An autopsy-based retrospective study of secondary thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a disseminated form of thrombotic microangiopathy. Formation of disseminated microthromboembolism is believed to be causative for TTP. When TTP occurs in association with other disorders it is regarded as secondary TTP. To investigate the clininco-pathologic findings of secondary TTP, we performed a retrospective autopsy-based study

Thrombotic thrombocytopenic purpura (TTP) is a disseminated form of thrombotic microangiopathy. TTP usually occurs in apparently healthy people, and it is believed that thrombotic lesions give rise to the characteristic manifestations of TTP. This type of disease is regarded as primary TTP. Inhibitors of von Willebrand factor (vWF)-cleaving protease and presence of unusually large vWF (UlvWF) multimers were reported as factors associated with the pathogenesis of primary TTP.[1] Plasma exchange is usually an effective treatment for primary TTP.[2] However, the syndrome is sometimes associated with other disorders such as infection and cancer. In this case it is regarded as secondary TTP. UlvWF is rarely observed in secondary TTP,[3] and plasma exchange is not effective.[4] The thrombotic microangiopathy in secondary TTP may not be identical in pathophysiology to that in primary TTP. We performed a retrospective autopsy-based study to clarify the clinicopathologic features of secondary TTP.

We reviewed all of the 1,043 autopsy protocols of patients who were admitted to our hospitals between 1980 and 1999. Six were diagnosed as having had secondary TTP. It is sometimes difficult to differentiate between hemolytic uremic syndrome and TTP. In general, the term TTP is preferred for cases in which neurologic dysfunction predominates, whereas cases involving predominantly renal damage are diagnosed as hemolytic uremic syndrome.[5] In the six patients, neurologic signs and thrombocytopenic purpura were predominant, and renal dysfunction was mild. They were therefore diagnosed as having TTP. The levels of von-Willebrand factor and factor VIII activity were markedly elevated in all of the samples, but UlvWF was not detected in any of them. Their clinical and pathologic characteristics are shown in Table 1. Pathologic findings were striking in that generalized thrombosis was not observed in any of the six patients. These findings were in contrast to those in patients with primary TTP. While four patients had thrombotic lesions in a variety of organs including the kidney (n=3), lung (n=1), spleen (n=1), bladder (n=1), brain (n=1) and colon (n=1), no thrombotic lesions were found in the other two patients despite thorough post-mortem examination. Lymphocyte infiltration into the vascular walls was observed in the kidney (patient #4), and demyelinating lesions with lymphocyte infiltration were observed in the brain (patient #3).

While thrombi might have disappeared as a result of intensive treatment, it is interesting that generalized thrombotic lesions were not observed in any of these patients. Although the presence of endothelial damage was supported by the marked elevation of vWF and factor VIII activity levels,[6] the autopsy findings suggest that the formation of thrombi resulting in vessel occlusion might not be essential in the pathogenesis of secondary TTP. Interestingly, symptoms of secondary TTP improved transiently with the administration of vincristine in the two patients who had pathologic evidences of lymphocyte infiltration in the brain and the kidney (patients #3 and 4). These pathologic changes might produce similar signs to those of primary TTP. Precipitating events in some cases of secondary TTP might be immune-mediated vasculopathy or myelinopathy. Pathologic examination directed towards the detection of thrombotic lesions is occasionally not useful for the diagnosis of secondary TTP.

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Table 1. Clinicopathologic findings of the six patients who were diagnosed as having secondary TTP.

No.	Age	Sex	Underlying diseases	Clinical features*	Interval between the day of diagnosis and that of autopsy (days)	Treatment	Pathological findings of secondary TTP				
							kidney	brain	heart	liver	other organs
1	15	F	dermatomyositis	fulfilled	2	plasma exchange (once), glucocorticoid	multiple thrombi	multiple thrombi	none	none	Multiple thrombi were found in arterioles of spleen and bladder.
2	62	F	autoimmune-induced angiitis	fulfilled	8	FFP°, glucocorticoid	none	none	none	none	none
3	75	F	lymphangioedema	fulfilled	29	plasma exchange (14times), FFP (10 units), glucocorticoid, vincristine	none	demyelinating lesions with lymphocyte infiltration	none	none	Several thronbi were found in colon and lung.
4	45	M	bone marrow transplantation for chronic myelocytic leukemia	fulfilled	52	plasma exchange (22 times), glucocorticoid, vincristine	multiple thrombi, lymphocyte infiltration of the vascular walls	none	none	none	none
5	60	F	dermatomyositis	fulfilled except for fever^	12	plasma exchange (5 times), FFP (70 units), glucocorticoid	multiple thrombi and red cell fragmentation.	none	none	none	none
6	64	M	liver cirrhosis, hepatocellular ca.	fulfiled	20	plasma exchange (10 times), FFP (67 units)	none	none	none	none	none

**The clinical features of TTP include thrombocytopenia, microangiopathic hemolytic anemia, fluctuating neurological symptoms, renal dysfunction and fever. ^The patient received gulcocorticoid for polymiositis at the onset of TTP . °FFP as fresh frozen plasma.*

Key words: TTP, microangiopathy.

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