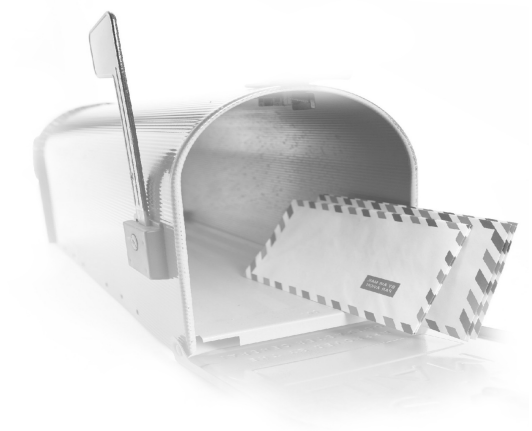

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Letters to the Editor

Myeloproliferative neoplasm with basophilia and abnormality of platelet-derived growth factor receptor a translocation: a case report

TO THE EDITOR: Translocation of platelet-derived growth factor receptor A (*PDGRFA*)-protein kinase cGMP-dependent 2 (*PRKG2*) is uncommon in myeloproliferative neoplasms. We report a rare case of a patient presenting Philadelphia-negative myeloproliferative neoplasms with peripheral basophilia. The patient was a 38-year-old man with splenomegaly and leukocytosis. Peripheral blood examination revealed normocytic and normochromic red blood cells, no polychromasia, an increased WBC count with no toxic granulation or vacuolations, some blasts, basophilia, and an increased platelet count. Laboratory tests revealed a white blood cell count of 30,000/μL, hemoglobin level of 11.6 g/dL, and platelet count of 789,000/μL. WBCs comprised 30% segmented neutrophils, 13% lymphocytes, 1% monocytes, 4% eosinophils, and 47% basophils. Bone marrow biopsy showed estimated cellularity of ~100%, and the numbers of immature cells and basophils were increased. Multifocal fibrosis was also observed. The *PDGRFA-PRKG2* fusion gene was observed through next-generation gene sequencing, and targeted imatinib therapy was selected using an artificial intelligence matching algorithm. Immediately after treatment, the patient's symptoms improved immediately, and his WBC count was normalized. Our results identify the first case of *PDGRFA-PRKG2* fusion in an unclassified myeloproliferative neoplasm. This case also shows that the use of imatinib is very effective in treating specific myeloproliferative neoplasms with the *PDGRFA-PRKG2* translocation.

INTRODUCTION

Patients, occasionally meet the general criteria for classifying their condition as a myeloproliferative neoplasm (MPN) but may not meet all criteria for a particular disease or may exhibit more than one category of diagnostic characteristics. These patients can be diagnosed as MPN unclassifiable (MPN-u). Symptoms are similar to typical MPNs and usually include hepatosplenomegaly and increased numbers of white blood cells (WBCs) and platelets. A bone marrow biopsy reveals megakaryocyte proliferation and hypercellularity in granulocytes or erythrocytes. As the disease progresses, the bone marrow becomes more fibrotic. However, in the current patient, *BCR-ABL, CARL, MPL*, and *JAK2* gene mutations, commonly observed in MPNs, were all negative. The patient was treated with hydroxyurea and ruxolitinib due to leukocytosis, hyperbasophilia, and splenomegaly, but there was no improvement. Myeloproliferative diseases often have mutations or rearrangements of protein tyrosine kinase genes such as *JAK2, FGFR1*, platelet-derived growth factor receptor A (*PDGFRA*), and *PDGFRB* [1, 2]. A variety of chromosomal translocations involving *PDGFRA* have been identified revealing that it can fuse with many different partner genes. *PDGFRA* and *PDGFRB* are transmembrane glycoproteins in the type III receptor tyrosine kinase family. This family also contains *KIT, FLT3*, and *c-FMS*. Platelet-derived growth factors (*PDGF*s) include a group of mitogens comprising five dimeric forms derived from pairs of A, B, C, and D peptide chains (*PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC,* and *PDGF-DD*). *PDGFRA* binds to the A, B, and C chains. *PDGFRB* binds to B and D chains. *PDGFRA* and *PDGFRB* are transmembrane glycoproteins belonging to the type III receptor tyrosine kinase family [3]. In 2003, the *FIP1L1-PDGFRA* mutation was described in relation to the MPN phenotype characterized by eosinophilia and mastocytosis [4]. The *FIP1L1-PDGFRA* fusion gene was highly sensitive to low-dose imatinib; complete molecular remission could be achieved with 100 mg/day and a 300 mg/week maintenance dose [5]. To date, four *PDGFRA* fusion genes have been identified including *FIP1L1-PDGFRA, BCR-PDGFRA, ETV6-PDGFRA*, and *CDK5RAP2-DGFRA* by the nested real-time polymerase chain reaction [6-8]. However, these mutations have been reported to exhibit clinical patterns of hyperbasophilia. In this study, we report a case of MPN-u associated with basophilia and the protein kinase cGMP-dependent 2 (*PRKG2*)-*PDGFRA* translocation, which

