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Case Series

Post-Polycythemia Vera Myelofibrosis (PPV-MF)-A Case Report of a Patient Transplanted after an Adverse Reaction to Covid Vaccination

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Abstract

Myeofibrosis is a natural evolution of polycythemia Vera (PV) disease in some patients. Although PV is a mild myeloproliferative neoplasm, the progression to myeolofibross, also known as Post-Polycythemia Vera Myelofibrosis (PPMF) can have unfavourable prognosis. In this case report, we discuss a case of 62-year-old male who was diagnosed with PV (positive JAK2 V617F type) in 2005. Initially, he was maintained on interferon alfa-2b treatment therapy. However, after 14 years, he presented with a triad of haematological abnormalities including anaemia, thrombocytopenia, and splenomegaly with a spleen size of 18.7 cm (10 cm below the costal margin). Upon investigation, he was diagnosed with myelofibrosis secondary to polycythaemia Vera, hyper cellular fibrotic stage. Since then, the patient was treated with ruxolitinib at various occasions. The major finding of current case is that the patient developed severe thrombocytopenia after Johnson & Johnson vaccine. Later the patient underwent an all transplantation and now he is in complete remission.

Keywords: Haematological Malignancy; Fibrotic Stage; Anaemia; Thrombocytopenia; Splenomegaly; Johnson & Johnson Vaccine

Introduction

Polycythemia Vera (PV) is a haematological malignancy with a relatively favourable prognosis [1]. The outcome of PV patients is influenced by various factors including the risk of life-threatening thrombosis and the development of the disease into the plastic phase or myelofibrosis with myeloid metaplasia [2]. Myeloproliferative neoplasms (MPN) are a category of disorders arising from clonal proliferation of hematopoietic stem cells. The most commonly diagnosed subtypes of MPN are primary myelofibrosis (PMF), polycythemia Vera (PV), and essential thrombocythemia (ET) [3]. Based on the empirical data, the likelihood of the progression of polycythemia Vera (PV) to the fibrotic stage is calculated as 4.9% and 9.4% at a ten and fifteen years, respectively after diagnosis [4]. The predictive determinants for Post-Polycythemia Vera Myelofibrosis (PPMF) are yet to be clearly established. Potential risk factors for PPMF include disease duration, prior exposure to cytoreductive therapy, leucocytosis, and the JAK2 allelic burden [5]. We present an extraordinary case

of PMF progression after initial diagnosis of PV.

Case Presentation

Our patient is a 62-year-old male who was registered in our clinic with the diagnosis of myelofibrosis secondary to polycythemia Vera (hyper cellular fibrotic stage, positive JAK2 V617F type). His prior history revealed that he was initially diagnosed with polycythemia Vera in 2005. Since then, the patient has been registered with different haematology clinics. During the initial three years after diagnosis, the patient was solely managed with periodic phlebotomies. In 2008, he was treated with interferon alfa-2b 3 mil units (3 times a week), without phlebotomy. The patient remained on IFN-α therapy until 2019 when he experienced a triad of haematological abnormalities including anaemia, thrombocytopenia, and splenomegaly with a spleen size of 18.7 cm (10 cm below the costal margin). His clinical picture led to the speculation of a possible progression to myelofibrosis. A bone marrow biopsy confirmed the appearance of myelofibrosis secondary to polycythemia Vera, hyper cellular fibrotic stage. At this stage, it was decided to discontinue the interferon therapy and initiate treatment with JAKAVI® (ruxolitinib) at a dose of 25 mg per day. A positive response was seen as a reduction in the size of the spleen was observed (splenomegaly at 4-6 cm below the costal margin). The patient's haematological status remained optimal until August 2021 when a routine laboratory evaluation revealed a decrease in haemoglobin levels to 7.9 g/dl, a decrease in platelet count to 90,000 mmc, and a slight increase in leukocyte count to 4000 mmc. Based on laboratory results, it was decided to adjust the dose of JAKAVI® (ruxolitinib) to 10 mg/12 h.

On September 2nd, 2021, laboratory analysis at the haematology department of Colentina Hospital revealed a haemoglobin concentration of 7.5 g/dL, a platelet count of 114,000 mmc, a leukocyte count of 4,400 mmc, and lactate dehydrogenase levels (LDH) of 499 IU/L. Considering low haemoglobin levels, it was decided to initiate substitution treatment (1U of packed red blood cells). The patient decided to undergo the substitution treatment in Iasi Hematology Department, leading to the discontinuation of JAKAVI® (ruxolitinib) treatment until completion of the substitution therapy. Upon completion of the substitution therapy, the JAKAVI® (ruxolitinib) treatment regimen was resumed. On September 14th, 2021, the patient received Johnson and Johnson's COVID-19 vaccine. Ten days post-vaccination, the patient presented with severe thrombocytopenia (8000/mmc). Further blood work showed a platelet count of 2000/mmc. At this point, treatment with JAKAVI® (ruxolitinib) was replaced with a platelet substitute treatment. Although an improved platelet count to 6000/mmc was seen after two days, however, severe thrombocytopenia persisted. Therefore, on September 29th the treatment with MEDROL® (methylprednisolone), 32mg-2 tabs/day was initiated which improved platelet count to 12000/mmc after three days. Following administration of MEDROL®, the patient's overall condition deteriorated, exhibiting symptoms such as excessive perspiration, rapid loss of body mass (5 kg), polydipsia (5-6 litters of water/day), and polyuria. Although MEDROL® administration improved platelet count to 60,000/mmc, adverse reactions persisted which led to the termination of treatment.

