Thrombotic thrombocytopenic purpura treated with vincristine in a Jehovah's witness

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Sir,

Thrombotic thrombocytopenic purpura (TTP) is a rare but fatal hematologic condition of considerable significance. TTP can be defined as severe microvascular occlusion, with accompanying systemic platelet aggregation, erythrocyte fragmentation, and organ ischemia.[1] Pathophysiologically, TTP is marked by the presence of large von Willebrand factor (vWF) multimers in the circulation.[2] Clinically, TTP is characterized by a pentad of microangiopathic hemolytic anemia, fever, thrombocytopenia, acute renal insufficiency, and neurologic disturbances. However, this classic pentad is not the common presentation and is seen in less than 40% of cases.[3]

TTP warrants prompt medical management. Left untreated, the mortality rate approaches 90%.[4] Since emerging as a treatment option, plasma exchange remains the preferred treatment modality.[2] Plasma exchange has decreased mortality and improved survival rates to as high as 80%–90%.[2] Generally, if TTP is clinically suspected, the findings of thrombocytopenia and schistocytosis are sufficient to institute plasma exchange.[4]

We report a case of TTP in a Jehovah's Witness that highlights the importance of diagnostic recognition. It is not our intention to describe the diagnosis or management of TTP but, rather, to highlight the challenging clinical, ethical, and legal issues involved in the management of this obscure and fascinating condition.

A 45-year-old African American woman presented with complaints of painless bleeding per rectum, with accompanying nausea, epistaxis, hematemesis, and hematuria over the past week. She stated that she had not been in her usual state of good health for the past ten days. She gave history of having had a fever of 102°F, a diffuse dull headache, vague joint pains, and disorientation to time and place, which had spontaneously resolved.

Upon initial examination, the patient was afebrile but appeared to be in mild discomfort; however, she was alert and had no obvious neurological deficits. Physical examination was remarkable for conjunctival injection, sublingual petechiae, presence of gross blood in the rectal vault, and multiple scattered petechiae over the abdomen and extremities.

Initial laboratory examination revealed leukocytosis, anemia, and marked thrombocytopenia. The coagulation profile was normal. Her blood chemistries revealed acute renal insufficiency. A haptoglobin level was low, lactic dehydrogenase (LDH) was elevated, fibrinogen was elevated, and D-dimer was elevated. Urinalysis revealed protein, hemoglobin, and red blood cells.

After the patient was admitted, a diagnosis of TTP was established in consultation with the hematology service. She was informed of the natural course of the disease and the utility of plasma exchange. The patient, however, was a Jehovah's Witness and firmly refused plasma exchange and any blood or blood product transfusion. Moreover, she elected to have a 'do not resuscitate'/'do not intubate' (DNR/DNI) status. Several members of her congregation were present with her throughout her hospitalization and verified that her current wishes were consistent with her known beliefs with regard to blood product transfusions and resuscitation or intubation.

Later in the course of her hospital stay her hemoglobin level started dropping, while the platelet count remained low. She complained of severe headaches, severe abdominal pain, and difficulty in breathing. Clinical exam was marked by a fluctuating mental status. Although her clinical condition worsened, she persisted in her desire to not receive any blood or blood product transfusion, including plasma exchange. She did, however, tearfully change her code status to wanting full medical intervention, including resuscitation and intubation. At the time of her rescinding DNR/DNI, she was in moderate discomfort and oriented only to person and place. Her congregation voiced the opinion that this was inconsistent with her normal wishes and that she was under stress and not in her senses. The patient did not have a health care surrogate to make decisions on her behalf and, as such, there was much controversy regarding her new desire to be resuscitated and intubated if necessary.

As she had refused plasma exchange, she underwent an alternative treatment with vincristine, aminocaproic acid, darbepoetin, and a dexamethasone taper. Fortunately, the patient tolerated the therapy well. Her clinical condition quickly improved and she soon returned to her usual state of health. Prior to discharge her hemoglobin and platelets had normalized.

Our patient fit the classic description of TTP, presenting with the characteristic pentad of symptoms and signs. This patient fortunately had a good outcome, but many issues were raised regarding etiology and treatment.

Our patient refused plasma exchange on numerous occasions despite being informed of the natural history of the disease, the benefits of plasma exchange, and the risks associated with non-treatment. She was offered alternatives to plasma exchange treatment and opted for vincristine therapy. Vincristine is a potent

immunosuppressant that is used alone or in combination with other cytotoxic agents.[3] The possibility of its use in TTP was suggested by the observation of thrombocytosis after its administration in cancer patients and the realization that it is the only antimitotic agent that lacks toxicity to megakaryopoiesis.[3] Despite *in vitro* data in its support, it is not a first-line therapy, and plasma exchange remains the mainstay of treatment in TTP.[5] However, vincristine has been considered a part of a multimodal therapy in light of the TTP US Medical Research Group's results, where they have detailed a standardized regimen of plasma exchange, vincristine, and corticosteroids.[3] One study reviewed TTP cases over 15 years and found that 8 out of 29 patients (28%) achieved remission with plasma exchange alone, while 7 out of 8 patients (88%) achieved remission with plasma exchange and early vincristine. This suggests a possible adjuvant role for vincristine in the treatment of TTP. Thus, most of the evidence regarding its utility in the therapy of acute TTP (in the absence of plasma exchange) is from case reports. Our case also showed a positive response to treatment with vincristine.

Our patient was treated with one dose of vincristine, aminocaproic acid, and darbepoetin, and a dexamethasone taper. It has been suggested that the precise dosing regimens for corticosteroids and antiplatelet drugs in TTP should be established via clinical trials[3] has and also that a randomized international trial, recruiting Jehovah's Witnesses with TTP, could be of value to establish standard guidelines. Our case report supports that suggestion by demonstrating the variability when treatment is with unconventional cytotoxic agents, without plasma exchange.

A major ethical question was whether our patient revoked her decision regarding her DNR/DNI status under the stress imposed by her deteriorating condition. Fortunately, we did not have to make a decision in this regard as the patient's condition improved, but this issue could clearly have posed an interesting ethical and legal challenge.

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