Idiopathic splanchnic vein thrombosis: is it really idiopathic?

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Splanchnic vein thrombosis (SVT) occurring in association with a clonal myeloproliferative neoplasm (MPN) is puzzling and difficult to manage for doctors who care for patients with myeloid disorders as well as those who care for patients with thromboembolic diseases. The phenotype of myeloproliferation is frequently that of a latent disease making diagnosis of an SVT-associated MPN challenging. Furthermore, the benefit of using cytoreductive agents is unproven, making therapy uncertain.

In this issue of *Haematologica*, Carrà and colleagues provide a new piece of the puzzle.[1] They report 15 consecutive cases of idiopathic SVT presenting with mutations involving one or more of the 30 myeloid genes of their next-generation sequencing panel. In seven cases, the authors found clonal hematopoiesis of uncertain potential (CHIP), i.e., acquired somatic mutations in leukemia-associated driver genes in individuals without underlying hematologic malignancies.

Even though Carrà's data mirror those recently published by Magaz *et al.* in 74 patients with idiopathic SVT,[2] the reported results have different points of interest. The first is that the authors, after setting the variant allele frequency threshold as >2%, reported a CHIP prevalence of 46% (95% confidence interval: 21%-73%), which is the highest ever reported. CHIP occurs in about 10% of healthy people after the age of 70 and in about 5% under 65 years old. This means the prevalence of CHIP in Carrà's study is nearly 10-fold higher than that expected in the general population of comparable age. This figure is higher than the 37.8% prevalence of CHIP in the study by Magaz *et al.* in idiopathic SVT, and the 25% prevalence in people with solid cancers.[3] These figures, even though obtained in small numbers of patients, support a role of CHIP in idiopathic SVT.

A second concept of clinical interest is that SVT-associated CHIP contrasts with the dominant notion that CHIP is linked to cardiovascular diseases, possibly related to pro-inflammatory interactions between clonal-derived leukocytes and vascular endothelial cells. Considerable data indicate risks of coronary heart disease and stroke are higher in people with CHIP than in those without CHIP.[4] The clinical relevance of these results is certified by the fact that specialized CHIP clinics with multidisciplinary teams of oncologists, hematologists and cardiologists have been recommended.[5]

Recently, a relationship between CHIP and risk of venous thromboembolism has been suggested. This suggestion was originated by a study testing whether individuals with *JAK2*^{V617F}-positive CHIP had a population of clonal neutrophils primed to produce neutrophil extracellular traps implicated in the pathogenesis of venous thrombosis. In a large case-control cohort (10,893 individuals), the authors documented that *JAK2*^{V617F}-mutant CHIP was powerfully associated with major venous thrombotic events.[6] Subsequent studies reported discordant results. In 11,695 patients with solid cancers no significant association between any CHIP mutations, including *JAK2*^{V617F}, and risk of thrombotic events was evidenced.[3] However, a pilot retrospective observational study of 61 subjects with unprovoked pulmonary embolism reported 20% CHIP-associated somatic mutations.[7]

The studies by Carrà *et al.* and Magaz *et al.* provide evidence that CHIP is a risk factor for venous thromboembolism. Since the study by Magaz *et al.* did not include patients with *JAK2*^{V617F}, whether the risk of venous thromboembolism is associated with mutations in specific genes, and whether these patients are exposed to a higher risk of recurrence are important questions that need to be addressed in large multicenter series.

The third feature of interest of Carrà's paper is the high frequency of *JAK2*^{V617F} considered part of the CHIP-associated mutations. Three of the seven patients (43%) with CHIP had *JAK2*^{V617F} mutations, together with three patients with *DNMT3A* mutations and one with an *EZH2* mutation. CHIP-associated mutations occur in many different genes, the most frequent of which are epigenetic regulators (*DNMT3A*, *TET2* and *ASXL1*), which account for approximately 70% of the mutations, followed by mutations in RNA splicing genes (*SF3B1*, *U2AF1*) and signaling, such as *JAK2*.[8]

The extraordinarily high frequency of *JAK2*^{V617F} among the CHIP-associated mutations in SVT subjects opens the

question on how to differentiate MPN-specific mutations from CHIP-associated ones. A similar question was raised by Steemsa *et al.* for CHIP in the normal population when the authors claimed that detection of a myelodysplastic syndrome (MDS)-associated somatic mutation in a cytopenic patient without other evidence of MDS causes diagnostic uncertainty.[9]

Carrà *et al.* claimed that their subjects lacked a myeloid disorder because bone marrow biopsies were inconsistent with a World Health Organization (WHO)-defined MPN. However, diagnosing a MPN in someone with SVT is challenging. The authors themselves noted that the patients had increased bone marrow cellularity, an increased erythroid component, and occasional hyperplasia of megakaryocytes with dysplasia. These data raise the suspicion of an early MPN.

We recently described a new subtype of MPN frequently associated with SVT.[10] The disorder is characterized by normal blood cell concentration, no signs of disease activity, with megakaryocyte hyperplasia and dysplasia, which we termed *clonal megakaryocyte dysplasia with normal blood values*. Here we emphasize that our dataset contains other MPN currently considered MPN-unclassifiable in the 2016 WHO classification of myeloid disorders. Many of these people have idiopathic thromboses (often SVT) and bone marrow histology showing minimal changes of megakaryocytes that deserve to be more precisely and usefully classified.

In their discussion, Carrà *et al.* propose that CHIP is a clue to the pathophysiopathology of SVT and a new, easily identifiable risk factor for SVT recurrence. I suggest that a more careful study of bone marrow histology in people with SVT, especially of megakaryocytes, is likely to identify new patients with MPN-associated SVT and consistently address them to a differential strategy of cure.

Disclosures

No conflicts of interest to disclose.

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