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Microangiopathic Hemolytic Anemia, a Frequent Complication of Mitomycin Therapy in Cancer Patients

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Abstract—*Microangiopathic hemolytic anemia (MAHA) has long been recognized as a rare complication in far-advanced malignant tumors. Recently several patients have been described in whom MAHA and renal insufficiency developed as a result of mitomycin therapy. We here describe another five such cases among 50 patients treated with mitomycin. All five cases were observed among the 14 patients who had received four or more doses of the drug. We conclude that MAHA is a frequent and potentially fatal complication of long-term mitomycin treatment. Careful monitoring for the early appearance of schistocytes is mandatory as the syndrome tends to be self-limited if this therapy is discontinued early.*

INTRODUCTION

MICROANGIOPATHIC hemolytic anemia (MAHA) has long been described as a rare cause of anemia in patients with malignancies. Among these, mucin-producing cancers of the gastrointestinal tract were the most frequently reported histological types [1–3]. The syndrome was usually found in patients with far advanced disseminated disease [2].

More recently, MAHA has been noted as a rare complication in cancer patients treated with mitomycin-containing chemotherapy [4–11]. The complication developed after several months of therapy with mitomycin either alone or in combination with other agents. A delayed onset several months after cessation of therapy was observed [7, 8, 10] in patients, who developed severe hemolytic anemia, thrombocytopenia and renal insufficiency as primary features. The reported deaths (Table 3) occurred from renal insufficiency usually aggravated by blood transfusions.

We describe here another five cases of this complication observed in the Klinikum Nürnberg among a total of 50 patients treated with mitomycin regimens. The fact that four of our five cases were diagnosed early by carefully looking for the complication—whereas most of the 13 cases reported to date in the literature were far advanced—suggests that this may be a frequent complication of mitomycin therapy and not a rare oddity.

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MATERIALS AND METHODS

Between July 1977 and July 1981, 50 patients were treated with mitomycin in combination schedules or as single-agent therapy. Forty-two patients received at least two courses of mitomycin and were evaluated for the development of the hemolytic complication. The 23 patients with adenocarcinomas of the gastrointestinal tract received 10–15 mg/m^2 mitomycin every 5–6 weeks in combination with fluorouracil, 600 mg/m^2 days 1–3 of each cycle. The 11 patients with breast cancer were treated with the same dose of mitomycin but in combination with daily medroxyprogesterone acetate. The other patients were treated with different regimens for various carcinomas, none of them developed the complication.

The duration of therapy varied. Among the 42 patients who received a minimum of two courses, 14 had four or more cycles of their treatment. After we observed our first case of severe hemolysis and renal failure all patients were specifically observed for the development of this complication. The following blood tests were regularly recorded: hemoglobin, erythrocytes, reticulocytes, thrombocytes, quantitative estimation of schistocytes, haptoglobin, direct Coombs test,

lactate dehydrogenase (LDH), creatinine, fibrinogen and fibrin degradation products (FDP).

RESULTS

Of the 14 patients who received four or more courses of mitomycin, five developed MAHA. Their diagnosis, stage of disease at time of therapy, doses of mitomycin and duration of treatment are given in Table 1. Four patients had carcinomas of the colon: in three patients the disease was metastatic but the first patient was treated in an adjuvant protocol after resection of a Dukes C lesion. Twenty-four months after the cessation of all chemotherapy this patient is still free of any detectable tumor.

The laboratory data are summarized in Table 2. The most sensitive early sign of the complication was the appearance of schistocytes in the peripheral blood in all our patients. Reticulocytosis, anemia, decreased levels for haptoglobin and high values for LDH were universally found, as signs of the hemolysis. The direct Coombs tests were negative in all patients. In patient No. 1 bone marrow biopsy and aspiration were done during the height of this illness. A marked increase in erythropoiesis compatible with a hemolytic state was seen. The number of megakaryocytes was unremarkable, as was the maturation of the granulocytes.

All patients were thrombocytopenic. Three patients developed impaired renal function. Their creatinine values rose, and they showed mild proteinuria and microscopic hematuria. One patient had impaired kidney function prior to his chemotherapy after several episodes of

Table 1. Clinical data of five cases of MAHA following mitomycin therapy

Patient No. [age (yr)/sex]	Stage of disease when MAHA was observed	Mitomycin, single dose (mg/m^2)	No. of courses	Course of malignant disease	Course of MAHA
1 (57/M)	adenocarcinoma colon, adjuvant	15	7	no evidence of tumor 24 months after end of therapy	complete recovery
2 (26/F)	adenocarcinoma colon, inoperable	12.5	5	very good regression of primary tumor, later progression	6 months after therapy minimal hemolysis
3 (60/F)	adenocarcinoma colon, liver metastases	12.5	6	PR, later progression and death	anemia contributing to death, syndrome aggravated by blood transfusions
4 (56/F)	adenocarcinoma colon metastases: liver ovary	15	4	NC over 4 months, then progression, died of malignant disease	mild persistent hemolysis
5 (70/F)	breast cancer metastases: lymph nodes, bone, liver	10	4	PR, later progression	persistent hemolysis

PR: partial remission. NC: no change.

