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Hemolytic-Uremic Syndrome in a Patient Receiving Mitomycin C and 5-Fluorouracil†

Glen R. Willie, MD,* Stanley M. Levy, MD,** Robert S. Michaels, MD,** and Richard M. Zirkin, MD***

Recently, an association was reported between a form of hemolytic-uremic syndrome and the use of adjuvant chemotherapy with mitomycin C and 5-fluorouracil. Our report presents the clinical course of a patient with this syndrome along with detailed renal pathological studies (including electron and immunofluorescence microscopy). This information is not available for most previous reports.

Hemolytic-uremic syndrome in the adult is often an illness of young women, associated with pregnancy or the use of birth control pills. It has also been associated in both sexes with many specific bacterial and viral illnesses. A third group of cases have no known predisposing factor, but some may have been related to earlier viral infections (1).

Recently, Gulati, et al (2) reported on two patients who received mitomycin C and 5-fluorouracil for epidermoid carcinoma, one of whom was free of detectable carcinoma when a previously unrecognized syndrome of hemolysis, thrombocytopenia, and uremia developed. Jones, et al (3) reported on two patients who received the same drugs as adjunctive chemotherapy after resection of gastric carcinomas; they developed the same syndrome, which was apparently exacerbated by transfusions. Both cases were fatal, and at autopsy no evidence of carcinoma was present. In an earlier report, Krauss, et al (4) probably observed this same syndrome. Two of 51 patients treated with the same drugs for recurrent or metastatic gastrointestinal cancer developed microangiopathic anemia, disseminated intravascular coagulation, and renal failure; one was free of tumor at autopsy. The authors speculated that either mitomycin C or metastatic carcinoma may have caused the syndrome. Since then, a few similar cases have been reported (2-7).

We wish to report an additional case of hemolytic-uremic syndrome associated with chemotherapy. The renal pathology, including glomerular electron microscopy and immune fluorescence microscopy findings, are detailed for the first time in this syndrome.

Case Report

A 74-year-old man had an abdominal-perineal resection for a mucin-secreting adenocarcinoma of the colon, which extended into the muscularis and had metastasized to one of six resected regional lymph nodes. His blood pressure was normal at that time, and otherwise he was robustly well. A liver scan was normal, and serial scans every three months remained normal.

He received adjuvant chemotherapy with mitomycin C, 20 mg/M² (day 1), and 5-fluorouracil, 1000 mg/M² x 5d, by continuous intravenous drip (days 1-5) on 35-42 day cycles. Mitomycin C was omitted on even cycles. The patient developed anemia, thrombocytopenia, proteinuria, and symptoms of congestive heart failure rather acutely two weeks after the seventh course. He was hospitalized and responded symptomatically to rest, digoxin, diuresis, and the transfusion of two units of packed erythrocytes; serum haptoglobin could not be detected. No further chemotherapy was given.

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Hemolytic-Uremic Syndrome with Mitomycin C and 5-FU

One month later, severe anemia and congestive heart failure recurred, and again the patient responded symptomatically to the same measures. The bone marrow was slightly hypocellular and showed absent iron stores, but the erythrocyte precursors that were present appeared active, and normoblasts were prominent. Serum folate, B12, and iron studies were normal. Review of his record showed gradual deterioration of renal function that began after the last course of chemotherapy (Table I). The patient was given iron and vitamins and started on prednisone (20 mg twice daily).

His final admission, one month later, was occasioned by pulmonary edema. He had noted progressive dyspnea for one week before he was admitted and had blood-tinged sputum one day before admission.

Physical examination: height 173 cm; weight 83 kg; blood pressure 205/90 mm Hg; pulse 120/min; afebrile. The patient was a well-developed, slightly obese white man who looked younger than his age. He was in no distress at rest. Rales were heard at both lung bases, and an S3 gallop was heard. The abdomen was soft and obese without tenderness, palpable mass, or organomegaly. His colostomy was well healed, and his stool was negative for occult blood.

