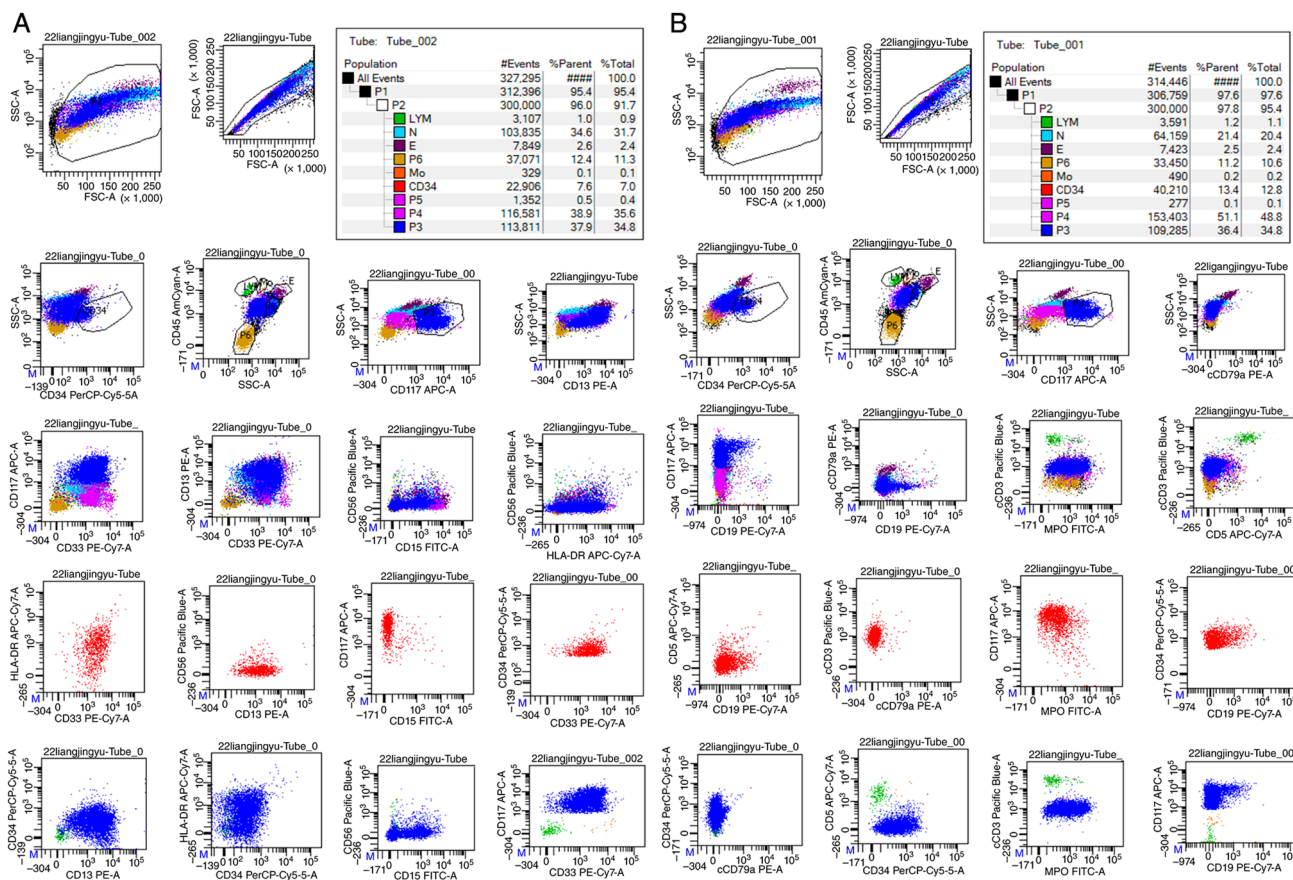


Figure 3. Multiparameter flow cytometry immunophenotyping of bone marrow aspirate. (A) Global FSC/SSC gating, population statistics and myeloid maturation markers (CD34, CD117, CD13, CD15, CD56 and HLA-DR). (B) Cytoplasmic MPO (myeloid-specific marker) and pan-lymphoid exclusion markers CD19, CD5 and cCD79a for lineage discrimination. CD34⁺ aberrant myeloblasts constitute 36.4% of marrow nucleated cells; positive CD33, CD117 and MPO alongside absent pan-lymphoid antigens indicate myeloid lineage. Granulocytes (population N on CD45/SSC plots) account for 47.94% of total nucleated cells; heterogeneous expression of maturation antigens CD13, CD15 and CD56 reveal granulocytic maturation dysplasia. FSC, forward scatter; SSC, side scatter; HLA-DR; human leukocyte antigen, DR isotype; MPO, myeloperoxidase.

and preventing re-ligation of DNA breaks. Normal hematopoietic stem cells (HSCs) can repair these damages through homologous recombination; however, long-term exposure may lead to the accumulation of gene repair errors in HSCs, predisposing them to chromosomal translocations. Cytogenetically, this often involves balanced translocations involving 11q23 (lysine methyltransferase 2A gene) or 21q22 (runt-related transcription factor 1 gene) (27). TOP II inhibitor-related t-AML typically has a shorter latency period (2-5 years), often presenting directly as acute leukemia without a preceding MDS phase. Platinum agents (cisplatin/carboplatin), belonging to alkylating agents, primarily form platinum-DNA adducts intra- or inter-strand, interfering with normal DNA replication and transcription. Unrepaired damages can lead to point mutations or gene deletions. Alkylating agent-related t-AML is frequently characterized by deletions of -5/del(5q) or -7/del(7q) and has a longer latency period (5-10 years) (28). The cumulative DNA-damaging