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CASE REPORT

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Philadelphia chromosome-like acute lymphoblastic leukemia with concomitant rearrangements of *CRLF2* and *ABL1*: a pediatric case report

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Abstract

Background *BCR::ABL1*-like or Philadelphia chromosome-like (Ph-like) acute lymphoblastic leukemia (ALL) was first reported in 2009. Ph-like ALL is characterized by gene signature similar to Philadelphia chromosome ALL, but without *BCR::ABL1* fusions. Molecularly, Ph-like ALL is divided into seven categories, with *CRLF2* and ABL-class rearrangements being the two most common subtypes, exhibiting alterations in distinct downstream signaling cascades.

Case presentation We report a rare case of pediatric Ph-like ALL with concomitant *CRLF2* and *ABL1* rearrangements. *CRLF2* was fused with *P2RY8*, its most common fusion partner, whereas *ABL1* was fused with *MYO18B*, a novel fusion partner that has not been previously reported. The 4-year-old female patient was treated using the national multicenter CCCG-ALL-2020 protocol with the addition of dasatinib at the end of induction when *ABL1* rearrangement was confirmed by RNA-seq. Morphologically and molecularly, the patient remained in continuous remission until the last follow-up. To the best of our knowledge, this is the first case of Ph-like ALL harboring two distinct rearrangement categories.

Conclusions Our results identified that ABL1 rearrangement and CRLF2 rearrangement can coexist. The application of FISH, whole transcription sequencing, PCR can help us to have a more comprehensive understanding of ALL cytogenetics and molecular biology. Further studies are needed to explore the role of targeted therapies in such rare clinical scenarios.

Keywords Acute lymphoblastic leukemia, Philadelphia chromosome-like, *CRLF2*, *ABL1*, *MYO18B*, Case report

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Background

BCR::ABL1-like or Philadelphia chromosome-like (Ph-like) acute lymphoblastic leukemia (ALL) is characterized by a poor early treatment response, high recurrence rate, and unfavorable clinical outcomes. The 5-year EFS/DFS of children Ph-like ALL varied widely across regions, ranging from around 30–90%. The 5-year EFS of adults Ph-like ALL were about 24% [1]. Ph-like ALL cases most commonly present with *CRLF2* or ABL class rearrangements [2, 3]; however, Ph-like ALL with concomitant rearrangements of both *CRLF2* and *ABL1* has not been identified previously. Here, we report a rare pediatric case of Ph-like ALL with concomitant *CRLF2* and *ABL1* rearrangements. *CRLF2* was fused with *P2RY8*, the most common fusion partner, whereas *ABL1* was fused with *MYO18B*, a novel fusion partner that has not been previously reported. Studies have shown that ABL-class-rearranged ALL has a good therapeutic response to the tyrosine kinase inhibitors (TKI) imatinib or dasatinib [4–8], similar to Ph positive ALL. However, effective therapies for *CRLF2* rearrangements are still under investigation. With the combination of chemotherapy and dasatinib, the patient has remained measurable residual disease (MRD)-negative for 18 months since therapy initiation.

Case presentation

A 4-year-old female was admitted to our hospital with intermittent fever and bilateral preauricular masses that persisted for 16 days. Approximately 16 days before admission, the painless preauricular lumps had grown steadily. Concomitantly, the patient presented with intermittent fever, exhibiting a maximum temperature of 38.8 °C. Her temperature normalized after intravenous penicillin administration at a local hospital. Before admission, the patient had no symptoms such as weariness, epistaxis, skin bleeding, or ostealgia. However, three kilograms of body weight were lost in the two weeks prior to admission. The patient had no history of illness. The patient had no specific personal and family history of similar illnesses. On admission, she was in a relatively stable condition but appeared pale. The size of the left preauricular was 2 by 2 cm and right preauricular was 2.5 by 2.5 cm, exhibiting moderate texture and was not tender. Abdominal palpation revealed hepatomegaly and splenomegaly 5 and 7 cm below the ribs, respectively. Physical examinations of the heart, lungs, and nervous system revealed negative results. White blood cell count was 5.4×10^9/L, lymphocytes were 51%, neutrophils were 19%, monocytes were 1%, blast cells were 25%, hemoglobin was 63 g/L, platelets were 36×10^9/L, reticulocytes were 0.14%, and absolute reticulocyte count was 0.0045×10^9/L on the complete blood count. Blood biochemical testing revealed normal renal function; alanine aminotransferase 42 U/L; aspartate aminotransferase 18 U/L; lactate dehydrogenase 157 U/L; and normal blood electrolyte levels. The results from the disseminated intravascular coagulation were normal. DNA tests for Epstein-Barr virus and Cytomegalovirus were negative. Abdominal ultrasonography revealed an enlarged liver and spleen. ALL was suspected based on a bone marrow smear, and the French-American-British classification was L2, with 88.5% lymphoblasts.

