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SHORT COMMUNICATION

Myeloid/lymphoid neoplasm with eosinophilia and *FIP1L1::PDGFRA* presenting as chronic myeloproliferative neoplasm in myeloid blast phase: case report and literature review

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Abstract

The authors present the case of a 39-year-old male with an initial diagnosis of *de novo* acute myeloid leukemia who, despite complete remission without measurable residual disease after conventional induction chemotherapy, presented with persistent splenomegaly and eosinophilia. As reactive eosinophilia was excluded and *CBFB::MYH11* and *RUNX1::RUNX1T1* gene fusions were not identified in additional molecular studies, we decided to test for other causes of clonal eosinophilia. Cytogenetic and molecular testing identified *FIP1L1::PDGFRA* gene fusion and prompted the introduction of imatinib. The initial diagnosis of *de novo* acute myeloid leukemia was changed to myeloid/lymphoid neoplasm with eosinophilia and *FIP1L1::PDGFRA* in the blast phase as myeloid blast count in the bone marrow at the diagnosis was >20%. The patient has maintained a complete molecular response with imatinib at a dose of 100 mg for more than two years.

Keywords: eosinophilia, chronic myeloproliferative neoplasm, MLN-TK, chronic phase, blast phase, *de novo* acute myeloid leukemia, AML, *FIP1L1::PDGFRA,* imatinib

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Introduction

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK) comprise a broad range of histologically distinct malignancies such as myeloproliferative neoplasms (MPN), myelodysplastic neoplasms (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), acute myeloid leukemia (AML), B- or T-lymphoblastic leukemia/lymphoma (B-/T-ALL) and mixed-phenotype acute leukemia (MPAL) [1–11]. These *BCR::ABL1*-negative diseases are driven by rearrangements of genes encoding tyrosine kinases including the platelet-derived growth factor receptor (*PDGFR*) alpha (*PDGFRA*) or beta (*PDGFRB),* fibroblast growth factor

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receptor 1 (*FGFR1*), Janus kinase 2 (*JAK2*), as well as FMS-like tyrosine kinase 3 (*FLT3*) and other defined tyrosine kinases. Products of these gene fusions possess a constitutively active tyrosine kinase domain; its activity disrupts cell signaling, resulting in uncontrolled cell proliferation. It is extremely important to identify such genetic abnormalities as some tyrosine kinase gene rearrangements imply the introduction of TK inhibitors (TKIs) to therapy with favorable outcomes, e.g. *PDGFRA* and *PDGFRB* rearrangements [1–10, 13, 14].

The most common fusion partner of *PDGFRA* is the factor interacting with PAPOLA and CPFS1 (*FIP1L1*) gene [1, 10]. MLN with *FIP1L1::PDGFRA* most commonly presents as MPN with eosinophilia in the chronic phase (CP) [3, 4, 13]. However, in rare instances, it is diagnosed in the blast phase (BP), which can mimic *de novo* AML [3, 4, 13]. In our Department of Hematology in 2011–2023, only 15 cases with *FIP1L1::PDGFRA*-positive MLN were diagnosed. Herein, we present the case of a 39-year-old male with MLN with *FIP1L1::PDGFRA* presenting as chronic MPN in the BP who had been initially diagnosed with *de novo* AML and received intensive chemotherapy induction, plus two cycles of consolidation, but reached and maintained complete molecular remission (CMR) only after therapy with imatinib had been initiated.

Case report

A 39-year-old male was admitted to our Department of Hematology after an outpatient complete blood count revealed leukocytosis (WBC 54.68 G/L) and thrombocytopenia (PLT 96 G/L). Peripheral blood smear noted a left shift (8% of blasts, 1% of promyelocytes, 19% of myelocytes, 5% of metamyelocytes, 3% of band neutrophils, 44% of neutrophils, 3% of eosinophils, 9% of monocytes, and 3% of lymphocytes).

