World Cancer Research Journal WCRJ 2022; 9: e2388

OVERT-STAGE PRIMARY MYELOFIBROSIS AFTER COVID-19 INFECTION: A CASE REPORT

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Abstract – *Objective:* *Primary Myelofibrosis (PMF) is an uncommon hematological condition where the bone marrow becomes progressively fibrotic, resulting in anemia, extramedullary hematopoiesis, and splenomegaly. It is considered one of the myeloproliferative neoplasms (MPNs). The mutations in some genes, one of which is JAK, play a role in the signaling pathway in COVID-19 (Coronavirus Disease 2019), and they are also found in PMF. Currently, the connection between these diseases is not yet established. This case report aims to describe a case of overt PMF in our patient after suffering from COVID-19.*

Case presentation: *A 57-year-old female was referred to our hospital with the symptoms of weakness, dyspnea, low-grade fever, splenomegaly, anemia, and a history of essential thrombocytosis for 17 years ago and was on treatment until January 2022. She was diagnosed with COVID-19 in February and March 2022, and during the treatment, she presented a progressive change in the disease course. A bone marrow biopsy was done, and the patient was diagnosed with Primary Myelofibrosis. She was treated with Ruxolitinib and showed significant improvement in the first week of the treatment before becoming irresponsive.*

Results: *The PMF diagnosis is based on the patient clinical presentation, laboratory, and pathological findings following the World Health Organization (WHO) 2016 Diagnostic Criteria. Ruxolitinib was the chosen treatment for the patient, and improvement in the patient clinical condition and laboratory finding was observed. After one week, she became irresponsive to the treatment and planned to undergo AHSCT.*

Conclusions: *No sufficient evidence proves that COVID-19 accelerates the disease progression of primary myelofibrosis. More studies on the MPN and its relation to COVID-19 are needed.*

KEYWORDS: *Primary myelofibrosis, Myeloproliferative neoplasm, COVID-19, IPSS, DIPSS, JAK2, Ruxolitinib.*

INTRODUCTION

Myelofibrosis (MF) is a type of chronic myeloproliferative neoplasm (MPN) characterized by extramedullary hemopoiesis with splenomegaly, recurrent anemia, peripheral blood leukoerythroblastosis, and a high symptom burden. It also has different degrees of bone marrow fibrosis and shows megakaryocytic proliferation and atypia. World Health Organization classifies polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) as "the JAK2MPNs". MF can develop as a new disease as primary myelofibrosis or roughly 15% of ET or PV patients develop post essential thrombocythemia or post polycythemia vera MF, with

DOI: 10.32113/wcrj_20229_2388

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comparable therapy and outcome. Primary myelofibrosis is a rare condition in the United States, with an annual incidence of about 0.5-1.5 cases per 100,000 people. The incidence rate of myelofibrosis ranged from 0.1 to 1 case per 100,000 per year, according to a survey from European data sources[1-4].

Currently, there is no information on the clinical status of MPN patients discharged following COVID-19. Despite the fact that SARS-CoV-2 infection has a variable clinical severity and primarily appears as a respiratory disease, mounting evidence suggests that the hematological system and vascular endothelium are damaged. This harm can continue long after the virus has cleared up. Following COVID-19, clonal disorders such as MPN, whose natural history is distinguished by vascular problems and the potential of clonal progression into myelofibrosis, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML), could be more common[5,6].

Patients can be diagnosed with PMF, or patients with PV or ET can develop post-PV or post-ET MF. The Janus Kinase (JAK) pathway is dysregulated in MF. Around 90% of MF patients have one of the three driver mutations (Janus kinase 2 [JAK2], calreticulin [CALR], or myeloproliferative leukemia viral oncogene [MPL])[5-7].

