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CASE REPORT Open Access

A new case of trisomy 5 with complex karyotype abnormalities in B-cell prolymphocytic leukemia: a case study

Musa Makongoro[1†], Mahmoud Matar Mohammad Abu Rakhey[1†], Yafei Yu[1], Jianzhi Sun[1], Guosheng Li[1], Na He[1], Samir Ali Abd El-Karem[2] and Daoxin Ma[1*†]

Abstract

Background: The B-cell prolymphocytic leukemia (B-PLL) diagnosis is challenging due to the superposition with mature B-cell leukemia and/or lymphoma.

Objective: An insight case study of trisomy 5 with complex karyotype abnormalities in B-cell prolymphocytic leukemia.

Subject and methods: A 72-year-old man was referred to the Hematology Department, Qilu Hospital, Shandong University, because of persistent fever (10 days) and lymphocytosis. A detailed diagnostic methods including complete blood count, bone marrow aspiration, flow cytometry, conventional karyotype analysis, fluorescence in situ hybridization (FISH), quantitative real-time polymerase chain reaction (qRT-PCR), next-generation sequencing technology (NGS) used to detect 41 kinds of mutant genes related to hematological malignancies were conducted and reasonable therapeutic regimens including emergent leukapheresis accompanied by basification of urine and hydrotherapy, followed by a regimen of cyclophosphamide and dexamethasone.

Results: Subject white blood cell count was 143.43 × 10^9/L, and 56% prolymphocytes. He did not show lymphadenopathy but splenomegaly. Immunophenotyping of prolymphocytes was CD5(+low), CD10(−), CD11c(−), CD19(+), CD20(+), cCD22(+), CD23(−), cCD79a(+), CD79b(+), FMC7(±), CD43(−), CD3(−), CD56(−), CD103(−), HLA-DR(+), and Lambda(+). R-banding and FISH revealed that leukemia cells carried extra chromosome 5. Considering the rare occurrence of trisomy 5 found in prolymphocytic leukemia, especially in Asians, with rapid disease progression. We know that median survival of B-PLL is three years after diagnosis, while survival time of this patient was only 1 month.

Conclusion: This study could provide the firsthand materials for precision, medicine and mechanism research in cytogenetics and molecular biology. It inferred that trisomy 5 might be a poor prognosis indicator, providing directions for clinical practice in the foreseeable future.

Keywords: B-cell prolymphocytic leukemia (B-PLL), Trisomy 5, Fluorescent in situ hybridization (FISH), Next-generation sequencing (NGS)

Introduction

B-cell prolymphocytic leukemia (B-PLL) is an aggressive, out of control growth of B- lymphocyte cells with scarce neoplasm that represents 1% of lymphocytic leukemia and accompanied by a low survival rate. B-PLL was first described as a variant form of B-cell chronic lymphocytic leukemia (CLL) in the early 1970s [1–7], while it

*Correspondence: daoxinma@sdu.edu.cn
†Musa Makongoro, Mahmoud Matar Mohammad Abu Rakhey and Daoxin Ma have contributed equally to this work
[1] Department of Hematology, Shandong University-Qilu Hospital, Jinan, China
Full list of author information is available at the end of the article

was implicated as an eminent clinic-pathologic entity and realized as a prolymphocytes malignancy influencing bone marrow (BM), blood, and spleen in the fourth edition of the 2008 World Health Organization (WHO) categorization [2–9]. 69 years is the mean age at diagnosis, with slightly male predominance. Patients typically exhibit B-symptoms, lymphocytosis, and splenomegaly, but lymphadenopathy is infrequent. It is considered by the WHO when more than 55% of the peripheral blood the lymphocytes are prolymphocytes, or when a lymph node or BM sample shows that prolymphocytes are the majority of lymphocytes. Molecular profiling and cytogenetic studies have failed to define and represent a single genetic aberration, instead abnormality of TP53/p53, deletion on 11q23, and/or 13q14, and trisomy 12 complex karyotypes have been documented. It is particularly worth mentioning that patient with karyotype abnormalities involving trisomy 5 is the first time to be reported in prolymphocytic leukemia [3–11].

