

# Acute myeloid leukemia with *CPSF6*–*RARG* fusion resembling acute promyelocytic leukemia with extramedullary infiltration

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**Abstract:** Some subtypes of acute myeloid leukemia (AML) share morphologic, immunophenotypic, and clinical features of acute promyelocytic leukemia (APL), but lack a *PML*–*RARA* (promyelocytic leukemia–retinoic acid receptor alpha) fusion gene. Instead, they have the retinoic acid receptor beta (*RARB*) or retinoic acid receptor gamma (*RARG*) rearranged. Almost all of these AML subtypes exhibit resistance to all-trans retinoic acid (ATRA); undoubtedly, the prognosis is poor. Here, we present an AML patient resembling APL with a novel cleavage and polyadenylation specific factor 6 (*CPSF6*)–*RARG* fusion, showing resistance to ATRA and poor response to chemotherapy with homoharringtonine and cytarabine. Simultaneously, the patient also had extramedullary infiltration.

**Keywords:** acute myeloid leukemia, *CPSF6*–*RARG* fusion, extramedullary infiltration, resemble acute promyelocytic leukemia, resistance to ATRA

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## Introduction

Acute promyelocytic leukemia (APL) is a special subtype of acute myeloid leukemia (AML), which is characterized by abnormal accumulation of promyelocytes in the bone marrow and peripheral blood. In these patients, the latter symptoms are often accompanied by serious coagulation abnormality. The majority of cases have a *PML*–*RARA* (promyelocytic leukemia–retinoic acid receptor alpha) fusion gene caused by a *t*(15; 17) translocation that leads to a unique sensitivity to therapy with all-trans retinoic acid (ATRA). The current treatment strategy combining with ATRA and arsenic trioxide (ATO) has greatly changed the prognosis of this once uniformly fatal disease.<sup>1</sup> Nevertheless, some AMLs resembling APL also revealed a proliferation of hypergranular promyelocytes and exhibited a life-threatening coagulopathy; unexpectedly, the *PML*–*RARA* fusion gene was negative. Instead, the retinoic acid receptor beta (*RARB*) or retinoic acid receptor gamma (*RARG*) gene was rearranged<sup>2–5</sup>; all of them were members of the nuclear receptor superfamily sharing high sequence homology (90%).<sup>6</sup> Almost

all of these subtypes of AML exhibit resistance to ATRA; undoubtedly, the prognosis is poor. Here, we present an AML patient resembling APL with a novel *CPSF6*–*RARG* fusion, showing resistance to ATRA and poor response to chemotherapy with homoharringtonine and cytarabine.

## Case description

A 67-year-old woman was admitted due to an oral hemorrhage and skin ecchymosis. Her blood test showed a white blood cell count (WBC) of  $1.6 \times 10^9/l$ , hemoglobin level (HGB) of 89 g/l, and platelet count (PLT) of  $49 \times 10^9/l$ . Fibrinogen and D-dimer levels were 0.5 g/l (reference 2.00–4.00) and 45,178 µg/l (reference 0–700). Positron emission tomography-computed tomography (PET-CT) revealed that masses of the right obturator internus and obturator externus had invaded the right pubic bone and affected the right edge of the cervix; multiple enlarged lymph nodes were present in the posterior peritoneum and beside the iliac arteries (Figure 1). A bone marrow (BM) smear revealed hypercellularity, with 72% hypergranular

