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Case Report

Treatment of Acute Promyelocytic Leukemia in a 94-Year-Old Male Patient: A Case Report

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SUMMARY

Acute promyelocytic leukemia (APL), more common in young and middle-aged people, is a unique subtype of acute myeloid leukemia. Recently, the experience in the treatment of elderly APL is limited. This report described the first case of APL in a patient older than 90 years in China. With the stealthy onset and no typical symptoms, the diagnosis was made timely based on close detection of laboratory examination. After a comprehensive evaluation of the patient's condition, the patient received half-dose arsenic trioxide (ATO) alone. The patient tolerated this dose well and achieved molecular complete remission. This report also provides clinical experience for the treatment of elderly APL.

1. Introduction

Acute promyelocytic leukemia (APL), a special subtype of acute myeloid leukemia (AML), favorably responds to differentiating agents and achieves complete remission (CR) rates of up to 90%.[1,2] However, because APL is relatively rare in elderly patients, studies focused on elderly APL patients are limited, and there is a lack of information regarding therapeutic strategies and outcomes for this group. Compared with younger patients, the prognosis of APL in the elderly has been poor after treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) alone or combined with chemotherapy.[3–5]

APL patients over the age of 80 usually have comorbidities and are intolerant to treatment; therefore, the treatment of elderly APL patients is challenging. Consequently, some patients do not receive effective treatment, only supportive care.

In this study, we report the case of a 94-year-old male patient with APL who was treated with half-dose ATO alone, achieving molecular CR.

2. Case report

A 94-year-old man was hospitalized for intermittent low fever with cough. His medical history included prostate cancer, which had been treated with LHRH analogs (Zoladex) for 2 years. His prostate-specific antigen level was below 4 ng/ml after one year of Zoladex withdrawal. He also had hypertension, type 2 diabetes, chronic kidney disease, severe osteoporosis, and an L2 compression fracture. Physical examination showed the following results: body temperature, 37.8 °C; pulse, 80 bpm; blood pressure, 153/56 mmHg, presence of pulmonary moist rales, and mild edema of lower extremity.

The patient's white blood cell (WBC) count was 3.88×10^9/L. The neutrophil (N) was 2.17×10^9/L, lymphocyte was 1.41×10^9/L, hemoglobin (HGB) was 116 g/L, and platelets were 115×10^9/L. Chest X-ray showed bilateral pulmonary exudation foci. He was diagnosed with pneumonia and treated with ceftazidime. The symptoms were relieved, but routine blood re-examination showed the following: WBC, 2.82×10^9/L; N, 0.91×10^9/L; HGB, 113 g/L; platelets, 99×10^9/L; coagulation function, 14.2 s (PT), 34.3 s (APTT); fibrinogen, 2.11 g/L; D-dimer level, 10.38 mg/L; and fibrinogen split product, 44.04 ug/ml. Arterial blood gas (ABG) analysis showed that PO_2 had decreased from 64 mm/Hg to 58 mm/Hg. Deep venous ultrasound showed no venous thrombosis. Echocardiography showed normal pulmonary artery pressure.

Low molecular weight heparin (0.3 ml; nadroparin calcium: 3075 IU) was administered once a day for 4 weeks (QD) to avoid potential venous thromboembolism. However, during anticoagulation therapy, the patient's D-dimer level continued to rise (up to 17.36 mg/L). WBC decreased to 1.71×10^9/L, neutrophils decreased to 0.76×10^9/L, HGB decreased to 97 g/L, and platelets decreased to 81×10^9/L within 40 days.

As the routine blood tests showed a simultaneous reduction of the ternary systems, we considered the adverse effects of ceftazidime. However, the adverse effects could not explain the fast reduction rate of the ternary systems and the gradually increased hypercoagulation state in the blood. Therefore, we considered the possibility of hematological disease. Accordingly, we conducted blood smears; the results suggested abnormal multigranular promyelocytes (Figure 1a). Next, we performed bone marrow aspiration. Promyelocytic leukemia cells were found with a proportion of 51.0% (Figure 1b). Immunophenotypic analysis revealed positivity for CD117, CD13, CD33, CD56, and CD38 antigens and negativity for CD34 and HLA-DR. Cytogenetic analysis revealed a karyotype with

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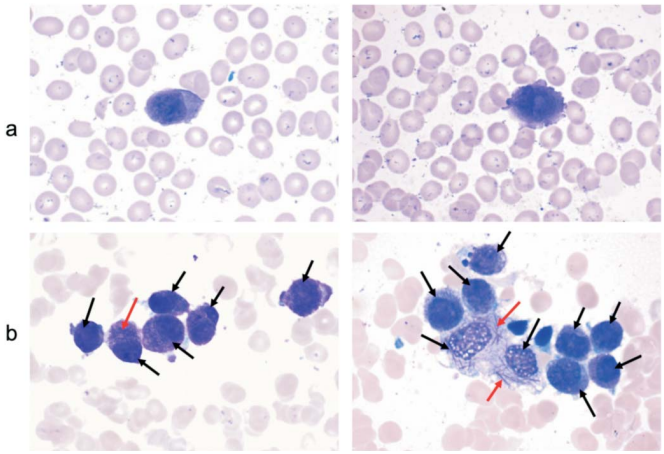

Figure 1. (a) Peripheral blood smears, the blue cells are abnormal promyelocyte. (b) Bone marrow smears, black arrows indicate abnormal multigranular promyelocyte, red arrows indicate Auer's corpuscle.

the t (15; 17) marker and positivity for PML/RARα with 13.09% copies. Therefore, we diagnosed APL.