Table 2. Laboratory values at time of most severe changes due to MAHA in mitomycin-treated patients

Patient	Hemoglobin (g/dl)	Reticulocytes ($\times 10^3/mm^3$)	Haptoglobin (mg/dl)	Schistocytes	LDH (U/dl)	Thrombocytes ($\times 10^3/mm^3$)	FDP ($\mu g/ml$)	Creatinine (mg/dl)
Normal values	male: 14–16 female: 12–16	20–90	<60	<1%	<240	150–350	<10	0.5–1.5
1	7.6	252	<10	5%	500	50	96	2.5
2	6.9	510	<10	7.5%	370	50	192	2.5
3	5.0	292	<10	8.5%	500	17	60	2.9
4	10.2	160	<10	*	410	57	*	0.8
5	9.1	242	10	*	600	79	96	†

*Not quantitated.
†Pre-existing elevation; see text.

hypercalcemia. There was a further increase in her creatinine value after MAHA developed. None of our patients developed hypertension.

All patients repeatedly showed elevated levels of FDP as a sign of a mild disseminated intravascular coagulation, but fibrinogen levels never fell below normal limits.

In one patient the anemia contributed to death. In all other patients the hemolytic condition improved spontaneously after discontinuation of chemotherapy.

No active treatment for the condition is known, with the possible exception of plasmapheresis [4, 9]. We carefully avoided blood transfusions, but patient No. 3 suffered severe heart failure and was transfused with washed packed red cells on two occasions. Each time she had an increase in her creatinine, FDP and LDH values and an aggravation of her thrombocytopenia. The effect of the transfusions on her hemoglobin levels was short. Attempts to treat the complication with steroids, heparin or aspirin were unsuccessful.

DISCUSSION

MAHA, often in combination with mild DIC, has been described as a complication of chemotherapy with mitomycin regimens. Hemolysis, thrombocytopenia and renal in-

Table 3. Clinical data of the eight reported cases of MAHA attributed to mitomycin therapy in the literature

Reference	Diagnosis	Mitomycin single dose	Therapy duration	Additional chemotherapy	Renal function	DIC	Course
[4]	epidermoid Ca. anal canal, adjuvant	15 mg q 5 weeks	11 months	FU	impaired on regular dialysis	—	after plasmapheresis remission of MAHA; 1 yr later still no detectable tumor
	metastatic epidermoid Ca. cervix	*idem*	12 months	FU	needed dialysis	—	after plasmapheresis improvement of hemolysis, MAHA contributed to death
[5]	gastric cancer, adjuvant	0.15 mg/kg q 3 weeks	15 cycles	FU	impaired possibly worse after transfusion	†	died, in renal failure, at autopsy no evidence of tumor
	gastric cancer	*idem* (frequent dose reduction)	24 cycles	FU	impaired got worse after transfusion	†	died in renal failure at autopsy no evidence of tumor
[7]	gastric cancer, adjuvant	10 mg/m² q 8 weeks	4 cycles	FU ADM	impaired	n.r.	anemia resolved, renal function impairment and hypertension persisted
[10]	breast cancer, osseous metastasis	30 mg per cycle	3 cycles	MPA	impaired, got worse after transfusion	n.r.	pulmonary fibrosis, died in renal failure
[9]	breast cancer	12 mg/m² q 5 weeks	5 cycles	TAM	impaired got worse after transfusions	—	congestive heart failure, pulmonary hypertension, died in renal failure
[6, 11]	gastrointestinal cancer 143 patients treated	15–20 mg/m²	>60 mg total	FU	impaired	+	14 patients developed renal toxicity, fatal in 9; signs of MAHA of varying severity
[8]	undifferentiated carcinoma (primary unknown)	10 mg/m² q 3 weeks	92 mg total	Vbl.	impaired needed dialysis	—	died with severe MAHA and renal failure at autopsy; no carcinoma
	adenocarcinoma, lung	20 mg q 3 weeks	5 cycles	Vbl.	impaired	—	developed severe hypertension died from cerebral hemorrhage with MAHA and renal insufficiency

FU, 5-fluorouracil; MPA, medroxyprogesteroneacetate; DIC, disseminated intravascular coagulation; ADM, adriamycin; TAM, tamoxifen; Vbl., vinblastine; n.r., not reported.

sufficiency are the results of this complication. Other reported signs include hypertension, proteinuria and mild hematuria. The severity of the different pathological findings, especially the degree of renal insufficiency, varies markedly in the different cases reported in the literature (Table 3). Not surprisingly, the syndrome is referred to as 'hemolytic uremic syndrome' (HUS) by one group of authors [8] or as 'renal disease after mitomycin' by others [11]. In fact our cases 1, 2 and 3 can be classified as HUS, but then it is reasonable to assume that all these cases have a common pathogenic mechanism. The first development is possibly damage to vascular epithelial cells leading to MAHA followed by extensive damage to the renal blood vessels [9, 11].