Case report

A 72-year Chinese male was admitted to our Hematology Department, Qilu Hospital, Shandong University, with a history of 10-day fever, fatigue, poor appetite, diarrhea, and abdominal pain. His previous medical history showed that he had a chronic hepatitis B for almost 40 years and painless splenomegaly for about ten years. He was a peasant and had no reported exposure to environmental carcinogen. On the admission day, he presents a brief syncopal episode. Upon inspection, he had a 38.3 °C temperature, conjunctiva and mucosal pallor was reported. The superficial lymph nodes were not palpable. About 7 cm below the left costal margin the spleen tip was palpable and confirmed through radiological investigations including: chest x ray, and abdominal ultrasound as conducted in previous studies and published leukemia diagnosis work [6, 10, 12]. Rest of the physical examinations was negative. The whole blood count revealed the white cell, hemoglobin, and platelet were 143.43×10^9/L, 101 g/L, and 79×10^9/L, respectively. The peripheral blood smear showed 87% of the nucleated cells were leukemic blasts with an elevated nuclear/cytoplasmic ratio, 56% of which were prolymphocytes with larger cell bodies and more prominent nucleoli. Renal and hepatic functions were normal. qRT-PCR displayed that serum level of Hepatitis B DNA and lactate dehydrogenase (LDH) was 1.25×10^3 IU/mL and 2014 U/L respectively, which was much higher than normal which could be also be related to post chemotherapy death. The current work was approved by Shandong University Research Ethical Committee, and written informed consent was obtained from participant family enrolled prior to sample collection.

Morphology and immunology

Bone marrow aspiration, smear and biopsy were carried out for morphological and immunological studies according to previous studies [6, 10–13]. The bone marrow smear represented 100% cellularity, with 91% blasts infiltration. Sixty-five percent among them were prolymphocytes characterized by large cell bodies, and prominent nucleoli. The blasts exhibit a high ratio of nuclear versus cytoplasm. Auer rods were not present (Fig. 1). Flow cytometry showed the blasts expressed CD19, CD20, CD5 (low), CD79a, cCD22, cCD79a, HLA-DR, FMC7 (low), and Lambda, but did not express CD10, CD23, CD34, myeloperoxidase (MPO), cCD3 and Kappa. All results above revealed the patient with mature B-cell neoplasm, in which B-PLL, mantle cell lymphoma (MCL), a variant form of hairy cell leukemia (HCL-V) and splenic marginal zone lymphoma (SMZL) were highly suspicious types (Fig. 1).

Cytogenetics

Cells were cultured in penicillin (100U/mL), streptomycin (100 fig/mL), and 10% fetal calf serum (FCS) in the presence of TPA (0.05 pg/mL final concentration) RPMI. Cells were harvested after 3 and 5 days of culture, and treated with hypotonic solution (075 mol/L, KCI0, 10 min, 37 °C) after (0.1 pg/mL colcemid, 60 min) mitotic arrest and with acetic acid/methanol (l:3) fixed. Metaphase chromosomes G banded were applied according to universal methods.

Fluorescence in situ hybridization (FISH) analysis: hypotonically fixed cells were placed drop-wise on slides and with fluorescent probes against 5q, 7q, 20q12, +8, −Y, RB1, 1q21, D13S319 and IgH hybridized for 16 h.

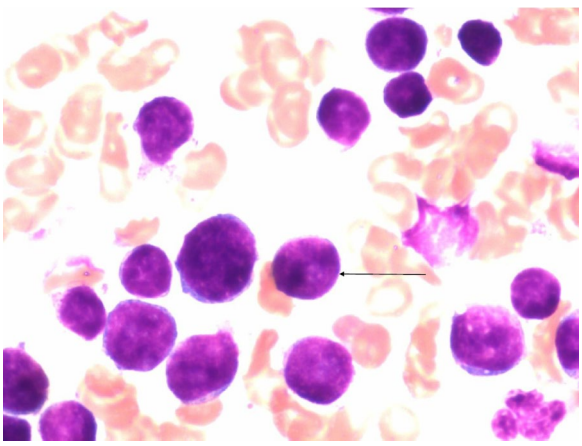

Fig. 1 The result of bone marrow morphology of B-cell prolymphocytic leukemia [() prolymphocytes are medium-sized lymphoid cells with a round nucleus, moderately condensed nuclear chromatin, a prominent central nucleolus, and basophilic cytoplasm]

