

Successful treatment with gilteritinib for popliteal extramedullary relapse of FLT-3-ITD acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation : a case report and literature review

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Abstract

Myeloid sarcoma represents a challenging clinical scenario, particularly when occurring as an isolated extramedullary relapse after allogeneic stem cell transplantation. In the case of concomitant FLT3-mutation, evidence supporting targeted therapy is limited.

We report the case of a 63-year-old man with primary myelofibrosis, who evolved to acute myeloid leukemia (AML) and subsequently underwent an allogeneic hematopoietic stem cell transplant (allo-HSCT) from an unrelated donor. Six years after transplant, the patient developed an isolated extramedullary relapse presenting as a large popliteal mass. Biopsy confirmed myeloid sarcoma with high proliferation index and bone marrow examination detected FLT3-ITD mutation. Due to age, comorbidities, and chronic GVHD, intensive chemotherapy or donor lymphocyte infusion (DLI) were not feasible. Gilteritinib was initiated at 120 mg daily, followed by local radiotherapy. Three months after TKI initiation, complete remission (CR) was achieved with molecular clearance of FLT3-ITD, achievement of full donor chimerism, and complete metabolic response at PET/CT. At the last follow up, 2 years after disease relapse, CR was maintained, with excellent tolerability and stable peripheral blood counts.

Gilteritinib led to rapid and durable remission of FLT3-ITD-positive post-HSCT myeloid sarcoma, suggesting that FLT3 inhibition may represent a valuable therapeutic option in extramedullary relapse settings where intensive treatment is not feasible.

Case Description

In 2011, a 63-year-old man was diagnosed with JAK2 V617F-positive primary myelofibrosis. His past medical history included hypertensive heart disease and hypercholesterolemia. At clinical onset, the DIPSS and DIPSS-plus scores were intermediate-1. The karyotype was normal, and the JAK2 allelic burden was 4.9%. There were no splenomegaly or constitutional symptoms.

He was treated with danazol, testosterone, and erythropoietin, and received iron chelation therapy because of progressive transfusion dependency.

In 2016, disease progression to acute myeloid leukemia (AML) was documented, with bone marrow aspiration showing 40% blasts and karyotype revealing a del(20) cytogenetic abnormality. Molecular testing detected JAK2 V617F positivity and WT1 overexpression, with negativity for FLT3 mutations. Trepine biopsy also revealed MF2. Spleen size had increased to 18 cm on ultrasound.

The patient received induction chemotherapy with ICE (idarubicin 12 mg/m² for three days, cytarabine 100 mg/m², and etoposide 100 mg/m² for seven days) and consolidation with cytarabine (1 g/m² for three days), achieving a partial response, followed by re-induction with FLAN (fludarabine 50 mg/m², cytarabine 1 g/m², and mitoxantrone 10 mg/m² for three days), with morphologic, molecular and cytogenetic complete response achievement.

He subsequently underwent peripheral allo-HSCT from a matched unrelated female donor. Conditioning consisted of fludarabine 30 mg/m² for five days and busulfan 0.8 mg/kg four times daily for two days; GVHD prophylaxis included cyclosporine, methotrexate, and anti-thymocyte globulin (ATG).

The post-transplant course was complicated by severe mucositis, probable invasive fungal infection, bacterial and viral infective complications, and moderate chronic cutaneous GVHD, which was treated with cyclosporine, prednisone 0.5 mg/kg/die, and PUVA phototherapy, leaving sclerodermic sequelae. He maintained stable engraftment and full donor chimerism for several years, and two secondary skin cancers were resected during follow-up.

Approximately six years after transplantation (May 2023) the patient presented with swelling and pain of the left lower limb. Magnetic resonance imaging (MRI) - Fig. 1- and PET/CT revealed a large popliteal lesion (8.8 × 8.6 cm; cranio-caudal extension 20 cm) with an SUV of 15.8. Ultrasound-guided biopsy confirmed myeloid sarcoma, consisting of blast-like cells expressing CD34, CD117, CD123, NPM1 (nuclear/cytoplasmic), and focal MPO, with a Ki-67 index of 80% (Fig. 2).

Peripheral blood count showed WBCs 4.2 (N 2.9) x10⁹/L, Hb 14.8 g/dl, MCV 93.2 fl, plts 168 x10⁹/L. Bone marrow biopsy showed hypocellular marrow with 2% blasts, donor chimerism of 68% in the CD34 + compartment, and no morphological signs of AML. Marrow molecular analysis demonstrated FLT3-ITD positivity, while JAK2 V617F was negative. Karyotype was normal (46 XX). FLT3 could not be assessed on the popliteal biopsy.

