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CASE REPORT

Bilineal T lymphoblastic and myeloid blast transformation in chronic myeloid leukemia with *TP53* mutation—an uncommon presentation in adults

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ABSTRACT

Bilineal blast transformation of myeloid and T lymphoid type is a rare event in chronic myeloid leukemia. Here, we report a case in which an adult presented with high white cell counts and lymphadenopathy. Bone marrow studies confirmed the presence of 9 and 22 chromosomal translocation, and a diagnosis of chronic myeloid leukemia in chronic phase was made. Examination of a lymph node showed both myeloid and T lymphoblastoid blast crisis. Molecular studies demonstrated the presence of *BCR-ABL* fusion transcripts in both the myeloid and the T lymphoblastic component, indicating that the myeloid and T lymphoid blast crisis components shared common progenitors. *TP53* deletion was demonstrated by fluorescence *in situ* hybridization.

KEY WORDS

Chronic myeloid leukemia, blast transformation, T lymphoblastic lymphoma, *BCR-ABL, TP53* mutation, myeloid sarcoma

1. INTRODUCTION

In chronic myeloid leukemia (CML), a T-cell lymphoid blast crisis is rare, although isolated cases have been described[1,2], including a recent report of a pediatric CML patient with nodal T lymphoblastic crisis[3]. In part because of the rarity of this condition, little is known about its cellular origins, pathogenesis, or clinical behaviour. Here, we report an adult CML patient with Philadelphia chromosome–positive bilineal blast crisis featuring myeloid sarcoma and T lymphoblastic lymphoma, with additional *TP53* mutation and expression of both major and minor *BCR-ABL* messenger RNA transcripts.

2. CASE REPORT

A 49-year-old woman presented to her general practitioner with a 3-month history of loss of weight, fever, and sweats. She had noticed lumps in her neck and groin. Blood tests revealed hemoglobin 7.2 g/dL, white cell count 520×10^9/L, and platelet count 422×10^9/L. Renal and liver function tests were normal. Peripheral blood and bone marrow were compatible with CML in chronic phase.

Computed tomography imaging revealed extensive cervical, axillary, mediastinal, retroperitoneal, pelvic, mesenteric, and inguinal lymphadenopathy. Reverse transcriptase-polymerase chain reaction for *BCR-ABL* in the marrow aspirate was positive for both the e14a2 and e1a2 transcripts. Metaphase analysis showed that the reciprocal translocation of chromosomes 9 and 22 [t(9;22)] was the sole cytogenetic abnormality. The *TP53* deletion was detected in 50% of 200 cells analysed by fluorescence *in situ* hybridization (FISH).

Our patient underwent an excisional lymph node biopsy that revealed two distinct cellular populations. The first population comprised nodules of CD117+, myeloperoxidase-positive, lysozyme-positive, terminal deoxynucleotidyl transferase (TdT)–negative immature myeloid precursors lacking in B- or T-cell markers (except for CD7) showing a low proliferation fraction of less than 20% by Ki-67 immunostaining, in keeping with myeloid sarcoma. They were surrounded by a predominant population of T lymphoblasts that expressed precursor lymphoid cell markers (CD34, TdT, CD99) and pan-T markers CD2, CD3, CD5, and CD7 (with diminution of CD2 and CD3). This T lymphoblastic lymphoma component displayed a high proliferation fraction of about 70% with Ki-67 immunostaining.