The chest x-ray revealed moderate cardiomegaly and pulmonary edema. An electroencephalogram showed sinus tachycardia with nonspecific ST-T changes that did not differ from a previous record. Laboratory investigations revealed hemoglobin 8.2 g/dl; hematocrit 26%; mean corpuscular volume (MCV) 106 μm³; reticulocyte count 3.2%; leukocytes 9,200/mm³; platelets 85,000/mm³. A peripheral smear showed slight hypochromasia, marked anisocytosis, slight poikilocytosis, and 2+ fragmented forms, and a differential of 4% band forms, 80% neutrophils, 12% lymphocytes, and 4% monocytes. Urinalysis revealed specific gravity 1.006, pH 5, albumin 4+, 4 RBC, 1 WBC/HPF, few epithelial cells, and moderate granular casts. Serum calcium was 8.4 mg/dl; glucose 291 mg/dl; lactate dehydrogenase 650 U/L; SGOT 25 U/L; CPK 23 U/L; sodium 138 mEq/L; potassium 4.4 mEq/L; chloride 110 mEq/L; bicarbonate 17 mEq/L; and total bilirubin 0.7 mg/dl.

Other laboratory data obtained over the next several days included negative urine and blood cultures; prothrombin time of 11 seconds (control 12); activated partial thromboplastin time, 19.7 seconds (control 25-40); fibrin split products, negative on several occasions; a weakly positive, diffuse ANA pattern; alpha-feto protein, negative; negative Coombs test; 24-hour urinary protein, 900 mg and 1,500 mg; fibrinogen, 280 mg/dl and 250 mg/dl. Haptoglobin was found to be 19 (normal 50-175); total complement, C3 and C4 were all normal or slightly elevated. A radionuclide renal scan indicated decreased renal blood flow bilaterally, and a retrograde pyelogram was normal. A second bone marrow biopsy showed increased iron stores, 50% cellularity; all cell lines were represented and active. There were increased numbers of normoblasts, and no metastatic tumor was seen.

TABLE I
Chemotherapy-Associated Hemolytic-Uremic Syndrome
Laboratory Values Before Final Admission

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Hb (g/dl)</th>
<th>MCV (μm³)</th>
<th>Retic (%)</th>
<th>Platelets x1000</th>
<th>Creatinine mg/dl</th>
<th>Proteinuria (0-4+)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13.6</td>
<td>85</td>
<td>1.0</td>
<td>330</td>
<td>1.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12.6</td>
<td>94</td>
<td>.7</td>
<td>210</td>
<td>1.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5 + 2 weeks</td>
<td>11.3</td>
<td>91</td>
<td>1.7</td>
<td>126</td>
<td>1.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10.4</td>
<td>98</td>
<td>1.1</td>
<td>330</td>
<td>1.3</td>
<td>0</td>
<td>B12, folate, normal</td>
</tr>
<tr>
<td>6 + 2 weeks</td>
<td>10.9</td>
<td>98</td>
<td>1.4</td>
<td>1.1</td>
<td>1.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10.3</td>
<td>100</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7 + 2 weeks</td>
<td>6.7</td>
<td>102</td>
<td>4.2</td>
<td>107</td>
<td>1.9</td>
<td>4+</td>
<td>Haptoglobin = 0. Admitted with CHF; transfused</td>
</tr>
<tr>
<td>7 + 4 weeks</td>
<td>10.1</td>
<td>96</td>
<td>.8</td>
<td>88</td>
<td>2.4</td>
<td>2+</td>
<td></td>
</tr>
<tr>
<td>7 + 6 weeks</td>
<td>7.0</td>
<td>4.5</td>
<td>150</td>
<td>3.1</td>
<td>3.1</td>
<td>2+</td>
<td>Admitted with CHF; transfused</td>
</tr>
<tr>
<td>7 + 8 weeks</td>
<td>8.8</td>
<td>98</td>
<td>3.5</td>
<td>137</td>
<td>3.4</td>
<td>2+</td>
<td>Prednisone started</td>
</tr>
<tr>
<td>7 + 10 weeks</td>
<td>8.8</td>
<td>104</td>
<td>3.2</td>
<td>94</td>
<td>6.2</td>
<td>4+</td>
<td>CHF; final admission</td>
</tr>
</tbody>
</table>

