# Efficacy of venetoclax and rituximab in the treatment of concurrent acute myeloid leukemia and untreated chronic lymphocytic leukemia: A case report and literature review

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**Abstract.** To date, few cases of concurrent acute myeloid leukemia (AML) and untreated chronic lymphocytic leukemia (CLL) have been reported. Due to the complexity of the pathogenesis and the absence of a uniform treatment regimen, the associated prognosis remains poor. The present study reports the case of a 58-year-old male with asymptomatic leukocytosis, who was previously healthy with no malignancies. Flow cytometry analysis revealed protocytosis, monocytosis and monoclonal B lymphocytosis in a bone marrow specimen. Results of a gene rearrangement assay demonstrated positive immunoglobulin heavy-chain variable region gene status in monoclonal B lymphocytes. Thus, the patient was diagnosed with AML with maturation (AML-M2) that co-existed with untreated CLL. The normative daunorubicin (40 mg/m$^2$ on days 1-3) and cytarabine (80 mg/m$^2$ on days 1-7) regimen combined with venetoclax (400 mg on days 1-7) and rituximab (375 mg/m$^2$ on day 0) was used as induction chemotherapy. The patient achieved morphological complete remission in both AML and CLL following the first course of chemotherapy. In addition, the present study retrospectively analyzed the data of 22 patients with concurrent AML and untreated CLL, and the results demonstrated that the median age at the time of AML diagnosis was 69 years (range, 52-86 years). Moreover, the male:female ratio was 6.33:1 and AML-M2 was the most frequent subtype at diagnosis. The presence of a complex karyotype was associated with the poorest prognosis, and patients who received venetoclax often exhibited an improved prognosis. In conclusion, the combination of venetoclax and rituximab improves the prognosis of patients with concurrent AML and untreated CLL.

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## Introduction

Chronic lymphocytic leukemia (CLL) is an indolent hematological malignancy characterized by the clonal proliferation of mature B lymphocytes (1). CLL is more prevalent in elderly patients, with a median patient age of 72 years at diagnosis (2). Results of a previous study demonstrated that CLL was associated with the development of secondary tumors, such as lung and skin cancer (3). In addition, CLL was associated with the development of hematological malignancies, such as myelodysplastic syndrome and acute myeloid leukemia (AML) (4). Notably, the number of patients diagnosed with concomitant AML and untreated CLL has increased in the last two decades due to advances in flow cytometry (FCM) analysis, as FCM can reduce the rate of misdiagnosis of this disease through immunophenotyping techniques. The prognosis of patients with concomitant AML and untreated CLL remains poor, due to limited treatment options. For example, as they are often older and more susceptible to infection, the majority of patients are not eligible for intensive chemotherapy and hematopoietic stem cell transplantation (5).

Bcl-2, an inhibitor of apoptosis, effectively suppresses apoptosis in diverse cellular systems (6). Results of numerous studies reported that members of the Bcl-2 family were abnormally expressed in various tumors, such as leukemia, lymphoma and breast cancer, and were associated with

pathogenesis and chemotherapeutic resistance (7,8). Venetoclax, which selectively binds to Bcl-2 to inhibit expression, thus inducing healthy apoptotic responses and protecting against cancer cell development, was the first Bcl-2 inhibitor to be discovered (5). Venetoclax was approved by the United States Food and Drug Administration for the treatment of CLL in 2016, and was approved for the treatment of AML that is ineligible for intensive chemotherapy in 2018. Venetoclax is considered an advance in traditional medicine methods for malignant hematology.

The pathogenesis, characteristics, treatment and prognosis of concomitant AML and untreated CLL remain poorly understood, due to a low incidence rate compared with CLL (4.9 per 100,000 individuals per year) and AML (4.34 per 100,000 individuals per year (1,9). The present study reports the case of a 58-year-old male diagnosed with concurrent AML and untreated CLL. In addition, the data of 21 patients diagnosed with AML and untreated CLL reported between January 2000 and December 2023 were retrospectively analyzed, and the clinical characteristics of these patients were summarized.