was improved following imatinib treatment.

CASE

A 38-year-old man presented to the Konyang University Hospital (Deajeon, South Korea) on March 10, 2017, with abdominal pain that started 2 months before, and thrombocytosis was identified at a local clinic. At the time of admission, the patient had a blood pressure of 130/90 mmHg, heart rate of 78 beats per minute, respiratory rate of 20 breaths per minute, and body temperature of 37°C. There was no significant previous medical history of hypertension, diabetes mellitus, or tuberculosis. On physical examination, we observed organomegaly in the right upper quadrant of the abdomen. However, there was no enlargement of the cervical, axillary, or inguinal lymph nodes. Other examinations were unremarkable. Laboratory tests showed WBCs at 30,300/μL, hemoglobin at 9.4 g/dL, and platelets at 836,000/μL. White blood cells were composed of 24% segmented neutrophils, 17% lymphocytes, 1% monocytes, 3% eosinophils, and 51% basophils. The reticulocyte count was within the normal range. Leukemic blasts were observed in 2% of the cells. Coagulation tests revealed a prothrombin time of 16.4 seconds and an activated partial thromboplastin time of 35.5 seconds. He had a fibrinogen level of 3.13 g/L, D-dimer level of 2.1 μg/mL, and antithrombin activity of 72% (not suggestive of disseminated intravascular coagulation). Peripheral blood showed normocytic and normochromic red blood cells, no polychromasia, a normal WBC count with no toxic granulation or vacuolations, and an increased platelet count. The serum lactate dehydrogenase level was 832 U/L (normal range, 120–240 U/I). The total bilirubin level was 1.04 mg/dL (normal range, 0–0.4 mg/dL). Results for other blood factors, including creatinine and bicarbonate, and liver function tests, were unremarkable. Computed tomography revealed hepatosplenomegaly (16 cm) without an intrasplenic mass. Bone marrow aspiration revealed no particles or peripheral dilution, and immature cells were observed occasionally (Fig. 1). Bone marrow biopsy showed estimated cellularity of approximately 100%, which was hypercellular for the patient's age. In cellular areas, trilineage hematopoiesis was observed, along with increased numbers of basophils and immature cells. In addition, there were increased numbers of dysplastic megakaryocytes, and diffuse fibrosis was observed in multiple focal areas throughout the bone marrow space (Fig. 2). The *JAK2* V617F, and *BCR/ABL1* mutations were not detected with the real-time polymerase chain reaction. In chromosome analysis, of the 20 metaphase cells that could be observed, all cells were subjected to 46, XY normal karyotype. The initial formal pathologic diagnosis was deferred, so the patients received hydroxyurea 200 mg twice daily. However, leukocytosis continued, and the basophilia did not improve. The WBC count eventually increased to 88,000/μL, and a bone marrow biopsy was performed again. The second formal pathologic diagnosis was MPN with myelofibrosis. The patient additionally received 20 mg ruxolitinib phosphate twice daily. Although the WBC count decreased to 32,000/μL, basophilia persisted. Various symptoms, such as splenomegaly, basophilia, and leukocytosis continued after more than a year of treatment. Finally, the patient was able to undergo next-generation gene sequencing (NGS). Targeted sequencing was performed for translocation detection using the HemaSCAN panel (Level.1), which includes the whole exomes of 427 cancer-associated genes, and the intronic regions of 23 genes. The sequencing library was constructed with DNA extracted from bone marrow