Given his age (75 years old at the time of relapse after HSCT), comorbidities, and chronic GVHD, intensive chemotherapy and donor lymphocyte infusions (DLI) were considered not feasible. Therefore, gilteritinib 120 mg once daily was initiated, followed by local radiotherapy on the mass in September 2023.

Three months later, complete morphological and immunophenotypic remission was achieved; FLT3-ITD became negative; donor chimerism increased to 98% in CD34 + cells; and oedema and limb dysfunction resolved. Radiologic re-evaluation showed substantial regression of the popliteal lesion, with a complete metabolic response (SUV max 2.3 versus 15.8 at baseline on PET/CT).

Treatment with gilteritinib was well tolerated, with only an initial increase in transaminases, which rapidly resolved and did not require dose adjustment or temporary drug interruption (Fig. 3)

In December 2024, bone marrow continued to show morphological and molecular complete remission, with full donor chimerism and FLT3 negativity.

At last follow up, 25 months after gilteritinib initiation, the patient was clinically well, with normal blood counts, and without relevant hematologic or biochemical toxicity. He had mild residual peripheral neuropathy, while chronic GVHD remained stable.

Discussion

We report a successful therapeutic case with gilteritinib in a complex scenario of post-transplant FLT3-mutated acute myeloid leukemia presenting with a localized myeloid sarcoma.

Gilteritinib is a potent and selective FLT3 inhibitor approved for relapsed or refractory (R/R) AML with FLT3-ITD or TKD mutations. Clinical evidence from pivotal trials has demonstrated superior overall survival compared with standard chemotherapy, together with deeper molecular responses and the possibility of sustained remission even in heavily pre-treated patients. The drug is generally well tolerated, also in older or unfit individuals, making it an increasingly relevant option both as a bridge to transplant and as post-transplant therapy.

In the pivotal phase III ADMIRAL trial, gilteritinib demonstrated a significant improvement in overall survival compared with salvage chemotherapy (median OS 9.3 vs 5.6 months), along with higher composite complete remission (CR/CRh) rates (34.0% vs 15.3%) [1]. These results were confirmed with longer follow-up, showing a sustained survival benefit and a manageable safety profile [2]. Real-world data have further supported the efficacy of gilteritinib in heavily pretreated patients, including those previously exposed to other FLT3 inhibitors such as midostaurin [3,4].

Extramedullary relapse of AML, including myeloid sarcoma, characterized by tumor masses of myeloid blasts occurring at extramedullary sites, either in isolation or in association with bone marrow disease, remains a major therapeutic challenge. Conventional treatment strategies, such as systemic chemotherapy, and radiotherapy, are often limited by toxicity and patient frailty. Molecularly targeted therapies, including FLT3 inhibitors, may offer an alternative, but clinical data regarding their use in this setting remain scarce, and no prospective studies are available.

Nevertheless, emerging data suggest that FLT3 inhibition with gilteritinib may be effective in this context. A recent review highlighted the growing number of reported cases of FLT3-mutated AML with extramedullary involvement treated with gilteritinib, showing encouraging responses, including complete or near-complete regression of extramedullary lesions [5]. Additionally, a multicenter retrospective analysis presented at ASH 2024, reported high response rates in patients with FLT3-mutated AML and myeloid sarcoma treated with gilteritinib, with complete remission achieved in a substantial proportion of cases and some patients successfully bridged to allo-HSCT [6].

These observations support the hypothesis that gilteritinib has activity not only in the bone marrow compartment but also at extramedullary disease sites.

The role of gilteritinib appears particularly appealing in the post-transplant setting, where extramedullary relapse represents a challenging clinical scenario associated with poor prognosis. Isolated extramedullary relapse after allo-HSCT is increasingly recognized and may occur despite full donor chimerism, suggesting mechanisms of immune escape and sanctuary-site disease [6]. Historically, outcomes in this setting have been unfavourable, and optimal management remains undefined. Therefore, treatment decisions in this setting are often individualized and based on extrapolation from systemic AML data.