On October 11th, 2021, laboratory assessments of the patient showed a blood glucose value of 900 mg/dl, for which he received insulin therapy for two days which stabilized blood sugar levels. Following the cessation of MEDROL®, the blood glucose value normalized but the haematological parameters showed decreased platelet count to 8000/mmc and hemoglobin to 8.5 g/dl. Again, platelet substitution therapy was initiated but platelet count remained abnormal. On October 16th, 2021, the patient was hospitalized at I.C Fundeni for further investigations. During this period, the patient underwent a series of investigations in order to establish the thrombocytopenia etiology. A medullary puncture was performed on September 27th, 2021 which showed hypoplasia and limited presence of hematopoietic cells. The erythroid series comprised a substantial proportion (62%) of the total nucleated cells, exhibiting a slight leftward shift in maturation (19% were proerythroblasts and basophilic erythroblasts). The arrangement of erythroblasts appeared to be isolated or in an island-like configuration. The myeloid blasts constituted approximately 2% of the nucleated cells.

The bone marrow findings demonstrated evidence of osteomyelofibrosis with MF3 severity which was characterized by distorted architecture, thick and irregular bone lamellae with osteosclerotic appearance, and relatively hypocellularized bone marrow spaces. The other cellular series were poorly represented. The Gordon-Sweet staining revealed severe reticulum fibrosis (MF3), while the Van Gielson staining showed discrete collagen fibrosis. The CD34 staining revealed frequent capillaries, but only very rare positive cells in the spinal cord series. On September 10th, 2021, peripheral blood cytology revealed anisopoikilocytosis among the erythrocytes, characterized by a mild degree of anisochromia and a relatively high frequency of polychromatophilic cells. The platelet population showed low density and marked anisocytosis, characterized by the presence of both large platelets and mega thrombocytes. On 12th September, abdominal ultrasound was performed. Upon partial examination of the liver through intercostal sections at the level of the right lobe, it was observed that the left lobe was enlarged to a dimension of 75 millimetres while the right lobe measured 145 millimetres. The liver exhibited a homogeneous structural composition. The spleen was noted to have a globular shape and increased dimensions, measuring 205/74mm. The splenic vein was measured at 8mm, exhibiting a positive Doppler signal.

At this stage, a post-vaccination reaction was suspected as the patient was vaccinated with Johnson & Johnson vaccine 10 days prior to severe thrombocytopenia. The patient was administered human immunoglobulin, resulting in a positive outcome, as evidenced by a hemoglobin level of 10.1 g% and platelet count of 86,000/mmc. On November 26th 2021, treatment with Ruxolitinib 5 mg x 2 / day was resumed for two weeks, and then the dose was increased to 10 mg x2 / day. On January 17th, 2022, the patient underwent a complete blood count analysis, including hemoglobin (hgb) levels, which were determined to be 8.4 g/dL, leukocyte (leu) count of 6000 cells/mm3, and a platelet (plt) count of 17,000 cells/mm3. Based on these results, it was deemed necessary to discontinue treatment with Ruxolitinib. On January 20th, 2022, a decrease in platelet count was observed, measuring 8000 per microliter. As a result, the patient received a subsequent administration of human immunoglobulin. This intervention resulted in a significant increase in platelet count, reaching a value of 75,000 per microliter. Additionally, a noticeable enlargement of the spleen was noted, measuring 210 millimetres in diameter. Following a reassessment of therapeutic options, it was determined that spleen irradiation would be implemented. The patient received 9 radiotherapy sessions between February 22nd, 2022 and March 3rd, 2022. However, despite the treatment, the patient presented with severe pancytopenia, exhibiting a white blood cell count (WBC) of 800 mmc, a platelet count (PLT) of 2000 mmc, and a hemoglobin (Hb) level of 7 g/dl. One month post-radiotherapy, a marked improvement was noted, with the size of the spleen decreasing to 169 mm. The patient's hemoglobin level increased to 8.1 g/dl, platelet count rose to 35,000 mmc, and the WBC count increased to 5000 mmc. Given that the patient has anaemia and severe thrombocytopenia under treatment with Ruxolitinib, he was considered refractory which left only option of stem cell transplantation. Compatibility tests were performed with the patient's children (50% compatibility) and a haploidentical transplant was being considered. Later the patient underwent an all transplantation and now he is in complete remission.

