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634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Clinical Characteristics and Outcomes of Unusual Venous Thrombosis Sites Among Veterans with Myeloproliferative Neoplasms

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Myeloproliferative Neoplasms (MPNs) may be complicated by venous thrombosis at unusual sites, which may include portal veins, hepatic veins, and cerebral sinuses. We have previously reported on the association of Agent Orange and the development of MPNs among Veterans. The incidence and timing from Service-Connected Exposures (SCE) of Veterans to the development of MPNs and thrombosis at atypical sites have not been defined. We examine the natural history, clinical characteristics, and outcomes of the Veterans with MPNs, who developed Renal Vein Thrombosis (RVT), Splanchnic Vein Thrombosis (SVT), Budd Chiari Syndrome (BCS), and Cerebral Venous Sinus Thrombosis (CVST).

Utilizing the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database from January 1, 2006 - January 26, 2023, Veterans with MPNs, RVT, SVT, BCS, and CVST were identified through ICD-9 and -10 codes, and, subsequently, a retrospective chart review was performed upon those Veterans with MPNs and unusual thrombosis sites. Military toxin exposures were verified through Veterans' duration and location of service. Time to MPN diagnosis refers to time from first year of cumulative SCE until year of MPN diagnosis.

Among 12,352,664 Veterans, there were 435 RVT, 156 SVT and BCS, 140 CVST, and 93,269 MPNs identified. Among those with MPNs, there were 9 BCS, 4 RVT, 5 SVT, 2 RVT & SVT, and 9 CVST. CVST was observed only in Vietnam Veterans; 13/20 (65%) of RVT, SVT or BCS cases had SCE from the Gulf War (Table 1).

Five/20 of the MPN subjects with RVT, SVT, or BCS had documented pre-existing thrombophilic risk factors, which included malignancy, heparin-induced thrombocytopenia, and splenectomy, whereas 2/9 CVST with MPN had associated alcohol abuse and tooth infection. All non-MPN Veterans with RVT, SVT, or BCS had thrombophilic risk factors, including malignancy, infection, and surgery. One had BCS from Paroxysmal Nocturnal Hemoglobinuria.

Median time to MPN diagnosis from SCE was 20 (3-62) years with 13 (65%) thrombotic events occurring at the same time of MPN diagnosis among Veterans with RVT, SVT, or BCS. Six (30%) had their thrombosis recognized prior to their MPN diagnosis, median 6 (1-10) years, while 1 had a thrombotic event 16 years after his MPN diagnosis (Figure 1). Veterans with MPN and CVST had a substantially longer median time from SCE to the time of MPN diagnosis, 42 (24-52) years. No CVST was observed concurrent to the time of MPN diagnosis. Among Veterans with MPN and CVST, 5 (56%) had thrombosis before MPN diagnosis and 4 (44%) had thrombosis after MPN diagnosis, median 5 (2-10) years and 7 (1-21) years, respectively.

Among Veterans with MPN and RVT, SVT, or BCS, 17 (85%) had portal hypertension complications, 8 (40%) had undergone endovascular interventions, and all individuals were placed on indefinite systemic anticoagulation, with warfarin most commonly prescribed. Among Veterans with BCS, 3 underwent liver transplantation. Among Veterans with CVST, 2 (22%) had concurrent CNS hemorrhage, 5 (56%) had persistent neurologic symptoms, and 1 had transformation of his MPN to Chronic Myelomonocytic Leukemia.

In summary, thrombotic episodes at unusual sites among Veterans with MPNs are rare events but convey substantial morbidity and mortality, particularly among those with RVT, SVT, and BCS. We describe a significantly shorter median time to MPN

diagnosis in Veterans with RVT, SVT, and BCS compared to CVST with a difference of 22 years. All MPN subjects with RVT, SVT, or BCS had JAK2 V617F mutations, with majority of thromboses noted at the time of MPN diagnosis. Future studies should include potential role of SCE in acquisition of driver mutations and CHIPs and progression of mutagenesis.

Disclosures Kessler: *Novo Nordisk:* Other: Scientific advisory board; *Octapharma:* Other: Scientific advisory board, Research Funding; *CSL Behring:* Other: Scientific advisory board; *Genentech:* Other: Scientific advisory board; *Bayer:* Consultancy, Other: Chair, DSMB, scientific advisory board, Research Funding.

Table 1. Baseline Demographics and Clinical Characteristics among Veterans with Myeloproliferative Neoplasms with Unusual Sites of Thrombosis