Recently, several case reports have described successful use of gilteritinib in post-transplant extramedullary relapse. Kida et al. reported a patient with isolated cutaneous myeloid sarcoma relapse after allo-HSCT, despite complete donor chimerism, who achieved marked lesion regression under gilteritinib [7]. Similarly, Kumode et al. described resolution of both medullary and extramedullary disease following gilteritinib administration in a post-transplant relapse [8]. Additional reports have documented complete and durable responses in isolated breast and other extramedullary relapses treated with gilteritinib, with minimal toxicity [9,10]. Other unusual presentations, including ocular myeloid sarcoma, have also shown responsiveness to FLT3-targeted therapy [11].

Conclusion

Our case and its peculiar presentation add to the growing body of evidence supporting the use of gilteritinib in extramedullary relapse of FLT3-mutated AML in the post-transplant setting, in particular when intensive chemotherapy, immunotherapy with DLI or even second transplant is not feasible.

Our experience also highlights the need to evaluate FLT3 status at post-transplant relapse, even in previously negative cases, as a distinct clone may emerge under the immunologic pressure of graft-versus-leukemia (GVL) effects. Moreover, FLT3 testing should be performed not only on bone marrow but also on tissue samples from extramedullary lesions, as these may harbor actionable mutations that can guide targeted therapy [12]

Declarations

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Nothing to declare.

Consent for publication

Patient provided written consent for publication of the case report and the accompanying images

Ethical approval. The manuscript was approved by the internal board of the institution.

Author contributions

GM wrote the manuscript and performed re-viewed of the literature. MC and LL provided the histopathological images in figure 2. The other authors (MF, VR, DA,EM,PC, FB, RD, SZ, LD, DR, MM) revised the manuscript and approved its final version