## Case report

A 58-year-old man was referred to Tianjin Union Medical Center of Nankai University (Tianjin, China) with asymptomatic leukocytosis, found via a routine blood test, in October 2022. The routine blood examination revealed a white blood cell (WBC) count of $11.71x10^9$/l (normal range, 3.5-$9.5x10^9$), with 48.51% lymphocytes (normal range, 20-50%), 6.32% monocytes (normal range, 3-10%) and 44.97% neutrophils (normal range, 40-75%). In addition, the routine blood examination revealed levels of hemoglobin at 104 g/l (normal range, 115-150 g/l) and a platelet count of $98x10^9$/l (normal range, 125-$350x10^9$). At 1 month prior to referral, the patient was diagnosed with acute cerebral infarction due to blurred vision in both eyes. The patient was previously healthy with no malignancies and no history of associated treatments. The patient did not present with a fever, night sweats or weight loss, and had no history of exposure to toxins or radiation. A physical examination revealed neither lymphadenopathy nor hepatosplenomegaly. The patient refused a bone marrow aspiration for personal reasons. A peripheral blood smear revealed small lymphocytes, and no blasts or abnormal monocytes. Results of the FCM analysis using a Navios 10 color flow cytometer with Kaluza analysis software (Beckman Coulter, Inc.) revealed a small B-cell population (41.43% of total cellularity), with positive CD5, CD19, CD20 and CD23 expression, negative CD10 expression and λ-light chain restriction in the peripheral blood. Thus, a diagnosis of CLL (Binet C and Rai IV) was made (1). As the patient was recovering from acute cerebral infarction, rituximab (375 mg/$m^2$ on day 0) plus cyclophosphamide (200 mg on day 1) and prednisone (60 mg/$m^2$ on days 1-3) chemotherapy was administered. In November 2022, the WBC count of the patient increased to $65.66x10^9$/l, with 13.27% lymphocytes, 73.00% monocytes and 13.23% neutrophils. Results of the peripheral blood smear revealed protocytosis, monocytosis and small lymphocytes (Fig. 1). The patient subsequently consented to a bone marrow aspiration. FCM analysis revealed a primitive myeloid cell population (expressing CD117, CD34, CD33, CD13, human leukocyte antigen-DR and CD7) accounting for 46.60% of total cellularity, an abnormal monocyte population (expressing CD4, CD11b, CD14, CD33, CD36 and CD64) accounting for 7.24% of total cellularity and a monoclonal B lymphocyte population (expressing CD5, CD19, CD22, CD23, CD200 and λ-light chain) accounting for 13.12% of total cellularity (Fig. 2). Cytogenetic analysis revealed a normal karyotype, and the hot spot fusion gene of leukemia was negative. Results of the gene rearrangement assay demonstrated positive immunoglobulin heavy-chain variable region gene expression in monoclonal B lymphocytes (IGH Somatic Hypermutation Detection Kit; Invivoscribe, Inc.). Based on these findings, disease progression was observed in the patient, and a diagnosis of AML-M2 with co-existing untreated CLL was determined. The corresponding treatment regimen consisted of 40 mg/$m^2$ daunorubicin on days 1 to 3 and 80 mg/$m^2$ cytarabine on days 1 to 7 (DA regimen), combined with a standard dose of 375 mg/$m^2$ rituximab on day 0 and 400 mg venetoclax on days 1 to 7 (VR regimen) every 28 days. This regimen was used as induction chemotherapy at 1 month after initial admission to the hospital. The patient achieved a morphological complete remission (CR) in both AML and CLL after the first course of chemotherapy. Notably, the patient refused further chemotherapy and died due to hemoptysis 1 month after the AML diagnosis.

## Discussion

On admission to the hospital, the patient presented with leukocytosis as the first symptom. As the patient refused a bone marrow aspiration at the first presentation, and results of the peripheral blood smear and FCM analysis revealed no blasts, it was not possible to accurately determine the pre-treatment disease status. However, a previous study revealed that secondary tumors associated with treated CLL often occurred 1-3 years after chemotherapy, and the development of AML associated with therapy often occurred after 5-7 years, with an incidence of ~1% (10). In the present case, the duration between the appearance of blasts and initial treatment was 1 month; thus, the development of secondary AML was considered unlikely. However, the distribution of myeloblasts in the bone marrow and peripheral blood were typical of AML (11); thus, the patient was diagnosed with concurrent untreated CLL and AML-M2.

The PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was screened for associated literature between January 2000 and December 2023, and the terms 'acute myeloid leukemia' and 'chronic lymphocytic leukemia' were used during the retrieval process. Patients with a history of CLL treatment were excluded. The data of 21 patients with concurrent untreated CLL and AML were extracted on July 2023. AML and CLL were defined based on the latest World Health Organization classification (12,13), and patients who had any history of exposure to chemotherapy or radiation were excluded. The clinical information of all patients is displayed in Table I (14-33). Results from the studies demonstrated a higher incidence of concurrent untreated CLL and AML in older individuals, with a median patient age at diagnosis of AML of 69 years (range, 52-86 years). Moreover, the male:female ratio was 6.33/1 and AML-M2 was the most

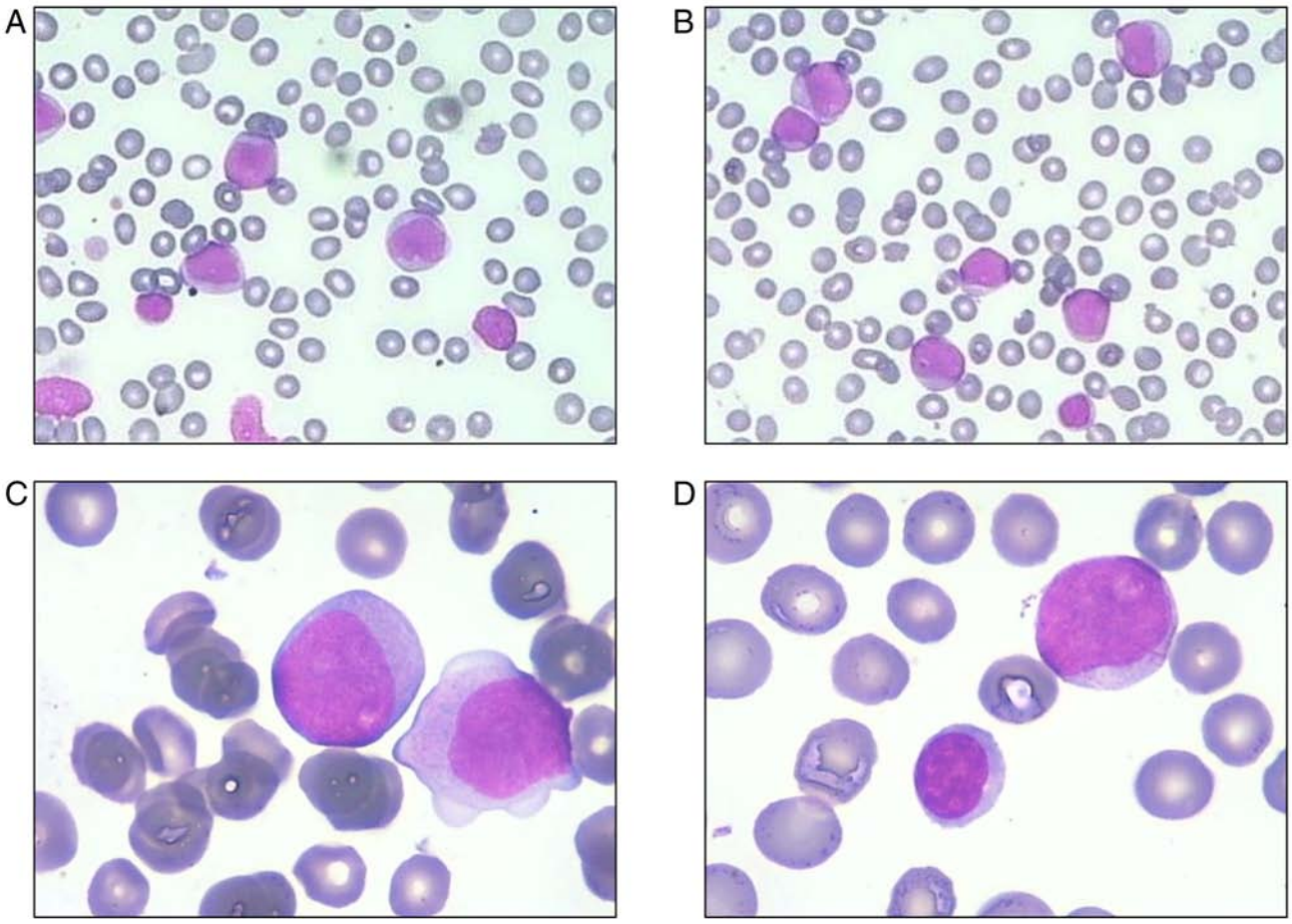


Figure 1. (A-D) Photomicrographs of peripheral blood smears. (A and B) Coexistence of blasts, promonocytes and small lymphocytes (Giemsa stain; x400 magnification). (C and D) Coexistence of blasts, promonocytes and small lymphocytes (Giemsa stain; x1,000 magnification).