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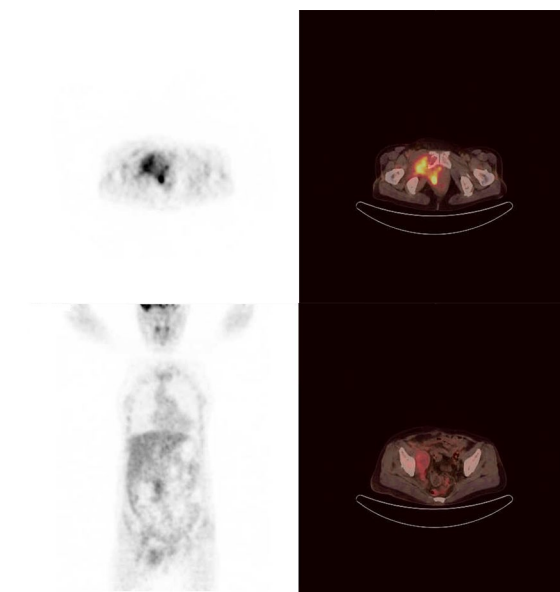
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promyelocytes (Figure 2A). The BM histochemistry showed a staining pattern of typical APL, being positive for POX, SB, and SE, and negative for NSE, PAS, and NAF. The leukemia cells expressed myeloperoxidase, CD13, and CD33, and partially expressed CD71, but lacked the expression of CD14, CD19, CD34, CD38, CD64, CD117, CD11b, CD11c, HLA-DR, and other T- or B-lymphoid-related markers (Figure 2D). Combining patient clinical manifestations, BM morphology, and immunophenotype, APL was highly suspected. She received ATRA starting on the second day of admission. However, *PML-RARA* was negative and fluorescence in situ hybridization (FISH) failed to detect the *PML-RARA* transcript in the BM (Figure 2B). Karyotype analysis revealed 46, XX [20] (Figure 2C). Meanwhile, we detected WT1 mutation by reverse-transcription (RT)-PCR. On day 9 after admission, blood tests showed a WBC of  $2.2 \times 10^9/l$ , HGB 56 g/l, and PLT  $37 \times 10^9/l$ .

Because there was no sign of differentiation and improvement of coagulopathy after 1 week of ATRA treatment, we initiated a homoharringtonine 2 mg d1-5, cytarabine 50 mg d1-7 (HA) regimen as induction therapy. To avoid exacerbating the coagulopathy, the doses of chemotherapy were decreased. On day 3 after chemotherapy, blood tests showed a WBC of  $5.2 \times 10^9/l$ , HGB 56 g/l, and PLT  $10 \times 10^9/l$ . At the same time, the patient progressed to anuria, a progressive increase in serum creatinine and BNP, with a poor diuretic effect. Considering acute renal failure, we discontinued ATRA and began continuous renal replacement therapy (CRRT) at the bedside for 6 days, then changed to three hemodialysis treatments per week. We performed a BM aspiration on day 12, revealed hypercellularity with 83% hypergranular promyelocytes. On day 15 after chemotherapy, a puncture of the right obturator internus mass was performed, and pathological analysis suggested that monocytelike cells had proliferated abnormally; a diagnosis of a hematopoietic malignant tumor was considered. Puncture flow cytometric analysis showed that AML cells accounted for 50.7%. The patient died due to an intracranial hemorrhage on day 17 after chemotherapy.

