SET-CAN Fusion Gene in Acute Leukemia and Myeloid Neoplasms: Report of Three Cases and a Literature Review

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Objective: To investigate the characteristics of hematological malignancies in patients with the SET-CAN fusion gene and provide a literature review.

Methods: We retrospectively analyzed the clinical data of three cases of acute leukemia and myeloid neoplasms harboring the SET-CAN fusion gene who were treated at our hospital. Their clinical manifestations, pathological results and treatment strategies were investigated.

Results: The three cases were diagnosed with T-cell acute lymphoblastic leukemia (T-ALL), acute myeloid leukemia (AML) and myeloid sarcoma (MS), respectively. Karyotype analyses identified a normal result in all three patients. Subsequently, we confirmed del(9q34) utilizing FISH analysis. Mutation of the BRAF gene was detected in case 1, while mutations in PHF6 and BCOR were detected in case 2, which have not been officially reported in patients with SET-CAN fusions. Finally, relevant literature focusing on adult patients with hematological malignancies harboring the SET-CAN fusion gene were summarized.

Conclusion: Adult patients with the SET-CAN fusion gene were rare among cases of hematological malignancies. There was a large degree of heterogeneity between different patients. Notably, some patients remained sensitive to chemotherapy. Overall prognosis may be related to the type of disease and other cytogenetic abnormalities. Systemic cytogenetic and molecular studies are needed to make accurate diagnoses. Additional cases need to be accumulated and summarized to better understand these diseases.

Keywords: T-lymphoblastic lymphoma/leukemia, acute myeloid leukemia, myeloid sarcoma, SET-CAN, ASCT, prognosis

Introduction

Recurrent genetic abnormalities are considered to be diagnostic and prognostic markers in patients with hematological malignancies.1,2 Although intensive chemotherapy and allogeneic stem cell transplantation have greatly contributed to therapeutic strategies, it is still difficult to guarantee long survival and predict clinical outcomes for many individuals. More studies focusing on cytogenetic aberrations and molecular abnormalities are required for further exploration.3 The SET-CAN/NUP214 fusion gene is a relatively rare genetic event in leukemia. It was first detected in a patient with acute undifferentiated leukemia (AUL)4 and was later detected in a patient with acute myeloid leukemia (AML).5 Subsequently, additional T-ALL patients with this fusion gene have been identified. Until now, fewer than 60 adult cases have been reported, among which over 40 cases have been diagnosed with T-ALL. The estimated incidence of the SET-CAN fusion gene in adult patients with T-ALL has been reported...
to be ~5%. On the cytogenetic level, it is unclear if the SET-CAN fusion is generated by a t(9;9)(q34;q34) or an interstitial deletion at 9q34. The precise role of the SET-CAN fusion in hematopoietic cells and its contribution to leukemogenesis remains unknown. It is generally believed that the prognosis of such patients is poor and that these patients are insensitive to traditional chemotherapy and corticosteroids, so hematopoietic stem cell transplantation (HSCT) may improve the prognosis of such patients.

Here, we report three patients carrying the SET-CAN fusion gene who were diagnosed with T-ALL, AML and myeloid sarcoma (MS), respectively. Furthermore, to the best of our knowledge, no cases of myeloid sarcoma carrying the SET-CAN fusion gene have been reported thus far. In the present study, the relevant literature regarding adult patients with the SET-CAN fusion gene was reviewed in order to provide a comprehensive profile of this rearrangement. This study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University. Written informed consent was obtained from all the three patients.

Case Presentation

Case 1

A 21-year-old male patient was admitted to our center in December 2019 due to lymphadenopathy with fever and fatigue. Ultrasonographic findings suggested splenomegaly and generalized lymphadenopathy on both sides of the diaphragm. Immunohistochemical staining for cervical lymph node biopsy displayed as diffused abnormal proliferative lymphoblastic cells with CD3(+) TdT(+) CD99(+) CD4(+) Ki67(70%), while a few scattered cells were positive for MPO, CD117 and CD8. The patient was diagnosed with T-lymphoblastic lymphoma (LBL). The complete blood cell (CBC) of the patient showed a white blood cell (WBC) count of $3.16 \times 10^9$/L, a hemoglobin (HGB) level of 150 g/L and a platelet level of $244 \times 10^9$/L. Intriguingly, a bone marrow aspirate revealed hypercellularity with predominant blasts (Figure 1A), and flow cytometry showed the T-lymphoblasts (P3 group, 85.9%) mainly expressed CD7, cCD3 and CD38; partially expressed CD5 and HLA-DR; and did not express CD33, CD117, CD34, CD19,

![Figure 1](image_url)

