

FORUM

Malignant benign hematology

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Abstract

When faced with a life-threatening non-cancerous blood disorder, the term “benign” is a misnomer. Devastating diseases like catastrophic antiphospholipid antibody syndrome, acquired hemophilia, and severe immune thrombocytopenia present a challenge to the hematologist. They are often difficult to treat and lack appropriately powered, unbiased evidence to support management. Moreover, the label “benign” does a disservice as it subconsciously triggers discrepancies in prioritization for the care provider, the system, the patient and his/her family. Despite our progressive advances in non-malignant hematology, there remain many knowledge and care gaps that can be effectively addressed by more international collaboration, more clinical and research infrastructure and more expertly trained clinicians. To highlight the need, is it time to reconsider the term “benign” hematology?

KEYWORDS

hemophilia A, hematology, idiopathic thrombocytopenic purpura, thrombophilia, thrombotic microangiopathy

I write this in reaction to the loss of another young patient to a rare, benign hematologic disease. I witnessed the vicious storm of acute, uncontrollable intravascular hemolysis and thromboembolism—a storm that would see no mercy. I am struck, yet again, by the malignant course of a benign disease and feel betrayed by the term “benign,” a term that ridicules the events of the last 48 hours—where his young blood was ravaged by unbridled disease and his organs tortured by consequence.

I know that my patients feel a sense of relief when they are told that their disease is noncancerous. “There is no chance of acute leukemia,” I say again and again. No matter the diagnosis, whether it be refractory autoimmune hemolytic anemia, severe immune thrombocytopenia, acquired hemophilia, thrombotic thrombocytopenic purpura, or catastrophic antiphospholipid antibody syndrome—my patients remain relieved.

Of course, most hematologic cancers are very serious and should be taken seriously. The problem is that many benign hematologic conditions are not given the same consideration and those with a fulminant course may go unrecognized and untreated. The challenge

when I am faced with the most severe, malignant forms of noncancerous blood disorders is that it is difficult for me to convey the profundity of risk without causing unnecessary alarm, particularly when the literature conveys heterogeneity, variable responsiveness to treatment, and rarity. I cannot find the comfort of appropriately powered, unbiased evidence to support guidelines and often rely on expert opinion or consensus. However, it is important to acknowledge that not every benign hematologic disorder behaves in devastating fashion. There are many blood conditions that are straightforward to diagnose, treat, and where there is a plethora of evidence to support management. Here I write about the severe, life-threatening blood disorders where the term benign is truly a misnomer.

Catastrophic antiphospholipid antibody syndrome (CAPS) is the perfect example of a malignant, benign disorder where advances in understanding and management have been stalled. CAPS is characterized by rapid, progressive, often diffuse thromboembolism of the small vessels with multiorgan failure. CAPS is a phenomenologic diagnosis that must meet laboratory and clinical criteria. The prevalence of CAPS is unclear but it seems to account for less than 1%

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of cases of antiphospholipid antibody syndrome.¹ CAPS is classified as a rare disease, defined by the European Union as a condition with a prevalence of less than 1 in 2000 and has a mortality rate as high as 50%.²⁻⁵ A recent best practice guideline for CAPS highlights the difficulty in making treatment recommendations given insufficient primary evidence, absence of randomized trials, and apprehension about making “weak” recommendations that could pose a barrier to treatment funding.^{5,6} Admittedly, the authors comment on “the main challenge in developing this guideline was the low certainty of evidence.”⁵ Hence, even our best attempt at finding cohesion and helpful treatment recommendations for this malignant benign hematologic disease is bracketed by the absence of certainty. This can be tremendously anxiety-provoking for the physician caring for the patient.

Moreover, for patients with CAPS the treatment involves blunt, highly toxic, and sometimes ineffective immunomodulatory therapies. Also, it must be appreciated that if the storm of CAPS can be effectively quieted, patients are then left with the chronic problem of antiphospholipid antibody syndrome and perpetual concern of disease relapse. Therefore, consideration of long-term effects of treatment must be weighed and choice of drug must be individualized; committed research is needed to inform the development of an evidence-based model to assist with shared decision making.

