BMC Pediatrics

CASE REPORT

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Methylmalonic acidemia with homocystinuria in acute myeloid leukemia: a case report

Yuxuan Cheng[1] and Aijun Zhang[1*]

Abstract

Background Methylmalonic acidaemia (MMA) is a genetic metabolic disorder caused by congenital defects that may result in multisystem damage. However, MMA complicated with acute myeloid leukemia (AML) is very rare.

Case presentation Here, we report a case of MMA with AML in a boy aged 7 years and 6 months. The boy was screened for MMA after birth and received long-term treatment with dietary control, vitamin B12, and L-carnitine. He was readmitted at the age of 7 years and 6 months with systemic bleeding spots and was diagnosed with AML by bone marrow cytology. When the diagnosis was clear, the patient received chemotherapy in addition to maintenance treatment for MMA. His blood routine, liver and kidney function, blood biochemistry, blood glucose, blood lipids, lactic acid and blood ammonia were monitored continuously. Bone marrow cytology one month after starting chemotherapy showed complete remission. Sorafenib was also added during chemotherapy and was discontinued 1 year after completion of chemotherapy. At the end of chemotherapy, he chose venetoclax for consolidation, and to date, the patient's condition is stable, with sustained CR and no relapse.

Conclusion MMA combined with AML is rare. The prevention of infection, comprehensive assessment of nutritional status, continuous monitoring of related indicators and overall situation should be prioritized and comprehensive and individualized treatment approaches are paramount.

Keywords Methylmalonic acidaemia, Acute myeloid leukemia, Pediatrics, Case report

Background

Methylmalonic acidaemia (MMA) is an autosomal recessive genetic disease. It is a disorder of organic acid metabolism caused by defective production or metabolic disorders of methylmalonyl-CoA mutase or its coenzyme cobalamin (vitamin B12). MMA can be divided into simple and complex MMA subtypes according to the presence of hyperhomocysteinemia. Children with severe MMA may experience drowsiness, vomiting, hypothermia, respiratory distress, severe ketoacidosis and hyperammonaemia during the neonatal period [1].

Leukemia is the most common malignant tumor in children, and acute myeloid leukemia (AML) is a hematological malignancy that accounts for approximately 15%-20% of childhood leukemia cases. Children with AML receive more intensive chemotherapy regimens but have a poor prognosis [2, 3].

In this article, we report the case of a 7.5-year-old boy with MMA and AML. At present, few similar cases have been reported; therefore, the condition and treatment of this child deserve special attention.

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Case presentation

The patient was a 7.5-year-old boy. After birth, MMA was detected via heel blood during screening for congenital diseases (DNA mass spectrometry): MMA (cblC type) complicated with hyperhomocysteinemia and had a mutation in the MMACHC gene (Coding region: Exon4. Nucleotide alteration: 609G > A. Amino acid change: p.W203X. Heterozygous mutations). His parents denied a family history of inherited metabolic diseases and a consanguineous marriage. The first onset occurred at 1 month after birth. He had poor milk intake, weak sucking power, and poor response and was subsequently taken to the Department of Neonatology, Qilu Hospital of Shandong University. Physical examination revealed that the child had a poor response to stimulation, weak crying, and slight abdominal distension. Routine blood examination revealed anemia (red-cell count 2.89*10^12/L, hemoglobin 93 g/L, mean corpuscular volume 93.8fL), and a blood ammonia concentration of 90 μmol/L suggested hyperammonaemia. Serum bilirubin measurements was 82 μmol/L (direct bilirubin 12.2 μmol/L, indirect bilirubin 69.8 μmol/L). Increased propionylcarnitine (C3, 5.29) was found in the amino acid and acylcarnitine profile analysis of inherited metabolic diseases. A comprehensive analysis of urinary organic acids revealed an increase in methylmalonic acid (8.2) and methyl citrate (0.3). Blood lipid analysis revealed that the homocysteine concentration was much greater than normal (93.4 μmol/L). The diagnoses made during this hospitalization were MMA and hyperbilirubinemia, and related treatment was given. Considering that the boy's hyperbilirubinemia was related to his poor feeding and metabolic condition and did not require phototherapy, no specific management was provided for his hyperbilirubinemia. During hospitalization, the MMA of the patient was treated with a special nutritional powder, vitamin B_{12} given by intramuscular injection, levocarnitine, and betaine to alleviate hyperhomocysteinemia. After discharge, the child continued to take L-carnitine, betaine, folic acid, and vitamin B_{12} regularly, and tried to avoid stress such as fever, fatigue, infection, and blood transfusion.