**Figure 1** (A) Morphology of leukemic cells at diagnosis (original magnification, ×1000) for case 1. (B) Flow cytometry result for case 1. (C) Morphology of leukemic cells at diagnosis (original magnification, ×1000) for case 2. (D) Flow cytometry result for case 2. (E) Karyotype analysis showed normal result of case 1. (F) Dual-color FISH analysis of case 1 with LSI BCR-ABL1 dual-color, dual-fusion translocation probe showing a monoallelic loss of the ABL gene. The ABL gene (9q34) was labeled as orange, and the BCR gene (22q11.2) was labeled as green.
CD10, MPO, cCD79a, CD2, CD1a, CD15, CD13, CD56, TdT, CD123, CD25, CD99, CD4, CD8, CD3, TCRα/β, TCRγδ and CD45RO, which indicated Pro-T-ALL (Figure 1B). Karyotyping analysis of a bone marrow (BM) sample illustrated that the patient had a 46,XY karyotype[20] (Figure 1E). In total, reverse transcriptase (RT)-PCR covering 56 commonly detected fusion genes in leukemia (listed in Supplementary Table 1) was performed on the bone marrow sample. The SET-CAN fusion gene was detected. To determine whether the SET-CAN fusion identified in this case was derived from deletion of 9q34, fluorescence in situ hybridization (FISH) analysis using the BCR/ABL fusion probe covering this region was applied to the cultured bone marrow cells. The ABL gene (9q34) was labeled as orange, and the BCR gene (22q11.2) was labeled as green (Figure 1F). A total of 200 cells were analyzed, and ~83% of the cells showed deletion of ABL and two copies of BCR. The remaining cells showed a normal hybridization pattern. The FISH result was nuc ish(BCR<2),(ABL<1) [166/200]. Then, next generation sequencing (NGS) was performed on 39 commonly mutated genes in ALL (listed in Supplementary Table 2), and we identified a missense mutation c.1803A>T (p.Lys601Asn) in BRAF (NM_004333). Based on the clinical course and laboratory findings, the patient was finally diagnosed with T-LBL/ALL and subsequently received an induction chemotherapy VICP (vinodesine 4 mg/d, d1, 8, 15, 22; idarubicin 8 mg/d, d8-10; cyclophosphamide 1.2 g/d, d8; dexamethasone 15 mg/d, d1-5, 11–14). Complete remission (CR) was achieved after the first cycle of chemotherapy. The patient will continue consolidation therapy and wait for allogeneic HSCT.

Case 2
A 24-year-old male presented with lymphadenopathy for half a month without fever and was admitted to our center in August 2019. The routine blood test showed a WBC count of 11.41×10⁹/L, a HGB level of 126 g/L and a platelet level of 211×10⁹/L. CT findings suggested mediastinal and bilateral axillary lymphadenopathy as well as splenomegaly. The proportion of blasts in bone marrow was 81.2% (Figure 1C), and flow cytometry (Figure 1D) showed the blasts (P3 group, 80.2%) mainly expressed CD7, CD33 and CD34; partially expressed CD11b, HLA-DR, CD123, CD64 and CD13; and did not express CD10, CD117, CD16, CD19, CD10, MPO, cCD3, cCD79a, CD14, CD3, CD15, CD4, CD8, CD2, CD25, CD9 and CD11c, which indicated AML. The karyotype result was normal. The SET-CAN fusion gene was detected in the bone marrow sample by RT-PCR. Then, NGS identified ainsertion mutation c.4834dupC (p.Leu1612fs) in the BCR gene (NM_01123383) (38.51%); a PHF6 (NM_001015877) mutation (85.21%): c.746C>T (p. Thr249Le); and a CEBPA (NM_004364) mutation (6.1%): c.857G>A (p.Arg286Gln). The patient was diagnosed with AML-M5. A standard DA (Daunorubicin 120 mg×3 days, Cytarabine 200 mg×7 days) was given for two cycles; then, Cytarabine 3.5g Q12h×3 days was given for five cycles. CR was achieved. The patient declined HSCT and has been alive for 8 months.

Case 3
A 32-year-old female presented with a mediastinal mass for 2 months with no fever and was admitted to our center in October 2018. The CBC of the patient showed a WBC count of 4.15×10⁹/L, an HGB level of 111 g/L and a platelet level of 128×10⁹/L. Ultrasonographic findings suggested generalized lymphadenopathy. The result of Lung CT+ enhancement showed left hilar and mediastinal space occupying lesions, 5.6×4.0 cm in diameter, with left upper lobe obstructive changes, pericardial effusion and left pleural effusion (Figure 2A). The PET-CT showed soft tissue shadow in the mediastinum and chest wall, wrapping mediastinal vessels, with SUVmax=10.1, which were considered to be malignant lesions. The left pleura was thickened with increased metabolism, and the metabolism of the left neck and upper and lower clavicle lymph nodes was also increased (Figure 2B). Immunohistochemical staining of the mediastinal mass biopsy (Figure 2C) displayed diffused abnormal proliferative cells with CD7(+)Pax8(+) CD33(+)CD43(+)CD99(+) CD4(+) LMO-2(+) Ki67 (85%), while a few scattered cells were positive for CD117, Pax5 and CD8. Other staining results showed CD1a(-), CD5(-), CD20(-), CD3(-), CK(-), CD19(-), CD21(-), CD163(-), EMA(-), P63(-), CD68(-), MPO (-), CD34(-), TdT(-), CAM5.2(-), TTF1(-), ALK(-), CD30(-), CD10(-), CD56(-), CgA(-), GB(-), SYN(-), TIA1(-) and EBER(-). The patient was diagnosed with myeloid sarcoma (MS). The results of bone puncture, bone marrow biopsy and bone marrow flow cytometry were all negative. The karyotype result was normal. The SET-CAN fusion gene was detected. Pericardial effusion was exudate. The Rivalta test was positive, and the cell count was 4481×10⁶/L. After the initial chemotherapy with an HIA regimen (Idarubicin 20 mg×2 days, cytarabine 100 mg m²×7 days, homoharringtonine 2 mg×4 days), the mediastinal mass was significantly reduced. However, the follow-up treatment did
not further alleviate the disease, and the negative effect of myelosuppression was particularly prominent, with a rapidly increased pericardial effusion. At last, the patient discontinued treatment due to intestinal infection.

