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ABOUT COVER

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CASE REPORT

Co-existing squamous cell carcinoma and chronic myelomonocytic leukemia with *ASXL1* and *EZH2* gene mutations: A case report

Lai-Jun Deng, Yang Dong, Mi-Mi Li, Chang-Gang Sun

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Abstract

BACKGROUND

Chronic myelomonocytic leukemia (CMML), a rare clonal hematopoietic stem cell disorder characterized by myelodysplastic syndrome and myeloproliferative neoplasms, has a generally poor prognosis, and easily progresses to acute myeloid leukemia. The simultaneous incidence of hematologic malignancies and solid tumors is extremely low, and CMML coinciding with lung malignancies is even rarer. Here, we report a case of CMML, with *ASXL1* and *EZH2* gene mutations, combined with non-small cell lung cancer (lung squamous cell carcinoma).

CASE SUMMARY

A 63-year-old male, suffering from toothache accompanied by coughing, sputum, and bloody sputum for three months, was given a blood test after experiencing continuous bleeding resulting from a tooth extraction at a local hospital. Based on morphological results, the patient was diagnosed with CMML and bronchoscopy was performed in situ to confirm the diagnosis of squamous cell carcinoma in the lower lobe of the lung. After receiving azacitidine, programmed cell death protein 1, and platinum-based chemotherapy drugs, the patient developed severe myelosuppression and eventually fatal leukocyte stasis and dyspnea.

CONCLUSION

During the treatment and observation of CMML and be vigilant of the growth of multiple primary malignant tumors.

Key Words: Squamous cell carcinoma; Chronic myelomonocytic leukemia; Myelo-

proliferative neoplasms; Myelodysplastic; *ASXL1* gene mutations; *EZH2* gene mutations; Case report

Core Tip: A 63-year-old male, with a long history of heavy smoking, was diagnosed with chronic myelomonocytic leukemia (CMML), with additional sex combs-like and enhancer of zeste homolog 2 gene mutations, as well as non-small cell lung cancer (squamous cell carcinoma). However, no such mutations were found in the lung cancer tissue. In CMML patients, pulmonary manifestations are non-specific, and the rare presence of malignant tumors in the lungs poses challenges in diagnosis. After receiving azacitidine, programmed cell death protein 1, and platinum-based chemotherapy drugs, the patient developed severe myelosuppression and eventually fatal leukocyte stasis and dyspnea. Therefore, during treatment and observation of CMML, medical practitioners should pay attention to the occurrence and evolution of solid tumors such as lung cancer, and be vigilant of the growth of multiple primary malignant tumors.

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INTRODUCTION

Chronic myelomonocytic leukemia (CMML), a rare clonal hematopoietic stem cell disorder characterized by myelodysplastic syndrome and myeloproliferative neoplasms, has generally poor prognosis and easily progresses to acute myeloid leukemia[1,2]. The simultaneous incidence of hematologic malignancies and solid tumors is extremely low[3], and CMML coinciding with lung malignancies is even rarer. Here, we report a case of CMML, with additional sex combs-like (*ASXL1*) and enhancer of zeste homolog 2 (*EZH2*) gene mutations, combined with non-small-cell lung cancer (lung squamous cell carcinoma).

CASE PRESENTATION

Chief complaints

A 63-year-old male, suffering from toothache accompanied by coughing, sputum, and bloody sputum for three months.

History of present illness

A 63-year-old male, suffering from toothache accompanied by coughing, sputum, and bloody sputum for three months, was given a blood test after experiencing continuous bleeding resulting from a tooth extraction at a local hospital. The results of the blood test included a white blood cell count of 111.34 × 10^9/L, monocyte count of 81.99 × 10^9/L, hemoglobin concentration 99 g/L, and platelet count of 150 × 10^9/L.

History of past illness

The patient was previously healthy.

Personal and family history

The patient in this case had a long history of heavy smoking, had no history of other major diseases nor any significant family history of disease.

Physical examination

The rest of physical examination was normal.