		Renal Vein Thrombosis (RVT), Splanchnic Vein Thrombosis (SVT), Budd Chiari Syndrome (BCS); N=20	Cerebral Venous Sinus Thrombosis (CVST) N=9
Age, Median (Range) in years		62 (32-89)	74 (56-76)
Race, N (%)	*Whites*	15 (75%)	7 (78%)
	Blacks	2 (10%)	0
	Pacific Islander	1 (5%)	1 (11%)
	Unknown	2 (10%)	1 (11%)
Male, N%		18 (90%)	9 (100%)
Service Location, N (%)	*Gulf War*	13 (65%)	0
	Vietnam War	5 (25%)	9 (100%)
	Korean War	2 (10%)	0
Duration of Service, Median (Range) in years		3 (1-20)	3 (1-12)
MPN Subtype, N (%)	*Polycythemia Vera*	13 (65%); all high risk	4 (44%); all high risk [1 has t(1;22)]
	Essential Thrombocythemia	5 (25%); all high risk	3 (33%); all high risk
	*Primary Myelofibrosis^*	1 (5%); high risk	2 (22%); 1 low [has t(2;12)] & 1 intermediate-2 risk
	*Secondary Myelofibrosis^*	1 (5%); intermediate-2 risk	0
Driver Mutations, N (%)	*JAK2*	20 (100%)	3 (33%)
	CALR	0	1 (11%)
	Unknown	0	5 (56%)
Prior Arterial Thrombosis, N (%)		4 (20%)	0
Prior Venous Thrombosis‡, N (%)		2 (10%)	1 (11%)
Recurrence of thrombosis, N (%)		3 (15%)	1 (11%) – 3 years later
Another Arterial Thrombosis, N (%)		2 (10%); 1 MI, 1 spinal cord infarction	0
Another Venous Thrombosis‡, N (%)		3 (15%); 2 PE, 1 DVT	1 (11%) – PE
Clinically Relevant Major Bleeding, N (%)		6 (30%)	2 (22%)
Anticoagulation, N	*Warfarin*	9	3†
	DOAC	2 Dabigatran*; 5 Apixaban*; 2 Rivaroxaban	1 Dabigatran†; 2 Apixaban; 1 Rivaroxaban
	LMWH	1	0
Antiplatelet, N (%)		6 (30%)	3 (33%)
Cytoreduction, N	*Phlebotomy*	8	1
	Hydroxyurea	9	4
	Ruxolitinib	3	1
	Interferon	2	0

DOAC – Direct Oral Anticoagulant; DVT – Deep Venous Thrombosis; LMWH – Low Molecular Weight Heparin; MI – Myocardial Infarction; PE – pulmonary embolism
*1 patient on Dabigatran switched to LMWH and 1 to Apixaban; 1 patient on Apixaban switched to Warfarin and 1 to LMWH
†1 patient on Warfarin switched to Dabigatran; 1 patient on Dabigatran switched to Apixaban
^DIPSS Plus Risk Score for Primary Myelofibrosis and MYSEC-PM Prognostic Model Risk Score for Secondary Myelofibrosis
‡Except the Unusual Thrombosis Sites

Figure 1. Timeline of Service-Connected Exposures to Myeloproliferative Neoplasm Diagnosis and Thrombosis at Unusual Sites

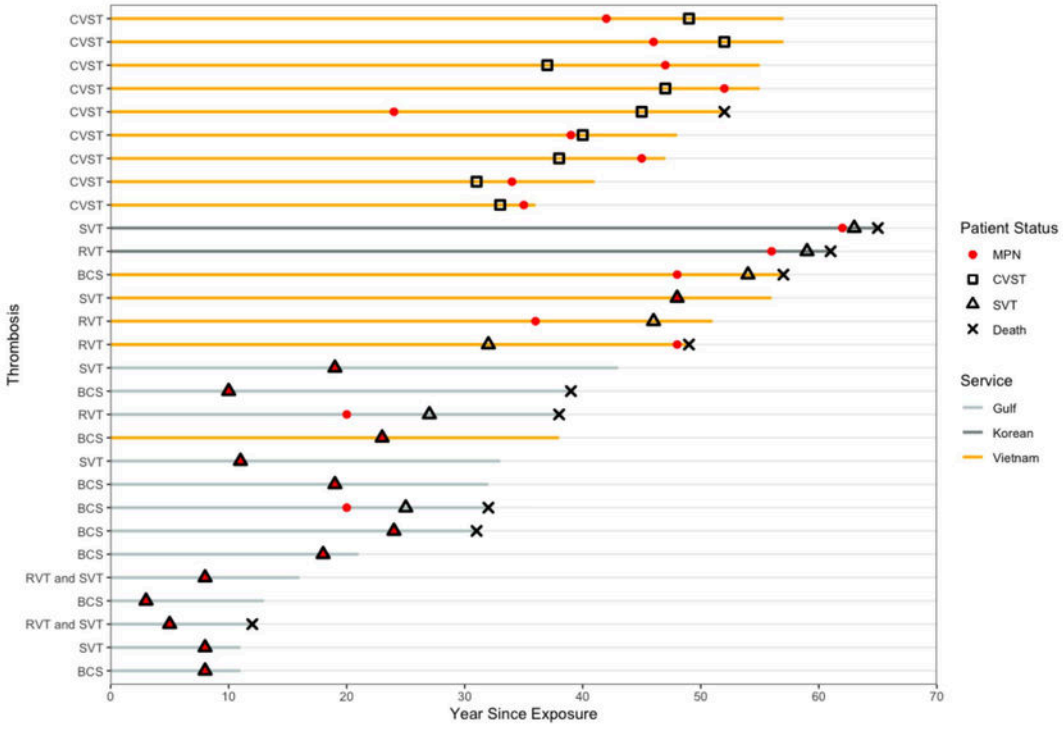

Figure 1

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