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Rare Gene Rearrangement t(11;22)(q23;q13)/*KMT2A-EP300* in Therapy-related Acute Myeloid Leukemia: A Case Report

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Dear Editor,

Therapy-related myeloid neoplasia (t-MN) describes leukemia and myelodysplastic syndrome in people who have undergone chemotherapy and/or radiation therapy for malignant tumors or non-malignant disorders [1].

t-MNs are divided into two categories based on the type of previous therapy. The first subtype usually occurs after the use of an alkylating agent and/or radiation therapy, and the second subtype occurs in patients taking topoisomerase II inhibitors or after radiation alone. Balanced translocations involving *KMT2A* (also known as *MLL*) or *RUNX1* are common in the second subtype. Approximately 104 different chromosomal rearrangements associated with *KMT2A* have been described to date, with 64 translocation partner genes characterized at the molecular level [2]. Therapy-related t(11;22)(q23;q13) involving a rare partner gene, *EP300*, has been reported in four different cases globally (Table 1) [1-4]. All four patients had a history of malignancy and chemotherapy, and three of them suffered from hematologic malignancies.

Here, we report the first case of a rearrangement involving *EP300*, in Korea. The patient had prostate cancer and subsequently developed AML with t(11;22)(q23;q13)/*KMT2A-EP300* fusion after receiving local palliative radiation therapies from March 2010 to May 2021. The Institutional Review Board of Severance Hospital, Seoul, Korea, approved this study (IRB No. 4-2021-1453) and waived the need for informed consent.

A 76-year-old male diagnosed as having prostate adenocarcinoma, who had undergone five radiotherapy treatments (55 Gy of tomotherapy to the pelvis, prostate, and L4-sacrum; 40 Gy of three-dimensional conformal radiation therapy to the cervical, thoracic, and sacrum vertebrae; and three rounds of intensity-modulated radiation therapy [60, 35, and 37.5 Gy, respectively]), was admitted five months after completing the last radiotherapy session, complaining of general weakness and fever. Regular hormonal treatments were administered, and no chemotherapy was initiated. The complete blood count showed pancytopenia: white blood cell count, 0.81×10^9/L; hemoglobin, 42 g/L; and platelet count, 51×10^9/L. Monocytosis was noted and nucleated red blood cells were frequently seen in the peripheral smear. The bone marrow biopsy showed h–ypercellularity (60%–80%) with markedly decreased number of megakaryocytes. Leukemic blasts up to 21.1% were observed in the bone marrow aspirate (Fig. 1A). Flow cytometry analysis showed that the blasts were positive for CD117, cMPO, CD38, CD11c, HLA-DR, CD33, CD13, CD64, and CD123, indicating AML with monocytic differentiation. G-banding analysis using the bone marrow sample revealed a

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Table 1. Summary of reported therapy-related leukemia cases with t(11;22)(q23;q13)

Characteristic	Present case	Ida, *et al.* [3]	Ohnishi, *et al.* [4]	Duhoux, *et al.* [2]	Takeda, *et al.* [1]
Sex/age (yr)	M/76	M/4	F/5	M/65	F/62
Underlying disease	Prostate cancer	Non-Hodgkin lymphoma	Neuroblastoma	PTCL NOS and AML with MRC	ATL
Leukemia type	Acute monocytic leukemia	AML without maturation	AML with maturation	AMML	CMML
Latent period (months)	138	67	36	16	10
Cytotoxic exposure	Radiotherapy	Chemotherapy including ETP	Chemotherapy including THP	CBDCA, CPA CHOP-14, ESHAP	mLSG+mogamulizumab*
Initial complete blood count	White blood cell: 0.81×10^9/L	-	-	White blood cell: 174×10^9/L	White blood cell: 4.9×10^9/L
	Hemoglobin: 42 g/L			Hemoglobin: 80 g/L	Hemoglobin: 96 g/L
	Platelet: 51×10^9/L			Platelet: 73×10^9/L	Platelet: 87×10^9/L
Cytogenetics	46,XY,t(11;22)(q23;q13)[13]/46,XY[7]	48,XY,+8,+8,t(11;22)(q23;q13)	46,XX,t(1;22;11)(q44;q13;q23)2,t(10;17)(q22;q21)	46,XY,t(11;22)(q23;q13)[15]/47,idem,+8[2]	46,XX,t(11;22)(q23;q13)
Breakpoint	*KMT2A* exon 10/*EP300* exon 15	*KMT2A* exon 9/*EP300* exon 15	*KMT2A* exon 7/*EP300* exon 15	*KMT2A* exon 10,11/*EP300* exon 15	*KMT2A* exon 10/*EP300* exon 15