CASE REPORT

A 57-year-old woman was referred to our hospital. The patient was previously diagnosed with essential thrombocytosis in 2005 (JAK2 V617F-positive) and was still on Hydrea treatment until January 2022. The Hydrea treatment was stopped because the hematologic panel was already in the normal range for several months, confirmed by a routine complete blood count test. Thrombocyte count at the time was 330,000 uL. The patient tested positive for COVID-19 in early February 2022 and came with mild symptoms. She decided to do self-isolation at home. However, she developed moderate symptoms of COVID-19 with shortness of breath and was admitted to our hospital for further treatment and observation. The symptoms improved, and she tested negative for COVID-19 after 11 days. She was discharged to continue with outpatient treatment and isolation at home. A week after, she was admitted to another hospital and diagnosed with congestive heart failure, renal failure, and post-COVID-19 pneumonia, and was treated by a cardiologist and internist. Upon inpatient treatment, it was discovered that she tested positive again for COVID-19 after 8 days and was treated in the isolation ward. She finally tested negative for COVID-19 after 7 days. The hematological data of the first and second COVID-19 infection can be seen on Table 1. During the course of the treatment, a complete blood count test proved that she had anemia (Hb 5.6 g/dL), leukocytosis (WBC 24,020/uL), thrombocytopenia (26,000/uL), elevated uric acid (7.2 mg/dL), and elevated lactate dehydrogenase/LDH (1,224 IU/L). Because of this, she was referred to our hospital to be treated by a hemato-oncologist. Physical examination revealed hepatosplenomegaly with tenderness on palpation, with liver 5 cm under the costal arch and schuffner 4 of the spleen. A peripheral blood smear was done, and the result shows normochromic normocytic anemia, leukocytosis, and thrombocytopenia. Ultrasonography of the abdomen shows hepatosplenomegaly. She got several transfusions, including packed red cell transfusion, thrombocytes concentrate transfusion, and thrombocytes concentrate apheresis. The patient still showed shortness of breath and occasional cough at the time. It was assessed as Long Covid Syndrome, and she was treated symptomatically by a pulmonologist. She was on oxygen supplementation with nasal canula with a dose of 3 Litre per minute. After her condition was stable, she underwent bone marrow punction and a biopsy procedure. Histopathology result shows that the bone marrow biopsy sample is consistent with the myeloproliferative neoplasm, and primary myelofibrosis (Figure 1 and 2). The patient has been treated with Ruxolitinib 5 mg twice a day. One week after the treatment, the patient's symptoms improved, the splenomegaly reduced to schuffner 1, and the hepatomegaly decreased to 2 cm below the costal arch, with no tenderness on palpation. The hematologic panel also improved, with hemoglobin of 9.4 g/dL and thrombocytes count of 103,000/uL. The patient was discharged and continued her medication at home. One week after discharge, the patient went to Hemato-oncologist Polyclinic for a routine blood test. The patient complained of fatigue and weakness. It was revealed that she had a low blood pressure of 83/58 mmHg at that time. At this time, the spleen size was still in schuffner 2. The blood test shows that the hemoglobin is 8.0 g/dL, and the platelet was 83,000/uL. The patient admitted again to get packed red cell transfusions and observation for clinical improvement while continuing the ruxolitinib. Her condition improved and was discharged after her hemoglobin level reach 10.5 g/dL and her platelet count was 63,000/uL.

TABLE 1. Patient's hematologic profile from first and second COVID-19 infection.

Hematological Data	*1st COVID-19 infection*	*2nd COVID-19 infection*	*Unit*	*Normal Value*
Hemoglobin	9.5	7.7	g/dL	12-16
Hematocrit	31.9	24	%	37-47
RBC count	3.43	2.92	10^6/µL	4.2-5.4
Leukocyte	15.6	5.95	10^3/ µL	4-10
Thrombocyte	299	62	10^3/ µL	150-400
MCV	93	82.2	fL	81-96
MCH	27.7	26.4	pg	27-36
MCHC	29.8	32.1	g/dL	31-37
RDW-SD	57.9	56.9	fL	37-54
RDW-CV	18.4	19.8	%	11-16
NEUT#	8.11	3.8	10^3/ µL	1.5-7
LYMPH#	2.23	1.4	10^3/ µL	1-3.7
MONO#	2.55	0.7	10^3/ µL	0-0.7
EOS#	0.96	0.0	10^3/ µL	0-0.4
BASO#	1.75	0.1	10^3/ µL	0-0.1
NEUT%	52	63.7	%	50-70
LYMPH%	14.3	23.7	%	20-40
MONO%	16.3	11.1	%	2-8
EOS%	6.2	0.2	%	0-4
BASO%	11.2	1.3	%	0-1
NLR	3.6	2.7	-	<3.13
D-Dimer	570	2525	ng/ml	<500

Abbreviations: RBC: red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW-SD: red cell distribution width standard deviation; RDW-CV: red cell distribution width coefficient of variation; NLR: neutrophil to lymphocyte ratio; NEUT#: neutrophil; LYPH#: lymphocyte; MONO#: monocyte; EOS#: eosinophil; BASO#: basophil; NEUT%: neutrophil; LYPH%: lymphocyte; MONO%: monocyte; EOS%: eosinophil; BASO%: basophil.