The boy was readmitted to the hospital because of systemic bleeding spots for 2 days when he was 7.5 years old. Two days before admission, the child was found to have bleeding spots scattered throughout the skin, which were partially clustered and accompanied by paroxysmal abdominal pain, with no obvious cause. He had no hematemesis, hematochezia, hematuria, epistaxis, fever, cough, fatigue, or sternal pain. Two days later, the boy developed gross hematuria. His parents took him to Jinan Maternal and Child Health Care Hospital for treatment. His routine blood tests revealed white blood cell counts of 276.92*10^9/L, hemoglobin levels of 101 g/L, and platelet counts of 38*10^9/L, and was recommended to visit a higher hospital for treatment. Then the child returned to Qilu Hospital of Shandong University for treatment and was admitted to the Pediatric Intensive Care Unit (PICU). The patient's physical examination revealed that in addition to scattered bleeding throughout the body, and he had a few lymph nodes on the neck that were palpable and enlarged, with good mobility and no pain, and his abdomen was slightly distended, with a palpable liver approximately 2 cm below the ribs. The mental development of children is still behind that of children of the same age. Although he was more than 7 years old, he could only simply express his demands and carry out simple communication, while other neurological examinations showed no obvious abnormalities. On admission, he completed the necessary examination again, and the blood routine test showed that the white blood cell count was 212.54*10^9/L, of which primitive immature cells accounted for 75%. Blood gas analysis showed pH 7.56, pCO_2 23 mmHg, pO_2 100 mmHg, BE-0.9, blood glucose 5.2 mmol/L, and electrolytes: Na + 132 mmol/L, K + 3.9 mmol/L, Cl- 102 mmol/L, Ca2 + 1.07 mmol/L, lactic acid 0.7 mmol/L, blood ammonia 19 μmol/L. Liver function: ALT 7 IU/L, AST 35 IU/L, AKP 151 IU/L, and renal function: BUN1.4 mmol/L, Cr 32 mmol/L, uric acid 364 μmol/L. His homocysteine concentration was 180.2 μmol/L. His routine urine test revealed microhematuria and pyuria. A gastric occult blood test was positive. After admission, the boy was given symptomatic and supportive treatment, such as hydration and alkalization of urine, oral allopurinol, and blood transfusion. He continued to monitor the blood gas analysis until the blood pH value roughly dropped to normal. At the beginning of the treatment, he had multiple infections and bleeding, and used parenteral nutrition for a short time when he had early gastrointestinal bleeding, as shown in Fig. 1. The main infection of the child at that time was urinary system infection, which was confirmed by urinary tract ultrasound and manifested as dysuria and purulent hematuria with a negative culture, and was controlled by timely anti-infection treatment with vancomycin. To establish the diagnosis, bone marrow aspiration and bone marrow cytology were performed in a timely manner, and the results revealed acute myeloid leukemia (M5): The monocytic lineage was abnormal, with primitive and naive monocytes accounting for 89% (Fig. 2). After admission, the patient developed fever with a maximum body temperature of 38.5°C, and his body temperature returned to normal after the administration of antipyretic drugs and physical cooling. However, he still had abdominal pain, for which the nature and specific location could not be described, and he still had brown urine with blood