*a humanized anti-CCR4 antibody.
Abbreviations: PTCL NOS, peripheral T-cell lymphoma not otherwise specified; AML with MRC, acute myeloid leukemia with myelodysplasia-related changes; ATL, adult T-cell leukemia/lymphoma; AMML, acute myelomonocytic leukemia; CMML, chronic myelomonocytic leukemia; ETP, etoposide; THP, pirarubicin; CBDCA, carboplatin; CPA, cyclophosphamide; CHOP-14, cyclophosphamide, doxorubicin, vincristine, and prednisolone; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; mLSG, VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone).

46,XY,t(11;22)(q23;q13)[13]/46,XY[7] karyotype (Fig. 1B). A schematic representation of the *KMT2A-EP300* fusion is provided in Fig. 1C. A next-generation sequencing (NGS) RNA fusion panel detected the fusion between exon 10 of *KMT2A* and exon 15 of *EP300* in 42.58% reads (Fig. 1D). To validate the *KMT2A-EP300* fusion transcripts, reverse transcription-PCR and direct sequencing were performed using *KMT2A*- and *EP300*-specific primers (Fig. 1E and 1F).

An NGS panel targeting 531 genes associated with myeloid malignancy detected variants of *BCOR* (c.4717+1G>A; 89.2% variant allele frequency [VAF]) and *PPM1D* (p.Arg572Ter; 44.3% VAF). Loss of *BCOR* can enhance the self-renewal of myeloid progenitors and promote leukemogenesis [5]. *PPM1D* is mutated in ~20% of patients with therapy-related AML or myelodysplastic syndrome and is associated with prior chemotherapy or radiotherapy [6]. In our case, a nonsense mutation in exon 6 of *PPM1D* produces a C-terminal-truncated protein resulting in the loss of the degradation motif [6]. A truncated form of *PPM1D* confers overexpression, resulting in chronic suppression of *p53* activity and tumorigenesis [7]. Induction chemotherapy with decitabine was administered for five days. No further bone marrow examination was conducted, and the patient was eventually sent to a hospital close to his hometown.

KMT2A-rearranged leukemia accounts for ~10% of acute leukemias in all age categories, which can occur *de novo* or after chemotherapy and/or radiotherapy [4]. A bimodal distribution is seen in patients with *KMT2A* rearrangements. The first peak typically manifests as ALL in newborns under the age of 12 months, and the second manifests as AML in older children and adults [8]. *KMT2A* and *EP300* are transcriptional co-activators involved in epigenetic chromatin remodeling, which induce leukemogenesis by transcriptional upregulation of target genes such as *HOXA9* and its cofactor *MEIS1*. The overexpression of *HOXA9* and *MEIS1* promotes the expansion of hematopoietic progenitor cells and self-renewal of stem cells [9]. The *MENIN-LEDGF* complex anchors and stabilizes KMT2A fusion proteins to their target genes [10]. The bromodomain of *EP300* transfers acetyl groups to lysine 27 of histone 3 (H3K27Ac)—an active transcription marker in hematopoietic epigenetics [1].

We represent the first worldwide report of *KMT2A-EP300* therapy-related leukemia following radiation-only therapy. Comprehensive molecular tests can help determine and characterize the rare gene rearrangements associated with leukemogenesis [11].