Under a fluorescence microscope cells were observed after staining with DAPI, the for fluorescence signals measurement. FISH was used to detect cytogenetic abnormalities. According to FISH results, three red, and three green fluorescent signals were observed by using two pairs of probes, CSF1R/D5S23, D5S7213(5q33) and EGR1/D5S23, D5S721(5q31), which were located in 5, that means it has an extra trisomy 5 (Fig. 2) and the detection of t (11;14) (q13; q32) translocation by CCND1/IGH probe was negative. We also used other probes, which are located in 7q31, 20q12,+8, ATM (11q22.3), RB1 (13q14), D13S25 (13q14.3), P53 (17p13.1), IGH, D13S319, and 1q21 that associated with chromosomal changes of CLL, MM, and MDS, but there was no positive result. The Karyotype analysis was performed using a standard protocol. It revealed that 49, XY,+ 5, del(5)(q13), add(8)(p23),+ 15, add(17)(q25),+19[cp20] (Fig. 3), which was the same as the FISH results (Figs. 2, 3).

Molecular biology

qRT-PCR was utilized to determine the molecular abnormality in bone marrow cells from the patient. However, we did not observe any positive result on 43 kinds of fusion genes detection, such as breakpoint cluster region/Abelsen (BCR/ABL), promyelocytic leukemia/retinotic acid receptor alpha (PML/RARA), a core-binding factor β myosin heavy chain11 (CBFB/MYH11), acute myeloid leukemia 1/eight-twenty one (AML1/ETO), mixed-lineage leukemia (MLL) gene rearrangement (Table 1). Genomic material was extracted for targeted gene mutation panel by NGS technology. Bioinformatics and statistics were used to determine the association between clinical features and gene mutations also discuss of our results with the Cancer Genome Atlas Research Network (TCGA) public dataset. NGST was used to detect 41 kinds of mutant genes related to hematological malignancies, and the results showed mutation rates of SETBP1 and PML were 51.06% and 98.54% (Table 2). PCR determination of B cell clonal immunoglobulin gene rearrangements showed the positive result of B cell monoclonality.

Treatment

The patient of study was diagnosed with B-cell prolymphocytic leukemia. He underwent emergent leukapheresis accompanied by basification of urine and hydrotherapy. Then, we started on a regimen of cyclophosphamide and dexamethasone instead of fludarabine, considering the patient and his family conditions, including their poor economic incomes and the patient's age. After 10-day therapy, the patient attained slightly stable and improving conditions with normal temperature, significantly decreased white cell count and safe levels of hemoglobin and platelet. He left our hospital against medical advice without continuous supportive treatment, and observation. He died at the local hospital 11 days after leaving our hospital. The family declined an autopsy. No further studies can be performed due to the patient's death.

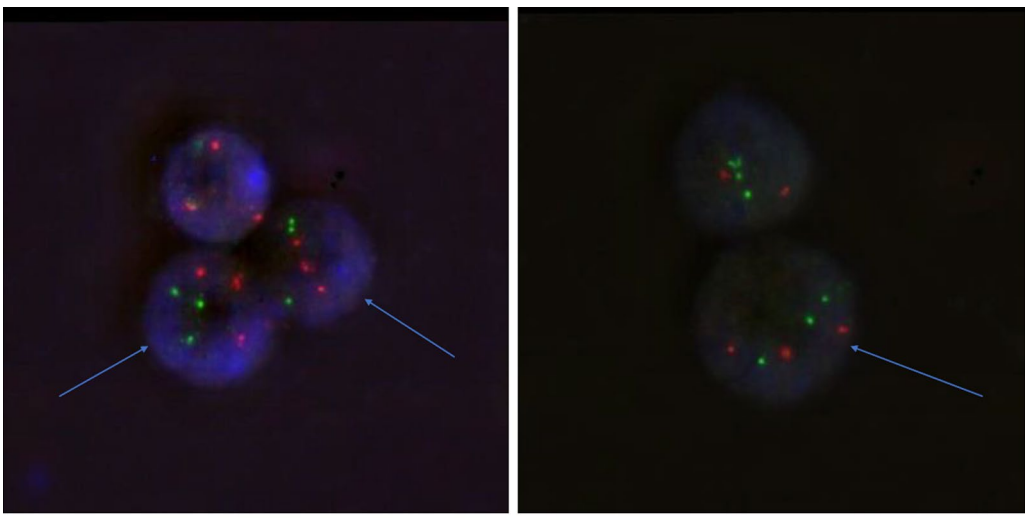

Fig. 2 The FISH analysis results with red (color) and green (color) probing of interphase B-cell prolymphocytic leukemia displaying **a** normal fusion signal and **b** split signal (arrow) red 5′ centromeric region and (arrow) green 3′ telomeric region

