BCOR mutation and *TLS-ERG* expression in acute myeloid leukemia with monoclonal immunoglobulinemia

This article was published in the following Dove Press journal:
OncoTargets and Therapy

Jingxia Jin
Shuna Luo
XingNong Ye
Jian Huang

Department of Hematology, The Fourth
Affiliated Hospital, Zhejiang University
School of Medicine, Yiwu, Zhejiang
322000, People's Republic of China

Abstract: Acute myeloid leukemia (AML) originates from the abnormal clonal proliferation of myeloblasts. Immunoglobulin is secreted by B cells. AML with monoclonal antibody often indicates a poor prognosis. Here we report a case of *BCOR* mutation and *TLS-ERG* expression in AML with monoclonal immunoglobulinemia. After chemotherapy, the patient achieved bone marrow complete remission. *BCOR* mutation and *TLS-ERG* fusion gene in patient's bone marrow were not detected, at the same time, peripheral blood monoclonal immunoglobulin also disappeared. *BCOR* mutation or *TLS-ERG* fusion gene expression is associated with poor prognosis, AML with monoclonal immunoglobulin may have the same prognostic significance.

Keywords: acute myeloid leukemia, bone marrow, monoclonal immunoglobulin, TLS-ERG, *BCOR*

Introduction

Acute myeloid leukemia (AML) originates from the abnormal clonal proliferation of myeloblasts which often combined with clinical symptoms such as infection, fever, hemorrhage and anemia. Cytogenetic and molecular abnormalities are frequent in AML patients. To date, the driver genes for leukemia remain largely undiscovered. Monoclonal immunoglobulinemia is a group of diseases caused by excessive proliferation of plasma cells or immunoglobulin-producing lymphoid plasma cells and B lymphocytes. It can develop into malignant plasma cell disease. Herein, we report an AML patient was concomitant with monoclonal immunoglobulinemia, the patient was also accompanied by *BCOR* mutation and *TLS-ERG* fusion gene.

Patients and methods

Patients

A 55-year-old female was admitted to the hospital due to “repeated edema of both lower limbs for 3 weeks, and white blood cells count increase for 1 day” on August 20, 2018. Before admission, she did not receive any treatment. On admission, physical examination: except for edema of both lower limbs, all other signs were negative, peripheral blood counts: PLT $142 \times 10^9/L$, Hb 77 g/L, and WBC $35.2 \times 10^9/L$.

Bone marrow examination showed the mononuclear cell system proliferated actively, and the primitive monocytes accounted for 86%. Cell morphology

Correspondence: Jian Huang
Department of Hematology, The Fourth
Affiliated Hospital, Zhejiang University
School of Medicine, N1 Shangcheng Road,
Yiwu, Zhejiang 322000, People's Republic
of China
Tel +86 1 886 796 1032
Fax +86 5 798 993 5555
Email househuang@zju.edu.cn

suggested M5b (Figure 1A). Bone marrow pathology: acute non-lymphocytic leukemia, with MPO (positive), CD34 (positive), CD117 (positive). Fusion gene screening in bone marrow revealed that *TLS-ERG* expression, all screened genes are shown in Table 1. Immunophenotype of bone marrow cell: Abnormal

myeloid primitive cells accounted for 96.39% of the nuclear cells, express CD33, CD13, CD123, CD34, CD9, MPO (Figure 1D). Medium express CD117, CD38, CD11b, CD64, CD56. Weak express HLA-DR. Karyotype analysis of bone marrow cells: 46, XX, +1, der(16)der(1:16)(q10;p10)t(16;21)(p11;q22), der(21)t

Figure 1 Laboratory results of this patient. (A) The morphology of bone marrow (BM). (B) The karyotype of BM cells. (C) Immunofixation electrophoresis of peripheral blood. (D) The immunophenotype of BM cells.

