Clinical Case Report

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Treatment-related acute granulocyte–monocytic leukemia from multiple myeloma

A case report and literature review

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Abstract

Rationale: To investigate the clinical features of treatment-related acute granulocyte–monocytic leukemia (t-AML) from multiple myeloma (MM) thereby improving the understanding of this disease.

Patient concerns: A 72-year-old woman patient was initially diagnosed as MM. Two years and 7 months after treatment, this patient developed AML M4 as confirmed by the analyses from clinical features, bone marrow morphology, flow cytometry, and cytogenetic examination.

Diagnosis: Treatment-related acute myeloid leukaemia (t-AML).

Interventions: Due to lack of the ability to pay the cost, she declined our recommendation to accept therapy as an inpatient and was discharged.

Lessons: The reported case was a rare t-AML, which is resistant to currently available treatments and has a poor prognosis.

Abbreviations: HB = haemoglobin, MM = multiple myeloma, PLT = platelets, RBC = red blood cells, t-AML = treatment-related acute myeloid leukemia, WBC = white blood cells.

Keywords: acute granulocyte–monocyte leukemia, multiple myeloma, treatment-associated acute granulocyte–monocyte leukemia

1. Introduction

Multiple myeloma (MM) is a common hematologic malignancy derived from pre-B cells and/or plasma cells. The abnormal proliferation of bone marrow plasma cells leads to osteolytic bone destruction and serum accumulation of monoclonal immunoglobulins or light chains (M proteins), resulting in recurrent infections, anemia and renal dysfunction. With the application of advanced chemo-radiotherapy and targeted therapy in cancers, increasing numbers of patients with cancers can obtain long-term survival. Treatment-related acute myeloid leukemia (t-AML) refers to the AML in patients after treatment of tumors or other benign diseases with radiotherapy and chemotherapy.[1] After treatment, the development of MM to t-AML, especially acute myelomonocytic leukemia, is rarely reported.[2] Herein, we report 1 case of an MM patient who developed AML (M4) 2 years and 7 months after treatment, and reviewed the related literature.

2. Case report

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Affiliated Hospital of Nantong University, China. Written informed consent was obtained from individual participant.

This patient was a 72-year-old woman who came to our hospital on April 8, 2014 and claimed dizziness, fatigue, and cough with expectoration for about a month. The routine blood examination results were white blood cells (WBC) 3.2×10^9/L, RBC 2.65×10^{12}/L, hemoglobin (HB) 85 g/L, and platelets (PLT) 120×10^9/L. The biochemistry tests showed normal creatinine and uric acid with globulin levels of 61.1 g/L. The immunoglobulin levels were IgA 42.3 g/L, IgG 3.19 g/L, IgM 0.29 g/L, kappa light chain 244 mg/dL, lambda light chain 738 mg/dL, and C-reactive protein 111.0 mg/L. The erythrocyte sedimentation rate was 123 mm/h. Immunofixation electrophoresis showed that the M component was an IgA-lambda light chain. Bone marrow cytology analysis demonstrated active proliferation of nucleated cells, with granule cells:red cell ratio = 3.03:1 without apparent alterations of granulocyte, mononucleocyte, lymphoid and erythroid proliferation; the PLT displayed clustered distribution. Moreover, we found 19 megakaryocytes in a slide with a whole area of 2.2×2.4 cm and myeloma cells accounted for 10%

