Thrombosis at Unusual Sites: Focus on Myeloproliferative Neoplasms and Paroxysmal Nocturnal Hemoglobinuria

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Abstract

Patients with thrombosis at an unusual site will need to be explored for rare causes of thrombosis. Two of these rare causes include myeloproliferative neoplasms (MPNs) and paroxysmal nocturnal hemoglobinuria (PNH). It is important not to overlook these causes, since they require specific management, in addition to antithrombotic treatment (anticoagulants, antiplatelet agents). Unusual sites of venous thrombosis include upper extremity veins, splanchnic veins, cerebral veins, and retinal veins, and unusual sites of arterial thrombosis include renal, adrenal, splenic and mesenteric arteries, and intracardiac and aortal locations. Suspicion for MPN and PNH should be raised if there are concomitant abnormalities, such as elevated or decreased blood cell counts or splenomegaly. Diagnosis of MPN and PNH should include JAK2V617F mutational screening as well as flow cytometric assessment of GPI-anchored proteins in the peripheral blood, respectively. Specific treatments for MPN may include phlebotomy or cytoreductive drugs such as hydroxyurea, anagrelide, pegylated interferon-alpha, or Janus kinase inhibitors. Drugs used for PNH treatment include terminal complement inhibitors, such as eculizumab and ravulizumab, as well as proximally acting inhibitors such as pegcetacoplan or iptacopan. Patients with MPN and PNH are at high risk for thrombosis during their entire lifetime and should thus be followed by specialists experienced in the care of these diseases.

Keywords

- thrombosis
- unusual sites
- myeloproliferative neoplasms (MPNs)
- paroxysmal nocturnal hemoglobinuria (PNH)
- complement

Zusammenfassung

Patienten mit einer Thrombose an einer ungewöhnlichen Lokalisation müssen auf seltene Thrombose-Ursachen hin untersucht werden. Zwei dieser seltenen Ursachen sind Myeloproliferative Neoplasien (MPN) und die Paroxysmale Nächtliche Hämoglobinurie (PNH). Es ist wichtig, diese Ursachen nicht zu übersehen, da Patienten mit diesen Erkrankungen neben einer antithrombotischen Behandlung (Antikoagulanzien, Thrombozytenaggregationshemmer) eine spezifische Behandlung benötigen. Ungewöhnliche Lokalisationen für Venenthrombosen sind Venen der oberen Extremitäten, Splanchnikusvenen, Hirnvenen und Netzhautvenen, während ungewöhnliche Stellen für arterielle Thrombosen Nieren-, Nebennieren-, Milz- und Mesenterialarterien sowie intrakardiale und aortale Lokalisationen darstellen. Der Verdacht auf das Vorliegen

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Schlüsselwörter
- Thrombose
- ungewöhnliche Lokalisation
- Myeloproliferative Neoplasien (MPN)
- Paroxysmale nächtliche Hämoglobinurie (PNH)
- Complement

einer MPN oder einer PNH sollte insbesondere dann geschöpft werden, wenn gleichzeitig weitere klinische Auffälligkeiten wie eine erhöhte oder verringerte Blutzellanzahl oder Splenomegalie vorliegen. Die Diagnose von MPN und PNH sollte ein JAK2V617F-Mutationsscreening bzw. eine durchflusszytometrische Bewertung von GPI-verankerten Proteinen im peripheren Blut umfassen. Zu den spezifischen Behandlungen für MPN können Aderlässe oder zytoreduktive Medikamente wie Hydroxycarbamid, Anagrelid, pegyliertes Interferon-alpha oder JAK-Inhibitoren gehören. Zu den zur Behandlung von PNH verwendeten Medikamenten gehören terminale Komplementinhibitoren wie Eculizumab und Ravulizumab sowie proximal wirkende Inhibitoren wie Pegcetacoplan oder Iptacopan. Patienten mit MPN und PNH haben während ihres gesamten Lebens ein hohes Thromboserisiko und sollten daher von Spezialisten betreut werden, die über Erfahrung in der Behandlung dieser Krankheiten verfügen.

