

Sudden Cardiac Death in Thrombotic Thrombocytopenic Purpura — —  
A Case Report and Review of the Literature

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Abstract

A 54-year-old man with thrombotic thrombocytopenic purpura ( TTP ) who developed sudden cardiac death is described. The clinical presentations of this case were typical including thrombocytopenic purpura, fever, neurologic deficit and renal abnormalities. On admission, plasma exchange was started soon after the diagnosis of TTP was made. Unfortunately, his condition deteriorated and went into a rapid outcome of death. The causes of mortality were discussed. We found that the reasonable cause of sudden death may be cardiac involvement of TTP. On the other hand, appearance of torsades de pointes during the therapy with plasma exchange could be considered as a contributing factor of his mortality. Understanding a high risk of sudden cardiac death in TTP and the possibility of lethal arrhythmia present in plasma exchange underlines the importance of early diagnosis, immediate treatment and prophylactic therapy in plasma exchange. ( J Intern Med Taiwan 2002;13:154-159 )

Key Words : Thrombotic thrombocytopenic purpura; Sudden cardiac death; Torsades de pointes; Hypocalcemia; Plasma exchange

Introduction

Thrombotic thrombocytopenic purpura ( TTP ) is an acute, uncommon and diffuse disorder resulting from occlusion of small arterioles and capillaries by microthrombi. It is defined as a pentad consisting of microangiopathic hemolytic anemia, thrombocytopenia, nonfocal neurologic abnormalities, renal function impairment and fever. TTP could involve many organs, most commonly the adrenals, heart, kidney, brain and pancreas 1,2. It carries a high fatality rate if untreated or delayed therapy. To our knowledge, previous reports described that cardiac involvement of TTP may cause myocardial damage, arrhythmias, and even sudden cardiac death. However, there has been no report stating that if sudden cardiac death could be induced by the treatment with plasma exchange, a principal management of TTP. Herein we describe

a case of TTP resulting in rapid death under therapy of plasma exchange. The causative factors of his mortality were discussed. We reckon that both the cardiac involvement of TTP and lethal torsades de pointes caused by hypocalcemia, a complication of plasma exchange should be the reasons.

#### Case report

A 54-year-old Taiwanese man presented to our emergency department with 3 days of gross hematuria and general weakness. He has been very well in the past. About one week before admission, the patient had the symptoms of dizziness, abdominal discomfort and fever. Urinary tract inflammation and severe anemia were told at local clinics.

At presentation, he was noted to be mild febrile, mild stupor in mental status and acute ill-looking in general. His blood pressure was 122/72 mmHg and pulse rate was 77 beats per minute. His respiratory rate was 19 beats per minute and body temperature was 37.2°C. Physical examination revealed anemic conjunctivae and petechiae on his lower trunk area. Cardiopulmonary examination was normal and abdominal examination showed hypoactive bowel sound with mild diffuse tenderness. Neurological examination demonstrated no special focal deficit but with disturbed consciousness. Laboratory investigations showed severe normocytic, normochromic anemia ( hemoglobin = 7.0 g/dL ) and thrombocytopenia ( platelet count =  $11 \times 10^9/L$  ) with normal white blood cell count ( including differentials ). The blood reticulocyte count was 2.0% ( normal, 0.5-1.5% ). Impaired renal function with blood urea nitrogen 26 mg/dL and serum creatinine 1.8 mg/dL was noted. His serum albumin level was 3.9 g/dL and total protein level was 6.3 g/dL. His serum total bilirubin level and lactate dehydrogenase were elevated ( 2.2 mg/dL and 1328 U/L, respectively ). Other serum biochemistry including sodium, potassium, calcium, phosphorus, alkaline phosphatase, glucose and liver enzymes were within normal values. Urinalysis showed protein, 100 mg/dL; bilirubin, negative; occult blood, 3+; white blood cell count, 4 to 6/high power field; red blood cell count, 3+/high power field. On the chest X-ray, neither cardiomegaly nor active lung lesion was noted. The electrocardiogram ( ECG ) showed no special abnormalities. Renal sonography revealed normal size of kidneys with uneven increased echogenicity of both renal cortices. Direct and indirect Coombs' tests revealed negative results. We examined his peripheral blood smear and it showed many fragmented red blood cells. Bone marrow aspiration and iliac-crest bone biopsy showed neither blast excess nor evidence of malignancy. The megakaryocytes showed increasing in number and mitotic figures and some micromegakaryocytes. The diagnosis of TTP was made on the basis of biochemical and clinical findings. Soon after admission to the intensive care unit, treatment with plasma exchange was started. We performed the plasma exchange of

higher volume ( 30ml/kg ) with fresh frozen plasma daily.