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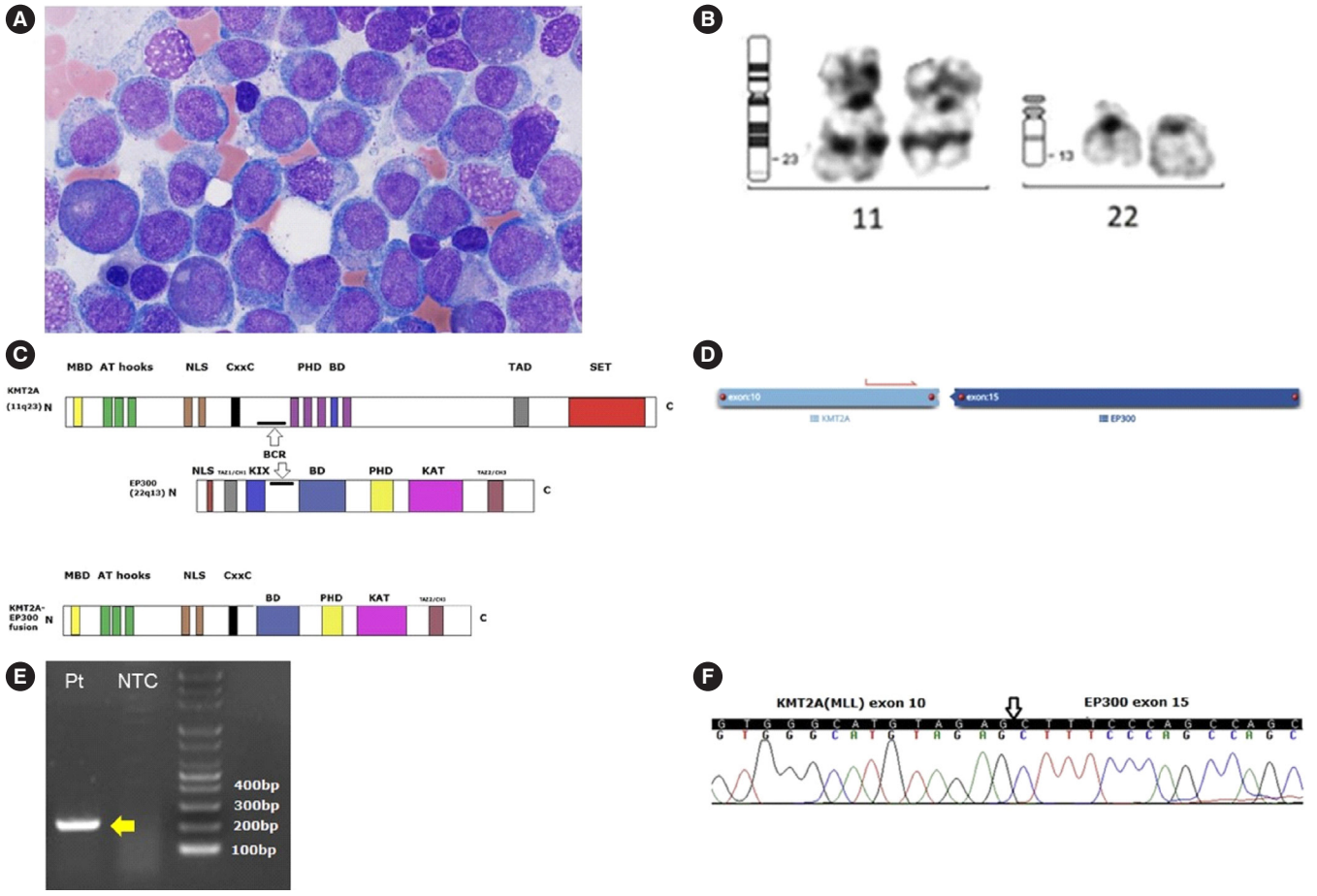

Fig. 1. (A) Bone marrow aspirate at initial diagnosis (×1,000 magnification). (B) G-banding karyotyping showing t(11;22)(q23;q13). (C) Schematic representation of the *KMT2A-EP300* fusion. (D–F) Fusion between exon 10 of *KMT2A* and exon 15 of *EP300* confirmed by (D) an NGS RNA fusion panel, (E) gel electrophoresis following reverse transcription-PCR (yellow arrow), and (F) Sanger sequencing of complementary DNA.

