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CASE REPORT

Breast Isolated *FLT3* Positive AML Relapse Treated with Gilteritinib in Monotherapy: Long- Term Follow-Up and Review of the Literature

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ABSTRACT

Extramedullary relapse of acute myeloid leukemia (AML) is a relatively common occurrence, with the FMS-like tyrosine kinase 3 (*FLT3*) mutation being a significant risk factor. While gilteritinib is approved for treating relapsed/refractory *FLT3*+ AML, its effectiveness in extramedullary relapse is still not well established. We report the case of a 69-year-old woman diagnosed with therapy-related nucleophosmin-1 (*NPM1*) and *FLT3*-internal tandem duplication (*FLT3*-ITD) positive AML. She was initially treated with induction and consolidation therapy using CPX-351 (liposomal daunorubicin plus cytarabine) and subsequently received off-label azacitidine maintenance. Although she achieved complete remission with persistent measurable residual disease, 19 months later she experienced an isolated breast relapse of *FLT3*-ITD+ AML. The patient was treated with single agent gilteritinib, which led to a rapid and sustained complete regression of the breast nodule, maintained after 44 courses of treatment. This case demonstrates that target therapy with gilteritinib can be an effective option for isolated extramedullary relapse of *FLT3*-ITD+ AML.

Introduction

Therapy-related acute myeloid leukemia (t-AML) is a disease that arises as a delayed complication following cytotoxic treatment for a primary cancer or a non-neoplastic disorder.

Until 2022, it was considered a category of AML [1], but with the updated 2022 European leukemiaNet (ELN) guidelines, it became a diagnostic qualifier for the AML-defining category [2]. This type of leukemia accounts for approximately 7% of all newly diagnosed AML cases [3] and it seems to be the direct consequence of mutational events induced by cytotoxic therapy (chemotherapy, including mostly treatment with topoisomerase II inhibitors, radiotherapy) and/ or selection of chemotherapy-resistant clones [3]. The diagnostic and prognostic workup for AML includes testing for several mutations, with about 30% of newly diagnosed AML cases carrying a mutation in the *FLT3* gene, which encodes a membrane-bound tyrosine kinase protein [4]. The most common *FLT3* mutations are *FLT3*-ITD and tyrosine kinase domain (TKD) mutations, present in roughly 20-30% and 7% of AML patients, respectively [5–7]. These *FLT3* mutations, especially *FLT3*-ITD, are considered poor prognostic factors in terms of relapse-free survival (RFS) and overall survival (OS), [8] irrespective of the *FLT3*-ITD allelic ratio [8]. Thus, patients with *FLT3*-ITD+ AML are generally recommended to undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT) after achieving complete remission (CR) [2]. Several studies have highlighted the frequent occurrence of *FLT3* mutations in patients with extramedullary involvement (EMI), which refers to the presence of leukemic cells outside of the blood or bone marrow, typically in organs such as the skin, bone, and lymphonodes [9,10]. EMI can develop simultaneously with, before, or after the initial AML diagnosis, and it may occur at diagnosis or relapse [9,10]. However, treatment guidelines for EMI remain lacking due to the rarity of this phenomenon, which affects only 3–8% of adult AML patients [11,12]. Some recent reports suggest that targeted therapies, including *FLT3* inhibitors, may be effective for treating EMI [13–18]. Gilteritinib, a second-generation selective *FLT3* inhibitor, is active against both *FLT3*- ITD and *FLT3*-TKD mutations. Gilteritinib has been approved as a monotherapy for *FLT3*+ AML in first or subsequent relapses, regardless of the *FLT3* status at diagnosis [19]. Generally, patients treated with gilteritinib obtain a CR in more than 30% of cases with an OS of about 10 months and a low toxicity profile [6]. Notably, up to 30% of AML patients who are *FLT3*-negative at diagnosis may acquire a *FLT3* mutation at relapse, highlighting the importance of re-testing for *FLT3* mutations at the time of relapse [20]. In this report, we present the case of a *FLT3*-ITD mutated AML patient with isolated breast EMI at relapse, who was successfully treated with gilteritinib.

