Multiple primary tumors in a patient with non-small-cell lung cancer harboring mutations in *ERCC6* and *LYL1*: A case report

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Abstract. Certain types of primary tumor, particularly triple primary tumors with germline mutations, are rare. The present study reports a novel case of the metachronous occurrence of three pathological conditions, namely, non-small-cell lung cancer (NSCLC), early T cell precursor acute lymphoblastic leukemia (ETP-ALL) and SCLC. The present study used next-generation sequencing to aid diagnosis. A 44-year-old male patient presented to The First Affiliated Hospital Zhejiang University School of Medicine (Hangzhou, China) in September 2016.) with a nodule in the right lower lung during an annual checkup. Then, the patient was diagnosed with poorly differentiated NSCLC (T1N2M0; stage IIIA) and underwent surgical resection and biopsy. In September 2018, the patient was diagnosed with ETP-ALL with superficial lymphadenopathy. Germline testing demonstrated germ cell variants of ERCC excision repair 6, chromatin remodeling factor (*ERCC6*; c.1322A>G) and LYL1 basic helix-loop-helix family member (*LYL1;* c.587T>A). In November 2020, the patient was diagnosed with SCLC by bronchoscopic biopsy following allogeneic hematopoietic stem cell transplantation. The patient was diagnosed with lung cancer in October 2016 and the treatment were: surgery, chemotherapy, radiotherapy, and targeted therapy. In October 2018, the patient was diagnosed with ETP-ALL and the treatment were: chemotherapy and allogeneic hematopoietic stem cell transplantation. In November 2020, the patient was diagnosed with small cell lung cancer and received chemotherapy and radiotherapy. The patient died at September 2022. The present case highlighted the importance of monitoring germline mutations in patients and their families to facilitate early diagnosis, appropriate treatment and prognostic evolution in the face of rapid recurrent cancer.

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Abbreviations: CT, computed tomography; ETP-ALL, early T cell precursor acute lymphoblastic leukemia; NSCLC, non-small cell lung cancer; ATG, anti-thymocyte globulin; IACR, International Association of Cancer Registries

Key words: triple primary tumor, gene mutation, multiple primary tumors, high-throughput sequencing, non-small-cell lung cancer

Introduction

Tumors that occur at different sites and/or belong to different histological or morphological groups are considered to be a multi-primary cancer (1). A study in 1921 reported that 4.7% of 3,000 patients with malignant tumors had multiple tumors (2). Epidemiological studies have reported that the frequency of multiple primary cancer was 2-17% in 2014 (3-7). Weir *et al* (5) reported that following Surveillance, Epidemiology and End Results guidelines (8), the incidence of multiple primary cancer was 19.7% in patients with colon cancer [16.9% as per International Association of Cancer Registries (IACR) guidelines (9)] and 21% in those with lung cancer (19.9% according to the IACR guidelines). The epidemiological factors contributing to occurrence of multiple primary cancer include host factors, such as genetic factors, hormones and tumor history, lifestyle factors, such as smoking and alcohol consumption, and environmental factors, such as occupation, pathogen exposure and geographical location (10). Among these, genetic factors have attracted increasing attention from researchers (3,11-16). It is estimated that between 5 and 10% of all breast cancer cases and ~20% of ovarian cancer cases are caused by an inherited pathogenic variant associated with hereditary breast and ovarian cancer syndrome (17-21). First- and second-degree relatives and first cousins have a 12.5-50.0% probability of inheriting the respective cancer predisposition variants (22,23). Therefore, timely identification of genetic variants decreases morbidity and mortality in individuals with inherited cancer risk and facilitates targeted therapy for patients with cancer (24). Table I provides a brief overview of germline mutations in patients with cancer from larger sequencing studies (25-32). Genetic testing serves as a robust and efficient auxiliary examination tool that provides information on molecular subtypes and therapeutic targets and

aids in the development of potential treatment strategies and selection of appropriate drugs (33).

