



# Myeloid and lymphoid neoplasm with novel complex translocation: unusual case report with T-lymphoblastic lymphoma, myeloid hyperplasia, eosinophilia, basophilia, and t(1;8;10)(p31;q24;q11.2)

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Received: 18 October 2022 / Accepted: 22 December 2022 / Published online: 29 December 2022

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## Abstract

Myeloid and lymphoid neoplasms with eosinophilia (M/Ls-Eo) encompass heterogeneous but aggressive hematopoietic disorders triggered by fusion genes or mutations that typically lead to constitutive overexpression of tyrosine kinase. The occurrence of T-lymphoblastic lymphoma in the setting of M/Ls-Eo has been reported rarely in the literature. Herein, we present an unusual case of a 28-year-old male patient who presented with massive lymphadenopathy and T-lymphoblastic lymphoma in the lymph node occurring concurrently with myeloid hyperplasia, eosinophilia and basophilia in peripheral blood and bone marrow biopsy. The syndrome was associated with a novel complex karyotype involving der(8)t(1;8;10)(p31;q24;q11.2). The FISH study was negative for *BCR::ABL1*, *JAK2*, *PDGFRA*, *PDGFRB*, and *FGFR1* rearrangements. The patient's clinical course was aggressive and resistant to multiple lines of intensive chemotherapy regimens. Therefore, he underwent allogeneic stem cell transplantation with a fully matched donor. A brief review of the occurrence of T-LBL in conjunction with M/Ls-Eo neoplasm was made with a special focus on molecular aspects.

**Keywords** Myeloproliferative neoplasm · Eosinophilia · T-Lymphoblastic lymphoma

## Introduction

T-Lymphoblastic lymphoma (T-LBL) is an aggressive malignancy that arises from the neoplastic transformation of immature precursor T cells and is characterized by the proliferation of T lymphoblasts in bone marrow, thymus, nodal and extra-nodal sites [1, 2]. On rare occasions, T-LBL occurs in the setting of myeloid and lymphoid neoplasm with eosinophilia (M/Ls-Eo). Such syndromes are highly aggressive and potentially lead to a diagnostic dilemma [3, 4].

Here we describe an unusual case of myeloid and lymphoid neoplasm with massive lymphadenopathy and T-lymphoblastic lymphoma in the lymph node occurring concurrently with myeloid hyperplasia, eosinophilia and basophilia in peripheral blood and bone marrow biopsy.

Moreover, it was associated with a novel complex karyotype and aggressive clinical course.

## Patient and methods

### Case report

A 28-year-old male patient presented to our hospital with a 3-week history of bilateral extensive and massive cervical, axillary and inguinal lymphadenopathy preceded by 3 months of mild sweating and loss of 9 kg of body weight. His past medical and family history were unremarkable. During the physical examination, no skin manifestations or hepatosplenomegaly were observed.

Laboratory investigations revealed a hemoglobin of 12 g/dL, platelet count was  $626 \times 10^9/L$ , and white cell count (WBC) of  $74.8 \times 10^9/L$ , with neutrophils of  $42.8 \times 10^9/L$ , lymphocytes were  $6.9 \times 10^9/L$ , monocytes were  $7.9 \times 10^9/L$ , eosinophils were  $11.5 \times 10^9/L$  and basophils were  $5.7 \times 10^9/L$ . Peripheral blood smear examination showed marked myeloid hyperplasia with left-shifted granulocytes,

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eosinophilia, basophilia, and monocytosis. The circulating blasts were 2%.

Both bone marrow aspirate and trephine biopsy yielded a markedly hypercellular bone marrow (100% cellularity) with myeloid hyperplasia and prominent eosinophilia (44%) without any significant dysplastic changes. Blasts were 4% with myeloid phenotype and no aggregates of immature-looking or lymphoid cells were detected (Fig. 1A).

A morphological diagnosis of chronic myeloid leukemia in chronic phase (CML-CP) was suspected and the patient was started on a short course of dasatinib 50 mg. However, *BCR::ABL1* (p210) mRNA transcript level was evaluated using Xpert *BCR::ABL1* ultra Assay (Cepheid) and was negative. The initial morphological suspicion of CML was thus re-evaluated.

