

# SET-NUP214 Fusion Gene Involved Early T-Cell Precursor Acute Lymphoblastic Leukemia in Adult with B Marker Expression

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**Abstract:** Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is rare and associated with poor clinical outcome especially in adults. ETP tumor cells that express cross-lineage antigens or lack pan T markers usually pose big challenges to diagnosis, and their prognostic implications are therefore more uncertain. This study reports the unique case of a 44-year-old woman with breast mass as the initial presentation of acute leukemia possessing both T- and B-cell features (cytoplasmic CD3<sup>+</sup>CD7<sup>+</sup>CD19<sup>+</sup>CD79a<sup>+</sup>). Despite the presence of gene rearrangements of *IGH* and *IGK* probably in a small amount of B cells, the patient was diagnosed with T-ALL mainly according to WHO criteria, and further ETP-ALL rather than mixed phenotype ALL based on additional positive expression of stem/myeloid lineage antigens (CD34<sup>+</sup>CD13<sup>+</sup>CD33<sup>+</sup>HLA-DR<sup>+</sup>). Moreover, in spite of normal karyotype, *SET-NUP214* gene fusion is identified, which has not been described in ETP-ALL with bi-phenotype. After intensive chemotherapy, the patient achieved short-term morphologic complete remission but relapsed within one month. This report may expand immunophenotype and clinical behavior of ETP-ALL in adults. Comprehensive evaluations are emphasized in making a differential diagnosis and distinguishing subtypes of acute leukemia.

**Keywords:** adult acute lymphoblastic leukemia, early T-cell precursor, mixed phenotype acute leukemia, breast infiltration, *SET-NUP214* fusion gene

## Introduction

Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) accounts for about 17% of T-ALL and is highly aggressive.<sup>1</sup> Besides the concurrence of myeloid/stem cell signatures, this hematopoietic malignancy with B marker expression is exceptionally rare, and usually poses big challenges to diagnosis. Additionally, patients with infiltration of the breast were only sporadically recorded over the last decades either at initial presentation or during relapse of acute leukemia, and their clinical outcomes varied.<sup>2,3</sup> Due to a general absence of ALL manifestations, differential diagnosis on ultrasonography and immunophenotyping is therefore essential in case patients are mistaken for benign breast mass or primary mammary carcinoma. Furthermore, the *SET-NUP214* fusion gene is an uncommon genetic event. It has been observed in mixed phenotype acute leukemia (MPAL), like acute undifferentiated leukemia and B/M MPAL,<sup>4</sup> and exists in only <6% of T-ALL. Data regarding its effects on prognosis remained controversial as some cases with *SET-NUP214* demonstrated no significant differences on survival, but better prognosis in a study containing a series of adult

