CHEST

A 42-Year-Old Woman With Anemia, Shock, and Ischemic Stroke After Lung Transplantation

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VIDEO

CASE PRESENTATION: A 42-year-old woman with mixed connective tissue disease-associated interstitial lung disease underwent bilateral lung transplantation. She had an uneventful surgery and was extubated 3 h later. Induction immunosuppression therapy included methylprednisolone 500 mg intraoperatively, basiliximab (anti-IL-2 monoclonal antibody) on days 0 and 4 after transplantation, and methylprednisolone 125 mg intravenously bid for 2 days following surgery. Maintenance immunosuppression therapy consisted of prednisone 20 mg daily, mycophenolate mofetil 750 mg bid, and enteral tacrolimus 0.5 mg bid. Both the donor and the recipient were seropositive for cytomegalovirus. Infectious disease prophylaxis consisted of valganciclovir, trimethoprim-sulfamethoxazole, and voriconazole.

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On postoperative day 1, the patient developed a fever, leukocytosis (12,600/cmm), shock requiring vasopressor support, and acute renal failure. The antibiotic regimen of cefepime and vancomycin was broadened to include levofloxacin and inhaled tobramycin. A transthoracic echocardiogram on day 1 was consistent with distributive shock, with no wall motion or valvular abnormalities. On postoperative day 2, the patient developed anemia and thrombocytopenia requiring frequent transfusions over the next few days to maintain a hemoglobin level and platelet count $>$ 8 mg/dL and 80,000/cmm, respectively (Table 1). There was no evidence of intrathoracic or intra-abdominal hemorrhage according to a CT scan. Chest tube output was not sanguineous, and there was no evidence of overt GI bleeding. On postoperative day 3, she developed right-sided hemiparesis.

Physical Examination Findings

The patient was intubated and sedated. Examination revealed warm, well-perfused extremities with vital signs of BP of 84/60 mm Hg on vasopressors, heart rate of 120 beats/min, respiratory rate of 14 breaths/min, and an oxygen saturation of 95% on 50% F_{IO_2}. The neck examination showed no jugular venous distention. Auscultation of the lungs revealed coarse crackles in the infrascapular areas bilaterally. Cardiac examination revealed sinus tachycardia. Heart sounds were normal with no murmur, gallop, or rub. Neurologic examination revealed right-sided weakness.

Diagnostic Studies

Results of laboratory evaluations through postoperative day 5 are detailed in Table 1. Notably, the platelet count fell rapidly from a baseline of 182,000/cmm

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TABLE 1] Laboratory Findings

Variable	Day −1	Day 1	Day 3	Day 5	ECU Day 6
Lactic acid (0.3-1.5 mmol/L)		0.9	8.4	11.7	8.2
Hemoglobin (12.0-16.0 g/dL)	11.9	11.9	6.9	6.9	6.9
Platelet (150-450 10^3/cmm)	182	146	58	32	66
Total bilirubin (0-1.0 mg/dL)	0.1	0.1	0.3	2.4	2.8
INR (0.9-1.2)	1.1	1.4	1.7	1.9	1.8
aPTT (23-38 s)	27	27	46	78	153

aPTT = activated partial thromboplastin time; ECU = eculizumab; INR = international normalized ratio.

preoperatively to reach a nadir of 32,000/cmm on day 4 after surgery. Hemoglobin levels dropped from 11.9 g/dL preoperatively to 6.9 g/dL on day 3. Hemolysis evaluation included an elevated total and indirect bilirubin and lactate dehydrogenase, low serum haptoglobin level (< 10 mg/dL), and presence of schistocytes on peripheral blood smear. Fibrinogen level and activated partial thromboplastin time were normal; the international normalized ratio was mildly elevated at 1.4. Lactic acid levels peaked at 11.7 mmol/L. The patient had severe proteinuria (300 mg %) and hematuria (139 RBC/hpf) on urinalysis.