Laboratory examinations

The results of the blood test included a white blood cell count of 111.34 × 10^9/L, monocyte count of 81.99 × 10^9/L, hemoglobin concentration 99 g/L, and platelet count of 150 × 10^9/L. Flow cytometry showed that myeloid blasts and monocytes (with a predominantly mature phenotype) accounted for 1.31% and

52.6% of nucleated cells, respectively. Next-generation sequencing (NGS) showed *ASXL1* gene mutation [exon12:c.1934 dupG:p.Gly646fs; variant allele frequency (VAF) = 33.72%], and *EZH2* gene mutation (exon18:c.2084C>T:p.Ser695Leu; VAF = 49.73%; exonc.2077A>T:p.Asn693Tyr; VAF = 46.05%). No abnormal chromosomal results were observed.

Imaging examinations

A subsequent ultrasound revealed an enlarged spleen.

FINAL DIAGNOSIS

Bone marrow cell morphology examination of the patient showed: (1) An abnormal proliferation of monocytes, interspersed with occasional naïve monocytes; (2) that well-differentiated monocytes accounted for 45% of total monocytes; and (3) a positive alkaline phosphatase score of 80% with 270 points (Figure 1A). Additionally, erythroid hyperplasia was inhibited, three megakaryocytes were observed, and PLT was rare (Figure 1A). Based on these morphological results, the patient was diagnosed with CMML. Flow cytometry showed that myeloid blasts and monocytes (with a predominantly mature phenotype) accounted for 1.31% and 52.6% of nucleated cells, respectively, thus supporting the diagnosis of CMML. A bone marrow biopsy, utilizing hematoxylin-eosin/periodic-acid–Schiff staining, showed naïve-stage monocyte hypercellularity, with an increased granulocyte-to-nucleated red blood cell ratio (Figure 1B). As determined using reticulocyte staining (MF-0 grade), the granular lineage predominantly comprised intermediate (lower-stage) and visible monocytes (Figure 1B). NGS showed *ASXL1* gene mutation [exon12:c.1934 dupG:p.Gly646fs; variant allele frequency (VAF) = 33.72%], and *EZH2* gene mutation (exon18:c.2084C>T:p.Ser695Leu; VAF = 49.73%; exonc.2077A>T:p.Asn693Tyr; VAF = 46.05%). No abnormal chromosomal results were observed. The patient was finally diagnosed with CMML-0 with an MD Anderson Prognostic Score (MDAPS) of 3[4]. Lastly, the patient had a 50-year history of smoking approximately two to four packs of cigarettes per day, and a computed tomography scan revealed associated lung inflammation. As treatment, hydroxyurea was administered on an outpatient basis for the next three months. The patient came to our hospital to begin treatment with the demethylating drug, azacitidine (administered at a daily dosage of 100 mg on days 1–7). However, bloody sputum symptoms did not alleviate with the improvement of CMML, and enhanced computed tomography showed soft tissue density shadows in the dorsal segment of the right lower lobe of the lung, and inflammation in both lungs (Figure 2). A subsequent tuberculin test and T-cell test for tuberculosis infection both returned positive results. To rule out tuberculosis, the patient was transferred to the Chest Hospital, where bronchoscopy was performed in situ to confirm the diagnosis of squamous cell carcinoma in the lower lobe of the lung. Immunohistochemistry revealed the presence of TTF-1(-), NapsinA(-), CK5/6(+), P40(+), and CK7(-) (Figure 3). Subsequent NGS tests conducted on the lung biopsy tissue slices revealed negative epidermal growth factor receptor, anaplastic lymphoma kinase, ROS1, and KRAS genes. The final resulting diagnosis was lung squamous cell carcinoma (T2N2M0). To determine whether the *ASXL1* and *EZH2* genes were involved in lung tumorigenesis, lung cancer tissue sections were tested for their presence, with negative results.

TREATMENT

After two courses of azacitidine treatment, leukocytes remained at normal levels, and partial remission was achieved. However, in response to subsequent lung tumor progression, the patient was administered with programmed cell death protein 1 (200 mg, q21) combined with DP (100 mg of docetaxel on day 1 and 30 mg of cisplatin on days 1–3), GP (1.2 g of gemcitabine on day 1, 8, and 30 mg of cisplatin on days 1–3), TP (200 mg of nab-paclitaxel on day 1 and 300 mg of carboplatin on day 1), and other chemotherapy regimens. Despite small doses of chemotherapy, the patient repeatedly suffered from grade IV myelosuppression, and multiple changes in chemotherapy regimens were similarly ineffective.

