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JAK2 V617F 양성 급성골수성백혈병의 임상병리학적 특징 2예

JAK2 V617F-Positive Acute Myeloid Leukemia: Clinicopathological Features of Two Cases

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Although the *JAK2* V617F mutation is a common genetic basis for the *BCR-ABL1*-negative myeloproliferative neoplasm (MPN), it is very rarely observed in acute myeloid leukemia (AML) without antecedent MPN. While *JAK2* V617F has a well-defined role as a driver mutation in MPNs, its role in *de novo* AML remains elusive. Here, we retrospectively identified two patients with *JAK2* V617F-positive AML by next-generation sequencing. These patients were diagnosed with AML without a history of an antecedent MPN. The presence of dysmegakaryopoiesis and a non-complex karyotype were consistent with the features reported in previous cases. Concurrent mutations in *JAK2* and *MPL* were identified in one of the patients. Presence of the *JAK2* V617F mutation in AML does not imply a blast phase of an occult MPN and suggests a separate clinical entity.

Key Words: Acute myeloid leukemia, *JAK2* mutation, Next-generation sequencing

INTRODUCTION

The *JAK2* V617F mutation is a common genetic basis for the *BCR-ABL1*-negative myeloproliferative neoplasm (MPN). The majority (~95%) of polycythemia vera and approximately half of the essential thrombocythemia and primary myelofibrosis patients carry this mutation [1]. However, it is rarely observed in *de novo* acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [2, 3]. While *JAK2* V617F has a well-defined role as a driver mutation in MPNs, its role in *de novo* AML remains largely unknown. We retrospectively identified two *JAK2* V617F-positive AML cases and analyzed them to investigate the clinical manifestations and genetic characteristics, as well as morphological features of the bone marrow (BM) from patients carrying this mutation. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B1711/435-004) and informed consent was obtained from the patients.

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CASE REPORT

1. Patient 1

A 37-year-old male patient visited Seoul National University Bundang Hospital for further evaluation of pancytopenia. His complete blood count (CBC) revealed a hemoglobin concentration of 79 g/L, an absolute neutrophil count of 523×10^6/L, and a platelet count of 69×10^9/L. Peripheral blood smear showed 26% blasts. Subsequently, BM biopsy was performed, which revealed an increase in myeloblasts positive for CD13, CD33, CD34, CD38 (partial), CD117, HLA-DR, and CD123, as confirmed with flow cytometry. Furthermore, the results revealed hypercellular marrow with dysmegakaryopoietic features such as monolobation, micro-

megakaryocytes (Fig. 1A), and grade 2 reticulin fibrosis (Fig. 1B). The initial cytogenetic study showed no mitosis. However, the fluorescence *in situ* hybridization results indicated trisomy 8. Next-generation sequencing (NGS) was performed with NextSeq500 (Illumina, San Diego, CA, USA) using a SureSelect Custom panel including 196 genes commonly mutated in myeloid neoplasms. The NGS analysis resulted in detection of the *JAK2*, *MPL*, and *ZRSR2* variants (Fig. 2A–C): NM_004972.3(*JAK2*):c.1849G>T (p.Val617Phe), variant allele frequency (VAF) of 22.2%; NM_005373.2(MPL):c.1543T>A (p.Trp515Arg), VAF of 5.7%; NM_005089.3(ZRSR2):c.1093_1103del (p.Glu365Profs*16), VAF of 60.2%, respectively. The patient had received his first stem cell transplantation in 2018, but relapsed and received a second stem cell transplantation in 2019. Dysmegakaryopoietic features partially remained in the BM biopsy performed after stem cell transplantation (Fig. 3). The patient is currently in a complete remission state.