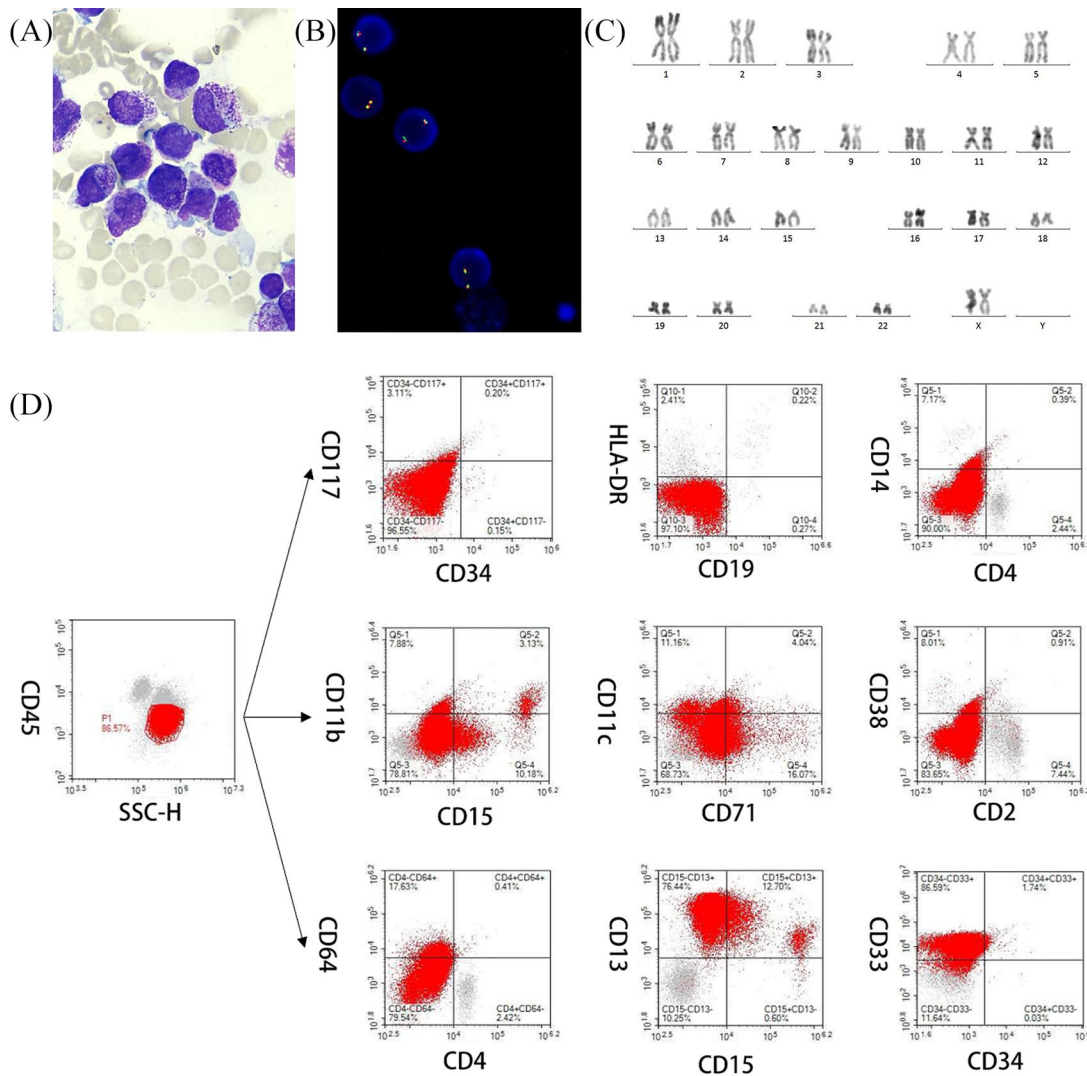
To clarify the molecular pathology, next-generation sequencing (NGS) was used on day 1 after chemotherapy. Total RNA from liquid bone marrow samples was extracted using the PureLink RNA Mini Kit (Thermo Fisher Scientific,



**Figure 1.** PET-CT revealed multiple swollen lymph nodes in the posterior peritoneum and beside the iliac arteries, accompanied by a slight increase in FDG metabolism. Masses of the right obturator internus and obturator externus invaded the right pubic bone and affected the right edge of the cervix, which were accompanied by increased FDG metabolism.

FDG,  $^{18}\text{F}$ -fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography.

Waltham, MA, USA). The library was constructed using a KAPA Stranded RNA-seq Kit with RiboErase (HMR) (KAPA Biosystems, Wilmington, MA, USA) according to manufacturer's instructions. Paired-end sequencing with a read length of 150bp were performed on an Illumina HiSeq<sup>TM</sup>4000 sequencer (Illumina Inc. San Diego, CA, USA). Raw data were mapped to human reference genome hg19 using FusionCatcher (version 0.99.4e). The NGS was based on genome GRCh37/hg19, which includes DNA sequencing and whole transcriptome mRNA sequencing. Mutational hotspots or whole coding regions of 88 genes that are known to be mutated frequently in hematologic malignancies were sequenced using a targeted gene panel (Nanjing Geneseeq Technology Inc., Nanjing, China). As expected, the NGS detected a fusion transcript within chromosome 12, in which *CPSF6* exon 4 (NM\_001300497) with *RARG* exon 4 (NM\_000966) were fused in-frame (Figure S1, Supplemental file S1). Furthermore, we identified co-mutations with *KRAS* exon 2 [NM\_004985.3: c.35G>C (p.G12A)] (Figure S2, Supplemental



