P1045 IS JAK2V617F BUT NOT CALR AS DRIVER MUTATION ENOUGH BY ITSELF IN THE PATHOGENESIS OF UNUSUAL TYPE VENOUS THROMBOSIS IN MPN PATIENTS?

**Topic:** 16. Myeloproliferative neoplasms - Clinical

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**Background:** Myeloproliferative neoplasms (MPN) are a heterogenous group of hematopoietic stem cell disorders and clinically they constitute the most frequent underlying cause of venous thrombosis (VTE) in unusual site, including splanchnic vein thrombosis (SVT) and cerebral vein thrombosis (CVT). This subgroup of patients has been showed to have distinct characteristics compared to MPN patients with VTE in usual site, including deep vein thrombosis and pulmonary embolism.

**Aims:**

The aim of this study is analyzed in a retrospective cohort of patients with MPN clinical characteristics, molecular features and outcome data in patients who have experienced an unusual site thrombosis.

**Methods:** In our study, we retrospectively analyzed a cohort of 577 consecutive patients with MPN according to WHO 2016 criteria who referred to our institute between 2009 and 2020. In all, 113 patients (19.58%) had a vascular event during a median follow up of 94.3 months (range, 2.4-416.0). Usual and unusual site venous thrombosis occurred in 40.7% and 33.6% in MPN patients with thrombosis, respectively.

**Results:**

From the 38 MPN patients with unusual site VTE, 19 (50%) were male. Twenty-seven patients had an SVT and 11 a CVT. The driven mutation was JAK2V617F in 79% with a median allelic burden of 20% using NGS. MPN patients with SVT and CVT are younger (ORR 0.87 (0.82-0.93), pValue < 0.0001), with higher PLT count at diagnosis (ORR 0.06 (0.01-0.38), pValue=0.0085), and higher splenomegaly rate (ORR 0.97 (0.90-0.99), pValue=0.0003) compared to MPN patients with usual site VTE. Globally survival data in our population reported an overall survival in MPN with thrombosis of 238 months (95% I.C. 177-336), poorer in patients with arteriosus events compared to VTE (usual and unusual sites; pValue=0.017). At all, only few patients experienced recurrence thrombosis during the follow up and the recurrence thrombosis free survival rate at 5 years in MPN with thrombosis was 85%. Moreover, older age and level of hemoglobin at time of thrombosis significantly influence survival in MPN patients with unusual site VTE. Using NGS on 20 MPN patients with unusual site VTE, molecular analysis identified the mutation in the hotspot exon 14 region of JAK2 in 13 patients, among them the 92% as isolated alteration. The most frequent additional mutations were found in CALR mutated patients, including high risk mutation as ASXL1 and U2AF1 (Figure 1).

**Image:**
Summary/Conclusion: This finding underlies the central role of JAK2V617F mutation in the pathogenesis of unusual type VTE in MPN, which occurs as sole molecular alteration in more than 90% of cases. However, in our cohort most patients who carried CALR as driver mutation seem to need one or more additional mutations. Our interpretation on these findings is that JAK2V617F is per se a strong risk factor for unusual venous thrombosis while CALR mutation must be enriched for additional non-driver alterations, needing a second hit to drive to thrombosis.