The 5-year survival rate of patients with 27 common types(including pancreas to testis) of cancer in the UK ranges from 7 to 88% (34). Depending on the type of combined tumor, survival times vary among patients with different recurring types of cancer, especially those with hematological disease (8), who exhibit rapid progression, high degree of malignancy, difficulty in treatment and a low survival rate. A number of patients with multiple primary tumors of hematological disease) carry germline driver gene mutations (CEBPA OR TP53 and so on) associated with a poor prognosis (35). Previous studies (36,37) have shown that a small number of patients carrying two germline mutations, ERCC excision repair 6, chromatin remodeling factor (*ERCC6*) and LYL1 basic helix-loop-helix family member (*LYL1*), develop non-small-cell lung cancer (NSCLC), early T cell precursor acute lymphoblastic leukemia (ETP-ALL) and SCLC. The present study describes a patient with *ERCC6*(+) and *LYL1*(+) mutations with triple primary tumors.

Case report

A 40-year-old male patient (healthy and non-smoker) was found to have a right lower lung space during an annual routine checkup in September 2016 (Fig. 1A) at The First Affiliated Hospital Zhejiang University School of Medicine (Hangzhou, China). The patient's father, who smoked for 40 years, had also been diagnosed with lung cancer but refused genetic testing. Radical resection of the lower right lung cancer was performed in October 2016. The pathological diagnosis was adenocarcinoma of the lower right lung (T1N2M0, stage IIIA) (38). Postoperative concurrent chemoradiotherapy included four cycles of pemetrexed + platinum, with a total radiotherapy dose of 50 Gy in 25 fractions (50 Gy/25 f). In March 2018, routine chest computed tomography (CT) scan demonstrated a new nodule near the pleura in the middle lobe of the right lung (Fig. 1B), which indicated local recurrence of adenocarcinoma. Gefitinib (250 mg, once daily) was administered orally and the nodules subsequently disappeared by July 2018, as confirmed by chest CT scan (data not shown).

In September 2018, at the Tongde Hospital of Zhejiang Province (Hangzhou, China) for the first presentation, the patient developed submental lymph node enlargement, which was diagnosed as ETP-ALL based on lymph node biopsy and bone marrow tests [CD7(++), CD1α(-), CD8(-), CD5(dim), CD34(+), CD2(+), cyCD3 (weakly positive) and CD4(+). Gefitinib was discontinued and hyper-cyclophosphamide, vindesine, liposomal doxorubicin and dexamethasone/methotrexate and cytarabine was initiated (Table II); however, this proved ineffective. Germline gene sequencing of skin tissue demonstrated *ERCC6* variant c.1322A>G and *LYL1* variant c.587T>A (Fig. 2).

The primers were as follows: ERCC6-E5 forward (F), 5'-GAGGAAGATGACGAGGTGGA-3' and reverse (R), 5'-GGCTGCAGAAATCCAACCTC-3' and LYL1-E4 F, 5'-CAGACCCATGAGTACACCCA-3' and R, 5'-CTGACGTCTTCACTGGTCCT-3'. The high-throughput sequencing was Aligent SureSelect. The method used to verify the quality/integrity of the processed samples was A