Introduction

Thrombosis and thromboembolism (TE)[a] are common diseases in the general population. They can be subdivided into venous and arterial thrombosis. Venous TE (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs at an incidence of 1.4 to 2.2 per 1,000 person-years,[1] with DVT being most commonly located in the lower extremity (81%[2]) and less commonly in the iliac veins (13%[2]) or the upper extremity veins (5%[3]). Acute arterial thrombosis most commonly occurs in the peripheral arteries (acute limb ischemia; 15 per 100,000 individuals[4]), the coronary arteries (acute myocardial infarction; age-adjusted incidence: 1.9–5.3 per 1,000 individuals; unpublished data from ARIC Surveillance 2005–2012, National Heart, Lung, and Blood Institute[5]), or the cerebral arteries (acute ischemic stroke; age-adjusted incidence: 0.88–1.91 per 1,000 individuals[6]).

Unusual or atypical sites of venous thrombosis include the upper extremity veins, splanchnic veins, cerebral veins, and retinal veins, or any other rarely affected veins.[7]

Due to the rare occurrence of thrombosis at these unusual sites, information on their diagnosis and management is scarce. Here, we review the specific clinical manifestations, diagnostic tests, and treatment of patients with thrombosis at unusual sites, with a focus on myeloproliferative neoplasms (MPNs) and paroxysmal nocturnal hemoglobinuria (PNH), since patients affected by these two entities will require specific management in addition to pure anticoagulation or antiplatelet therapies.

Diagnostic Approach to Thrombosis at Unusual Sites

In addition to the standard diagnostic procedures which are necessary to establish the diagnosis of thrombosis (medical history, clinical signs, D-dimers [in case of venous thrombosis], imaging of site of thrombosis, exclusion or detection of PE, and/or stroke), thrombosis at an unusual site should trigger additional diagnostic steps (see ►Table 1). In particular, thrombophilia should be ruled out, including thrombophilia caused by MPN or PNH. Here, genetic testing for MPN and flow cytometric analysis of Glycosyl phosphatidylinositol (GPI)-anchored proteins are essential, since the treatment of thrombosis may require additional therapy in addition to antiplatelet agents and/or anticoagulants, such as cytoreductive therapy for MPN[8–11] or mandatory complement inhibition for patients with PNH suffering from a TE event.[12–14]

Unusual Sites of Thrombosis in Myeloproliferative Neoplasms

The following atypical presentations of patients with thrombosis should raise a suspicion for an underlying MPN: thrombosis at young age, lack of cardiovascular risk factors (particularly in cases of arterial thrombosis), concomitant expansion of blood cells (e.g., isolated leukocytosis, erythrocytosis, or thrombocytosis, or three-lineage expansion), splenomegaly, and/or MPN-associated symptoms (e.g., aquagenic pruritus, bone pain, night sweats, weight loss, fatigue), and an unusual site of thrombosis.

In such cases, the presence of an MPN should be ruled out, employing a thorough clinical exam, blood tests, including genetic testing, and imaging modalities (see ►Table 1).

Real-world evidence from registries has informed us that, in patients with MPN, the prevalence of thrombosis, all sites of the body combined, was approximately 20%.[15] In our own series, taken from an MPN bioregistry, it was 33.6% (►Table 2).[9]

There was a high frequency of splanchnic vein thrombosis (SVT) in MPN patients, ranging from 15.2%[9] to up to 40%.[16] In a large meta-analysis, the prevalence of venous thrombosis was around 6%, with 53, 22, 14, and 11% of these cases located in extremity veins (DVT), splanchnic veins, pulmonary arteries, and cerebral veins, respectively.[15]

Interestingly, MPN patients with SVT were more likely to exhibit an elevated gamma-glutamyl transferase (GGT) serum levels than MPN patients without SVT,[16] and elevated GGT levels were independently associated with poor

[a] In this review, thrombosis and thromboembolism will be termed "thrombosis" unless otherwise indicated.

