Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/thrombotic-risk-and-ivh-is-there-something-more-to-pnh/14302/

Released: 08/12/2022
Valid until: 08/12/2023
Time needed to complete: 1h 54m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Thrombotic Risk and IVH – Is There Something More to PNH?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Weitz:
Hello, everyone, my name is Dr. Ilene Weitz. I am a professor of medicine at the Jane Anne Nohl Division of Hematology, Keck-USC School of Medicine. We're going to talk today about thrombosis and PNH I thought I'd start with a brief history of a patient of mine. 29 years old, presented with chest pain and shortness of breath. She had a 9-month history of abdominal pain, had a cholecystectomy done 3 months prior to presentation, and then presented with persistent abdominal pain and shortness of breath. On physical examination, she had evidence of ascites, she was jaundiced, and a bilateral edema. Her CTPA showed a pulmonary embolus in the left main pulmonary artery extending into the left lower lobe, as well as evidence of hepatic, portal, and mesenteric vein occlusion due to clot that extended into the IVC, and she had bilateral DVTs. On laboratory studies, she had a hemoglobin of 9. She had a platelet count count of 69,000, markedly elevated dimers. LDH was elevated at 750, bilirubin was increased and her reticulocyte count was 169,000, haptoglobin was low. Work up for a variety of hypercoagulable states was negative, but a PNH flow showed a 68% granulocyte and monocyte clone, and her red cell clone was type 2 and type 3s equaled 30%.

As you know, thrombosis is experienced by 40-plus percent of patients, perhaps more, and accounts for most of the deaths in PNH. Common sites are common affecting the DVTs and PEs, are most common, but unusual sites should be evaluated for PNH. In particular, intraabdominal or Budd-Chiari syndrome and cerebral vein thrombosis. Arterial events occur six times more frequently than the general population, and at a much younger age. If you have a thromboembolic complication in PNH, your likelihood of staying alive at 4 years is less than 40%.

So complement activation is very important in driving the thromboembolic complications. In particular, C5a is a very potent inflammatory protein as well as prothrombotic protein. There are receptors on monocytes, neutrophils and platelets four C5a, and this results in the generation of cytokines, as well as platelet aggregation and endothelial injury. Thrombin generation, as a result of the complement activation also then further creates more C5a, generating even more activation of the granulocytes, monocytes, and platelets.

So what are the consequences of complement activation in PNH? Well, we know that with complement activation, you generate terminal complement causing cellular damage to the red cells, that causes hemolysis, but you also induce platelet activation due to C5a and leukocyte activation, which generate cytokines. So you get platelet aggregation, you get cytokine release, which results then in thrombosis as well as other end-organ damage.

So we know that certain clinical situations place the patient at increased risk for thromboembolic events. Interestingly enough, hemoglobinuria itself is not an increased risk factor for thrombosis. However, it is interesting that when combined with the LDH, you can see an increased risk, abdominal pain, chest pain, and dyspnea are all increased risk factors for thromboembolic complications in PNH.

So what's the pathophysiology? Why do you get thrombosis in PNH? It's really due to the complement activation with the generation of

C5a inducing cytokines, as well as complement injury to the granulocytes, monocytes, platelets and endothelial cells.

What happens when you inhibit complement in PNH? Well, we know that there's a significant decrease in thromboembolic events, although this was not a primary outcome of the trial study. Nevertheless, 92% of reduction was noted with a P value of 0.00001.

We also know that there's a significant reduction in D-dimer and thrombin antithrombin, complex markers of hemostatic activation, as well as cytokine reduction in IL-6 and a reduction in tissue factor microparticles, and untreated PNH patients have evidence of excess thrombin generation as measured by dimers and TATs, as well as an inflammatory state as measured by IL-6. That probably correlates with the fatigue symptoms that the patients experience. It also correlates with thrombin generation. We know that in some patients, the platelet counts go up as the dimers go down, which really is reflective of thrombin-mediated platelet consumption, DIC. Overall, what's the most important benefit of complement inhibition in PNH? It's really a normalization improvement in overall survival because the patients aren't dying of thrombosis.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.
To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.