**Discussion**

Both the *SET* and *CAN* genes are located at chromosome 9q34. The *SET* protein is a potent endogenous inhibitor of protein phosphatase 2A (PP2A). It is overexpressed in
numerous cancer types.\textsuperscript{10,11} The SET protein has multiple functions, being involved in, for example, apoptosis, the cell cycle and nucleosome assembly.\textsuperscript{12} CAN/NUP214 is a type of nucleoporin, which is the main component of the nuclear pore complex and plays a role in nuclear protein import, mRNA export and cell cycle progression.\textsuperscript{13} The SET-NUP214 fusion protein consists of almost the whole SET protein fused to the C-terminus of NUP214 (Figure 2D).

LBL/ALL is an aggressive malignant proliferative disease of the hematopoietic system. It is characterized by uncontrolled proliferation of T-lineage progenitor cells with a 5-year-overall survival of \( \approx 48\% \).\textsuperscript{14} The clinical features include presentation with hyperleukocytosis and extramedullary infiltration of the lymph nodes and other organs. This form accounts for 25\% of total adult ALL cases.\textsuperscript{15} Most patients with T-ALL have a high tumor load, with rapid disease progression and a high risk of disease recurrence. Until now, just over 40 adult T-ALL patients with the SET-CAN fusion gene have been reported. Relevant articles with detailed information on patients have been collected in Table 1. Here, we collected eight studies, including 35 adult T-ALL patients with the SET-CAN fusion gene.\textsuperscript{6,9,16-21} Another two studies also mentioned patients with the SET-CAN fusion gene but were not included because they lacked the detailed information.\textsuperscript{22,23} Most of the reported T-ALL cases with the SET-CAN fusion gene occurred in young and middle-aged men. Flow cytometry analysis showed that patients not only had the differentiation antigen of T lymphocytes, but also expressed many myeloid antigens, suggesting that the tumor cells of these patients may be in the early stage of T lymphocyte development. The deletion or translocation of the small segment on chromosome 9 is difficult to detect using conventional cytogenetic methods, and the aberration needs to be further confirmed by FISH or array. More than one-third of the patients described in the literature had normal karyotype results. Complex karyotypes and other abnormal karyotypes have also been reported. However, del(9q34) can be detected in all patients who received FISH or array tests. Most of the patients presented with the SET exon7-NUP214 exon18 (S7N18 type) fusion transcript (13/14). Only one patient presented with the SET exon7-NUP214 exon17 (S7N17 type) fusion transcript (1/14). Mutation of the NOTCH1 gene as well as the PHF6 gene has also been identified in several patients.

It is reported that patients with a SET-CAN fusion have poor prognosis and are not sensitive to chemotherapy, especially to high dose glucocorticoids. It is suggested that HSCT should be carried out as early as possible after remission. Yang, et al\textsuperscript{9} reported three patients with T-ALL harboring the SET-CAN fusion gene, all of whom were refractory to high dose glucocorticoid-based chemotherapy. The authors sorted CD34\(^+\)Lin- cells from one patient as primary T-ALL cells and found that these cells were insensitive to dexamethasone. Additionally, SET-CAN mediated the loss of regulation of histone H3 acetylation, which might be a potential mechanism of glucocorticoid resistance. Furthermore, CLAG chemotherapy in combination with asparaginase might be a potential treatment option for adult SET-CAN\(^+\)T-ALL patients. The SET-CAN fusion gene is also considered to be a contributor to the poor responsiveness of SET-CAN-harboring leukemic cells to glucocorticoids. In one study, the SET-CAN fusion protein did not interact with the glucocorticoid receptor, was constitutively co-precipitated with glucocorticoid response elements and suppressed glucocorticoid receptor transcriptional activity and histone acetylation.\textsuperscript{24} In our case report, patient 1 showed a normal karyotype result accompanied with del(9q34) confirmed by FISH. A missense mutation of BRAF, which has not been previously reported in patients harboring the SET-CAN fusion gene, was identified by NGS. The mutant BRAF protein continuously activates the Ras/BRAF signaling pathway, which is essential for tumor growth, proliferation, invasion and metastasis.\textsuperscript{25}