Abbreviations: MBD, menin-binding domain; NLS, nuclear localization signal; CxxC, motif recognizing unmethylated CpG dinucleotides; PHD, plant homeodomain fingers; TAD, transactivation domain; SET, H3K4 histone methyltransferase domain; TAZ, transcriptional-adaptor zinc-finger domain; CH, cysteine/histidine-rich regions; KIX, kinase-inducible domain of the CREB-interacting domain; BD, bromodomain; KAT, lysine acetyltransferase domain; Pt, patient; NTC, no template control.

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AUTHOR CONTRIBUTIONS

Kim SW collected the data and wrote the manuscript. Lee S, Shin S, and Lee ST performed genetic and flow cytometric analyses. Shin S supervised the study and edited the manuscript.

CONFLICTS OF INTEREST

There are no potential conflicts of interest relevant to this article to report.

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REFERENCES

1. Takeda R, Yokoyama K, Kobayashi S, Kawamata T, Nakamura S, Fukuyama T, et al. An unusually short latent period of therapy-related myeloid neoplasm harboring a rare MLL-EP300 rearrangement: case report and literature review. Case Rep Hematol 2019;2019:4532434.
2. Duhoux FP, De Wilde S, Ameye G, Bahloula K, Medves S, Légé G, et al. Novel variant form of t(11;22)(q23;q13)/MLL-EP300 fusion transcript in the evolution of an acute myeloid leukemia with myelodysplasia-related changes. Leuk Res 2011;35:e18-20.
3. Ida K, Kitabayashi I, Taki T, Taniwaki M, Noro K, Yamamoto M, et al. Adenoviral E1A-associated protein p300 is involved in acute myeloid leukemia with t(11;22)(q23;q13). Blood 1997;90:4699-704.
4. Ohnishi H, Taki T, Yoshino H, Takita J, Ida K, Ishii M, et al. A complex t(1;22;11)(q44;q13;q23) translocation causing MLL-p300 fusion gene in therapy-related acute myeloid leukemia. Eur J Haematol 2008;81:475-80.
5. Kelly MJ, So J, Rogers AJ, Gregory G, Li J, Zethoven M, et al. Bcor loss perturbs myeloid differentiation and promotes leukaemogenesis. Nat Commun 2019;10:1347.
6. Kahn JD, Miller PG, Silver AJ, Sellar RS, Bhatt S, Gibson C, et al. PPM1D-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. Blood 2018;132:1095-105.
7. Lu X, Nguyen TA, Moon SH, Darlington Y, Sommer M, Donehower LA. The type 2C phosphatase Wip1: an oncogenic regulator of tumor suppressor and DNA damage response pathways. Cancer Metastasis Rev 2008;27:123-35.
8. Huret JL, Dessen P, Bernheim A. An atlas of chromosomes in hematological malignancies. Example: 11q23 and MLL partners. Leukemia 2001;15:987-9.
9. Kawagoe H, Humphries RK, Blair A, Sutherland HJ, Hogge DE. Expression of HOX genes, HOX cofactors, and MLL in phenotypically and functionally defined subpopulations of leukemic and normal human hematopoietic cells. Leukemia 1999;13:687-98.
10. Yokoyama A and Cleary ML. Menin critically links MLL proteins with LEDGF on cancer-associated target genes. Cancer Cell 2008;14:36-46.
11. Lim HJ, Lee JH, Lee YE, Baek HJ, Kook H, Park JH, et al. The First Korean Case of NUP98-NSD1 and a Novel SNRK-ETV6 Fusion in a Pediatric Therapy-related Acute Myeloid Leukemia Patient Detected by Targeted RNA Sequencing. Ann Lab Med 2021;41:443-6.

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