Pre-B ALL was identified by bone marrow flow cytometry based on the expression of CD19, cCD79a, CD22, CD10, TDT, CD34, HLA-DR, CD9, CD66c, and CD38, and lack of expression of CD3 or MPO. A positive *MYO18B::ABL1* fusion gene (Fig. 1A), positive *P2RY8::CRLF2* fusion gene (Fig. 1B), positive *PTPN11* mutation (E76G, mutation frequency 31.2%), and positive *ETV6* mutation (R105*, mutation frequency 1.6%) were identified using whole-transcriptome sequencing. The *MYO18B::ABL1* fusion was verified by polymerase chain reaction (PCR) and sanger sequencing (Fig. 2). With positive rates of 49% and 85%, respectively, the *ABL1* and *CRLF2* probes demonstrated signal separation using fluorescence in situ hybridization (FISH) (Fig. 3). The probes used to detect the ABL1 break site were located at 9q34.12 and the CRLF2 break site were located at Xp22.33. *CRLF2* overexpression was also observed, with an expression percentage of 99.4%. 47, XX, +21[2]/47, idem,?t(1;9)(p34;q34),del [22](q11)[6]/46, XX[12] were the chromosomal karyotypes found. Analysis of karyotype results can sometimes be inaccurate and subjective, and our karyotype results suggest abnormalities of 9q.34 and 22q. ABL1 is located at 9q.34 and MYO18B is located at 22q. No *IKZF1* gene deletions were found using multiplex ligation-dependent probe amplification. The methods and materials used for this patient's assay are provided in the Supplementary Materials.

Combined with the typical clinical signs and symptoms of the patient, the laboratory examination, especially the bone marrow morphology and genetic examination, confirmed the diagnosis of ALL beyond doubt. Based on the FISH and whole-transcriptome test results, we concluded that the child was Ph-like ALL.

Acute Lymphoblastic Leukemia-2020, an ongoing project of the China Children's Cancer Group, was used to treat the patient once ALL was confirmed (CCCG-ALL-2020; www.chictr.org.cn; Date of registration: August 5, 2020; Registration number: ChiCTR2000035264). On day 6 after chemotherapy, the enlarged lymph nodes were no longer palpable, and on day 18, the enlarged liver was restored to its normal size. Following chemotherapy, routine complete blood count revealed that the red blood cells, white blood cells, and platelets in the peripheral blood were all stabilized around day 28. A satisfactory response to early

