ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Thrombotic Complications of Influenza and COVID-19 Infections

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H&O How often do influenza and COVID-19 lead to thrombotic complications?

PN The true incidence of thrombotic complications with influenza and COVID-19 is unclear. A study by Kwong and colleagues published in *The New England Journal of Medicine* a couple of years ago found that patients who had influenza had 6 times the risk of a heart attack.[1] In addition, a 2022 paper in *Nature Medicine* found an elevated risk of heart attacks in a veteran population in the year after a diagnosis of COVID-19.[2] However, not all heart attacks are related to thrombosis. Thrombotic heart attacks, in which a ruptured plaque interrupts blood flow to the heart, are known as type 1 heart attacks. Demand ischemia heart attacks, in which the blood flow to the heart is not limited but is inadequate to match the demands of an increased workload, are known as type 2 heart attacks.

H&O Which patients are at the highest risk for thrombotic complications from influenza and COVID-19?

PN There is some uncertainty about which patients are at the highest risk for thrombotic complications from influenza and COVID-19 because we do not know the exact mechanism for type 1 heart attacks. All adults have plaques, and these plaques can rupture at any time. One of many possible heart attack triggers is a viral illness, which can activate the immune system and increase inflammation. Cardiologists tend to focus on cholesterol in heart patients, even though heart attacks can occur when cholesterol levels are low. Inflammation, however, is a critical piece of the puzzle. We now have an approved anti-inflammatory medication for secondary prevention of cardiovascular disease events. In June 2023, the US Food and Drug (FDA) approved colchicine (Lodoco, Agepha Pharma) for use in secondary prevention of cardiovascular disease events. Despite this breakthrough, there is still a need to better understand how the immune system contributes to thrombotic complications so we can develop additional anti-inflammatory medications for treating residual inflammatory risk. As physicians, we have long used agents such as aspirin, clopidogrel, and prasugrel to reduce thrombotic risk, and antiglycemic agents to treat diabetes.

In a study on heart transplant recipients published in *Circulation Research* in 2022, we found that molecular mimicry can occur. This occurs when a patient has T cells that cross-react with viral peptides and self-peptides.[3] Although the patients were not infected with a virus at the time of transplant, we found that T cells isolated from their plaque expressed specificity to viral epitopes, including influenza and COVID-19. We confirmed that the plaque T cells reacted with viruses in a cell culture system. Because active infection is a contraindication to heart transplant, we wondered why these T cells reactive to viral peptides were in the plaque. We hypothesized that the T cells specific to viruses may cross-react with self-peptides, explaining their presence in the plaque. To identify self-peptides that may cross-react with these viral-specific plaque T cells, we used a computational algorithm to identify proteins in the human vasculature that may share the same amino acid sequence as viral

proteins. After identifying a few candidate self-peptides with similar amino acid sequences, we exposed these self-peptides to the plaque T cells. Indeed, some self-peptides were able to activate the viral-specific T cells in a cell culture dish. These findings suggest that when some patients with plaque have viral infections, T cells found in their plaque can activate and cause an inflammatory cascade that results in plaque rupture and thrombotic complications. Unfortunately, we currently do not know how to identify these patients. If we can identify those at the highest risk with a diagnostic assay, we can develop therapy to target those at the highest risk for thrombotic complications related to molecular mimicry.

H&O Are hospitalized patients more likely to experience thrombotic complications from influenza and COVID-19?

PN The development of thrombotic complications and myocarditis related to COVID-19 tends to be unpredictable, whether the person is in the hospital or not, because we do not fully understand the underlying mechanisms. It is known that people with influenza or COVID-19 are more likely to experience type 2 heart attacks if they are hospitalized, because hospitalized patients are sicker by definition. However, we do not know if the same is true for those with type 1 heart attacks.

H&O What are some other approaches to reducing the risk of thrombotic complications of viral illnesses?

PN We have long been looking for the holy grail of what defines a vulnerable plaque and the best ways to stabilize it. Current medications, some of which have anti-inflammatory effects, are helpful but imperfect. The next step should be looking at ways to modulate the elements of the immune system that contribute to plaque development. Targeting the immune system in general causes problems because the immune system is our friend. With the advent of chimeric antigen receptor T cells and other T-cell therapies for cancer, we are optimistic that we can develop more-specific agents to target thrombosis.

H&O What do you recommend for patients who are at high risk for thrombotic complications from influenza and COVID-19?

PN We know that influenza and COVID-19 vaccines can reduce the risk of type 2 heart attacks by reducing the increased demand on the heart that these illnesses cause. What we do not know is whether vaccines can reduce the risk of type 1 heart attacks.

H&O Are thrombotic complications from influenza and COVID-19 treated just like any other thrombotic complications?

PN Yes, we use the standard treatment of coronary artery catheterization and stenting, followed by the use of aspirin, a statin, and P2Y12 receptor blockers (eg, clopidogrel or prasugrel). We also conduct a highly sensitive test for levels of C-reactive protein to see if the patient has an elevated degree of inflammation. At the same time, we treat influenza or COVID-19 because these conditions increase the demands on the heart. I hope that someday we will be able to figure out which patients have cross-reactivity and provide effective therapies to block this autoimmune reaction.

H&O What additional questions would you like to see answered?

PN We have demonstrated that there are T cells specific to viruses in the plaque, and we have also shown that both self-peptides and viral peptides activate these T cells in vitro. What I would like to do next is show in an animal or in vitro cell culture model whether the development of cross-reactive T cells leads to heart attacks. We can also employ an in vitro cell culture model that uses patient-specific cells derived from the patient's stem cells to model the reaction between vasculature and the immune system. That is an avenue we will continue to explore. We want to be able to understand exactly what triggers plaque rupture and predict which people will develop thrombotic complications in the settings of influenza and COVID-19.

Disclosures

Dr Nguyen has no disclosures to report.

References

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