OUTCOME AND FOLLOW-UP

Six months later, after rapid lung tumor progression, 17% blasts were detected in the peripheral blood, with a white blood cell count of 122 × 10^9/L, a monocyte count of 43.4 × 10^9/L, hemoglobin concentration of 95 g/L, and platelet count of 71 × 10^9/L. Nine months after diagnosis, the patient developed leukocyte stasis and dyspnea. His condition deteriorated thereafter, and he died.

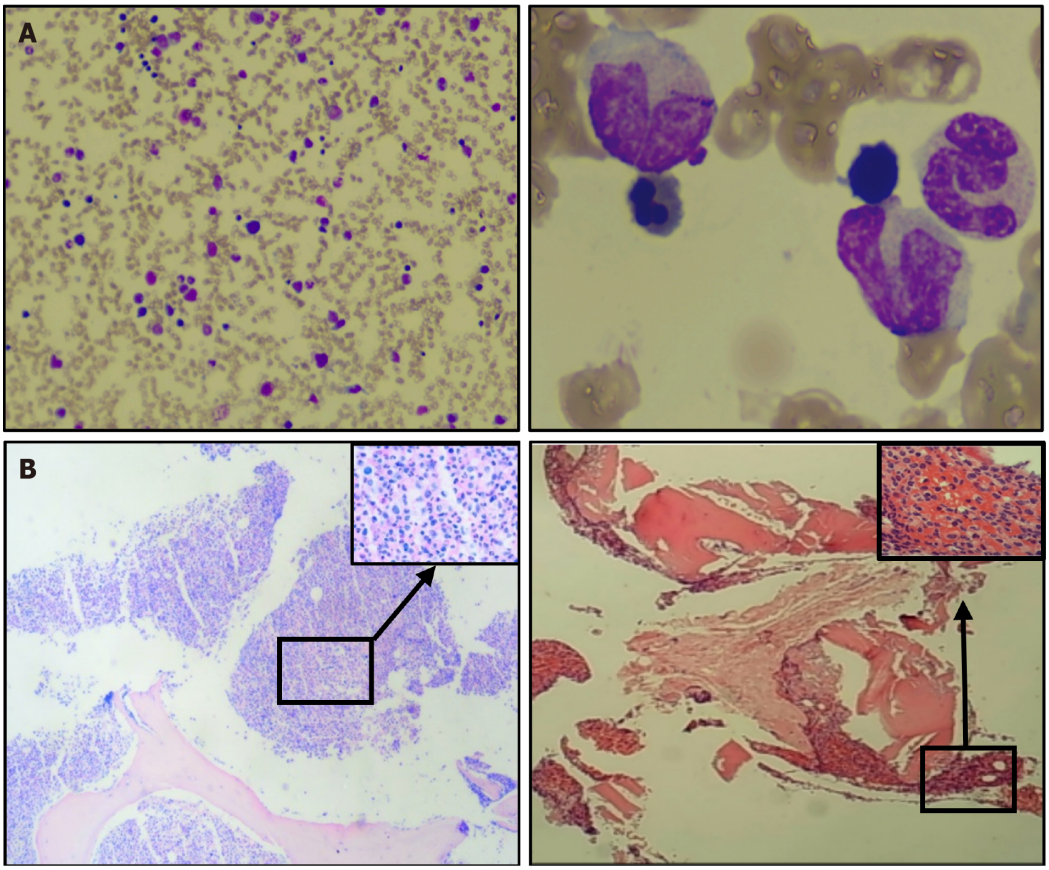

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Figure 1 Morphological and biopsy results of chronic myelomonocytic leukemia bone marrow analysis. A: Pelger deformed granules (100× magnification), exhibiting abnormal proliferation of monocytes and occasional naïve monocytes (with well-differentiated monocytes accounting for 45% of total monocytes), inhibited erythroid hyperplasia, three megakaryocytes, and rare platelet; B: Increased naïve-stage cells, with an increased granulocyte-to-nucleated red blood cell ratio. The granular lineage predominantly comprised intermediate (lower-stage) and visible monocytes, based on reticulocyte staining (MF-0 grade; ×4 and ×40 magnification).

DISCUSSION

The global incidence of CMML is extremely low, occurring in approximately 0.3 per 100000 people[4]. Based on the MDAPS and CMML Prognostic Scoring System results, the median survival period in CMML is 5–72 mo[5,6]. Approximately 20% of CMML patients have some form of systemic inflammatory or autoimmune disease affecting other organ systems[7-9]. However, the relationship between CMML and solid tumors is unclear[10,11]. To our knowledge, this is the first reported case of CMML alongside squamous cell carcinoma. As such, there is currently no standard treatment plan for the co-occurrence of these associated malignant tumors.