Upon admission, the patient denied having systemic or any other symptoms. He had no significant past medical history. Physical examination revealed a spleen 5 cm below the left costal margin. Leukocytosis (WBC 49.61 G/L), eosinophilia (AEC 3.43 G/L), mild normocytic anemia (Hb 11.8 g/dL, MCV 84.0 fL) as well as moderate thrombocytopenia (PLT 69 G/L) were noted in a complete blood count. Vitamin B12 level was highly elevated (>2,000 pg/mL), ferritin level was high (678.5 ng/mL), and there was folate deficiency (2.62 ng/mL). Bone marrow cytology indicated the presence of 16% of blasts and 4.8% of eosinophils. Immunophenotyping by multiparameter flow cytometry (MP-FCM) detected 11% of myeloblasts and 5% of eosinophils. Conventional cytogenetic analysis revealed complex karyotype with clonal trisomies of chromosomes 8, 13 and 22. *BCR::ABL1* gene fusion, *JAK2* V617F mutation and pathogenic variants in exon 9 of *CALR* and exon 10 of *MPL* were excluded. Histopathological examination of bone marrow trephine biopsy specimens showed a hypercellular bone marrow with 30–35% of blasts expressing myeloid phenotype: CD33+/–MPO+CD34+CD117+CD19-CD3-Tdt-. Eosinophil infiltration was detected, and this constituted 15–20% of the granulocyte lineage cells. Only single erythroblasts were identified. Megakaryocyte count was decreased. Marked bone marrow fibrosis was noted (MF-2) (see Figure 1). Additional molecular studies excluded *CBFB::MYH11* and *RUNX1::RUNX1T1* gene fusions as well as *FLT3* and *NPM1* mutations. An initial diagnosis of *de novo* AML was established and, due to adverse cytogenetic risk, the patient was assessed as a candidate for allogeneic stem cell transplantation (alloSCT).

He received a conventional induction chemotherapy regimen consisting of daunorubicin and cytarabine (DA 3+7), achieving complete remission without measurable residual disease [CR MRD(–)]. MRD was assessed by MP-FCM. Upon admission for consolidation therapy, the patient was asymptomatic. However, physical examination was still notable for splenomegaly. Persistent eosinophilia (AEC 1.19 G/L) was present in a peripheral blood count (see Fig. 2). These findings prompted additional studies to establish the cause of eosinophilia. As core binding factor translocations and secondary eosinophilia were excluded, we decided to analyze for the *FIP1L1::PDGFRA* gene fusion using the fluorescence *in situ* hybridization (FISH) technique for the cysteine-rich hydrophobic domain 2 (*CHIC2*) at 4q12 using archived material from initial diagnosis and reverse-transcriptase polymerase chain reaction (RT-PCR) using RNA isolated from blood marrow collected during initial diagnosis. First-strand cDNA was synthesized from RNA isolated from mononuclear cells using a Transcriptor First Strand cDNA Synthesis Kit (Roche) and random primers. The fusion of *FIP1L1* to *PDGFRA* was analyzed by RT-PCR and nested PCR according to the method of Pardanani et al. [14], and then visualized using horizontal agarose gel electrophoresis (see Fig. 3). While anticipating the results, the patient received a first consolidation cycle with intermediate-dose cytarabine. FISH for the *CHIC2* deletion that leads to *FIP1L1::PDGFRA* gene fusion was detected in 88% of cells. Molecular testing identified the *FIP1L1::PDGFRA* gene fusion. These findings prompted the introduction of imatinib at 100 mg daily. Imatinib was initiated eight days after the start of the first consolidation cycle. A final diagnosis of MLN with *FIP1L1::PDGFRA* presenting initially as chronic MPN in the BP was established. Chemotherapy based on intermediate-dose cytarabine was canceled after the second cycle of consolidation.