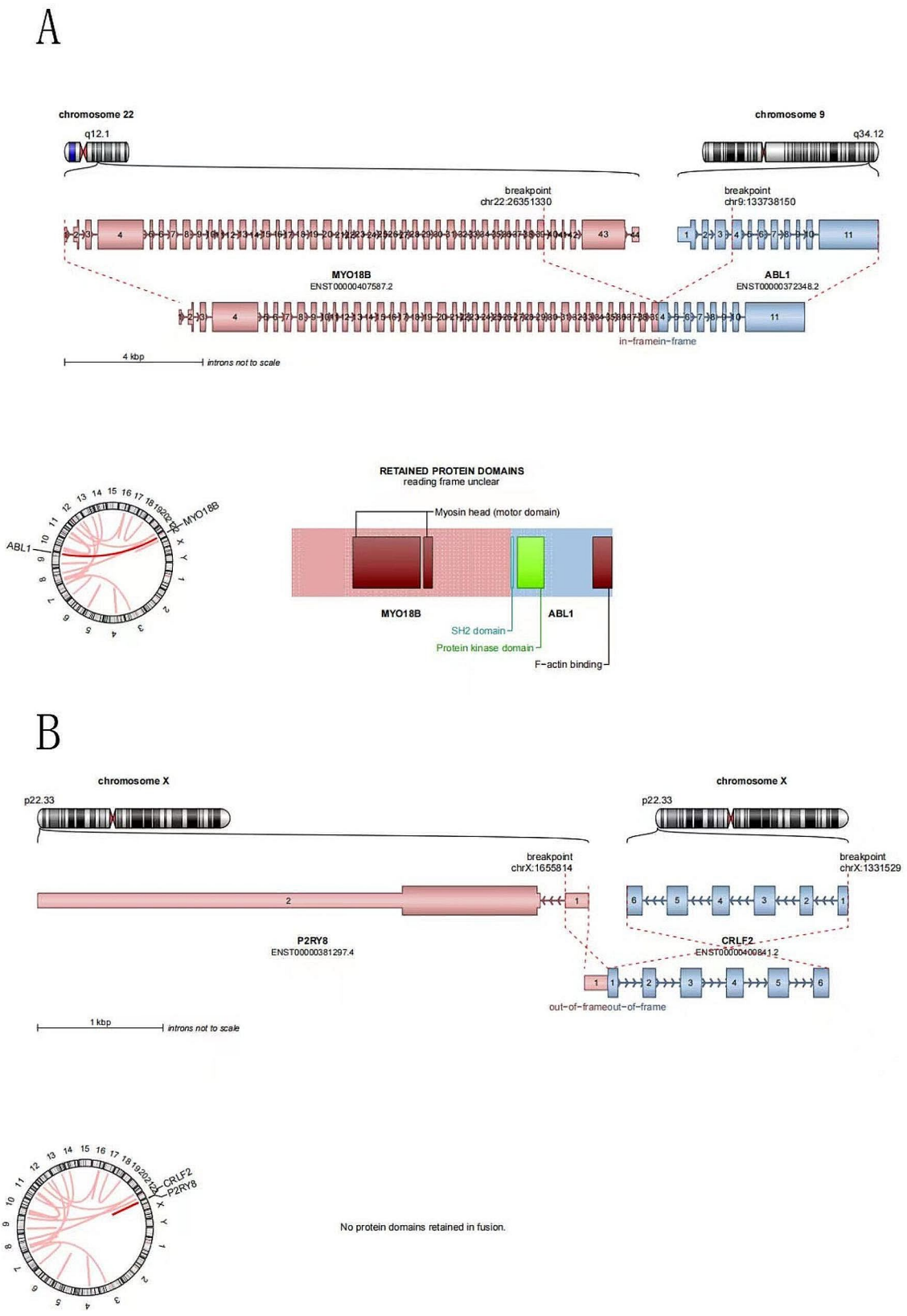

Fig. 1 A positive *MYO18B-ABL1* fusion gene and a positive *P2RY8-CRLF2* fusion gene were suggested by whole-transcriptome sequencing. Diagram of the *MYO18B/ABL1* fusion gene. The fracture point of *MYO18B* is located at chr22:26251330, and the fracture point of ABL1 is located on chr9:133738150, respectively. Diagram of the *P2RY8-CRLF2* fusion gene. The fracture point of *P2RY8* is located on chrX:1,655,814, and the fracture point of *CRLF2* is located on chrX:1,321,529, respectively