effect of cisplatin may provide a cellular background with increased chromosomal instability, facilitating etoposide-induced chromosomal translocations. ICIs activate antitumor immune responses by releasing the inhibition of immune cells by immune checkpoints (such as programmed cell death protein 1/PD-L1 and cytotoxic T lymphocyte-associated protein 4) (29); however, the mechanism underlying their induction of second malignant

neoplasms remains unclear. Additionally, the present patient had a heavy smoking history. Nicotine metabolites in tobacco (such as nicotine-derived nitrosamine ketone) can induce DNA damage in bone marrow hematopoietic cells, increasing the risk of hematological malignancies (30,31). In the present case, smoking may have contributed to the disease process through a dual oncogenic effect: On one hand, it induced SCLC (6); on the other hand, it impaired the genomic stability of bone marrow HSCs, reduced their tolerance to chemotherapeutic agents and accelerated the development of t-AML (32). This synergistic effect may have served as a contributing factor to the exceptionally short latency period observed.

The development of t-AML following chemotherapy for SCLC is a doubly rare event, rendering the report of each case particularly valuable. To the best of our knowledge, this is the first report of t-AML with the complex karyotype t(11;20)(p15;q11) and add(6)(p25) secondary to SCLC chemotherapy, expanding the cytogenetic spectrum of t-AML with a novel subtype. The present case suggests that even conventional doses of etoposide may induce t-AML within a short latency period, especially in high-risk populations such as smokers and patients aged ≥ 50 years. Therefore, long-term routine blood monitoring should be established. In the presence of unexplained or persistent pancytopenia, abnormal blood count patterns or the appearance of blasts in