Table 1 Diagnostic management of thrombosis at an unusual site

Prior history	• Medical history, previous thrombosis, risk factors • History of MPN or PNH? Cancer? Family history? • Thrombosis provoked or unprovoked? • Anticoagulants? Antiplatelet agents? Other medication?
Clinical exam	• Splenomegaly? Signs of portal hypertension? Ascites? • Signs of hemolysis? • Headache? • Multiple sites of thrombosis? Signs of previous thrombosis? • Indwelling venous catheters? Anatomical obstruction?
Clinical chemistry	• D-dimers • Hemolysis parameters (haptoglobin, bilirubin, LDH, Coombs tests) • Hepatic function tests • Iron deficiency?
Coagulation factors	• Antithrombin (AT III), protein C, and protein S activities • Rule out antiphospholipid syndrome (APS): lupus anticoagulant, anticardiolipin, and anti-beta-2-glycoprotein antibodies
Hematology	• Complete blood count (leukocytosis? erythrocytosis? thrombocytosis? polycythemia? cytopenias?) • Reticulocyte count • Blood smear (blasts? leukoerythroblastosis? dysplasias?) • Bone marrow aspiration/biopsy to rule out MPN and/or aplastic anemia
Flow cytometry	• PNH diagnostics (e.g., GPI-anchored proteins CD55 and CD59 in two blood cell lineages [granulocytic and erythrocytic]) according to Manning et al[91] and Giannotta et al[92]
Genetics	• Molecular genetics (peripheral blood) – MPN driver oncogenes: JAK2V617F, calreticulin (CALR), or MPL mutations, Bcr-Abl transcript – Coagulation factor genes: F. V Leiden or prothrombin (F. II) mutations • Cytogenetics (bone marrow)
Imaging	• CT: specific imaging according to affected site (e.g. rule out cervical rib in thoracic outlet syndrome), rule out pulmonary embolism • Echocardiography: rule out atrial defect (in case of atypical stroke) • MRI: sinus vein thrombosis?

Abbreviations: CT, computed tomography; LDH, lactate dehydrogenase; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; PNH, paroxysmal nocturnal hemoglobinuria.

Table 2 Location of thrombosis in MPN (as published in Kaifie et al[9])

Type of thrombosis	Site of thrombosis	Frequency in MPN, *n* (%)[a]
All (venous and arterial)	All sites	147/438 (33.6%)
Venous	Deep vein (extremity)	46/146 (31.5%)
	Splanchnic vein	22/145 (15.2%)
Arterial	Coronary artery (heart)	41/148 (27.7%)
	Cerebral artery	28/145 (19.3%)

Abbreviation: MPN, myeloproliferative neoplasm.
[a]Previous and current thrombosis cases.

survival.[16] Thus, GGT serum levels should be assessed in patients with SVT.

Overall, in a non-MPN-selected population, the fraction of atypical venous thrombosis was 12% in a series of 2,293 patients who underwent thrombophilia testing after venous thrombosis.[17] Here, the fractions of SVT and cerebral vein thrombosis were only 3.6% each,[17] suggesting that these atypical locations of thrombosis were much more prevalent in MPN patients.