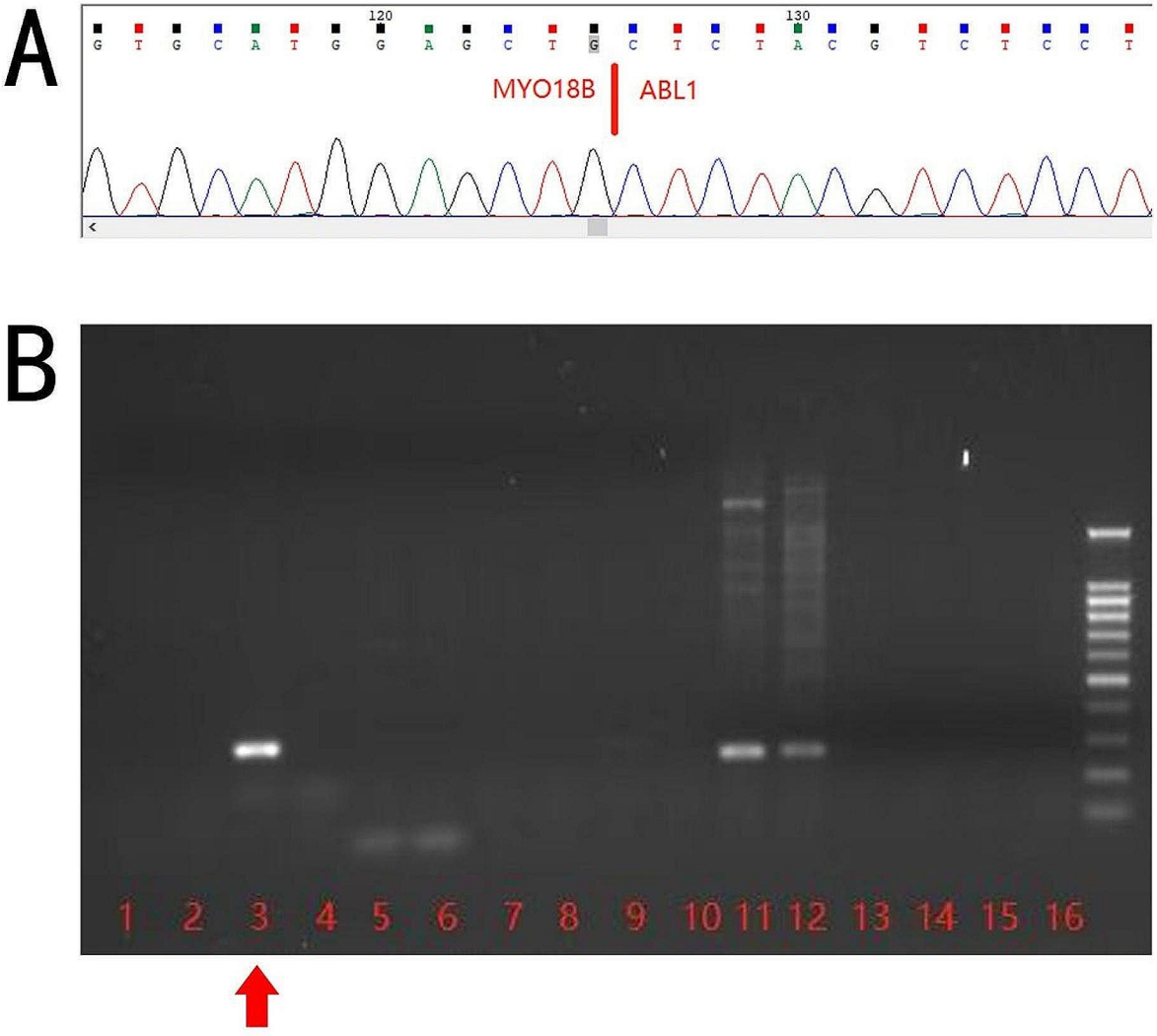

Fig. 2 Sanger sequencing and PCR electrophoresis of *MYO18B/ABL1*. (**A**) Sanger sequencing peak figure of *MYO18B/ABL1*. The fusion gene sequence is GCAGCGGGAGGCAGAGGCCAGCCGGCGGTGCATGGAGCTTCTACGTCTCCTCCGAGAGCCGCTTCAACACCCTGGCCGAG [GC]. (**B**) PCR electrophoresis shows that lane 3 is the PCR product of *MYO18B-ABL1* while lane 4 is the negative control

chemotherapy was indicated on day 19 following chemotherapy, when the bone marrow smear showed complete remission and the flow cytometry (FCM)-MRD was less than 0.01%. On day 46, RT-PCR showed negative results for the *MYO18B::ABL1* and *P2RY8::CRLF2* fusion genes, and Sanger sequencing showed negative results for *PTPN11* and *ETV6* mutations. On day 28 of induction therapy, targeted therapy with dasatinib (80 mg/m^2/day) was initiated. The patient developed severe serous cavity effusions and shortness of breath approximately 10 days after oral delivery. We immediately discontinued dasatinib, and these symptoms gradually improved. Fourteen days after discontinuation of dasatinib, a reduced dose of dasatinib (60 mg/m^2/day) was re-administered at the beginning of consolidation therapy and continued until the end of consolidation therapy. At the beginning of continuous treatment, approximately four months after the initial treatment, we attempted to adjust the dose of dasatinib to 80 mg/m^2/day, and the patient had no further adverse reactions.

It has been 18 months since the initiation of chemotherapy. Every four months, bone marrow smears, FCM-MRD, fusion gene qualification, and gene mutation quantification were performed, with consistently negative results (Fig. 4).