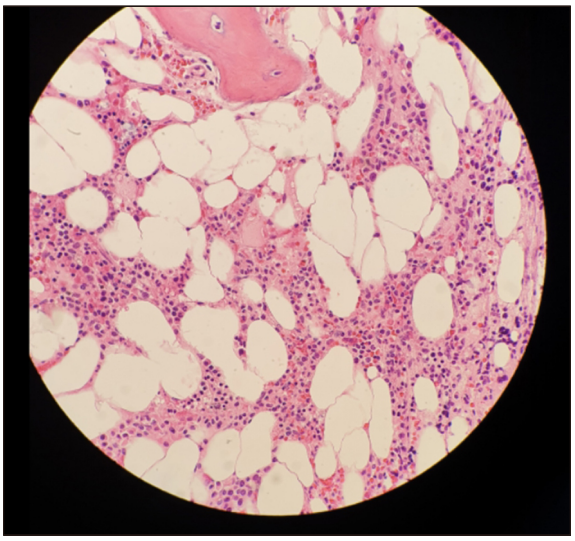

Fig. 1. Bone marrow aspiration demonstrating a lack of particles and peripheral dilution. Immature cells are occasionally noted (×200).

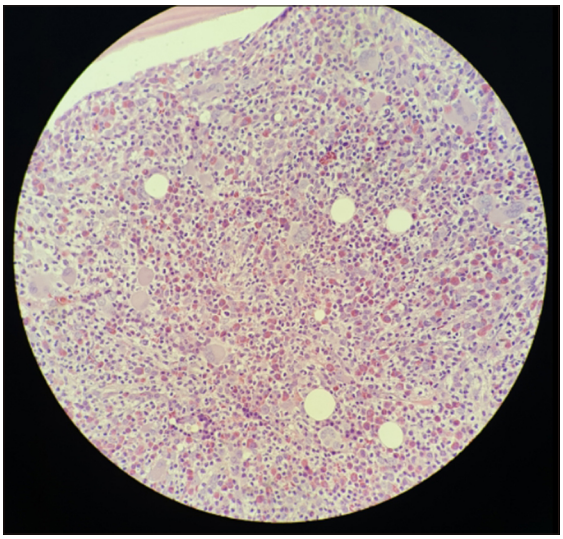

Fig. 2. Trephine bone marrow biopsy showing approximately 60% cellularity, with increased atypical megakaryocytes and fibrosis (Hematoxylin & Eosin staining, ×200).

Table 1. Results of next generation gene sequencing before imatinib treatment. PRKG2-PDGFRA translocation with 33.6% variant allele frequency and breakpoints at exon 10 of PRKG2 and exon 12 of PDGFRA.