A right submandibular lymph node biopsy was performed and revealed diffuse infiltration with monotonous small to medium immature-looking cells (Fig. 1B). The immunohistochemistry stains (GA-R2; Ventana Medical System, Inc.) showed strong positivity for CD1A, CD2, CD3, CD4, CD5, CD7, and TDT while Ki 67 was 90%. (Fig. 1C and D). They were negative for CD8, CD30, CD156, CD20, CD34, and granzyme B. The final report of lymph node biopsy was consistent with acute T-lymphoblastic lymphoma (T-LBL).

Chromosomal karyotyping was performed on 20 metaphases that demonstrated the presence of complex

translocation involving  $\text{der}(8)\text{t}(1;8;10)(\text{p}31;\text{q}24;\text{q}11.2)$  in 100% of the analyzed cells (Fig. 2). An extended panel of fluorescent in situ hybridization (FISH) was carried out on the bone marrow cells and yielded negative results for *BCR::ABL1*, *JAK2*, *ETV::RUNX1*, *KMT2A* gene, *C-MYC* gene, *TCF3::PBX1*, *IGH::IL3*, *TCR* gene, *PDGFRA*, *PDGFRB*, and *FGFR1*. Bone marrow specimen was sent out to a reference laboratory for repeating the FISH study for *PDGFRA*, *PDGFRB*, and *FGFR1* rearrangements, the results of which were within normal limits for all genes.

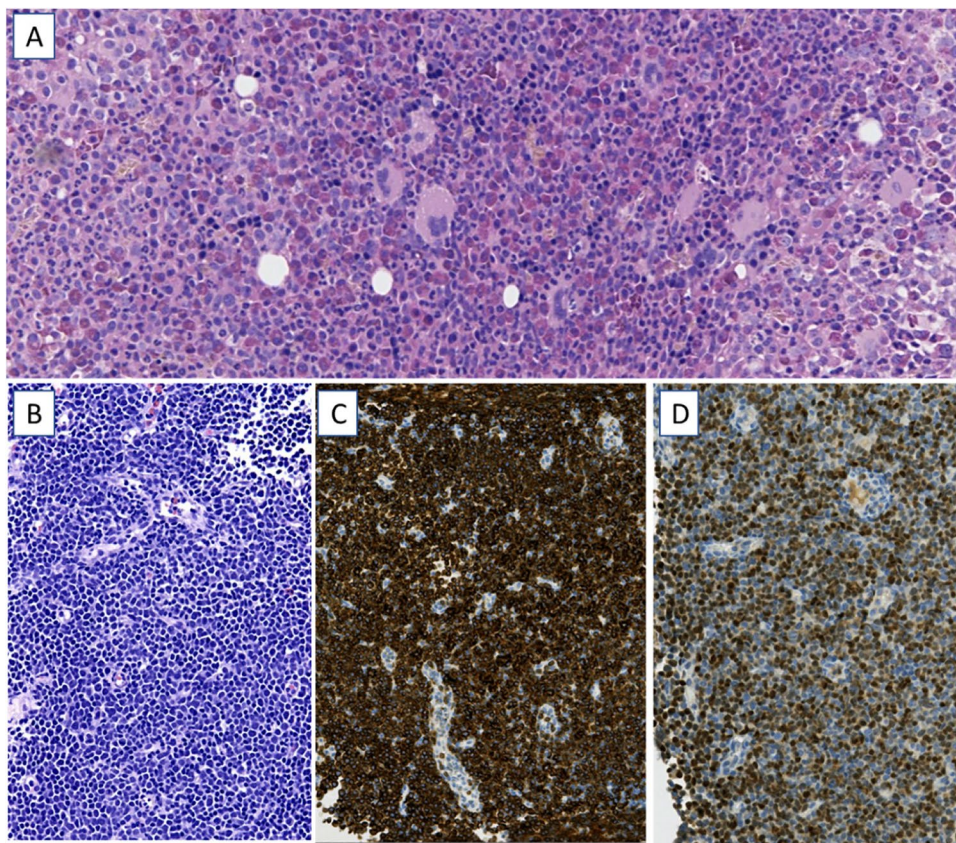
CT scan confirmed the presence of widespread lymphadenopathy including mediastinal and abdominal lymph nodes with increased metabolic activity in the PET scan. There was a heterogenous increase in bone marrow tracer uptake as well.

