Recovery From Mitomycin C-Induced Hemolytic Uremic Syndrome

A Case Report

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Mitomycin C (MMC) is a cytotoxic agent that may induce a hemolytic uremic syndrome (HUS) with severe renal insufficiency. Of all reported patients with terminal renal failure only two survived with chronic hemodialysis. A patient with advanced gastric cancer in complete remission, who developed MMC-induced HUS, is reported; hemodialysis was necessary because of oliguria. Hemolysis subsided, and after addition of captopril renal function recovered partially. The patient is alive 6 months after discontinuation of hemodialysis. Recently she developed brain metastases. Symptoms of hemolysis did not recur. The pathogenesis and treatment of HUS are discussed.


MITOMYCIN C (MMC) is an alkylating antibiotic that was isolated from Streptomyces cespitosus in 1956. It has cytotoxic activity against a variety of human neoplasms, such as stomach cancer, breast cancer, pancreatic cancer, and cancer of the uterine cervix.

Side effects include delayed myelosuppression, lethargy and, less frequently, skin rash, nausea, and vomiting. In the last few years serious and sometimes lethal side effects have been reported. These are pulmonary fibrosis, cardiac failure, and a microangiopathic hemolytic anemia often combined with renal failure (hemolytic uremic syndrome, HUS).

Treatment possibilities of MMC-induced HUS remain disappointing. Progressive renal failure caused death in all patients, except in two who survived with chronic hemodialysis. We report a patient with a HUS induced by MMC, who recovered from this syndrome.

Case Report

A 49-year-old woman with an advanced undifferentiated adenocarcinoma of the stomach presented in September, 1981. There were metastases in a left supraclavicular lymph node, in the para-aortic lymph nodes, and subcutaneously in the region of the left scapula. Treatment with 5-fluorouracil, Adriamycin (doxorubicin), and mitomycin C(FAM) was initiated. Following two cycles of FAM, a complete remission was achieved. There was histologic confirmation, based on biopsy specimens from the original gastric tumor site.

In April, 1982, 1 month after another two cycles of FAM, at a cumulative dose of MMC of 60 mg, the patient developed clear symptoms of hemolysis (Fig. 1). Hemoglobin level was 4.6 mmol/l (normal, 8–10 mmol/l), platelet count was 39 × 10⁹/l, and in the peripheral blood smear large numbers of fragmented erythrocytes were seen. Bilirubin value was normal, serum lactate dehydrogenase (SLDH) activity was 260 U/l (normal, 175 U/l), serum creatinine level was 103 µmol/l, and creatinine clearance was 40 ml/minute. Microscopic hematuria and moderate proteinuria were found. Haptoglobin was absent and a Coombs' test had negative results. Fibrin degradation products were not increased, nor were there other signs of disseminated intravascular coagulation. Circulating immune complexes were absent, but platelet autoantibodies could be detected. As other causes could be excluded, the hemolytic anemia was considered to be caused by MMC, and cytotoxic treatment was discontinued. Erythrocyte transfusions aggravated the hemolysis and also the thrombocytopenia. Neither a trial with high-dose corticosteroids nor frequent plasmapheresis with substitution of fresh donor plasma improved symptoms.

In August, 1982, the patient had to be admitted to the hospital because of cardiac failure, a hypertension of 180/110 mmHg, and oliguria with a creatinine clearance rapidly decreasing to below 5 ml/minute. Hemodialysis was started three times a week and resulted in disappearance of cardiac failure. Within 1 month, platelet counts returned to normal (150 × 10⁹/l), platelet autoantibodies became negative, and the frequency of erythrocyte transfusions decreased. In October, all signs of hemolysis had disappeared, but oliguria persisted.

A percutaneous renal biopsy specimen at that time showed a histologic pattern consistent with HUS: focal glomerular
sclerosis, swelling of endothelial cells with nuclear degeneration, as well as rarefaction of basement membrane. The glomeruli showed deposition of fibrin and protein casts. Deposits of fragmented erythrocytes were not seen. Urine analysis showed a low sodium excretion (17 mmol/l) and a high creatinine excretion (12 mmol/l), while serum sodium level was normal. Serum renin proved to be 30 mcg/l/hour (normal 0.4–4.5 mcg/l/hour), consistent with reduced renal blood flow. Persistence of the glomerular changes might have stimulated renin secretion, but a concomitant functional component could not be excluded. Captopril therapy was started, increasing the dose to three times 25 mg/day. Shortly thereafter, diuresis improved to 200 to 500 ml/24 hours, and extension of fluid administration did not reintroduce signs of cardiac failure. Blood pressure decreased to normal. Finally, diuresis became normal with a creatinine clearance of 12 ml/minute.