The mere detection of SVT should trigger genetic testing of the peripheral blood for the presence of the JAK2V617F mutation, since this mutation occurred in 94.7% of patients with an SVT and a concomitant MPN, but also in 21.5% of patients with an SVT but without an overt MPN.[18] Patients with a JAK2V617F but without a known MPN should then undergo full testing for MPN (potentially including bone marrow histology). Interestingly, the JAK2V617F mutation was also detected in 4.8% of patients with cerebral vein thrombosis in the absence of an MPN.[18] In a large meta-analysis[19] of 1,062 patients with Budd–Chiari syndrome (BCS) and 855 patients with portal vein thrombosis (PVT), 41.1 and 27.7% were JAK2V617F-positive, most of whom had an MPN.[19] However, even BCS and PVT patients without MPN features harbored a JAK2V617F in 17.1 and 15.4%, respectively.[19]

In addition to the occurrence of atypical venous thrombosis in MPN patients, these patients are at an increased risk of arterial thrombosis. The prevalence of arterial thrombosis in MPN patients was approximately 16%, with predominant locations in cerebral arteries (stroke), coronary arteries, and peripheral arteries in 7.4, 6.1, and 3.3%, respectively.[15]

Atypical sites of arterial thrombosis may occur in MPN and non-MPN patients, but they should trigger the search for unusual and rare prothrombotic states, such as MPN, PNH, antiphospholipid syndrome, and hereditary increase of lipoprotein(a).[20] The vessels affected by atypical arterial thrombosis include renal and adrenal as well as splenic and mesenteric arteries, and intracardiac and aortal locations.[20]

Therapeutic Management of Patients with MPN and Thrombosis

One of the reasons why patients with thrombosis at an unusual site should be thoroughly assessed for the cause of their thrombosis is the fact that these patients often have an indication for specific treatment, in addition to antiplatelet agents and/or anticoagulants.[8,10,11]

MPN patients with a history of thrombosis or current thrombosis are at high risk for thrombosis recurrence.[21,22] In order to decrease this recurrence rate, an extended and even life-long duration of anticoagulation has been advocated, particularly in patients with recurrent thrombosis, SVT, or life-threatening thrombosis/TE, or in cases of progressing MPN and, in general, MPN patients with a low bleeding risk.[10] Limited-duration anticoagulation should be reserved for patients with clearly provoked thrombosis or those with unprovoked distal DVT.[23]

However, although the recurrence rate is decreased by anticoagulant treatment, it remains elevated even in the presence of anticoagulation,[21] particularly in patients with MPN and SVT.[22]

Thus, the use of additional cytoreductive therapy has been investigated in such high-risk MPN patients. Thrombosis risk assessment is part of the diagnostic workup of MPN patients. In patients with essential thrombocythemia (ET), the IPSET-thrombosis (International Prognostic Score of thrombosis in Essential Thrombocythemia) score assesses four factors: age 60 years or more (1 point), presence of a cardiovascular risk factor (hypertension, diabetes mellitus, and/or active smoking) (1 point), presence of a prior thrombotic event (2 points), and presence of the JAK2V617F mutation (2 points).[24] Low, intermediate, and high risk scores are characterized by 0–1, 2, and 3–6 points, respectively.[24] Patients with low, intermediate, and high IPSET risks have an annual thrombosis risk of 1.03, 2.35, and 3.56%, respectively.[24] High-risk patients with ET should receive cytoreductive therapy in order to decrease their thrombotic risk, based upon the results of the randomized study comparing hydroxyurea with placebo and showing increased thrombosis-free survival in the hydroxyurea-treated group of patients.[25]

Patients with polycythemia vera (PV) are stratified according to age and previous thrombosis in order to assess their risk of thrombosis.[11] In high-risk patients with PV (i.e., those with previous thrombosis and/or an age of 60 years or more), primary prophylaxis with acetylsalicylic acid led to superior thrombosis event-free survival as compared to placebo, as shown in the randomized ECLAP trial.[26] In addition, high-risk patients with PV benefitted from cytoreductive therapy with hydroxyurea, which, when added to phlebotomy, led to a higher overall survival and cardiovascular event-free survival than phlebotomy alone.[27]

Together, these results demonstrate that patients with thrombosis occurring at an unusual site should be screened for the presence of an underlying MPN and, if an MPN is confirmed, should be treated with a combination of cytoreductive therapy and either antiplatelet agents (in the case of sole arterial thrombosis) or anticoagulants (patients with venous thrombosis or combined arterial and venous thrombosis).[8,10,11]

