**Red Blood Cell Morphological Changes and Enlarged Platelets Found in Idiopathic Multicentric Castleman Disease**

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**Background:** Idiopathic multicentric Castleman disease (iMCD) is a rare polyclonal lymphoproliferative disorder characterized by systemic inflammatory symptoms, cytopenias, generalized lymphadenopathy, and multiple organ system dysfunction. iMCD is subclassified into iMCD-TAFRO, with thrombocytopenia, anasarca, fever/elevated C-reactive protein, reticulin myelofibrosis/renal failure, and organomegaly, and iMCD-NOS (not otherwise specified), with high platelet counts and hypergammaglobulinemia. Despite recent diagnostic guidelines, iMCD diagnosis remains challenging because many of the histopathologic features and clinical/laboratory abnormalities are non-specific. Characterization of easily measurable findings from minimally invasive procedures, such as peripheral blood smear, could help to improve the accuracy of diagnosis as well as potentially providing insights into disease pathogenesis. Peripheral blood smears are often performed during routine clinical evaluation and enable morphologic evaluation of red blood cells (RBCs) and white blood cells (WBCs). In this study, we systematically characterized peripheral blood smear morphologic findings in iMCD for the first time.

**Methods:** Peripheral blood smear morphologic findings in medical records from 68 iMCD patients, who were enrolled in an international registry for CD patients and had been confirmed to meet iMCD criteria by an expert panel, were reviewed and analyzed. Patients were also categorized into iMCD-TAFRO (N=39) or iMCD-NOS (N=29) based on clinical and laboratory data. Two-sample proportion tests were used to compare the frequency of features between iMCD-TAFRO and iMCD-NOS, when the abnormality was present in ≥ 5 subjects in both subtypes. P-value correction was not performed as findings are preliminary and hypothesis generating.

**Results:** Among the 68 iMCD patients, average age was 35.8 years (14-61); 46% were female, 54% were male; racial distribution was 62% white; 10% Black; 15% Asian; 13% other. The most common peripheral blood smear findings across all iMCD patients included abnormalities in RBC size and color, with anisocytosis (58.8%), polychromasia (57.4%), hypochromia (55.9%), and microcytosis (50.0%) being the most prevalent findings in the overall cohort (**Table 1**). Other RBC abnormalities were observed but less frequently, including abnormalities in shape such as poikilocytosis (44.1%). Giant or large platelets were found in 47% of iMCD cases. Abnormalities in WBCs, including toxic granulation, atypical lymphocytes, and toxic vacuolization, were detected less frequently. When comparing the two clinical subtypes, patients with iMCD-TAFRO had more frequent anisocytosis ($p=0.043$), hypochromia ($p=0.002$), polychromasia ($p=0.022$), and giant/large platelets ($p<0.001$) versus iMCD-NOS.

**Discussion:** Here, we have characterized peripheral blood morphologic abnormalities in iMCD for the first time. The most common findings in this cohort included abnormalities in RBC size and color. These abnormalities can be found in a number of conditions, including myelofibrosis, autoimmune diseases, and other inflammatory conditions. In iMCD, they are likely related to cytokine-driven anemia of chronic inflammation. The presence of large or giant platelets in nearly half of iMCD patients, with significantly more in iMCD-TAFRO than iMCD-NOS, is particularly notable since this has not been described in iMCD. These enlarged platelets, which can be found in immune thrombocytopenic purpura, myeloproliferative disorders, pseudothrombocytopenia, and inherited platelet disorders, may reflect hyperactivity of megakaryocytes and/or early release from the bone marrow in response to peripheral platelet sequestration. Though less common in this cohort, there are additional changes in RBC shape and WBC features that may be more specific to iMCD and potentially informative in increasing the index of suspicion for iMCD. These findings suggest that the peripheral blood smear may be able to support the diagnosis of iMCD and result in faster treatment administration. Future work is needed to determine whether the constellation of findings in the peripheral blood identified herein is unique to iMCD or seen in various other infectious, malignant, and autoimmune diseases.