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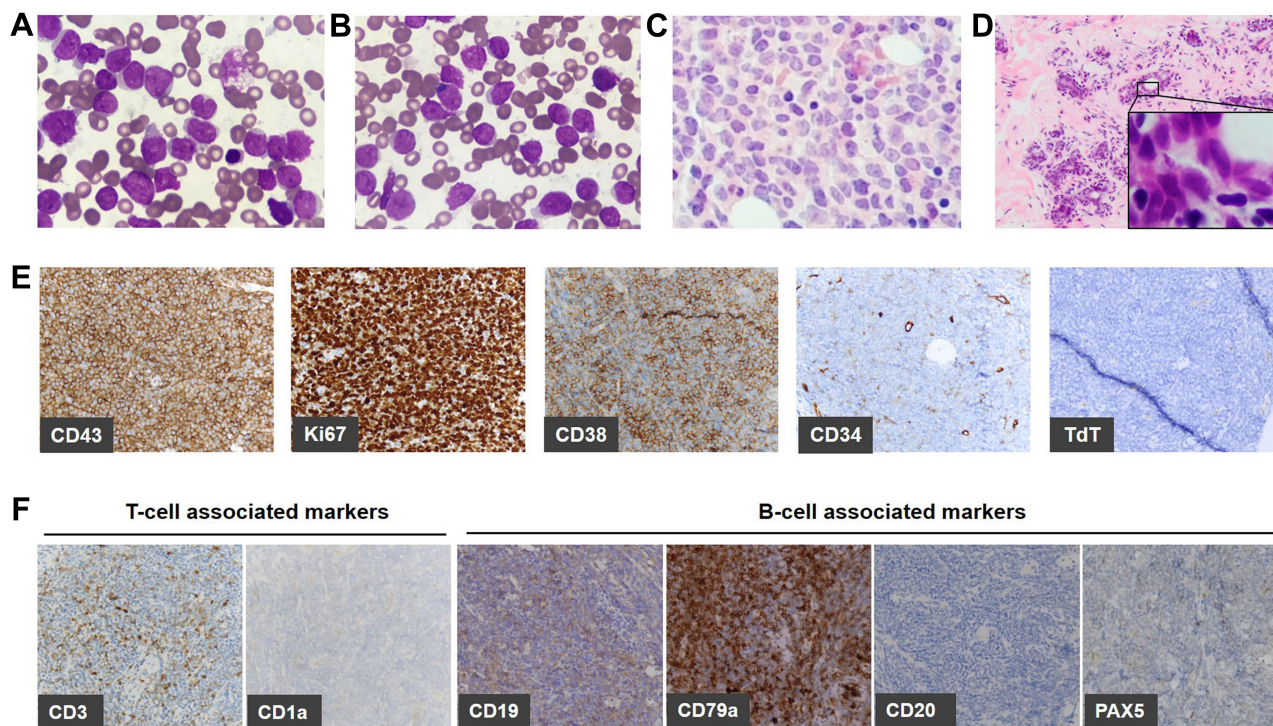
T-ALL was shown by Chen et al.<sup>5,6</sup> However, it was recently proposed as a risk predictor.<sup>7,8</sup> To date, clinical manifestations of ETP-ALL with this fusion gene are quite limited. Herein, we present a unique *SET-NUP214* fusion involved ETP-ALL with B marker expression. The patient experienced mild clinical course with breast masses as first presentation, but progressed fast. After ALL strategy treatment, she just got temporary complete remission (CR) and soon relapsed. This case may help expand the expression profile and clinical behavior of ETP-ALL, and might provide more clues in tracking the cell of origin of ETP-ALL in adults.

### Case Presentation

A 44-year-old woman was admitted with a chief complaint of painless masses in the breast found by chance, and had no history of malignancy. Results of physical examination including body temperature, blood pressure and superficial lymph node were within normal limits. Serum laboratory tests showed normal hemoglobin (140 g/L) and platelets - ( $111 \times 10^9/L$ ), but high levels of lactic acid dehydrogenase (507 U/L),  $\beta_2$ -microglobulin (1.47 mg/L) and white blood cells ( $21.1 \times 10^9/L$ ). Subsequently, the hemoglobin decreased to 97 g/L along with severe thrombocytopenia ( $33 \times 10^9/L$ ),

and white blood cells soared to  $78.95 \times 10^9/L$  in a half-month. Morphologically, hypercellular marrow was observed, and aberrantly increased white blood cells were detected in peripheral blood (PB). The majority of cells in both bone marrow (BM) and PB were medium- to large-sized leukemic blasts (>90%), which were irregularly shaped with high nucleus/cytoplasm ratio, fine chromatin and inconspicuous nucleoli (Figure 1A–C). Less residual mammary ducts remained and were shown by tumor biopsy (Figure 1D).