A. Annotated variants
TRANSLOCATION:

GeneA	GeneB	cnt_ ReadA	cnt_ ReadB	Total_ read	ChrA	ChrB	Read. posA	Read .posB	Direction
PDGFRA	PRKG2	154	129	283	chr4: 55141064	chr4: 82065407	NM_006206_ Exon(12/23)_ Frame(0,1)	NM_006259_ Exon(10/19)_ Frame(2,2)	PRKG2→ PDGFRA

B. Known variants
SNV:

Gene	Refseq ID	Exon	DNA change	AA change	Func	ChrPos	Read depth	VAF	COSMIC	dbSNP
MKI67	NM_ 002417	exon14	c.9670C>T	p.R3224W	nonsynonmous SNV	chr10:129899557	1746	42.55%	COSM916078	rs754802357
MCU2	NM_ 002457	exon30	c.5356A>C	p.K1786Q	nonsynonmous SNV	chr11:1093537	697	8.03%	COSM4145288	rs80200693
LRRK2	NM_ 198578	exon11	c.1256C>T	p.A419V	nonsynonmous SNV	chr12:40646786	1020	44.41%	COSM147473	rs34594498
BCL7A	NM_ 020993	exon4	c.359A>C	p.N120T	nonsynonmous SNV	chr12:122481879	724	46.55%	COSM5880386	rs34821485
WDR90	NM_ 145294	exon16	c.1804C>T	p.R602W	nonsynonmous SNV	chr16:705658	758	44.2%	COSM3273238	rs201699835
PALB2	NM_ 024675	exon4	c.925A>G	p.I309V	nonsynonmous SNV	chr16:23646942	1710	45.5%	COSM3957351	rs3809683
ZNF24	NM_ 006965	exon3	c.427C>T	p.L143F	nonsynonmous SNV	chr18:329919934	1054	43.93%	COSM5854150	rs148053646

INDEL:

Gene	Refseq ID	Exon	DNA change	AA change	Func	ChrPos	Read depth	VAF	COSMIC	dbSNP
MSH6	NM_ 000179	exon10	c.4065_4066 insTTGA	p.T1355fs	frameshift insertion	chr2:48033981	764	40.45%	COSM3186044	NA

C. Novel Variants
SNV:

Gene	Refseq ID	Exon	DNA change	AA change	Func	ChrPos	Read depth	VAF	COSMIC	dbSNP
SDHC	NM_ 003001	exon2	c.25G>A	p.V9I	nonsynonmous SNV	chr1:161293408	689	55.15%		rs774768866
ALK	NM_ 004304	exon18	c.3035C>T	p.T1012M	nonsynonmous SNV	chr2:29449820	1332	46.1%		rs35073634
ERBB4	NM_ 005235	exon24	c.2935C>G	p.R979G	nonsynonmous SNV	chr2:212286761	1177	45.2%		rs574197848
BARD1	NM_ 000465	exon4	c.722C>G	p.S241C	nonsynonmous SNV	chr2:215645876	2397	46.06%		rs3738885
HIST1H2BJ	NM_ 021058	exon1	c.215A>G	p.E72G	nonsynonmous SNV	chr6:27100315	1660	47.89%		NA
KDM4C	NM_ 015061	exon18	c.2447G>A	p.R816Q	nonsynonmous SNV	chr9:7103707	1055	44.36%		rs180710573
ABL1	NM_ 007313	exon10	c.1601T>C	p.V534A	nonsynonmous SNV	chr9:133755917	559	40.97%		rs776483252
NUP98	NM_ 016320	exon11	c.1192A>G	p.S398G	nonsynonmous SNV	chr11:3774621	937	46.42%		rs144302699
PTPRO	NM_ 030667	exon17	c.2648A>T	p.Y895F	nonsynonmous SNV	chr12:157133183	1553	49.45%		rs759525747
FANCA	NM_ 000135	exon42	c.4232C>T	p.P1411L	nonsynonmous SNV	chr16:898055318	1230	45.61%		rs201494304
GTSE1	NM_ 016426	exon9	c.1688G>C	p.R563T	nonsynonmous SNV	chr22:467225515	1135	47.84%		rs760482340
PCLO	NM_ 033026	exon2	c.1561C>G	p.P521A	nonsynonmous SNV	chr7:82784396	618	14.24%		NA

