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Case report

Mitomycin C-related hemolytic uremic syndrome in cancer patients

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In rare cases mitomycin C (MMC) may induce cancer-associated hemolytic uremic syndrome, which is characterized by hemolytic anemia, thrombocytopenia and progressive renal failure. Treatment possibilities of this multisystem disease up to now remain disappointing. We report a case of MMC-related hemolytic uremic syndrome, and discuss the etiologic parameters, clinical aspects, prognosis and treatment modalities of this severe syndrome. [© 1998 Lippincott-Raven Publishers.]

Key words: Chemotherapy, hemolytic uremic syndrome, mitomycin C.

Introduction

Mitomycin C (MMC) is an alkylating cytotoxic agent, widely used in chemotherapy of solid tumors, mainly of gastrointestinal and breast origin.[1] Adverse events of this treatment include myelosuppression, alopecia, nausea, vomiting, skin rash, cardiotoxicity, pulmonary fibrosis and nephrotoxicity.[2,3]

In rare cases, MMC may induce serious and lethal side effects, such as hemolytic uremic syndrome (HUS). HUS is a multisystem disease characterized by microangiopathic hemolytic anemia, thrombocytopenia and progressive renal failure.[5] Additionally, pulmonary edema may often occur after blood transfusion. Thrombotic microangiopathic processes play a major role in pathogenesis, but the etiologic mechanisms are not yet exactly known.[6,7]

We report the clinical course of a patient presenting the typical characteristics of HUS during treatment with MMC, and discuss the relationship between prognosis and patient conditions.

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Case report

A 42-year-old woman underwent a radical left mastectomy for adenocarcinoma (T1 N1 M0) in 1990, followed by postoperative irradiation of the chest wall with a total dose of 50 Gy. In addition, adjuvant chemotherapy (6× CMF) was administered.

In 1994 disease relapsed with hepatic and bone metastases. Due to hepatic tumor progression several courses of systemic treatment with CMF, epirubicin and taxol were performed from April 1994 through October 1995.

Starting in November 1995 the patient received five courses of chemotherapy with vindesin and MMC (cumulative dose 47 mg/m^2) achieving partial remission of the liver metastases. During this period all parameters related to hematopoietic and renal function were normal.

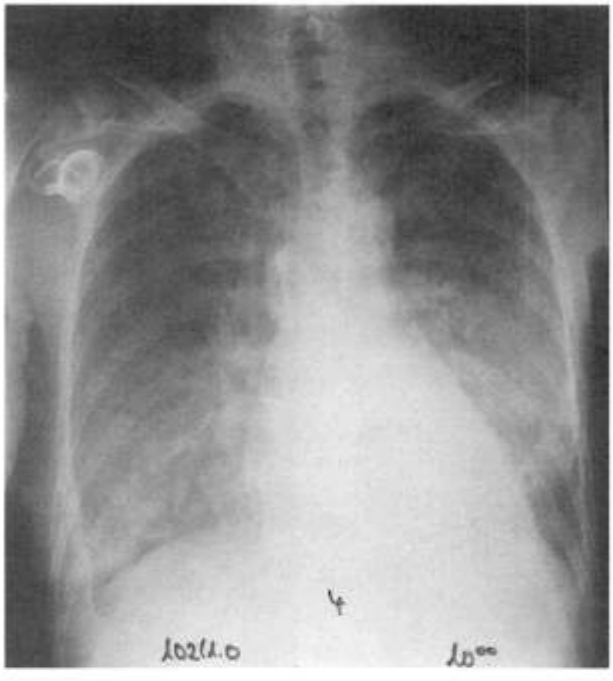
After four cycles of treatment with vindesin/MMC the patient developed acute dyspnea induced by a non-cardiogenic lung edema, but therapy with high-dose corticosteroids led to a rapid improvement of symptoms. Six weeks after completion of the fifth course she complained of weakness and progressive respiratory distress. Chest X-ray and CT scans (Figure 1a and b) demonstrated all signs of massive lung edema.

Laboratory findings showed a pronounced hemolytic anemia, thrombocytopenia and impairment of renal function. Hemoglobin was 6.0 g/dl, reticulocytes 6%, platelets 18 000/μl, lactate dehydrogenase (LDH) 980 U/l, PTT 72 s and plasma creatinine 2.6 mg/dl. Erythrocyte transfusions aggravated the hemolysis and the thrombocytopenia. In the peripherial blood smear, large numbers of fragmented erythrocytes were seen (Figure 2). Microscopic hematuria was found. Haptoglobin was absent, and the direct and indirect Coombs' test had a negative result.

Neither a trial with high-dose corticosteroids nor frequent plasmapheresis improved symptoms; therefore this treatment was discontinued.