2. Patient 2

A 47-year-old male patient with dysarthria was admitted to the neurology department of Seoul National University Bundang Hospital. He had never been diagnosed with hematologic disorders or cancer. Severe left middle cerebral artery stenosis and multifocal territories embolic infarction were confirmed with brain magnetic resonance imaging. The CBC profile of the patient revealed a hemoglobin concentration of 136 g/L, an absolute neutrophil count of $2,320 \times 10^6$/L, and a platelet count of 183×10^9/L, indicating no cytopenia but presence of more than 20% peripheral blasts. Next, BM biopsy was performed, which revealed an increase in

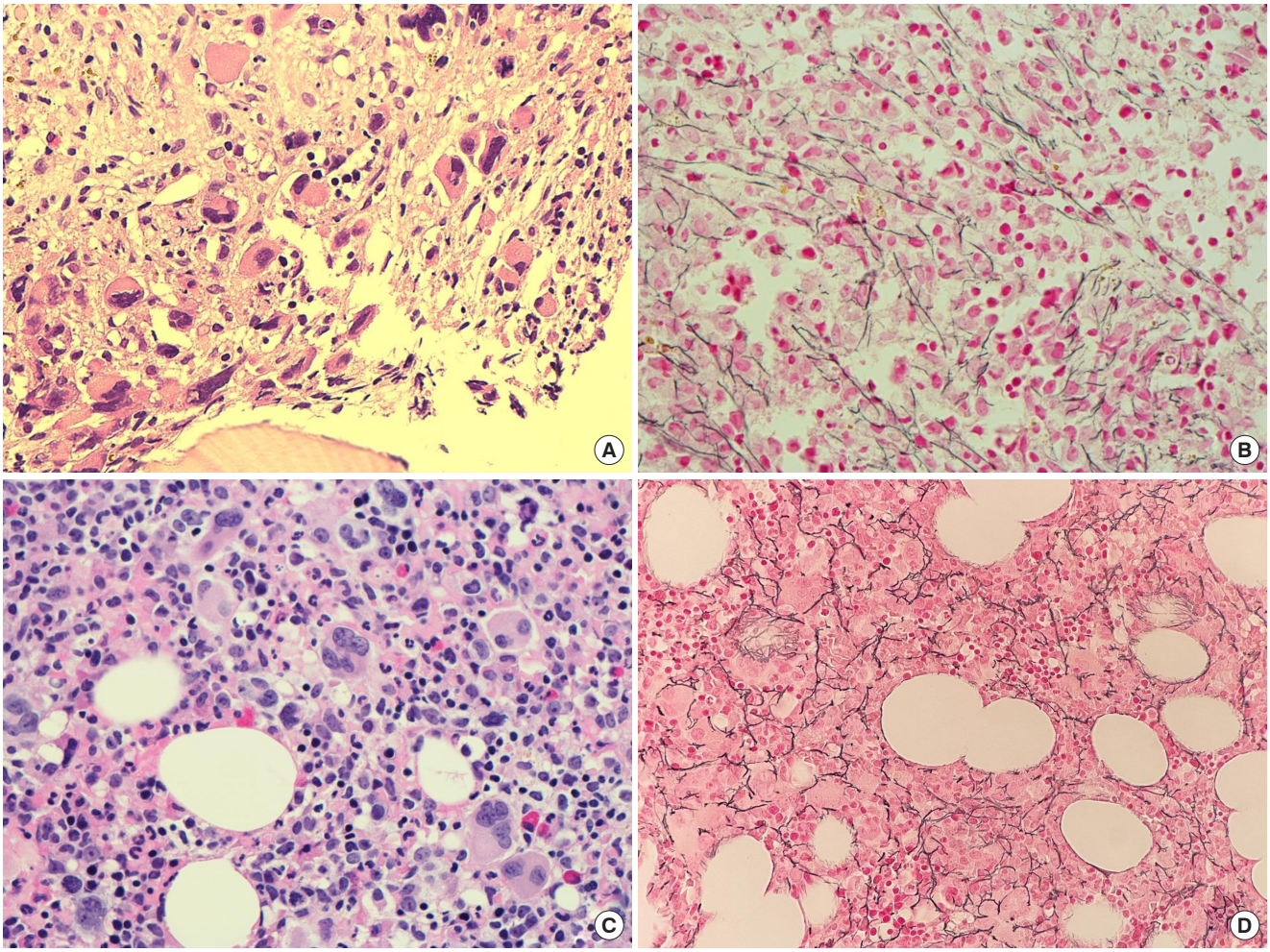

Fig. 1. Morphological features of the bone marrow from patients with AML carrying the *JAK2* V617F mutation. (A) Patient 1: Micromegakaryocytes (hematoxylin-eosin, 400×). (B) Patient 1: diffuse reticulin fibrosis (MF-2) (reticulin, 400×). (C) Patient 2: Hypolobated, dysplastic megakaryocytes (hematoxylin-eosin, 400×). (D) Patient 2: diffuse reticulin fibrosis (MF-2) (reticulin, 200×).

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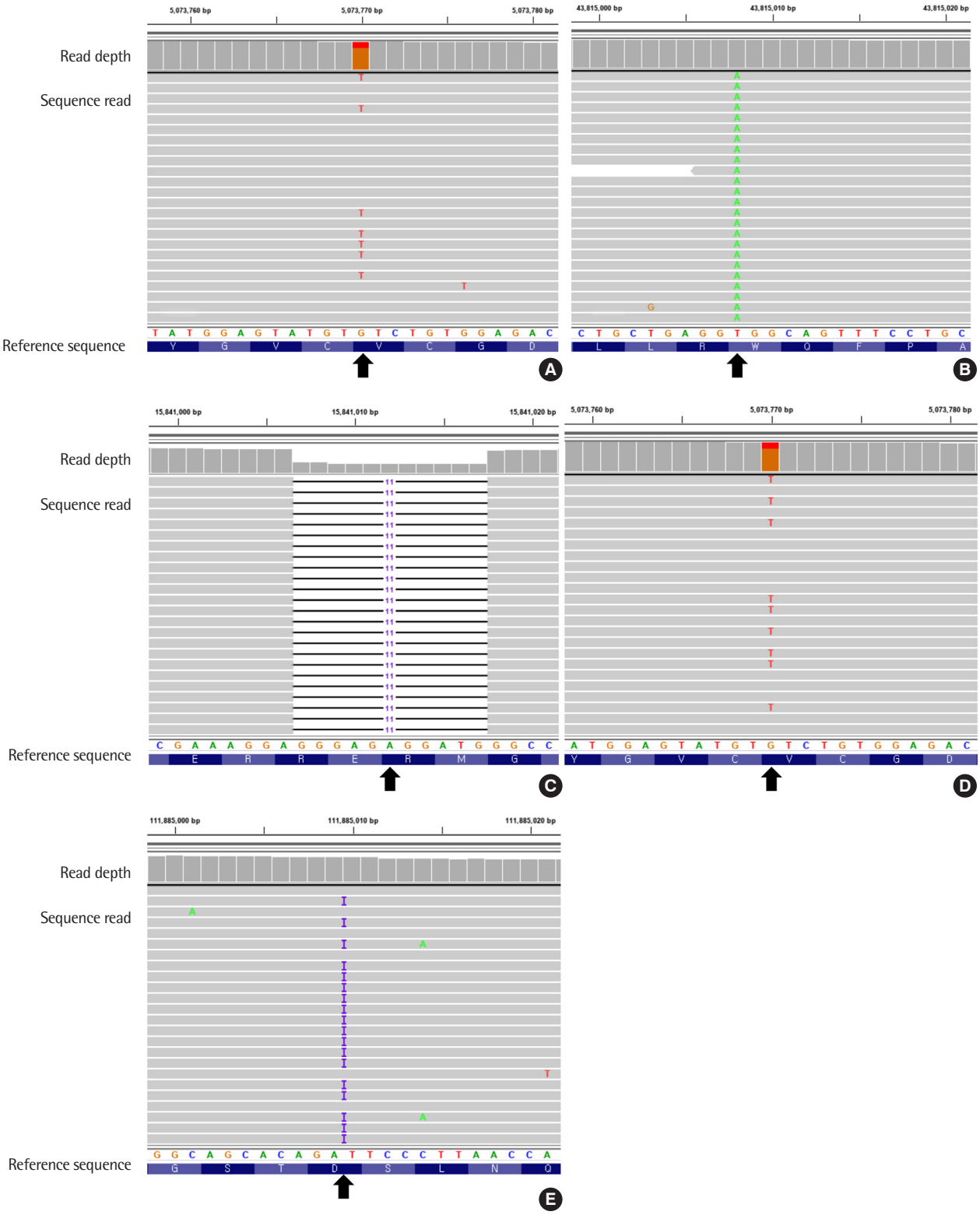

