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Acute Respiratory Distress Syndrome as a Major Clinical Manifestation of Thrombotic Thrombocytopenic Purpura

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ABSTRACT: *Background:* Although the classical triad of thrombocytopenia, microangiopathic hemolytic anemia, and neurological changes has been well recognized, thrombotic thrombocytopenic purpura (TTP) sometimes presents with atypical clinical features. Some cases of acute respiratory distress syndrome (ARDS) were suspected to be a manifestation of TTP. *Methods:* We examined retrospectively the medical records of patients with known TTP from 1981 to 1998. The patients who developed ARDS simultaneously with TTP were identified. Clinical, laboratory, and other pertinent data were reviewed; the clinical outcome was documented. *Results:* Seven out of 56 patients with an established diagnosis of TTP were identified as having ARDS. All 7 patients had progressive dyspnea, persistent hypoxemia with diffuse pulmonary infiltrates, and no evidence of localized pneumonia, pulmonary emboli, congestive heart failure, or other identifiable lung diseases. In addition to ARDS, 4 patients developed progressive neurological (mental) changes, 3 developed fever, and 2

developed renal failure. Six patients were treated with ventilatory support in the ICU. Upon establishing the diagnosis of TTP, 6 patients were treated with exchange plasmapheresis (EP) and 1 patient with an infusion of fresh frozen plasma. Within 2 days of initiation of EP, 4 patients showed marked respiratory improvement; shortly thereafter, mechanical ventilation was ended. Complete and long-lasting remission was achieved in all 4 patients. Three patients died because of delayed diagnosis and untimely employment of EP. *Conclusion:* Life-threatening ARDS can be associated with TTP. It is recommended that all patients with ARDS and unexplained thrombocytopenia be evaluated for unrecognized TTP. Early recognition of ARDS associated with TTP and timely EP is critical to a favorable outcome.

KEY INDEXING TERMS: Thrombotic thrombocytopenic purpura; Acute respiratory distress syndrome; Exchange plasmapheresis; Microangiopathic hemolytic anemia; Thrombotic microangiopathy. [Am J Med Sci 2001; 321(2):124-128.]

Classical cases of thrombotic thrombocytopenic purpura (TTP) are characterized by the pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurologic abnormalities, renal dysfunction, and fever.¹ A related disorder in children with renal failure caused by glomerular damage, in addition to thrombocytopenia and MAHA, has been named the hemolytic-uremic syndrome.² Also, another variant characterized by elevated liver enzymes, thrombocytopenia, and MAHA in association with pregnancy, has been called HELLP syndrome.³ Now, these syndromes are considered to be different clinical manifestations of a similar pathophysiologic process, and the term *thrombotic mi-*

croangiopathy has been proposed to include them in one pathophysiologic entity.⁴

The main pathologic features of proposed thrombotic microangiopathy are disseminated arteriolar capillary microthrombosis and thrombocytopenia, which are caused by the activation and aggregation of platelets and the adhesion to capillary endothelial walls.⁵ MAHA is the hematologic change, which is caused by red cell fragmentation from shear stress-altered endothelial surface because of arteriolar capillary microthrombi. Neurological, renal, and hepatic dysfunction is the manifestation of organ impairment caused by hypoxemia, which is in turn caused by extensive microthrombi in the particular organ. Other atypical manifestations of TTP, including pancreatitis,^{6,7} cardiac dysfunction,^{8,9} and skin gangrenes,¹⁰ have also been described. These conditions are considered to be the result of microthrombi in those organs.

Respiratory dysfunction has not been recognized as a major manifestation of either TTP or other thrombotic microangiopathy. In this article, 7 cases

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Table 1. Patient Clinical Data

Patient	Age (years)	Underlying Pathology	ARDS Onset	Days to diagnosis of TTP after ARDS	TTP Criteria ^a
1	68	Coronary artery disease and mitral and tricuspid valve insufficiency	6 days after 3 vessel CABG and valves replacement	2	TAN
2	57	Coronary artery disease	2 days after 3 vessel CABG	2	TA
3	43	Enterocutaneous fistula after bowel resection for Crohn disease	21 days after bowel resection ^b	1	TANF
4	72	Intestinal obstruction due to intestinal adhesions	5 days after lysis of adhesions	3	TAN
5	74	Probable <i>Legionella</i> infection	1 day after admission	9	TA
6	85	None, but admitted due to hemoptysis, fever and dyspnea	1 day after admission	1	TARF
7	77	Non-Hodgkin lymphoma	1 day after admission	2	TANRF

All patients were female.