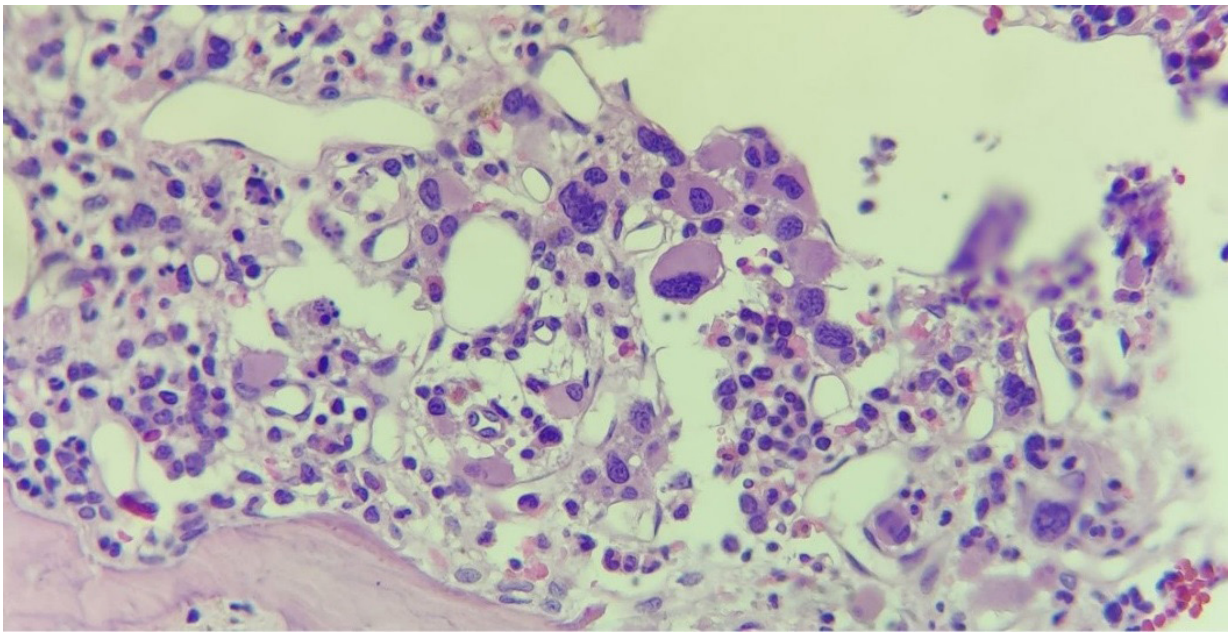

Fig. 1. Clusters of atypical megakaryocytes in bone marrow biopsy (photo courtesy of Herman Saputra).