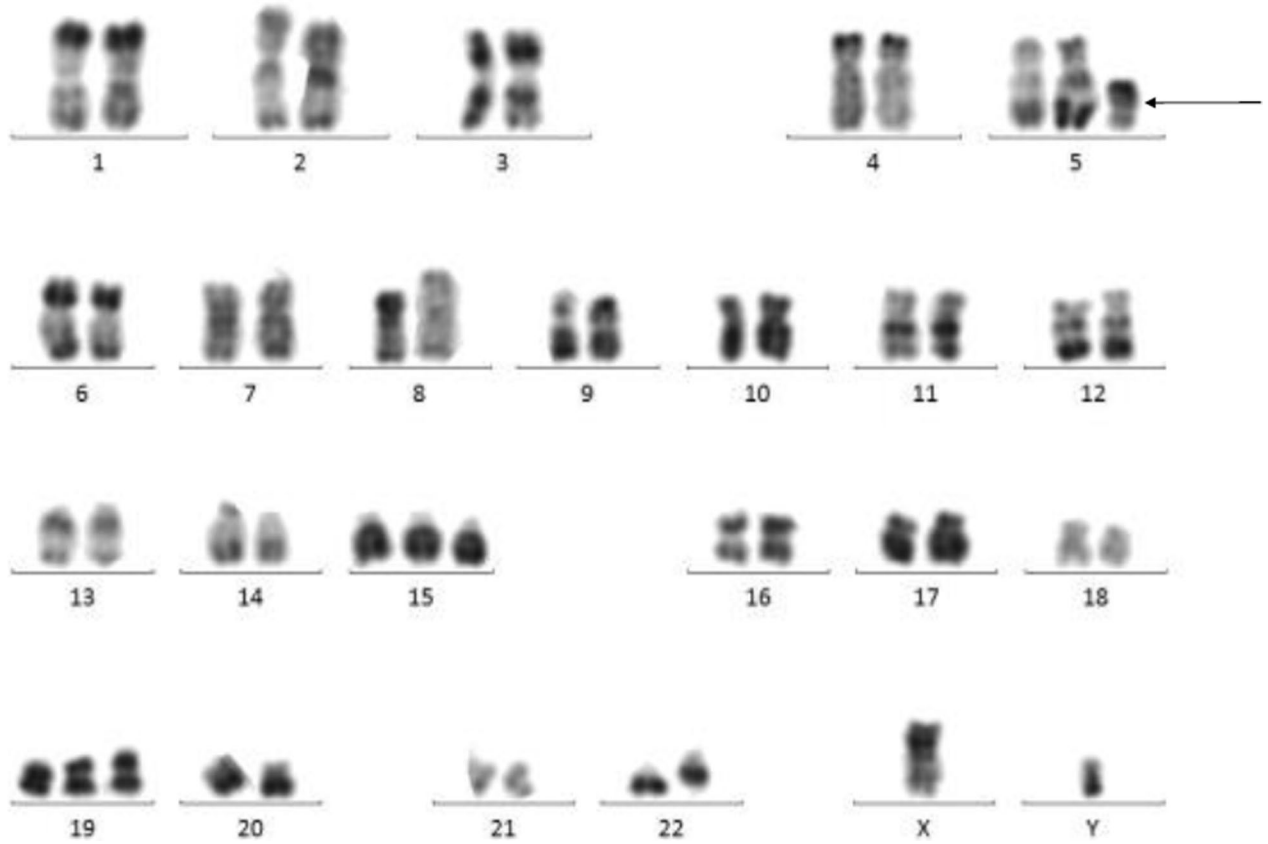

Fig. 3 The R-banded complex karyotype results representing the new B-cell prolymphocytic leukemia trisomy of 15, 19 and 5 (arrow)

