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## Acute myeloid leukemia with t(11;19)(q23;p13.1) in a patient with a gastrointestinal stromal tumor undergoing imatinib therapy: A case report

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**Author contributions:** Kim HJ reviewed the literature and contributed to manuscript drafting; Baek SK was the patient's physician until acute leukemia developed, and reviewed the literature; Maeng CH and Kim SY contributed to manuscript drafting; Park TS performed the molecular biological analyses and interpreted the imaging findings; Han JJ was the patient's physician treating acute leukemia, and reviewed the literature; all authors issued final approval for the version to be submitted.

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### Abstract

#### BACKGROUND

Acute myeloid leukemia (AML) harboring 11q23 translocations is classified as therapy-related AML in patients who have undergone prior treatment with cytotoxic agents. There have been only a few reports of AML that subsequently developed during imatinib mesylate (IM) treatment for gastrointestinal stromal tumors (GISTs).

#### CASE SUMMARY

A 63-year-old woman was diagnosed with a hepatic GIST recurrence in April 2012; she was administered IM 400 mg/d. In November 2015, she developed dyspnea with pancytopenia while IM treatment was continued for 42 mo. A chromosome study using a bone marrow sample showed a 46, XX karyotype with t(11;19)(q23;p13.1) in 22 of 26 analyzed metaphase cells. Fluorescence *in situ* hybridization using the locus-specific indicator (11q23) gene break-apart probe showed positive rearrangement in 82% of interphase cells. Reverse-transcription polymerase chain reactions subsequently confirmed the KMT2A/ELL transcript. She achieved complete response with incomplete neutrophil recovery with two decitabine treatment cycles. After the third cycle of decitabine, the disease relapsed, and she refused further treatment. She died of hemorrhagic stroke 5 mo after diagnosis. To the best of our knowledge, this is the first report of AML with KMT2A gene rearrangements in a patient with a GIST receiving IM treatment.

#### CONCLUSION

Physicians should consider the potential risks of developing hematologic malignancies, including therapy-related AML, in patients with GISTs receiving IM treatment.



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**Core tip:** To the best of our knowledge, this is the first report of acute myeloid leukemia with *KMT2A* gene rearrangements in a patient with a gastrointestinal stromal tumor receiving imatinib mesylate (IM) treatment. Although there is no known mechanism by which IM causes acute leukemia, there have been reports supporting the speculation that IM may have a direct mutagenic effect on normal hematopoietic precursors. Physicians should consider the potential risks of developing hematologic malignancies, including therapy-related acute myeloid leukemia, in patients with gastrointestinal stromal tumors receiving IM treatment.

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## INTRODUCTION

Gastrointestinal stromal tumors (GISTs), the most common mesenchymal tumors of the digestive tract, generally occur in the stomach (60%) and small intestine (35%)<sup>[1]</sup>. The interstitial cells of Cajal were identified as the precursor cells, and the mutational activations in receptor tyrosine kinases, c-KIT, or platelet-derived growth factor receptor- $\alpha$  (PDGFRA) were involved in the main pathogenesis<sup>[1,2]</sup>. This understanding of the pathogenesis led to the application of imatinib mesylate (IM), a c-KIT/PDGFRA tyrosine kinase inhibitor, for the treatment of advanced or metastatic GISTs<sup>[3]</sup>.

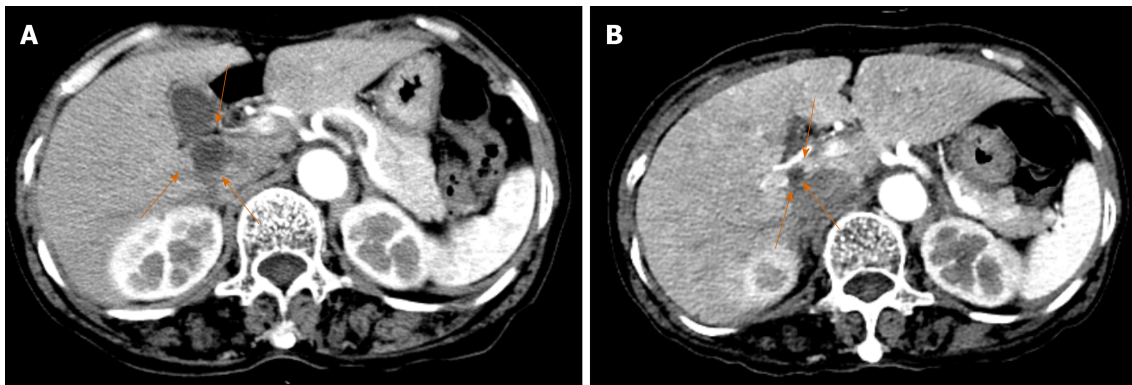
Acute myeloid leukemia (AML) with 11q23 translocations involving the *KMT2A* (previously called *MLL*) gene has been categorized as AML with recurring genetic abnormalities according to the 2016 World Health Organization classification<sup>[4]</sup>. However, AML with 11q23 translocations should be classified as therapy-related AML (t-AML) in patients who have undergone prior treatment with cytotoxic agents, including topoisomerase inhibitors such as etoposide.

