G53 The Pattern of Immunoreactivity for von Willebrand Factor in a Variety of Thrombotic States

Stacey A Simons, MD, Miami Dade County Medical Examiner Department, Number One on Bob Hope Drive, Miami, FL 33136; Paul*
E. Swanson, MD, University of Washington Division of Anatomic Pathology, 1959 Northeast Pacific Street, Seattle, WA 98195; and Aldo
J. Fusaro, DO, King County Medical Examiner's Office, 908 Jefferson Street, Seattle, WA 98104

After attending this presentation, attendees will understand the role of von Willebrand Factor (vWF) in thrombotic thrombocytopenic purpura (TTP) and recognize variations in patterns of immunohistochemical staining against von Willebrand Factor antigen in thromboemboli from thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, non-bacterial thrombotic endocarditis, renal allograft vascular rejection, and stasis thrombosis.

This presentation will impact the forensic science community in cases of precipitous deaths with little or no antemortem workup that are characterized by a thrombotic state. Although previous reports have discussed the value of immunohistochemical staining against von Willebrand Factor antigen in deaths where thrombotic thrombocytopenic purpura is suspected, this is the first case report to provide images that demonstrate the staining patterns of several other entities within the differential diagnosis.

Although previous reports have detailed the value of this stain in deaths where TTP is suspected, this is the first case report to provide images that demonstrate the staining patterns of several other entities within the differential diagnosis. The variations appear to reflect the etiology of the thromboemboli and their relative content of vWF. The visual references included here will be especially helpful to the medical examiner in cases of precipitous death when there has been little or no antemortem workup.

TTP is a thrombotic microangiopathy, historically requiring a pentad of symptoms for clinical diagnosis: microangiopathic hemolytic anemia; thrombocytopenia with or without purpura; acute renal insufficiency; fever; and neurologic abnormalities. It is now understood that few patients present with all features; however, the presence of neurologic abnormalities is often helpful in distinguishing TTP from hemolytic uremic syndrome (HUS).

The case of an adult male is presented with microangiopathic hemolytic anemia, thrombocytopenia, and an episode of hematuria two days prior to hospital admission. The patient did not report diarrhea or fever, and did not exhibit neurologic symptoms. Pulseless electrical activity and renal failure were present at the time of admission. The patient had a rapid clinical decline and died before a diagnosis could be made. Autopsy did not reveal significant gross pathology. Histologic sections contained myocardial necrosis with relatively widespread microthrombi in small cardiac vessels and, less frequently, microthrombi within glomeruli and renal arterioles. Vascular lesions also included intimal thickening and disruption, and fragmented red cells.

TTP is currently thought to be driven by a deficiency in ADAMTS- 13, a metalloprotease that cleaves vWF to render it ineffective in its role in intravascular platelet aggregation. Deficiencies may be inherited or acquired, and may lead to unchecked formation of vWF-rich thrombi in those vessels subject to shear stress (including arterioles and capillaries). Because vWF is produced in arterial endothelial cells and megakaryocytes, thrombotic lesions in TTP, non-bacterial thrombotic endocarditis (NBTE) and allograft vascular rejection will demonstrate immunoreactivity to vWF antigen. The characteristically fibrin-rich thromboemboli formed in states that are not mediated by vWF will exhibit minimal-to-no immunoreactivity.

Tissue controls in the current report included a single example of

control case, internal positive controls (arterial endothelium), and internal negative controls (hepatic veins and sinusoids). In TTP, there was dense, relatively homogeneous staining of the entire vWF-rich thrombus. In NBTE, there was variably dense, granular staining of characteristically platelet-rich bland vegetations (both on valves and in embolized material). In renal allograft rejection, there was heterogeneous staining, most dense in areas of vascular damage, with only minimal peripheral staining of the thrombi.

In HUS, there was minimal peripheral staining of thrombi. In disseminated intravascular coagulation (DIC), and in stasis thrombosis (the latter secondary to a myocardial infarct), there was focal dense staining only within the more cellular "layered" regions of organizing thrombi, where platelets may become entrapped.

Tissue from the presented case demonstrated vWF-rich thrombi in cardiac and renal vessels as well as in rare small cerebellar vessels, and looked most similar to the mixed immune-TTP control tissue, supporting myocardial necrosis secondary to TTP as the cause of death.

Overall, this case with its corresponding array of tissue controls represents a spectrum of patterns that correlates well with the pathophysiology of each specific pathologic entity. In conclusion, when interpreted in combination with anatomic findings at autopsy, vWF staining provides support for a diagnosis of

 ** Presenting Author*

TTP even when the clinical history is limited or atypical.
TTP, von Willebrand, Hemolysis

 ** Presenting Author*