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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/16238
DOI URL: http://dx.doi.org/10.21474/IJAR01/16238

RESEARCH ARTICLE

JAK 2 NEGATIVE POLYCYTHEMIA VERA IN A TERTIARY CARE CENTER IN WEST UP POPULATION IN INDIA :A RARE PRESENTATION OF 5 CASES

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Manuscript Info

Manuscript History
Received: 10 December 2022
Final Accepted: 14 January 2023
Published: February 2023

Abstract

Introduction: Polycythaemia vera (PV) belongs to the group of myeloproliferative neoplasms with an excessive increase in hemoglobin levels.(1). It has been seen that JAK2 V617F mutation present in 80-90% of MPNs and JAK2 exon12 mutations are seen in 4%-5% cases of MPNs like PV.As per an Indian data the JAK2V617F mutational frequency in Indian population was 81.8% for PV, which was different from that reported in western literature as more than 95% for PV.Activation of JAK2 by either point mutation or fusion protein causes activation of the JAK-STAT pathway. While mutations in JAK2 are reported in numerous MPN phenotypes, exon 12 mutations specifically result in erythrocytosis due to increased EPO signalling. In India, the incidence of JAK2-negative polycythemia is relatively high, reaching up to 18%. (2,3)

Case series: Case 1-A 21-year male presented to the hematology OPD with complains of paresthesias and off and on headache for the past 6 months. He was on multiple symptomatic medications but to no relief. On routine investigations it was seen that he had a persistent hemoglobin level fluctuating between 17.5gm/dl and 18.5 gm/dl. He has iron deficiency for which he is on single oral iron tablet. No definite organomegaly was seen. In hematology OPD he was investigated for polycythemia vera keeping in mind the WHO criterias.His Serum EPO levels are within normal range,JAK2 V617F/exon 12mutation analysis is negative.A bone marrow aspiration and biopsy study done shows Hypoplastic marrow for age with erythroid predominance. In view of clinical suspicion of JAK 2 negative PV he is being treated with ecosprin, phlebotomy every 3 months and supplemental iron orally. The patient is clinically relieved of his symptoms of peripheral neuropathy. His last hemoglobin value is stable at 16.5gm/dl.Case 2-A 32 -year male presented to hematology OPD with mild headache and weakness for 6 months. A routine CBC investigation showed a high hemoglobin level of 18.4 gm/dl. Mildly raised RBC count was also seen. A subnormal serum EPO levels of 3.7 mIU/Ml (4.3-29.0 mIU/ML) was seen. JAK 2V617F/exon 12 mutation analysis was negative. The patient has been started on ecosprin and phlebotomy every 3 months and is symptomatically relieved.Case 3- A

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29-year male presented to hematology OPD with paresthesias and weakness for 3 months. A routine CBC investigation showed a high hemoglobin level of 19.7 gm/dl. Mildly raised RBC count was also seen. Rest all parameters were within normal limits. On examination no hepatosplenomegaly or lymphadenopathy was seen. A low serum EPO levels of <1 mIU/Ml (4.3-29.0 mIU/ML) was seen. JAK 2V617F/exon12 mutation analysis was negative. The patient has been started on ecosprin and phlebotomy every 3 months and is symptomatically relieved. Case4-33 year male presented to OPD with fatigue and paresthesias.CBC showed increased hemoglobin of 18gm/dl.Patient was a non-smoker.Vitamin B12 was>1000gm/dl.Bone marrow showed mildly predominant myeloid series.JAK2 mutation profile was negative but the patient responded to phlebotomy.Case5:A 28 year female had recurrent headaches however MRI and other investigations were normal. A serum EPO level done on suspicion of PV showed subnormal ranges.Bone marrow was reported as reactive.JAK2 mutation analysis was negative however patient responds to ecosprin and hyroxyurea.

Conclusion-All five cases that presented to the department had been undiagnosed before they reached our setup. The unique feature of all these cases was negativity for both JAK2V617F as well as JAK2 exon 12 mutation despite its clinical behaviour being that of PV .These cases are being actively managed as low risk polycythemia vera and since the start of the treatment comprising of phlebotomy once every 3 months their hemoglobin and hematocrit concentrations are maintained.No cytoreductive therapy is being given .Such unique presentations need to be reported and discussed extensively.