Finally, the patient died after fatal deterioration of renal function with the clinical symptoms of respiratory distress.

a



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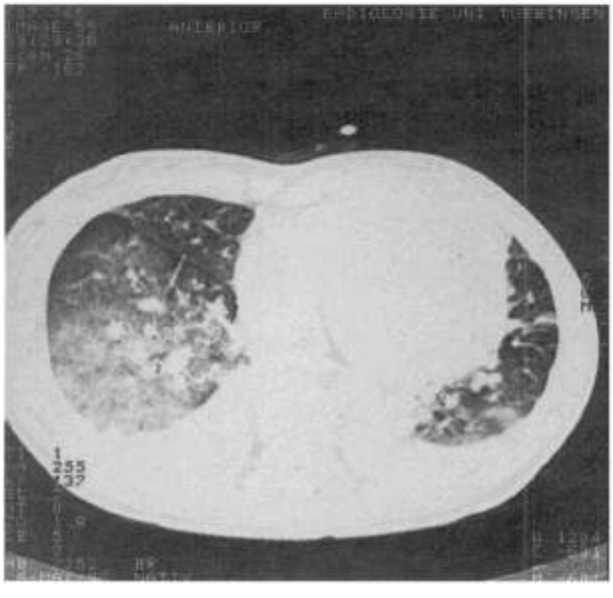

Figure 1. Signs of lung edema are shown in chest X-ray (a) and CT scans (b) 6 weeks after completion of chemotherapy with vindesin and MMC.

Discussion

MMC is known to cause cancer-associated HUS, which consists of microangiopathic hemolytic anemia, thrombocytopenia and progressive renal failure. According to previous reports it affects about 10% of patients treated with this agent.[5,8]

The etiology of MMC-associated HUS is not yet exactly explained. This process may result from red blood cells shearing in microcirculation, partially obstructed by fibrin strands due to disseminated intravascular coagulation or intimal proliferation.[4,9] Whether circulating tumor cells are a main factor causing these changes remains uncertain, because more than 50% of patients observed were free of tumor.[10] Possibly, immune-mediated tissue damage plays an additional role in the pathogenesis.[9] Furthermore MMC may induce primary damage to the vascular endothelium, and therefore trigger platelet aggregation and fragmentation of erythrocytes (Figure 2). MMC led to a deficiency in prostacycline biosynthesis by endothelial cells and consecutively may support disseminated intravascular coagulation (DIC).[8]

The patient described presented all signs of HUS with Coombs' negative microangiopathic hemolytic anemia, renal failure and low platelet count 6 weeks after completion of chemotherapy with MMC. This rapid onset of symptoms seems to be a risk factor and is commonly associated with a worse prognosis. Usually, the latency period between the last dose of MMC and development of HUS is about 3-6 months.[8,11] Further, patient's and clinical characteristics, such as age, histology of primary cancer, total dose of MMC and pulmonary impairment, can be determined as prognostic parameters.[10,12] Patients less

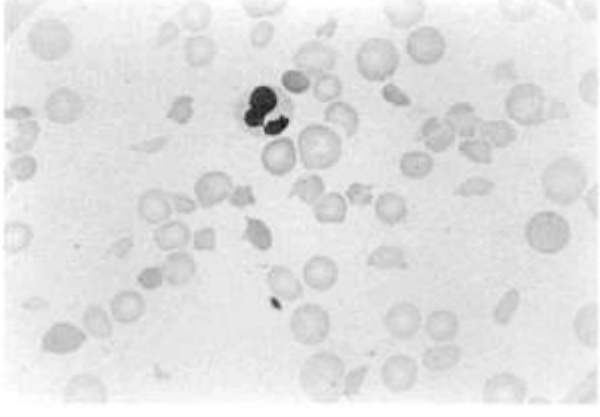

Figure 2. Fragmentation of erythrocytes due to damage of the vascular endothelium is seen in peripheral blood smear.

than 60 years old or treated with plasma exchange were found to be significantly associated with a more favorable outcome.[11] Moreover, nephrotoxicity is related to the cumulative dose; the risk of renal failure is about 2% at doses higher than 50 mg/m^2, but more than 30% at doses higher than 70 mg/m^2.[12] Cumulative dose in our 42-year-old patient was 47 mg/m^2, but the therapeutic interventions failed to control HUS and a rapid deterioration of clinical signs occurred. Initial diagnosis of adenocarcinoma, receipt of combination chemotherapy containing MMC and pulmonary edema during the course of syndrome are features and risk factors presented by the described patient, which appear in about two-thirds of HUS patients. In addition, an adverse reaction to blood transfusions is seen in almost 50% of cases.[11]

HUS associated with MMC is highly resistant to treatment. Therapy with immunosuppressive drugs, anticoagulants and inhibitors of platelet aggregation has been unsuccessful. In some cases corticosteroids revealed symptomatic improvement of the lung edema. In about 30% of patients plasmapheresis resulted in the reduction of hemolysis by removal of circulating immune complexes and substitution of deficient clotting-inhibitor factors.[9] In rare cases partial recovery of renal function has been described after prolonged treatment with hemodialysis and the institution of captopril therapy.

Conclusion

In conclusion, treatment possibilities of MMC-induced HUS up to now remain disappointing with a high mortality of this syndrome of about 60–80%. Therefore MMC treatment must be carefully monitored for the onset of side effects, especially for hemolysis and renal impairment. MMC chemotherapy should be discontinued immediately if the syndrome is suspected and blood transfusions should preferably be avoided. Early institution of plasmapheresis is always indicated in patients presenting with minor manifestations of this severe syndrome.

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