An MRI of the brain on day 3 demonstrated changes consistent with an early left middle cerebral artery (MCA) territory ischemic stroke. A transesophageal echocardiogram on the same day demonstrated 7- to 8-mm mobile vegetation on the atrial surface of the tricuspid valve (Fig 1A), small vegetation on the mitral valve, and mobile vegetation on the papillary muscle of the right ventricle (Fig 1B; Videos 1 and 2). Additional studies to investigate the cause of thrombocytopenia and cardiac thrombi revealed negative heparin-induced thrombocytopenia (HIT) antibodies. Similarly, an extended antiphospholipid antibody panel to check for IgG and IgM isotypes of anticardiolipin/aCL and anti-$\beta_2$glycoprotein 1 antibodies was negative. Serum complement protein C3 and C4 levels were 72 mg %

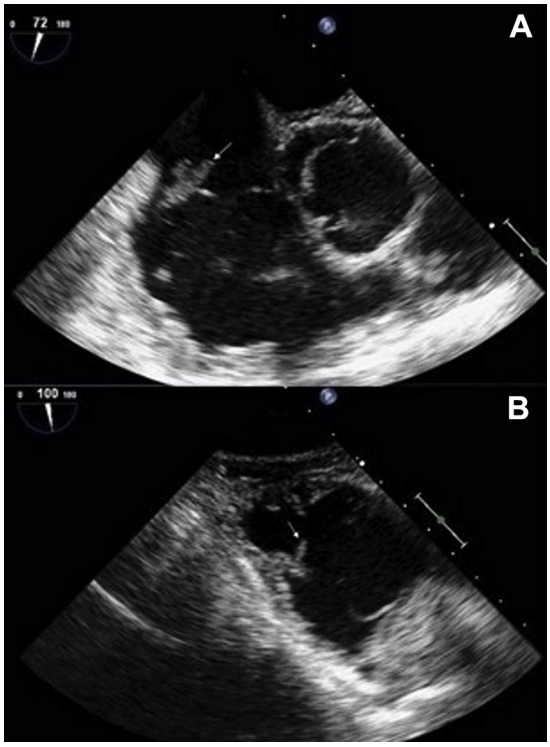

Figure 1 – *A, Mid-esophageal view at the level of the aortic valve with transesophageal echocardiography demonstrates a 7- to 8-mm mobile mass (arrow) attached to the atrial surface of the tricuspid valve. B, Transesophageal echocardiogram (transgastric right ventricular view) demonstrates a linear, independently mobile structure (arrow) attached to a papillary muscle in the right ventricle.*

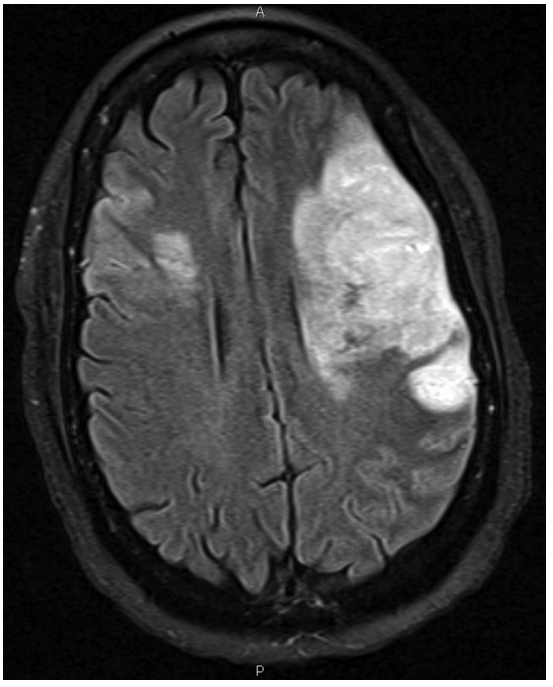

Figure 2 – *Diffusion-weighted MRI of the brain demonstrates restricted diffusion in the left middle cerebral artery vascular distribution consistent with evolution of infarction. New patchy areas of restricted diffusion can now be seen in the left thalamus, right caudate head, and right anterior middle cerebral artery vascular territory.*

(90-180 mg %) and 13 mg % (15-46 mg %) and CH50 of 54 complement activation enzyme immunoassay units (60-144), respectively, indicating complement consumption. The patient also had a normal ADAMTS13 level of 91% (normal value, $>$ 80%). A stool enzyme-linked immunosorbent assay for Shiga-like toxin antigen was negative.