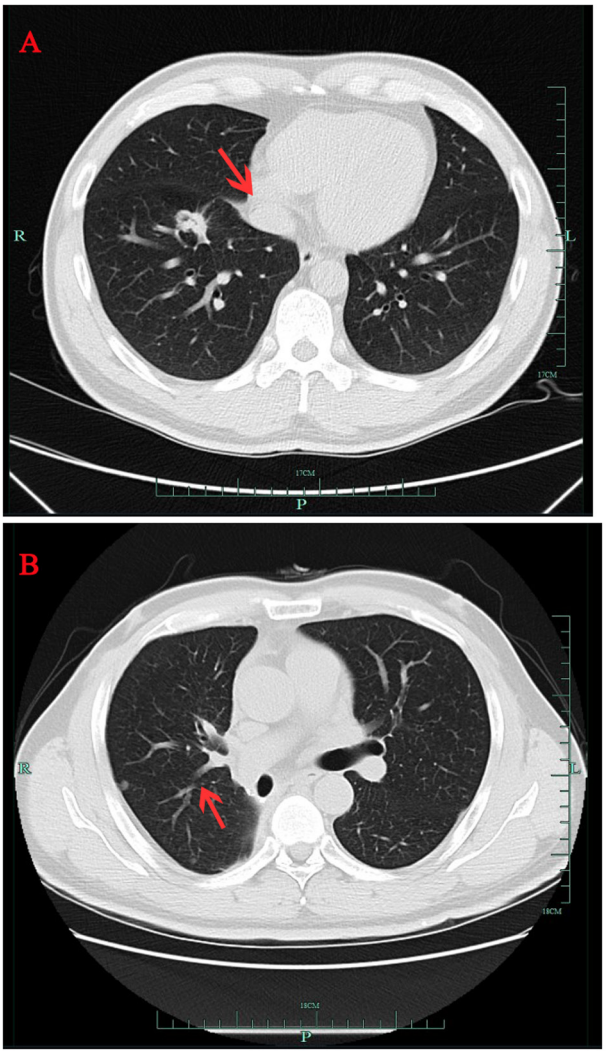

Figure 1. Serial chest CT scans of patient with non-small cell lung cancer. (A) CT scan from September 2016 showing a right lung mass (red arrow). (B) CT scan from March 2018 showing a small nodule (red arrow) near the pleura in the middle lobe of the right lung. CT, computed tomography.

2200 bioanalyzer for genomic DNA or RNA. The type of sequencing was 300 bp for length and paired end for direction of sequencing. The loading concentration of the final library, including how concentrations were measured:5 pM for DNA sequencing). i) The patient received two courses of venetoclax combined with granulocyte colony-stimulating factor, cytarabine and aclacinomycin chemotherapy (Table II). February 2019 bone marrow reexamination indicated complete remission (data not shown).

Modified busulfan-cyclophosphamide pretreatment (Cytarabine 7.3 g-10d,-9d; busulfan 54 mg q6h8d,-7d,-6d; cyclophosphamide 3.3 g-5d,-4d; oral semustine 450 mg-3d. Cytarabine-busulfan and cyclophosphamide intravenous infusion. Semustine was Oral administration, the purpose of this were to fully eliminate or suppress the patient's immune system to prevent graft rejection; reduce the number of tumor cells to a minimum; remove the patient's hematopoietic stem cells from the bone marrow niche to provide sufficient space for the engrafted donor hematopoietic stem cells to support proliferation and differentiation. ii) was performed in March 2019.

Table I. Common genes with germline mutations in patients with cancer.

Gene	Prevalence of mutation (globally)	Disease	Clinical characteristics	(Refs.)
BRCA1	1/500-1/300	Breast, ovary, prostate and pancreas cancer	Sensitivity to platinum-containing therapy or PARP inhibitors	(25)
p53	1/5,000-1/500	Li-Fraumeni syndrome	Breast cancer, soft tissue sarcoma and osteosarcoma	(26)
Adenomatous polyposis coli	1/10,000-1/8,000	Colorectal cancer	Familial occurrence, a younger age of onset, and is commonly seen in children.	(27-29)
MutL homolog 1, MSH2, MSH6 and PMS2	1/3,000	Lynch syndrome	Colorectal, endometrial and ovarian cancer and gastric and ureteral carcinoma	(30)
Von Hippel-Lindau tumor suppressor	1/36,000	Von Hippel-Lindau syndrome	Retinal angioma, hemangioblastoma, pancreatic cyst and renal carcinoma	(31)
SDHB	6/100-8/100	SDHB-deficient paraganglioma/ pheochromocytoma syndrome	Hypertension, headache, palpitations, hyperhidrosis and catecholamines in blood or urine	(32)

SDBH, succinate dehydrogenase complex iron sulfur subunit B; MSH, mutS homolog; PMS2, PMS1 homolog 2, mismatch repair system component.

Table II. Timeline of early T cell precursor acute lymphoblastic leukemia treatment.