During the course of plasma exchange, hypocalcemic status was noted ( serum total calcium level was 6.8 mg/dL and free calcium level was 3.8 mg/dL ) and calcium supplement was prescribed. ECG monitoring showed sinus bradycardia sometimes during the treatment. The clinical manifestations including thrombocytopenia, neurological deficit and renal dysfunction did not improve under this adequate therapy. Five days later, his consciousness level deteriorated and intracranial hemorrhage was suspected. Brain computed tomography revealed no definite acute intracranial parenchymal hemorrhage or infarction. We checked his electrolytes and found hypocalcemia was present ( serum total calcium level was 7.0 mg/dL and free calcium level was 3.5 mg/dL ). Calcium supplementation was restarted.

Unfortunately, the patient became comatous and hypotensive. Elevated cardiac enzyme was noted. Echocardiogram revealed general hypokinesia of the heart without pericardial effusion. ECG monitoring showed bradycardia with QT prolongation then torsades de pointes. Immediate direct-current cardioversion was done with partial response. The patient soon suffered from torsades de pointes again and asystole that did not respond to inotropic agents and resuscitation attempts and ended up with mortality.

#### Discussion

Thrombotic thrombocytopenic purpura is an uncommon hematologic syndrome characterized by the clinical pentad of microangiopathic hemolytic anemia, thrombocytopenic purpura, non-focal neurological signs, renal abnormalities and a febrile course. It is a life-threatening, sometimes suddenly fatal disorder of unknown etiology. Children are rarely affected and women are more common than men<sup>1</sup>. The main clinical presentations of TTP include petechiae, palpable purpura, ecchymoses, and hemorrhage of gastrointestinal tract, upper respiratory tract, or genitourinary tract. Other symptoms, signs and physical findings of TTP are fever, headache, nausea, abdominal discomfort, jaundice, weakness, neurologic deficit, hepatosplenomegaly and renal dysfunction<sup>1,2</sup>. Clinical features of microangiopathic hemolytic anemia and thrombocytopenic purpura should be sufficient diagnostic criteria since other findings are not always present<sup>2,3</sup>. The clinical manifestations of our case were typical: severe thrombocytopenia with hematuria, anemia, fever, neurologic deficit and renal function impairment all were present. The peripheral blood smear, showing numerous fragmented red blood cells, confirmed the diagnosis of TTP. Negative finding in bone marrow examination and Coombs' test ( direct/indirect ) could rule out other related hematologic disorders. TTP is a diffuse disease and it affects multiple organ systems. In addition to manifestations in central

nerve system and kidney, involvement of the heart, spleen, pancreas, adrenals and other organs is well described 4. Cardiac involvement has been documented in some necropsy studies references. Furthermore, it seems that cardiac involvement in the course of TTP is a constant autopsy finding 5. It may lead to myocardial necrosis, myocarditis, myocardial hemorrhage, conduction system defects, arrhythmias, signs and symptoms of coronary artery occlusion, and even sudden death 2, 4-7. We reviewed previous literatures which had reported sudden cardiac death in patients with TTP and summarized the duration, clinical presentations and ECG findings of all patients ( including our reported case ) in the tabulation ( Table 1 ). Wajima et al 2 reported a patient with TTP who developed to a rapid outcome of death caused by coronary artery microthrombi. Podolsky et al 4 described a fatal case of TTP in a patient who presented with signs and symptoms of diffuse myocarditis. The autopsy findings showed that multiple macroscopic and microscopic areas of hemorrhagic necrosis were present in the myocardium of left and right ventricles. Webb et al 5 reported four patients with TTP who developed severe cardiac dysfunction. Three of them got improvement in cardiac function with treatment of the underlying hematologic disorder, but the other one died because of extensive intramyocardial and subepicardial confluent hemorrhages. Ridolfi et al 6 studied the relation between the heart lesions of TTP and clinical cardiac dysfunction in 17 autopsied patients. Some of whom had symptoms suggestive of congestive heart failure before death and all patients had cardiac arteriolar microthrombi or petechial hemorrhages. Geisinger et al 7 reported a patient with TTP who died suddenly secondary to an arrhythmia induced by diffuse myocardial hemorrhage. The pathological findings showed that patient's myocardium contained massive confluent hemorrhages in the walls of all four chambers and the interventricular septum. According to the previous reports aforesaid, it appears that the cardiac involvement of TTP is caused by the presence of microthrombi leading to arrhythmia, heart failure or sudden cardiac death. A spectrum of cardiac involvement may be dependent on the degree and distribution of microvascular compromise 2,5. However, these pictures are not pathognomonic lesions of TTP and can be found in many conditions that simulate TTP, such as disseminated intravascular coagulation, hemolytic-uremic syndrome, systemic lupus erythematosus, paroxysmal nocturnal hemoglobinuria, vasculitis, and microangiopathic hemolytic anemia 2. In our case, the patient developed cardiopulmonary arrest with unsuccessful response to resuscitation attempts and ended up with mortality. Before his death, the elevated cardiac enzyme and echocardiogram finding could show that the cardiac involvement of TTP was present. Bell et al 1 stated that microvascular involvement of the heart and cardiac conduction system is the most common mechanism of sudden death in TTP. Therefore, we reckon