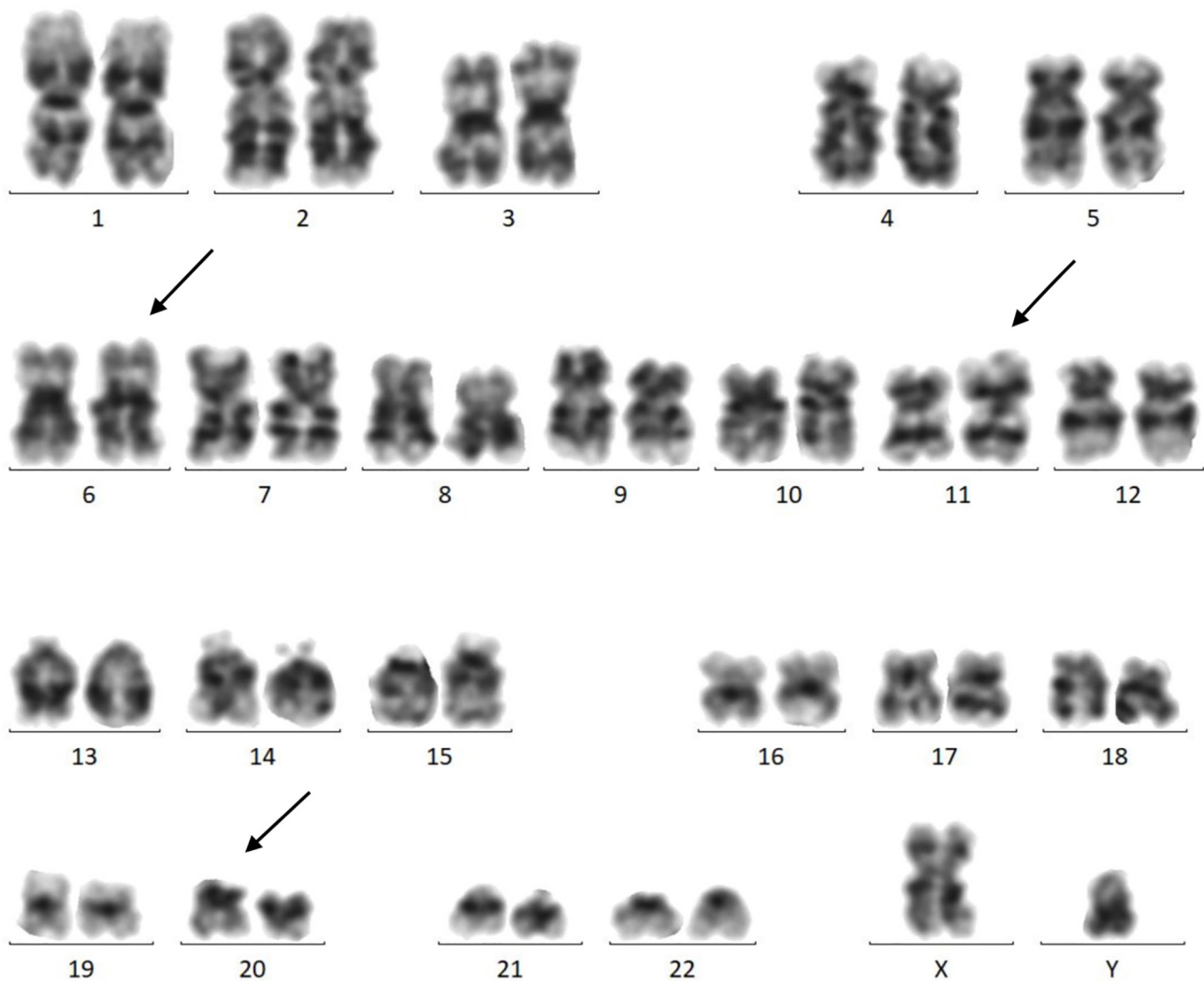


Figure 4. Chromosome karyotype analysis. G-banded karyotype showing multiple clonal abnormalities, spread with $t(11;20)(p15;q11)$ and $add(6)(p25)$ represented by black arrows.

