

Hemolytic Uremic Syndrome

Dawn Camp-Sorrell, MSN, FNP, AOCN®

A.P., a 42-year-old woman, presented with rectal bleeding to her primary care physician. Endoscopic examination revealed a mass in the anal canal. Biopsy was positive for squamous cell carcinoma. A.P. underwent local excision and was established as stage II (T2N0M0). After surgery, she received 5-fluorouracil (FU) 1,000 mg/m² by continuous infusion on days 1–4 and on days 29–32, mitomycin-C 10 mg/m² days 1 and 29, and radiation therapy (4c500 cGY). Minimal nausea was the only side effect. A.P. achieved complete remission.

Approximately eight weeks after completing therapy, A.P. presented for an implantable port flush. The nurse noted that A.P. was pale, weak, and short of breath. A complete blood count (CBC) was obtained and revealed a hematocrit of 17.1% (normal range 37%–48%), hemoglobin of 4.9 (normal range 12.3–15.3 g/dl), and platelet count of 50,000 (normal range 150,000–450,000 cells/ml). A physical examination revealed paleness with generalized anasarca. A.P. was afebrile; her blood pressure was 180/100 mm Hg, pulse rate was 72, and respiration was 24. A.P. was admitted to the hospital for further evaluation and possible blood transfusion.

Other laboratory results included a serum creatinine 3.5 mg/dl (normal range 0.7–1.4 mg/dl), lactic dehydrogenase (LDH) 342 units/L (normal range 140–280 units/L), and serum haptoglobin < 38 mg/dl (normal range

60–270 mg/dl). Peripheral blood smear demonstrated prominent schistocytes with overall low blood cells. The coagulation profile was within normal limits. Mitomycin-C–induced hemolytic uremic syndrome (HUS) was diagnosed.

A.P. initially underwent plasmapheresis every other day with daily plasma infusions and IV methylprednisolone. Her blood pressure continued to increase and was treated successfully with a combination of antihypertensive agents, including a calcium channel blocker, an angiotensin-converting enzyme, and a beta blocker. Weekly erythropoietin-stimulating agent (ESA) injections were initiated. Within three weeks, A.P. had significant improvement of hematologic parameters and daily plasma infusion was stopped.

Plasmapheresis continued twice a week. A.P.'s blood pressure had stabilized. Unfortunately, her renal function continued to worsen and she was placed on renal dialysis three times per week with an initial creatinine of 5.6 mg/dl, potassium of 5.6 mEq/l, and LDH of 580 units/L. Symptoms improved with diuretic administration, and A.P.'s creatinine was maintained at 3.2 after one week on dialysis. After eight weeks in the hospital, A.P.'s hematologic parameters stabilized as well as her renal function on dialysis. She was discharged with close monitoring of her counts and continued dialysis three times per week.

What is hemolytic uremic syndrome?

HUS is a rare condition with a clinical triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. Thrombotic microangiopathy dominated by renal impairment usually is referred to as HUS. Systemic hypertension and noncardiogenic pulmonary edema commonly occur during the course of the syndrome. Variable signs of organ failure occur because of platelet thrombi in the microcirculation (Pisoni, Ruggenti, & Remuzzi, 2001).

Little is known about the disease. HUS was first described in 1924 (Wu et al., 1997; Zakarija & Bennett, 2005), but little nursing literature exists concerning risks and management. Because of the complexities identified with this syndrome, a cancer-associated HUS national registry was established in 1984 and ran through 1986 (Lesesne et al., 1989). The registry defined HUS as patients with hematocrit less than 25%, a platelet count less than 100,000, and a serum creatinine greater than 1.6 mg/dl. Clinical characteristics were common among 85 patients identified through the registry, including diagnosis of adenocarcinoma (particularly of the gastrointestinal tract), partial to complete tumor response from treatment, use of mitomycin-C, noncardiogenic pulmonary edema associated with blood product transfusions, and poor response to treatment of HUS with significant mortality.

Do You Have an Interesting Clinical Experience to Share?

Clinical Challenges provides readers with a forum to discuss creative clinical solutions to challenging patient care issues. Case studies or descriptions may be submitted with or without discussion or solutions. References, tables, figures, and illustrations can be included. Materials or inquiries should be directed to *Oncology Nursing Forum* Associate Editor Susan Moore, RN, MSN, ANP, AOCN®, at smoore46@yahoo.com.