While the majority of the adult patients experienced T-ALL, other subtypes of acute leukemia with the SET-CAN fusion gene are summarized in Table 2. Here, we collected seven studies\textsuperscript{4,5,7,8,26-28} including nine adult patients with the SET-CAN fusion gene. Three patients were diagnosed with AUL, four patients were diagnosed with AML and the other two were diagnosed with B-ALL. Another study conducted by Choi et al\textsuperscript{23} also mentioned two cases of AML, but was not included in our table because it lacked detailed information. According to the literature, only one B-ALL patient was female, while all the patients with AML and AUL were male. The median age was 36.5 years (19–46 years). In our report, case 2 was diagnosed with AML-M5. A mutation in PHF6 was identified in this patient, which has also been mentioned in other patients with the SET-CAN fusion gene.\textsuperscript{19} PHF6, located in the nucleolus, is an X-linked tumor suppressor gene which functions in transcriptional regulation. PHF6 mutations can be found in 15\% of AML patients and is associated with poor prognosis.\textsuperscript{29} Additionally, BCOR gene mutations have been found in 8–10\% of AML.
| Sex    | Age (y) | Country | WBC (*10^9/L) | Blast (%) | Karyotype | Array            | FISH                | Immunophenotype          | Gene Mutation | Fusion Position | Treatment                | Follow-Up                  |
|--------|---------|---------|---------------|-----------|-----------|------------------|----------------------|------------------------|----------------|----------------|----------------------------|----------------------------|
| Male   | 20      | China   | 34.1          | NR        | 46,XY     | NR               | del(9q34)/ABL1      | Positive for CD7,     | PHF6, NOTCH1           | 5'SET exon7-NUP214        | NR                        | Relapse and death, 9 months |
| Female | 56      | China   | 6.81          | NR        | 92-93,XXXX,+1, +3,+4-5,-6,-7, +10,-18, +dmin # 3–4[CP10] | NR               | del(9q34)/ABL1      | Positive for CD7,     | NA                     | 5'SET exon7-NUP214        | NR                        | NR                        |
| Male   | 23      | China   | 2.65          | NR        | 46,XY     | del(9)(q34, lq34.13),del (12) (p13.2p11.23) | del(9q34)/ABL1      | Positive for CD7,     | PHF6, NOTCH1           | 5'SET exon7-NUP214        | NR                        | Relapse and survive in CR2, 17.8 months |
| Male   | 27      | China   | NA            | NR        | 46,XY     | del(1) (p36.33, p36.12),del (2) (q37.1), del (9) (q34, lq34.13) | NR               | Positive for CD7,     | NOTCH                 | 5'SET exon7-NUP214        | NR                        | Relapse and death, 15 months |
| Male   | 45      | China   | 33.3          | NR        | 46,XY     | NR               | NR                   | Positive for CD7,     | PHF6, NOTCH1           | 5'SET exon7-NUP214        | NR                        | Relapse and death, 30 months |
| Male   | 23      | China   | 15.1          | NR        | 46,XY     | del(9)(q34, lq34.13),del (11)(p13),del (12) (p13.2p11.21), del(17)(q11.2) | del(9q34)/ABL1      | Positive for CD7,     | PHF6, NOTCH1           | 5'SET exon7-NUP214        | NR                        | NR                        |
| Name                          | Gender | Age  | Country | karyotype                                                                 | FISH/BFU   | WBC     | FAB   | Therapy | CR, relapse, SCT, alive | Time to event |
|-------------------------------|--------|------|---------|----------------------------------------------------------------------------|-------------|---------|-------|---------|------------------------|---------------|
| Chae (2011)                   | Female | 55   | Korea   | 47,XX, del(11)(q22q23), del(12)(p13), +14                                | del(9)(q34.11–34.13)/ ABL1 | CD34, CD34, CD13, CD7, cy-CD3 | NR    | S'ET exon7-NUP214 exon18 3' | Relapse 31 months |
|                               | Male   | 32   | Korea   | 46,XY, del(13)(q12q14)                                                   | del(9)(q4)/ ABL1   | CD33, CD34, CD13, CD7, cy-CD3 | NR    | S'ET exon7-NUP214 exon18 3' | Relapse and death, 42 months |
|                               | Male   | 32   | Korea   | 46,XY, del(6)(q21q23), del(12)(p11.2)                                    | del(9)(q4)/ ABL1   | CD33, CD34, HLA-DR, CD7, cy-CD3 | NR    | S'ET exon7-NUP214 exon18 3' | Relapse and death, 21 months |
|                               | Female | 20   | Korea   | 46,XX+, del(3)(q11.2) del(12)(p13), -13 del(17)(p11.2)                   | del(9)(q4)/ ABL1   | CD33, CD34, CD7, CD5, CD8, cy-CD3 | NR    | S'ET exon7-NUP214 exon18 3' | 33 months |
| Ben Abdelali (2014)           | Male   | 34   | France  | 46, XY, t(3;10)(q27; q32)[20]                                            | NR          | NR      | CD34, CD33, CD7, cCD3 | NR | GRAALL trail | CR, relapse, SCT, died 49 months |
|                               | Female | 37   | France  | 46,XX,t(4;16)(q25; q23)[30]                                             | del(9)(q34.11–34.13) | CD34, CD7, cCD3 (ETP-ALL) | NR    | NR | GRAALL trail | CR, SCT, alive 64 months |
|                               | Male   | 29   | France  | 46,XY, del(6)(q14q24), del(11)(q21), del(12)(p12)[9]/46, XY[3]          | del(9)(q34.11–34.13) | CD34, CD13, CD33, CD7, cCD3 (ETP-ALL) | NR    | NR | GRAALL trail | CR, relapse, SCT, alive 44 months |
|                               | Male   | 41   | France  | 47,XY,+4[15]                                                            | NR          | NR      | CD34, CD33, CD7, cCD3 (ETP-ALL) | NR | NR | GRAALL trail | CR, SCT, alive 46 months |