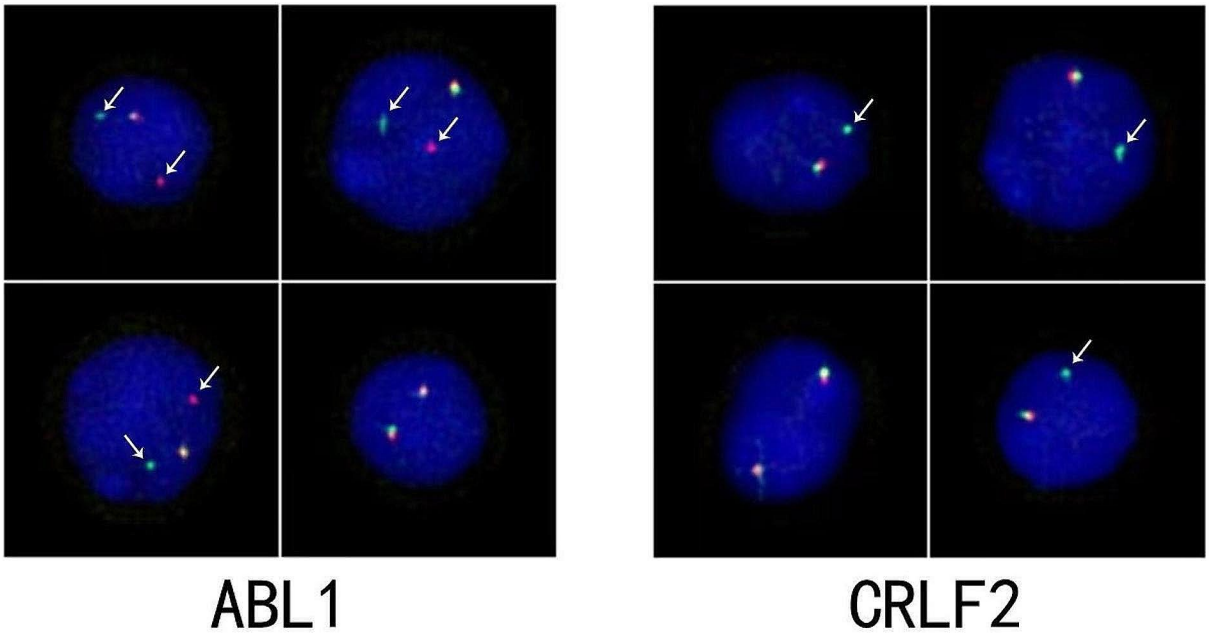

Fig. 3 FISH detection indicates signal separation in both ABL1 and CRLF2 (indicated by the white arrow). The ABL1 separation probe showed signal separation with a positive rate of approximately 49%, while the CRLF2 separation probe showed an abnormal signal mode with a positive rate of approximately 85%

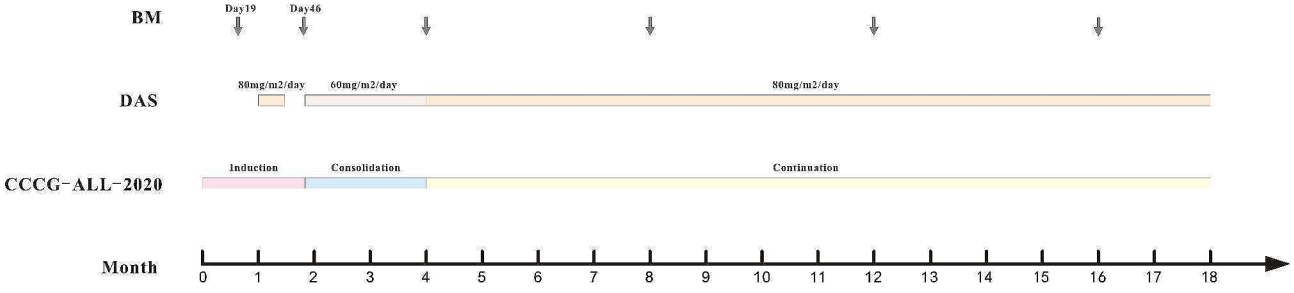

Fig. 4 The treatment timeline of the patient. On day 28 of the induction therapy, targeted therapy of dasatinib (80 mg/m^2/day) was added. The patient had severe serous cavity effusions and shortness of breath approximately 10 days after oral delivery. We immediately stopped the dasatinib administration and these symptoms gradually abated. Fourteen days after dasatinib was discontinued, a reduced dose of dasatinib (60 mg/m^2/day) was added again at the beginning of the consolidation therapy and continued until the end of the consolidation therapy. Complete response at the genetic level of the bone marrow was achieved from 19 days after chemotherapy. DAS: dasatinib