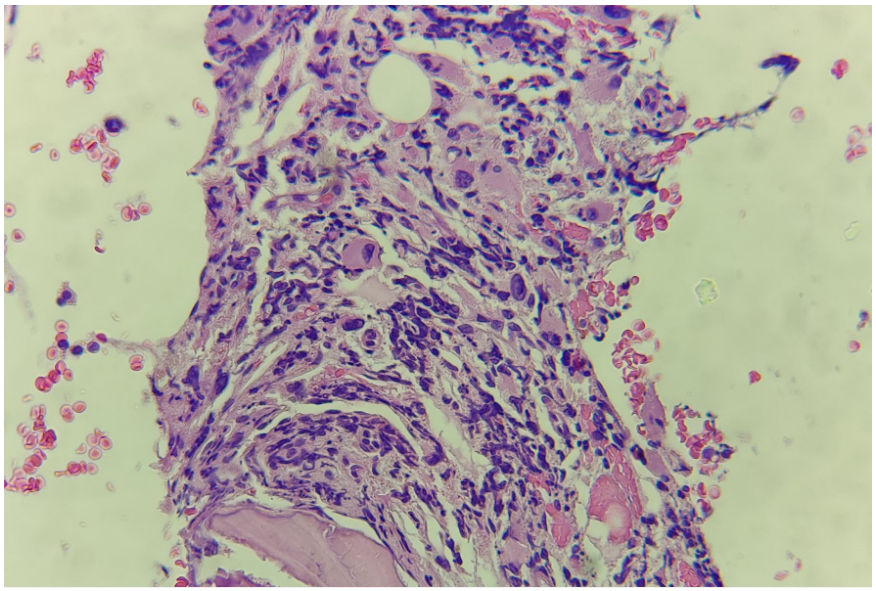

Fig. 2. Bone marrow biopsy shows pale stroma and fibrosis impression (photo courtesy of Herman Saputra).

Ten days after, she experienced similar symptoms and started to get headaches, and bone aches in her back and legs. She was admitted again because her hemoglobin level was 8.5/uL and her thrombocyte level was 20,000 uL. From the physical examination, we found that the spleen enlarged again to schuffner 4, and hepatomegaly of 5 cm below the costal arch. She planned to do another packed red cells transfusion and thrombocytes concentrate transfusion. The Ruxolitinib was discontinued. She needed AHSCT (Allogeneic Hematopoietic Stem Cell Trasplantation) and still searching for the donor that is available. Clinical and laboratory improvement are important before she can undergo the AHSCT.

DISCUSSION

Primary myelofibrosis (PMF) is a rare disease that has a similar rate of incidents in males and females, usually first diagnosed in the later stage of life – 60-70-years-old on average. Hereditary predisposition, ionizing radiation, and exposure to benzene are some etiologies that have been reported to cause PMF. The disease itself can appear asymptomatic, especially in the early stage (pre-fibrotic stage PMF). Patients can have complaints of constitutional symptoms (low-grade fever, weakness, fatigue, dyspnea, night sweats), or severe anemia, and some can exhibit bleeding or thrombosis. Some patients may feel bloated or have an enlarged abdomen due to hepato-splenomegaly. Gouty arthritis and renal stones also can appear as symptoms because of elevated uric acid secondary to the PMF[1,7,8].

We present a case of a 57-year-old woman who had been diagnosed with PMF. No history of ionizing radiation and exposure to benzene was recorded. There was no family history of hematological disease or neoplasms. The patient did state that she once had massive epistaxis before the ET diagnosis, but it was thought to be caused by her elevated blood pressure at that time. She experienced constitutional symptoms like fatigue, dyspnea, low-grade fever, and bloated sensation. From the physical examination, we found that she was anemic and had an enlarged spleen palpable at schuffner 4 and enlarged liver, with the right lobe of 5 cm below the costal arch with tenderness on palpation.

Laboratory findings of this patient were suitable with PMF, showing anemia (5.6 g/dL), leukocytosis (24,020/uL), elevated uric acid (7.2 mg/dL), elevated lactate dehydrogenase (LDH) (1224 IU/L), and JAK2V16F mutation, along with bone marrow biopsy showing atypical megakaryocytes, dilated sinusoid, immature cell, and chromatin clumping, and fibrosis impression from the pale stromal area. Abdominal ultrasonography also showed the presence of hepato-splenomegaly.

The patient's symptoms were in line with the 2016 WHO criteria for overt PMF. Previous diagnosis of ET could not be proven because the bone marrow biopsy result was unavailable at the time of diagnosis. The characteristic of ET and pre-PMF is similar and requires more laboratory and genetic examination to decide the most likely diagnosis. The previous WHO criteria were not sufficient and overlapped when compared to the newest 2016 WHO criteria to determine the diagnosis at that time in 2005.

COVID-19 pandemic has a big impact worldwide, but even more on the patients with chronic disease or comorbidity, including those with MPN. The progression of the patient disease from the pre-fibrotic stage to the overt stage is fast and questionable. Our patient was diagnosed with COVID-19 twice in a rather close timeline, only one month apart. The signaling pathway for the COVID-19 virus included the JAK pathway, which in patients with MPN includes the genetic mutation that occurred in JAK2V617F. There are reports on a similar case of progression in pre-PMF and other hematologic malignancies after COVID-19 infection. Currently, no evidence is present showing that COVID-19 is affecting or accelerating MPN disease progression[5,6,9].