Management of Patients with Paroxysmal Nocturnal Hemoglobinuria

Three pioneering PNH specialists in 2011 stated that "PNH is the most vicious acquired thrombophilic state known in medicine,"[28] as "the life-time risk in untreated PNH patients is in the order of 50%" while "thrombosis is highly unpredictable and tends to target abdominal and/or cerebral veins." While this drastic statement fortunately refers to times when complement inhibition was not available, the unacceptable high lifetime risk of thrombosis for PNH patients has recently been verified,[29] and it is true that patients with unrecognized PNH suffer from a relative risk for VTE, which by far outweighs those of other thrombophilic states.[30,31] This stems from the fact that PNH is "the" complement model disease,[32] in which the deficiency of complement regulatory proteins on the surface of peripheral blood cells due to an acquired mutation of hematopoietic stem cells leads to uncontrolled intravascular complement activation and manifestations resulting primarily in intravascular hemolysis, which in itself is accompanied by thrombophilic sequelae.[33,34] Complement and coagulation cascades are tightly intertwined and are known to enhance each other,[35,36] but dissection of the plethora of known mechanistic links between both serine protease networks is beyond the scope of this article; readers are referred to excellent overviews.[34,35,37–39] Thrombosis rates in patients with PNH differ between populations studied, from $<5\%$ in Japanese patients to around 20% in South Koreans and Norwegian PNH patients, and to $>30\%$ in patients from the United States, Great Britain, and France.[40–46]

PNH, in a nutshell, comprises of three major clinical features: bone marrow dysfunction resulting in various degrees of cytopenia, hemolysis, and thrombophilia. These are accompanied by smooth muscle dystonia, which can further facilitate the development of thrombotic events through platelet activation and aggregation.[47] The coagulation cascade in turn further aggravates complement activation—through various mechanisms—which leads to the well-described vicious cycle.[48] Studies have shown that the terminal part of the complement cascade seems to be the major culprit aggravating the thrombotic state.[35]

Table 3 Location of thrombosis in PNH (as published in Gurnari et al[29])

Type of thrombosis	Site of thrombosis	Frequency in PNH, *n* (%)
All (venous and arterial)	All sites	56/267 (21%)
Venous	Deep vein (extremity)	15/56 (26, 7%)
	Splanchnic vein (including Budd–Chiari)	25/56 (44.6%)
Arterial	Coronary artery (heart)	–
	Cerebral artery	5/56 (9.1%)

Abbreviation: PNH, paroxysmal nocturnal hemoglobinuria.

Thrombosis in PNH can occur at arterial or venous sites alone or in combination (►**Table 3**). Typical sites include cerebral,[49] gastrointestinal (hepatic and mesenteric), as well as lower extremities and pulmonary veins.[38,50] Other sites include cutaneous veins[51] or coronary[52] and cerebral arteries.[29,53] Patients with PNH can present with very severe thrombotic complications or even multiple-site thrombosis, as well as with multiple TE episodes, which is why early diagnosis of this ultra-rare disease is paramount.[54–58]

The scenarios depicted above suggest that PNH should not be overlooked as the cause for an unexplained thromboembolic event, due to the grim potential consequences. The high incidence of thrombosis in PNH patients over the course of the disease and the rarity of the disease itself in combination with the unspecific symptoms most patients experience before their often-delayed diagnosis often lead to a dilemma between not overlooking and on the other hand not overemphasizing PNH as a cause for thrombosis.

This has often prompted physicians to check for PNH clones in unselected patient groups. However, the true rate of PNH as the sole cause for a TE event in unselected patients is most likely overestimated.[59,60] While, for example, SVT should always prompt adequate flow cytometric analysis of peripheral blood, as already described in the 2015 Baveno VI Consensus Workshop recommendations ("work-up in primary thrombosis of the portal venous system or hepatic venous outflow tract a close collaboration with haematologists ...for complete work-up for prothrombotic factors including ... paroxysmal nocturnal haemoglobinuria (PNH) ..."),[61] in patients with thrombosis without further clues for PNH (►**Table 1**), flow cytometric testing in most cases can be neglected.