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Figures

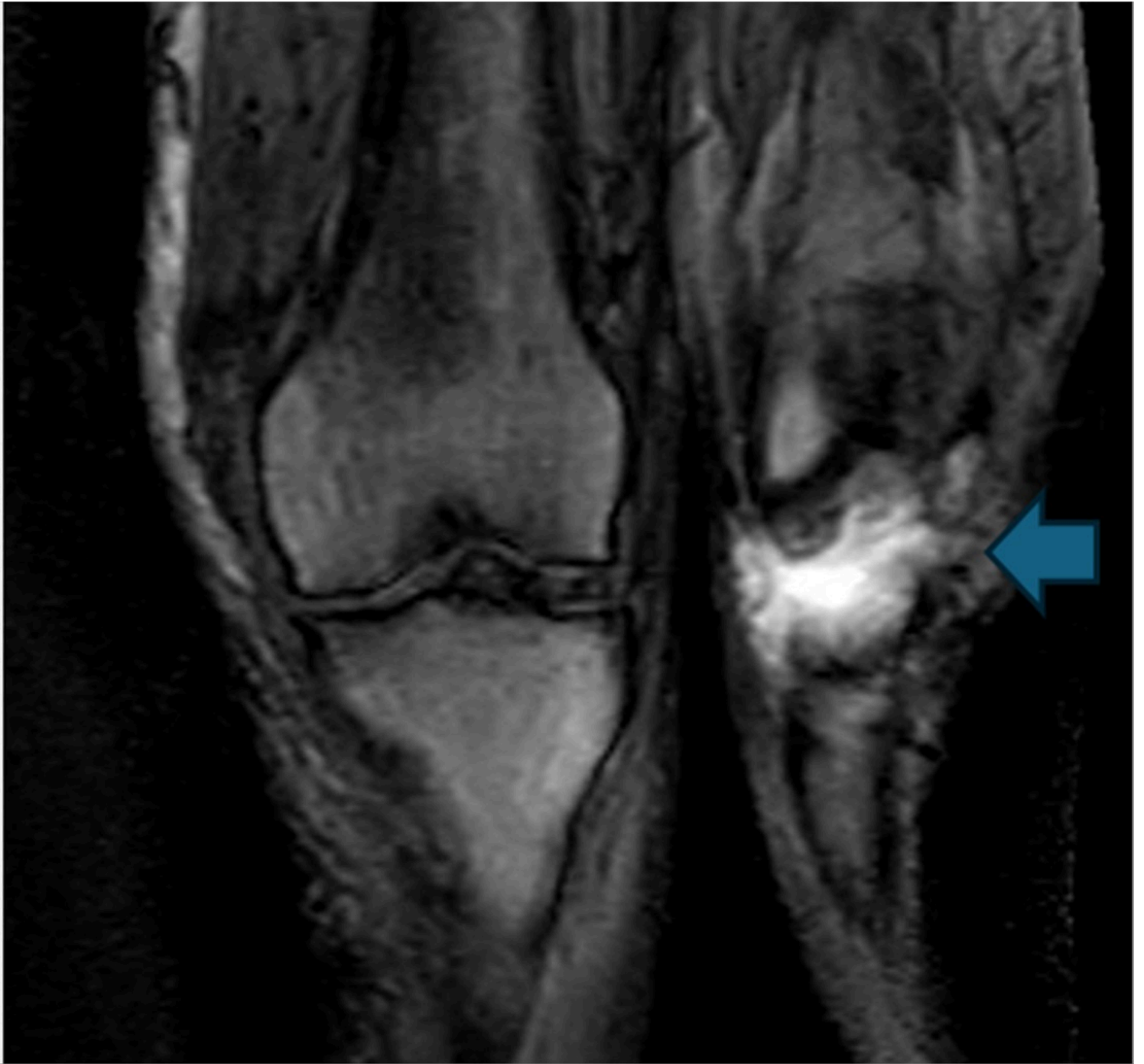


Figure 1

MRI findings of the left popliteal myeloid sarcoma

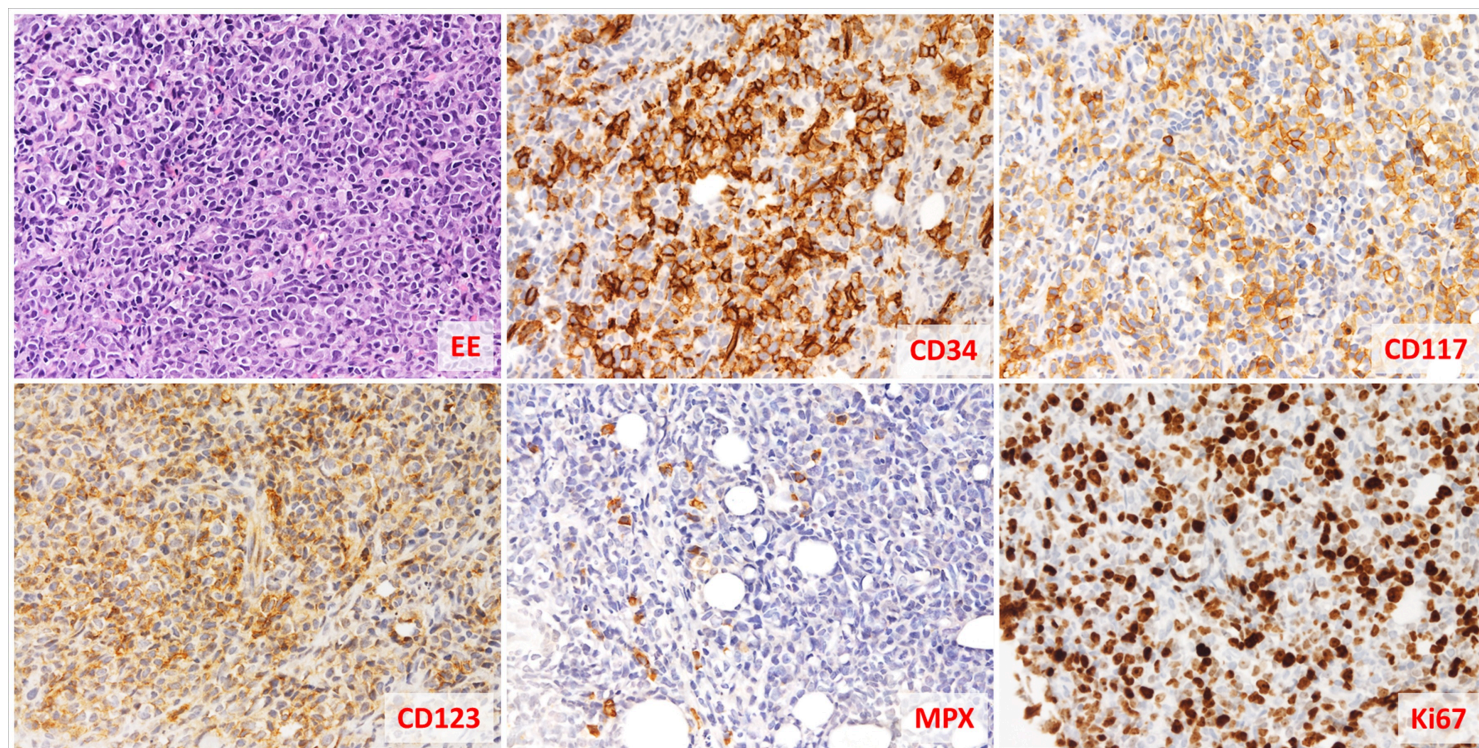


Figure 2

Histopathological and immunohistochemical features of the popliteal myeloid