In keeping with the finding of *TP53* deletion, double immunostaining showed inactivation of *TP53,* with loss of downstream *p21/WAF1* and stabilization of p53 protein. Figure 1 shows the histology and phenotype of the nodal biopsy. Interphase FISH confirmed the presence of t(9;22) translocation using duo-colour, duo-fusion probes (Abbott Laboratories, Abbott Park, IL, U.S.A.). Combined immunofluorescence and FISH (FICTION technique)[4,5] confirmed the

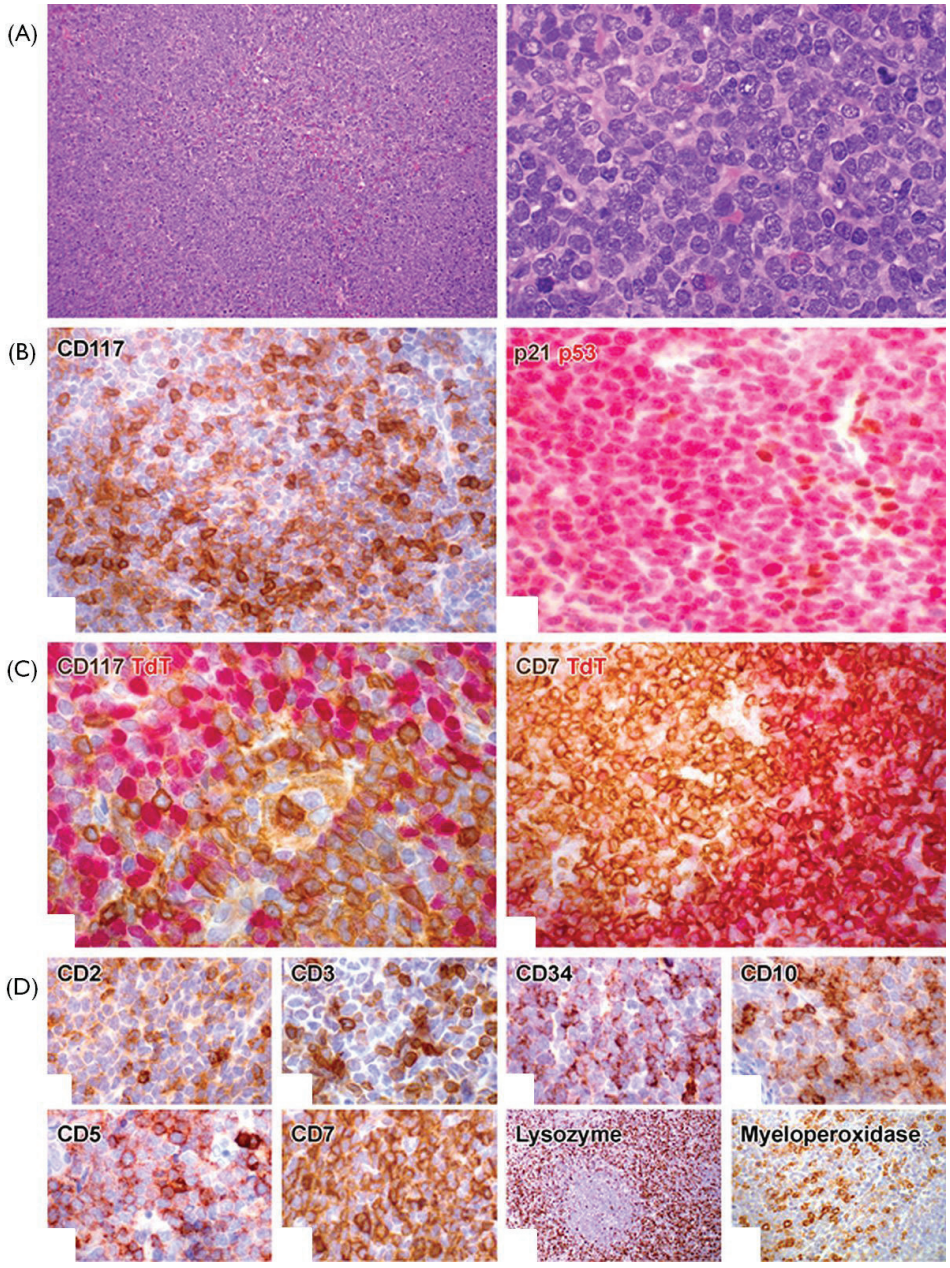

FIGURE 1 *Histologic features and phenotype. (A) Microscopic appearance of the lymph node biopsy shows a diffuse infiltrate of blast cells. (B,C) Immunophenotype demonstrates nodular aggregates of CD117+ terminal deoxynucleotidyl transferase (TdT)–negative myeloid blasts (left panels), surrounded by sheets of T lymphoblasts that express TdT but not CD117, although co-expression of CD7 is seen in both blast populations (right panels). (B) Double immunostaining shows expression of p53 but not p21, in keeping with mutated* TP53 *(right panel). (D) In addition, the T lymphoblastic lymphoma component expresses pan-T markers CD2 (weak), CD3 (weak), CD5, CD7, and precursor lymphoid markers CD34 and CD99; meanwhile, the myeloid sarcoma component expresses myeloperoxidase and CD10.*

presence of this translocation in both the CD117+ myeloid sarcoma population and the second subset of CD34+ CD3+ TdT+ T lymphoblasts (Figure 2).

In summary, our patient presented with features of chronic-phase CML in the bone marrow, with bilineal acute transformation into myeloid sarcoma and T lymphoblastic lymphoma in the lymph node. Both blast populations harboured the *BCR-ABL* translocation as demonstrated in the immunoFISH study. The bone marrow aspirate showed isolated t(9;22) translocation on karyotyping, and the FISH analysis picked up an additional *TP53* deletion.

Our patient was treated with hyper-CVAD (course A: cyclophosphamide, vincristine, doxorubicin, dexamethasone; course B: methotrexate, cytarabine) and imatinib. After 2 cycles of therapy,