aspiration blood, and sequencing was performed on a NextSeq550Dx with a 75 bp read (Illumina). Post-sequencing data were analyzed using a bioinformatics pipeline (HemaSCAN version 1.0) from Labgenomics. This test identified a driver mutation, that is, the *PRKG2-PDGFRA* translocation (Table 1). Based on artificial intelligence matching algorithm (HemaSCAN version 1.0), imatinib treatment was immediately initiated. Within a month of treatment, the WBC level was within the normal range, and the basophil level was reduced to 1%. The patient was treated with imatinib for more than a year, and the *PDGFRA-PRKG2* translocation disappeared in a repeated NGS test (Table 2). All of the patient's blood tests results returned to normal and splenomegaly improved.

DISCUSSION

Translocation of *PDGFRA-PRKG2* is uncommon in MPNs. Here, we report a rare case of a patient presenting with a Philadelphia-negative MPN with peripheral basophilia. These results are the first report of *PDGFRA-PRKG2* fusion in an MPN-u case. This case shows that the use of imatinib is very effective in specific MPNs with the *PDGFRA-PRKG2* translocation. The most intensively studied *PDGFRA* mutation is *FIP1L1-PDGFRA*, a karyotypically occult del(4)(q12) described in 2003 as an imatinib-sensitive activation mutation. The *FIP1L1-PDGFR* fusion gene is an ~800 kb interstitial deletion within 4q12 that fuses the 5′ portion of *FIP1L1* to the 3′ portion of *PDGFRA* and is a novel molecular mechanism for generating

Table 2. Results of next generation gene sequencing after imatinib treatment. The oncogenic mutation (PRKG2/PDGFRA translocation) has disappeared.

A. Annotated variants
B. Known variants
SNV:

Gene	Refseq ID	Exon	DNA change	AA change	Func	ChrPos	Read depth	VAF	COSMIC	dbSNP
MKI67	NM_002417	exon14	c.9670C>T	p.R3224W	nonsynonmous SNV	chr10:129899557	2254	41.33%	COSM916078	rs754802357
ZNF24	NM_006965	exon3	c.427C>T	p.L143F	nonsynonmous SNV	chr18:32919934	1447	44.3%	COSM5854150	rs148053646

INDEL:

Gene	Refseq ID	Exon	DNA change	AA change	Func	ChrPos	Read depth	VAF	COSMIC	dbSNP
MKI67	NM_002417	exon13	c.4991_4992del	p.T1664fs	frameshift insertion	chr10:129905112	3486	2.35%	COSM916119	rs145960091

C. Novel variants
SNV:

Gene	Refseq ID	Exon	DNA change	AA change	Func	ChrPos	Read depth	VAF	COSMIC	dbSNP
SDHC	NM_003001	exon2	c.25G>A	p.V9I	nonsynonmous SNV	chr1:161293408	633	52.45%		rs774768866
ERBB4	NM_005235	exon24	c.2935C>G	p.R979G	nonsynonmous SNV	chr2:212286761	1620	44.88%		rs574197848
BARD1	NM_000465	exon4	c.722C>G	p.S241C	nonsynonmous SNV	chr2:215645876	2889	46.49%		rs3738885
FGFR4	NM_002011	exon13	c.1817G>A	p.R606Q	nonsynonmous SNV	chr5:176522720	243	48.56%		rs757092386
HIST1H2BJ	NM_021058	exon1	c.215A>G	p.E72G	nonsynonmous SNV	chr6:27100315	2154	50.0%		NA
ABL1	NM_007313	exon10	c.1601T>C	p.V534A	nonsynonmous SNV	chr9:133755917	718	42.9%		rs776483252
NUP98	NM_016320	exon11	c.1192A>G	p.S398G	nonsynonmous SNV	chr11:3774621	1283	45.91%		rs144302699
PTPRO	NM_030667	exon17	c.2648A>T	p.Y895F	nonsynonmous SNV	chr12:157113183	1521	48.06%		rs759525747
FANCA	NM_000135	exon42	c.4232C>T	p.P1411L	nonsynonmous SNV	chr16:898055318	1747	46.48%		rs201494304
GTSE1	NM_016426	exon9	c.1688G>C	p.R563T	nonsynonmous SNV	chr22:467225515	1415	46.08%		rs760482340
RUNX1	NM_001754	exon9	c.1270T>G	p.S424A	nonsynonmous SNV	chr21:361646605	225	25.33%		NA