Table 1 The screening results of fusion genes detected with qRT-PCR method

Fusion gene	Result	Fusion gene	Result	Fusion gene result	Result	Fusion gene	Result
BCR-ABL	–	SIL-TAL1	–	MLL-AF4	–	FIP1L1-PDGFRA	–
AML1-ETO	–	NPM-MLF1	–	MLL-AF6	–	ETV6-PDGFRA	–
AML1-MDS1/EVI1	–	NPM-ALK	–	MLL-AF9	–	DEK-CAN	–
AML1-MTG16	–	CBFB-MYH11	–	MLL-AF10	–	SET-CAN	–
PML-RARa	–	E2A-HLF	–	MLL-AF17	–	NUP98-HoxA9	–
NPM-RARa	–	E2A-PBX1	–	MLL-ELL	–	NUP98-HoxA11	–
FIP1L1-RARa	–	TLS-ERG	–	MLL-ENL	–	NUP98-HoxA13	–
PRKAR1A-RARa	–	TEL-JAK2	–	MLL-AF1q	–	NUP98-HoxC11	–
NUMA1-RARa	–	TEL-AML1	–	MLL-AF1p	–	NUP98-HoxD13	–
PLZF-RARa	–	TEL-ABL	–	MLL-AFX	–	NUP98-PMX1	–
STAT5b-RARa	–	TEL-PDGFRB	–	MLL-SEPT6	–		

"–" Means there was no positive result found

Discussion

We described a case of B-PLL carrying trisomy 5 with complex karyotype abnormalities, which was determined by conventional karyotype analysis and interphase/metaphase FISH. It is known that the B-PLL diagnosis is challenging because of superposition with MCL, HCL-V, or SMZL mature B-cell leukemia and lymphoma. The 72-year-old patient exhibited the typical features of B-PLL, lymphocytosis, splenomegaly, and B-symptoms. Though the patient was old, the results of morphology and immunology detection, as well as rapid and marked increase in the peripheral white cell count, were

Table 2 The screening results of gene mutation detected by next-generation sequencing

Gene	Result	Gene	Result	Gene	Result	Gene	Result
FLT3	–	ASXL1	–	SETBP1	51.06%[a]	PML	98.54%[a]
NPM1	–	PHF6	–	ETV6	–	WT1	–
KIT	–	TP53	–	IKZF1	–	PTPN11	–
CEBPA	–	SF3B1	–	PAX5	–	CDKN2A	–
DNMT3A	–	SRSF2	–	JAK1/JAK2	–	CDKN2B	–
IDH1	–	U2AF1	–	CRLF2	–	NT5C2	–
IDH2	–	ZRSR2	–	NOTCH1	–	SMC1A	–
TET2	–	NRAS	–	FBXW7	–	SMC3	–
EZH2	–	CBL	–	PTEN	–	STAG2	–
FAM5C	–	RUNX1	–	CREBBP	–	RAD21	–

"–" Means there was no positive result found

[a] Percentage means the mutant proportion of mutant gene in detected samples

observed, which were both different from the features of CLL. The diagnosis requirements of more than 55% of the lymphocytes in the peripheral blood are prolymphocytes, medium-sized cells with prominent central clumped chromatin nucleoli, and typical immune-phenotype, the expression of the B-cell antigens CD19, 20, 22 and 79a were present [8, 9]. Moreover, the absence of t(11;14)(q13;q32) helped exclude MCL. Smooth outline of the blast cells, B-symptoms, higher WBC ($>100\times10^9$/L), and clinical course much more attributes of B-PLL compared to HCL-V or SMZL. Research in sixty subjects showed that splenomegaly was the most prevalent feature of B-PLL [7]. However, the molecular pathogenesis of B-PLL is still largely unknown. As for studies reported, complex karyotype and abnormalities in the TP53 tumor suppressor gene might be common events in B-cell PLL [9–12]. Moreover, deletions at 11q23, 13q14, and trisomy (especially 12) were found [11, 14–17]. A few case studies have reported transformed B-PLL and CLL, MYC translocations, including t(8;14) [11, 12, 16–18].

Because gene fusions are crucial factors for risk stratification in leukemia risk-adapted therapy, gene fusion is indispensable diagnostic testing part. In the present work, fusion gene panels and clinical utility were analyzed based on targeted NGS for leukemia diagnosis. 41 kinds of mutant genes related to hematological malignancies, and the results showed mutation rates of SETBP1 and PML were 51.06% and 98.54% (Table 2). PCR determination of B cell clonal immunoglobulin gene rearrangements showed the positive result of B cell monoclonality [19, 20].