Chemotherapy over several months seems to be required for the complication to develop, but it is not clear whether the total cumulative dose of mitomycin or the duration of treatment is the more important factor. Mitomycin was the only agent given to all patients reported with this syndrome, yet all but two patients received fluorouracil as well. Whether other cytostatic drugs—or hormones—increase the likelihood for this complication to occur is unknown.

This complication led to death in most of the reported cases (Table 3). The cause of death was renal insufficiency in them all. Blood transfusions had usually led to a marked worsening of the already impaired kidney function. In patients recovering from the hemolytic episode renal function usually improved only partially. The one patient in our series in whom MAHA contributed to death showed the same pattern with worsening of the hemolysis and kidney function after red cell transfusions.

Mitomycin has also been suspected as a possible nephrotoxic agent. These data are summarized by Ratanatharathorn *et al.* [12]. In some of the reported cases fibrin thrombi were found in the glomeruli. This may suggest that some of these patients showed the same complication. Wahid *et al.* [11] report 14 cases of renal disease after mitomycin therapy. They distinguish between a fulminating, rapidly fatal form and a chronic, slowly progressive one. Severe MAHA was only recognized in two of their patients, but many more showed abnormal numbers of schistocytes.

MAHA undoubtedly occurs in cancer patients independent of any chemotherapy [1–3]. In the presence of advanced metastatic disease it therefore may be impossible to be certain about the cause of the hemolysis. In our cases this difficulty is seen in patient No. 3. In all the other cases we cannot attribute the findings to the malignant disease itself.

Lohrmann *et al.* [2] describe eight cases of MAHA in untreated patients with cancer. All patients died within a short period. There was only one patient whose hemolytic syndrome improved temporarily and this was the only patient who responded to chemotherapy. The fact that the hemolysis subsided spontaneously after discontinuation of chemotherapy in our surviving patients makes it very likely that the syndrome was due to the treatment. Also our first patient is still alive 24 months after recovery from severe anemia without any chemotherapy and without detectable tumor.

Kressel *et al.* [13] recently described six patients with adenocarcinomas who developed MAHA, thrombocytopenia and renal failure. Five of the 6 patients were treated with mitomycin combinations; the sixth patient received no mitomycin but had far-advanced disease. The authors attribute the complication to the malignant tumor itself, but three of their patients had either no evidence of malignant tumor or minimal microscopic foci found at autopsy. We therefore cannot follow their conclusions.

We are impressed by the high frequency of this complication in our patient population. MAHA was observed five times among 50 patients treated with any mitomycin regimen. Of those, 42 had received two or more courses of treatment and only 14 had four or more doses of mitomycin. On the other hand, no patient developed the syndrome after less than four cycles of treatment. It is likely that this complication passes unrecognized in many instances, as a slow drop in hemoglobin and a rise in LDH are easily attributed to progressive disease in patients with metastatic cancer. Renal insufficiency develops slowly and thrombocytopenia may be interpreted as being caused by the myelotoxicity of the chemotherapy. The important findings of the markedly increased number of schistocytes and reticulocytes are easily overlooked.

The true prevalence of this complication will become known only if patients are specifically checked for its early signs. To us, the search for schistocytes seems the most reliable and practical screening. Jones *et al.* [5] also state in their publication that they saw the syndrome in their cooperative trial with increasing frequency and that the two reported lethal cases were only the extreme of the syndrome.

Wahid *et al.* [11] report nine (6.9%) deaths from renal impairment among a total of 143 patients treated with mitomycin.

No effective therapy for the complication is known. Plasmapheresis was the only possibly effective treatment [4, 9] and further evaluation of its value is indicated. Steroids, heparin, aspirin, cyproheptadine and dialysis have all been tried

without success. Discontinuation of chemotherapy at the early signs of complication and avoidance of blood transfusions allow time for spontaneous recovery.

In our opinion published data and our own observations allow the conclusion that MAHA is a frequent and potentially fatal complication of mitomycin treatment. The use of this drug is only justified when careful monitoring for the early signs of the complication is carried out. Furthermore, at present we suggest that the drug is not used in adjuvant chemotherapy programs.

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