Table 1 All screened fusion gene

1. BCR-ABL	2. PML-RARA	3. AMLI-ETO	4. CBFβ-MYH11	5. MLL-AF9
6. MLL-AF4	7. MLL-ENL	8. MLL-AF10	9. MLL-SEPT6	10. MLL-ELL
11. MLL-AF17	12. MLL-AF1q	13. MLL-AF1p	14. MLL-AF6	15. NPM-RARA
16. PLZF-RARA	17. AMLI-MDS1/EV11	18. AMLI-MTG16	19. TEL-ABL	20. TELJAK2
21. TEL-AML1	22. TEL-PDGFRB	23. E2A-PBX1	24. E2A-HLF	25. SIL-TAL1
26. FIP1L1-PDGFR	27. DEK-CAN	28. NPM-MLF1	29. STAT5B-RARA	30. ETV6-PDGFR
31. NUP98-HOXA13	32. UP98-HOXC11	33. UP98-HOXD13	34. NUP98-HOXA9	35. NUP98-HOXA11
36. NUP98-PMX1	37. MLL-AFX	38. FIPL1-RARA	39. PRKARIA-RARA	40. NUMAI-RARA
41. NPM-ALK	42. SET-CAN	43. TLS-ERG		

Table 2 Next-generation DNA sequencing of bone marrow

Gene	Mutation site	Nucleotide	Amino acid	DbSNP	Rate%
BCOR	Exon12	c.4586_4589del	p.G1529Efs*4	—	51.7
PLCG1	Intron29	c.3556+4A>G	—	—	49.9
DIS3	Exon14	c.1760C>T	p.s587F	rs144957541	48.4
JAK3	Exon6	c.665G>A	p.R222H	rs19986895	49.0
BRAF	Exon1	c.64G>A	p.D22N	rs397507456	51.6
JAK2	Exon5	c.380G>A	p.G127D	Rs56118985	45.1

(16;21)(p11;q22) (Figure 1B). Thus, next-generation DNA sequencing (NGS) technology showed that *BCOR* (51.7%), *PLCG1* (49.9%), *DIS3* (48.4%), *BRAF* (51.6%), *JAK2* (45.1%), *JAK3* (49.0%) were mutated in bone marrow (Table 2). Surprisingly, we found that peripheral blood immunofixation electrophoresis showed that gamma region is seen with a monoclonal light chain lambda component (Figure 1C). Laboratory examinations showed high level of LDH 3261 U/L (range 120–250 U/L), globulin 28.1 g/L (range 20–40 g/L), albumin 37.3 g/L (range 40–55 g/L), β -MG 2.08 mg/L (range 1.0–3.0 mg/L), calcium 2.12 mmol/L (range 2.11–2.52 mmol/L), IgM 1.61 g/L (range 0.46–3.04 g/L), IgA 1.8 g/L (range 0.82–4.35 g/L), and IgG 10.7 g/L (range 7.51–15.60 g/L). Urine kappa light chain 13.7 mg/L (range 0–20 mg/L), urine lambda light chain <3.72 mg/L (range 0–50 mg/L), blood kappa light chain 2.12 g/L (range 1.70–3.70 g/L), blood lambda light chain 1.62 g/L (range 0.9–2.1 g/L), creatinine: 61 μ mol/L (range 41–73 μ mol/L). According to the clinical symptoms and pathological results, final diagnosis of acute monocytic leukemia, subtype M5b, with *BCOR* mutation and *TLS-ERG* expression was confirmed.

Methods

High-throughput gene sequencing was carried out by ultra-high multiple PCR exon enrichment technology with an average sequencing depth of 800 $\times$. Mutation analysis was performed by Ion Reporter System and Variant Reporter Software. Once diagnosed, the patient underwent one cycle of IA (Idarubicin 10 mg d1-4, cytarabine 0.075 g q12 h d1-7).

Ethics statement

This study has been approved by the Ethics Committee of the Fourth Affiliated Hospital of Zhejiang University. Before collecting clinical isolates from the patient, we

informed her of our research purposes and written informed consent for participation in the study was obtained. Written informed consent for publication of the case details and clinical images was obtained from the patient.

Results

Twenty-five days after chemotherapy onset, bone marrow examination showed that primitive and immature monocytes accounted for 3%. Chromosome analysis showed 46, XX karyotype without any cytogenetic abnormalities. Minimal residual disease: Abnormal myeloid primitive cells accounted for 0.01%. Fusion gene detection showed that *TLS-ERG* turned negative. *BCOR* mutation was not detected by NGS. Mutations of *PLCG1*, *DIS3*, *BRAF*, *JAK2*, *JAK3* still exist. The disease reached complete remission (CR). Peripheral blood immunofixation electrophoresis turned negative.