Induction therapy with ATO alone (5 mg/day) was administered after conducting a comprehensive assessment and full communication with the patient. One week after treatment, D-dimer levels decreased to 2.99 mg/L without any anticoagulation therapy. However, the patient developed a low-grade fever and gained 2 kg of weight. His WBC increased to 4.65×10^9/L, accompanied by a marked increase in LDH (172 U/L to 378 U/L). ABG showed a decrease in PO_2 (58 mmHg to 52 mmHg). These results suggested mild differentiation syndrome. Therefore, hydroxyurea (500 mg QOD) was administered. Nine days later, the WBC stabilized at 7.0×10^9/L, LDH decreased to 250 U/L, and PO_2 increased to 56 mmHg; therefore, we stopped hydroxyurea administration.

After 33 days of induction therapy, we performed peripheral blood smears, which revealed no abnormal promyelocytes, and bone marrow smears. After APL treatment (Figure 2a), genetic analysis showed positivity for PML/RARα with 5.45% copies. No abnormal phenotypic cells were found after immunophenotypic analysis, and ATO was stopped on the 34th day. Three weeks later, consolidation therapy was started (Figure 2b), which comprised ATRA (20 mg BID for 2 weeks), then intermittently for 2 weeks, as a course of treatment, for a total of seven courses; and ATO (5 mg QD for 4 weeks), then intermittently for 4 weeks, as a course of treatment, for a total of four courses. The patient completed five cycles of ATRA and one cycle of ATO, as planned. The second cycle of ATO was discontinued at the 4th week because of elevated creatinine levels (101 umol/L to 156 umol/L).

After treatment, we re-examined the bone marrow smears, the APL remained in CR and PML/RARα gene was not detected. The creatinine level decreased to 113.4 umol/L after 5 days of ATO withdrawal; therefore, the elevated creatinine was considered an adverse effect of ATO. Thereafter, the patient refused to complete the remaining therapy because he feared adverse effects.

One and a half years have passed since the treatment, and the patient is alive and in good health. On his latest re-examination, his WBC count was 6.74×10^9/L, neutrophil level was 4.13×10^9/L; HGB,

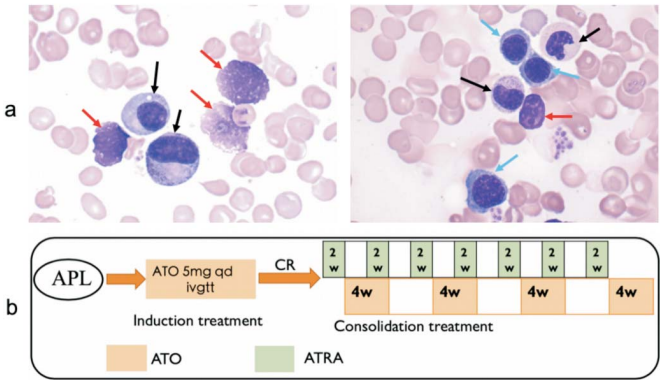

Figure 2. (a) Bone marrow smears reexamined, black arrows indicate neutrophilic myelocyte, red arrows indicate degenerated cells, blue arrows indicate erythrocytoblasts. (b) The diagram of the treatment schedule.

