International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Association of Solitary Tumors in Polycythemia Vera with 3p Deletion

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Abstract: ***The association of JAK2 (Janus kinase-2) V617F mutation in myeloproliferative neoplasms has long been established. We report a case of a 48 years old male a known case of JAK 2 positive polycythemia vera presenting with anaemia who was incidentally detected to have carcinoma of distal stomach. His cytogenetic study revealed 3p deletion which is said be associated with both haematological and solitary tumors. Hence we emphasise the importance of cytogenetics in diagnosis and prognosis of patients with both haematologicalsolitary malignancies.***

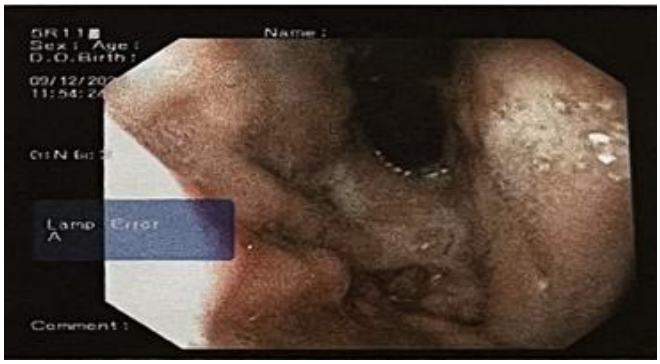
Keywords: Polycythemia Vera, JAK2 V617F, 3p deletion, Gastric cancer

1. Introduction

Polycythemia vera (PV) is a clonal and acquired stem cell disease characterized by an abnormal erythropoiesis, with some erythroid progenitors being erythropoietin (Epo)-hypersensitive and independent.[1] The molecular characterization of PV came in 2005 with the discovery of the JAK2 V617F mutation in about 90% of PV patients.[2] JAK2 V617F mutation activates JAK2 kinase and therefore, the JAK kinase - signal transducer and activator of the transcription signaling (JAK/STAT) pathway.[3]The significance of JAK2 mutation in gastric cancer is not well established. A study by Xu et al. indicates that the dysregulation, mutation, and amplification of JAK2 are associated with cancer progression.[4]3p deletion (most commonly 3p14.[2] and 3p25-26) which is frequently associated with solitary tumorsis a chromosomal abnormality associated with hematological malignancies as well.[5] Here, we report a case of gastric carcinoma in a patient with PV, JAK 2 mutation and 3p deletion.

2. Case Report

A 48year old male, reformed smokerpresented with urinary tract infection 4 years ago and was found to have Hb - 18.5g/dl, MCV-82.6, Hct-49.5, WBC-11200, Platelets-9.12L and a diagnosis of polycythemia was made according to WHO (World Health Organization) diagnostic criteria. Serum EPO (erythropoietin) level was 5.2mU/ml (2.6-18.5 mU/ml) and JAK 2 V617F (Janus Kinase) mutation was detected. He was treated with phlebotomies initially and later maintained on hydroxyurea 500mg. In the course of 4 years, he went on to develop Addison's disease with fasting cortisol of 4.2mcg/dl (5-20mcg/dl) and serum ACTH (adrenocorticotropic hormone) of 251pg/ml (0-46 pg/ml). CECT (contrast enhanced computed tomography) abdomen at the time showed bilateral adrenomegaly(14.8mm on right and 13mm on left) with no focal lesion. Since the gland was inaccessible for biopsy via CT, biopsy was deferred, other infective, infiltration, thrombotic, autoimmune causes were ruled out with other investigations, patient was started on steroids and kept under follow up. Subsequently patient improved clinically and repeat CT abdomen showed normal adrenals. About 3 and half years later, patient presented again with generalized fatiguability, dyspnoea on exertion and early satiety. On evaluation, he was found to have microcytic hypochromic anaemia (Hb-7.2g/dl, MCV- 72, Hct- 27.4, WBC- 10800, Platelets- 5.7L, serum iron-28, ferritin- 19.3, total iron binding capacity- 300, transferrin saturation-56%) Secondary myelofibrosis was ruled out with bone marrow studies. Though he did not give any history of bleeding per rectum or malena, stool occult blood was positive for three consecutive days. Hence an OGD (oesophageo-gastro-dudenoscopy (figure 1) was done. It showed and ulceroproliferative mass lesion causing gastric outlet obstruction was found and biopsy revealed an infiltrating neoplasm suggestive of poorly differentiated adenocarcinoma.