that TTP with heart involvement could be a causative factor of patient's sudden cardiac death, though the postmortern examination was not performed. Treatment of TTP includes anti-platelet agents, high doses of glucocorticoids, combination of chemotherapy and plasma exchange. Plasma exchange is now the treatment of choice due to apparent good results. Exactly how plasma exchange works is not well known. It may remove some substance in plasma that facilitates platelet aggregation or, alternatively, it may replace a factor abnormally absent from plasma 5,8. This procedure should be initiated as soon as the diagnosis is made. In our case, the diagnosis of TTP was early established and plasma exchange was started without delay. However, the patient developed to a fatal result. Was sudden death of the patient associated with the treatment of TTP---plasma exchange? Mokrzycki et al 9 described that the most frequent complications of plasma exchange were symptoms of hypocalcemia, hypovolemia, and anaphylactoid reactions. The incidence of hypocalcemic symptoms could be lowered with the prophylactic administration of calcium. Our patient had been in hypocalcemic status during treatment with plasma exchange even though calcium supplement was prescribed. Before his death, the ECG finding showed bradycardia with QT prolongation then torsades de pointes. Torsades de pointes is a unique and polymorphic form of ventricular tachycardia that usually occurs in the presence of prolonged QT interval. The QT prolongation may be either congenital or acquired. Previous reports stated that etiologies for the acquired form of QT prolongation include hypokalemia, hypomagnesemia, hypocalcemia, starvation, sick sinus syndrome, atrioventricular block and drug effect. Medications that have been implicated comprise of most antiarrhythmic agents, some nonsedating histamine blockers, erythromycin, ketoconazole and others 10,11. Reviewing medications prescribed for our reported patient, there was no special drug aforementioned that could cause QT prolongation. Result of brain computed tomography excluded the presence of intracranial lesion. The reasonable causality of the appearance of torsades de pointes was hypocalcemia induced by plasma exchange. Therefore, we think that hypocalcemia, namely, complication of plasma exchange may contribute to sudden cardiac death.

In conclusion, TTP is an uncommon disorder that carries a high fatality rate. Its cardiac involvement is always present by several autopsied studies and could lead to many heart damage including sudden cardiac death. On the other hand, the mainstay of management of TTP--- plasma exchange may induce complication of hypocalcemia that causes lethal arrhythmia, torsades de pointes. Awareness of this uncommon syndrome together with its high risk of sudden cardiac death underlines the importance of early diagnosis and immediate treatment 2,12. Furthermore, complications of plasma exchange during treatment of TTP should be considered and

prophylactic therapy must be initiated. By doing these, we believe, could improve the prognosis and survival of these patients.

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血栓性血小板低下紫斑症造成突發心臟性死亡 —— 一病例報告及文獻回顧

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## 摘 要

本篇報告描述一位五十四歲男性患有血栓性血小板低下紫斑症而造成突發心臟性死亡的病例。此血栓性血小板低下紫斑症病例的臨床表現非常典型，包括血小板低下紫斑、發燒、神經受損及腎功能異常。入院後，診斷此症確定即刻施予血漿置換術治療。病人經過治療後情況沒有好轉，最後造成突發心臟性死亡。本文討論其造成心臟性死亡的原因，並參考之前文獻報告，發現血栓性血小板低下紫斑症影響心臟器官乃其產生突發性死亡的合理解釋。另一方面，在施予血漿置換術治療期間產生的致命性心律不整，亦認為是一項促因。在瞭解血栓性血小板低下紫斑症產生突發心臟性死亡的高危險性及血漿置換術治療期間產生致命性心律不整的可能性之後，醫者應注重對此症的早期診斷、早期治療與施予血漿置換術治療期間的預防性處置。

Table 1. Presentations of patients with TTP died in sudden cardiac involvement

Authors	Age& Sex	Duration	Clinical presentations	ECG findings	Treatment
Ridolfi et al	29/F	6 weeks	petechiae, others: unknown	atrioventricular dissociation, bradycardia	unknown
	41/F	7 days	petechiae, dyspnea	acute bradycardia	unknown
Bell et al	24/F	2 days	unknown	not available	unknown
	37/M	3 days	petechiae, others: unknown	not available	unknown
Geisinger et al	20/F	6 days	fever, headache, petechiae, convulsions	acute cardiac arrest	dipyridamole, aspirin, prednisone
Wajima et al	59/M	1-2 days	petechiae, chest pain, consciousness change	bradycardia, ST elevation	no
Webb et al	29/F	few weeks	unknown	electro- mechanical dissociation	plasma exchange, steroids, antiplatelet
Podolsky et al	47/F	4-5 days	gross hematuria, petechiae, fever, consciousness	QRS prolongation, electro-	supportive therapy

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			change	mechanical	
				dissociation	
present	54/M	2 weeks	fever, petechiae,	bradycardia,	plasma
			gross hematuria,	torsades de	exchange
			consciousness	pointes	
			change		

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