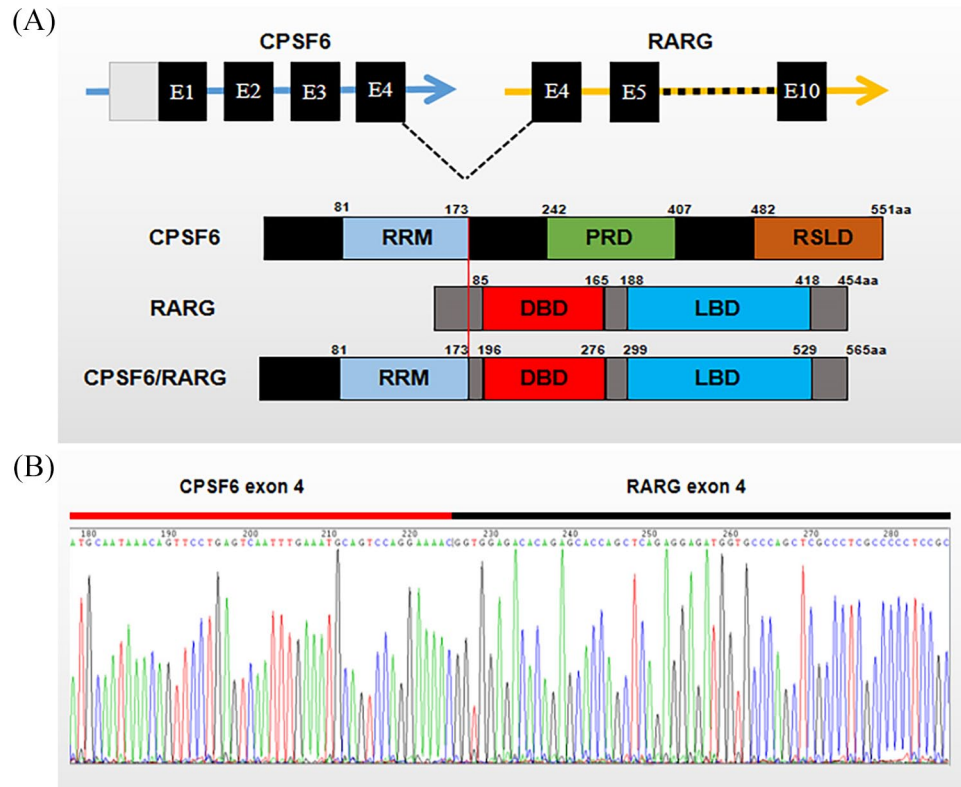
**Figure 2.** Morphology, immunophenotype, FISH analysis, and karyotyping. (A) Several promyelocytes, with hypergranulated cytoplasm and invaginated nuclei, are shown (Wright-Giemsa stained bone marrow smear,  $\times 1000$ ). (B) Interphase FISH revealed the absence of *PML-RARA* fusion signals in AML using *PML-RARA* dual-color, dual-fusion translocation probes. (C) G-banded karyotype showing 46, XX[20]. (D) The leukemia cells expressed myeloperoxidase, CD13, and CD33, and partially expressed CD71, but lacked the expression of CD14, CD19, CD34, CD38, CD64, CD117, CD11b, CD11c, and HLA-DR. AML, acute myeloid leukemia; FISH, fluorescence in situ hybridization; *PML-RARA*, promyelocytic leukemia-retinoic acid receptor alpha.

file S1), *EZH2* exon 20 (NM\_004456.4: c.2196\_2201delATACAG [p.R732\_Y733del]) (Figure S3, Supplemental file S1), and *EZH2* exon 20 [NM\_004456.4: c.2204\_2211delAGGCTGAT (p.Q735Rfs\*25)] (Figure S4, Supplemental file S1). To confirm the *CPSF6-RARG* fusion, we performed RT-PCR using the bone marrow sample and the following primers: forward (at *CPSF6* exon 2), 5'-TGGTGGACAA CAGATGAAGACT-3' and reverse (at *RARG*

exon4), 5'-CTTGCAGCCTTCACAAGAGC-3'. Sanger sequencing revealed that the fusion gene was the in-frame fusion of *CPSF6* exon 4 with *RARG* exon 4 (Figure 3B).