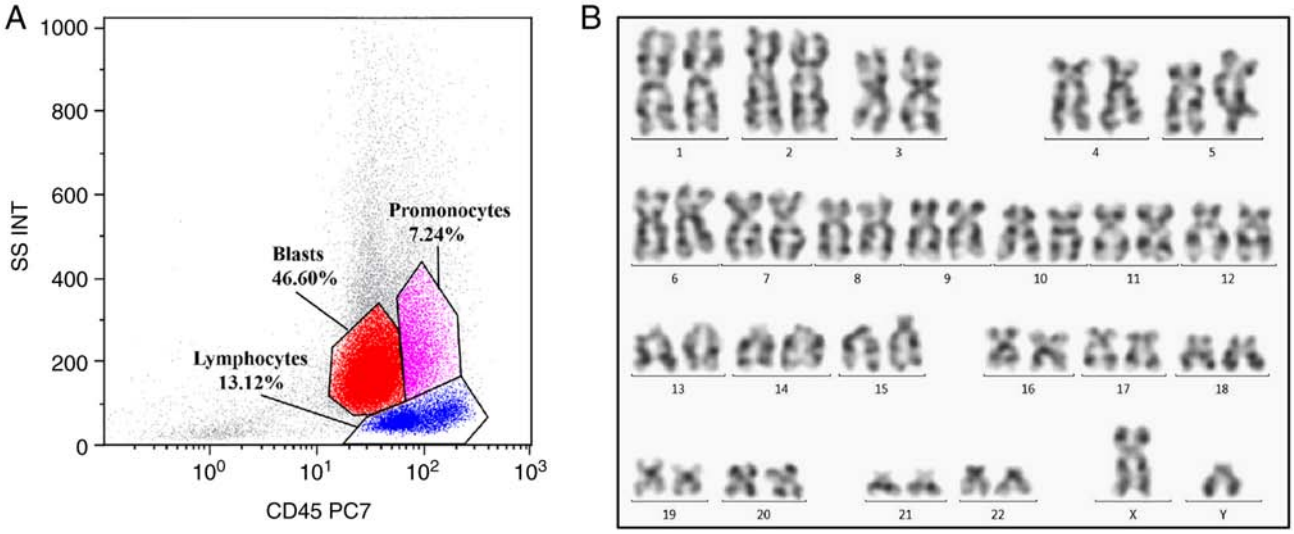


Figure 2. (A) Immunophenotyping of the bone marrow specimen. The red area indicate blasts, which accounted for 46.60% of total cellularity. The blue area indicates monoclonal small B lymphocytes, which accounted for 13.12% of total cellularity. The pink color indicates promonocytes, which accounted for 7.24% of total cellularity. (B) Normal karyotype: 46,XY. SS INT, side scatter intensity.

frequent subtype. Complex karyotype was observed in 4 cases, and this was associated with the poorest prognosis. In addition to the patient described in the present study, 2 patients were treated with venetoclax, and they exhibited an improved prognosis. The CR rate of patients with AML was 27.27%, and the median overall survival time was only 3 months after the AML diagnosis. Moreover, patients who achieved CR tend to survive longer than those who did not.