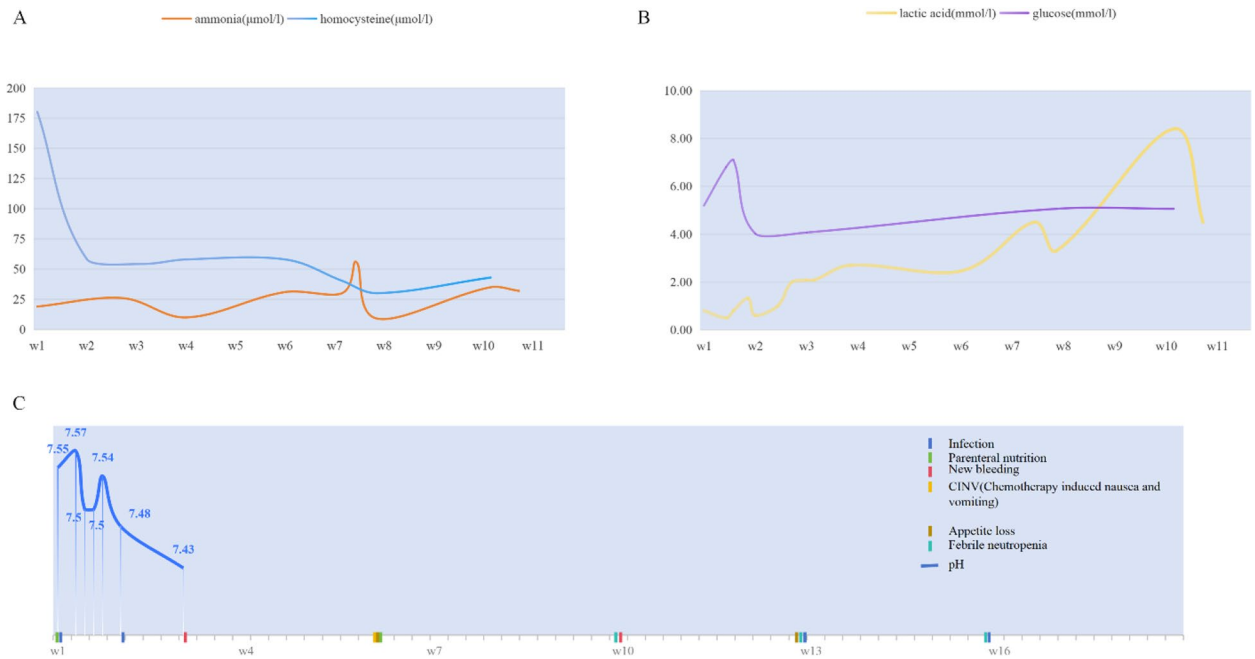

Fig. 1 The course of the patient's conditionand monitoring of important metabolic indicators. **A** Monitoring of blood ammonia (orange) and homocysteine (blue) in the treatment process. **B** Monitoring of blood glucose (purple) and lactic acid (yellow) in the treatment process. **C** Monitoring of blood gas analysis in the early treatment phase and the special events that occur throughout the course of treatment that may aggravate MMA

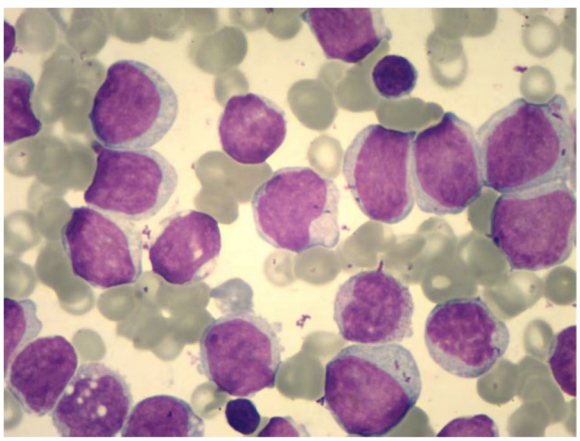

Fig. 2 The bone marrow cytology of the boy (cell morphology). Description: 1. Abnormal proliferation of monocytes, the primitive and naive monocytes accounted for 89%, with round and oval cell bodies and round and oval nuclei. Deformed nuclei were common, such as notched, sunken and twisted nuclei, with dense chromatin which is purple staining. One or two fuzzy nucleoli can be seen in part of the nucleus, the amount of cytoplasm is small, with gray blue color, and some fine purplish red particles can be seen in the cytoplasm. MPO (-) ~ (±) AS-DCE (-) PAS was weakly positive. 2. Proliferation of granulocytic series, erythron and lymphocytic series was inhibited. 3. There were 8 megakaryocytes in the whole film, and Platelets were rare. Diagnosis: Acute leukemia; Morphological support for acute myeloid leukemia (M5)

clots. The boy was diagnosed with AML, MMA, urinary tract infection, and mental retardation, and transferred to the pediatric hematology unit for continued treatment. After the transfer, additional workup for AML was completed. His leukemia immunophenotyping suggested possible AML-M4/M5 (67.58% cells were positive for CD33, CD13, CD34, cMPO, CD117, CD38, CD64, CD7 and HLA-DR, but negative for other antigens). Whole transcriptome profiling of hematologic malignancies (next-generation sequencing) and gene mutation screening of myeloid neoplasms (next-generation sequencing) suggested that: CEBPA (double mutation), FLT3-ITD (high), WT1 high expression (positive rate 9.115%), NRAS gene missense mutation (Table 1). Karyotype analysis: 46, XY,? inv(16)(p13q22)[2]/46,XY[18]. The child was put at high risk and soon started chemotherapy (Low-dose group chemotherapy regimen: details of the complete regimen shown in Table 2). During chemotherapy, the patient developed left eyelid conjunctival hemorrhage and hematuria due to low platelet count and was treated with platelet transfusion (Fig. 1). Throughout the treatment, he continued to receive hydroxocobalamin(10 mg/day), betaine(4 mg/day), levocarnitine(1 g/day), and leucovorin(15 mg/day) for MMA throughout the treatment period, and homocysteine, lactic acid and blood ammonia were monitored regularly (Fig. 1). During the entire course of chemotherapy, the patient consistently received