Dawn Camp-Sorrell, MSN, FNP, AOCN®, is an oncology nurse practitioner at Hematology Oncology Associates of Alabama in Sylacauga. No financial relationships to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum or the Oncology Nursing Society.

Digital Object Identifier: 10.1188/08.ONF.593-596

Agents implicated in the pathogenesis of HUS include mitomycin-C, cyclosporine, quinine, ticlopidine, bleomycin, cisplatin, fluorouracil, gemcitabine, alpha interferon, and fludarabine (Muller et al., 2005; Pisoni et al., 2001; Wu et al., 1997). The most common chemotherapy agent reported to induce HUS is mitomycin-C, with a reported incidence of 2%–10% (Wu et al.).

What is the relationship of mitomycin-C to hemolytic uremic syndrome?

Mitomycin-C was approved in 1974 to treat a wide variety of malignancies, including gastric, pancreatic, renal, and anal carcinoma. Mitomycin-C is classified as an alkylating agent and is isolated from the broth of streptomyces and caespitosus. The first cases of mitomycin-C–induced HUS were described in 1985 by Cantrell, Phillips, and Schein. Several syndromes have been recognized describing mitomycin-C–induced issues, such as microangiopathic hemolytic anemia, cancer-related thrombotic thrombocytopenic purpura, mitomycin-C–induced nephrotoxicity, and chronic glomerular microangiopathy (Cantrell et al.).

What is the pathophysiology of hemolytic uremic syndrome?

Pathogenesis of mitomycin-C–induced HUS is not well understood. Tissues from renal biopsy and at autopsy show a thrombotic microangiopathic process. Pathology features include endothelial cell injury and development of platelet aggregatory immune complexes (Zakarija & Bennett, 2005). Mitomycin-C can cause direct damage to the kidney vascular endothelial cells and inhibit prostacyclin production, which results in promotion of platelet aggregation and microthrombi formation, predominately in the kidney vasculature, resulting in severe renal failure (Wu et al., 1997). Significant immune complex levels dissociated into antigen and antibody components have been found to be elevated in the serum of patients diagnosed with HUS (Lesesne et al., 1989).

What is the course of this syndrome?

Clinically, HUS can consist of variable combinations of microangiopathic hemolytic anemia, thrombocytopenia, renal failure, pulmonary edema, systemic arterial hypertension, and neurologic abnormalities (Wu et al., 1997). However, blood transfusions often will exacerbate any or all of these clinical abnormalities. Other clinical features include rash, fever, interstitial pneumonitis, hematuria, and proteinuria.

HUS typically occurs four to eight weeks after completion of mitomycin-C therapy; however, reports of HUS occurring

immediately following or up to nine months after treatment do exist (Wu et al., 1997). Incidences of mitomycin-C–induced HUS appear to be dose-related. A total cumulative dose of mitomycin-C greater than 40–60 mg increases the risk for HUS (Lesesne et al., 1989). Renal insufficiency usually is progressive and dialysis is required in almost a third of patients (Pisoni et al., 2001). The majority of patients will die from renal failure, with a median time-to-death of four weeks from the initial HUS presentation.

What are the presenting signs and symptoms?

The most common symptoms of HUS include anorexia, weight gain, weakness, fatigue, jaundice secondary to hemolysis, dyspnea, and neurologic issues (headache, confusion, hemiplegia, hemiparesis, or coma). Patients may experience anxiety or feelings of impending doom. A dry cough may be present in patients with pulmonary edema.

A review of systems and physical examination findings are vague; neither is definitively diagnostic of the syndrome. Patients may have generalized anasarca (soft tissue swelling or edema), pallor, and hypertension. Jaundice may be present in the dermis or sclera.

Abnormal breath sounds with scattered wheezing will be present with pulmonary edema.

How is hemolytic uremic syndrome diagnosed?

HUS is primarily diagnosed from laboratory findings (see Table 1), with the presence of schistocytes helpful in confirming the diagnosis (Gordon & Kwaan, 1999). The absence of coagulopathy with normal prothrombin time and normal partial thromboplastin time differentiates HUS from a diagnosis of disseminated intravascular coagulation. Rapidly declining renal function is noted with proteinuria and hematuria. A chest x-ray may be useful in detecting pulmonary edema or interstitial pneumonitis.

What is the treatment?

