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Title: FEATURES OF POLYCYTHEMIA VERA WITH THE JAK 2 EXON 12 MUTATION.

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Background: One of the diagnostic criterion for polycythemia vera (PV) by the WHO 2016 guidelines is molecular detection of JAK2 mutation (V617F or exon 12). JAK2 exon 12 mutations are seen in about 2-5% of JAK2V617F-negative cases of PV. Mutations in JAK2 cause constitutive activation of JAK-STAT pathway which results in variable phenotypes. PV patients with exon 12 mutations in JAK2 present characteristically with erythrocytosis. Clinical characteristics, therapy, response to treatment are not well described due to the small number of cases of polycythemia vera with JAK2 exon 12 mutation.

Aims: Clinical, laboratory characteristics, outcome of a group of patients with PV JAK 2 exon 12 mutation.

Methods: From 2013 to 2022, 10 patients with PV with a JAK2 exon12 mutation were observed at the National Medical Research Center for Hematology. The male:female ratio was 1.5:1 (6:4). The median age of patients was 54.5 years (range 27 to 82 years).

Results: Bone marrow investigation was performed in 8 patients. The degree of stromal fibrosis was assessed as MF0 - 7, MF1 - 1 cases. There were no comorbidities in 2 patients. Concomitant diseases were registered in 8 cases: cardiovascular system - 5, hematopoiesis (MGUS) - 1, respiratory system - 2, gastrointestinal tract - 5, CNS - 1, endocrine system - 2, reproductive system - 1. In 7 cases in one patient ≥ 2 diseases reported. Asymptomatic course of the disease was observed in 3 cases. 7 patients complained. The leading complaint was: headache, dizziness - 4, sweating - 1, aquagenic pruritus - 1, fatigue - 1. During physical examination, the plethora was determined in 9 patients. Thrombosis in history and/or at the time of diagnosis was registered in 4 patients (40%). In all cases, arterial thrombosis: myocardial infarction - 1, splenic artery thrombosis - 2, TIA - 1. The risk group for thrombotic complications was defined as low risk - 5, intermediate risk - 4, high risk - 1 case. The median of RBC is 8.39 $x10^{12}$/l (5.40 - 9.98 $x10^{12}$/l). Median hemoglobin 200.5 g/l (158 – 222 g/l).Median hematocrit 60.55% (47 – 71.8%). Median platelets 254 $x10^{9}$/l (151 - 503 $x10^{9}$/l).Median WBC 7.8 (5.25 - 11.6 $x10^{9}$/l). The study of LDH activity was performed in 5 patients. Above normal LDH was determined in 3 cases. Thrombophilia markers were studied in 2 cases: in one case the risk was defined as low, in the second case the risk was defined as high (F2Thr165Met). With splenomegaly, the disease proceeded in 6 patients. All patients received therapy aimed at preventing thrombotic complications: acetylsalicylic acid - 4, dipyridamole - 1, clopidogrel - 2, rivaroxaban - 2, dabigatran - 1. Phlebotomy was performed in 9 cases. 2 patients were under observation, therapy was carried out in 8 patients: hydroxycarbamide - 5, interferon alfa - 2, pegylated interferon alfa - 1.In 3 cases, after the diagnosis was established, the patients did not appear for a second appointment. The follow-up period for 7 patients ranged from 8 to 76 months. The effect of therapy was assessed in 5 cases: a complete hematological response was obtained in 5 patients, partial - in 1, stabilization - in 1 patient.

Summary/Conclusion: JAK2 exon 12 mutation analysis contributes to diagnostics in PV or erythrocytosis. Mouse models have demonstrated the ability of JAK2 exon 12 mutations to induce a MPN phenotype with prominent erythrocytosis. This is consistent with the results of our study on a small group of patients.

Keywords: Myeloproliferative disorder, Polycythemia vera