### Discussion

APL is a special subtype of AML. The majority of the patients express the *PML-RARA* fusion gene, which is the target for treatment with ATRA. Indeed,



**Figure 3.** Molecular analysis of the *CPSF6-RARG* fusion. (A) Schematic diagram of *CPSF6*, *RARG*, *CPSF6-RARG* fusion transcript, and the fusion protein of the patient. The breakpoint is indicated by a red line. (B) Sanger sequencing of the PCR product analysis of the *CPSF6-RARG* fusion transcript junctions revealed a fusion between exon 4 of the *CPSF6* gene and exon 4 of the *RARG* gene. *CPSF6*, cleavage and polyadenylation specific factor 6; *DBD*, DNA binding domain; *LBD*, ligand-binding domain; *PRD*, proline-rich domain; *RARG*, retinoic acid receptor gamma; *RRM*, RNA recognition motif; *RSLD*, arginine/serine-like domain.

ATRA must be initiated immediately after the diagnosis is suspected due to the life-threatening coagulopathy. The application of the current standard therapy makes APL the most curable subtype of AML. AMLs with *RARG* or *RARB* rearrangements share morphologic, immunophenotypic, and clinical features of APL, but lack the *PML-RARA* fusion gene. These patients have high mortality on account of lack of response to ATRA. *CPSF6-RARG* is the most common fusion in these subtypes of AML; early identification can help change treatment strategies in time and improve prognosis. Cleavage and polyadenylation specific factor 6 (*CPSF6*) is a subunit of cleavage factor I, which is involved in messenger RNA (mRNA) precursor 3'-end processing.<sup>7</sup> *RARG* has a unique function in maintaining the self-renewal of hematopoietic stem cells (HSCs).<sup>8</sup> Four cases of *CPSF6-RARG* fusion and one case of *RARG-CPSF6* fusion have previously been reported (Table 1)<sup>5,9-11</sup>; in our patient, clinical manifestations, cell morphology and immunophenotype were

similar to APL, but they did not respond to ATRA. As listed in Table 1, Patient #1, *DNMT3A* mutation and a tetraploidy karyotype of 92, XXXX[2] were detected. NGS revealed that the 3'-region of the *RARG* gene (from exon 4 to exon 9) was reversed and fused in-frame with the 5'-region of the *CPSF6* gene (from exon 1 to exon 4). The patient received ATRA, ATO (arsenic trioxide), and IDA (idarubicin), the IAG regimen [IDA, cytosine arabinoside, and granulocyte-colony stimulating factor (G-CSF)], and decitabine treatments. Unfortunately, all treatments were ineffective.<sup>5</sup> Like patient #1, patient #2 was resistant to ATRA, ATO, and the MA regimen (mitoxantrone and cytarabine). A *CPSF6-RARG* rearrangement within chromosome 12 was detected, accompanied by a *WT1* mutation; the main transcript was the fusion of *CPSF6* exon 4 with *RARG* exon 2.<sup>9</sup> For patient #3, the 3'-region of the *RARG* gene (from exon 1 to exon 9) was reversed and fused in-frame with the 5'-region of the *CPSF6* gene (from exon 1 to exon 4), co-mutations with *WT1*, *KRAS*.