Immunohistochemistry (IHC) performed on core-needle biopsy at the mammary gland exhibited strong CD43 expression on tumor cells illustrating lymphoid/hematopoietic lineage commitment. Ki67 was high (>90%). The expression of CD38 was positive, while CD34 was merely punctate positive and terminal deoxynucleotidyl transferase (TdT) was negative (Figure 1E). Besides scattered positive expression of CD3, most lineage markers were negative (CD4<sup>-</sup>CD8<sup>-</sup>CD1a<sup>-</sup>CD10<sup>-</sup>CD20<sup>-</sup>PAX5<sup>-</sup>MPO<sup>-</sup>CD117<sup>-</sup>) except for CD19 and CD79a (partial results are shown by Figure 1F, Supplementary Figure S1). Consistently, flow cytometry (FCM) analyses using BM aspirate indicated a large single population of CD34<sup>+</sup>CD38<sup>+</sup>HLA-DR<sup>+</sup>



**Figure 1** Morphological and histological view.

**Notes:** (A) BM aspirate (1000×), (B) PB smear (1000×) and (C) BM biopsy (400×) indicated typical characteristics of leukemic blast. (D) Tumor tissue biopsy by hematoxylin–eosin staining showed residual mammary ducts (100×; local oil immersion view: 1000×). (E) Mammary gland biopsy showed positive expression of CD43, Ki67 and CD38, and negative TdT (400×). (F) Mammary gland biopsy presented positive expression of both T and B markers: CD3 (scattered), CD19 (weak) and CD79a, and negative CD1a, CD20 and PAX5 (400×).

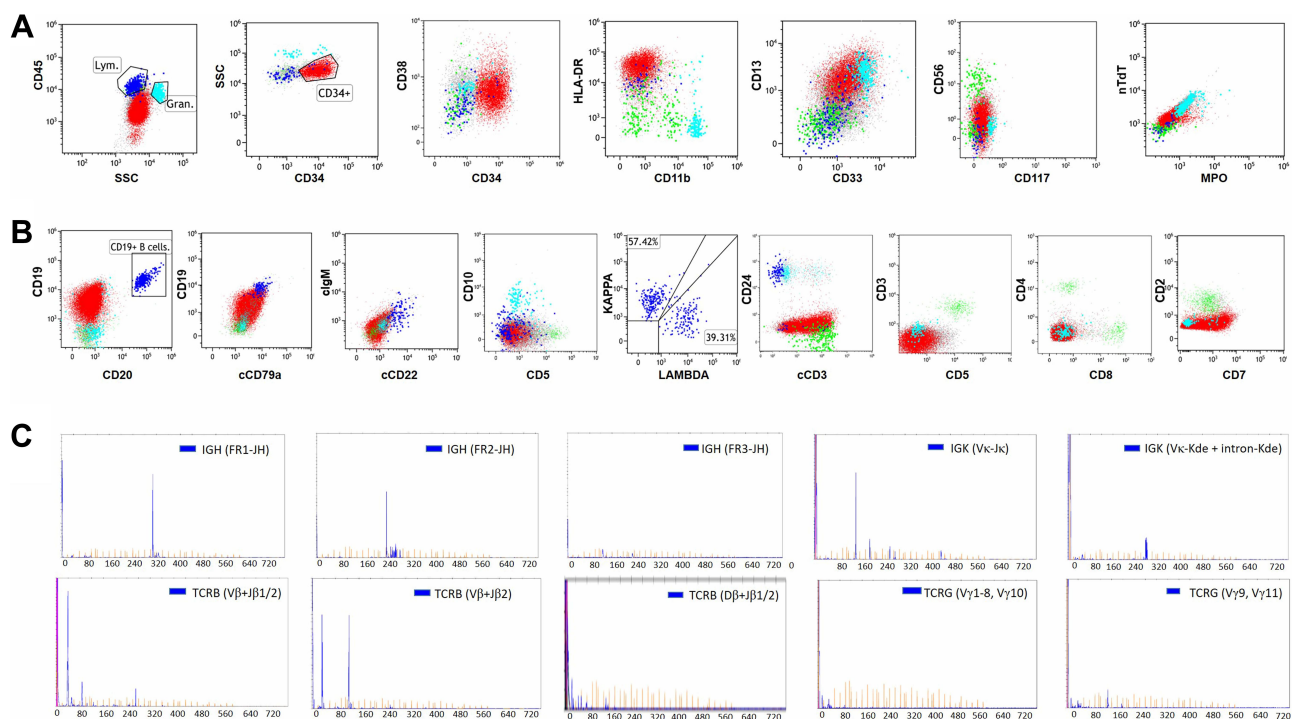
nTdT<sup>-</sup> tumor cells (75.31% of karyocytes) (Figure 2A). Myeloid marker MPO and additional B markers including cytoplasmic CD22 (cCD22), CD24 and cIgM were undetectable. As regards clonality assessment, restricted expression of B-cell immunoglobulin light chain was not found (Figure 2A and B). Noteworthy, these cells expressed cCD3, generally the most specific marker in T lineage assignment, and CD7, whereas other T antigens including surface CD3, CD2, CD4, CD8, CD5, CD1a and CD99 were negative (partial results are shown by Figure 2B).