(Continued)
Table 1 (Continued).

| Sex | Age (y) | Country | WBC (*10^9/L) | Blast (%) | Karyotype | Array | FISH | Immunophenotype | Gene Mutation | Fusion Position | Treatment | Follow-Up |
|-----|---------|---------|---------------|-----------|-----------|-------|------|-----------------|---------------|----------------|-----------|-----------|
| Male | 23      | France  | 604.4         | NR        | 46,XY[31] | NR    | NR   | CD7, cCD3       | NR            | NR             | GRAALL    | Died 5 months |
| Male | 30      | France  | 24.9          | NR        | 46,XY[21] | NR    | NR   | CD7, cCD3       | NR            | NR             | GRAALL    | CR, SCT, relapse, CR, alive 66 months |
| Male | 36      | France  | 181.8         | NR        | 46,XY,add(5)(q22), del(12)(p11q13), 2q/46,XY,der(5)(t 5;12)(q11.2;p13), del(12)(p11q13), der(12)t(5;12) (q11.2;p13)add(5) (q22)[2]/46,XY [16] | NR    | NR   | CD34, CD33, CD7, cCD3 | NR            | NR             | GRAALL    | CR, SCT, alive 24 months |
| Male | 45      | France  | 50.8          | NR        | 46,XY,del(5)(q112), 7q/46,XY,del(11) (q12q14),inv(14) (q11q32),del(116) (p11p13),del(12)(q11q13)]5/46, XY[5] | NR    | NR   | CD7, cCD3       | NR            | NR             | GRAALL    | CR, alive 33 months |
| Male | 38      | France  | 2.8           | NR        | 88,X,Y,-Y,[46], add[2]q24],+4,5,- 5add[5]q15),-7,- add[9]q21],del (9)(q11q21),+10, del(12)(p11q13)x2,- 17x2,+2mar[cp7]/ 77~89,1+Y+Y, add[9]-del[9],+9, +9,+1~2mar[cp3]/ 78~88,del[1],-9add (15)(p11)[cp6]/46, Y[1] | NR    | NR   | CD34, CD33, CD7, cCD3 (ETP-ALL) | NR            | NR             | GRAALL    | CR, SCT, died 9 months |
|   | Gender | Age | Country | First | karyotype | LSI FISH | CD34 | CD33 | CD7 | cCD3 | CD38 | CD34 | CD3+ | CD4- | CD8- | CD33+ | CD1a- | CD5 dim | CD117+ | MPO+ | 5'SET exon7- | NUP214 exon18 3' | combination chemotherapy | HSCT | Induction therapy | Disease status |
|---|--------|-----|---------|-------|-----------|---------|------|------|-----|------|------|------|------|------|------|-------|-------|-------|-------|-------|-------|----------------|----------------|----------------------|------|-------------------|-----------------|
|   | Male   | 28  | France  | 41.8  | 46,XY,del(5) (q31q33),del(6)(q12q16),del(7) (q24),del(12)(p12),del(16)(q21)29]/47.idem.del(11q),+mar[4]/46,XY[3] | NR     | NR   | NR   | NR  | CD34, CD33, CD7, cCD3 | NR   | NR   | GRAALL trail | CR, SCT, alive 30 months |
|   | Male   | 20  | France  | 30.9  | 48,XY,del(5) (q31q33),del(6)(q12q16),del(7) (q24),del(12)(p12),del(16)(q21)29]/47.idem.del(11q),+mar[4]/46,XY[3] | NR     | NR   | NR   | NR  | CD7, cCD3 | NR   | NR   | GRAALL trail | CR, SCT, alive 28 months |
| Prokopiou C 201519 | Female | 48  | Cyprus  | NR    | del(17) (q11.2), del(6)(q16.1-q21) and del(12)(p12.1-13.1) | NR     | NR   | NR   | NR  | CD7+, CD5 dim, sCD3+, cCD3+, CD4+, CD8-, CD34+, HLA-DR+, CD117+, MPO+, 5'SET exon7- NUP214 exon18 3' | combination chemotherapy | ASCT from her fully matched sibling, relapsed one year after ASCT, died during induction therapy |
|   | Male   | 45  | Cyprus  | NR    | NR ### del (17) (q11.2), del(6)(q16.1-q21) and del(12)(p12.1-13.1) ### | NR     | NR   | NR   | NR  | CD7+, CD38+, CD34+, CD3+, CD4-, CD8-, CD34+, CD1a- | NR   | NR   | combination chemotherapy | ASCT from a fully matched unrelated donor, died six months after ASCT |
| Lee 201120 | Male   | 28  | Korea   | 37.2  | 47,XY,del(1) (p13p22),del(6)(q13q21),del(9)(q12),del(11)q13), -12,add(15) (p11.2),del(16)(q22),+19,+mar[3]/46,XY[17] | NR     | NR   | NR   | NR  | positive expression of CD5 (67%), CD7 (95%), CD33 (79%), and CD34 (53%), negative for CD3, CD10, CD19, and CD20 | NR   | NR   | prednisolone, vincristine, L-asparaginase, daunomycin, cytarabine, and methotrexate, CR, SET-NUP214 fusion transcript* | The patient is scheduled to receive HSCT from an unrelated donor. |