An additional benign disease that is invariably voracious is acquired hemophilia A (AHA). Also rare, the incidence of AHA has been estimated at 1.48 per million individuals per year⁷ and carries a mortality rate of nearly 22%.⁸ Given its rarity, our understanding of AHA is guided largely by reports from prospective registries. Thus guidelines come from consensus and are based on observations of natural history with historically employed treatment algorithms. The absence of effectively tested hypotheses, due to the significant rarity of the disease, can leave the treating physician perplexed, questioning whether s/he is providing treatment on the basis of medical ritualism or a sound expectation of efficacy and safety. This becomes particularly concerning when the treatments provided include potent pro-hemostatic and immunosuppressive therapies to vulnerable, elderly patients.

Yet another benign disease that can behave in malignant fashion is severe immune thrombocytopenia (ITP). Severe ITP is characterized by clinically significant bleeding.⁹ ITP is a disorder that usually follows a benign route but every hematologist in practice has witnessed ITP with a shattering, tragic, and bloody course. In fact, because of the admittedly critical nature of the situation, the American Society of Hematology’s current guideline on the emergency management of ITP suggests that “physicians may wish to try treatments with evidence limited to case reports but which may be in theory more rapidly acting than intravenous immunoglobulin and/or corticosteroids.”¹⁰ What is interesting about ITP, is that it is not less common than many of the lymphomatous malignancies where the activity in research has been more publicized to date and where said activity has translated into relatively significant changes in health policy.¹¹ What accounts for this difference is unclear—perhaps it simply comes down to human emotion, as we can easily connect to

the physically visible plight of the patient affected with cancer while it is harder to understand the silent struggle of the one with ITP. The above narrative about ITP, however, would not be balanced if I did not describe the development of therapeutic agents in recent years to manage chronic ITP. The advent of thrombopoietin receptor agonists has certainly diminished the burden of severe cases but drug access remains an issue as the criteria for public or private funding substantially restrict their use.

We are familiar with the divide in hematology—benign or malignant, often positioned benign versus malignant based on discrepancies in hospital, regional, and/or national support. In fact, I, like many others, depend on compassionate drug access as the evidence to support the use of agents routinely funded for malignant conditions is lacking in fulminant benign hematology. I often hope that my call will be heard and that the reserved infusion clinic “chemo” chair will be liberated for my “benign” patient. The conceptual separation of nonmalignant hematology and oncology in itself is not the problem as there are important differences that must be acknowledged. Perhaps it is simply the label “benign” that does a disservice to these grave hematologic diseases as it subconsciously triggers discrepancies in prioritization for the care provider, the system, the patient, and his/her family.¹²

My expression of the difficult plight of the “benign” hematologist when faced with the most challenging forms of “benign” hematologic disease is not meant to disregard the plethora of research advances that have been and continue to be made in the realm of nonmalignant hematology. There have been many important breakthroughs in many different diseases and researchers dedicated to the field continue to conduct large multicenter trials and registry studies to develop evidence to guide therapeutic decisions. Moreover, this discussion is also not meant to trivialize the importance of clinical experience, collective narrative, and practice of the art of medicine. Indeed this is an exciting time to be a “benign” hematologist as many of the advances made have been career-altering for the practitioner and life-altering for the patient.

That being said, I believe that we can do better and perhaps it starts with a change in nomenclature. Is it time for us to reconsider the term “benign” hematology? Adoption of an alternative descriptive term such as “complex hematology” may be more fitting and helpful for conditions that fall in the realm of the aforementioned. Despite our progressive advances, there remain many knowledge and care gaps that can be effectively addressed by more international collaboration, more clinical and research infrastructure, and more expertly trained clinicians. Thus, in the wake of the recent loss of my brave, resilient patient I find a sense of purpose as I see the solutions are within grasp if we collectively highlight the needs in complex hematology and collaboratively address them.

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