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“Philadelphia negative myeloproliferative neoplasms – morphological and immunohistochemical characteristics”

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The concept of personalized medicine, based on an increasingly differentiated understanding of the causes and features of the disease in each individual, goes deeper and deeper into medical practice. Medical oncology is increasingly relying on the rapid transmission of fundamental knowledge in the clinic. From these positions, clinical and molecular pathology worldwide faces the challenge of detecting morphological traits, including genetic ones, in order to identify and implement new prognostic and predictive factors and targeted therapy. In this regard, breast carcinomas, colorectal, lung and malignant melanoma already have certain molecular targets for individualized therapy. There is still little information and research on Ph(-) myeloproliferative neoplasms. A JAK 2 mutation was found in them, which can lead to the phenotypic manifestation of three separate diseases.

The aim of the present study is to detect morphological features distinguishing the different types of Ph(-) myeloproliferative neoplasms, to study the signaling pathways and mechanisms by which these changes occur. To elucidate the molecular mechanisms, it is necessary to deepen research by applying innovative methods to prove the importance of growth and transcription factors.

The expected results are related to the identification of factors influencing the initiation, transformation, progression, angiogenesis and metastasis that could serve as “targets” for targeted therapy.

**Achieved results:** Ph(-) myeloproliferative neoplasms occur with equal frequency in both sexes and in all age groups with a peak incidence between 61-70 years. More than half of patients with Ph(-) myeloproliferative neoplasms have the JAK2 mutation, with a mutation load between 2 and 50% occurring slightly more frequently than a mutation load above 50%. Half of the patients with Ph(-) myeloproliferative neoplasms lack fibrosis. In other cases, there is fibrosis, with Grade 1 and Grade 2 being more common than Grade 3. In Ph(-) myeloproliferative neoplasms, megakaryocytes with vesicular nuclei (cloudlike) are most common, followed by dysmorphic nuclei and nuclei such as staghorn. Hypercellular bone marrow occurs in more than two-thirds of cases, with cellularity, fibrosis, spleen size,

and mutational load showing no sex dependence. Deceased patients with Ph(-) myeloproliferative neoplasms are more often male. The JAK2 mutation does not depend on the type of Ph(-) myeloproliferative neoplasms: essential thrombocythemia, polycythemia vera and primary myelofibrosis. There is no significant difference between patients with and without JAK2 mutation in terms of cytoplasmic and nuclear area, nucleus/ cytoplasm ratio, largest cytoplasmic and nuclear diameter of megakaryocytes. Cloud-like nuclei are more commonly found in patients with the JAK2 mutation. In patients with polycythemia vera, the nuclei are more often dysmorphic and “Cloud-like”, in essential thrombocythemia “Staghorn” nuclei predominate, and in primary myelofibrosis the nuclei are most often of the “Cloud-like” type and only in primary myelofibrosis there are “bare nuclei” type nuclei. Patients with polycythemia vera and essential thrombocythemia more often have hyperlobulated nuclei, while in patients with primary myelofibrosis the nuclei of megakaryocytes are hypolobulated. In the absence of the JAK2 mutation in polycythemia vera, megakaryocytes are evenly distributed without cluster formation, loose clusters are more common in patients with essential thrombocythemia, while dense clusters in the bone marrow are present in patients with primary myelofibrosis. YAP1 expression is higher in patients with the JAK2 mutation compared to JAK2-negative patients regardless of the type of Ph(-) myeloproliferative neoplasms, but there is no significant difference between essential thrombocythemia, polycythemia vera, and primary myelofibrosis. Bcl-XL expression is high at low platelet counts. Calreticulin expression was higher in Ph(-) myeloproliferative neoplasms compared to controls. In patients with essential thrombocythemia and the JAK2 mutation, Calreticulin expression was higher compared to JAK2-negative patients, whereas in polycythemia vera and primary myelofibrosis did not differ.