sarcoma. Representative images showing hematoxylin and eosin staining (EE) and immunohistochemical staining for CD34, CD117, CD123, myeloperoxidase (MPX), and Ki-67.

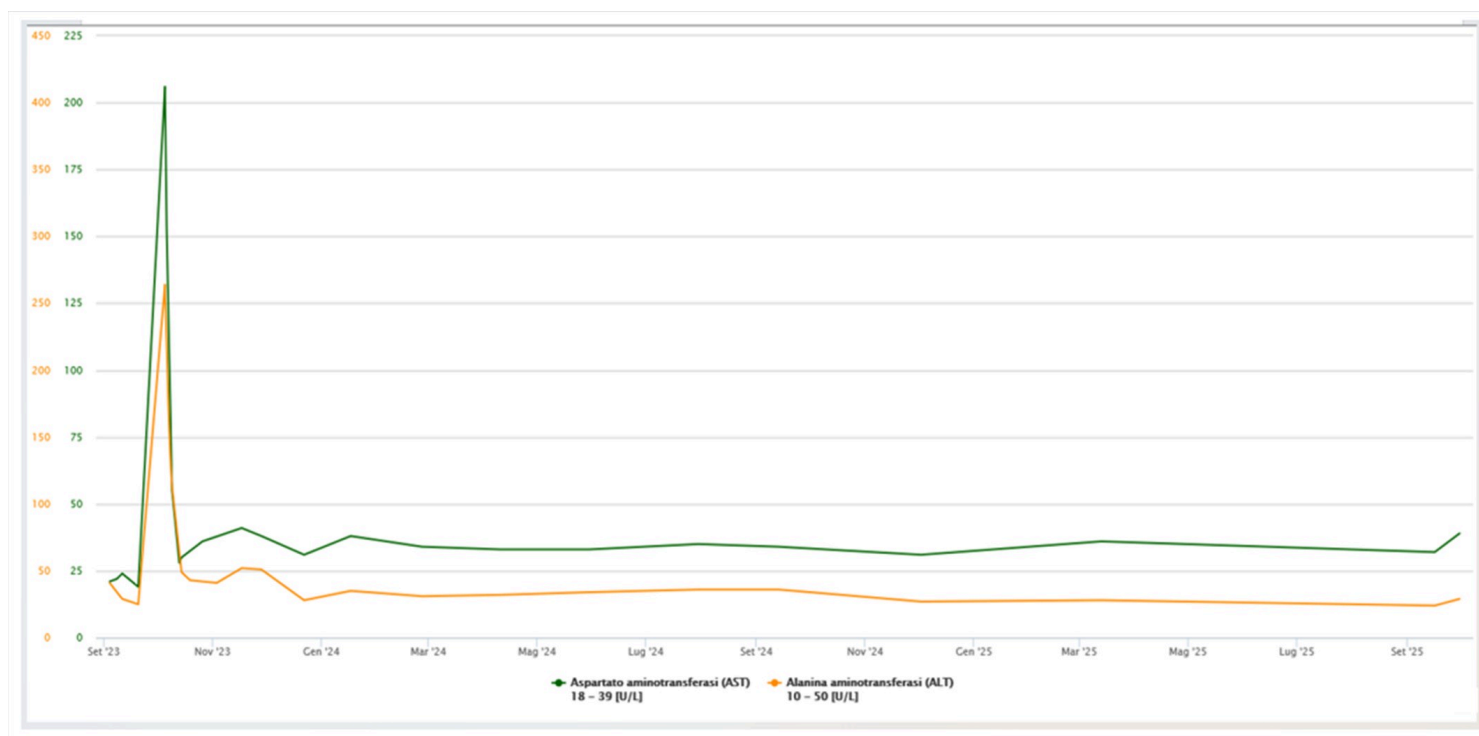


Figure 3

Trend of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels during gilteritinib administration