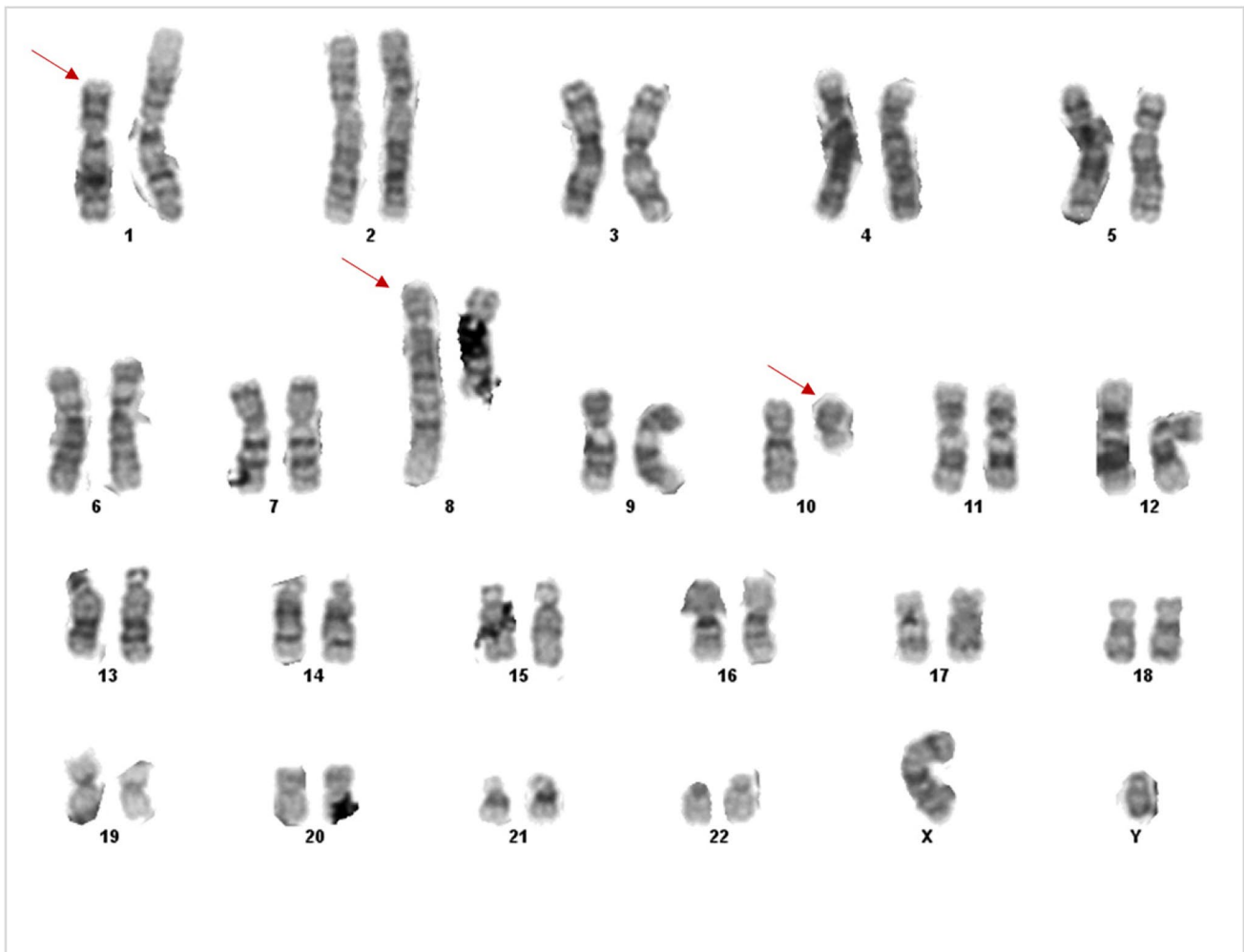
The final report was released as a myeloid and lymphoid neoplasm with T-LBL, eosinophilia, basophilia, and  $\text{der}(8)\text{t}(1;8;10)(\text{p}31;\text{q}24;\text{q}11.2)$  translocation.