Discussion

AML is the most common malignancy in the hematologic system which mainly derives from the malignant-cloned monoclonal of the granulocyte stem cell.^{1,2} The pathogenesis of monoclonal immunoglobulinemia is unknown, as clones derive from plasma cells, mutations and tumors of B-generation hematopoietic precursor cells, chronic infections, connective tissue diseases, etc., can stimulate excessive proliferation of monoclonal immunoglobulins in plasma B cells.³ According to WHO 2008 diagnostic criteria, the serum monoclonal immunoglobulin (Ig) concentration in monoclonal gammopathy of undetermined significance (MGUS) patients was <30 g/L, and the bone marrow plasma cells were <10%, and there were no lytic bone lesions, hypercalcemia, anemia or renal insufficiency associated with the proliferation of monoclonal plasma cells. Monoclonal immunoglobulinemia and AML are both clonal diseases, but originated from different clones. Clinically, hematological diseases with

MGUS are frequent, but there are few literature reports and researches. Roeker L E observed 605 cases of MGUS and found that the risk of developing acute leukemia (ALL or AML) or myelodysplastic syndromes (MDS) was 1.83 times higher in MGUS patients than controls.⁴ Mailankody S also observed a higher risk for AML/MDS following MGUS (SIR 8.01, 95% CI 5.40–11.43).⁵ Fei Li has reported two cases of MDS with high monoclonal immunoglobulin, one of which was classified as MDS-RAEB-t according to the original FAB classification and AML according to the WHO classification in 2008.⁶ But none of them elucidated the underlying biological mechanisms. According to WHO 2008 diagnostic criteria, this case was diagnosed as MGUS. In this case, through NGS, it was found that AML patients with MGUS may have abnormal-mutated genes, which may provide a little clue.

Genetic changes are a danger for clonal diseases. With the application of next-generation sequencing in leukemia, more and more genes are being discovered. In this case, AML patients with MGUS, by comparing CR before and after we found that while the patient's M protein turned negative, the *TLS-ERG* fusion gene and *BCOR* gene mutation also disappeared. The *TLS-ERG* fusion gene is formed by the rearrangement of *TLS* and *ERG* genes on chromosomes 16 and 21. The *TLS-ERG* leukemia fusion protein inhibits E1A pre-mRNA splicing.⁷ The current study holds that the expression of this fusion gene indicates rapid disease progression and poor prognosis.⁸ *BCOR* mutations can be found in AML, chronic myelomonocytic leukemia (CMML), MDS, aplastic anemia, and often coincide with *DNMT3* gene mutations, suggesting that it may affect the occurrence of leukemia through epigenetics.⁹ Through whole-exome Sequencing, some scholars found that *BCOR* mutations in AML with normal karyotype (3.8%), in AML without *NPM1*, *CEBPA*, *FLT3-ITD*, or *IDH1* and *MLL-PTD* mutations (17.1%), in with *DNMT3A* mutated (43.5%).¹⁰ Frederik Damm also found that *BCOR* mutations in MDS (4.2%) and CMML (7.4%).¹¹ The *BCOR* gene is located on p11.4 of chromosome X and encodes an ubiquitously expressed nuclear protein.¹² *BCOR* mutations are often coincided with other genes, and *BCOR* mutations are associated with poor prognosis.¹¹ *BCOR* is a newly discovered corepressor of BCL-6, which can play a supporting role when *BCOR* combines with DNA; when *BCOR* is overexpressed, it can enhance the inhibition of BCL-6. BCL-6 is highly expressed in tumor

cells,^{13,14} it encodes transcriptional repressors which are required for the formation of the germinal center and may affect apoptosis.¹⁵ Bcl-6 inhibits the differentiation of germinal center B cells into plasma cells.

Conclusion

Patients with *TLS-ERG* fusion gene which is a poor prognosis gene. AML with monoclonal antibody also indicates a poor prognosis. *BCOR* abnormal expression may increase the inhibitory effect of BCL-6 and affect the apoptosis of B cells, and B cells continue to secrete immunoglobulin. *BCOR* may affect plasma cell function. Indicating that monoclonal immunoglobulinemia may have relationships with *BCOR* mutation. However, little studies have focused on the *BCOR* gene mutation site up to now. Whether the *BCOR* gene mutation results in the combination of the AML and MGUS requires further investigation.

