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

**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 142×10⁹/L, Hb 77 g/L, and WBC 35.2×10⁹/L.

Bone marrow examination showed the mononuclear cell system proliferated actively, and the primitive monocytes accounted for 86%. Cell morphology...
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. AML1-ETO | 4. CBFI-MYH11 |
| 6. MLL-AF4 | 7. MLL-ENL | 8. MLL-AF10 | 9. MLL-SEPT6 |
| 11. MLL-AF17 | 12. MLL-AF1q | 13. MLL-AF1p | 14. MLL-AF6 |
| 16. PLZF-RARA | 17. AML1-MDS1/EVI1 | 18. AML1-MTG16 | 19. TEL-ABL |
| 21. TEL-AML1 | 22. TEL-PDGFRB | 23. E2A-PBX1 | 24. E2A-HLF |
| 26. FIP1L1-PDGFRA | 27. DEK-CAN | 28. NPM-MLF1 | 29. STAT5B-RARA |
| 31. NUP98-HOXA13 | 32. UP98-HOXC11 | 33. UP98-HOXD13 | 34. NUP98-HOXA9 |
| 36 NUP98-PMXI | 37. MLL-AFX | 38. FIP1L1-RARA | 39. PRRKARIA-RARA |
| 41. NPM-ALK | 42. SET-CAN | 43. TLS-ERG | 44. FIP1L1-RARA |
| 45. FIPLL1-RARA | 46. SET-CAN | 47. TLS-ERG | 48. PRKARIA-RARA |
| 49. PRKARIA-RARA | 50. NUP98-PMXI | 51. MLL-AFX | 52. SET-CAN |
| 53. FIP1L1-RARA | 54. PRKARIA-RARA | 55. NUP98-PMXI | 56. MLL-AFX |
| 57. SET-CAN | 58. TLS-ERG | 59. NUP98-PMXI | 60. MLL-AFX |
(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 µmol/L (range 41–73 µmol/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×. 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

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   | p.s587F   | rs14957541  | 49.9  |
| DIS3  | Exon14        | c.1760C>T     | p.R222H   | rs19986895  | 49.0  |
| JAK3  | Exon6         | c.665G>A      | p.D22N    | rs397507456 | 51.6  |
| BRAF  | Exon1         | c.380G>A      | p.G127D   | Rs56118985  | 45.1  |

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MGUS are frequent, but there are few literature reports and researches. Roeker LE 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. Mailankody S also observed a higher risk for AML/MDS following MGUS (SIR 8.01, 95% CI 5.40–11.43). Fei Li has reported two cases of MDS with monoclonal immunoglobulin, one of which was classified as MDS-RAEB-1 according to the original FAB classification and AML according to the WHO classification in 2008. 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 premRNA splicing. The current study holds that the expression of this fusion gene indicates rapid disease progression and poor prognosis. 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. 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%). Frederik Damm also found that BCOR mutations in MDS (4.2%) and CMML (7.4%). The BCOR gene is located on p11.4 of chromosome X and encodes an ubiquitously expressed nuclear protein. BCOR mutations are often coincided with other genes, and BCOR mutations are associated with poor prognosis. 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, it encodes transcriptional repressors which are required for the formation of the germinal center and may affect apoptosis. 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.

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**Disclosure**

The authors report no conflicts of interest in this work.

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