Table I. Characteristics of previously reported patients with concomitant acute myeloid leukemia and untreated chronic lymphocytic leukemia.

| First author, year | Age, years | Sex | FAB subtype | BM immunophenotype | | Cytogenetics | Treatment | CR | Survival time, months | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Blasts, % | Lymphocytes, % | | | | | |
| Xie *et al*, 2000 | 64 | M | M5 | 78.00 | 0.75 | -7 | Cytarabine | | | (14) |
| Ornellas De Souza *et al*, 2001 | 70 | F | M2 | 27.00 | 49.00 | 47,XX,+12[10]/ 46,XX,del(5)(q31), t(8;13)(q22; q21)[4]/46,XX[6] | Hydroxyurea | No | <1 | (17) |
| Miller *et al*, 2001 | 55 | M | M4 | | | | | | | (15) |
| Muta *et al*, 2002 | 84 | M | M2 | 21.30 | 56.60 | 56,XY,+1,+6,+ 8,add(10)(q26), +11,+11,+13,+14,+15,+21,+21 [19/20]/46,XY[1/20] | No chemotherapy | No | 3 | (16) |
| Lu *et al*, 2006 | 59 | M | M4 | | | inv(16)/+22 | DA | Yes | >12 | (18) |
| Gottardi *et al*, 2006 | 69 | M | M2 | | | 46,XY | Hydroxyurea | No | 9 | (19) |
| Katz *et al*, 2010 | 76 | F | M5 | | | | Hydroxyurea | No | <1 | (22) |
| Zhang *et al*, 2011 | 80 | M | M0 | | | 46,XY,t(2;5;11) (q31,3;q21,2;p15), t(5,11)(q21.1;q14.2),t(5,11) (q35.2;p15) | | | | (23) |
| DeFilipp *et al*, 2012 | 55 | M | M2 | 46.50 | 26.60 | -7q | 7+3+3, HiDAC, allo-HSCT | Yes | >12 | (24) |
| Su *et al*, 2017 | 52 | M | M3 | | | t(15;17)(q22;q12) | ATRA hydroxyurea | No | <1 | (33) |
| Kajtar *et al*, 2015 | 74 | M | M1 | 28.00 | 40.00 | 46,XY | No chemotherapy | No | 9 | (25) |
| Milosevic, 2016 | 76 | M | | 30.00 | 65.00 | 46,XY | | No | 2 | (26) |
| Al Mussaed *et al*, 2016 | 77 | M | M5 | 60.00 | 30.00 | 46,XY | Hydroxyurea | No | <1 | (28) |
| Ito *et al*, 2017 | 65 | M | | 30.00 | 17.00 | 46,XY | DA | No | 6 | (29) |
| Lee *et al*, 2017 | 76 | M | | 21.60 | 16.60 | 46,XY,del(13)(q14),add(14)(q32) [3]/46,XY[17] | Decitabine | No | | (30) |
| Boddu *et al*, 2019 | 71 | M | M3 | 18.00 | 0.07 | 46,XY,t(15;17)(q24;q21)[5]/ 46,XY[15] | ATRA + ATO | Yes | >12 | (32) |
| Shoyele and Gupta, 2018 | 65 | M | M4 | 34.00 | 3.20 | inv(16)(p13.1q 22) | DA | No | <1 | (21) |
| Licci, 2020 | 86 | M | | | | | | No | <1 | (27) |

Table I. Continued.

| First author, year | Age, years | Sex | FAB subtype | BM immunophenotype | | Cytogenetics | Treatment | CR | Survival time, months | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Blasts, % | Lymphocytes, % | | | | | |
| Chen *et al*, 2021 | 66 | M | M2a | 46.57 | 14.70 | 45,XY,-7[10]/46,XY[5] | Cytarabine + azacitidine, venclexta + azacitidine | Yes | >12 | (20) |
| | 62 | F | M1 | 29.78 | 50.42 | | HA, cytarabine + VP16, HA + VP16 | Yes | >12 | |
| Kiso *et al*, 2021 | 69 | M | | 21.40 | 34.80 | 46,XY,add(1)(p36.1),del1(1)(p?), -5,-7,-8,-10,-12,-13,-14,-16,add (19)(p13),-21,+8mar [4]/46, XY[16] | BR, venetoclax | No | 3 | (31) |
| Present study | 58 | M | M2 | 46.6 | 13.12 | 46,XY | DA, venetoclax, rituximab | Yes | 1 | |

FAB, French-American-British classification system; M, male; F, female; BM, bone marrow; CR, complete remission; DA, daunorubicin + cytarabine; 7+3+3, cytarabine + doxorubicin + etoposide regimen; HiDAC, high-dose cytarabine; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; HA, harringtonine + cytarabine; VP-16, etoposide; BR, bendamustine + rituximab.