**Table 1.** AML with *CPSF6-RARG* and *RARG-CPSF6* fusion in literature.

No	Age/sex	PB	Morphology	Immunophenotype	Cytogenetics	Gene fusion site	Other related gene mutations	Therapy	Outcome	Reference
1	48/F	WBC: $0.81 \times 10^9/l$ HB: 4.2 g/dl PLT: $92 \times 10^9/l$	89% hypergranular promyelocytes with auer rods	CD13+ CD33+ MPO+ CD9partial+ CD64partial+ CD117- CD34- HLA- DR- CD11b- CD14-	92,XXXX[2]	<i>CPSF6</i> exon4 was fused with <i>RARG</i> exon4	DNMT3A mutation	ATRA+ATO+IDA, IAG+ATRA+ATO, Decitabine as induction therapy	No response and die of cerebral hemorrhage	Liu <i>et al.</i> <sup>5</sup>
2	38/M	WBC: $1.68 \times 10^9/l$ HB: 8.0 g/dl PLT: $79 \times 10^9/l$	65% promyelocytes	CD13+ CD33+ CD34+ MPO+ CD117+ CD9partial+ CD64partial+ CD11b- HLA- DR- CD38- CD14-	46,XY[20]	<i>CPSF6</i> exon4 was fused with <i>RARG</i> exon2	WT1 mutation	ATRA+RIF d1-25, MA started at d26	Died of diffuse alveolar hemorrhage	Qin <i>et al.</i> <sup>9</sup>
3	51/F	WBC: $20.15 \times 10^9/l$ HB: 6.5 g/dl PLT: $45 \times 10^9/l$	87.5% hypergranular promyelocytes	CD13+ CD33+ cMPO+ CD9+ CD34partial+ HLA-DR- CD11c- CD38- CD14-	46,XX,del(12)(p12)[2]/46,XX[18]	<i>CPSF6</i> exon4 was fused with <i>RARG</i> exon1	WT1, KRAS mutation	ATRA+DNR, DA as induction therapy, two cycle HD-Ara-C followed by two cycle 3+7 regimens	Resistant to ATRA+DNR, but sensitive to DA, CR at last followed	Liu <i>et al.</i> <sup>5</sup>
4	55/M	WBC: $1.23 \times 10^9/l$ HB: 7.6 g/dl PLT: $60 \times 10^9/l$	93% hypergranular promyelocytes with auer rods	CD13+ CD33+ CD117+ CD6+ CD34- CD38- HLA- DR-	46,XY	<i>CPSF6</i> exon 5 was fused with <i>RARG</i> exon 1	NA	ATRA+ATO, IA, HA as induction and consolidation therapy	Resistant to ATRA, ATO, IA. But sensitive to HA and achieved CR	Zhang <i>et al.</i> <sup>10</sup>
5	26/M	WBC: $16.4 \times 10^9/l$ HB: 10.5 g/dl PLT: $120 \times 10^9/l$	60% blasts, 15% promyelocytes	CD13+ CD33+ CD64+ CD117partial+ CD34- HLA- DR ± CD14- CD11b-	45,X,-Y[10]/45, idem, add (6)(q?13)[2]/46,XY[18]	<i>RARG</i> intron 9 was fused with <i>CPSF6</i> exon 6	BMPR1A, NEAT1, WT1 mutation	ATRA was started on d1 added IA on d2	NA	Miller <i>et al.</i> <sup>11</sup>

AML, acute myeloid leukemia; ATO, arsenic trioxide; ATRA, all-trans acid; *CPSF6*, cleavage and polyadenylation specific factor 6; CR, complete remission; DA, daunorubicin and cytarabine; DNR, daunorubicin; F, female; G-CSF, granulocyte-colony stimulating factor; HA, homoharringtonine and cytarabine; HB, hemoglobin; IA, idarubicin and cytarabine; IAG, idarubicin, cytosine arabinoside and G-CSF; IDA, idarubicin; M, male; MA, mitoxantrone and cytarabine; NA, not available; No., number; PB, peripheral blood; PLT, platelet; *RARG*, retinoic acid receptor gamma; Ref, reference; RIF, retinoic acid receptor gamma; RIF, Realgar-Indigo naturalis formula; WBC, white blood cell.

In this patient, ATRA and DNR (daunorubicin) were not effective, but she was sensitive to the DA (daunorubicin and cytarabine) regimen, followed by two cycles of high dose Ara-C. She remained in complete remission (CR) until last follow up<sup>5</sup>; these results are consistent with the report of Zhang in that *RARG*-rearranged APL-like AMLs are sensitive to a 3 + 7 regimen; in their report, this regimen benefited *NUP98-RARG*-positive AML patients.<sup>12</sup> However, the IA (idarubicin and cytarabine) regimen failed to work in patient #4. In contrast, after one course of standard HA regimen, the patient achieved CR and remained in CR until the last follow up; this patient's *CPSF6-RARG* fusion transcript was the longest, and was generated by the fusion of exon 5 of *CPSF6* and exon 1 of *RARG*.<sup>10</sup> The author of that report claimed that homoharringtonine is an effective drug for the novel subtype AML with *CPSF6-RARG* fusion. Nevertheless, in our case, considering the patient's severe coagulation dysfunction and thrombocytopenia, we adopted a dose-adjusted HA regimen (Hom 2mg d1-5, Ara - C 50mg d1-7). Unfortunately, the treatments were ineffective for our patient and she eventually died due to an intracranial hemorrhage.