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Introduction:-

Polycythemia vera is a part of the umbrella group of Philadelphia-negative myeloproliferative neoplasms (MPNs) which are a group of clonal hematopoietic disorders involving a disordered proliferation of hematopoietic elements.Polycythaemia vera (PV) belongs to the group of myeloproliferative neoplasms with excessive increase in hemoglobin levels. The condition affects an estimated 44 to 57 per 100,000 individuals in the United States.1 It is clinically characterized by nonspecific symptoms such as fatigability, pruritus, early satiety due to splenomegaly, increased risk of infections, and thrombotic events. It has been seen that JAK2 V617F mutation present in 80-90% of MPNs and JAK2 exon12 mutations are seen in 4%-5% cases of MPNs like PV.As per an Indian data the JAK2V617F mutational frequency in Indian population was 81.8% for PV, which was different from that reported in western literature as more than 95% for PV(2). Activation of JAK2 by either point mutation or fusion protein causes activation of the JAK-STAT pathway. While mutations in JAK2 are reported in numerous MPN phenotypes, exon 12 mutations specifically result in erythrocytosis due to increased EPO signalling. In India, the incidence of JAK2-negative polycythemia is relatively high, reaching up to 18%. (3)

Exon 12 is present in the region between SH2 and JH2 domains of JAK2. Mutations in this region contribute to approximately 3% of PV cases [4-7]. Rare JAK2 mutations have also been reported in exons 12, 13, 14, and 15 [6]. Patients with exon 12 mutations typically present with isolated erythrocytosis and suppressed erythropoietin. In contrast to the trilineage hyperplasia characteristic of patients with V617F mutation, the bone marrow from patients with exon 12 mutations often exhibits nonspecific morphology, with isolated erythroid proliferation and absence of prominent megakaryocyte atypia and clustering. Demonstration of exon 12 mutations in these patients is particularly helpful for ruling out reactive erythrocytosis [7]. JAK2 exon 12 mutations are included as a major criterion for diagnosis of PV in the most recent World Health Organization guidelines [8]. There are limited reports describing JAK 2 negative Polycythaemia veras.[9–11]. Here, we describe a series of 5 cases of PV suspected clinically with JAK 2 negative mutation.

Case series

Case 1-A 21-year male presented to the hematology OPD with complains of parasthesias and off and on headache for the past 6 months. He was on multiple symptomatic medications but to no relief. On routine investigations it was seen that he had a persistent hemoglobin level fluctuating between 17.5gm/dl and 18.5 gm/dl. He has iron deficiency for which he is on single oral iron tablet. No definite organomegaly was seen. In hematology OPD he was investigated for polycythemia vera keeping in mind the WHO criterias. His Serum EPO levels are within normal range,JAK2 V617F/exon 12mutation analysis is negative. A bone marrow aspiration and biopsy study done shows Hypoplastic marrow for age with erythroid predominance. In view of clinical suspicion ofJAK2 negative PV he is being treated with ecosprin, phlebotomy every 3 months and supplemental oral iron therapy.The patient is clinically relieved of his symptoms of peripheral neuropathy. His last hemoglobin value is stable at 16.5gm/dl.

Case 2-A 32 -year male presented to hematology OPD with mild headache and weakness for 6 months. A routine CBC investigation showed a high hemoglobin level of 18.4 gm/dl. Mildly raised RBC count was also seen. Rest all parameters were within normal limits. There was no hepatosplenomegaly or lymphadenopathy. A subnormal serum EPO levels of 3.7 mIU/Ml (4.3-29.0 mIU/ML) was seen. JAK 2V617F/exon 12 mutation analysis was negative. The patient has been started on ecosprin and phlebotomy every 3 months and is symptomatically relieved.

Case 3- A 29-year male presented to hematology OPD with paresthesias and weakness for 3 months. A routine CBC investigation showed a high hemoglobin level of 19.7 gm/dl. Mildly raised RBC count was also seen. Rest all parameters were within normal limits. There was no hepatosplenomegaly or lymphadenopathy. A low serum EPO levels of <1 mIU/Ml (4.3-29.0 mIU/ML) was seen. JAK 2V617F/exon12 mutation analysis was negative. The patient has been started on ecosprin and phlebotomy every 3 months and is symptomatically relieved.