Case report

In September 2019, a 69-year-old woman presented to the emergency department of the University Hospital Città della Salute e della Scienza – Turin (Italy), reporting extreme fatigue and dyspnea. She had no comorbidities except for a medical history of papillary thyroid cancer, treated with thyroidectomy and radiotherapy 13 years before. Her complete blood count revealed anemia, thrombocytopenia and leukocytosis (Hb: 7.8 g/dL, PLT: 37×10^9/L, WBC: 45×10^9/L), while her physical examination was normal. The bone marrow smear showed 84% of blasts with myeloid immunophenotype (CD45, CD13, CD33, HLA-DR, lysozyme, CD36, CD64, CD11bc, partial CD14, and CD4 positive), molecular biology showed *NPM1* mutation and *FLT3*-ITD positivity, while karyotype was normal (46, XX, 20/20).

Consequently, a diagnosis of *FLT3*-ITD+ and *NPM1* mutated t-AML was made. Induction chemotherapy was started with CPX-351 (liposomal daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2), obtaining CR with a 3-log *NPM1* reduction (0.177). She was consolidated with CPX-351 (liposomal daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 day 1 and 3), remaining in CR with persistent low level of measurable residual disease (MRD), *NPM1* 0.34. Meanwhile, we found a suitable HLA matched donor, but the patient refused the transplant procedure. Thus, we decided to start off-label azacitidine as maintenance therapy (50 mg/m^2 subcutaneous daily for 5 days, every 28 days) [21]. Maintenance therapy was globally well tolerated, and the patient experienced only positivity for COVID-19 without need of hospitalization or additional care. She remained in CR with persistent MRD in BM (*NPM1* 0.044 after 12 cycles). During the fifteen course (May 2021), we found a palpable right mammary nodule on physical examination, confirmed on ultrasound, with a diameter of 18 x 11 mm (Fig.1a). We stopped azacytidine and we promptly biopsied the nodule with a diagnosis of breast infiltration by AML blasts carrying the *NPM1* mutation. CT scan and PET of chest, neck and abdomen were negative, and BM evaluation showed 1% blasts, with *NPM1* 0.044. The *FLT3*-ITD mutation resulted positive on breast cells while negative on medullary blasts. Thus, concluding for extramedullary relapse of AML *FLT3*-ITD mutated, we decided to start gilteritinib as single agent, at a dose of 120 mg daily. After 30 days, mammary ultrasound showed a reduction in diameter of the nodule (Fig.2), and in 4 months, the lesion has completely disappeared (Fig.3). The PET scan performed after 5 months of treatment was persistently negative and confirmed the absence of other uptakes. BM revaluation showed no blasts, with *NPM1* 0.006. Today, after 44 months of treatment, our patient is still in CR without signs of clinical and radiologic relapse (Fig.4). We continue monitoring her MRD status every two months on peripheral blood (PB), as shown in table 1. Globally, therapy has been always well tolerated. In January 2024, we had to stop gilteritinib for 28 days due to pyelonephritis and sepsis treated with broad spectrum antibiotics. During this time, she remained in complete remission without any sign of relapse. After some months, in September, our patient has undergone exeresis of basal cell carcinoma, without complications and without need of stopping gilteritinib.