Date	Chemotherapy regimen	Drug
October 2018	Hyper CVAD-part A	Cyclophosphamide, 0.55 g q12h d-3; dexamethasone, 40 mg qd d1-4; liposomal doxorubicin, 60 mg qd d4; vindesine, 4 mg qd d4
November 2018	Hyper CVAD-part B	Methotrexate, 2 g qd d1; cytarabine, 1g q12h d2-3
November 2018	V + CAG	Venetoclax, 400 mg qd d1-28; cytarabine, 25 mg q12h d1-14; aclarubicin, 20 mg qd d1-4; G-CSF, 300 μg d1-14
January 2019	V + CAG	Venetoclax, 400 mg qd d1-28; cytarabine, 100 mg q12h d1-7; aclarubicin, 20 mg qd d1-4; G-CSF, 300 μg d1-14

G-CSF, granulocyte colony-stimulating factor; CVAD, cyclophosphamide, dexamethasone, liposomal doxorubicin and vindesine; V + CAG, venetoclax, cytarabine, aclarubicin and G-CSF; qd, once daily; q12h, once every 12 h; d, day.

Haploidentical hematopoietic stem cell transplantation was performed following stem cell donations from the patient's son (March 2019). During transplantation, anti-thymocyte globulin (ATG; total dose 700 mg), cyclosporin A and short-course methotrexate(cyclosporin A 75 mg q12h qd Intravenous infusion; methotrexate 10mg +1d,+3d,+6,+11d, were Intravenous infusion) were administered on days 1, 3, 5 and 11 following transplantation, to prevent acute graft vs. host disease. After ATG was administered, leukocyte count (Table III) was monitored. In April 2019, bone marrow examination showed that the ETP-ALL was in remission, the short tandem repeat was of the complete donor type and the right lung lesion was smaller, as observed through CT scan (data not shown). During the cyclosporin anti-rejection treatment, routine Positron Emission Tomography-CT examination indicated multiple small nodules in both lungs, which prompted clinical consideration of lung adenocarcinoma recurrence. Gefitinib (250 mg, once daily) targeted therapy was re-administered for 10 months to alleviate the increase in the number of lung nodules.-we decided to switch from gefitinib to osimertinib (80 mg/d). The number of nodules in both lungs decreased following this treatment.

Sudden hemoptysis occurred in November 2020 and a new obstruction in the lumen was noted following bronchoscopy (Fig. 3). Pathological examination of brush cytology smear under a microscope demonstrated SCLC (Fig. 4). Immunohistochemistry was negative for CK7 and positive for pancytokeratin (PCK), chromogranin A) and SyN(Synaptophysin). A marked decrease in foreign body count was observed after combining chemoradiotherapy with osimertinib treatment through chest CT (data not shown). A