After the introduction of imatinib, there was no palpable splenomegaly. Eosinophilia was not detected in complete blood counts. Control cytogenetic testing revealed normal karyotype and control histopathological examination of

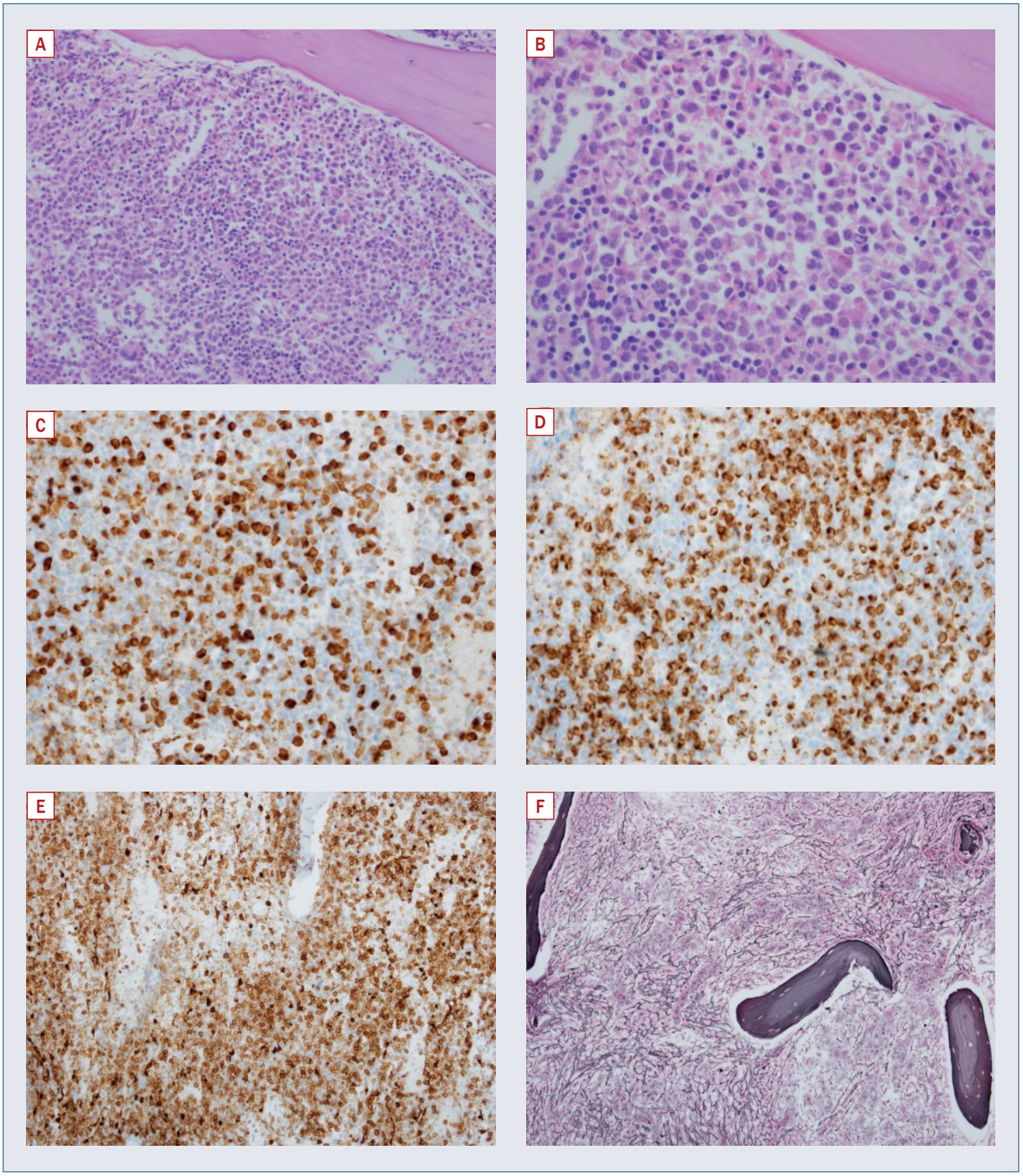
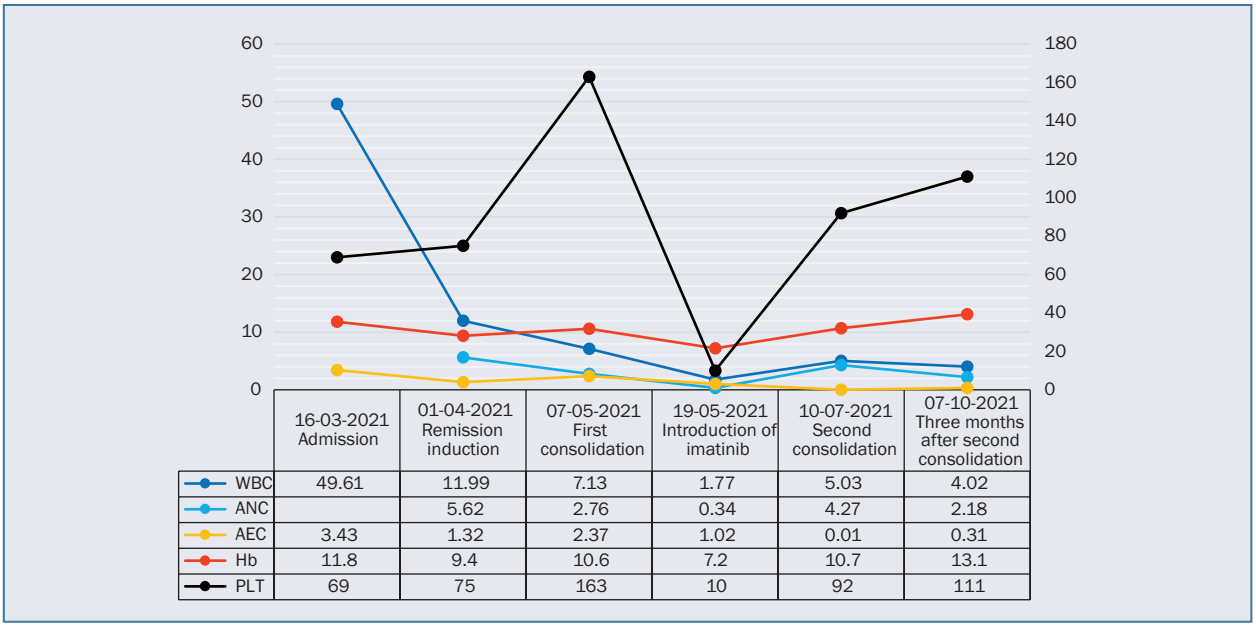