CABG, coronary artery bypass graft.

^a T, thrombocytopenia; A, MAHA; N, neurologic changes; R, renal dysfunction; F, fever.

^b Readmitted after the intestinal surgery.

of acute respiratory distress syndrome (ARDS) associated with acute TTP are described. Clinical evidence that ARDS may be another manifestation of TTP is presented, and the possible pathophysiologic mechanism of ARDS occurring in TTP is discussed.

Patients and Methods

All identifiable cases of TTP seen at Good Samaritan Hospital in Dayton, Ohio, were carefully documented and recorded in the computer system retroactively to 1981. The medical records of all patients diagnosed with TTP simultaneously associated with ARDS between 1981 and 1998 were reviewed. The essential diagnostic criteria for TTP were unexplained thrombocytopenia and MAHA.¹¹ In some patients, additional clinical features, including neurological changes, renal dysfunction, and fever, were present. The causes of thrombocytopenia were evaluated, with an assessment of clinical history and findings, including previous history of thrombocytopenia, drug administration, blood transfusion, and presence of infection. Appropriate laboratory studies were also reviewed. Consumption coagulopathy was ruled out by normal fibrinogen level, prothrombin time, and activated partial thromboplastin time. Heparin-induced thrombocytopenia was excluded according to criteria described previously¹² and normal ¹⁴C serotonin release assay.¹³ Thrombocytopenia caused by such infections as sepsis and pneumonia was ruled out by appropriate examinations, including blood cultures and imaging studies.

The diagnosis of ARDS, when the data was available, was based on the guideline of the American-European Consensus Conference on ARDS.^{14,15} The criteria of the diagnosis for ARDS was as follows: (1) acute onset of respiratory distress; (2) bilateral pulmonary infiltrates seen on frontal chest radiographic examination; (3) pulmonary artery occlusion pressure (PaOp) equal to or less than 18 mm Hg when measured or lack of clinical evidence of increased left arterial pressure; and (4) impaired oxygenation as indicated by the decreased ratio of arterial-to-alveolar partial pressures of oxygen (PaO₂/PAO₂) equal to or less than 200.

Hematologic data reviewed were the hemoglobin, hematocrit, platelet count, reticulocyte count, lactic acid dehydrogenase levels, and haptoglobin levels. The reports of the peripheral blood film also were reviewed and blood smears examined when available. The degree of schistocytosis was estimated as follows¹¹: the score of 0 for less than 1% of schistocytes among red blood cells, 1+ for 1–2%, 2+ for 2–5%, 3+ for 5–10%, and 4+ for more than

10%. The treatments for TTP and final outcomes were recorded. Pathologic findings were reviewed from 1 autopsied case.

Results

There were 56 patients with the diagnosis of TTP between 1981 and 1998 in our institution. Among these patients, ARDS was the major clinical manifestation in 7 patients; in all of them, the diagnosis of ARDS was established before TTP. In 4 patients, ARDS developed as a surgical complication; the other 3 patients presented to the hospital with respiratory distress. In all of these patients, TTP was not considered initially. In fact, in all 7 patients, unexplained thrombocytopenia prompted hematologic consultations. Table 1 summarizes the patients' clinical characteristics. The age of the patients ranged between 43 and 85 years. All patients were women. Four patients developed ARDS after major surgeries: 2 after coronary artery bypass grafts and 2 after exploratory laparotomy and bowel surgeries. The others developed ARDS in association with, respectively, positive serology for *Legionella pneumophila*, sudden onset of hemoptysis, and chemotherapy for stage IV non-Hodgkin lymphoma. Two patients (patients 5 and 6) were admitted to the hospital because of increasing shortness of breath. The time to the diagnosis of ARDS was between 1 and 6 days from the date of admission or surgery, and the time to the diagnosis of TTP after the diagnosis of ARDS was between 1 and 9 days. ARDS was suspected on the basis of initial clinical picture and subsequently confirmed by radiographic and laboratory examination.