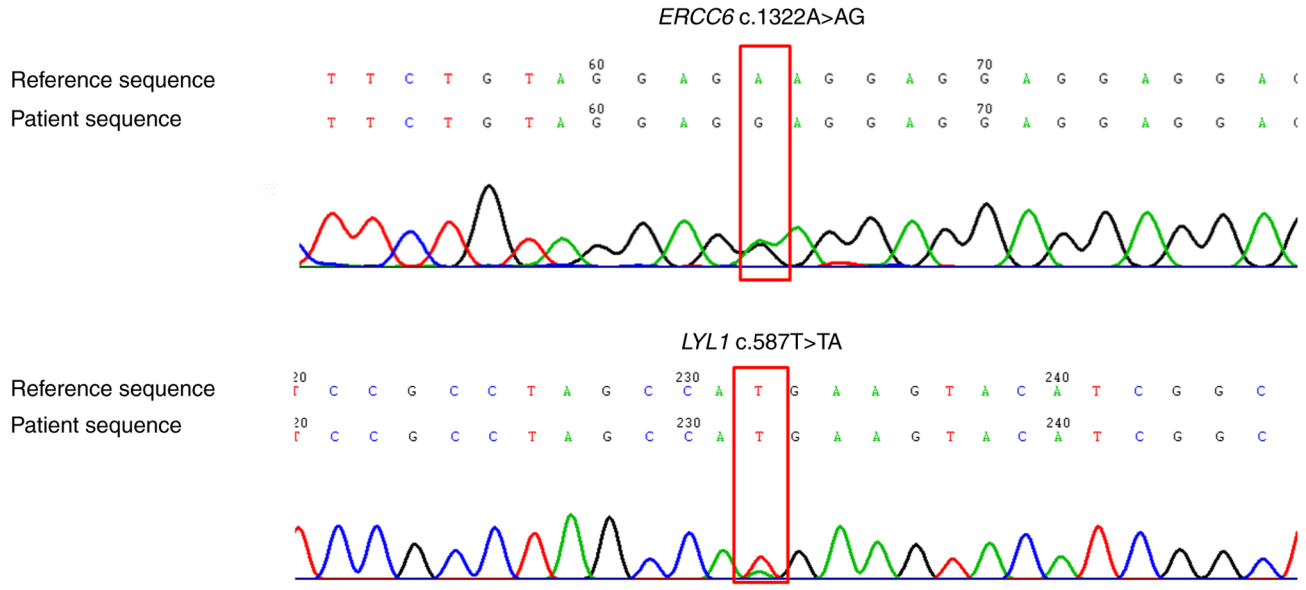

Figure 2. Next-generation sequencing demonstrated *ERCC6* and *LYL1* mutations (red box). ERCC6, ERCC6 excision repair 6, chromatin remodeling factor; LYL1, LYL1 basic helix-loop-helix family member.

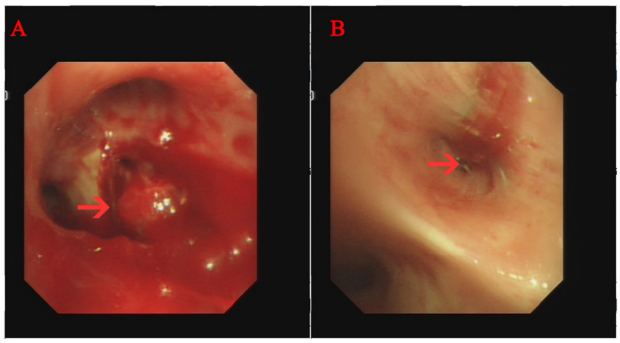

Figure 3. Bronchoscopic findings at time of diagnosis of small cell lung cancer. (A) Polypoid endobronchial mass (red arrow) blocked the right upper lobe bronchus (red arrow). (B) Tracheal occlusion after resection of the right lower lobe bronchus.

timeline of the three types of cancer diagnosed is presented in Table IV. No metastases in the skull, bones or gastrointestinal area were observed during treatment. In August 2022, the patient succumbed to progressive lung cancer and no autopsy was performed.

Discussion

Germline gene mutations implicated in development of multiple primary tumors warrant investigation. Paired tumor germline genomic analyses have identified at least one pathogenic or potentially pathogenic germline variant of cancer susceptibility genes in 8-18% of patients with cancer (39-41). Oncologists increasingly recommend genetic testing for pathogenic germline variants in patients with cancer to advise on individual risk of developing cancer and the likelihood of family members carrying the same genetic predisposition to cancer (42,43). For example, inactivating mutations in the cancer suppressor genes *BRCA1* and *BRCA2* predict response to drugs, such as PARP inhibitors docetaxel and cisplatin, and are associated with increased genetic susceptibility (44).

ERCC6 encodes a DNA-binding protein key for excision and repair during transcriptional coupling. The protein exhibits ATP-stimulated ATPase activity, interacts with numerous transcription and excision repair proteins and may promote complex formation at DNA repair sites. ERCC excision repair 6, chromatin remodeling factor (alternatively named Cockayne syndrome complementation group B), encoded by *ERCC6*, recruits nucleotide excision repair factors to the DNA damage site and serves a key role in the repair process. Mutations in *ERCC6* are commonly observed in patients with Cockayne syndrome type B and cerebro-oculofacial bone syndrome type I (45,46). Several population-based studies have shown that *ERCC6* polymorphisms markedly affect risk of certain types of cancers, including lung cancer (47-49), and the recurrence of superficial bladder cancer (50). In a case-control study of lung cancer in a Chinese population, Ma *et al* (51) reported that each single nucleotide polymorphism may serve only a small role individually, and multiple loci in *ERCC6* may collectively contribute to lung cancer susceptibility.