CHF = Congestive heart failure
MCV = Mean corpuscular volume
The patient was treated with rest, fluid and dietary restrictions, digoxin, high dose steroids, and antacids. After four days, a chest x-ray indicated mild cardiomegaly, and resolution of pulmonary edema. Peritoneal dialysis was started. The hemoglobin fell to 6.2 g/dl over three days without evidence of bleeding, and the patient was transfused with two units of packed erythrocytes. The platelet count fell to 14,000 cu mm, and the patient was given 20 units of platelets from random donors. He remained in renal failure with poor urine output; steroids, peritoneal dialysis, red cell and platelet transfusions were continued. Mild glucose intolerance persisted.

Three weeks after admission, the patient vomited fresh blood and began passing melanotic stool, without hypotension. The bleeding was stopped by means of gastric lavage, nasogastric suction, and continued antacids. Two days later, the patient complained of abdominal pain. Slight rebound tenderness was noted. A peritoneal fluid stain showed gram-positive cocci in clusters and eventually grew out Staphylococcus aureus. The patient was treated with gentamycin and a cephalosporin. On the following day, when the platelet count was 5,000 cu mm, the patient was transfused with platelets again. The same day the patient became hypotensive, developed an idioventricular rhythm, and died.

An autopsy four hours after death revealed no gross or microscopic evidence of residual adenocarcinoma. There was acute focal peritonitis, probably related to the peritoneal dialysis, and focal hemorrhagic esophagitis and gastritis, with evidence of recent hemorrhage. An incidental unsuspected finding was a 2x2 cm aspergilloma in the right upper lung, without evidence of systemic aspergillosis. There was no evidence of generalized microthrombi in the extrarenal tissues.

The kidneys were of normal size and gross appearance, except for slight mottling of the cortical surface and small pelvic mucosal petechiae. Microscopically, the glomeruli were diffusely involved, with a lobular, hypocellular, ischemic appearance (Fig. 1). The capillary wall and mesangium were thickened, filled with a granular eosinophilic material. Some areas showed calcific deposits in degenerating glomeruli. Vascular changes of marked intimal fibroplasia, edema, and luminal narrowing were evident in all vessels, including the arcuate and interlobular arteries (Fig. 2). The tubules showed considerable change with nephronal atrophy and dilation of the tubular spaces. In some areas, the intact tubules exhibited hyaline droplet change of the cytoplasm. Jones' silver stain showed thickened capillary walls with occasional double basement membrane formation without silver-positive spikes. Congo red stain and thioflavin-s stains were negative for amyloid. A phosphotungstic acid hematoxylin stain for fibrin indicated occasional areas of positivity in and within the glomerular capillary walls. The Slidders-Dundee modification of Fraser-Lendrum stain for fibrin/fibrinogen was negative. Occasional glomeruli revealed foam cells and fragments of red blood cells in the capillary lumina.

Immunofluorescence studies performed on tissues frozen at the time of autopsy showed focal vascular IgC deposits, no IgA glomerular deposits, and occasional IgA tubular deposits. The mesangium stained focally for
IgM, and the vessels stained strongly for IgM in focal areas. C3 was seen only as weak, finely granular deposits along the tubular basement membranes. C4 was not seen. C1q was found in a moderately strong focal and segmental pattern in the mesangial areas. Fibrinogen deposits were found in the arteries and arterioles but not in the glomeruli; albumin staining was negative.

Electron microscopy revealed that the material stuffing the capillary walls in subendothelial locations and extending into the mesangium was loosely fibrillar (Figs. 3, 4) and accompanied by lipid-like material. The basement membrane was wrinkled in some areas.