Table 2 shows physical, radiographic, and laboratory findings. Physical findings were nonspecific. Tachypnea was the main symptom and rales were present in the bilateral lungs. In radiographic and

Table 2. Patient ARDS Data

Patient	Respiratory Rate (bpm)	Auscultation of the Lung	Radiographic Chest Findings	PaOp (mm Hg)	PaO ₂ /PAO ₂ Ratio	Ventilatory Support
1	30	Bilateral diffuse rales	Left pleural effusion & infiltrate	12	279	Yes
2	V	Few rales	Bilateral diffuse infiltrate		127	Yes
3	24	Bilateral diffuse rales	Bilateral diffuse infiltrate	16	196	Yes
4	30	Bibasilar rales	Bilateral diffuse infiltrate	15	98	Yes
5	35	Bibasilar rales	Bilateral diffuse infiltrate	12	72	Yes
6	24	Bibasilar rales	Extensive bilateral infiltrate			No
7	40	Bilateral rales	Bilateral diffuse infiltrate		127	Yes

bpm, breaths per minute; V, on ventilator; PaOp, pulmonary artery occlusion pressure; PaO₂/PAO₂, arterial-alveolar difference in partial pressure of oxygen.

imaging studies, bilateral diffuse infiltrates were detected without well-defined pneumonia, evidence of pulmonary emboli, significant pleural effusion, or congestive heart failure. The pulmonary artery occlusion pressure (PaOp) was available in 4 patients. The values ranged between 12 and 16 mm Hg at the time of the diagnosis of ARDS. The PaO₂/PAO₂ ratio was between 72 and 279. The ratio was less than 200 in 5 patients. The consistent finding was persistent hypoxemia, even after administration of a high flow of oxygen. Six patients needed ventilatory support.

Table 3 shows the hematologic data. All patients had evidence of MAHA and unexplained thrombocytopenia when evaluated by a hematologist. The level of hemoglobin fluctuated because of multiple blood transfusions in all patients. However, the degree of anemia was moderate to severe and worsened during the postoperative period. The platelet count ranged between 10 and 100 × 10³/μL. The peripheral blood smear showed variable degree of schistocytosis as reported in the examination by technologists and hematologists. Schistocytosis, reticulocytosis, an elevated level of lactic acid dehydrogenase, and decreased haptoglobin level confirmed the diagnosis of MAHA in all 7 patients.

As soon as the diagnosis of TTP was established, as seen in Table 4, 6 patients were begun on exchange plasmapheresis and 1 patient was treated

with an infusion of fresh frozen plasma. Four of these patients showed significant clinical improvement of ARDS within 48 hours and eventually achieved complete remission of both TTP and ARDS. However, patient 7 required prolonged plasmapheresis. Three patients died because of untimely employment of exchange plasmapheresis; their ARDS was too advanced before the diagnosis of TTP. Over 3 years' follow-up after complete remission, none of 4 patients has had a relapse of TTP or ARDS.

An autopsy was performed on patient 3, who died of multiorgan failure 23 days after admission. Microscopic examination of the lung showed marked congestion, fresh hemorrhage within alveoli, and foci of pneumonia. Many of the alveolar blood vessels showed hemorrhage and some fibrinous materials occluding the lumen. However, no extensive hyaline fibrinoid deposits were noted in arteriolar capillaries, possibly because the patient had undergone 11 exchange plasmaphereses by the time of death.

Discussion

There have been reports of ARDS presenting as a clinical feature of TTP.^{16,17} One of our patients (patient 7) has been described in a case report.¹⁸ Our

Table 3. Patient Hematologic Data

Patient	Hemoglobin (g/dL)	Hematocrit	Platelets (×10 ³ /μL)	Reticulocytes (%)	Blood Smear (schistocyte)	LDH (U/L)	Haptoglobin (mg/dL)
1	8.4	.242	55	9.1	1+	757	<5
2	9.4	.282	29	5.7	2+	1391	
3	5.6	.170	100	3.2	3+	773	<5
4	8.6	.255	62	8.6	2+	697	65
5	9.1	.254	9	3.0	1+	1984	<5
6	9.5	.282	53	4.1	1+	1678	<5
7	9.0	.282	48	4.5	2+	375	8

Control values: hemoglobin, 14–18 g/dL (male), 12–16 g/dL (female); hematocrit, .40–.50 (male), .38–.45 (female); platelets, 140–440 × 10³/L; reticulocyte, 0.5–1.5%; haptoglobin, 20–150 mg/dL; schistocytes: 0, less than 1%; 1+, 1–2%; 2+, 2–5%; 3+, 5–10%; 4+, more than 10%.