Table 1 The leukemia cell genetics information (RNAseq) of the child

Gene	Details	Type	Proportion
CEBPA	NM_004364.4:exon1:c.939_940insAAG:p.K313_V314insK	Non-frameshift insertion	42.55%
	NM_004364.4:exon1:c.117delC:p.A40Rfs*120	Frame shift missing	52.18%
FLT3-ITD (high)	NM_004119.2:exon14:c.1793_1794insCGTTGATTTCAGAGAATATGA: p.Y597_E598insDVDFREY	Tandem repeat mutations	41.97%
NRAS	NM_002524.5:exon2:c.G35A:p.G12D Missense point mutation	Missense point mutation	5.81%
WT1	NM_024426.6:exon9:c.C1399G:p.R467G	Missense point mutation	16.67%

Table 2 The complete chemotherapy regimen the patient received

Stage	Chemotherapy regimens	Note
Induction therapy 1[a]	Idarubicin 5 mg/m^2 /day d1,d3,d5 (> 2 h) Ara-C 10 mg/m^2/dose q12h d1-10 G-CSF 5 μg/kg/day d1-10 IT: d1	D26 BM + MRD
Induction therapy 2	Idarubicin 5 mg/m^2 /day d2,d4,d6 (> 2 h) Ara-C 10 mg/m^2/dose q12h d1-10 (> 30 min) G-CSF 5 μg/kg/day d1-10 IT: d1	
Consolidation therapy 1	HHT 3 mg m^2 /day d1-5(> 3 h) Ara-C 3 g/m^2/dose q12h d1-3 (> 3 h) IT: d0	
Consolidation therapy 2	VP-16 150 mg/m^2 /day d1-3(> 3 h) Ara-C 3 g/m^2/dose q12h d1-3 (> 3 h) IT: d0	
Consolidation therapy 3	Ara-C 3 g/m^2/dose q12h d1-2, d8-9 (> 3 h) L-ASP 6000U/m^2/dose, 3 h after the 4th and 8th dose of Ara-C	
Consolidation therapy 4	Fludarabine 30 mg/m^2 /day d1-5 (> 1 h) Ara-C 2 g/m^2/d d1-5(> 3 h), 3 h after fludarabine) Dexamethasone 5 mg/ m^2 /day d1-5, 0.5 h before Ara-C G-CSF 300 μg/m^2/day d0-5, 12 h before fludarabine	

The interval between each stage was 3 weeks

[a] Considering that the patient may not be able to tolerate the complete protocol, the physician adjusted the protocol:Idarubicin 5 mg/m^2 /day d1,d3,d5 (> 2 h),G-CSF 5 μg/kg/day d1-6,IT: d1

Ara-C cytarabine, *VP-16* etoposide, *HHT* homoharringtonine, *L-ASP* L-asparaginase, *G-CSF* granulocyte colony stimulating factor, *IT* Intrathecal injection, *BM* bone marrow puncture, *MRD* minimal residual disease

compound sulfamethoxazole as a prophylactic measure against fungal infection. Additionally, he regularly gargled with compound borax solution to prevent stomatitis and were placed in a laminar flow bed for protective isolation in order to minimize the risk of cross-infection during bone marrow suppression. However, there were still some unavoidable adverse reactions, such as vomiting, appetite loss, infection, febrile neutropenia, bleeding, etc. (These are all marked in Fig. 1), but none of them caused aggravation of MMA. Infection and febrile neutropenia usually occured during the period of bone marrow suppression following intensive chemotherapy. The loss of appetite commonly manifests in the middle and late stages of intensive chemotherapy, necessitating intravenous nutritional support when it became severe. Meanwhile, he concurrently received appropriate dietary guidance, with a low-protein, high-calorie diet as the primary approach, specifically targeting reduced protein intake, particularly valine-, isoleucine-, threonine-, and methionine-rich proteins. Daily protein consumption ranged from 0.8–1.2 g/kg while ensuring sufficient energy intake and considering oral medium-chain triglyceride supplementation if necessary. It is noteworthy that the child's intravenous nutrition regimen included a diverse range of amino acids (including isoleucine, threonine, and valine, but no methionine), medium- and long-chain fat emulsion, as well as other essential electrolytes and vitamins. Notably, no MMA attacks were observed during treatment. Bone marrow cytology one month after starting chemotherapy showed complete remission