Unfortunately, we did not carry on an optimal individualized treatment regimen considering his economic income and their wishes. However, the choice of personalized treatment regimen is always the critical point in research of hematological disorders. A study on four patients with PLL was carried out, whose age ranged between 55 and 84 years, with the leucocyte count above 180/nL, β2-microglobulin and LDH higher with a median of 4.2 mg/L and284 U/L, respectively. The results showed that 4 patients achieved a complete remission with immune-chemotherapy fludarabine, epirubicin, and rituximab (FER regimen). It provided an impetus for further evaluation of the treatment schedule offered in a larger number of PLL patients [16–21]. Previous reports report the successful B-PLL treatment with monotherapy rituximab, while the durability responses were short [16–22]. All in all, integration of rituximab together with bendamustine or fludarabine with epirubicin or mitoxantrone (FER, BMR, and FMR) as anthracycline has been showed to be efficient in B-PLL [16, 22–26]. Some experts suggest that to patients with no TP53 abnormalities the usual approach is applying this regimen as cornerstone therapy. Alemtuzumab is vital in the treatment for B-PLL patients with mutations and/or deletions of TP53. Also, antagonists targeting molecules for the B-cell receptor as PI3 Kinase delta (PI3Kd) and Burton's Tyrosine Kinase, may also have efficacy in B-PLL, including TP53 abnormalities cases. However, ofatumumab, GA101, or new anti-CD20 mAbs have not been assessed in B-PLL. Recent researches revealed that idelalisib, a powerful oral and selective PI3Kd inhibitor, combined with rituximab responses was found to be clinically meaningful and rapid in B-PLL patients with disrupted TP53 [21–27]. Also, Gordon et al. stated that two B-PLL patients, with del(17p), responded to ibrutinib single therapy, an oral inhibitor of Burton's tyrosine kinase, involved in signal transduction of B-cell receptor. Two patients treated with ibrutinib for months reached normal absolute count of lymphocyte, hemoglobin and platelet [26–36]. At last, the only therapeutic approach

in B-PLL and should be taken into account for younger subjects remain the allogeneic hematopoietic stem cell transplant (allo-HSCT).

Conclusion

In conclusion, complex karyotypic abnormalities and aberrations in TP53 probably indicated the B-PLL poor prognosis. Even deficiency of efficient established therapeutic modalities, FMR, FER, BMR, alemtuzumab, idelalisib-rituximab and ibrutinib all exhibited remarkable effect on therapy of B-PLL patients. Taking the cost of treatment into account, more economical and effective regimens should be researched to make sure that patients can afford them. Further molecular profiling and cytogenetic studies remain to be performed to define genetic aberration clearly, such as trisomy 5. While we did not demonstrate the role of trisomy 5 on B-PLL, we put emphasis on specific cytogenetic and molecular abnormalities, which could promote the deep-going research in the field of B-PLL.

Abbreviations

B-PLL: B-cell prolymphocytic leukemia; FISH: Fluorescence in situ hybridization; qRT-PCR: Quantitative real-time polymerase chain reaction; NGS: Next-generation sequencing; CLL: Chronic lymphocytic leukemia; BM: Bone marrow; LDH: Lactate dehydrogenase; BCR/ABL: Breakpoint cluster region/Abelsen; PML/RARA: Promyelocytic leukemia/retinotic acid receptor alpha; CBFB/MYH11: Core-binding factor β myosin heavy chain11; AML1/ETO: Acute myeloid leukemia 1/eight-twenty one; MLL: Mixed-lineage leukemia; WHO: World Health Organization.

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Authors contributions

MM, MM MAR, YY, JS, GL, NH, SAAEK, DM are shared in designing the research report, processing the samples, interpretation the patient data regarding the hematological disease and writing the case report and read and approved the final manuscript. All authors equally contributed.

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Availability of data and materials

Data and materials are available upon request.

Declarations

Ethics approval and consent to participate

The research methodology in the present work was approved by research ethical committee of Shandong University, and written informed consent was obtained from participant family enrolled in the case report prior to sample collection. Experimental procedures and sampling followed the international and national regulations in accordance with the Declaration of Helsinki.

Consent for publication

The authors grant the publisher permission to publish this work.

Competing interests

All authors declare that they have no competing interests.

Author details

[1]Department of Hematology, Shandong University-Qilu Hospital, Jinan, China. [2]Department of Applied Medical Chemistry, Alexandria University-Medical Research Institute, Alexandria, Egypt.

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