LYL1 encodes a basic helix-loop-helix (bHLH) transcription factor that is hypothesized to serve roles in vascular maturation and hematopoietic processes (52,53). *LYL1* was first reported to be associated with the translocation t(7;19)(q35;p13) in patients with T cell acute lymphoblastic leukemia (T-ALL) (54). As a super enhancer (55,56), *LYL1* induces transcription of target genes and shows closer association with oncogenes compared with typical enhancers (such as PARP inhibitors for breast cancer (BRCA1 mutation), oncogenes LYL1 is associated with DNMT3A/IDH2) (57). It has been hypothesized that the antitumor activity of GNE-987 drug that is still under development and has not yet been released to the market.) targeting bromodomain-containing protein 4 in acute myeloid leukemia (AML) involves downregulation of various super enhancers and associated oncogenes,

Table III. Leukocyte levels following anti-thymocyte globulin treatment.

Day	1	4	7	9	10	11	12	14	15	17	22	24	26	28	30
White blood cell count, $x10^9$/l	3.4	0.1	0.2	0.4	0.1	0.1	0.1	0.1	0.1	0.1	2.0	2.8	2.4	2.8	3.4
Absolute neutrophil count 10^9/l	3.3	0.1	0.2	0.4	0.1	0.0	0.0	0.0	0.0	0.0	1.5	1.5	1.8	2.0	2.6