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|        | Sex  | Age (y) | Country | WBC (*10⁹/L) | Blast (%) | Karyotype | Array | FISH | Immunophenotype | Gene Mutation | Fusion Position | Treatment                     | Follow-Up                           |
|--------|------|---------|---------|--------------|-----------|-----------|-------|------|-----------------|---------------|----------------|--------------------------------|-------------------------------------|
| Yang 2020³ | Male | 26      | China   | 12.3         | 97        | 46, XY, del(11) (q13), del(13)(q14), inv(16)p13.3q23 | NR    | NR   | Positive for CD7, CD99; partial expressed cCD3, CD33, CD34, CD10; weak expressed CD2; negative for Surface CD3, cCD79a, CD117, CD13, CD19, HLA-DR, cTDT, CD56, CD4, CD5, CD1a, CD8, CD33, CD56, CD15, CD64 | NR | NR | VICP with cytarabine 2 g, d1-3 | Candida tropicalis septicemia, died +15 days |
| Male   | 51   | China   | 109.1   | 89.7         | Normal    | NR       | NR    | NR   | Positive for CD7, CD33, CD99, CD10; partial expressed CD34, cCD3, CD5; weak expressed cTDT; negative for surface CD3, CD1a, CD4, CD2, CD3, CD8, CD117, CD13, CD19, HLA-DR | NR | NR | VICP, mitoxantrone, etoposide and cytarabine | Infected with Pseudomonas aeruginosa and Stenotrophomonas maltophilia, died +37 days |
| Male | 37 | China | 131.5 | 89.5 | 45, XY, der (17;19) (q10;q10)/46,XY | NR | NR | Positive for CD7, CD99, CD38, CD34, CD33, HLA-DR; partial expressed cCD3; weak expressed cTdT; negative for surface cCD79a, CD1a, CD4, CD2, CD3, CD117, CD13, CD19, CD10, cMPO, CD56, CD16, CD5 | NR | NR | CALGB9111; CLAG Combined with asparaginase Infected by Stenotrophomonas maltophilia, partial remission, alive, 10 months |
|------|----|-------|--------|------|---------------------------------|-----|-----|-------------------------------------------------|-----|-----|-------------------------------------------------|
| Lee 2012 Female | 43 | Korea | 60.6 | 85 | 46,XX,dup(1)(p22p36.1) | del(9q34.11–9q34.13)dup(1p36.11–1p22.3) | del(9)(q34)/ABL1 | Positive for CD3 (84%), CD5 (78%), CD7 (99%), CD13 (43%), CD33 (48%), and CD34 (80%). Negative for CD10, CD19, CD20, cCD22, CD14, HLA-DR, and myeloperoxidase. | NR | 5'SET exon7-NUP214 exon18 3' | NR | NR |
| Gorello 2010 Male | 38 | Italy | 24 | NR | 46,XY[15] | NR | del(9)(q34)/ABL1 | Pre-T NOTCH 1 | NR | CR, ASCT, alive +29 months |
| Male | 19 | Italy | 3.28 | NR | 46,XY[15] | NR | del(6)(q16)/GRK2 del(9)(q34)/ABL1 del(12p)/ETV6 | Pre-T NOTCH 1 | NR | CR, SCT, relapse, Cord blood transplant, died +23 months |
| Male | 47 | Italy | NR | NR | Failed | NR | del(9)(q34)/ABL1 | Cortical FBW7 | NR | NR | Refused treatment |

(Continued)
| Sex   | Age (y) | Country | WBC (*10^9/L) | Blast (%) | Karyotype | Array | FISH | Immunophenotype | Gene Mutation | Fusion Position | Treatment | Follow-Up       |
|-------|---------|---------|---------------|-----------|-----------|-------|------|-----------------|---------------|----------------|-----------|----------------|
| Female | 27      | Italy   | NR            | NR        | Failed    | NR    | del(9) (p21)/CDKN2A-B del(9) (q34)/ABL1 del(11) (p13)/LMO2 del (11)(q14)/CALM | Pre-T | NOTCH1           | NR         | NR             | Resistant died +12 months |
| Male   | 19      | Italy   | NR            | NR        | Failed    | NR    | del(9) (q34)/ABL1 del (11)(p13)/LMO2 del (11)(q14)/CALM del (12)(p13)/ETV6 | Pro-T | NR              | NR         | NR             | CR, alive +3 months       |
| Male   | 18      | Italy   | NR            | NR        | Failed    | NR    | del(9) (q34)/ABL1 del (5)(q35)/TLX3 | Pre-T | NR              | NR         | NR             | CR, relapse, died +24 months |
| Male   | 23      | Italy   | NR            | 46,XY[12] | NR        | del(9) (q34)/ABL1 | Pre-T | NR              | NR         | NR             | CR, relapse, ASCT, died +17 months |