Discussion and conclusions

BCR::ABL1-like or Ph-like ALL was first reported in 2009 [9, 10]. Ph-like and Ph+ALL have similar gene expression profiles and are both likely to be complicated by gene mutations in *IKZF1*, transcription factor 3 (E2A), early B-cell factor, and paired box 5 [5, 11, 12]. Mutations in *PTPN11* and *ETV6* were also detected in our patient. According to the literature, both *PTPN11* and *ETV6* mutations are common genetic lesions in Ph-like ALL [13–15]. Similar to *BCL::ABL1*-positive ALL, the prognosis of Ph-like ALL is worse than that of other types of B-cell precursor-ALL. According to the WHO classification of lymphopoietic tumors updated in 2022, Ph-like ALL is classified as a recurrent genetic abnormality of B-cell lymphoblastic leukemia/lymphoma [16] and is characterized by a poor early treatment response, high recurrence rate, and unfavorable clinical outcome.

The incidence of Ph-like ALL gradually increases with age and is approximately 10–15% in children, 20% in adolescents, and 20–27% in adults [5, 17, 18]. Ph-like ALL is more common in male patients. The male-to-female ratio is approximately 1.5:1 in children and 4:1 in adults [5]. In the CCCG-ALL-2020 protocol, methods used to screen for Ph-like ALL include PCR, FISH, and RNA-seq. These three methods are routine tests for all patients with ALL, according to our protocol.

Poor prognosis of patients with Ph-like ALL is associated with genetic abnormalities at the molecular level. The molecular biological abnormalities of Ph-like ALL mainly involve kinase and cytokine receptor activation. The kinase genes and cytokine receptors involved can be divided into the following major categories: *CRLF2* rearrangement, ABL-class rearrangement (*ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*), *JAK2* rearrangement, *EPOR* rearrangement, JAK/STAT aberrations (*TSLP*, *IL2RB*, and *TYK2*), RAS pathway mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*, *CBL1*, and *BRAF*), and other types of genetic abnormalities (*NTRK3*, *PTK2B*, *BLNK*, *FLT3*, *FGFR1*, *DGKH*) [2, 19, 20]. In addition, it has been reported that patients with positive *ETV6::RUNX1*, *TCF3::PBX1*, *KMT2A-r*, and *BCR::ABL1* rearrangements usually do not have the above gene changes of Ph-like ALL simultaneously [21, 22].

Among the above categories, *CRLF2* rearrangement is the most common genetic abnormality in Ph-like ALL at all ages, accounting for approximately 40–60% of cases [5]. The *CRLF2* gene is located at Xp22.3 (OMIM: *300357)/Yp11.3 (OMIM: *400023), encoding the thymic stromal lymphopoietin receptor, which binds with the ligand of the α-chain heterodimer IL-7R to mediate the downstream signal transduction of lymphogenesis, anaphylaxis, and inflammation [23]. The vast majority of *CRLF2* rearrangements have positive *IGH::CRLF2* and *P2RY8::CRLF2* fusion genes, and a few have *CRLF2* point mutations [24–27]. Approximately 50–60% of patients with *CRLF2* rearrangements are complicated by genetic abnormalities of the JAK or RAS pathways, such as *NRAS*, *KRAS*, *PTPN11*, and *NF1*, and often have loss of heterozygosity (LOH) of *IKZF1* and *iAMP21*. *CRLF2* rearrangements are also found in non-Ph-like ALL, specifically in Down Syndrome-associated ALL [28]. *CRLF2* overexpression is associated with high MRD during early treatment and poor outcomes in high-risk ALL [29–31]. We carefully considered whether the JAK inhibitor ruxolitinib should be administered to our patient. Overall, ruxolitinib efficacy in patients with *CRLF2*-rearranged ALL remains unclear. Clinical studies on the ruxolitinib in patients with *CRLF2* rearrangement ALL are limited, with only a small number of ongoing clinical trials in children and adults with Ph-like ALL (NCT02723994, NCT03571321, NCT03117751, NCT02420717, and NCT02723994) and a recently initiated European trial (EudraCT number 2020-005017-41). However, the final findings have not yet been published. Ruxolitinib is primarily used as an adjuvant treatment for ALL with abnormalities in *JAK2* or the JAK-STAT pathways. RNA-seq clearly showed that there were no genetic aberrations in any genes in the JAK-STAT signaling pathway in our patient, and we presumed that the off-label use of ruxolitinib would not provide additional benefits. In addition, it has been suggested that P2RY8::CRLF2 could represent a secondary event because this fusion can be found concomitantly with other subtype-defining alterations such as iAMP21 or hyperdiploid ALL. In patients with ABL rearrangement, perhaps ABL1 fusion is more likely to be the key driver also [32–34].