Interventions generally fail to control the syndrome and patients usually die from HUS rather than cancer. Administration of red blood cells (RBCs) and platelets usually produces a transient reversal of the anemia and thrombocytopenia; however, blood product transfusions often will cause an exacerbation of HUS as a result of rapid worsening of hemolysis and induce noncardiogenic pulmonary edema within a few hours after

Table 1. Laboratory Findings

Parameter	Laboratory Results	Description
Bone marrow	Usually normal	No effect on bone marrow function
Coagulation parameters	Normal	No effect on coagulation factors
Direct bilirubin	Increased	Reflects red blood cell hemolysis
Direct Coombs	Negative	Lack of red cell auto-antibodies
Hematocrit	Decreased, usually less than 25% in 40% of cases	Direct effect of hemolysis
Hemoglobin	Decreased, usually less than 6.5 mg/dl, in 40% of cases	Direct effect of hemolysis
Lactate dehydrogenase	Increased	Reflects intravascular hemolysis
Peripheral smear	Schistocytes, fragmented red blood cells, helmet cells	Result of fibrin and platelet deposits that shear red blood cells in microvasculature
Platelets	Decreased, usually less than 50,000 cells/ml	Direct effect of hemolysis
Renal biopsy	Thrombotic microangiopathy	Renal damage
Reticulocyte	Increased	Compensates for low red blood cells
Serum creatinine	Increased, usually greater than 2.5 upper limit of normal	Declining renal function
Serum haptoglobin	Decreased	Hemolysis process
Urinalysis	Hematuria and protein	Declining renal function

Note. Based on information from Gordon & Kwaan, 1999; Pisoni et al., 2001; Wu et al., 1997.

the initial transfusion (Lesesne et al., 1989). Subsequently, blood product transfusions are reserved for patients with life-threatening bleeding or markedly symptomatic anemia. Weekly ESA injections can enhance RBC production without causing HUS exacerbation (Catalano, Gianesini, & Fabbian, 2002). No reports have been documented regarding efficacy of oprelvekin in reversing thrombocytopenia.

Because elevated levels of circulating immune complexes may play a role in HUS, plasma therapy has been used to remove these complexes (Pisoni et al., 2001). Treatment is given every day to every other day according to the patient's hematologic parameters. The procedure usually normalizes the blood count but rarely reverses renal insufficiency. Plasma exchange usually is considered over high-volume plasma infusion because renal insufficiency and heart failure limit the amount of volume that can be infused. Renal dialysis eventually will be necessary to rid the body of waste products and reduce serum creatinine (Coppo et al., 2003).

Immunoperfusion to alter or deplete circulating immune complexes has been a promising treatment based on a hypothesis that HUS is related to the presence of the complexes that are believed to suppress the body's immune response. Immunoperfusion involves plasmapheresis with the reinfusion of plasma over a column of staphylococcal protein-A (SPA). SPA is a component of the cell wall of pathogenic *Staphylococci* that nonspecifically binds the Fc portion of the immunoglobulin G (IgG) molecule and is capable of binding to the complex forms of IgG molecules found in patients

Nursing Education Key Points

- Avoid using or over-inflating a blood pressure cuff.
- Avoid using a tourniquet.
- Avoid invasive procedures, such as bladder catheterization, venipunctures, and rectal temperatures.
- Apply pressure to venipuncture or implantable port sites for approximately five minutes.

Patient Education Key Points

- Reduce risk of trauma by maintaining clear hallways, using hand rails going up and down stairs, and avoiding physical activity that may lead to trauma.
- Wear shoes or thick-soled slippers during ambulation.
- Avoid sharp objects such as cutting with a knife or using a straight-edge razor.
- Avoid constipation and implement a bowel regimen.
- Call a healthcare professional for bleeding episodes or go directly to the emergency room.

Figure 1. Thrombocytopenia Precautions

- Avoid sudden changes in position such as sitting to standing.
- Ask for assistance with walking and self-care activities.
- Conserve energy and allow for frequent rest periods as needed.
- Eat a nutritionally balanced diet and use vitamins or mineral supplements as directed.
- Call a healthcare professional for symptoms related to anemia complications, such as shortness of breath, confusion, chest palpitations, or headaches.

Figure 2. Patient Education Key Points for Anemia

with HUS (Korec et al., 1986; Pisoni et al., 2001). After the patient undergoes immunoabsorption, plasma is then reinfused. As with plasma exchange, hematologic abnormalities usually normalize, yet rarely does the renal failure reverse.

Splenectomy may be considered in patients with disabling disease requiring frequent plasma therapy. Bilateral nephrectomy has been an option for patients with severe renal impairment in imminent danger of death from thrombocytopenia associated with refractory hypertension and hypertensive encephalopathy (Pisoni et al., 2001). Kidney transplantation may be an option for patients on chronic dialysis with normalized hematologic parameters.