Table 4. Patient Treatment and Outcome

Patient	Treatment Modality	Outcome
1	PE (4)	CR
2	PE (9)	CR
3	PE (11)	Died
4	PE (7)	Died
5	FFP infusion	Died
6	PE (15)	CR
7	PE (39)	CR

PE (no), plasma exchange (number of PE in days); CR, complete remission; FFP, fresh frozen plasma.

additional cases of ARDS associated with acute TTP and hematologic and clinical remission of both conditions after exchange plasmapheresis support the idea that ARDS may be a manifestation of TTP. In all 7 patients, the diagnosis of TTP was well established on the basis of characteristic hematologic findings and clinical picture. MAHA and thrombocytopenia were the cardinal features, and, in addition, fever, neurologic changes, and renal dysfunction were present in some patients. Additionally, persistent hypoxemia with diffuse pulmonary infiltrates and absence of pulmonary emboli, pneumonia, significant pleural effusion, congestive heart failure, and other lung diseases were consistent with ARDS. Reported cases followed a rapidly fatal course of ARDS when associated with TTP.^{16,17} An autopsy showed the classical multiorgan involvement with platelet aggregation and widespread hyaline occlusion of terminal arterioles and capillaries.¹⁷

ARDS is a descriptive term that has been applied to many acute, diffuse infiltrative lung diseases of diverse causes that have been accompanied by severe arterial hypoxemia.^{14,15} Despite various causes of ARDS, its clinical manifestation and respiratory pathophysiologic derangement is remarkably similar and, even in the best intensive respiratory care setting, the prognosis is poor once a fulminating course of ARDS is developed. A favorable outcome may be anticipated if the precise cause of ARDS is established at an earliest possible time and a specific treatment is rendered. Ventilatory support and correction of hypoxemia are important; however, without management of the underlying pathology, the recovery from ARDS is dependent upon correction of the pathologic process of pulmonary function through natural physiological adjustment.

Although a cause-and-effect relationship cannot be ascertained, because in our patients ARDS was simultaneously associated with acute TTP and also achieved a complete remission to exchange plasmapheresis in 4 patients, ARDS was suspected to be a manifestation of TTP. TTP might have resulted in extensive platelet microthrombi in the pulmonary alveolar capillaries and led to thrombocytopenia, persistent hypoxemia, and nonspecific diffuse pulmonary

infiltrate.¹⁸ However, the possibility that ARDS resulted in TTP through platelet activation and aggregation caused by acute inflammatory process cannot be ruled out. Nonetheless, the benefit of exchange plasmapheresis for both ARDS and TTP tend to support the contention that a common pathophysiologic mechanism is involved. Considering the life-threatening nature of ARDS, without exchange plasmapheresis, 4 more patients would have succumbed to ARDS alone, even without the complications of TTP.

The pathogenesis of TTP is still not well defined. However, recent studies have shed some light on the understanding of its pathogenesis. Documented findings are deficiency of a von Willebrand factor (VWF)-cleaving protease due to inhibitors^{19,20} and existence of unusually large von Willebrand factor (uLVWF) multimers in active patients with TTP.²¹ It is also known that the protease cleaves uLVWF multimers to smaller multimers; uLVWF multimers, if not cleaved, promote the aggregation of platelets.²² Accordingly, it is likely that endothelial cells that produce and store VWF contribute to the pathogenesis. When there is a disease or physical injury in the endothelial cells, uLVWF multimers are released into the circulation; these multimers, if the VWF-cleaving protease is deficient, induce the aggregation of platelets in the arteriolar capillaries. Undoubtedly, alveolar capillaries could also serve as the site of extensive microthrombi of platelets that can result in ARDS.

The most effective treatment for TTP is timely employment of exchange plasmapheresis.^{23,24} Theoretically, this treatment would replenish the deficient VWF-cleaving protease and remove the inhibitors of VWF-cleaving protease, such as its antibodies, if present, and additionally may remove uLVWF multimers. As observed in TTP, exchange plasmapheresis was an effective treatment for ARDS in our patients. Three patients died because the TTP was unrecognized until ARDS and TTP were too far advanced.

In conclusion, our experience suggests that ARDS may occur as a clinical feature of either de novo or secondary TTP; therefore, all patients with ARDS should be evaluated for unrecognized TTP. A high index of suspicion is crucial when a patient with ARDS presents with unexplained thrombocytopenia and MAHA, with or without neurological or mental changes. Because exchange plasmapheresis is a life-saving measure, unexplained thrombocytopenia and MAHA should be sufficient criteria to make the presumptive diagnosis of TTP for the initiation of exchange plasmapheresis.

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