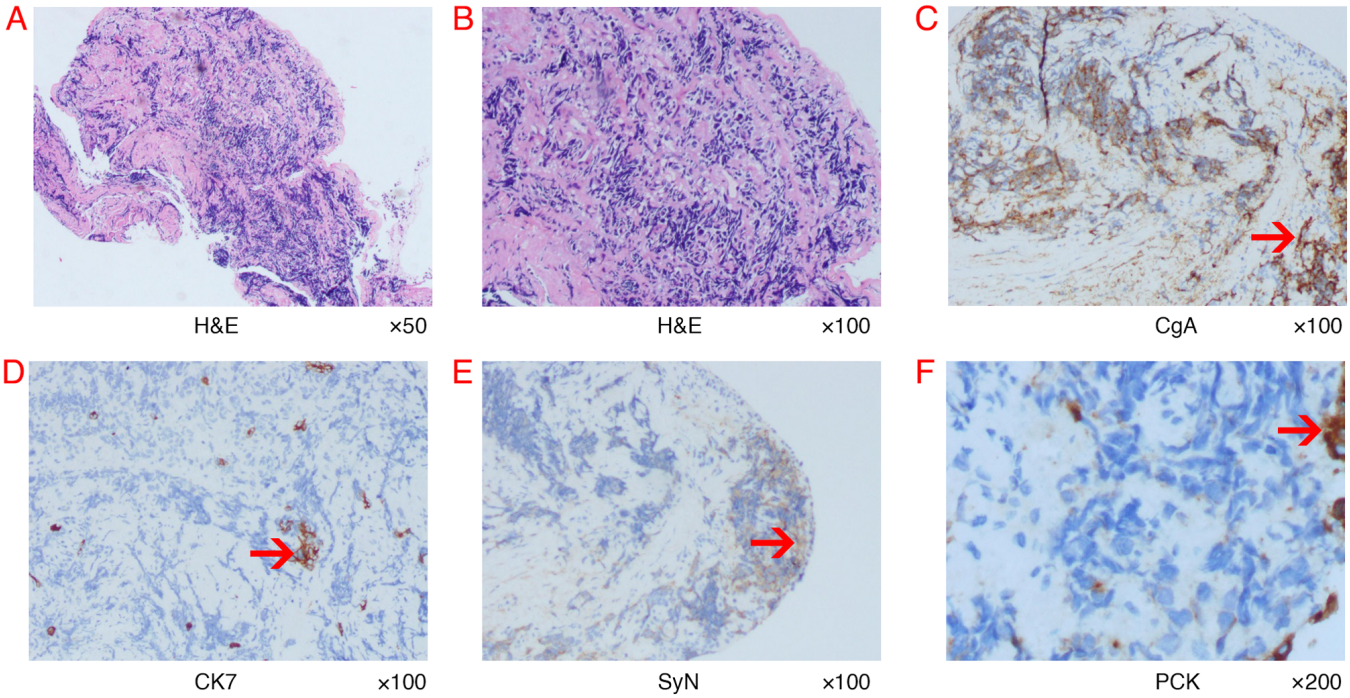

Figure 4.Histopathological findings of bronchoscopic biopsy and representative IHC-labelled tumor tissue. (A and B) Representative images of tumor morphology. Magnification, x50 and x100, respectively. The histological results of (C) CgA, (D) CK7, (E) SyN and (F) PCK. The red arrows indicate positive IHC labelling. IHC, immunohistochemistry; PCK, Pancytokeratin; H&E, hematoxylin and eosin; CgA, Chromogranin A; SyN, Synaptophysin; CK7, Cytokeratin 7.

including *LYL1* (58). Furthermore, LYL1 expression levels in bone marrow of patients with AML is reported to be higher compared with that in normal bone marrow (44). Structurally, both LYL1 and its homolog T cell acute lymphocytic leukemia protein 1 (TAL1) that form DNA-binding heterodimers with E proteins (such as E2A:transcription factor 3 and HEB: transcription factor 12), are bHLH factors (59). For example, TAL1 forms a complex with E2A, LDB1 (LIM domain-binding protein 1), LMO2 (LIM-domain-only protein 2), GATA3 (endothelial transcription factor 3) and RUNX1 to mediate a core transcriptional regulatory circuit in T-ALL (60). LYL1 expression levels are associated with poor prognosis of AML (61). In the present case of a patient harboring mutations in *ERCC6* and *LYL1*, three tumors developed within a short period (1.5-2 years). These two germline gene mutations could potentially influence cancer recurrence.

In addition to driver genes, radiotherapy and chemotherapy are considered risk factors for recurring types of cancer (62). In a previous study, four patients with heterochronous manifestations received chemotherapy and/or radiation therapy for lung cancer before developing AML (63). In all four patients, lung cancer preceded AML by 5-10 years and the patients died within 2 months of being diagnosed with AML. In the present case, the patient initially developed NSCLC and ETP-ALL occurred within 2 years of treatment with pemetrexed combined with cisplatin chemotherapy and radiotherapy, which progressed rapidly. The patient harbored the driver genes *ERCC6*(+) and *LYL1*(+), which promoted the occurrence of acute leukemia following radiotherapy and chemotherapy. Later, owing to the high degree of malignancy of ETP-ALL, the patient received allogeneic hematopoietic stem cell transplantation, requiring strong immunosuppression to prevent rejection. These anti-rejection drugs act by removing T cells, resulting in T cell exhaustion (42). According to Chan *et al* (64), a recurrent SCLC subpopulation may exist in an immunosuppressed tumor microenvironment characterized by exhausted CD8+ T cells, as described by Guo *et al* (65). Research has

Table IV. Timeline of triple cancer progression.

Cancer	Date of diagnosis	Key pathological features	Molecular findings	Treatment
Non-small cell lung carcinoma	October 2016			Surgery, radiotherapy, chemotherapy[a] and targeted therapy[b]
Early T cell precursor acute lymphoblastic leukemia	October 2018	CD7(+), CD1α(-), CD8(-)[c], CD5<75%, CD34(+), CD2(+), CD3(+) and CD4(+)	LYL1 and ERCC6[d]	Chemotherapy[e] and haplo-hematopoietic stem cell transplantation
Small cell lung carcinoma	November 2020	PCK(+), CgA(+), SyN(+), CK7(-)	Not applicable	Radiotherapy and chemotherapy