(CR), MRD was less than 0.01%, FLT3-ITD turned negative, but CEBPA remained positive. Then, sorafenib (0.2 g/day) was added to chemotherapy and was not discontinued until 1 year after the end of chemotherapy. Because the initial dose of chemotherapy was low in the patient's chemotherapy regimen, in order to reduce the risk of recurrence, the patient chose to add venetoclax (100 mg/day) for consolidation after the completion of chemotherapy. The child was followed up regularly after the end of chemotherapy. At present, the patient's condition is stable with a sustained CR and there is no recurrence of leukemia.

Discussion

This case report describes a 7-year and 6-month-old boy who was diagnosed with AML on the basis of MMA. Under standard treatment and reasonable monitoring and management, the treatment process for this child was smoother than expected, and the prognosis was better than expected.

MMA is a disorder of organic acid metabolism and is a group of inborn errors that can cause multisystem damage [4]. Some important amino acids, such as isoleucine, threonine, methionine and valine, are metabolized to methylmalonic acid, which is well metabolized by MCM and cobalamin, which is converted to succinic acid. When the corresponding gene mutation occurs, metabolic wastes such as methylmalonic acid cannot be metabolized, and these products will accumulate in the blood and urine, which will cause multisystem involvement and damage [5]. The main principle of treating MMA is to reduce the accumulation of toxic substances, which can be generally achieved by two methods: reducing the production of toxic substances and increasing the excretion of toxic substances. On the one hand, restriction of protein intake and vitamin B12 supplementation can reduce the generation of metabolic waste products, and on the other hand, the administration of L-carnitine increases the excretion of metabolites. L-carnitine converts methylmalonyl-CoA to methylmalonyl-carnitine, which is nontoxic [6, 7].

Childhood AML patients generally have better outcomes than adult AML patients because of the more frequent presence of favorable prognostic genetic features and greater tolerance to intensive therapy [3, 8] The treatment of AML is based on intensive multidrug chemotherapy. The standard intensive chemotherapy regimen mainly includes cytarabine and anthracyclines. Intensive chemotherapy regimens involving cladribine or fludarabine and further treatment, such as allogeneic hematopoietic stem cell transplantation (HSCT), should also be considered [3, 9]. The child in this case chose a low-dose chemotherapy regimen at the initial treatment, which reduced the dose and duration. Because he tolerated chemotherapy better than expected, subsequent chemotherapy was not reduced in intensity.

By searching the subject terms "methylmalonic acidaemia" and "leukemia" in databases, including PubMed and Web of Science, we found very few relevant articles, indicating that MMA combined with leukemia is rarely reported. We found one similar case report [10] in which the child was a girl with acute lymphoblastic leukemia (ALL) complicated with MMA. This case is similar to but also significantly different from this reported case. In the case report obtained by the search, the patient presented with metabolic disorders and clinical manifestations of multisystem involvement during chemotherapy for ALL. Through metabolic disease screening, she was also diagnosed with complex MMA (cblC type). Her subsequent treatment included intermittent chemotherapy with low-dose vindesine and chimeric antigen receptor T-cell (CAR-T) immunotherapy [11].

For this rare condition, it is particularly important to manage MMA reasonably under the premise of chemotherapy and disease status of leukemia to avoid metabolic crisis.

Repeated infections can lead to metabolic decompensation in patients with MMA because of the increased metabolic demands at the time of infection, aggravating the underlying disease. Patients with both MMA and AML are prone to recurrent infection. Pancytopenia can be observed in many patients with MMA, and neutropenia may be the main cause of infection [12]. Prevention of infection is therefore particularly important for this boy with both MMA and AML. If the child inevitably has an infection, broad-spectrum antibiotics can be used to control the infection and prevent metabolic crisis. However, during acute metabolic decompensation, the corresponding treatment should be administered more quickly. The intake of protein should be stopped in a timely manner for a maximum of 24–48 h because a lack of protein intake may cause the body to break down its own protein, leading to metabolic crisis. Attention should also be given to age-appropriate intravenous glucose, insulin to avoid hyperglycemia, and sodium and potassium electrolytes. If necessary, the dosage of L-carnitine should be doubled. If the child cannot tolerate it orally, the drug should be given intravenously. The pH and blood ammonia and electrolyte levels need to be monitored continuously throughout the process [7].