The downstream signaling pathways JAK/STAT and P13K/AKT/MTORC1 were abnormally activated in *CRLF2*-rearranged cell lines. In *IGH::CRLF2*-positive cell lines, activation of the MTORC1 and RAS pathways plays a crucial role in their survival, but the survival of *CRLF2*-rearranged cell lines does not depend on JAK activation [35]. The MEK inhibitor trametinib and Akt inhibitor MK2206 have been shown to enhance the sensitivity of *CRLF2*-rearranged cell lines to hormones [36]. Moreover, the combined use of trametinib and gilteritinib can simultaneously inhibit MEK (RAS pathway) and receptor tyrosine kinases (RTKs) (P13K/AKT/MTORC pathway), playing an inhibitory role in *CRLF2*-rearranged cell lines [37].

ABL class rearrangement is also a common genetic abnormality in Ph-like ALL, accounting for approximately 10% of all Ph-like ALL cases. Children with Ph-like ALL have a higher proportion of ABL class rearrangements than adults [5]. Studies have shown that ABL class-rearranged ALL has a good therapeutic response to imatinib or dasatinib [4–8], similar to the response in patients with Ph+ALL. At present, many clinical trials have evaluated the efficacy and safety of dasatinib (ClinicalTrial.gov: NCT 02420717, NCT02883049, NCT03564470, and NCT02143414). Using the CCCG-ALL-2015 regimen, our randomized controlled study confirmed that dasatinib was significantly superior to imatinib in reducing recurrence in the bone marrow and central nervous system without increasing adverse reactions [8]. Therefore, in the CCCG-ALL-2020 regimen, dasatinib is recommended as the preferred drug for the targeted therapy of ABL-class Ph-like ALL.

A total of 13 *ABL1* partner genes have been reported to date; however, the partner gene *MYO18B* (myosin-XVIIIb) identified in this case has not been previously reported [1, 3, 19]. *MYO18B* (OMIM, *607295) is located at 22q12.1. LOH of 22q and is common in patients with lung, ovarian, and colorectal cancers, suggesting that a tumor suppressor gene may be in this region. The research results of Nishioka et al. showed that the deletion, mutation, promoter methylation, and histone deacetylation of *MYO18B* in 22q lead to the reduction or inactivation of *MYO18B* activity, which is closely related to the occurrence of lung, ovarian, and colorectal cancers [38–42]. The low expression of *MYO18B* has been reported to be related to the poor prognosis of squamous cell carcinoma of the skin [43]. Therefore, *MYO18B* is currently considered a tumor suppressor gene.

Ph-like ALL with a positive *MYO18B::ABL1* fusion gene has not yet been reported. To our knowledge, this is the first report of an *MYO18B::ABL1* fusion gene in ALL. Because of the fusion of *MYO18B* and *ABL1*, the activity of *MYO18B* may be reduced. In this case, the 3' breakpoint of *ABL1* was at chr9:133738150 (GRCh38), which is a common breakpoint of *ABL1* and can affect the function of ABL1. Therefore, we speculate that the formation of the *MYO18B::ABL1* fusion gene may have been related to the occurrence of leukemia in this case. In addition, other genetic abnormalities relevant to the pathogenesis of leukemia were detected in our patient, including *P2RY8::CRLF2* fusion gene-positivity, and mutations in *PTPN11* and *ETV6*. We believe that these genetic abnormalities are potential therapeutic targets for our patient.

CRLF2 and ABL-class rearrangements are the two most common Ph-like ALL subtypes. To the best of our knowledge, patients with ALL featuring both *CRLF2* and *ABL1* rearrangements are rare. An adult patient with chronic myelogenous leukemia was reported to be *BCR::ABL1*-positive at initial diagnosis and presented with a new *CRLF2* rearrangement during the B-lymphoblast phase [44]. Both FISH and RNA-seq in this case confirmed simultaneous *CRLF2* and *ABL1* rearrangements.