### Therapy and hospital course

The patient was started on induction treatment according to Dana Farber Consortium Protocol (DFCP) with vincristine, doxorubicin, prednisone, asparaginase, and methotrexate. He had a good response within the first week with complete disappearance of the lymphadenopathy and

**Fig. 1** Morphology and Immunohistochemistry findings of bone marrow and lymph node biopsy. **A** BM biopsy is markedly hypercellular with myeloid hyperplasia and prominent eosinophilia. **B** Lymph node biopsy is diffusely infiltrated with monotonous small to medium immature-looking cells. **C** IHC stains show strong positivity for CD3 (C) and TDT (D)





**Fig. 2** Complex karyotype with 3 chromosomal aberrations: 46,XY,der(8)t(1;8;10)(p31;q24;q11.2)

normalization of the blood counts. Post-induction PET scan showed a complete metabolic response. He received CNS treatment and intensification as well.

Three months later, the patient presented with generalized lymphadenopathy, leukocytosis, eosinophilia, and thrombocytosis. A repeat bone marrow aspirate and trephine biopsy showed marked hypercellularity with granulocytic hyperplasia, eosinophilia (23%), and 11% of T lymphoblasts confirmed immunophenotypically and immunohistochemically. The cytogenetic analysis found the same abnormal translocation in 65% of cells. The PET scan also confirmed the relapsed disease.

He received fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) chemotherapy followed by complete hematological resolution of the disease. The CT scan confirmed the disease's resolution. However, cytogenetic analysis detected the persistence of the complex translocation t(1,8,10) in 5% of

the analyzed cells indicating the persistence of molecular disease despite morphological remission.

The patient then underwent an allogeneic hematopoietic stem cell transplantation (HSCT). The conditioning regimen included fludarabine, etoposide, and total body irradiation. Additionally, he also received ATG with cyclosporine as graft-versus-host disease (GVHD) prophylaxis. The patient was engrafted on day 17 with 100% chimerism on day 60 post-allogeneic HSCT. In the first few weeks, his post-transplant course was associated with nausea and dry mouth with features of mild gut and liver GVHD. Tapering of cyclosporine was delayed to day 100. He was started on imatinib 100 mg daily, Prednisolone 20 mg and artificial saliva, antiviral, and antifungal prophylaxis.

The patient had one episode of neutropenia and pneumonia requiring hospital admission and GCSF support. PET scan at 12 months post-transplant showed no disease. His immunosuppressive therapy was gradually tapered. His



chimerism studies at 12 months post-transplant showed full donor chimerism. His lung function and bone densitometry tests were within normal limits.

## Discussion

Myeloid and lymphoid neoplasms with eosinophilia (M/Ls-Eo) encompass heterogeneous but aggressive hematopoietic disorders derived from pluripotent lymphoid/myeloid stem cells. The pathogenesis of M/Ls-Eo is triggered by fusion genes or mutations that typically lead to constitutive overexpression of tyrosine kinases [5]. According to the 5th edition of the WHO classification of hematolymphoid tumors, this category includes M/Ls-Eo with either PDGFRA, PDGFRB, FGFR1, JAK2, FLT3 rearrangement, ETV6, ABL1 fusion gene or with other tyrosine kinase fusion genes [6, 7]. The neoplasm can present as chronic eosinophilic leukemia, myeloproliferative neoplasms (MPN), myelodysplastic syndrome/MPN, and acute myeloid or lymphoid leukemia. Eosinophilia is a constant feature reported in more than 90% of the cases while basophilia is an uncommon finding [8].

Our patient presented with an MPN picture associated with both eosinophilia and basophilia in the bone marrow along with massive lymphadenopathy and T-LBL in lymph nodes simultaneously. Basophilia has been observed more with certain genetic abnormalities such as t(1;8)(q31;p11.2) resulting in TPR-FGFR1 fusion gene and (8;22)(p11.2;q11) resulting in BCR-FGFR1 gene.