**Discussion**

During life, the patient's renal diagnosis remained in some doubt. Hemolytic-uremic syndrome was tentatively diagnosed, but several laboratory findings were unusual. The anemia was not purely hemolytic, as the reticulocyte count never exceeded 5% (uncorrected). Hemolysis was indicated by 1) the peripheral smear (fragmented red cells and later nucleated red cells); 2) a rise in the reticulocyte count simultaneous with worsening anemia two weeks after the seventh chemotherapy cycle; 3) bone marrow examinations showing adequate cellularity and precursors; 4) haptoglobin levels always low and zero on several occasions; and 5) a moderate transfusion requirement without evidence for hemorrhage (until the preterminal stage). We attribute the low reticulocyte count to an incomplete marrow response secondary to the earlier chemotherapy and/or to high doses of vitamin C which he had received, which may reduce the apparent staining of reticulocytes.

Evidence for disseminated intravascular coagulation can often be found in the hemolytic-uremic syndrome by noting a prolonged prothrombin time and partial thromboplastin time, or low levels of fibrinogen. This finding is not constant, however, and depends upon relative rates of synthesis and consumption. We cannot explain the normal tests for fibrin split products, except that we measured these late in the illness when others have also found fibrin split products to be absent (7). Different clinical laboratories may also have different lower levels of detection. Coagulation tests were not prolonged nor fibrinogen levels low (when reported) in other cases of chemotherapy-associated hemolytic-uremic syndrome (2,3,5). Fibrin split products were documented in one case only (3).

The renal pathology at autopsy was interpreted as most compatible with the hemolytic-uremic syndrome. Similar findings may also be seen in only a few conditions, namely, in malignant hypertension, sclerodema kidney, thrombotic thrombocytopenic purpura, postpartum renal failure, severe eclampsia, and some cases of renal transplant rejection. Most of these diagnoses are easily excluded in our case on clinical or pathological grounds.

Cases of scleroderma kidney have been reported that occurred before clinical manifestations of the systemic disease were evident, but in our case no evidence for scleroderma was found in any other organ system at autopsy (8). Moreover, such brisk, persistent hemolysis and platelet consumption are not usually seen in scleroderma kidney or in malignant hypertension. The patient's blood pressure was as high as 200/90 only upon admission when he was overloaded with fluids due to his renal failure;
throughout his course he never had visual complaints or findings. Although hypertension may have aggravated the vascular process, we do not feel the overall clinical course can be ascribed to malignant hypertension.

Thrombotic thrombocytopenic purpura has similar renal anatomic abnormalities but clinically is associated during its course with fever and prominent neurological signs in over 90% of cases (9). Widespread microthrombi are usually found at autopsy.

At autopsy, a small undiagnosed aspergilloma was found. However, to our knowledge, no fungal infection has been associated causally with the hemolytic-uremia syndrome (10), and in this case we feel it was incidental. Thus, we believe this patient had a variant of the hemolytic-uremic syndrome.

The staining characteristics of the fluffy, fibrillar, fibrin-like material found in the capillary wall were the reverse of those usually seen in the hemolytic-uremic syndrome. Characteristically, fibrin in the glomeruli and vessel walls can be demonstrated in this condition only by immunofluorescent staining (10,11). Our immunofluorescent stain for fibrin in the glomeruli was totally negative (with positive controls). On the other hand, our phosphotungstic-acid-hematoxylin stain, while not absolutely specific for fibrin-fibrinogen, was positive, although only small portions of the massive deposits so stained. We do not know if these atypical reactivities of the fibrin-like material deposited in the renal microvasculature are typical of other chemotherapy-associated cases, since detailed pathological studies have not been previously reported in most cases. Our patient had a fairly indolent course over three months from first abnormal urinalysis to death. Perhaps, deposited fibrin was partially degraded in situ to a material no longer recognized immunologically as fibrin. By electron microscopy, the material appeared similar to fibrin, mixed with lipid-like material which might have been derived from platelets.