Figure 1. MLN with *FIP1L1::PDGFRA* in BP. Hypercellular bone marrow with hyperplasia of poorly differentiated cells of granulocytic lineage and presence of eosinophils (**A**, **B**); MPO expression on nondifferentiated cells of granulocytic lineage (**C**); Blasts with expression of CD34+ (**D**) and CD117+ (**E**) which constitute 50% of bone marrow cells; Focal marked fibrosis (MF-2) (**F**)

bone marrow showed normal erythroblast and megakaryocyte counts as well as the absence of aberrant blasts and fibrosis. The patient still remains in a CMR of MLN with *FIP1L1::PDGFRA* 32 months after the initiation of imatinib. The drug is continued at a dose of 100 mg and the CMR is monitored by nested PCR for *FIP1L1::PDGFRA* every three months using RNA isolated from peripheral blood. The patient has not been regarded as a candidate for alloSCT since achieving the CMR due to imatinib's good tolerance, safety, and efficacy.



	16-03-2021 Admission	01-04-2021 Remission induction	07-05-2021 First consolidation	19-05-2021 Introduction of imatinib	10-07-2021 Second consolidation	07-10-2021 Three months after second consolidation
WBC	49.61	11.99	7.13	1.77	5.03	4.02
ANC		5.62	2.76	0.34	4.27	2.18
AEC	3.43	1.32	2.37	1.02	0.01	0.31
Hb	11.8	9.4	10.6	7.2	10.7	13.1
PLT	69	75	163	10	92	111

Figure 2. Trend analysis of white blood cells (WBC), absolute neutrophil count (ANC), absolute eosinophil count (AEC), hemoglobin (Hb), and platelet count (PLT) from admission, through day one of induction, first and second consolidation, introduction of imatinib, and until three months after second consolidation

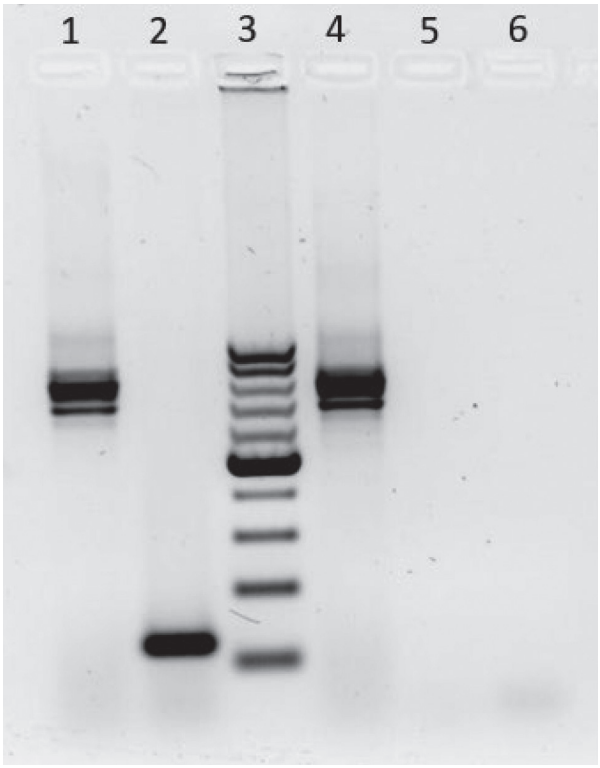


Figure 3. Gel electrophoresis of *FIP1L1::PDGFRA* fusion gene;. (1) real-time polymerase chain reaction (RT-PCR) product confirming presence of *FIP1L1::PDGFRA* fusion gene in tested material. Visibly different sizes of products indicate alternative splicing within *FIP1* gene, as described in literature; (2) Control gene [ABL1]; (3) 100 bp size marker; (4) Positive control of PCR reaction; (5) and (6) Negative controls for PCR reaction

Discussion

In MLN-TK, different disease presentations have variable incidence depending on specific genetic fusions [3]. None of the underlying genetic abnormalities is associated with a single clinicopathological phenotype [3]. Although eosinophilia is prominent, it is not an invariable feature [1–3, 10].

FIP1L1::PDGFRA is the most common fusion gene within MLN-TK [1, 2, 10]. This genetic abnormality results from 800-kb submicroscopic deletion in chromosome 4q12. Thus, it is cytogenetically occult and is diagnosed by FISH for the detection of *CHIC2* deletion and/or nested RT-PCR.

The most salient feature of *FIP1L1::PDGFRA*-positive MLN is sensitivity to TKIs, primarily imatinib, the first-line TKI [1–7, 10, 12–14]. Identifying *FIP1L1::PDGFRA* early in the diagnostic process is of key importance, because the introduction of imatinib leads to and maintains durable remission of the disease. Resistance to imatinib in *FIP1L1::PDGFRA*-positive MLN is rare, and is most commonly associated with the acquisition of the T674I mutation [2, 3, 13]. *PDGFRA* D842V is also associated with development of resistance to imatinib. In spite of favorable *in vitro* sensitivity to other TKIs, e.g. nilotinib and sorafenib, they seem to be of limited efficacy in clinical practice [16]. AlloSCT may be the only therapeutic option in such cases, although data regarding alloSCT in *FIP1L1::PDGFRA*-positive MLN-TK is scarce [2–4]. von Bubnoff et al. [13] reported the progression of *FIP1L1::PDGFRA*-positive MLN in the CP to the BP during imatinib therapy. Despite a good initial response, six months after imatinib had been started

the patient was diagnosed with progression to the BP of chronic MPN with *FIP1L1::PDGFRA*. Although cytogenetic analysis at diagnosis revealed a normal karyotype, an aberrant karyotype with a gain of chromosome 8 was detected during progression. Resistance to imatinib emerged due to acquiring the T674I mutation within the ATP-binding domain of *PDGFRA*. Despite chemotherapy with mitoxantrone and high-dose cytarabine, the patient succumbed to the disease two months after the transformation was diagnosed.