In February, 1983 dialysis treatment was discontinued. Dose reduction of captopril, however, immediately resulted in fluid retention. The patient returned to an active life. Unfortunately, she later presented with brain metastases, which were treated by radiotherapy. The patient died because of progressive brain metastases in September 1983.

Discussion

Our patient presents another example of MMC-induced HUS, but hemolysis completely disappeared and renal failure partially improved.

Renal disease induced by MMC was first reported in animals in the early 1960s. The drug was shown to cause necrotizing nephrosis. In 1971, Liu and associates described renal toxicity in humans, presumed to be caused by MMC. Over the last few years about 50 cases have been reported. The clinical picture often fits HUS, but some patients have been reported with renal failure without hemolysis. Furthermore, a microangiopathic hemolytic anemia, which is always Coombs’ negative, seems to be possible without renal failure. Patients with HUS have had cumulative MMC doses of 30 to 260 mg. The latency period between the last dose of MMC and development of HUS is 2 to 5 months. In our patient, symptoms of HUS started within 1 month after the last course of FAM at a cumulative dose of MMC of 60 mg. All reported patients had an adenocarcinoma, several in complete remission, and in most cases MMC treatment was combined with 5-fluorouracil and/or Adriamycin.

In contrast to the MMC-induced tubular changes found in animals, the pathologic findings in humans are mainly confined to the glomeruli and consist of deposition of fibrin in the glomerular capillaries, basement membrane thickening, small infarcts, and protein casts in the tubuli, as is seen in HUS because of other causes. In these patients, however, bizarre giant glomerular nuclear forms and degenerated nuclei were also present. Immunofluorescence studies did not reveal specific changes. The primary pathologic event seems to be
damage to the endothelial lining cells, especially the glomerular capillaries.\textsuperscript{26}

Whether circulating tumor cells\textsuperscript{29,30} are a main cause of these changes in MMC-induced HUS remains uncertain, since more than 50% of the patients appear to be free of tumor. The role of immune-mediated tissue damage needs further attention, because in two patients circulating immune complexes were reported\textsuperscript{22,23} and three additional patients (including our own) had platelet autoantibodies. Local fibrin deposition preceded by thromboplastin release from erythrocytes or from tumor cells\textsuperscript{30,32} or by a deficient plasma factor\textsuperscript{33,34} has to be considered as well. Increased platelet aggregation does not seem to be present in the early phase of HUS.\textsuperscript{15}

Fragmentation of erythrocytes on fibrin strands\textsuperscript{17} or by contact with tumor emboli\textsuperscript{29,30} may be the reason for the accompanying hemolysis.

Until recently, treatment of MMC-induced HUS has been disappointing. Progression after blood transfusion has been reported\textsuperscript{12,13,21} and was also noticed in our patient. This may be caused by activation of the intravascular clotting as was suggested by Agnelli et al.\textsuperscript{36} In our patient we observed a rapid fall in platelet count after an erythrocyte transfusion, but further coagulation tests were not done. If possible, blood transfusions should be avoided in these patients. Attempts at controlling the complications with steroids,\textsuperscript{13,17,20,25} aspirin,\textsuperscript{14,17,20} cyproheptadine,\textsuperscript{17} and dipyridamole\textsuperscript{13,14} were unsuccessful, except in three patients in whom heparin led to recovery of anemia.\textsuperscript{18} Plasmapheresis, with the aim of removing circulating immune complexes or of substituting a deficient plasma factor necessary for clotting inhibition,\textsuperscript{12} resulted in improvement of hemolysis in some reported cases,\textsuperscript{12,20} although renal function did not improve. Almost all patients who required hemodialysis because of renal failure have died.

Among the three patients who survived, one patient had HUS\textsuperscript{12} with disappearance of hemolysis and another had renal failure only.\textsuperscript{25} In the third (our patient), hemodialysis could be discontinued following partial recovery of renal function. The inappropriately high renin secretion probably caused both hypertension and the inability to excrete excessive sodium and water.\textsuperscript{37} Captopril, an angiotensin-converting enzyme inhibitor, reduced pre- and afterload through arteriolar and venous dilation in the kidney.\textsuperscript{38} This facilitates the administration of fluids in cases of oliguria with concomitant hyperreninism. In our patient, captopril treatment improved diuresis as well as renal function. Based on our experience, the role of captopril in the treatment of renal failure in MMC-induced HUS merits further attention.

In conclusion, there is substantial evidence that MMC may induce lethal HUS. The incidence and pathogenesis remain unclear. Physicians should be alerted by the appearance of proteinuria, microscopic hematuria, and anemia with fragmented erythrocytes. MMC treatment should be discontinued immediately if the syndrome is suspected. Blood transfusions should preferably be avoided. Plasmapheresis or heparin might be useful in the control of hemolysis. Those patients in whom hemolysis disappears and who survive on chronic hemodialysis may have partial recovery of renal function with captopril.

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