Discussion

Although polycythemia Vera is usually considered a benign condition, however, they share a proclivity towards progression into a fibrotic stage, known as post-Polycythemia Vera Myelofibrosis (PPV-MF) [6]. Our case initially was diagnosed with PV (positive JAK2 V617F type) but later developed MF. In the vast majority of PV cases, a V617F mutation in exon 14 of the JAK2 gene is present, which results in the constitutive activation of JAK2 [7]. Interferon Alfa has been shown to not only ameliorate the normal blood cell count in patients with PV but also to reduce the prevalence of the mutant JAK2V617F allele [8-10]. Our patient was maintained in interferon alfa-2b for a long period of time from 2005 to 2009. In our case, the progression of MF was reported after fourteen years of initial diagnosis. These findings were in-line with Alvarez-Larrán et al. who investigated 116 patients with PV [11]. Their results showed that the probability of MF was 16% at ten years and 34% at fifteen years. Primary myelofibrosis presents with the most heterogeneous clinical manifestations, encompassing anaemia, splenomegaly, leucocytosis or leukopenia, thrombocytosis or thrombocytopenia, and a constellation of constitutional symptoms [12]. In our case, the triad of major haematological abnormalities including anaemia, thrombocytopenia, and splenomegaly was observed. Generally, various palliative treatment options are employed for the management of anaemia, splenomegaly, bone pain, and other systemic symptoms in PPV-MF patients. Several studies have demonstrated the efficacy of ruxolitinib for the treatment of MF [13,14]. In the current report, ruxolitinib resulted in improved spleen size after treatment. These findings have been reported in a previous study as well [15]. Elevated LDH levels are a characteristic feature of MF and are frequently associated with alteration following myelofibrotic changes in PV patients [16]. In current case the patient developed severe thrombocytopenia ten days post vaccination. Acquired immune thrombocytopenia is a haemostatic disorder resulting from the antibody-mediated destruction of platelets. The presentation of thrombocytopenia in patients may range from being asymptomatic to exhibiting symptoms of severe haemorrhage, including bleeding in mucosal and cutaneous tissues that may pose a threat to the patient's life [17]. A similar case of thrombocytopenia has been reported by Banerjee et al. in 63-year-old women after receiving Johnson and Johnson's COVID-19 vaccine [18]. Muir et al. documented a case of a 48-year-old female who exhibited substantial thrombosis, coupled with severe thrombocytopenia and disseminated intravascular coagulation that was analogous to autoimmune heparin-induced thrombocytopenia subsequent to Ad26.COV2.S vaccination (Johnson and Johnson's COVID-19 vaccine) [19]. Recently, Greinacher et al. reported that vaccine-induced immune thrombotic thrombocytopenia was associated with IgG antibodies that recognize PF4 and activate platelets through their Fcγ receptors [20]. Currently, the data on PPV-MF, with no studies describing follow-up of patients in detail, however, a prospective cohort study investigated the progression of MF post PV diagnosis. Bonicelli et al. evaluated 327 individuals with a confirmed diagnosis of polycythemia Vera (PV) to assess the incidence of secondary myelofibrosis (MF) over time. The study found that after a median follow-up duration of 116 months from the time of diagnosis, 11.5% of participants had developed secondary MF. The cumulative incidence of secondary MF was estimated to be 6% after 10 years, 14% after 15 years, and 26% after 20 years [21]. The median survival duration for individuals suffering from PPV-MF has been estimated to be approximately 6 years, however, the survival rate can vary greatly, ranging from over 15 years to less than 2 years [22]. The current recommendation for allogeneic hematopoietic cell transplantation (allo-HCT) is limited to patients under 70 years of age with a projected median survival

of no greater than 5 years [23]. Multiple investigative reports have indicated inferior clinical outcomes for transplant recipients utilizing HLA-compatible or incompatible allogeneic donors from non-familial sources, as compared to those receiving grafts from HLA-identical siblings [24,25]. In conclusion, in some patients with polycythemia Vera, which are relatively benign MPN, MF develops as a natural evolution of the disease, resulting in post-polycythemia Vera myelofibrosis (PPV-MF). In current case report, we share long-term follow up of the PV patient who ultimately developed myelofibrosis. Our case developed post vaccine reaction after COVID-19 vaccine. Although currently no data is available to identify the underlying mechanism of vaccine reaction in myelofibrosis patients, we found that disease progression was hastened after COVID-19 vaccine reaction. However, further studies are required to look at this aspect of disease progression.

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