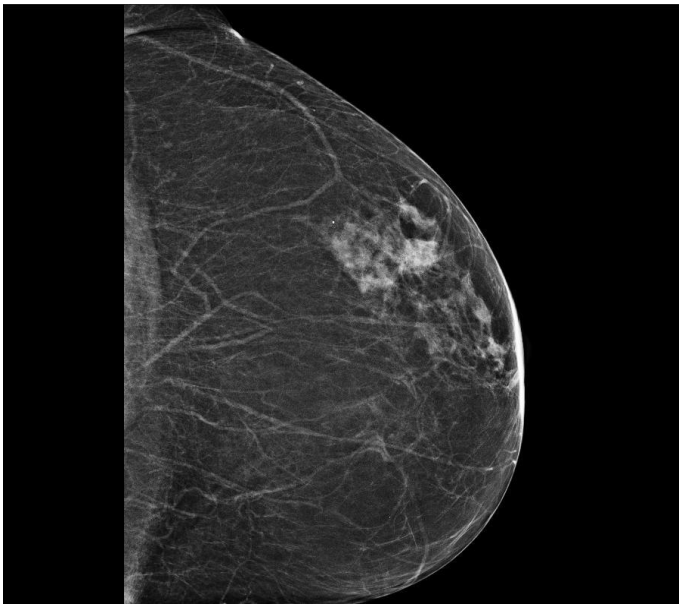

Figure 1a. Breast mammography at relapse

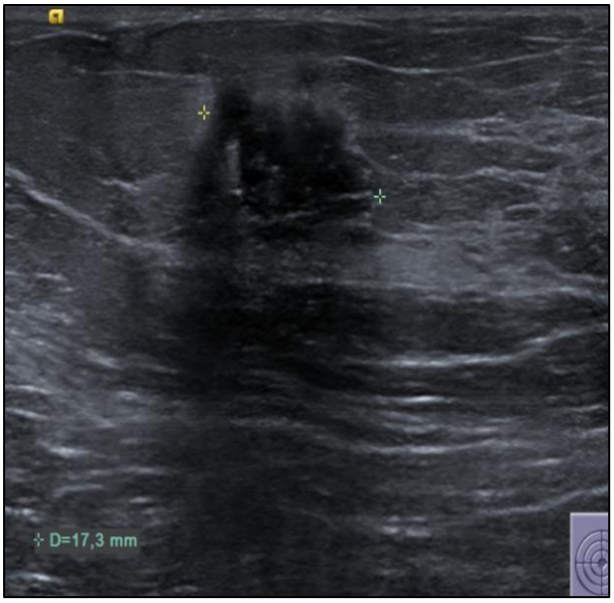

Figure 1b. Breast ultrasound at relapse

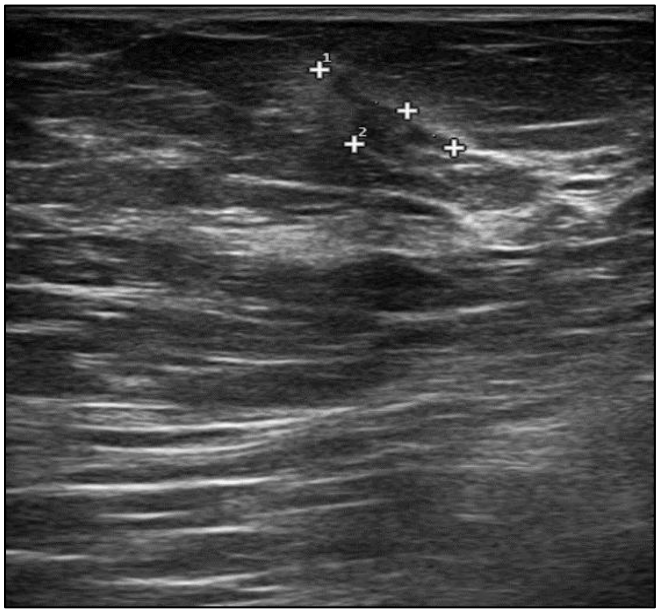

Figure 2. Breast ultrasound after 1 month of gilteritinib (diameter 11 mm x 5 mm)

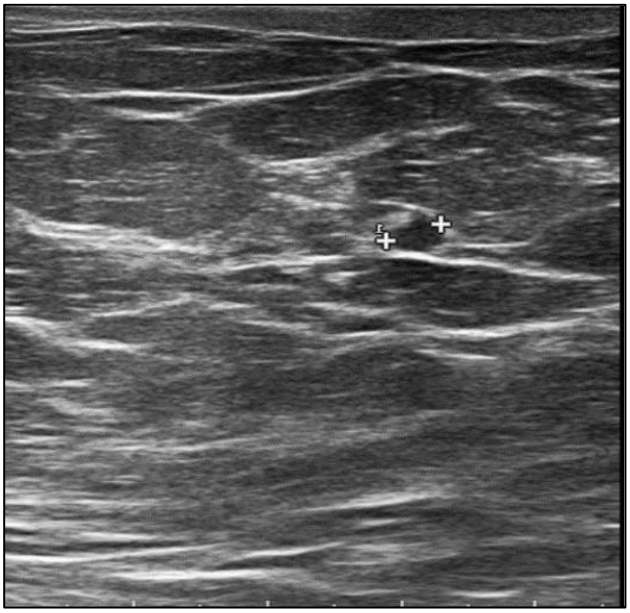

Figure 3. Breast ultrasound after after 4 months of gilteritinib (no significant detectable lesions).