Fig. 2. IGV browser visualization of the NGS results. (A) Patient 1: NM_004972.3(JAK2):c.1849G>T (p.Val617Phe) in the *JAK2* gene. (B) Patient 1: NM_005373.2(MPL):c.1543T>A (p.Trp515Arg) in the *MPL* gene. (C) Patient 1: NM_005089.3(ZRSR2):c.1093_1103del (p.Glu365Profs*16) in the *ZRSR2* gene. (D) Patient 2: NM_004972.3(JAK2):c.1849G>T (p.Val617Phe) in the *JAK2* gene. (E) Patient 2: NM_005475.2(SH2B3):c.1009dup (p.Ser337Phefs*3) in the *SH2B3* gene.

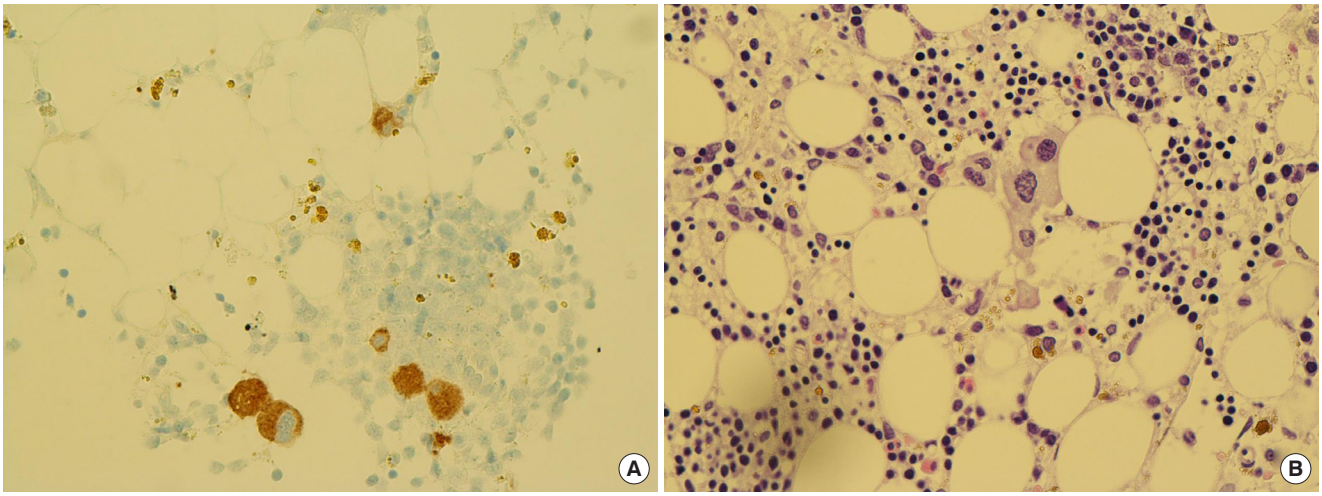

Fig. 3. Morphological features of the bone marrow from patient 1 after stem cell transplantation (SCT). (A) BM biopsy after 1st SCT (CD61, 400×). (B) BM biopsy after 2nd SCT (hematoxylin-eosin, 400×). Micromegakaryocytes could be occasionally observed in a small cellular area.

myeloblasts positive for CD13, CD33, CD34, CD117 (partial), HLA-DR, and myeloperoxidase (partial), as confirmed with flow cytometry. Additionally, normocellular marrow with dysmegakaryopoietic features, such as widely separate nuclei and monolobation (Fig. 1C), and grade 2 reticulin fibrosis (Fig. 1D) were also observed. The initial cytogenetic study indicated a normal karyotype. Based on these findings, a diagnosis of AML, not otherwise specified was made. The NGS analysis identified *JAK2* V617F with a VAF of 23.7%. An additional mutation, NM_005475.2(SH2B3):c.1009dup (p.Ser337Phefs*3), was found in the *SH2B3* gene (Fig. 2D and E). Despite the need for chemotherapy, the patient refused to receive treatment and was discharged.