A follow-up MRI 10 days later revealed evolution of the left MCA infarct but also new restricted diffusion in the left thalamus, right caudate head, bilateral cerebellar hemispheres, and right anterior MCA vascular territory; these findings indicate evolving multifocal infarctions (Fig 2).

What is the diagnosis?

Diagnosis: Atypical hemolytic uremic syndrome

Discussion

The occurrence of microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure, and the presence of thrombi in multiple organs is consistent with a diagnosis of thrombotic microangiopathy (TMA) syndromes. TMA is a broad term encompassing diverse syndromes, including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), and medication-induced TMA. These syndromes are united by common clinical and pathologic features of microangiopathic hemolytic anemia, intravascular thrombi, thrombocytopenia, and organ injury. TTP is characterized by endothelial injury associated with the formation of large multimers of von Willebrand factor in serum due to lack of ADAMTS13, the von Willebrand factor-cleaving protease. The ADAMTS13 deficiency is either genetic or secondary to the presence of ADAMTS13 inhibitor antibodies.

In the present case, a normal ADAMTS13 level excludes a diagnosis of TTP. Moreover, the rapid onset of symptoms in the postoperative period, the absence of diarrhea, and the extensive thrombus formation, along with a negative enzyme-linked immunosorbent assay for Shiga-like toxin antigen, are inconsistent with a diagnosis of HUS. The two remaining possibilities are medication-induced TMA and aHUS. The patient's symptoms started before the initiation of tacrolimus, and she had an undetectable serum tacrolimus level on the second day after transplantation, making the diagnosis of calcineurin inhibitor-induced TMA unlikely. Therefore, a diagnosis of aHUS seemed to be most plausible after careful exclusion of other possibilities.

The differential diagnosis for TMA is HIT, catastrophic antiphospholipid syndrome (CAPS), and disseminated intravascular coagulation (DIC). Negative HIT antibody and antiphospholipid antibody panel test results, in addition to the presence of extensive microangiopathic hemolytic anemia, exclude the diagnosis of HIT and CAPS in this patient. Similarly, DIC is characterized by consumptive coagulopathy and multiorgan failure in the setting of extensive surgery or septic shock; however, a normal serum fibrinogen level, persistent severe hemolysis, and the presence of large intravascular thrombi are inconsistent with this diagnosis.

aHUS is a rare condition (incidence of 2/1,000,000 in the United States) that results from uncontrolled activation of the alternate complement pathway and is characterized by microangiopathic hemolytic anemia, low platelet count (thrombocytopenia), the formation of intravascular platelet-rich thrombi, and multiorgan failure. Nearly 5% of all HUS cases are thought to be due to aHUS. There is both a familial (<20%) and a sporadic form of the disease. aHUS may rarely present as a potentially fatal complication after solid organ transplantation (SOT). Ischemia/reperfusion injury, use of calcineurin inhibitors (eg, tacrolimus, cyclosporine), and viral infections such as cytomegalovirus can precipitate aHUS after SOT. Other well-known precipitants for the sporadic form of atypical HUS include the following: HIV infection; cancer; organ transplantation; pregnancy; and the use of certain anticancer drugs, immunotherapeutic agents (eg, cyclosporine, tacrolimus), and antiplatelet drugs (eg, ticlopidine, clopidogrel).

aHUS commonly presents as TMA syndrome resulting from microvascular injury and thrombosis, leading to hypoxic organ failure as well as microangiopathic hemolytic anemia. Hemolytic anemia, thrombocytopenia, and renal failure are the hallmarks of this disease. The most common organ failure occurs in the form of acute kidney failure but in approximately 20% of cases, strokes, seizures, cardiac ischemia, and ischemic infarction of multiple organs such as the gut, liver, and distal extremities can be encountered.