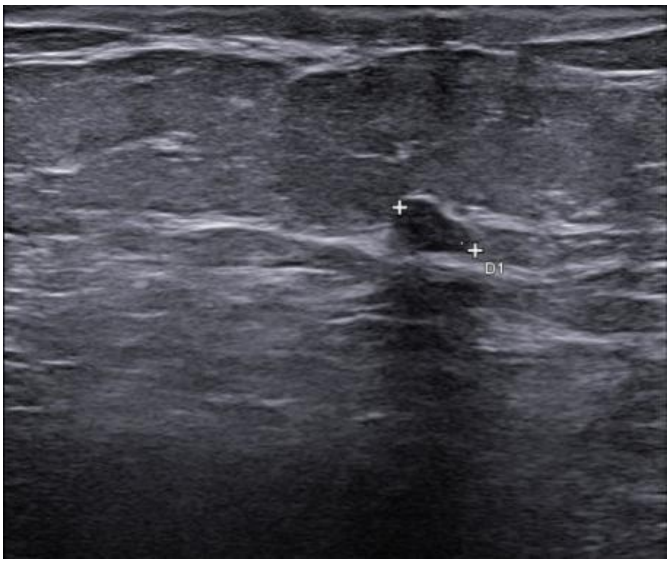

Figure 4. Last breast ultrasound performed, January 2025 (no significant detectable lesions).

Table 1: MRD status (*NPM1* level in BM and PB)

Date	Time	Source	Result [(*PM1-A*/*ABL* copies) %]
September 2019	At diagnosis	BM	481
October 2019	After induction	BM	0.177
December 2019	After first consolidation	BM	0.034
August 2020	After 6° cycle of azacitidine	BM	0.006
February 2021	After 12° cycle of azacitidine	BM	0.044
May 2021	At extramedullary relapse	BM	0.006
January 2022	After 7m of gilteritinib	PB	0.0006
January 2022	After 7m of gilteritinib	BM	Negative
June 2022	After 12m of gilteritinib	BM	Negative
August 2022	After 14m of gilteritinib	PB	Negative
September 2022	After 15m of gilteritinib	PB	0.0026
December 2022	After 18m of gilteritinib	PB	Negative
February 2023	After 20m of gilteritinib	PB	0.0043
Avril 2023	After 22m of gilteritinib	PB	Negative
July 2023	After 25m of gilteritinib	PB	Negative
August 2023	After 27m of gilteritinib	PB	Negative
September 2023	After 28m of gilteritinib	PB	Negative
October 2023	After 29m of gilteritinib	PB	Negative
November 2023	After 30m of gilteritinib	PB	Negative
December 2023	After 31m of gilteritinib	PB	Negative
February 2024	After 33m of gilteritinib	PB	Negative
Avril 2024	After 35m of gilteritinib	PB	Negative
June 2024	After 37m of gilteritinib	PB	0.0009
August 2024	After 39m of gilteritinib	PB	Negative
September 2024	After 40m of gilteritinib	PB	Negative
November 2024	After 42m of gilteritinib	PB	Negative
January 2025	After 44m of gilteritinib	PB	Negative

MRD, measurable residual disease; *NPM1*, nucleophosmin-1; BM, bone marrow; PB, peripheral blood; *ABL*, Abelson proto-oncogene 1; m, months.