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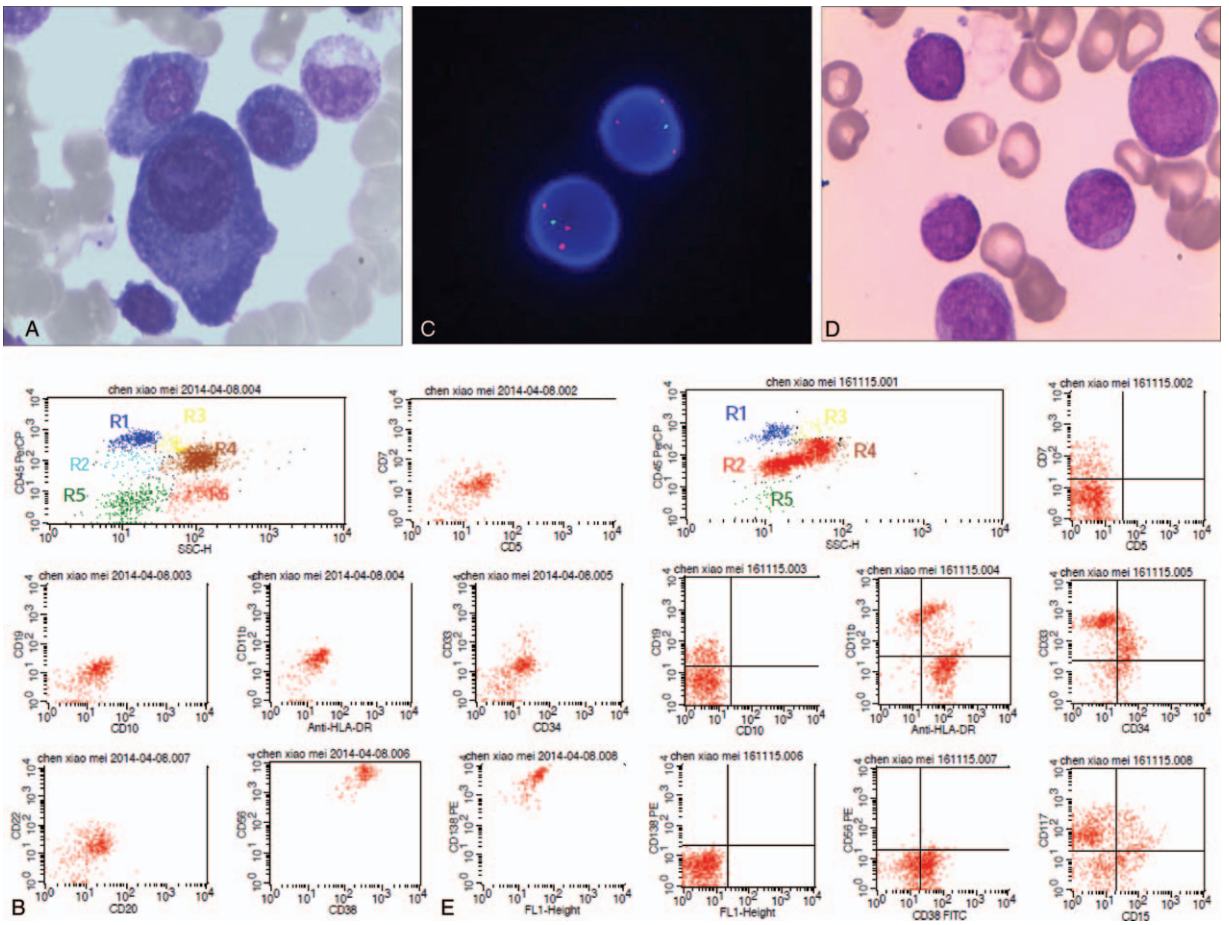

Figure 1. (A) Bone marrow smears showed myeloma cells (Wright staining, ×1000). (B) Immunological typing at the time of initial diagnosis. (C) FISH tests at the time of initial diagnosis. (D) Wright staining showed t-AML (M4), ×1000. (E) Immunophenotyping of t-AML (M4). FISH = fluorescence in situ hybridisation.

(Fig. 1A). Leukemia/lymphoma immunotyping found that R1-lymphocytes, R2-early bone marrow cells, R3-monocytes, R4-differentiated myeloid cells, R5-nucleated red blood cells (RBCs), and R6-CD38++/CD56++/CD138++CD20−/CD22− MM cells accounted for 18.80%, 2.81%, 5.14%, 47.04%, 14.69%, and 8.46%, respectively (Fig. 1B). Fluorescence in situ hybridization analysis found 1q21 gene amplification in 16% cells but normal D13S319, RB1, and immunoglobulin heavy chain (Fig. 1C). No apparent bone hyperplasia or signs of destruction in the head, cervical spine, and thoracic vertebra, or pelvis lumbar degeneration were observed. Based on these tests, the patient was diagnosed as MM (IgA λ light chain type; stage II group A).