In this case, we evaluated the patient's lung condition and leukemic cell burden after lung cancer diagnosis. We gave priority to treatment with the demethylating drug azacitidine. Azacitidine is the preferred treatment for CMML, and there is increasing evidence that HMAs play an important role in the treatment of proliferative CMML[12]. Azacitidine and diazepam acetabine are the only lines of therapy approved by the US Food and Drug Administration for the treatment of CMML[13]. Unfortunately, the lung malignancy did not go into remission as CMML symptoms improved, but rather progressed. Mutation-targeting and immunologic agents are rapidly improving the treatment of advanced non-small cell lung cancer[14]; however, there is no standard treatment for lung squamous cell carcinoma, given the low rate of target mutations and its poor response to chemotherapy.

In patients with CMML, the precursors to normal blood cells in the bone marrow are either damaged or suppressed, and tolerance to myelotoxic drugs is reduced. This may be the main reason for the severe myelosuppression observed here. There is currently no evidence of azacitidine leading to the progression of lung malignancies. However, since the 1970s, studies have reported a risk of myelodysplastic syndrome and acute myeloid leukemia transformation linked to platinum drugs commonly used to treat solid tumors, such as cisplatin and carboplatin, with carboplatin posing a smaller carcinogenic risk than cisplatin[15-17]. Chronic myelomonocytic leukemia is at risk of transforming into acute myeloid leukemia. After three courses of platinum-based drug therapy, more blasts had appeared in the peripheral blood of the patient, suggesting that the rapid progression of the disease may be related to