The results of the present study demonstrate that the prognosis of patients with concurrent untreated CLL and AML remain poor due to a limited response to chemotherapy. However, a combination regimen of venetoclax and rituximab may improve outcomes in this subset of patients. Results of previous studies demonstrated that the limited response to chemotherapy in these patients may be due to poor humoral and cell-mediated immunity, including hypogammaglobulinemia and abnormal T-cell subsets, resulting in both impaired antitumor responses and increased susceptibility to infection (29,34). In addition, aberrant TP53 expression also played a key role in the poor prognosis of patients with untreated CLL and AML (35).

The mechanisms underlying concurrent untreated CLL and AML remain to be fully elucidated. The majority of studies supported the interpretation that the emergence of myeloblasts was not associated with that of monoclonal B lymphocytes. In some cases, the presence of different cytogenetic and biomolecular alterations has been reported (17). Lu *et al* (18) reported a case of concurrent AML with inversion (16) and CLL, and revealed that the CLL cells did not possess the same chromosome aberrations as myeloblasts, indicating that the myeloblasts and monoclonal B lymphocytes originated from disparate clones. Shoyele and Gupta (21) revealed that the myeloblast nuclei exhibited MYH11/CBFB fusion without trisomy 12 (in ~33% of patients with CLL); thus, supporting the hypothesis that AML and CLL were clonally independent. Results of an immunoglobulin H gene rearrangement assay demonstrated that AML and CLL had different origins (19). Moreover, Graf (36) confirmed that progenitor cells with plasticity undergo neoplastic transformation in the process of hematopoietic differentiation, and may develop into two independent lineages; namely, myeloid and lymphoid. Thus, patients may exhibit characteristics associated with leukemia, as well as certain tumor susceptibility factors affecting two or more hematopoietic stem cells, highlighting that CLL and AML may originate from different cell lines. In the present case, the patient refused a bone marrow aspiration at the onset of disease, and next-generation sequencing and single-cell sequencing were not performed. Thus, the origin of the disease was not determined. The coexistence of CLL and AML is inferred from previous domestic and international reports, and the patient's disease progression. We consider that these are two different groups of cells with different origins and different driving genes. Further investigations into the pathogenesis of concurrent untreated CLL and AML are required.

Due to the nature of the disease, timely treatment is required. In previous cases, the treatment of concurrent untreated CLL and AML was based on the treatment of AML; however, the response was not optimal. As patients with concurrent untreated CLL and AML are often older and more susceptible to infection, the development of an effective combination therapy regimen is required. Following advances in medicine, the treatment of hematological diseases tends to include targeted treatment regimens using small molecule inhibitors and antibodies. Since its approval, venetoclax has demonstrated efficacy in the treatment of both AML and CLL (37-39). Results of a previous study demonstrated that the progression-free survival time of patients treated with a combination of venetoclax and rituximab was significantly longer than that of patients treated with a combination of bendamustine and rituximab. In addition, patients treated with a combination of venetoclax and rituximab demonstrated a higher minimal residual disease negativity rate, compared with those treated with a combination of bendamustine and rituximab (40). At present, numerous combination therapies that include venetoclax are considered for the treatment of CLL. Thus, the patient described in the present study was treated with a standard DA + VR regimen and achieved morphological CR after one course of chemotherapy. This response highlights that this combination therapy may be effective in patients diagnosed with concurrent AML and untreated CLL. However, future clinical trials are required to validate the findings of the present study.

In conclusion, together with the present study, the results of previous studies demonstrated that venetoclax is effective in the treatment of numerous types of leukemia. Thus, the comprehensive use of targeted drugs with different mechanisms may improve the prognosis of patients with relapse and refractory hematological malignancies, and improve the life quality of patients.

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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**

XLZ, XFW and YFC made substantial contributions to the conception and design of the manuscript. XLZ provided suggestions for patient treatment and gave final approval of the version to be published. YFC and LYY drafted the manuscript and revised it critically for important content. YFC, LYY, XXL, XW and QQZ retrieved data from the literature, and analyzed the data. QQZ managed the patient, provided suggestions for patient treatment, and collected and analyzed patient data. XLZ, XFW and YFC confirm the authenticity of all the raw data. 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 publication of the article was obtained from the patient on diagnosis.

## Competing interests

The authors declare that they have no competing interests.

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