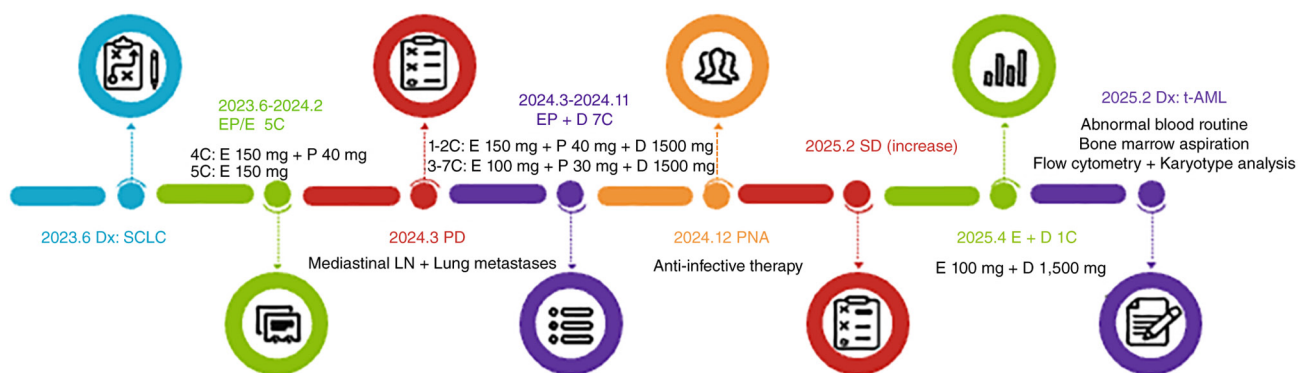


Figure 5. Clinical timeline of SCLC progression to t-AML in the present patient. Total cumulative doses: Etoposide 4,950 mg, cisplatin 1,170 mg and durvalumab 12,000 mg. Cycle length: 21 days; dosing on days 1-3 via ivgtt. SCLC, small cell lung cancer; Dx: diagnosis; E, etoposide; P, cisplatin; C, cycle; D, durvalumab; LN, lymph node; PNA, pneumonia; SD, stable disease; ivgtt, intravenous guttae.

peripheral blood, timely bone marrow aspiration combined with cytogenetic testing should be performed to avoid misdiagnosis of t-AML.

The present patient faced dual therapeutic demands for both SCLC and newly diagnosed t-AML, presenting a prominent

therapeutic dilemma: t-AML requires intensive chemotherapy for induction of remission, but the poor performance status of the patient following multiple cycles of intensive chemotherapy resulted in extremely low tolerance; meanwhile, maintenance therapy for SCLC may further exacerbate myelosuppression.

In such circumstances, the treatment goal needs to strike a delicate balance between achieving remission and maintaining quality of life. Although novel regimens such as azacitidine combined with venetoclax offer new hope for patients with AML intolerant to intensive chemotherapy, the prognosis of t-AML is notably worse than that of *de novo* AML, particularly in patients with complex karyotypes. Allogeneic hematopoietic stem cell transplantation remains the only curative treatment for t-AML.

In the present case report, a comprehensive description and in-depth analysis of a case of a 53-year-old man with SCLC who developed t-AML with a short latency of ~23 months after standard treatment. The t-AML harbored a complex karyotype characterized by t(11;20)(p15;q11) combined with add(6)(p25), and was potentially driven by the NUP98-TOP1 fusion gene. The present case is notable for the co-occurrence of two highly malignant neoplasms, a short latency period and rare cytogenetic abnormalities, thereby enriching the cytogenetic spectrum of t-AML.

As survival outcomes of patients with SCLC continue to improve, t-AML has emerged as a key, life-threatening late complication. The present case highlights the imperative to establish long-term hematological monitoring and multidisciplinary management in clinical practice. Meanwhile, it provides insights into the clinicopathological features, molecular mechanisms and individualized diagnostic and therapeutic strategies of t-AML following treatment for SCLC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SY and LL authenticated all the raw data and were responsible for data collection. LL drafted the manuscript, performed the critical revision and edited the final version. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for the publication of this case report and any associated images was obtained from the patient's next-of-kin prior to submission. The next-of-kin was informed that all personally identifiable information would be anonymized to safeguard confidentiality.

Competing interests

The authors declare that they have no competing interests.

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