Risk of stratification and prognostication in PMF relied upon the IPSS (International Prognostic Scoring System) and DIPSS (Dynamic International Prognostic Scoring System) score[10-12,14]. The patient had constitutional symptoms, anemia with Hb 5.6 g/dL, and peripheral blood blast of more than 1%, so the total score for IPSS was 3 and was categorized as a high-risk group. However, with DIPSS, it earned 4 points and was categorized as Intermediate-2 risk with an estimated 4 years of survival.

There are some therapeutic approaches to PMF, with the best choice of Allogeneic Hematopoietic Stem Cell Transplantation (AHSCT) if the patient is eligible for transplant. AHSCT is a high-risk procedure with a 50% rate of transplant-related death, graft *vs*. host disease (GvHD), infections, secondary malignancies, and a low survival rate. The procedure requires the patient condition to be stable with no comorbidities and a combination of sufficient knowledge, operator, and facility. A conventional approach with drug therapy is not opted to cure the disease but rather to reduce the symptoms and spleen size. First-line drug for PMF is Ruxolitinib, which is the JAK2-inhibitor drug. Dysregulation of JAK1 and JAK2 in MPN is associated with hematopoiesis and immune functions. JAK-STAT signaling and cell proliferation of cytokine-dependent hematological malignancies are inhibited by JAK2-inhibitor such as Ruxolitinib. It is working as a JAK1 and JAK2 inhibitor, which is used to treat disease-related splenomegaly and symptoms in AHSCT-ineligible patients[14]. In patients with IPSS intermediate-2/ high-risk MF, randomized clinical trials showed how Ruxolitinib is well-tolerated and reduces spleen size, also provides symptom improvements compared with other treatments or placebo. Hydroxyurea, androgens, thalidomide, steroid, and a few drugs are still in the clinical trials[10,14-19].

The patient started with 5 mg Ruxolitinib twice a day because she was still searching for the compatible donor candidate for AHSCT, and her platelet count was >50.000/uL. Patient exhibited improvement in symptoms after a week of treatment, as shown in the physical examination and laboratory results. Constitutional symptoms were improving, spleen size was reduced to schuffner 2, and the liver size was reduced with no tenderness on palpation. The therapy improved her symptoms for a while before she was becoming unresponsive for Ruxolitinib. The hemoglobin and thrombocyte level started to decline again, with the presence of hepatomegaly and spleen enlargement become more prominent. The best choice is the AHSCT, after she found the right donor, and her condition improved, but AHSCT also have several side effects and can't be done in our province.

CONCLUSIONS

A case of a 57-year-old female with PMF and a history of COVID-19 infection was presented. The disease progressed rapidly into overt PMF after the diagnosis of COVID-19. There was no strong evidence that shows that COVID-19 infection influenced the disease progression of PMF or other MPNs. More research should be conducted to prove the relationship between COVID-19 and the disease progression of MPNs, especially PMF. The Patient is currently treated with ruxolitinib and shows significant improvement in clinical and laboratory parameters for one week before becoming unresponsive. For the treatment of her condition, she needs AHSCT. Further evaluation of the disease course is warranted.

Acknowledgement:

The authors are grateful to the patient and her family. The authors also acknowledge the hospital director and colleagues at Siloam Hospitals Bali who supported the publication of this report.

Funding:

No funding is declared for this article.

Author Contribution:

Putu Dewinta Darmada contributed to the data collection, physical examination, evaluation, literature review, and writing and arrangement of the manuscript. Nyoman Gede Grenata Nanda Ustriyana worked on the literature review, writing, and evaluation of the report. Ni Gusti Ayu Arini Junita Putri Kardinal served as the primary physician, supervised the report, and reviewed the manuscript. Herman Saputra was responsible for the interpretation of pathological results of bone marrow biopsy and advised the writing of this manuscript.

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Conflict of Interest:

There is no conflict of interest in this case report.

Ethical Approval:

This article was submitted and approved by the responsible Ethics Committee of Siloam Hospitals Denpasar (Bali, Indonesia).

Informed consent:

The patient signed the informed consent.

Consent For Publication:

Consent to publish was obtained from the patient.

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