Data from various groups show that the chances to detect PNH increase with the following diagnostic clues: thrombosis + signs of hemolysis, thrombosis at unusual sites, and/or thrombosis and cytopenia.[39] Some of these diagnostic clues were validated in a Spanish and Brazilian cohort of 873 blood samples, in which cytopenia in combination with thrombosis led to PNH diagnosis in 14% of 73 patients, while thrombosis without anemia and/or other cytopenia was identified only in 0.4% out of 800 cases.[94] Studies from the United States, Canada, Turkey, and other European countries confirmed the rather low rates of PNH in patients without typical clues in addition to thrombosis.[59,62–64] However, as flow cytometry-based diagnosis of PNH is straightforward and takes just one rather quick and inexpensive analysis in experienced laboratories,[65] it should rather be ordered in cases of doubt, as a negative result including white blood cell analysis reliably rules out PNH.[66]

It is important to remember that other factors can contribute to an increased thrombosis risk in patients with known PNH, such as hormonal factors (e.g., estrogen-based contraception)[67] or the transfusion of plasma products, which are known to be high in complement and should be avoided in PNH patients.[39] Other risks for thrombosis even in patients during complement inhibitor treatment include pregnancy[68] and breakthrough hemolytic events, which in some cases can be caused by complement-amplifying conditions (CACs) such as infections.[69]

Although used regularly in patients not treated with complement inhibitor therapy (especially in countries in which complement inhibitors are not available), therapeutic anticoagulation has not proven to reliably prevent thrombotic events in PNH patients.[38,70] The central role of complement in the pathogenesis of thrombosis in PNH was demonstrated through blocking of the terminal complement at the C5 level with eculizumab (and later ravulizumab). This intervention efficiently decreased TE events from 7.37 to 1.07 per 100 patient-years, corresponding to a relative reduction of 82%.[38,71] This protective effect of eculizumab has recently been re-assessed in a large patient cohort with high-risk features, defined by lactate dehydrogenase (LDH) $\geq 1.5 \times$ ULN (upper limit of normal) and a history of major adverse vascular events (MAVEs).[72] In general, larger PNH clones >30% within the granulocyte compartment "appear to indicate a greater disease burden and risk of TEs and MAVEs."[73,74] However, registry data show that also patients with clones of 10 to 49% are at risk to develop thrombosis.[75]

Treatment

Treatment of TE in PNH patients has to be divided between patients with unknown PNH presenting with thrombosis and subsequent PNH diagnosis and those with a known history of PNH who newly develop a TE.

In a recent series of 267 patients from four U.S. centers, 21% experienced a TE with 43% of these 56 patients experiencing their TE as initial disease manifestation (with venous thrombosis in the majority of cases).[29] Hence, thrombosis as first PNH manifestation is still common. In addition, the data also demonstrated that the amount of so-called type II red blood cells might be correlated with the appearance of TEs in PNH patients, a correlation that has been described similarly before.[76]