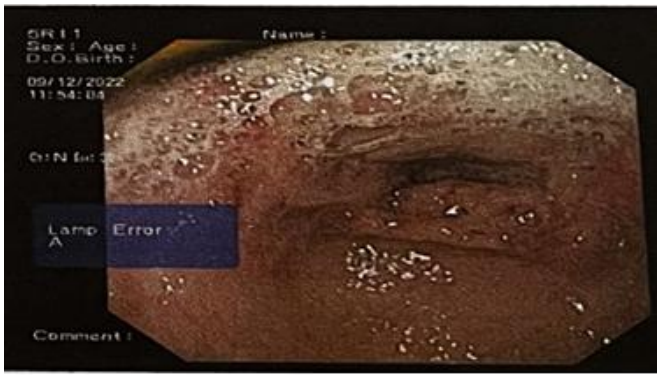


Figure 1: OGD showing mass lesion causing GOO

Later cytogenetic study for 3p deletion was sent which came out to be positive. Patient underwent distal gastrectomy (figure 2) and is doing well.

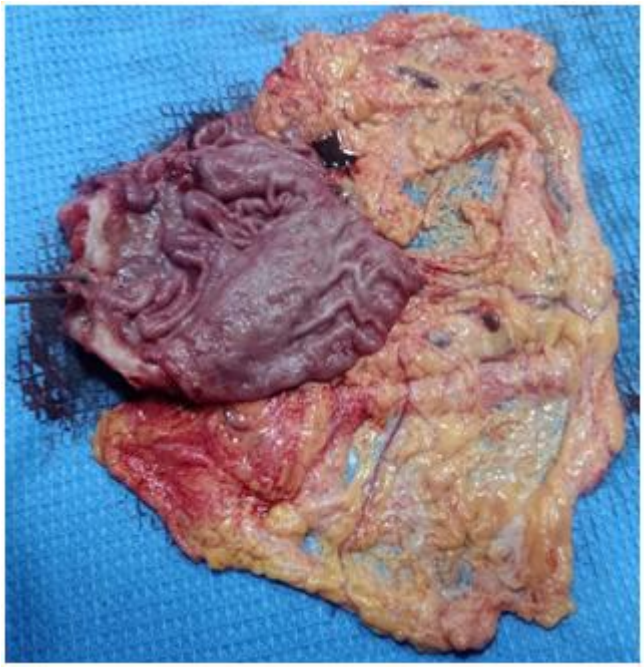


Figure 2: Resected specimen of distal gastric carcinoma

3. Discussion

Cytogenetic aberrations resulting in deletion of 3p are common in solid tumors, indicating the presence of tumor suppressor genes (TSG) on this chromosome arm.[6]Deletions in this region are very frequent in lung and kidney carcinomas and were also observed in a variety of other common tumors, such as breast cancer, head and neck cancer, gastrointestinal cancer, esophageal cancer, and cervical cancer.[7] 3p deletion is also frequently seen in some hematological malignancies. These are 3p25 in acute myeloid leukemia, 3p26 and 3p25 in acute lymphoblastic leukemia, 3p26 in myelodysplastic syndrome, 3p14 in MPD, 3p25, 3p23, and 3p21 in chronic myeloid leukemia, 3p26 and 3p25 in chronic lymphoproliferative disorders, 3p26 in Hodgkin's disease, and 3p26 in non-Hodgkin's lymphomas.[6] However presence of 3p deletion in PV (polycythemia vera) has rarely been described.

Signal Transducer and Activator of Transcription-3 (STAT3) is constitutively activated in many cancers where it promotes growth, inflammation, angiogenesis and inhibits apoptosis. It has been shown that JAK2/STAT3 is constitutively activated in human gastric cancer, and that chronic IL-11-driven STAT3 transcriptional activity induces gastric tumourigenesis.[8] Aberrant JAK-STAT signaling has also been demonstrated in various MPN patient subgroups, including PV. JAK2 V617F is a common pathogenetic mutation in myeloproliferative neoplasms (MPNs) and is sufficient to produce a myeloproliferative phenotype[9]

With this background, we retrospectively went on to do cytogenetic study on finding out gastric carcinoma. Hence it is imperative to do cytogenetic study in any neoplasm for detection and prognostication.

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