For patients with both *CRLF2* and ABL-class rearrangements, it is also necessary for clinicians to consider the selection of reasonable targeted therapeutic drugs. In our report, our patient was treated with dasatinib in combination with chemotherapy, which mainly resulted for the following reasons. First, the targeting effect of dasatinib in ABL-class Ph-like ALL has been confirmed in several studies [1, 45, 46]. In addition, no clinically effective *CRLF2*-targeted drug is currently available. Third, after the induction therapy, flow cytometry of the bone marrow on day 19 showed that the FCM-MRD of the child was <0.01%, suggesting a good early therapeutic response. Therefore, we selected dasatinib, which has a proven efficacy against ABL-class ALL, for targeted therapy. Moreover, guided by FCM-MRD and fusion-gene PCR monitoring, post-chemotherapy follow-up and bone marrow monitoring were performed. At present, 13 months after chemotherapy, the bone marrow smear, FCM-MRD, *MYO18B::ABL1*, and *P2RY8::CRLF2* genes of the patient remain negative. We plan to regularly monitor and follow up on the bone marrow characteristics of the patient.

Whether children with Ph-like ALL require hemopoietic stem cell transplantation (HSCT) is a matter of concern for clinicians. At present, it is believed that chemotherapy combined with TKI can be considered for patients with continuously negative FCM-MRD results after induction therapy; however, the bone marrow smear, FCM-MRD, and genetic examination of children should be closely monitored. However, for children with Ph-like ALL whose FCM-MRD is not negative and high-risk patients with a 5-year disease-free survival of <30%, HSCT may be needed [47]. Currently, the long-term relapse rate in patients with negative bone marrow FCM-MRD results prior to HSCT is relatively low. Therefore, it is recommended that combining chemotherapy with TKIs or administration of CAR-T cells to achieve bone marrow FCM-MRD negativity is recommended before HSCT [48]. After HSCT, it is also necessary to continuously monitor MRD and continue the oral administration of TKIs. However, the optimal course of TKI treatment after transplantation remains unclear. Some studies suggest that TKI withdrawal may be considered in patients with persistently negative MRD for 6 months to one year after HSCT [49, 50].

Overall, the incidence of Ph-like ALL in children is low; however, the prognosis for this specific malignancy is poor. Due to the extensive application in recent years of next-generation sequencing in clinical practice, more cases of Ph-like ALL have been reported. At present, only the ABL-class has TKIs as approved treatments. In contrast, targeted therapies for *CRLF2* rearrangements, and other types of Ph-like ALL need to be evaluated in additional trials. More research and exploration are needed on the indications for HSCT in children with Ph-like ALL and whether they would benefit from HSCT.

Abbreviations

BCR	Breakpoint cluster region
MYO18B	Myosin-XVIIIb
CRLF2	Cytokine receptor-like factor 2
P2RY8	Pyrimidinergic receptor p2y, g protein-coupled,8
IGH	Immunoglobulin heavy chain
PTPN11	Protein-tyrosine phosphatase, nonreceptor-type, 11
ETV6	ETS variant transcription factor 6
IKZF1	Ikaros family zinc finger 1
ALL	Acute lymphoblastic leukemia
FISH	Fluorescence in situ hybridization
FCM	Flow cytometry
PCR	Polymerase chain reaction
MRD	Measurable residual disease
LOH	Loss of heterozygosity
CCCG-ALL-2020	China Children's Cancer Group Acute Lymphoblastic Leukemia 2020
HSCT	Hemopoietic stem cell transplantation
TKI	Tyrosine kinase inhibitors
CAR-T	Chimeric antigen receptor T cell
DAS	Dasatinib

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
He GQ and Lei YP wrote the manuscript with contributions from all other authors; Huang DW drafted and revised the paper. Gao J and Yang R performed the topic selection, designed the study and edited the manuscript. All authors contributed to and reviewed the final manuscript.

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Data availability
Sequence data that support the findings of this study have been deposited in the Sequence Read Archive with the primary accession code PRJNA1000109.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of West China Second Hospital, Sichuan University. The patient's parents were informed and consented to participate.

Consent for publication
Written informed consent was obtained from the parents for the publication of any potentially identifiable images or data included in this article.

Competing interests
The authors declare no competing interests.

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