From April 14, 2014, the patient was subjected to liposomal doxorubicin; vindesine; dexamethasome (DVD) chemotherapy (doxorubicin liposomes: 20 mg × 2 d intravenous injection (i.v.); vindesine: 1 mg × 4 d i.v.; dexamethasone: 20 mg × 4 d i.v.). After a 4-day interval, the patient was discharged and underwent continuous oral administration of dexamethasone at 20 mg × 4 d, followed by an interval for 4 days, and then oral administration of dexamethasone at 20 mg × 4 d. On May 12, 2014, the patient underwent routine blood tests. The results showed immunoglobulin levels of IgA 18.70 g/L and lambda light chain levels of 373 mg/dL. This treatment cycle was repeated on May 13, June 13, July 13, and August 13, 2014. During this treatment period, IgA and lambda light chain levels decreased, HB level increased, and erythrocyte sedimentation rate decreased. Examination on August 22, 2014 showed an IgA level of 5.72 g/L, a lambda light chain level of 306 mg/dL, and trace IgA-lambda light chain levels by immunostaining electrophoresis. The patient demonstrated significantly improved condition. Then the patient was discharged and subjected to thalidomide dexamethasome chemotherapy (dexamethasone 20 mg qw; thalidomide 100 mg qn).

On October 10, 2016, she had a fever with dizziness, fatigue, and cough accompanied with some yellow purulent sputum, and was treated as cold without apparent improvement. On November 11, 2016, she was admitted to our hospital. The routine blood examination results were WBC 16.8×10^9/L, RBC 1.5×10^{12}/L, HB 52 g/L, and PLT 17×10^9/L. The immunoglobulin levels were IgA 5.81 g/L and lambda light chain 708 mg/dL. Immunofixation electrophoresis showed that the M component was an IgA-lambda light chain. Bone marrow cytology analysis demonstrated obviously active proliferation of nucleated cells with pathological changes of granule cells (I + II accounted for 35.5%), positive for myeloperoxidase staining; mononuclear cells demonstrated hyperplasia with 48.5% of primary mononuclear cells, partly negative for myeloperoxidase staining. There were no lymphoid abnormalities (Fig. 1D). Leukemia/lymphoma immunotyping revealed that R1-lymphocytes, R2-early bone marrow cells, R4-differentiated myeloid cells, and R5-nucleated RBCs accounted for 8.85%, 84.2%, 1.05%, and 1.43%, respectively (Fig. 1E). These tests demonstrated a phenotype of

AML-M4. Analysis of chromosomes revealed no karyotype abnormality. TP53 gene mutation analysis found TP53 was wild type. Due to lack of the ability to pay the cost, she declined our recommendation to accept therapy as an inpatient and was discharged.

3. Discussion and literature review

MM is a common blood system malignancy and accounts for 10% of hematopoietic malignancies and about 1% of all malignant tumors.[3] The treatment of MM has improved greatly since the 1960s traditional melphalan combined with prednisone treatment and the 1980s multidrug combination chemotherapy (such as doxorubicin; vindesine; dexamethasome, DVD, M2 programs) and autologous hematopoietic stem cell transplantation. Particularly, the advent of molecular targeted drugs has greatly prolonged the survival time of MM patients. Development of MM to t-AML has become a major challenge. Although MM and AML originate from 2 distinct clones with low incidences of second tumor, t-AML is an aggressive disease with a very poor prognosis.[4] Recently, there have been several case reports of t-AML, including plasma cells, acute lymphoblastic and acute nonlymphotropic subtypes; however, there have been few reports of AML-M4 with only 1 case reported in China.[2]