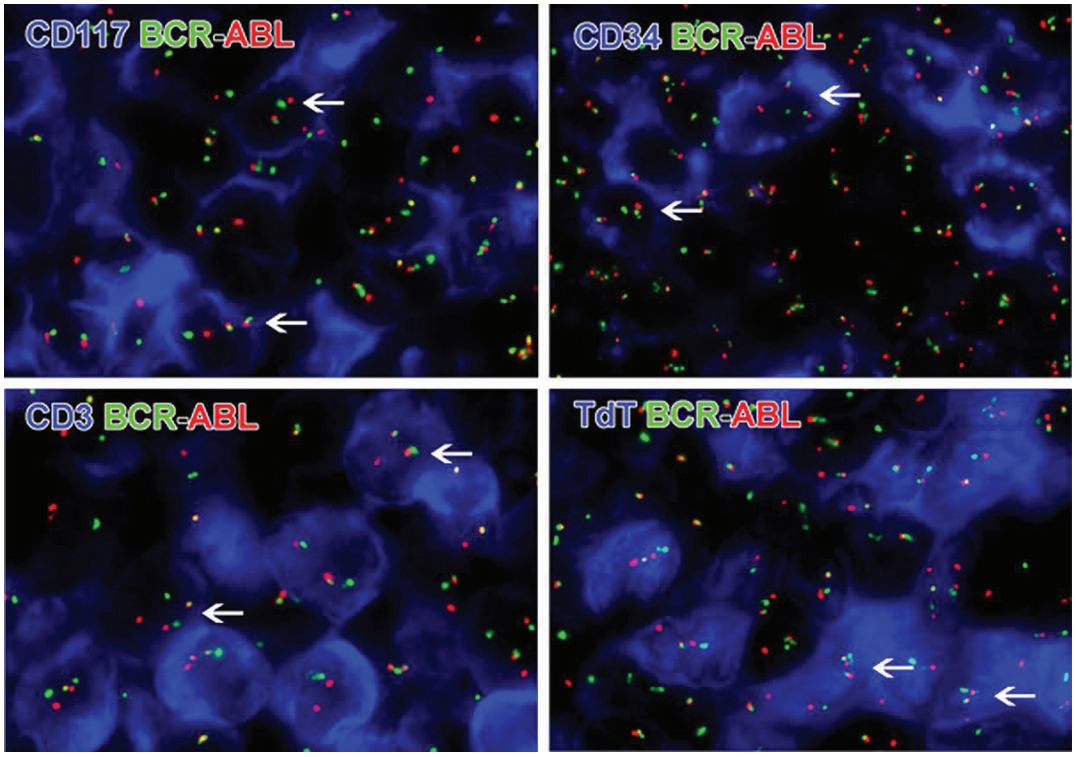

FIGURE 2 FICTION *(fluorescence immunophenotyping and interphase cytogenetics as a tool for the investigation of neoplasms) technique. Combined interphase fluorescence* in situ *hybridization for* BCR-ABL *fusion, with immunofluorescence, confirms the presence of t(9;22) translocation in the CD3+ CD34+ terminal deoxynucleotidyl transferase (TdT)–positive T lymphoblastic lymphoma and the CD117+ myeloid sarcoma components.*

blood counts normalized, with regression of the previously demonstrated lymphadenopathy. Copies of the *BCR-ABL* transcript were steadily decreasing on quantitative polymerase chain reaction. After 4 cycles of chemotherapy, this woman underwent allogeneic bone marrow transplantation from a sibling donor. She is currently 6 months post-transplant, having achieved a major molecular remission.

3. DISCUSSION

This case is interesting for a number of reasons and may throw light on the pathogenesis of this entity.

3.1 Origin from Pluripotent Hematopoietic Stem Cells

Although lymphoblastic crises constitute one third of blast crises in CML, most show a pre-B phenotype; T lymphoblastic transformation is rare. A T lymphoblastic crisis has been reported in CML patients, simultaneously[1] or metachronously after the diagnosis of CML. A bilineal T lymphoblastic and myeloid blast crisis in CML is even rarer, with isolated cases being reported in adults[1] and children[2,6]. In the present case, a bilineal blast transformation of the myeloid and T lymphoblastic types, both of which displayed *BCR-ABL* translocations proved by both quantitative polymerase chain reaction and interphase FISH, a finding which suggests that T lymphoid and myeloid blasts share common progenitors that are positive for *BCR-ABL* translocations. In other words, the acquisition of the *BCR-ABL* translocations in CML may occur in a hematopoietic stem cell before separation into common myeloid and lymphoid precursors.