a compositionally activated fusion tyrosine kinase. The breakpoint of *FIP1L1* has been observed at various positions, but the *PDGFRA* breakpoint is specific to exon 12, which encodes part of the protein-protein interaction module with two fully conserved tryptophans containing the JM region. As a result, automatic prohibition activities are suspended, leading to disruption of its autoinhibitory activity [9]. Although *FIP1L1-PDGFRA* occurs in a small number of patients with phenotypic features of systemic mastocytosis or hypereosinophilic syndrome, the presence of this mutation reliably predicts complete hematological and molecular responses to imatinib therapy [10]. In addition, *PDGFRA* activation associated with chronic eosinophilic leukemia is described by karyotypically apparent fusion mutations such as *KIF5B-PDGFRA* t(4:10)(q12;p11) [11], *BCR-PDGFRA,* t(4;22)(q12;q11) [12], and *CDK5RAP2-PDGFRA*, ins(9;4)(q33;q12q25) [13].

KIF5B is the third *PDGFRA* partner gene identified after *BCR* and *FIP1L1*, and encodes kinesin family member 5b, a microtubule-based motor protein involved in organ transport. The *KIF5B* protein is composed of three structural regions: an N-terminal region that hydrolyzes ATP and binds microtubules, a large central helicoil region, and a C-terminal region that interacts with other proteins, blood vessels, and membrane organs. The *KIF5B-PDGFR* fusion protein contains most of the first two structural domains of *KIF5B*, including six of the seven coil domains and the entire kinase domain of *PDGFRA* [11].

CDK5 regulatory subunit-related protein 2 (*CDK5RAP2*) encodes a protein that is thought to be involved in regulating the formation and stability of microtubules from the centrosome. A new mRNA in-frame fusion between exon 13 of the *CDK5RAP2* gene, and truncated *PDGFRA* exon 12, were identified by rapid amplification of cDNA ends with the polymerase chain reaction. The *CDK5RAP2-PDGFRA* protein, which is composed of 1,003 amino acids, preserves both the tyrosine kinase domain of *PDGFRA* and several potential dimerization domains of *CDK5RAP2* [13]. In 1994, the Golub and Gililand groups described *ETV6-PDGFRB* fusion as the first of these fusion genes in patients with chronic myelomonocytic leukemia with eosinophilia and t(5;12) [14]. This gene encodes a protein that belongs to the serine/threonine protein kinase family of proteins. The encoded protein then binds to and inhibits the activation of several receptor tyrosine kinases. Alternate splicing results in multiple transcript variants encoding distinct isoforms whose regulatory N-termini differ in length but whose C-terminal catalytic domains are identical.

The *PRKG2* gene encodes a protein that belongs to the serine/threonine protein kinase family of proteins. The encoded protein binds to and inhibits the activation of several receptor tyrosine kinases and plays a role in regulating fluid balance in the intestine. Membrane-bound proteins are regulators of the intestinal secretion, bone growth, and renin secretion. Diseases associated with *PRKG2* include chromosome 4Q21 deletion syndrome and cystic fibrosis. Among its related pathways are Sertoli-Sertoli cell junction dynamics and signaling by G-protein coupled receptors [15]. The *PRKG2-PDGFRB* fusion gene associated with t(4;5)(q21;q33) has been reported previously in only a few patients that presented with systemic mastocytosis, basophilia, thrombocytosis, and massive splenomegaly, with a myeloid neoplasm and *PRKG2-PDGFRB* rearrangement [16]. Our case, together with those cases in the literature, suggests an association between *PDGRFA-PRKG2* and basophilia without mastocytosis. Our patient responded well to imatinib therapy. Further studies are needed to determine if the *PDGRFA-PRKG2* fusion is harbored by basophils, which would suggest that cases may represent a distinct clonal disorder. In conclusion, this case highlights the fact that patients with *PDGRFA-PRKG2* fusion respond favorably to imatinib. Genetic analysis by NGS in ambiguous blood cancers is essential for identifying appropriate targeted treatment, and further research is warranted.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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COVID-19 pneumonia concurrent with newly diagnosed chronic myelogenous leukemia