Mucinous adenocarcinoma (which can induce a hypercoagulable state) was suspected to be the cause of this patient’s illness before he died, but at autopsy no residual tumor was found. Mitomycin C, perhaps in combination with 5-FU, may have caused this syndrome. In addition to the literature cited by Jones, et al (3), we found an earlier reported case of hemolytic-uremic syndrome associated with 5-FU and mitomycin therapy, but in that case the syndrome was attributed to the bulk destruction of tumor by the chemotherapy (12). In our case, the bulk tumor was removed surgically, and there was never any evidence for recurrence. Thus, this mechanism is very unlikely in our case or in the other cases with no evidence of carcinoma at autopsy. It seems more likely that mitomycin C is somehow directly able to induce this syndrome. In one case report, only mitomycin C had been given (7). However, a previous report of three cases of renal toxicity secondary to mitomycin C (when given alone) noted only what appeared to be direct toxic effects on the glomeruli and tubules, and no pathological evidence of the hemolytic-uremic syndrome (13). The type of resulting toxicity may relate to the dosage schedule of mitomycin C.

Other unknown factors, or the combination with 5-fluourouracil, may promote a primarily endothelial (rather than tubular/glomerular) toxicity in some patients, triggering local activation of coagulation and the hemolytic-uremic syndrome. Although we did see tubular degeneration and atrophy in our case, it could have been secondary to the hemolytic-uremic syndrome and vascular damage. According to Churg (14), tubular degeneration is common, and more severe cases may progress to tubular necrosis. Some correlation seems to exist between the extent of necrosis and the unfavorable course of the disease (14).

Discovery of this association may provide the basis for the development of an animal model, perhaps even a primate model, which would greatly improve research progress and provide answers of direct benefit to patients with the hemolytic-uremic syndrome of other causes.

Finally, in an effort to provide guidelines for the oncologist who may be able to note early laboratory changes and discontinue mitomycin C and 5-FU before the full-blown syndrome develops, we reviewed the laboratory findings before the patient developed the acute hemolysis that occurred two months before his last admission. A mean corpuscular volume of 100 μm³, mild anemia, and trace proteinuria were noted at the beginning of the seventh and last cycle of chemotherapy (Table 1). Two weeks later, evidence of severe hemolysis was already present before any transfusions were performed. For several weeks before his acute episode of hemolysis, the patient’s MCV had been gradually increasing. Mild anemia and an increased MCV is a rather nonspecific finding which is common in patients undergoing chemotherapy, sometimes due to the reticulocytosis of marrow recovery, sometimes unexplained. Trace proteinuria is also not uncommon. Even in retrospect, routine laboratory values gave no real warning of this syndrome in our patient before he received his last dose of mitomycin C (the seventh course of chemotherapy). Perhaps the serum haptoglobin would have provided earlier and more specific warning of hemolysis if it had been measured. We advise that patients receiving mitomycin C be
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followed closely with awareness of the possible development of this serious syndrome.

Summary

We have presented an additional case of chemotherapy-associated hemolytic-uremic syndrome. This syndrome is probably a manifestation of mitomycin C toxicity, perhaps as modified by 5-FU or additional factors. Hemolysis and renal failure may develop with little warning, and an increased urinary protein in conjunction with a high MCV may provide an early clue to its detection. The discovery of this association may provide the basis for developing a good animal model for the hemolytic-uremic syndrome in humans.

Addendum

After our manuscript was completed and submitted for publication, another case report was brought to our attention. A further computer-based literature search uncovered additional cases (15-17). In two cases of Hanna, et al and one case of Pavy, et al, autopsies were performed, and no evidence of residual tumor was present. Detailed renal pathology (biopsy or autopsy) is reported for three cases of Hanna and the case of Rabadi. These authors reported material immunologically positive for fibrin in the mesangium. Renal pathology was otherwise essentially as we observed.

Acknowledgments

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