There have been only a few reports of AML that subsequently developed during IM treatment for GISTs. Herein, we describe a patient who developed AML with an 11q23 translocation while receiving IM for GISTs.

## CASE PRESENTATION

A 63-year-old woman was diagnosed with a gastric GIST in March 2007 and underwent subtotal gastrectomy. The GIST recurred in the liver in April 2012, and she was administered IM 400 mg/d (Figure 1A). She was transferred to our department in May 2012, and a partial response was observed while IM treatment was continued for 42 mo (Figure 1B). In November 2015, she developed dyspnea with pancytopenia. Her hematological data were as follows: Hemoglobin level, 4.0 g/dL; platelet count,  $27 \times 10^9/L$ ; and white blood cell count,  $1.05 \times 10^9/L$ . Bone marrow examination showed hypercellularity with 70% blasts containing abundant cytoplasm, which were moderately-to-intensely basophilic, and some of them exhibited pseudopod formations and scattered fine azurophilic granules.

Leukemic blasts stained positively upon myeloperoxidase staining. However, the results of periodic acid-Schiff (PAS) and non-specific esterase (NSE) stains were negative. A chromosome study using a bone marrow sample showed a 46, XX karyotype with t(11;19)(q23;p13.1) in 22 out of 26 analyzed metaphase cells (Figure 2A). Fluorescence *in situ* hybridization using the locus-specific indicator (11q23) gene break-apart probe showed positive rearrangement in 82% of interphase cells (Figure 2B). Reverse-transcription polymerase chain reactions subsequently confirmed the *KMT2A/ELL* transcript.



**Figure 1** Four-phase computed tomography images. A: Computed tomography on arterial phase performed in May 2012 showing a 2.0-cm mass with central necrosis and peripheral solid portions; B: Computed tomography on arterial phase performed in November 2015 showing a partial response of the mass.

## FINAL DIAGNOSIS

The final diagnosis of the presented case is AML with *KMT2A*/*ELL* rearrangement.

## TREATMENT

The patient was not considered for intensive treatment because of poor performance status. Therefore, decitabine (20 mg/m<sup>2</sup>) was administered for 5 d.

## OUTCOME AND FOLLOW-UP

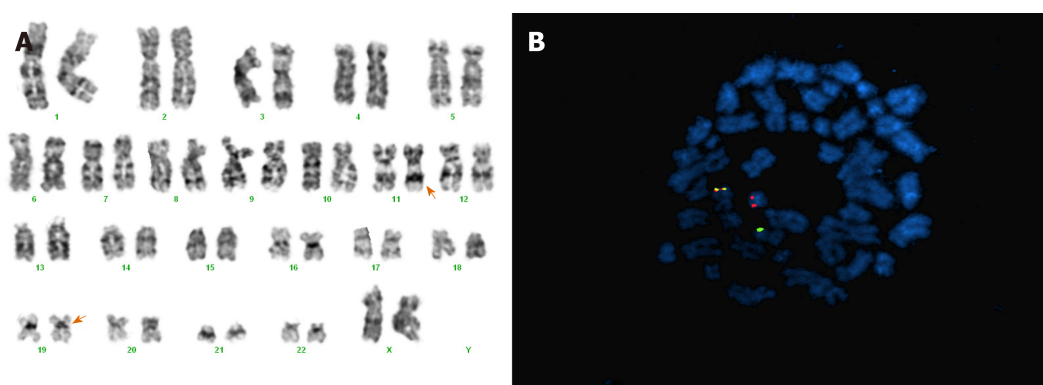
She achieved a complete response with incomplete neutrophil recovery after two treatment cycles. Cytogenetic analysis showed a response with residual disease with the 46, XX, t(11;19)(q23;p13.1) karyotype remaining in 18% of metaphase cells. After the third decitabine treatment cycle, the disease relapsed with 66% blasts in the bone marrow, and cytogenetic analysis showed an additional cytogenetic abnormality of del(13)(q12a14). The patient died of severe intracerebral hemorrhage 5 mo after diagnosis.

## DISCUSSION

To the best of our knowledge, this is the first report of AML with *KMT2A* gene rearrangements in a patient with a GIST receiving IM treatment. Although there is no known mechanism by which IM causes acute leukemia, there have been reports supporting the speculation that IM may have a direct mutagenic effect on normal hematopoietic precursors.

Previously, there have been sporadic reports suggesting the association between hematologic malignancy and GISTs<sup>[5,6]</sup>, and in the late 2000s, a non-random association between GISTs and myeloid leukemia was suggested in a retrospective study that enrolled 1892 patients with GISTs diagnosed between 1970 and 1996<sup>[7]</sup>. Six (0.3%) of the study patients developed AML 1.7–21 years after the diagnosis of GISTs. Although IM was not available at the time of diagnosis, some of the patients could have received IM during the course of their treatments. In another report, 12 of the 314 patients developed hematologic malignancies after the diagnosis of GISTs<sup>[8]</sup>. These studies revealed no information on *KMT2A* gene rearrangements.