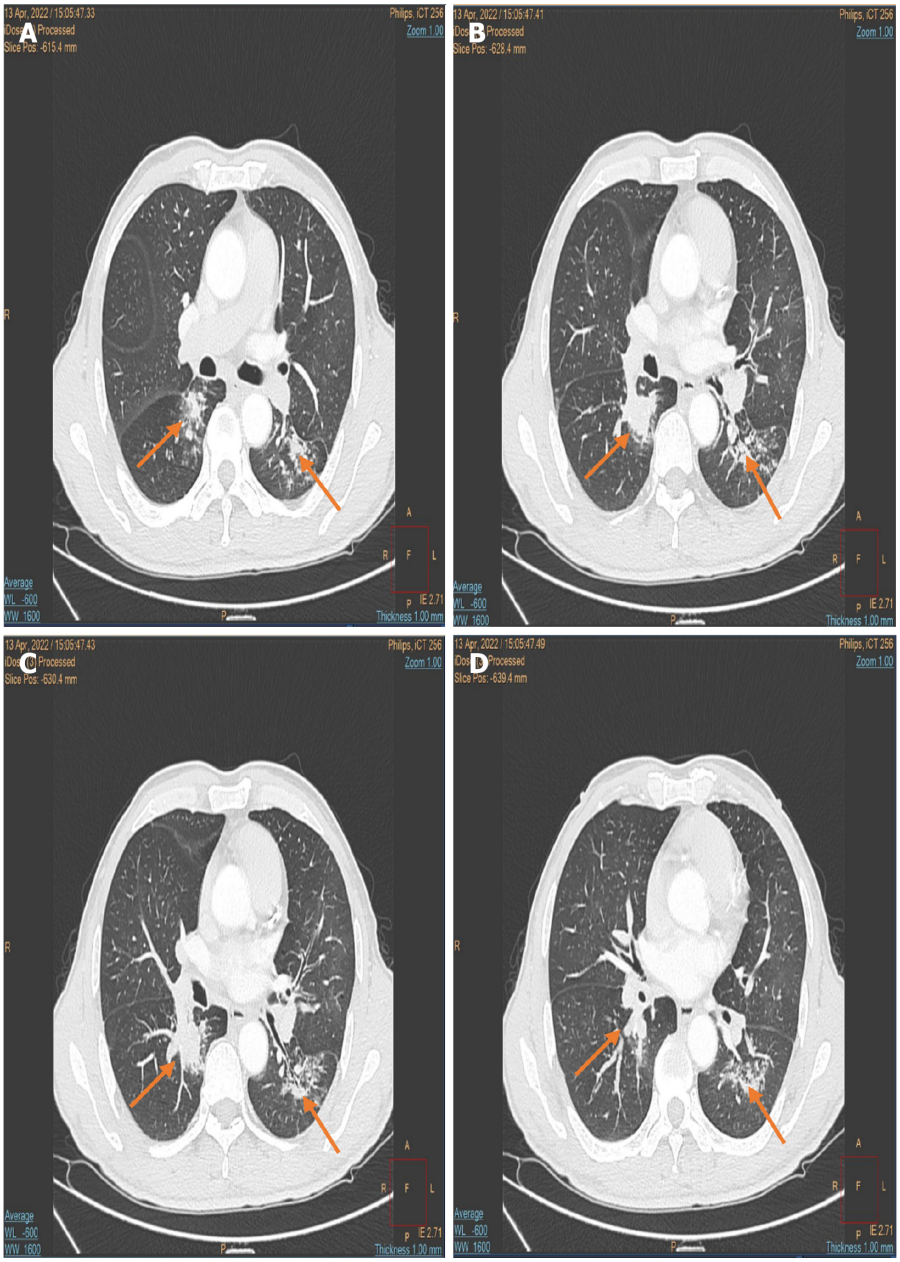

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Figure 2 Enhanced computed tomography results for non-small cell lung cancer. A: Squamous cell carcinoma, showing soft tissue density in the dorsal segment of the right lower lobe of the lung and inflammatory lesions in both lungs; B: Next slice chest enhanced computed tomography (CT) image; C: Next slice chest enhanced CT image; D: Next slice chest enhanced CT image.

the use of platinum-based drugs and the presence of *ASXL1* gene mutation may accelerate this progression. Currently, no biomarkers are available to predict treatment responses to demethylating agents in CMML. Nonetheless, the presence of the *ASXL1* gene mutation in patients with CMML may reduce the benefits of demethylating-agent treatment. While another deduction is the complex mechanisms involved in multiple primary tumors, including genetic factors, gene abnormalities, or low immunity. These factors may result in accelerated evolution of malignant clone cells from earlier naïve cell clones. The pathogenesis of multiple primary malignant tumors is complex, the early "field cancerization" theory[18] revealed the occurrence of multiple primary malignant tumors in specific areas (such as in the respiratory tract). The patient reported here has a long history of heavy smoking, and studies have shown a direct relationship between smoking and the occurrence of cancers[19]. Alternatively, multiple primary malignant tumors may arise *via* extensive migration of cancerous cells, in which tumor progenitor cells carrying mutant genes migrate to new sites and continue to divide and grow[20].

With the development of molecular biology, the pathogenic mechanisms of multiple primary cancers have been revealed at the genetic level; these include *BRCA1* and *BRCA2* gene mutations, *ALDH2* gene inactivation, microsatellite instability, DNA replication errors, and aneuploidy of chromosome 17[21,22].