[a]Pemetrexed and platinum. [b]Gefitinib. [c]Method of detection was flow cytometry. [d]Tissue sample taken from skin of the leg. [e]Hyper cyclophosphamide, dexamethasone, liposomal doxorubicin and vindesine, methotrexate, cytarabine;V+CAG, venetoclax, cytarabine, aclarubicin and G-CSF. ERCC6, ERCC6 excision repair 6, chromatin remodeling factor; LYL1, LYL1 basic helix-loop-helix family member; PCK, pancytokeratin; CgA, Chromogranin A ; SyN, Synaptophysin; CK7, cytokeratin-7.

shown that the genetic profile of activated tumor regulatory T cells is associated with a poor prognosis in lung adenocarcinoma: Chan *et al* (64) has shown that SCLC exhibits increased immune isolation and decreased immune infiltration compared with lung adenocarcinoma. Here, 1.5 years after transplantation, the patient developed SCLC, which was possibly linked to use of immunosuppressants such as ATG.

In the present study, the patients father's long-term smoking may have exposed the patient to tobacco smoke for numerous years and may represent a carcinogenic exposure factor. Epidemiological studies of exposure to environmental tobacco smoke, along with the detection of tobacco-specific carcinogens in blood and urine of non-smokers in such environments, have indicated that long-term inhalation of tobacco smoke is a cause of lung cancer (66,67) Subsequent studies (68-70) have similarly confirmed that exposure to environmental tobacco smoke significantly increases risk of lung cancer for non-smokers.

The National Comprehensive Cancer Network guidelines recommend genetic screening for breast, ovarian, pancreatic, lung, colorectal and prostate cancer based on previous studies (71). Genetic screening is performed according to American College of Medical Genetics and Genomics, which offers the advantage of early identification of tumors and effective treatment (72,73). For example (74,75), positive screening of commonly inherited breast cancer gene *BRCA1*/2 mutations can prompt appropriate treatment measures such as surgery or enhanced monitoring of patients who refuse surgery. However, screening faces a number of challenges, such as cost, invasiveness of the procedure. Therefore, in clinical decision-making, patients should receive information on the advantages and disadvantages, with their preferences respected.

Management of multiple primary tumors poses challenges, with implications for overall survival and quality of life, such as decreasing infections, avoiding transfusions and shorter hospital stays. Therefore, multidisciplinary collaboration to develop a personalized treatment plan is essential. In the present case, when the ETP-ALL diagnosis for the second tumor was made, multiple multidisciplinary discussions with oncology, respiratory and radiotherapy departments were conducted regarding the choice of chemotherapy regimen for ETP-ALL and the decision on whether to proceed with a transplant. The patient and their family were also consulted. Finally, a chemotherapy regimen for AML that combined venetoclax with cytarabine, aclarubicin and G-CSF was chosen, which achieved complete remission. Subsequently, one consolidation cycle was administered, followed by a related donor allogeneic hematopoietic stem cell transplant. Treatment plans for lung cancer post-transplant due to emergence of the third SCLC tumor were similarly coordinated with oncology, respiratory and radiotherapy specialists.

The present study had several strengths, such as genetic testing of germline genes upon development of a second tumor, successful management of ETP-ALL with hematopoietic stem cell transplantation and sustained remission. However, there were also limitations, which included the absence of sample testing from the patient's father, inability to verify the genetic pattern and the need for case reports.

In summary, the present study described a patient with NSCLC harboring mutations in the germline genes *ERCC6* and *LYL1* who developed ETP-ALL and SCLC shortly after remission. Considering the rapid progression of recurring types of cancer, clinicians should prioritize screening for germline mutations in patients and their family members to facilitate early diagnosis, treatment and prognosis assessment.

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Availability of data and materials

The sequencing data generated in the present study may be found in the National Centre of Biotechnology database under accession number PRJNA1146555 or at the following URL: https://dataview.ncbi.nlm.nih.gov/?archive=bioproject.

Authors' contributions

XFX conceived the study and revised the manuscript. HFJ interpreted the radiological findings. YXJ and MXH interpreted the pathological findings. HYW interpreted the genetic findings and wrote the manuscript. XFX and HYW confirm the authenticity of all the raw data All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Review Committee of Tongde Hospital of Zhejiang Province (approval no. 106-JY.2022; Hangzhou, China).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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