In children with AML, malnutrition is thought to be associated with chemotherapy-related adverse effects and reduced survival [13, 14]. Nausea, diarrhea, constipation, and fatigue caused by chemotherapy and cachexia all eventually lead to malnutrition [15]. Since children with MMA cannot directly receive protein and important

essential amino acids such as threonine and leucine, the nutritional status of these children is limited. In a malnourished state, the patient's tolerance to chemotherapy and ability to fight infection are affected. Children with leukemia often need supplemental nutrition. When it is clinically possible, enteral nutrition is generally preferred over parenteral feeding, although the latter may be necessary, especially in patients with AML [16]. However, for children with MMA, more attention should be given to nutritional supplements. To maintain metabolic stability, children with MMA usually receive enteral emergency feed containing a glucose polymer solution with the occasional addition of fat during nutritional supplementation [7]. Clinicians should be particularly cautious when trying to supply protein and amino acids to kids. It is necessary to take into account the child's illness and general conditions. Protein intake should be stopped or partially reduced depending on the severity of clinical symptoms [7]. For the child with vitamin B12-dependent MMA, it is important to pay attention to whether he or she needs timely supplementation with vitamin B12,. Other nutritional supplements, such as omega-3 fatty acids, have been shown to be beneficial for children with leukemia [17]. However, due to objective circumstances, there may be a lack of availability of specialized formula milk powder or nutrition sometime. For children with vitamin B12 dependent MMA, the dietary restrictions can be not overly strict. For instance, in this case report, the short-term administration of intravenous nutrition containing amino acids like isoleucine that can potentially result in the production of methylmalonic acid as a metabolite did not exacerbate MMA. At the same time, blood ammonia and lactic acid levels, as well as blood glucose, blood lipids, and other nutrition-related indicators, need to be monitored regularly.

For patients with MMA, many treatments are also the cause of stress response [7]. The child in this case report did not experience metabolic crisis and stress response caused by infection, chemotherapyand other events during the treatment, which was due to the regular and timely application of vitamin B12, L-carnitine, betaine and other drugs in his daily life, and also related to the initial adjustment of the dose and time of chemotherapy and the reduction of the intensity of chemotherapy. And it can be seen that the adjustment of the initial dose did not affect the efficacy. At the same time, this child belongs to a high-risk group but did not opt for HSCT due to factors such as the significant impact of chemotherapy, the exorbitant cost of transplantation, and the substantial adverse reactions. Ultimately, venetoclax was selected to consolidate therapeutic efficacy, thereby exemplifying personalized treatment and significantly alleviating the burden on children with MMA.

Conclusion

For the rare case of AML with MMA, the prevention of infection, comprehensive assessment of nutritional status, continuous monitoring of related indicators and overall situation should be prioritized. If deemed necessary, treatment intensity can be reasonably adjusted to strike a balance between efficacy and potential complications. Comprehensive and individualized treatment approaches are paramount.

Abbreviations

MMA	Methylmalonic acidemia
AML	Acute myeloid leukemia
RHG-CSF	Recombinant Human Granulocyte Colony-stimulating Factor
MRD	Minimal residual disease
ALL	Acute lymphoblastic leukemia
CAR-T	Chimeric Antigen Receptor T-Cell
CINV	Chemotherapy induced nausea and vomiting

Authors' contributions

Yuxuan Cheng was responsible for the clinical information and drafted the manuscript. Aijun Zhang analyzed the information, provided guidance and revised the manuscript. Both authors approved the manuscript for submission.

Funding

This work was supported by National Key Research and Development Plan (2023YFC2706402), Shandong Provincial Natural Science Foundation (ZR202010220039).

Data availability

The datasets generated and/or analyzed during the current study are available in the Genome Sequence Archive with code PRJCA028986 (https://ngdc.cncb.ac.cn/gsa) and the data used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This case report has been approved by Scientific Research Ethics Committee of Qilu Hospital of Shandong University, and obtained the informed consent of the parents.

Consent for publication

We state that the written informed consent was obtained from the patient's parents for publication of the case report in a public publication.

Competing interests

The authors declare no competing interests.

Received: 26 March 2024 Accepted: 19 August 2024
Published online: 12 February 2025

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