Although the long-term experience of IM in patients with chronic myeloid leukemia (CML) was reported as only one case (0.2%) of secondary AML on an IM treatment arm after more than 10 years of follow-up<sup>[9]</sup>, there have been some reports of hematologic malignancies associated with IM treatment. Despite its low prevalence (0.5%), the emergence of 11q23 translocations has been reported in patients with CML during IM treatment. In two cases, the translocation companion for 11q23 was t(11;19)<sup>[10]</sup>. Subsequent AML or MDS after treatment with second generation Bcr-Abl tyrosine kinase inhibitors including dasatinib, nilotinib, and ponatinib for CML was also reported<sup>[11–13]</sup>. Spadaro *et al*<sup>[14]</sup> studied the bone marrow of 49 patients with unresectable or metastatic GISTs before and during IM treatment. They found that 8



**Figure 2 A chromosome study and fluorescence in situ hybridization study.** A: Giemsa-banding karyogram at initial diagnosis: 46, XX, t(11;19)(q23;p13.1). The arrows indicate the involved chromosomes; B: Metaphase fluorescence *in situ* hybridization with the KMT2A probe revealed a red signal on the derivative chromosome 19, a green signal on the derivative chromosome 11, and a fusion signal on the normal chromosome 11.

(16%) of 49 patients acquired chromosomal abnormalities, 7 of whom had trisomy 8. Three patients with trisomy 8 developed myelodysplastic syndrome (MDS), and one patient who had monosomy 7 developed MDS with excess blasts, which rapidly transformed into AML. Ganjoo *et al*<sup>[15]</sup> reported three cases of AML in patients with GISTs during IM treatment. Bone marrow cytogenetic analyses revealed trisomy 8 in one patient and *MLL* duplication in another patient. Summary of data of the patients with GISTs who subsequently developed AML is shown in Table 1. These findings suggest that IM may play a role in the acquisition of specific cytogenetic abnormalities associated with t-AML or MDS.

The important issue in previous findings and the current case is whether IM has mutagenic effects on normal hematopoietic cells. Direct induction of an oncogene leading to the outgrowth of the transformed cell is one of the suggested pathogenic models for t-AML development in association with topoisomerase inhibitors<sup>[16]</sup>. Topoisomerase inhibitors stabilize double-strand breaks and delay the ligation of free DNA ends during replication. Free DNA ends can easily recombine with DNA from another chromosome, which could produce specific gene fusions such as *KMT2A/MLL-MLL3*. IM induces apoptosis in human CML cell lines by inhibiting topoisomerase I and II<sup>[17]</sup>, supporting the idea that similar pathophysiologies may be responsible for the development of t-AML with 11q23 translocations after IM treatment in patients with GISTs. Since the pathogenesis is not yet elucidated, it is impossible to clearly demonstrate that AML occurred due to IM administration even in the present case. The risk of leukemia may be increased with IM treatment alone, but may not be increased without a combination of IM and some predisposing genetic abnormalities, such as an isocitrate dehydrogenase mutation.

## CONCLUSION

In conclusion, physicians should consider the potential risks of developing hematologic malignancies, including t-AML, in patients with GISTs receiving IM treatment. Systematic collection of data on the occurrence of t-AML or MDS during long-term IM treatment in patients with GISTs should be considered along with cytogenetic analysis to better understand the mechanism of t-AML or MDS during IM treatment. Finally, further studies are warranted to identify the off-target effects of tyrosine kinase inhibitors in association with the mechanisms of therapy-related myeloid neoplasms.



**Table 1 Summary of clinicopathologic data of the 11 patients with gastrointestinal stromal tumors who subsequently developed acute myeloid leukemia**

No.	Age (yr)	Sex	Location of GIST	KIT expression/ KIT mutation	AML type	Bone marrow cyto-genetics	Interval of GIST and leukemia	Administration of imatinib mesylate	Ref.
1	57	Male	Perirectal	+ /ND	M4eo	46, XY, add(6)(p25), inv(16)(p13q22), trisomy 8	33	+	[12]
2	74	Male	ND	+ /ND	NOS	ND	38	+	[12]
3	70	Female	Small bowel	+ /ND	M2	46, XX, del(11)(9q21q23) 11q23 (MLLx2)	27	+	[12]
4	63	Female	Small bowel	+ /ND	Preceded by MDS	ND	216	ND	[8]
5	84	Female	Small bowel	+ /ND	NOS	ND	21	ND	[8]
6	40	Male	Small bowel	+ /c.1689_1701 del	Promyelocytic leukemia	ND	30	ND	[8]
7	70	Female	Stomach	+ /c.1689_1701 del	NOS	ND	153	ND	[8]
8	49	Male	Stomach	ND /ND	NOS	ND	252	ND	[8]
9	58	Female	Small bowel	+ /ND	Acute myelomonocytic leukemia	ND	20	ND	[8]
10	63	Female	Stomach	+ /ND		46, XX, t(11;19)(q23;p13.1)	96	+	The present case

GIST: Gastrointestinal stromal tumor; AML: Acute myeloid leukemia; ND: No data; NOS: Not otherwise specified; MDS: Myelodysplastic syndrome.

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