**Abbreviations:** SCT, stem-cell transplantation; ASCT, allogeneic stem cell transplantation; CR, complete remission; NR, not report; VICP, vindesine, idarubicin, cyclophosphamide, dexamethasone; CALGB9111, cyclophosphamide, doxorubicin, vincristine, prednisone, L-asparaginase; CLAG, cladribine, cytarabine, granulocyte colony-stimulating factor (G-CSF).
| Sex       | Age (y) | Country | Diagnosis | Blast (%) | WBC (*10^9/L) | Karyotype | Array | FISH | Immunophenotype | Gene Mutation | Fusion Position | Treatment                  | Follow-Up                                      |
|-----------|---------|---------|-----------|-----------|---------------|------------|-------|------|-----------------|---------------|----------------|----------------|--------------------------------|
| Vonlindern 1992 | Male 19 | Netherlands | AUL       | NR        | NR            | 46,XY     | t(9;9)(q34;q34) and no del(9) (q34.1;q34.13) | NR | NR | 5'SET exon7- NUP214 exon18 3' | NR | NR |                                                                 |
| Kim 2010 | Male 40 | Korea | AUL       | 84        | 53            | 46,XY(20) | del(9) (q34.1;q34.13) del(9)(q22) | del(9) (q34)/ ABL1 | CD7 (95.6%), CD33 (51.7%), CD117 (73.8%), and CD38 (94.8%), CD3 (13%), MPO(-), CD22 (0.1%), CD79a (2.6%), CD19 (0%) | 5'SET exon7- NUP214 exon18 3' | 5'SET exon7- NUP214 exon18 3' | Cytosine arabinoside and idarubicin | CR, alive 7 months, lost to follow-up |
| Dong 2017 | Male 31 | China | AUL       | 56.8      | 3.6           | 46,XY[2] | positive for CD34, CD117, CD7, CD71, CD38, CD33, CD123, HLA-DR | NR | NR | 5'SET exon7- NUP214 exon18 3' | 5'SET exon7- NUP214 exon18 3' | 5'SET exon7- NUP214 exon18 3' | Mitoxantrone, cytarabine (MA) | CR was achieved after 2 cycles of MA regimen, but in the fourth course of consolidation chemotherapy central nervous system leukemia was suspected, and the patient refused further treatment |
| Male 35 | China | M1      | 91.2      | 8.0        | 46–49,XY, del(1) (p13p31), t (6;6) (q27; q21), del(3) (p11), inc [cp13] / 46,XY(7) | NR | NR | Positive for CD34, CD117, CD38, HLA-DR, CD33, CD11b, CD7, CD71, CD123, CD4 | NR | NR | 5'SET exon7- NUP214 exon18 3' | Mitoxantrone, etoposide, cytarabine (MEA) | CR, relapse 14 months after diagnosis |
| Male 38 | China | M2      | 56        | 1.6        | 46,XY [20]   | NR | NR | positive for CD34, CD38, HLA-DR, CD33, CD13, CD123, CD19, CD7, CD71, MPO | NR | NR | 5'SET exon7- NUP214 exon18 3' | Daunorubicin, cytarabine (DA) | CR, die of septic shock during the second treatment course |

(Continued)
Table 2 (Continued).

|                  | Sex | Age (y) | Country | Diagnosis | Blast (%) | WBC (*10^9/L) | Karyotype                                      | Array | FISH | Immunophenotype | Gene Mutation | Fusion Position | Treatment                        | Follow-Up                                      |
|------------------|-----|---------|---------|-----------|-----------|---------------|------------------------------------------------|-------|------|-----------------|---------------|----------------|----------------------------------|-----------------------------------------------|
| Jeong 2019⁸      | Male| 46      | Korea   | M1        | 89        | 17.1          | 59–90, XXXY,1, −2,5, −7,7, −10,13,13, −16, −17, −18, −21[cp23] | NR    | del(9)(q34)/ ABL1 | positive for MPO, CD33, CD7, CD34, and CD71 antigens | NR   | 5’SET exon18- NUP214 exon18 3’ | idarubicin and cytosine arabinoside           | CR and MR, the patient received allogenic peripheral blood stem cell transplantation from a full-matched sibling donor; still alive for 8 months |
| Rosati 2007⁵     | Male| 35      | Italy   | M4        | 90        | 40            | Normal | del(9)(q34) / ABL1 | positive for myeloperoxidase, CD34, CD33, CD13, CD45, CD66b, CD15 and CD11b antigens | none | 5’SET exon7- NUP214 exon18 3’ | daunorubicin and cytosine arabinoside       | CR, HSCT from his HLA-identical brother four months after diagnosis |
| Zhu 2016⁶        | Male| 19      | China   | B-ALL (pro-B) | 92.5        | 217           | 56,XY,+6, +8,12,+13, +15,+19, +20,+21, +21,+mar (11)45-49 and 48,XY, +12,+15, +16,+17 (q10), +21, +22,+mar2 (q5)46,XY (4) | NR    | NR | HLA-DR+, CD34+, CD38 +, CD58+, cytoplasmic (c) CD79a+, CD19+ (dim), CD22+ (dim), CD33+, CD13+, CD7+, CD11b+, CD10, CD17, cCD3-, CD3-, CD4-, CD8-, CD20, CD25-, CD103+, CD14, CD64, CD11b, FMC7-, c myeloperoxidase (MPO)-, c immunoglobulin (Ig)M, IgG-and IgA- | NR   | 5’SET exon7- NUP214 exon18 3’ | cyclophosphamide, vindesine, daunorubicin and prednisone | Not remission, waiting for allo-HSCT |
| Nowak 2010⁵⁶     | Female| 42     | The USA | B-ALL     | NR         | NR            | Normal | del(9)(q34) | del(9)(q34) | NR | 5’SET exon8- NUP214 exon17/18 3’ | NR | NR | NR | |
cases and is usually associated with poor prognosis and secondary AML.\textsuperscript{30} The detected mutations in the present case have not been reported in the related literature.