The pathogenesis of aHUS is not well understood. An uncontrolled activation of the alternate complement pathway and endothelial injury are the cornerstones of this syndrome. Under normal circumstances, the alternative complement pathway is constitutively active as a result of spontaneous hydrolysis of C3 to C3b. Complement regulatory proteins (CRPs) such as complement factor H, complement factor I, and membrane cofactor protein work together to inactivate endothelial cell surface-bound C3b, thus protecting endothelial cells from complement attack. When this system is aberrant, C3b deposition on tissue increases, resulting in the formation of the C5b-9 terminal complement complex (membrane attack complex). Deposition of the membrane attack complex on the endothelium leads to a prothrombotic state through the exposure of subendothelial collagen, von Willebrand factor, and fibrinogen.

Various mutations of CRPs have been described in patients with aHUS. In addition to genetic abnormalities

in CRPs, a fraction of patients with aHUS may have a functional deficiency of CRPs due to the formation of antibodies, such as anti-complement factor H antibody, which accounts for about 10% of aHUS cases. Genetic defects account for only a fraction of aHUS cases. Therefore, the absence of these mutations does not rule out the diagnosis. The classic pattern of abnormality seen on complement testing is a low C3 and a normal C4 level. It is also well recognized that a normal C3 level does not rule out the diagnosis and could indicate dysregulated activation at the cell surface.

The first step toward a diagnosis of aHUS is identifying the TMA syndrome. Serum complement levels should be checked when aHUS is suspected. Other causes of TMA syndromes such as TTP, HUS, and medication effects should be eliminated. Other mimickers to consider in the differential diagnosis would be HIT, DIC, and CAPS.

Treatment options for aHUS include plasmapheresis (PPH) and targeted therapies to inhibit the terminal component of the complement cascade. Theoretically, PPH removes antibodies to CRPs and simultaneously replaces defective CRPs by adding fresh frozen plasma. However, the majority of available evidence supporting therapy with PPH was based on studies that included a heterogeneous group of patients, including those with TTP for which PPH is the treatment of choice. More recently, the use of eculizumab, a humanized monoclonal antibody that binds to C5, has gained significant interest for the management of aHUS. It works by blocking the cleavage of C5 to C5b, halting the formation of C5b and subsequently C5b-9. Current recommendations suggest that empiric PPH be started as early as possible, preferably within 24 h of diagnosis. However, if there is a persistence of hemolysis or lack of improvement in renal function after an appropriate trial of PPH, switching to eculizumab is then required. In view of a recent trial that demonstrated an impressive 80% TMA event-free status, eculizumab treatment can be considered as the new standard of care for patients with aHUS. Eculizumab has been successfully used in the management of aHUS after renal and heart transplantations wherein initial therapy with PPH had failed.

In general, the prognosis of aHUS varies widely based on the acuity of presentation and the degree of organ failure.

Clinical Course

A course of PPH was attempted in the patient. However, she could not tolerate this therapy due to hemodynamic instability and malignant cardiac arrhythmias. Thus, therapy aimed at terminal complement inhibition with an IV infusion of eculizumab (an anti-C5 monoclonal antibody) was initiated, which resulted in the prompt achievement of hemodynamic stability and almost complete resolution of hemolysis and platelet