What are the nursing implications with regard to hemolytic uremic syndrome?

Preventing HUS is extremely difficult because mitomycin-C often is the best or only chemotherapy option in certain cancers. During mitomycin-C administration, strict monitoring of the patient's renal function and the CBC for anemia and thrombocytopenia is important. Urinalysis is useful in detecting hematuria and proteinuria. Markers for microangiopathic process include monitoring LDH levels, reticulocyte count, and peripheral smears for the presence of schistocytes. When abnormalities are detected, mitomycin-C administration should immediately be discontinued. Patients should be monitored for several months following completion of therapy because HUS may occur at any time.

Monitoring and documenting the cumulative dose of mitomycin-C are important and consideration should be given to hold further mitomycin-C when the cumulative dose of 40 mg is reached. Nurses should cautiously administer blood products and monitor for complications. During plasmapheresis, nurses should monitor patients for fever, chills, nausea, or vomiting, and provide supportive care as needed. Although

rare, hypotension and bronchospasm can occur during plasmapheresis. Thrombocytopenic precautions should be instituted when platelets are less than 50,000 cells/ml to minimize the occurrence of bleeding (see Figure 1). Patient and family education should include interventions that may be beneficial with anemia (see Figure 2). Early recognition is vital to prompt treatment and hope for a full recovery.

Author Contact: Dawn Camp-Sorrell, MSN, FNP, AOCN[®], can be reached at onpdawn@bellsouth.net, with copy to editor at ONF Editor@ons.org.

References

- Cantrell, J.E., Phillips, T.M., & Schein, P.S. (1985). Carcinoma-associated hemolytic-uremic syndrome: A complication of mitomycin C chemotherapy. *Journal of Clinical Oncology*, 3(5), 723-734.
- Catalano, C., Gianesini, C., & Fabbian, F. (2002). Erythropoietin is beneficial in mitomycin-induced hemolytic-uremic syndrome. *Nephron*, 91(2), 324-326.
- Coppo, P., Bussel, A., Charrier, S., Adrie, C., Galicier, L., Boulanger, E., et al. (2003). High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. *Medicine*, 82(1), 27-38.
- Gordon, L.L., & Kwaan, H.C. (1999). Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the cancer patient. *Seminars in Thrombosis and Hemostasis*, 25(2), 217-221.
- Korec, S., Schein, P.S., Smith, F.P., Neefe, J.R., Woolley, P.V., Goldberg, R.M., et al. (1986). Treatment of cancer-associated hemolytic uremic syndrome with staphylococcal protein A immunoperfusion. *Journal of Clinical Oncology*, 4(2), 210-215.
- Lesesne, J.B., Rothschild, N., Erickson, B., Korec, S., Sisk, R., Keller, J., et al. (1989). Cancer-associated hemolytic-uremic syndrome: Analysis of 85 cases from a national registry. *Journal of Clinical Oncology*, 7(6), 781-789.
- Muller, S., Schutt, P., Bojko, P., Nowrousian, M.R., Hense, J., Seeber, S., et al. (2005). Hemolytic uremic syndrome following prolonged gemcitabine therapy: A report of four cases from a single institution. *Annals of Hematology*, 84(9), 621-622.
- Pisoni, R., Ruggenti, P., & Remuzzi, G. (2001). Drug-induced thrombotic microangiopathy. *Drug Safety*, 24(7), 491-501.
- Wu, D.C., Liu, J.M., Chen, Y.M., Yang, S., Liu, S.M., Chen, L.T., et al. (1997). Mitomycin-C-induced hemolytic uremic syndrome: A case report and literature review. *Japanese Journal of Clinical Oncology*, 27(2), 115-118.
- Zakarija, A., & Bennett, C. (2005). Drug-induced thrombotic microangiopathy. *Seminars in Thrombosis and Hemostasis*, 31(5), 681-690.

Clinical Highlights: Hemolytic Uremic Syndrome

Definition

Hemolytic uremic syndrome (HUS) is a clinical triad of acute renal failure (serum creatinine > 1.6 mg/dl), microangiopathic hemolytic anemia (hematocrit < 25%), and thrombocytopenia (platelet count < 100,000 cells/ml) (Lesesne et al., 1989).