Case 3 in our report was diagnosed with MS. This is a manifestation of extramedullary soft tissue masses which may develop as part of AML, myeloproliferative neoplasm, myelodysplastic syndrome or at relapse, especially in patients following allogeneic HSCT.\textsuperscript{31} Additionally, most of the literature about MS consists of case reports and small retrospective studies, and thus there is limited clinical knowledge of the cases and their presentation and management plans.\textsuperscript{32} Remarkably, this present case did not show any blast infiltration into the bone marrow, which is termed isolated or primary MS. Because high proportions of isolated MS patients may progress to AML, the recommended treatment regimen is conventional AML protocols.\textsuperscript{33}

At present, research on the \textit{SET-CAN} fusion gene mainly focuses on T-ALL. Although many studies have been performed on the \textit{SET-CAN} fusion gene, the related clinical characteristics and the pathogenesis of leukemia are still unclear. Van Vlierbergh et al\textsuperscript{34} analyzed 92 patients with T-ALL. The \textit{SET-CAN} fusion gene was identified in three patients and in the T-ALL cell line LOUCY. Further study revealed that the \textit{SET-CAN} fusion gene inhibited the differentiation of T-cells by increasing the expression level of \textit{HOXA}, thus promoting the occurrence of T-ALL. Similarly, another study conducted by Gorello et al\textsuperscript{35} showed that the \textit{SET-CAN} fusion gene was identified in seven out of 152 patients with T-ALL. Subsequently, gene expression profiling identified a signature characterized by \textit{HOXA} and \textit{NUP214} upregulation and \textit{SET} downregulation. Quentmeier et al\textsuperscript{11} performed RT-PCR-based screening of 141 leukemia/lymphoma cell lines of T-, B- and myeloid cell origin to detect the \textit{SET-NUP214} fusion gene. That study only demonstrated the presence of the \textit{SET-NUP214} gene in the T-ALL cell line LOUCY and in the AML cell line MEGAL. Moreover, quantitative RT-PCR confirmed a positive correlation between \textit{SET-NUP214} and \textit{HOX} gene expression in the cell line LOUCY when compared to six other T-ALL cell lines. Meanwhile, genomic sequencing localized the breakpoints of the \textit{SET} gene to regions downstream of the stop codon and to \textit{NUP214} intron 17/18 in both the LOUCY and MEGAL cell lines.

As for the study of the \textit{SET-CAN} fusion in the pathogenesis of leukemia, it has been reported that it may be related to aberrant intracellular localization of hCRM1, a nuclear export factor. Current research results indicated that SET and CAN were found in the nucleus and the nuclear envelope, respectively, whereas SET-CAN was primarily localized in the nucleus and interacts with hCRM1. Thus, the export of SET-CAN could be affected by hCRM1, which may lead to oncosenescence.\textsuperscript{36} Kandilci, et al\textsuperscript{36} verified that the \textit{SET-CAN} fusion gene not only inhibits the differentiation of primitive progenitors but also committed myeloid cells (U937T) and therefore contribute to leukemogenesis. Subsequently, that same research group presented a transgenic mouse model that expresses the \textit{SET-CAN} fusion gene in hematopoietic progenitor cells to further explore the role of \textit{SET-CAN} in leukemogenesis.\textsuperscript{37} However, \textit{SET-CAN} mice were not leukemia-prone and did not show shortening of disease latency after retroviral tagging. Surprisingly, \textit{SET-CAN} mice developed spontaneous hyperplasia of the stomach mucosa, which indicated a role of \textit{SET-CAN} in the proliferation of certain epithelial cells. A study conducted by Saito et al\textsuperscript{38} revealed that the \textit{SET-CAN} fusion gene affected hematopoietic cell differentiation in a mouse model. Erythroid and megakaryocytic differentiation was impaired in SET-CAN transgenic mice.

Conclusion
In conclusion, the \textit{SET-CAN} fusion gene was very rare in patients with leukemia, but was more prevalent in young men, most of whom are diagnosed with T-ALL. Conventional karyotype analysis was unable to detect this chromosomal abnormality, and the overall prognosis may be relatively poor. Allogeneic HSCT may improve the prognosis. However, there was a great heterogeneity between different patients. The clinical characteristics of \textit{SET-CAN} positive patients and the pathogenesis of leukemia are not clear at present. The treatment efficacy and prognosis of patients may be also correlated with other genetic changes. More cases should be accumulated and summarized to better understand diseases related to this translocation.

Ethical Statement
Written informed consent to have the case details published was obtained from all the three patients, and the study was approved by Ethics Committee of the First Affiliated Hospital of China Medical University.

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Disclosure

The authors report no conflicts of interest for this work.

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