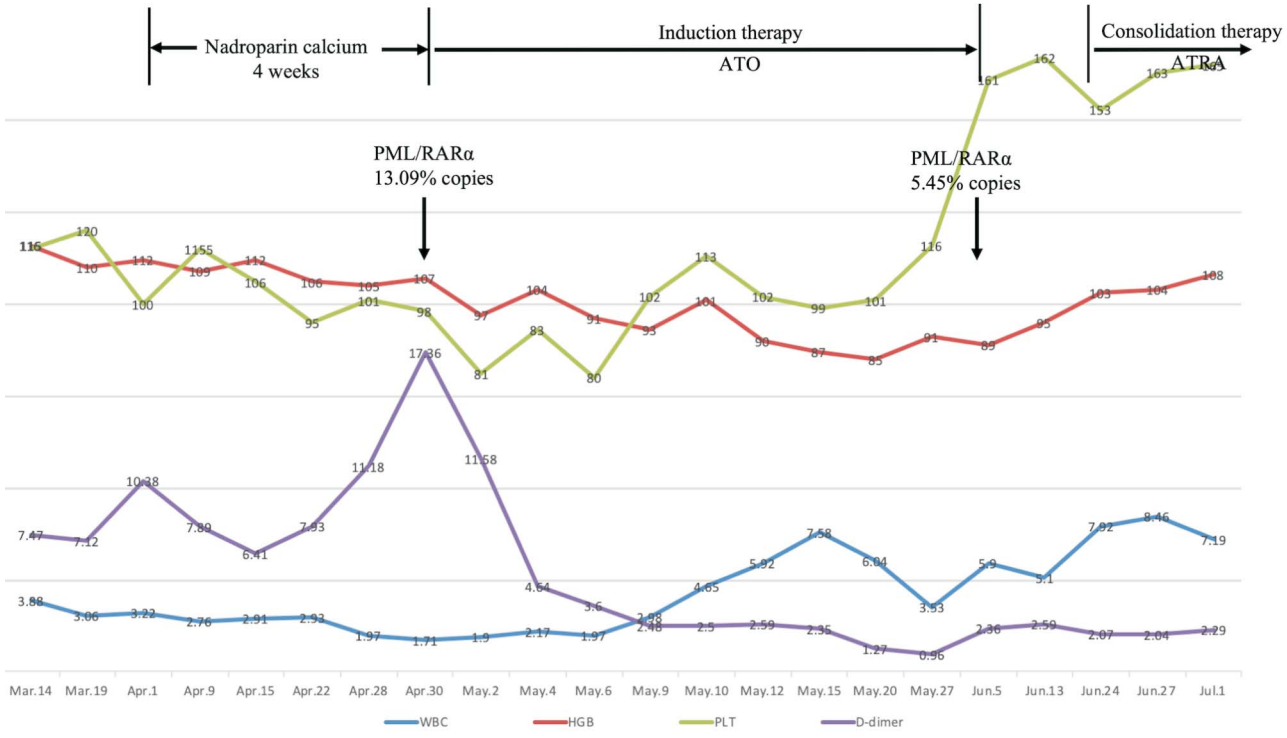

Figure 3. Illustration of the cell count, the treatment and the PML/RARA gene copies along the timeline.

101 g/L; platelets, 194 $\times$ 10^9/L; D-dimer level, 2.42 mg/L, and his peripheral blood smears were within normal ranges.

3. Discussion

APL, a unique subtype of AML, is characterized by the specific chromosomal translocation, t (15; 17) (q22; q12), which generates a PML/RARα fusion gene. The resulting fusion proteins induce a differentiation blockage at the promyelocyte stage, the main molecular mechanism of APL.[6] In the early phase of APL, life is threatened by coagulation disorders and hemorrhages.[7] Because of the standardized application of ATRA and ATO, the outcome of APL has improved considerably, and many patients can be cured.[8]

The elderly patient in this study had no symptoms such as fatigue, bleeding, or tenderness of the sternum. Only laboratory tests showed a slight decrease in WBC count and elevation of D-dimer level. If the blood and coagulation functions had not been closely monitored, diagnosis could easily have been missed. In a short time, D-dimer level increased significantly and fibrinogen and platelets decreased progressively, showing the tendency of DIC, and progressed quickly. APL was diagnosed based on bone marrow examination.

According to the risk stratification, the patient was at low risk of relapse; therefore ATRA combined with ATO was considered based on the latest guidelines.[9] However, these guidelines were developed based on clinical trials that rarely recruited APL patients older than 80. In addition, previous studies have reported that elderly APL patients are more vulnerable to complications, such as differentiation syndrome and infection, in the early induction stage.[3,10] Furthermore, these patients often have multiple comorbidities and can be intolerant to treatment. Treatment of APL in the elderly therefore remains a great challenge.

In this case, we first conducted a comprehensive geriatric assessment. Although the activity of daily living and frailty scores showed some functional deficiency and weakness, the general condition and biochemical indicators were acceptable, and the patient's personal willingness to receive treatment was strong. APL is the only disease that has a high cure rate without chemotherapy, but if it is left untreated, life expectancy is less than 3 months. ATO alone was demonstrated to exert excellent outcomes in APL.[11,12] Therefore, we used ATO alone and the dose was reduced by half.

In the early stage of treatment, the appearance of hypoxia, low fever and increased leucocyte, LDH, and uric acid supported mild differentiation syndrome. After hydroxyurea treatment, the above symptoms gradually improved. During induction treatment, the evident adverse effects were not observed, except for slight elevation of serum creatinine and liver enzymes. With these treatments, the patient achieved complete molecular remission. Although this patient did not finish the consolidation therapy as planned, the prognosis was still good.

In summary, this is the first reported case of APL in a patient older than 90 years. For very elderly, low-risk APL patients, half-dose ATO is recommended for induction therapy and alternate application of ATO and ATRA is recommended for consolidation therapy. In future, with the extension of the average lifespan and the pursuit of a better quality of life, positive treatments for very elderly patients with malignancy will be common and necessary. The successful experience with this patient provides clinicians with a viable treatment strategy and indicates a good prognosis for very elderly APL patients. Cautious use of the differentiated agents can result in sustained remission and excellent life quality for these patients.

Conflicts of interest

There is no financial and non-financial conflicts of interest.

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