Although *FIP1L1::PDGFRA* most commonly presents as chronic MPN in the CP, it can also be diagnosed in the BP or present as AML [3, 4, 13]. Distinguishing between MLN-TK presenting as chronic MPN in the BP and *de novo* AML is sometimes difficult, as described above. In such cases, the diagnosis requires a combination of clinical, laboratory, cytogenetic, molecular and histopathological analyses [2–4]. It is worth noting that after exclusion of reactive eosinophilia and core binding factor translocations, patients with AML with prominent eosinophilia should be tested for the presence of *FIP1L1::PDGFRA* fusion. In *FIP1L1::PDGFRA*-positive MLN-TK in the BP, imatinib should be administered at a dose of 400 mg daily.

In our case, imatinib was introduced at 100 mg daily because of CR MRD(–) after induction chemotherapy and cytopenia because the imatinib was introduced eight days after the start of the first consolidation cycle.

Patients with MLN harboring *FIP1L1::PDGFRA* can present with splenomegaly and the involvement of such organs as skin, lungs and heart [4]. Elevated vitamin B12 and/or serum tryptase are associated with *FIP1L1::PDGFRA*-positive neoplasms of myeloid origin [3, 10, 12]. Left-shifted leukocytosis, leukoerythroblastosis, and dysplasia are observed in peripheral blood smears [3]. Histomorphological bone marrow features such as hypercellularity with prominent eosinophilia, absence of normal blood cell precursors, clusters of atypical mast cells, and fibrosis are characteristic [3, 13]. Data regarding quantitative chromosomal aberrations is scarce. Trisomy 8 and 13 seem to be disease-modulating secondary events [13, 15]. In *FIP1L1::PDGFRA*-positive MLN, the underlying genetic abnormality is detected by RT-PCR or FISH for the *CHIC2* deletion [1, 3, 12, 14]. Mutations of myeloid-related genes such as *FLT3, IDH1/2, RUNX1, ASXL1, TP53* are rare in *FIP1L1::PDGFRA*-positive MLN [11, 12].

At diagnosis, our patient presented with splenomegaly, eosinophilia, and highly elevated vitamin B12. We did not test for serum tryptase as we were unaware of underlying genetic fusion at that time. Hypercellular bone marrow with >20% of myeloid blasts and 15–20% of eosinophils, decreased erythroblast and megakaryocyte count, and prominent fibrosis were noted in the histopathological examination of bone marrow. Cytogenetic testing revealed an abnormal karyotype with the addition of chromosomes 8, 13 and 22. FISH for the *CHIC2* deletion was positive in 88% of cells. *FIP1L1::PDGFRA* was identified by RT-PCR. The patient did not harbor *FLT3, ASXL1* and *SRSF2* mutations.

After risk-benefit analysis, due to imatinib safety and a long-term CMR despite the adverse genetic risk, our patient has not been regarded as a candidate for alloSCT. In cases of loss of hematological, cytogenetic, or molecular response, a patient should be evaluated for cytogenetic clonal evolution and tested for *PDGFRA* T674I and D842V mutations. Because of the limited clinical activity of other TKIs, such as nilotinib and sorafenib, a patient with genetic abnormalities associated with imatinib resistance should be referred to a clinical trial with avapritinib or be considered for alloSCT.

Article information and declarations

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Authors' contributions
All authors wrote and revised manuscript.

Conflict of interest
The authors declare no conflict of interest.

Ethic statement
An ethical statement was not necessary to publish this data, as it is impossible to identify the patient based on this description.

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There are no additional data.

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