Acknowledgments

The research was supported by fundings of the Science and Technology Department of Zhejiang Province, China (2016C33160), the Public Technology Research Projects of Yiwu, China (2016-S-05), and the Key Medical Discipline of Yiwu, China (Hematology, 2018-2020).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Passequé E, Jamieson CH, Ailles LE, Weissman IL. Normal and leukemic hematopoiesis: are leukemias a stem cell disorder or a reacquisition of stem cell characteristics? *Proc Natl Acad Sci U S A*. 2003;100(Suppl 1):11842–11849. doi:10.1073/pnas.2034201100
2. Hope KJ, Jin L, Dick JE. Acute myeloid leukemia originates from a hierarchy of leukemic stem cell classes that differ in self-renewal capacity. *Nat Immunol*. 2004;5(7):738–743. doi:10.1038/ni1080
3. Bida JP, Kyle RA, Therneau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. *Mayo Clin Proc*. 2009;84(8):685–693. doi:10.1016/S0025-6196(11)60518-1
4. Roeker LE, Larson DR, Kyle RA, et al. Risk of acute leukemia and myelodysplastic syndromes in patients with monoclonal gammopathy of undetermined significance (MGUS): a population-based study of 17,315 patients. *Leukemia*. 2013;27(6):1391–1393. doi:10.1038/leu.2013.34
5. Mailankody S, Pfeiffer RM, Kristinsson SY, et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). *Blood*. 2011;118(15):4086–4092. doi:10.1182/blood-2011-05-355743
6. Fei L, Hai-Yan Z. A report of two cases of myelodysplastic syndrome with increased monoclonal immunoglobulin. *J Clin Exp Med*. 2011;10(10):735-736. doi:10.3969/j.issn.1671-4695.2011.10.008

7. Yang L, Embree LJ, Hickstein DD. TLS-ERG leukemia fusion protein inhibits RNA splicing mediated by serine-arginine proteins. *Mol Cell Biol.* **2000**;20(10):3345–3354. doi:10.1128/MCB.20.10.3345-3354.2000
8. Zhang Z, Zou J, Yuantang LI, et al. Clinical characteristics and laboratory analyses of acute myeloid leukemia with t(16;21)(p11; q22). *Oncol Lett.* **2015**;9(5):2244–2248. doi:10.3892/ol.2015.3051
9. Fan Z, Yamaza T, Lee JS, et al. BCOR regulates mesenchymal stem cell function by epigenetic mechanisms. *Nat Cell Biol.* **2009**;11(8):1002. doi:10.1038/ncb1826
10. Damm F, Chesnais V, Nagata Y, et al. BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. *Blood.* **2013**;122(18):3169–3177. doi:10.1182/blood-2012-11-469619
11. Grossmann V, Tiacchi E, Holmes AB, et al. Whole-exome sequencing identifies somatic mutations of BCOR in acute myeloid leukemia with normal karyotype. *Blood.* **2011**;118(23):6153–6163. doi:10.1182/blood-2011-07-365320
12. Wamstad JA, Bardwell VJ. Characterization of Bcor expression in mouse development. *Gene Expr Patterns.* **2007**;7(5):550–557. doi:10.1016/j.modgep.2007.01.006
13. Ye BH, Lista F, Lo Coco F, et al. Alterations of a zinc finger-encoding gene, BCL-6, in diffuse largecell lymphoma. *Science.* **1993**;262(5134):747–750. doi:10.1126/science.8235596
14. Ye BH, Cattoretti G, Shen Q, et al. The BCL-6 proto-oncogene controls germinal-centre formation and Th2-type inflammation. *Nat Genet.* **1997**;16(2):161–170. doi:10.1038/ng0697-161
15. Huynh KD, Fischle W, Verdin E, Bardwell VJ. BCOR, a novel corepressor involved in BCL-6 repression. *Genes Dev.* **2000**;14(14):1810–1823.

OncoTargets and Therapy

Dovepress

Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic

agents and protocols on patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/oncotargets-and-therapy-journal>