Gene rearrangements of BCR immunoglobulin genes ( $V_H$ - $J_H$  framework region of *IGH* and *IGK*) and *TCR-beta* (*TCRB*) and *-gamma* (*TCRG*) were determined by the BIOMED-2 multiplex RT-PCR system (effective region scope is shown by Supplementary Table 1).<sup>9</sup> Both *IGH* and *IGK* rearrangements rather than TCR genes were revealed (Figure 2C). Moreover, a gene fusion test was carried out using a 43-gene panel that was frequently involved in ALL by quantitative RT-PCR (listed in Supplementary Table 2), and the *SET-NUP214* fusion gene was identified. Karyotype was normal (46, XX) (data not shown). Positron emission tomography and computed tomography (PET-CT) scan showed the largest mass at the right internal mammary region (3.0×3.6 cm<sup>2</sup>). Additional suspicious malignant

tumors observed at the anterior mediastinum, bilateral axillar, uterus corpus and cervix suggested multiple organ involvement (Figure 3A–D). Upon comprehensive evaluations, diagnosis of T-ALL was made mainly according to the WHO principle, and ETP-ALL was concluded finally. The patient did not respond to primary VDCLP (vincristine, daunorubicin, cyclophosphamide, L-Asp, and prednisone) chemotherapy. After the following one cycle of CAM (cyclophosphamide, cytosine arabinoside, 6-mercaptopurine) and chidamide strategy treatment, she achieved temporary morphologic CR (lymphoid cells <5% in either BM or PB), but unfortunately progressed soon within one month. Now, the patient is kept under ICU monitoring.