Pathophysiology

The most common chemotherapy agent to cause HUS is mitomycin-C, which can cause a thrombotic microangiopathic process with endothelial cell injury and the development of platelet aggregatory immune complexes (Zakarija & Bennett, 2005). Mitomycin-C also can cause direct damage to the kidney vascular endothelial cells and inhibit prostacyclin production, resulting in promoted platelet aggregation and microthrombi formation, predominately in the kidney vasculature, leading to renal failure (Wu et al., 1997).

Risk Factors

Agents implicated in the pathogenesis of HUS include mitomycin-C, cyclosporine, quinine, ticlopidine, bleomycin, cisplatin, fluorouracil, gemcitabine, alpha interferon, and fludarabine (Muller et al., 2005; Pisoni, Ruggenti, & Remuzzi, 2001; Wu et al., 1997). A total cumulative dose of 40–60 mg of mitomycin-C increases the risk of HUS. The syndrome usually occurs four to eight weeks after completion of therapy.

Clinical Findings

The most common presenting symptoms of HUS include anorexia, weight gain, weakness, fatigue, jaundice, dyspnea, and neurologic issues. Patients may experience anxiety or feelings of impending doom. A dry cough may be present in patients who present with concurrent pulmonary edema.

Differential Diagnosis

Initially, HUS may appear to be from severe anemia or thrombocytopenia. Hemolytic anemia or disseminated intravascular coagulation can present with similar clinical features. Acute renal failure from dehydration may be suspected. Laboratory values will confirm HUS.

Treatment

Blood product transfusions often will cause an exacerbation of HUS and induce noncardiogenic pulmonary edema within a few hours of transfusion. Erythropoietin-stimulating agents have been found to be useful in restoring red blood cells without the use of transfusions (Catalano, Giancesini, & Fabbian, 2002).

Plasma therapy every day to every other day, according to the patient's hematologic parameters, can remove circulating immune complexes. The procedure usually normalizes the blood count but rarely reverses renal insufficiency. Renal dialysis is eventually necessary to reduce serum creatinine.

Immunoperfusion has been a promising treatment. Plasmapheresis is performed with the reinfusion of plasma over a column of staphylococcal protein-A. After the patient undergoes immunoabsorption, plasma is reinfused. Splenectomy, bilateral nephrectomy, and kidney transplantation may be options for patients with severe renal impairment.

Nursing Implications

Strict monitoring of patients' renal function and complete blood count for anemia and thrombocytopenia during mitomycin-C administration is important. Urinalysis is useful in detecting hematuria and proteinuria. Patients must continue to be monitored for several months following completion of therapy because HUS may occur at any

time. Nurses should monitor and document the cumulative dose of mitomycin-C and consideration should be given to hold further mitomycin-C when the cumulative dose of 40–60 mg is reached.

Nurses should monitor patients for fever, chills, nausea, and vomiting during plasmapheresis and provide supportive care as needed. Thrombocytopenic precautions should be instituted when platelets are less than 50,000 cells/ml to minimize the occurrence of bleeding. Educating patients and families about interventions that can minimize the effects of anemia may be helpful to reduce anemia-induced symptoms.

References

- Catalano, C., Giancesini, C., & Fabbian, F. (2002). Erythropoietin is beneficial in mitomycin-induced hemolytic-uremic syndrome. *Nephron, 91*(2), 324–326.
- Lesesne, J.B., Rothschild, N., Erickson, B., Korec, S., Sisk, R., Keller, J., et al. (1989). Cancer-associated hemolytic-uremic syndrome: Analysis of 85 cases from a national registry. *Journal of Clinical Oncology, 7*(6), 781–789.
- Muller, S., Schutt, P., Bojko, P., Nowrousian, M.R., Hense, J., Seeber, S., et al. (2005). Hemolytic uremic syndrome following prolonged gemcitabine therapy: A report of four cases from a single institution. *Annals of Hematology, 84*(9), 621–622.
- Pisoni, R., Ruggenti, P., & Remuzzi, G. (2001). Drug-induced thrombotic microangiopathy. *Drug Safety, 24*(7), 491–501.
- Wu, D.C., Liu, J.M., Chen, Y.M., Yang, S., Liu, S.M., Chen, L.T., et al. (1997). Mitomycin-C induced hemolytic uremic syndrome: A case report and literature review. *Japanese Journal of Clinical Oncology, 27*(2), 115–118.
- Zakarija, A., & Bennett, C. (2005). Drug-induced thrombotic microangiopathy. *Seminars in Thrombosis and Hemostasis, 31*(5), 681–690.