Bergsagel et al conducted that the first prospective clinical study evaluating the effects of a combination of 3 alkylating agents in the treatment of MM: melphalan, cyclophosphamide, and carmustine. They observed higher incidence of all forms of acute leukemia than expected in all age groups.[5] It was reported that the incidence of acute leukemia in MM patients after chemotherapy is in the range of 0.2% to 7% with a peak time of 3.5 to 5 years after initiation of treatment.[6] Other studies also demonstrated that conventional chemotherapy before autologous stem cell transplantation, rather than pretransplant myeloablative therapy, maintenance therapy, or additional treatment after transplantation, more likely contributes for acute leukemia.[7] Moreover, patients with MM who undergo continuous treatment have a higher incidence of acute leukemia than those who undergo intermittent treatment. The exact mechanisms of the development of t-AML from MM are largely unknown. The potential mechanisms may include chemotherapy-induced recurrent bone marrow suppression and regeneration results in clonal changes of stem cells; chemotherapy results in genetic alteration of marrow hematopoietic stem cells, thereby leading to clone expansion of leukemia stem cells; chemotherapy triggers an activation of potential leukemia initiating factors; chemotherapy or radiotherapy impairs the immune surveillance system leading to loss of the killing and removal of abnormal cells and leukemia clones; abnormal proliferation of leukemic cells inhibits MM cell differentiation and proliferation.[2] Nevertheless, some scholars believe that the history of chemotherapy is not an essential factor for MM patients to develop AML. Since MM patients are prone to immune deficiencies often accompanied by intermittent and recurrent infections, the long-term immune response may lead to mononuclear cell hyperplasia and finally AML.

In addition, the evolution of MM to AML may also be associated with cancer susceptibility of the patient.[8–10] Indeed, it has been estimated that genetic variations can account for up to 95% of variability in drug disposition and effects.[11] In addition to drug disposition and response to treatment, polymorphisms in genes encoding drug-metabolizing enzymes, DNA repair pathways, drug transporters, and drug targets may contribute to a person's susceptibility to subsequent malignancies as well.[12] Furthermore, the bone marrow microenvironment may be important in the pathogenesis of AML. MM depends on mutual interactions between cells and extracellular components of the bone marrow for survival and growth. Interactions between MM cells with the bone marrow microenvironment activate a pleiotropic proliferative and antiapoptotic cascade, including the nuclear factor-kappa B signaling pathway, resulting in the growth, survival, drug resistance, and migration of MM cells.[13] Moreover, many growth factors secreted by MM and bone marrow stromal cells stimulate osteoclastogenesis and angiogenesis.[14] It is thus conceivable that the resultant changes in bone marrow microenvironment may play a role in the development of AML after MM.

In this case, the patient did not receive alkylating agents such as carmustine, cyclophosphamide, melphalan, and busulfan, but was subjected to 5 cycles of DVD chemotherapy for nearly 3 years. The relatively early development of AML in this MM patient might be related to her old age, since compared with young patients, chemotherapy-induced bone marrow suppression is stronger in old patients, likely leading to difficulty in short-term recovery, increased clonal changes in stem cells, and accelerated loss of immune surveillance. In addition, this patient took thalidomide for nearly 3 years. It has been warned that thalidomide increases the risk of secondary blood cancers.[15] It is possible the early development of AML in this MM patient might be related to the usage of thalidomide. However, all patients with myeloma in our hospital have taken thalidomide. Except for those patients who cannot tolerate thalidomide-induced hand and foot numbness, edema and other adverse reactions and discontinued thalidomide, all the other patients take thalidomide at the beginning of treatment and continue long-term oral administration for treatment maintenance with the maximum dose of 200 mg/d. Only 1 case of secondary M4 in all MM patients was found in our hospital. Therefore, further studies are needed to investigate the association of thalidomide with the development of AML from MM. Furthermore, several proposed environmental risk factors are shared between MM and second malignancies. Chronic antigen stimulation from prior autoimmune, infectious, inflammatory, allergic disorders, and immune dysregulation may play a role in the pathogenesis of both MM and AML.[16–18] In addition, socioeconomic status has been shown to influence survival of both MM and AML, suggesting that lifestyle factors in these disorders are important.[19]

Taken together, it seems reasonable to propose that the development of second malignancies after MM is most likely an outcome from the multifactorial process. With the extension of survival time in MM patients, there will be increasing numbers of reports regarding t-AML derived from MM. However, MM-derived t-AML progresses rapidly with a very poor prognosis. To avoid t-AML, it will be critical to better characterize the molecular features of patients who develop second malignancies after MM, which would allow us to better define the role of treatment and nontreatment-related factors and how they influence each other.

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