Other than *CPSF6-RARG* fusion, in our patient, *WT1* mutation was detected by RT-PCR before chemotherapy. It was not, however, found in the NGS of the genes submitted after chemotherapy. *WT1* mutation occurs in 5.5% of AML cases and is expressed recurrently in APL, reaching 11%.<sup>13</sup> Similar to typical APL, the mutation frequency of *WT1* in *CPSF6-RARG* fusion AML is much higher than in other subtypes of AML.<sup>14</sup> It is very clear that patients #2, #3, and #5 (Table 1) all have *WT1* mutations. It is speculated that *WT1* mutation may influence ATRA sensitivity.<sup>15</sup> we also found other co-mutations of this patient, including a *KRAS* gene mutation, which can cause continuous activation of Ras protein and participate in tumorigenesis.<sup>14</sup> In addition, *EZH2* is a member of the PRC2 family, coding for a histone methylation enzyme. It has been shown that the *EZH2* mutations themselves have no effect on overall survival (OS) or progression-free survival (PFS) in AML.<sup>16,17</sup> However, the co-existence of *EZH2* mutations with *FLT3* or *IDH2* mutations seem to be connected with poor OS and PFS.<sup>18,19</sup> Only *EZH2* mutations were present in our patient, which may have little prognostic significance.

An important clinical characteristic of our patient was extramedullary infiltration, which

has never been reported in published studies.<sup>5,9-11</sup> In our patient, the right obturator internus, obturator externus, and some lymph nodes confirmed the extramedullary involvement of AML. Indeed, typical APL rarely has extramedullary involvement.<sup>20</sup> Research showed that the factors associated with extramedullary infiltration in APL including youth, WBC count  $>10 \times 10^9/l$ , and bcr3 *PML-RARA* breakpoint.<sup>21</sup> Obviously, our patient did not have the above characteristics. It has never been reported previously that five patients had extramedullary infiltration, presumably because no systemic examination such as a PET-CT was conducted. Whether AML with *CPSF6-RARG* fusion tends to extramedullary infiltration remain uncertain, but it is certain that identification of extramedullary infiltration has an important impact on treatment. The appearance of extramedullary infiltration indicates a poor prognosis and may need radiotherapy, more intensive chemotherapy, or even allogeneic hematopoietic stem cell transplantation (allo-HSCT).<sup>22</sup> PET-CT may play a critical role in the diagnosis and treatment of this subtype of AML.

In summary, in our APL-like patient, *CPSF6-RARG* fusion was simultaneously accompanied by extramedullary infiltration. She showed a poor response to ATRA and HA regimen. The available evidence suggests that the prognosis is poor, active treatments such as allo-HSCT in CR deserve further research.

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### Author contributions

**Xiaoyan Han:** wrote part of the manuscript; reviewed literature; manage the patient; provided clinical data.

**Chunxiang Jin:** wrote part of the manuscript and reviewed literature.

**Gaofeng Zheng and Yi Li:** reviewed and wrote part of the manuscript.

**Yungui Wang and Enfan Zhang:** performed molecular studies and provided images.

**Honghu Zhu:** reviewed and wrote part of the manuscript.

**Zhen Cai:** supervised and formulated case report; wrote the manuscript; review of the literature.

All authors reviewed the manuscript and contributed to the final draft.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of interest statement

The authors declare no competing financial interests.


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### Ethics approval and consent to participate

Our study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, and informed consent was obtained from this patient. The approval number is (2020) IIT (338).

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### Supplemental material

Supplemental material for this article is available online.

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