## Discussion

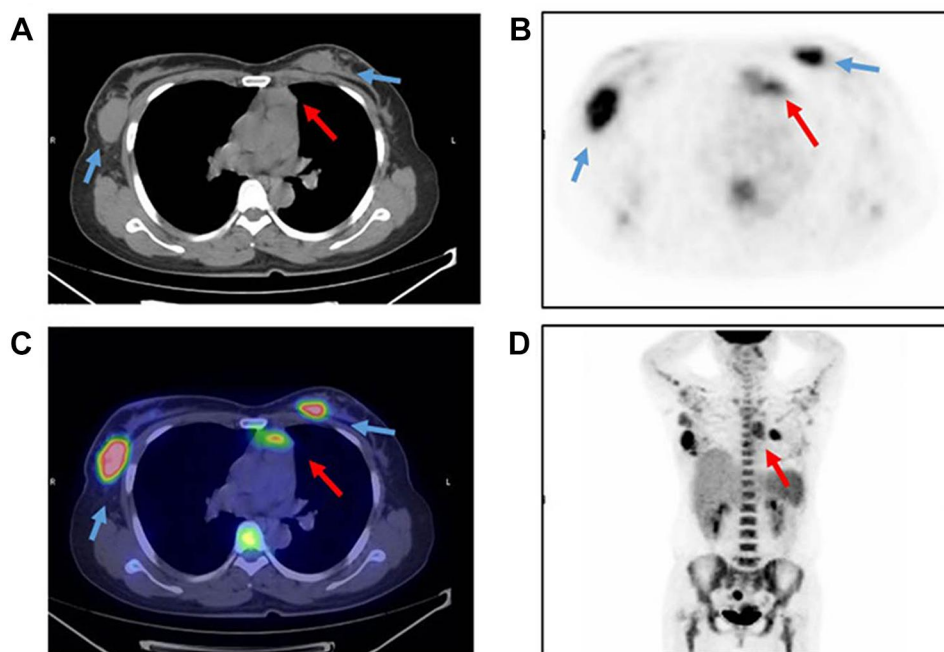
Among ALL cases presenting as a breast mass, MPAL is extremely rare,<sup>2,10</sup> and to our knowledge, there has been no similar case report of ETP-ALL infiltration of the breast. Upon combination therapy or hematopoietic stem cell transplantation (HSCT), lasting clinical remission could be achievable at initial presentation, but not for relapsed settings. Besides, bilateral breast infiltration may imply a diffuse leukemic process involving sanctuary organs. Unlike those previous cases of predominantly young girls (median age is about 20),<sup>2</sup> the



**Figure 2** Detection of immunophenotype by FCM analyses (tumor cells indicated in red).

**Notes:** (A and B) Co-expression of partial myeloid/stem cell-, T- and B-associated markers in tumor cells. (C) Clonality is assessed by the BIOMED-2 system showing single peaks at *IGH* (*FR1*, *FR2*) and *IGK* (*Vκ-Jκ*) (clonal peaks are indicated in nt by horizontal axis), and no rearrangement at either *TCRB* or *TCRG* genes.





**Figure 3** Imaging by PET-CT scan.

**Notes:** (A) CT plain scan showed multiple soft tissue shadows in the bilateral breast, bilateral axillar, uterus corpus, cervix and anterior mediastinum. (B) Cross-sectional view with radioactive concentration by PET ( $SUV_{max}$  is 5.6). (C) Hybrid imaging from CT (A) and PET (B). (D) Whole body MIP image. Red arrow shows the mass in the anterior mediastinum where accumulative uptake of  $^{18}F$ -FDG was presented. Two masses in the mammary region are shown by blue arrows.

patient described here is older. She remained asymptomatic except for breast masses initially, but the immunophenotype was fairly complex, making it challenging to distinguish the diagnosis of ETP-ALL from MPAL. Despite limited lineage clues upon primary IHC results, from the view of the European Group for Immunological Characterization scoring system, MPAL (B/T bi-phenotype) was possible for the patient ( $>2$  points for either lineage due to co-expression of CD19, cCD79a and cCD3).<sup>11</sup> However, the WHO definition cannot be satisfied because of dim or negative expression of CD10, CD22 and cCD79a besides dim CD19, and instead, a T-ALL diagnosis was made.<sup>12</sup> Actually, an arbitrary conclusion often occurs, partially because the latter further takes expression intensity into consideration although sometimes underpowered.<sup>13</sup> Additionally, the mediastinal mass, frequently presented in T-cell lymphoblastic lymphoma or T-ALL, might also prompt the T lineage malignancy assignment. Finally, based on concurrence of myeloid/stem cell-associated markers ( $CD34^+CD13^+CD33^+HLA-DR^+CD4^-CD8^-CD1a^-CD5^-$ ), the patient was diagnosed with ETP-ALL. In addition to the absence of TdT expression as extra evidence, this diagnosis could be further confirmed by other immunophenotypic score-based algorithms.<sup>14–16</sup>