The occurrence of T-LBL concurrent with M/Ls-Eo has been reported rarely in the literature [3, 4]. Zanelli et al reported 11 cases of this neoplasm in which T-LBL diagnosis was made in conjunction with (M/Ls-Eo). The majority of the patients (6/11) had shown FGFR1 gene rearrangement with either ZMYM2-FGFR1 or BCR-FGFR1 fusion genes. Two cases of T-LBL were associated with the FIP1L1-PDGFR fusion gene and one case was associated with *PCMI::JAK2* fusion gene. In the same report, two additional cases were confirmed to have MPN with eosinophilia and T-LBL by both bone marrow and lymph node biopsies however, no cytogenetic or molecular abnormalities were detected [3].

Roger et al described two patients with a syndrome of T-LBL, eosinophilia, and myeloid hyperplasia associated with t(8;13)(p11;q11). Both patients presented with lymphadenopathy and peripheral eosinophilia [4].

In the current case, the syndrome was associated with a novel complex karyotype composed of a derivative of chromosome 8 and (1;8;10)(p31;q24;q11.2) translocation. To the best of our knowledge, no such genetic abnormalities have been reported previously.

The 10q11.2 encodes RET protooncogene, which is a tyrosine kinase surface receptor, that regulates cellular proliferation and survival through activation of the Raf/Mek/ERK1/2 cascade and PI3K/Akt signal transduction pathway respectively [9]. Two tyrosine kinase fusion genes have been recently recognized by the 5th edition of the WHO classification of hematolymphoid tumors under the category of myeloid/lymphoid neoplasms with tyrosine kinase fusion genes (NOS). The fusion genes are *FGFR1OP::RET* and *BCR::RET* resulting from t(6;10)(q27;q11), and t(10;22)(q11;q11) balanced translocation, respectively [6, 10]. No evidence of such balanced translocations was detected in the current case despite the presence of a complex karyotype with three chromosomal aberrations. Conventional karyotype revealed that 10q11.2 has translocated and moved to 8q24 along with 1p31. High-throughput techniques such as RNA sequencing are required to elucidate the nature of the potential RET fusion gene resulting from such novel translocation [11].

M/Ls-Eo with FGFR1 rearmament is an aggressive disorder with rapid blastic transformation to either T lymphoid, myeloid, or bi-phenotypic acute leukemia. 8p11 translocation is the genetic defining event involving the gene of FGFR 1 tyrosine kinase and its multiple partner genes and thereby leading to constitutive activation of the oncogenic signal transduction pathway [12]. So far, 14 different reciprocal translocations have been linked to the syndrome, out of which, t(8;13)(p11;q12) resulting in the *ZMYM2::FGFR1* fusion gene being the most common genetic abnormality [2, 13, 14]. The TPR-FGFR1 fusion gene arising from t(1;8)(q31;p11.2) is the least common chromosomal translocation reported only in two cases to the best of our knowledge [15–17].

Clinically, M/Ls-Eo with T-LBL is characterized by refractory disease with poor outcome even with intensive chemotherapy. The majority of the reported cases had shown poor responses to different chemotherapy regimens [3, 4, 18]. Moreover, the response to the available tyrosine kinase inhibitors is still suboptimal except for PDGFRA and PDGFRB rearrangements. Therefore, all-HSCT is the only therapeutic modality to achieve long-term disease-free survival [6].

Similarly, the clinical course of our patient was aggressive and resistant to intensive chemotherapy regimens. The patient relapsed shortly, within 3 months, after the initial response to the DFCEP chemotherapy and re-induced again with the FLAG-IDA regimen. Despite there being a complete hematological and radiological response, the cytogenetic study revealed the persistence of the disease. Therefore, he underwent allogeneic stem cell transplantation with a fully matched donor.

## Conclusion

The diagnosis of M/Ls-Eo with T-LBL might be quite peculiar and challenging due to the bi-phenotypic nature of the syndrome especially when associated with an aggressive clinical course and novel complex translocation. High throughput NGS technology such as RNA sequencing provides clear insight and a more detailed view of the implicated gene rearrangement. Furthermore, additional scientific reports might help to identify the resulting fusion gene from such a novel and complex translocation.

## Declarations

**Funding** No funding was received.

**Conflict of interest** The authors declare no competing interests.

**Ethical approval** The institute board review IRB was obtained for this study.

**Informed consent** Not applicable.

**Consent for publication** Not applicable.

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