TO THE EDITOR: A 62-year-old-lady visited the emergency room for diarrhea followed by fever in December 2020 when she had leukocytosis (187,400/μL with 72% neutrophils) and pneumonia predominantly at the lower lobes (Fig. 1). She looked relatively well with no respiratory distress in WHO performance score of I, but febrile up to 39.0°C. Pallor, jaundice, lymphadenopathy, and bleeding tendency were absent. Heart rate was rapid and regular without murmurs. Crackles were heard on the lung bases. The abdomen was scaphoid with a palpable spleen. The remainder of the physical exam was unremarkable. A diagnosis of chronic myeloid leukemia (CML) in the chronic phase was immediately made using peripheral blood polymerase chain reaction (PCR) for the *BCR-ABL* fusion gene and later by marrow study. Pneumonia was confirmed to be coronavirus disease 2019 (COVID-19) by reverse transcription (RT)-PCR of a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS CoV-2 RNA). Her fever ranged from 38.1 to 39.0°C, lasted for 3 days, and disappeared right after starting remdesivir. Following remdesivir treatment at 100 mg for five consecutive days, imatinib was started at 600 mg daily, higher than the usual dose, for the risk of leukostatic hemorrhage. The drug was continued and reduced to 400 mg QD on the 13th day as leukocyte count returned to normal (Fig. 2). She tolerated imatinib very well and the drug did not deteriorate the clinical course of COVID-19. She was COVID-19 positive via RT-PCR for 6 weeks and became negative when her pneumonia resolved. Pneumonia was completely gone after two and a half months (Fig. 1).

There has been concern about the susceptibility for con-

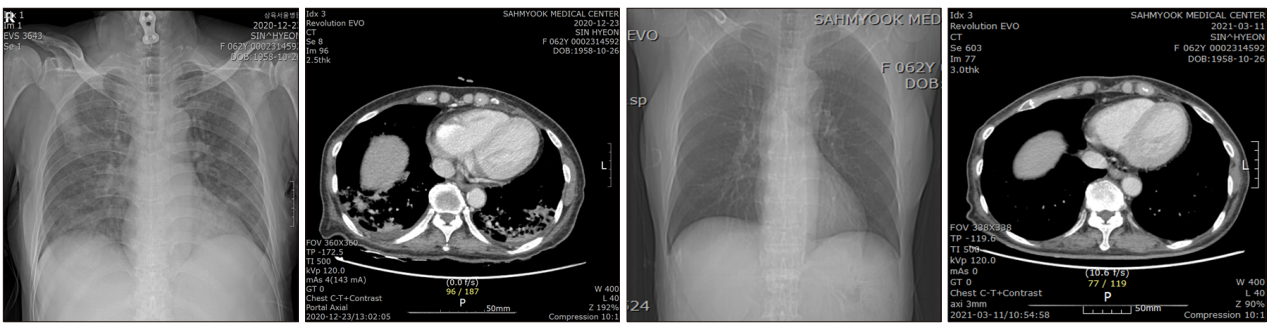

Fig. 1. Pneumonia shown on chest radiograph and CT scan taken day 1 was completely gone on radiograph and CT scan taken day 78.