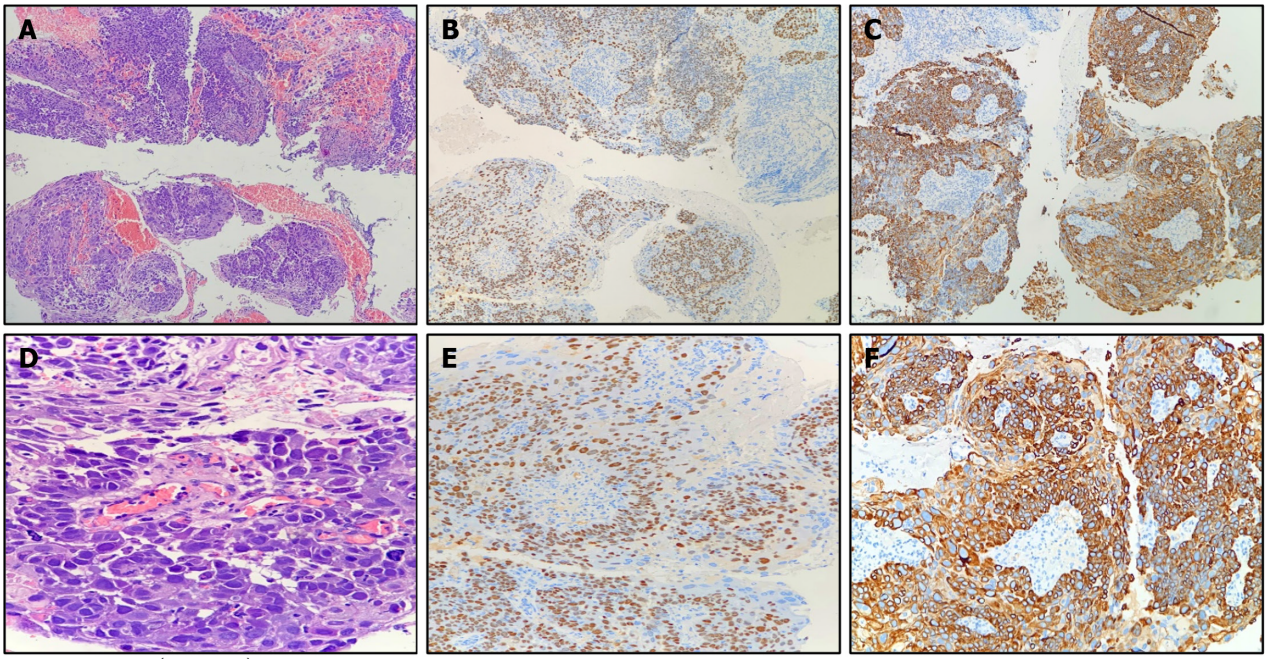

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Figure 3 Immunohistochemistry results and pathological manifestations of non-small cell lung cancer squamous cell carcinoma. A: HE staining was used to observe the pathological manifestation (×100 magnification); B: Nuclear positive (P40, ×100 magnification); C: Cytoplasmic positive (CK5/6, ×100 magnification); D: Tumor cells with large and deeply stained nuclei, significant nucleoplasmic heterogeneity, keratinization in some areas, rich blood vessels, tumor cells growing around blood vessels, and polarity disappearing in some areas, showing solid nests (HE, ×400 magnification); E: Nuclear positive (P40, ×200 magnification); F: Cytoplasmic positive (CK5/6, ×200 magnification).

With a positivity rate of 40%, *ASXL1* gene mutation is thought to be an independent adverse prognostic factor affecting survival in CMML. In contrast, with a positivity rate of 5%, almost always occurring simultaneously with *ASXL1* mutations, *EZH2* gene mutations have no clear clinical impact on CMML. Both of these genes affect epigenetic regulation and histone modification[23,24]. Patients with two co-occurring mutations exhibited shorter survival periods and worse prognosis than those with a single mutation or without co-occurring mutations[25,26].

In this case, using NGS, we detected no mutations in *ASXL1* or *EZH2* in the patient's lung squamous cell carcinoma tissue. Pulmonary manifestations in CMML patients are non-specific, and careful evaluation of leukemic involvement in the lungs is required to differentiate between infection, bleeding, leukemic infiltration, and the rare occurrence of pulmonary manifestations, presenting challenges in diagnosis. Computed tomography scan results are usually inconclusive, and bronchoscopy and bronchoalveolar lavage are typically recommended to exclude leukemic infiltration, bleeding, and infection. Lung biopsy[27] may be required for accurate diagnosis. The presence of this rare population should be given due consideration in clinical practice.

CONCLUSION

Although the simultaneous occurrence of CMML and lung malignancy is rare, two cases have so far been reported. Koopman *et al*[28] reported the case of a male patient with CMML exhibiting an *IDH2* mutation; the patient was diagnosed with non-small cell lung cancer (adenocarcinoma) during the observation period. Adenocarcinoma and the same mutation were observed in a lung cancer biopsy, suggesting its origin in CMML. Kim *et al*[29] reported that a male patient with non-small cell lung cancer developed CMML within two years after receiving platinum-based chemotherapy; furthermore, their cytogenetic study revealed trisomy 8. Although our case also concerned an elderly male patient, it involved simultaneous CMML and lung cancer, with no evidence of CMML infiltrating the lung cancer tissue. Therefore, we emphasize the importance of: (1) Paying attention to the occurrence and evolution of solid tumors, such as lung cancer, when treating and monitoring CMML treatment; and (2) being vigilant of the presence of multiple primary malignancies.

FOOTNOTES

Author contributions: Deng LJ designed the research study; Deng LJ and Dong Y performed the research and wrote the manuscript; Li MM and Sun CG analyzed the data; all authors have read and approve the final manuscript.

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