Discussion

Myeloid sarcoma (MS), also referred to as extramedullary myeloid infiltration, was first described in 1811 by Burns [22]. Initially, the tumor was called "chloroma" because of its greenish hue, which was later linked to the presence of the MPO (myeloperoxidase) enzyme by King in 1853 [23]. The tumor was identified as a mass composed of myeloid blasts, causing disruption in the normal tissue structure. The connection between MS and myeloid leukemia was first established in 1893 by Dock [24,25]. Histologically, MS consists of immature.

granulocyte precursors, such as myeloblasts, promyelocytes, myelocytes, and granulocytes [26]. Core biopsy is preferred over fine needle aspiration for the histologic and immunophenotypic evaluation, FISH, PCR and NGS allows a better understanding of the patient's prognosis and identification of potential treatment targets [27]. It is observed in 3-8% of adult patients with acute myeloid leukemia [9,10]. It can occur in the context of intramedullary AML (synchronous extramedullary AML), or in an isolated form with an essentially normal bone marrow (isolated extramedullary AML; also called “nonleukemic” or “aleukemic”), which is usually followed by the development of metachronous intramedullary AML. Its frequency is higher in the post-allo-HSCT relapse setting with about 15% of all post allo-HSCT AML relapses being isolated EMI [27]. While the exact cause of MS development remains unclear, it is thought to involve the migration of leukemia blasts to extramedullary sites, facilitated by specific adhesion molecules found on the blast cell surfaces[11]. Age might influence the presence of MS; most studies have reported a median age at diagnosis ranging from 46 to 59 years, with approximately 52–59% of affected patients being male [27]. Certain genetic features, including trisomy 8, monocytoid differentiation of blasts, *MLL* rearrangements, as well as CD56 positivity and the absence of CD117 (c-kit), are associated with an increased risk of developing MS in AML. These factors enhance the ability of leukemic cells to migrate to areas beyond the bone marrow [11]. Recent reports have highlighted the frequent occurrence of *FLT3* mutations in patients with EMI [9,10]. *FLT3*-ITD mutations were the first molecular abnormalities to be identified in MS cells with initial studies detecting the mutation in up to about 30%, which is similar to the frequency noted for typical AML. *NPM1* mutations are detected in up to 50% of cases, again comparable to conventional AML [27]. MS in the breast is extremely rare, making up only about 3% of all MS cases, according to a Mayo Clinic study [28]. Due to its infrequency, it is often mistaken for other breast malignancies, such as lobular carcinoma, non-Hodgkin’s lymphoma, or small round blue cell tumors [26]. A recent review by Sharma et al. examined 67 previously reported cases, 66 of which were women and only one was a man [29]. In most instances, breast MS presents as a rapidly enlarging mass, which may affect one or both breasts. Nipple retraction is generally not observed. Right-sided breast involvement is more common than left-sided [30]. In terms of imaging, MS in the breast typically appears as a large, irregular, non-calcified mass with poorly defined, "feathery" margins [30], a characteristic finding consistent with the mammograms of the patients in the study (Fig.1b). FDG-PET/CT at diagnosis, after treatment completion and at the time of suspected relapse is an important tool that allows for timely adjustments to the management strategy [27].

Recent data indicate that the prognostic significance of EMI depends on the combination of involved sites, as well as the biological and cytogenetic characteristics of the disease [31]. It remains unclear whether EMI generally correlates with a poor prognosis. In a large recent study involving patients with extramedullary lesions at diagnosis - both with and without central nervous system involvement - EMI did not appear to significantly affect the prognosis in terms of CR or survival [32]. There is currently no consensus regarding the optimal treatment for AML patients with EMI due to its rarity and the absence of randomized controlled trials [12]. In clinical practice, patients with isolated EMI typically receive AML-like induction therapy, followed by consolidation treatment, which may include chemotherapy or allo-HSCT [12,33]. Some case reports suggest that local radiation therapy can lead to long-term remission in patients with persistent or relapsed extramedullary disease [34]. However, while RT can be effective for local control, its long-term benefits have not been thoroughly established [12].

In the case of our patient, who had a good performance status and no significant comorbidities, we proposed a treatment regimen involving debulking therapy followed by consolidation with allo-HSCT from a fully matched unrelated donor. Unfortunately, the patient declined this treatment.