3.2 Secondary Genetic Alterations

The incidence of *TP53* deletion in CML blast crisis is reported to be approximately 10%[7,8] and is more often associated with myeloid blast crisis[7]. A series of 92 CML patients published by Uike *et al.*[8] reported that *TP53* deletions were associated mostly with myeloid blast crisis: *TP53* deletion was found in 4 of 10 myeloid blast crisis samples and in only 1 of 8 lymphoid blast crisis samples. Okazuka *et al.*[9] reported a T lymphoblastic crisis in CML with an additional t(6;8)(q25;q22) translocation. To our knowledge, however, *TP53* deletion has not been described in a CML T lymphoid blast crisis. Although composite myeloid and T lymphoid blast crisis has recently been described in two reports[3,6], such an event is reportedly infrequent in adults; a search of PubMed located only one case report[1]. As best we can determine, no cases of composite T lymphoblastic and myeloid

blast crisis in CML demonstrating *TP53* deletion have been reported.

Our case closes a gap in the understanding of CML blast crisis with demonstration of a *TP53* deletion in a bilineal T lymphoblastic and myeloid blast crisis, which is very uncommon and not to our knowledge previously reported.

4. ACKNOWLEDGMENT

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5. CONFLICT OF INTEREST DISCLOSURES

SK, CC, and SYT designed the research, performed the research, contributed bio-resources and data, analyzed data, and wrote the paper. KS performed research and analyzed data. All authors declare that there are no competing financial interests with respect to the preparation of this work.

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