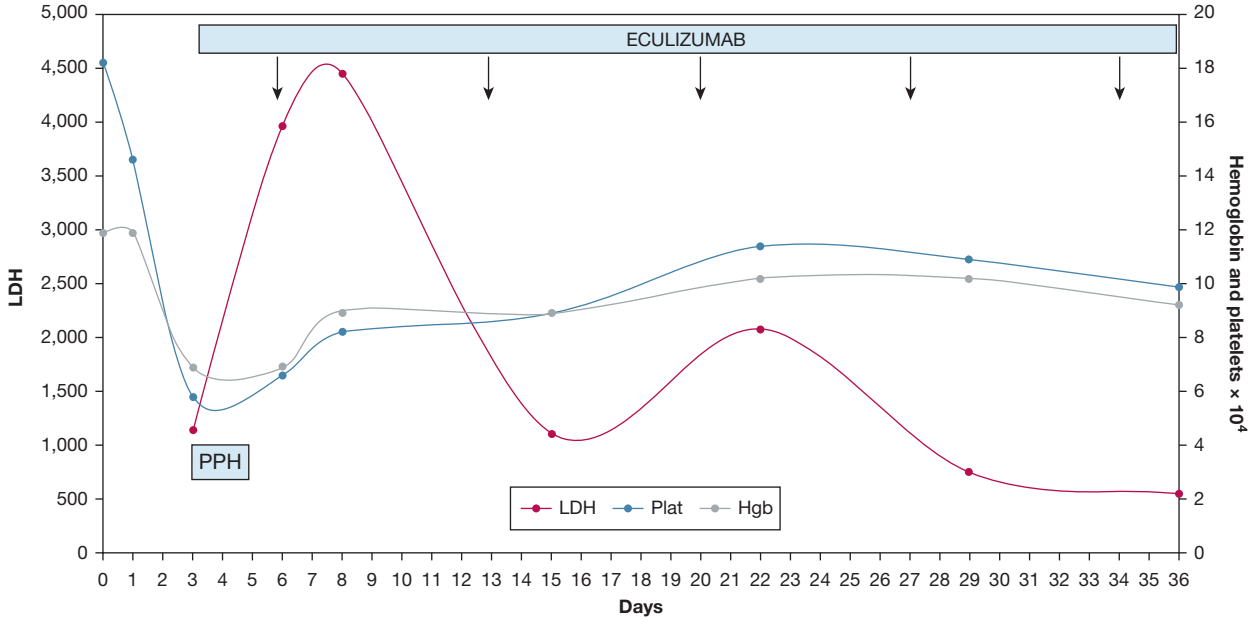

Figure 3 – *Evolution of changes in platelet count, hemoglobin level, and LDH levels after transplantation and stabilization following treatment with eculizumab. Hgb = hemoglobin; LDH = lactate dehydrogenase; Plat = platelets; PPH = plasmapheresis.*

destruction (Fig 3). Vasopressor support was discontinued in the next few hours, and the patient required no further blood product transfusion over the next few days. She received eculizumab infusions weekly for five doses with no further episodes of hemolysis or thrombocytopenia.

A repeat transesophageal echocardiogram 2 weeks after initiation of therapy with eculizumab was negative for any valvular vegetation. Unfortunately, the extensive embolic events caused irreversible CNS, renal, and extremity ischemic sequelae that resulted in cognitive and motor impairment, chronic renal failure requiring dialysis, and gangrene of the fingers and forefeet. The patient remained on mechanical ventilation due to an altered mental status and weakness. The introduction of calcineurin inhibitors was avoided to prevent precipitation of TMA.

Although the patient had no further evidence of hemolysis, consumptive coagulopathy, or new embolic stroke, she continued to be dialysis- and ventilator-dependent for the next 3 months. She did not have complete recovery of her neurologic function and died following 3 months of complications resulting from another episode of sepsis.

Clinical Pearls

1. *A combination of microangiopathic hemolytic anemia, thrombocytopenia, and intravascular thrombosis is a rare scenario encountered after SOT. The differential diagnosis includes HIT, TTP, HUS, DIC, CAPS, and aHUS. A systematic approach is necessary to identify the cause and to institute appropriate treatment in a timely fashion.*
2. *aHUS is the result of unchecked activation of a complement cascade. It can present as systemic inflammatory syndrome and TMA after stressful conditions such as SOT in patients with predisposed genetic susceptibility. Early identification and effective treatment are necessary to prevent morbidity and mortality associated with aHUS. Checking complement levels when suspicious can help in the early diagnosis of this condition.*
3. *Eculizumab is an effective treatment for syndromes caused by aberrant complement cascade activation such as seen in aHUS.*

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Additional information: The Videos can be found in the Supplemental Materials section of the online article.

Suggested Readings

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