In recent years, targeted therapies for EMI have shown promising results, such as humanized anti-CD33 monoclonal antibodies, tyrosine kinase inhibitors (TKIs) for FIP1L1-PDGFR and *FLT3*-ITD, and DNA methyltransferase inhibitors [13–15,20]. Efforts to develop protein kinase inhibitors that target mutated forms of the *FLT3* receptor have led to the development of multiple generations of *FLT3* inhibitors. First-generation *FLT3* inhibitors included tandutinib, sunitinib, lestaurtinib, sorafenib, and midostaurin, while second-generation inhibitors include quizartinib, crenolanib, and gilteritinib [35]. These inhibitors vary in their ability to block *FLT3*, their selectivity for the mutated receptor, and their toxicity profiles [1]. In a phase III randomized trial involving 371 relapsed or refractory AML patients with *FLT3* mutations, gilteritinib at a daily dose of 120 mg showed a CR rate of 34% compared to 15.3% with salvage chemotherapy. Furthermore, the median OS was significantly longer for the gilteritinib group (9.3 months versus 5.6 months). As a result, gilteritinib has been approved for use in relapsed/refractory *FLT3*-mutated AML patients [6,36]. In our case, the *FLT3*-ITD mutation was detected in the leukemic blasts of breast tissue. Since the patient declined the transplant, we initiated single agent gilteritinib therapy. Remarkably, the patient responded rapidly, and after 4 months of treatment, the breast lesions had completely disappeared. To date, there are few published case reports on the use of gilteritinib in *FLT3*+ myeloid sarcoma, with none involving breast tissue. Kida et al. [13] reported a case of a 56-year-old man with *FLT3*-ITD+ AML who developed subcutaneous masses after undergoing allo-HSCT. Upon detecting *FLT3*-ITD in the tissues, gilteritinib treatment was initiated, resulting in significant tumor regression. Similarly, Kumode et al. [14] reported a case of *FLT3*-ITD+ AML relapse post allo-HSCT with both bone marrow and extramedullary tumor involvement. Treatment with gilteritinib led to remarkable responses in both sites, and a second allo-HSCT was performed with complete molecular response. Kim et al. [16] treated a patient with relapsed *FLT3*-ITD+ AML and an iridociliochoroidal MS, as well as nodular lesions in the axilla and scalp, with gilteritinib, resulting in substantial tumor regression. However, the patient eventually passed away less than a year later due to progressive disease. Perrone et al. [15] described the use of gilteritinib in a patient with meningeal relapse of AML. After reinduction chemotherapy failed, gilteritinib was initiated, leading to a complete response in the central nervous system within 3 months. A French study conducted by Saint Louis Hospital, explored the distribution and in vitro efficacy ofgilteritinib in cerebrospinal fluid (CSF) in AML patients with CNS relapse, reporting favorable pharmacokinetic and pharmacodynamic properties [18]. Thus, the use of gilteritinib in SNC relapse of *FLT3* AML is increasing in the last years, obtaining encouraging results [17]. The positive antileukemic effect of gilteritinib may bring new hope for the treatment of *FLT3*- mutated AML with CNS relapse. Angotzi et al. [37] conducted an Italian multicentric retrospective study including 24 patients diagnosed with *FLT3*-mutated AML and histologically confirmed MS presenting concurrently with AML either at diagnosis or at disease relapse. MS localization was skin, central nervous system, gastrointestinal tract, ovary, mammary gland, muscle, and soft tissues. 14 patients were treated by gilteritinib, administered for a median of 5 cycles. CR rate was 69% with successful bridging of 25% of patients to allo-HSCT.

Conclusion

Gilteritinib seems to be effective in the treatment of EMI with a good toxicity profile. We present the first reported case of a successful single agent treatment of isolated extramedullary breast relapse in *FLT3*-ITD+ AML, with a persistent remission at the extended follow-up. CR has been sustained from 44 months, without any consolidation treatment with allo-HSCT. Further research is required to confirm the efficacy of gilteritinib in treating extramedullary relapse. Include and enroll patients with EMI onto AML clinical trials is necessary to find new treatment options and prospectively to evaluate their outcomes in comparison to patients without extramedullary AML

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