DISCUSSION

The valine-to-phenylalanine substitution at codon 617 in the *JAK2* protein is a common mutation in *BCR-ABL1*-negative MPNs. However, this mutation is reported at a low frequency (<5%) in *de novo* AML [2, 3]. These cases appeared in the literature from 2005 onwards, mostly as case reports or as small case series. Hidalgo-López et al. [4] reported the comparison between *de novo* AML with *JAK2* V617F mutation and age-, sex-, and WHO classification diagnosis-matched *JAK2* wild type AML. The *JAK2* V617F mutation has been frequently identified in patients with BM dysplasia and myelofibrosis, an abnormal karyotype, and mutations in genes involved in DNA methylation and epigenetic-modifying pathways, and in the absence of gene mutations in activating signaling pathways other than *JAK2*. In 2018, Aynardi et al. [5] reported the largest-to-date case series, which included 15 patients. They compared *de novo* AML with the *JAK2* V617F mutation and secondary AML transformed from an underlying MPN. Splenomegaly, MPN-like megakaryocytic atypia at the time of AML diagnosis, and complex karyotype were less commonly observed in *de novo JAK2* V617F-positive AML compared to those in secondary AML from underlying MPN. Normal karyotype and mutations in the genes encoding DNA methylation mediators were more commonly observed in *de novo* AML, and the mean *JAK2* V617F allele frequency was higher in secondary AML (50%) than in *de novo* AML (32%). These previous studies did not reveal the specific role of the *JAK2* V617F mutation in AML pathogenesis, but proposed that this entity exhibits features distinct from those of secondary AML.

In this case report, we presented two cases of *JAK2* V617F-positive AML. The patients were diagnosed with AML without any evidence of antecedent MPN. The presence of dysmegakaryopoiesis and a non-complex karyotype were consistent with the findings of previous studies. Both patients carried the *JAK2* V617F mutation and the variant allele frequency was 22.2% and 23.7%. As previous studies reported that mutations in the activating signaling pathways other than *JAK2* are rarely observed in *de novo JAK2* V617F-positive AML, the additional mutation in the *MPL* gene was a rare finding. Patient 1 exhibited *MPL* W515R with a VAF of 5.7%. The coexistence of driver mutations is also a rare event in MPN patients [6, 7]. Most *MPL* mutations substituted at the amino acid position 515 (W515) reportedly lead to the activa-

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tion of MPL and result in constitutive activation of JAK2 and STAT protein signaling [8]. It is noteworthy that the allele burden of *MPL* W515R was significantly lower (5.7%) than that (22.2%) of *JAK2* V617F. This could be explained by pre-existing clonal hematopoiesis, followed by the acquisition of a second oncogenic mutation [9]. Considering that Patient 2 visited the hospital with a history of cerebral infarction and no previous diagnosis was established, he could potentially have underlying MPN. However, in previous reports, *JAK2* V617F allele frequency tended to be lower in *de novo JAK2* V617F-positive AML than in secondary AML [5]. The *JAK2* V617F allele frequency of Patients 1 and 2 was 22.2 and 23.7%, respectively, which could be considered low.

JAK2 V617F-positive AML is a distinct biological entity from secondary AML transformed from underlying MPNs. Presence of the *JAK2* V617F mutation in AML does not imply a blast phase of an occult MPN. The cases described here support the presence of this unique entity. In patients newly diagnosed with *JAK2* V617F-positive AML without a history of previously diagnosed hematologic disease, dysmegakaryopoiesis, myelofibrosis, and non-complex karyotype are common. Splenomegaly and the mean VAF of the *JAK2* mutation are also important in discriminating between *de novo JAK2* V617F-positive AML and secondary AML progressed from antecedent MPN.