Co-expression of B antigens has been already reported in both T-ALL and mature T-cell lymphoma with

controversial prognosis.<sup>17,18</sup> However, to our knowledge, there were only three ETP-ALL cases with B marker expression once discussed. They were immunophenotypically and genetically distinct.<sup>19,20</sup> The seemingly confusing result here was conjunction of gene rearrangements of both *IGH* and *IGK*, which were highly sensitive in detecting tumorous B cells,<sup>21</sup> although they could occasionally occur in either T-cell malignancy or in non-cancerous condition.<sup>22</sup> Considering that no detectable clonality of light chain protein expression was observed among either B cells or ETP tumor cells by FCM analyses, there is probably reactive proliferation existing in a small amount of mature monoclonal B cells, while less likely is a B lineage commitment potential of tumor cells. In contrast, the absence of TCR gene rearrangement could be explained by the most immature stage of T-cell development before CD1a starts to express.

ETP-ALL is believed to originate from thymus seeding progenitors (TSP). Since the immunophenotype of migrants from BM is highly heterogeneous as lineage commitment progresses, the cell of origin especially in adult ETP-ALL remains elusive. Here, the  $CD10^-CD7^+CD24^-$  tumor cells could be postulated to originate from lineage-negative  $CD34^+CD10^+CD24^-$  progenitors capable of circulating in blood throughout life and

generating a thymic TSP1 population.<sup>23,24</sup> Meanwhile, they also phenotypically overlap with TSP2 (CD10<sup>-</sup>CD7<sup>+</sup>), which was primed by *NOTCH* signals but transcriptionally distinct from TSP1 (Supplementary Figure S2).<sup>24</sup> Further gene expression profiling is needed to exploit the potential path involved.

Furthermore, *NUP214* gene fusion, critical in nuclear export of proteins and mRNA, is frequently involved in glucocorticoid chemotherapy resistance. Mechanically, it is capable of inhibiting histone 3 acetylation, which could eventually repress transcription activity of corticosteroid receptor. Thus far, 65% of patients involved are T-ALL (including ETP-ALL) with a male predominance. As far as we know, this is the first report showing *SET-NUP214* fusion in ETP-ALL with B antigen expression, suggesting its potential role in hematopoietic differentiation. In terms of clinical practice, ALL-based treatment is likely more effective than an acute myeloid leukemia-based strategy for ETP-ALL. However, the treatment outcome of this case is worse in comparison to that of three previous cases who relapsed within 120 to 505 days. Considering that *SET-NUP214* fusion was proven to be a good factor for clinical outcome when an intensive Hyper-CVAD-based regimen was used,<sup>6</sup> the poor clinical course is probably mainly ascribed to the ETP immunophenotype and concurrence of cross-lineage markers. In addition, although HSCT is performed more frequently in ETP-ALL than that in non-ETP-ALL,<sup>25</sup> it is not clear whether such cases with rapid progression could be benefited or not once the first morphologic CR is achieved. More recently, a “triple mutation” model was provided by Booth et al to highlight mutations of *RUNX1*, *EZH2* and *FLT3-ITD* genes in transformation of ETP, upon which bromodomain inhibitor involved treatment could be hopefully effective.<sup>26</sup> Meanwhile, certain novel strategies like monoclonal antibody against CD33, CD38 or CD123, and combination treatment are potentially promising.<sup>27</sup>

Collectively, we report the first *SET-NUP214* fusion involved ETP-ALL case with B-cell features, and emphasize the importance of comprehensive evaluations for diagnosis of ETP-ALL with extramedullary infiltration of the breast and ambiguous immunophenotype. Also, this case might add more evidence to blocked extrathymic differentiation of T precursors in adults. Further follow-up and more similar cases will facilitate the exploration of consensus on ETP-ALL treatment.

## Ethics Statement

This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital. Written informed consent was obtained from the patient’s family for the publication of all data and accompanying images.

## Author Contributions

All authors made substantial contributions to conception and design of this manuscript, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

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