Case 4- 33 year male presented to OPD with fatigue and paresthesias. No definitive examination findings were noted.CBC showed increased hemoglobin of 18gm/dl. Patient was a non-smoker.Vitamin B12 was>1000gm/dl.LFT was mildly deranged with SGOT BEING 68gm/dL and SGPT being 90 gm/dl. Bone marrow showed mildly predominant myeloid series.JAK2 mutation profile was negative but the patient responded to phlebotomy,Patient responded to phlebotomy every 3 months with ecosprin 75mg/dl daily.

Case 5-:A 28 year female had recurrent headaches however MRI and other investigations were normal.No definitive examination findings were noted. A serum EPO level done on suspicion of PV showed subnormal ranges.Bone marrow was reported as reactive.JAK2 mutation analysis was negative however patient responds to ecosprin and hyroxyurea.

Discussion:-

Polycythemia vera is a rare disorder involving specific mutation markers. In early 2005, a novel Janus kinase 2 (JAK2) mutation was described in association with PV, Essential thrombocythemia (ET), and primary myelofibrosis. JAK2 associates with the cytoplasmic portions of various receptors for key hematopoietic cytokines, such as erythropoietin (EPO), thrombopoietin (THPO), and granulocyte colonystimulating factor (G-CSF). Constitutive activation of JAK2 by either point mutation or fusion protein causes activation of the JAK-STAT pathway. (5)Few studies show that only 50% of PV cases with exon 12 mutations had low serum EPO.Our case had variations as mentioned above with 1 case having subnormal levels ,one case being on the lower side of normal and one case having almost normal levels of EPO. [7].

Sporadic patients with PV do not carry JAK2, and the proportion of familial cases of PV that are negative is definitely higher.[6] Very few cases with negative JAK2 and clinically suspected PV responding to therapy have been documented as of now(ref2).The World Health Organization (WHO) introduced criteria for diagnosing PV which included, an increased red cell mass or an Hb above 18.5 g/dl in men or 16.5 g/dl in women, as well as additional criteria like bone marrow hypercellularity, JAK 2 mutation profile and subnormal serum EPO levels. These criteria were adapted in the British Committee for Standards in Hematology (BCSH) guidelines for diagnosis and management.[4]

The discovery of JAK2 mutations in the majority of patients with PV simply showed the presence of clonal disease. This allowed for revision and simplification of the diagnostic criteria in those with a JAK2 mutation. The WHO also revised their criteria in view of the presence of JAK2 mutations in the majority of patients.[4] BCSH criteria are the most accurate diagnostic criteria for PV as they have an acceptable level of sensitivity and can differentiate between

PV and other erythrocytosis.[8] In the newly proposed diagnostic criteria for PV, the presence of JAK2V617F mutation has been integrated as a major criterion. It has been suggested that JAK2V617F mutation analysis can be used to screen individuals with polycythemia.[9] There is no significant difference in the clinical presentation of the JAK2 mutation in positive and negative PV patients.

In general, patients who do express JAK2V617F are older than those who do not, but they do not have a longer duration of disease.[5] In recent times, mutations of JAK2 exon 12 have been described in JAK2V617F negative patients with PV.[10] Most patients with PV, carrying an exon 12 mutation, had isolated erythrocytosis at clinical onset, unlike patients with JAK2 positive PV, who had elevations in leucocytes and / or platelet count.[6] Both leucocytes and platelet counts were within normal limits in the present case

The mutations described recently in JAK2V617F-negative polycythemia are JAK2 exon12 mutation [11] and CALR mutations [12]. Among this, JAK2 exon12 mutation was associated with isolated erythrocytosis compared to the JAK2V617F-positive PV where there is elevated leukocyte and/or platelet count. there is a noted significant difference in the clinical outcome of JAK2V617F-positive and negative PV [13,14]; JAK2-positive PV has a worse prognosis compared to JAK2-negative PV.

However, there is very small percentage of patient group not expressing JAK2 mutation yet responding to therapy for the same with phlebotomy.In our case we continue with a 3 monthly phlebotomy only without adding additional hydroxyurea and the cases are well. This matches with another similar case of JAK 2 negative PV.

Conclusion:-

All five cases that presented to the department had been undiagnosed before they reached our setup. The unique feature of all these cases was negativity for both JAK2V617F as well as JAK2 exon 12 mutation despite its clinical behaviour being that of PV .These cases are being actively managed as low risk polycythemia vera and since the start of the treatment comprising of phlebotomy once very 3 months their hemoglobin and hematocrit concentrations are maintained. No cytoreductive therapy is being given .Such unique presentations need to be reported and discussed extensively.

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