요 약

JAK2 V617F는 *BCR-ABL1* 음성 골수증식종양(MPN)에서 높은 빈도로 발견되는 유전자 돌연변이이다. 그러나 이전 MPN 병력이 없는 급성골수성백혈병(AML)에서는 매우 드물게 관찰된다. 골수증식종양에서는 암 유발 돌연변이로서 *JAK2* V617F의 역할이 잘 알려져 있지만, 일차성 AML에서 *JAK2* V617F의 역할은 명확하지 않다. 본 연구에서는 후향적으로 차세대염기서열분석에 의해 두 명의 *JAK2* V617F 양성 AML 환자를 찾았기에 문헌고찰과 함께 보고하는 바이다. 두 환자 모두 이전에 MPN 진단을 받지 않은 상태에서 AML 진단을 받았다. 거핵구 이형성(dysmegakaryopoiesis)과 비복합성 핵형(non-complex karyotype)이 관찰된다는 점은 이전 연구와 일치했다. 한 환자에서는 *JAK2*와 *MPL* 두 유전자에서 동시에 돌연변이가 있었는데 이는 드문 소견이었다. *JAK2* V617F 양성 AML은 기저 MPN으로부터 진행하여 발생하는 이차성 AML과는 생물학적으로 구분되는 질환이다. AML 진단을 받은 환자에서 확인된 *JAK2* V617F 돌연변이 양성이 반드시 기저 MPN의 급성기를 의미하지는 않으며, 별개의 질환임을 본 증례를 통해 확인할 수 있다.

Conflicts of Interest

None declared.

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REFERENCES

1. Swerdlow SH, Campo E, et al. eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Lyon, France: International Agency for Research on Cancer, 2017:39-53.
2. Steensma DP, McClure RF, Karp JE, Tefferi A, Lasho TL, Powell HL, et al. *JAK2* V617F is a rare finding in de novo acute myeloid leukemia, but STAT3 activation is common and remains unexplained. Leukemia 2006;20:971-8.
3. Lee JW, Kim YG, Soung YH, Han KJ, Kim SY, Rhim HS, et al. The *JAK2* V617F mutation in de novo acute myelogenous leukemias. Oncogene 2006;25:1434-6.
4. Hidalgo- López JE, Kanagal-Shamanna R, L. Medeiros LJ, Estrov Z, Yin CC, Verstovsek S, et al. Morphologic and molecular characteristics of de novo AML with *JAK2* V617F mutation. J Natl Compr Canc Netw 2017;15:790-6.
5. Aynardi J, Manur R, Hess PR, Chekol S, Morrissette JJD, Babushok D, et al. *JAK2* V617F-positive acute myeloid leukemia (AML): a comparison between de novo AML and secondary AML transformed from an underlying myeloproliferative neoplasm. A study from the Bone Marrow Pathology Group. Br J Haematol 2018;182:78-85.
6. De Roeck L, Michaux L, Debackere K, Lierman E, Vandenberghe P, Devos T. Coexisting driver mutations in MPN: clinical and molecular characteristics of a series of 11 patients. Hematology 2018;23:785-92.
7. Jang MA, Seo MY, Choi KJ, Hong DS. A rare case of essential thrombocythemia with coexisting *JAK2* and *MPL* driver mutations. J Korean Med Sci 2020;35:e168.
8. Defour JP, Chachoua I, Pecquet C, Constantinescu SN. Oncogenic activation of MPL/thrombopoietin receptor by 17 mutations at W515: implications for myeloproliferative neoplasms. Leukemia 2016;30:1214-6.
9. Mansier O, Luque Paz D, Ianotto JC, Le Bris Y, Chauveau A, Boyer F, et al. Clinical and biological characterization of MPN patients harboring two driver mutations, a French intergroup of myeloproliferative neoplasms (FIM) study. Am J Hematol 2018;93:E84-6.