Management of an acute TE in complement-inhibitor-naïve PNH patients calls for immediate initiation of complement inhibition. While reliable data from larger patient groups in this regard are available for eculizumab and ravulizumab, data from the newly introduced group of proximal complement inhibitors are still immature.[77] However, the mechanism of action of drugs, such as pegcetacoplan, iptacopan, and others, would suggest that they also lead to immediate inhibition of the terminal complement cascade, hence, not precluding them from being a therapeutic alternative in countries in which they are available.[78,79] Currently, we would, however, prefer immediate commencement of complement inhibition with eculizumab (or its biosimilars) or ravulizumab given the amount of data demonstrating their efficacy available. In addition to the immediate blockade of the terminal complement cascade, patients also need therapeutic anticoagulation with low-molecular-weight heparin (LMWH), unfractionated heparin (switched to warfarin or phenprocoumon in the course of time), or direct oral anticoagulants (DOACs). While data with DOACs used to be scarce, more and more data are published validating this approach.[29,80] It is still unclear whether anticoagulation has to be given indefinitely if a patient is treated effectively with a complement inhibitor or if it can be discontinued after some time as done in other conditions.[69,81,82] Data about the necessity for concomitant anticoagulant therapy together with complement inhibition are too scarce to offer a general recommendation with regards to dosing and timing, and, so far, no general guideline exists.[80,81] While the approach of anticoagulant discontinuation has been successfully performed in a (limited!) number of PNH patients, it cannot be generally recommended and should be—whenever possible—discussed within a team experienced in PNH and coagulation. Potential clues to discontinue might me normalized LDH (<1.5 ULN), normalized D-dimers, clinical and radiological absence of signs of thrombosis as well as early introduction of efficient DOAC therapy.[29,81] As stated above, patients with PNH and TE should also be evaluated for other thrombogenic risk factors.

Patients with a history of PNH who develop a TE event have a high likelihood of developing a recurrent TE event. While experiencing either a relevant CAC such as pregnancy or a severe infection leading to a pharmacodynamic breakthrough hemolysis or will suffer from insufficient complement control due to pharmacodynamic reasons.[83] Depending on which type of anticomplement therapy these patients are on, additional doses or a switch from, e.g., proximal to terminal inhibition might be warranted.[84–86]

In patients with aplastic anemia (AA)/PNH overlap syndromes presenting with very low platelets, the decision for the right dose of anticoagulation can be challenging. However, low platelet counts do not prevent AA/PNH patients from developing thromboembolic complications.[87,88]

Pregnancy in patients with hemolytic PNH[89] as well as in AA/PNH patients[68] can be challenging as well and should always be cared for by a multidisciplinary team; expert guidelines for this delicate patient group are published elsewhere and often focus on optimal dosing of eculizumab (increase in dose or frequency of administration) in addition to treatment with LMWH.[13,90,91]

Finally, it should not be forgotten that PNH and MPN are manifestations at different ends of the spectrum of hematologic diseases with proliferative characteristics and can occur within the one and the same patient; recent data report a prevalence of PNH clones in MPN patients of about 10%,[92,93] which means that any unusual symptom (e.g., the development of significant hemolysis in an MPN patient or splenomegaly in a PNH patient) should prompt the search for PNH in the first and for MPN in the latter.

As has been pointed out elsewhere,[70] "the importance of complete and relevant data sets in rare diseases" should prompt us to establish "a well-constructed, professionally run academic registry …to understand the impact of new diagnostics and therapies on this phenomenon and others." Such a registry has been established by the International PNH Interest Group, and enrolling patients in this registry "should be a valuable resource for research into this fascinating disease," enabling us to answer more and more questions regarding prevention and treatment of TE in patients with PNH.

Conflicts of Interest

Steffen Koschmieder received research funding from Geron, Janssen, AOP Pharma, and Novartis; received advisory board or consulting fees from Pfizer, Incyte, Ariad, Novartis, AOP Pharma, Bristol Myers Squibb, Celgene, Geron, Janssen, CTI BioPharma, Roche, Bayer, GSK, Sierra Oncology, PharmaEssentia, and MSD; received payment or honoraria from Novartis, BMS/Celgene, Pfizer; received travel/accommodation support from Alexion, Novartis, Bristol Myers Squibb, Incyte, AOP Pharma, CTI BioPharma, Pfizer, Celgene, Janssen, Geron, Roche, AbbVie, GSK, Sierra Oncology, Kartos, and MSD; had a patent issued for a BET inhibitor at RWTH Aachen University.

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