# Haemolytic Uraemic Syndrome Associated with Bleomycin, Epirubicin and Cisplatin Chemotherapy

## *A Case Report and Review of the Literature*

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Microangiopathy resembling haemolytic uraemic syndrome is a rare complication of cancer therapy, which is usually associated with mitomycin C. This report describes a patient who developed haemolytic uraemic syndrome and haemoptysis after chemotherapy with bleomycin, epirubicin and cisplatin for a recurrent poorly differentiated carcinoma of the nasopharynx. This syndrome, which has an uncertain aetiology and very poor prognosis, has been reported in association with cisplatin and bleomycin in only 12 cases to date, and has not previously been reported in nasopharyngeal carcinoma. We hypothesize that the combination of cisplatin and bleomycin can cause disseminated vascular endothelial injury manifest as pneumonitis and haemolytic uraemic syndrome.

*Case report*. A 54-year-old woman presented in January 1993 with conductive deafness of the left ear and a left trigeminal nerve palsy in the mandibular division. A diagnosis of poorly differentiated carcinoma of the left nasopharynx (T4N3) was made on a biopsy. Initial treatment with high-dose radiotherapy resulted in a complete clinical and radiological response. In April 1994 increasing left facial pain and a left third cranial nerve palsy developed. These symptoms and signs were relieved with dexamethasone. A CT scan and an MRI scan confirmed a recurrence in the region of the left cavernous sinus.

Chemotherapy began on 17 May 1994. Three cycles at 3-week intervals were planned, consisting of bleomycin 15 mg IV bolus on day 1 and 16 mg/m$^2$ as a continuous infusion from day 1 until day 4, epirubicin 80 mg/m$^2$ on day 1 and cisplatin 100 mg/m$^2$ on day 1 (BEC) (1, 2). A pre-treatment white blood cell count (WCC) was $12.1 \times 10^9$/l (normal range: $4.0–11 \times 10^9$/l), Hb was 147 g/l (115–165 g/l) and platelets were $276 \times 10^9$/l ($150–400 \times 10^9$/l). The blood film was normal. All biochemistry processes including the liver function tests and LDH were normal. Nadir blood cell counts were recorded on day 8 of the first cycle of chemotherapy as WCC $4.6 \times 10^9$/l, Hb 143 g/l and platelets $77 \times 10^9$/l.

On day 8 of cycle 2 of BEC the full blood count showed a WCC of $1.2 \times 10^9$/l (neutrophils $0.9 \times 10^9$/l), Hb of 104 g/l, haematocrit of 28.6% and platelets $7 \times 10^9$/l. The blood film showed mild anisocytosis and poikilocytosis with occasional spherocytes and irregularly contracted red blood cells (schistocytes). A platelet transfusion was given on day 8, without complication. On day 10 the serum creatinine was elevated to 0.13 mmol/l (normal range 0.06–0.10 mmol/l). Liver function tests were also abnormal: GGTP 178 U/l (1–25 U/l), ALT 49 U/l (1–30 U/l), AST 28 U/l (1–30 U/l), ALP 79 U/l (40–115 U/l) and LDH 906 U/l (120–260 U/l). Bilirubin was 9 $\mu$mol/l (normal range 1–11 $\mu$mol/l). On day 15 Hb had fallen to 78 g/l and haematocrit to 22.4% with mild polychromasia and an occasional schistocyte; however, the WCC and platelet count had recovered. A transfusion of 3 units of packed red cells was given, again without complication. On day 18 the liver function tests had recovered except for LDH 718 U/l, GGTP 97 U/l, and bilirubin 13 $\mu$mol/l. At this time the patient's only significant complaints were general malaise, lethargy and postural dizziness. The CT scan after 2 cycles of chemotherapy showed a partial response.

A third cycle of chemotherapy in the same doses was begun on 4 July 1994. At this time the pre-treatment full blood count showed Hb 10.5 g/dl, WCC $6.1 \times 10^9$/l and platelets $318 \times 10^9$/l. The blood film showed mild anisocytosis, poikilocytosis and polychromasia. Serum LDH was 442 U/l and other liver function tests showed GGTP 193 U/l, ALP 119 U/l, ALT 67 U/l, AST 51 U/l and bilirubin 5 $\mu$mol/l.

Six days later the patient presented to the emergency department with sharp, well-localized pleuritic pain in the right anterior chest, breathlessness and left basal crepitations. WCC was $2.8 \times 10^9$/l, Hb 86 g/l, platelets $32 \times 10^9$/l and the blood film again showed occasional spherocytes and irregularly contracted red blood cells. A chest x-ray showed some consolidation over the right upper zone, suggesting bilateral basal pneumonic changes compared with results from the previous x-ray of June 1994. Arterial blood-gases showed pH 7.39, $pCO_2$ 40.3 mmHg, $pO_2$ 73.9 mmHg and $O_2$ saturation 93.3% in room air. On day 1 after

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admission, a ventilation-perfusion lung scan showed a medium-high probability of pulmonary embolus and the patient was heparinized with 14 000 units given over 24 h. Pre-heparin, the prothrombin time was 10 s (normal range 10–13 s) and the aPTT was 25 s (22–35 s). The patient's WCC was $2.1 \times 10^9$/l (neutrophils $2.0 \times 10^9$/l), Hb 73 g/l, haematocrit 20% and platelets $23 \times 10^9$/l. The blood film was unchanged and reported as pancytopenia with red cell changes consistent with microangiopathic haemolytic anaemia. Urinalysis showed pH 5, microscopic haematuria, nitrates and a trace of leucocytes. On day 2 the patient developed haemoptysis and anuria was noted. The WCC was $0.9 \times 10^9$/l, Hb was 55g/l and platelets were $6 \times 10^9$/l. The aPTT was more than 100 s and the heparin infusion was stopped. The blood film showed occasional fragmented red cells and moderate numbers of spherocytes and was reported as consistent with disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura or haemolytic uraemic syndrome (HUS). The serum creatinine rose from 0.34 U/l on admission to 0.43 U/l on day 2. Bilirubin was 18 $\mu$mol/l, GGTP 136 U/l, ALT 24 U/l, AST 79 U/l, ALP 88 U/l and LDH was 2 362 U/l.

Later, on day 2, the patient became critically ill with hypotension (BP 90/50 mmHg) and increasing haemoptysis. A differential diagnosis of pulmonary haemorrhage, neutropenic sepsis or bleomycin-induced interstitial pneumonitis was considered (3, 4). The coagulation profile showed PT 13 s, aPTT 97 s (therapeutic range for heparin 40–80 s), thrombin time $>60$ s (correcting to normal with protamine sulphate, consistent with heparin effect) fibrinogen 4.4 g/l (normal range 2.0–4.0 g/l) and XDPs $<0.25$ g/l (normal range $<0.25$ g/l). Platelets and fresh frozen plasma were transfused. Treatment with gentamicin and timentin (ticarcillin and clavulanic acid) was started, but despite all resuscitation efforts the patient died on day 2 after admission.

An autopsy showed:

- The kidneys had a normal weight and the external surface of the kidneys was unremarkable. A few of the glomeruli showed chronic ischaemic changes with wrinkling of the basement membrane and peri-glomerular fibrosis. Microthrombi were seen in glomerular tufts.
- Nasopharyngeal carcinoma with extension into the left middle cerebral fossa. Histology showed necrosis and fibrosis with no viable tumour in the nasal mucosa. However, the left middle fossa showed an area of fibrous tissue infiltrated by a few strands of poorly differentiated carcinoma cells.
- Pulmonary fibrosis with superimposed intra-alveolar haemorrhage. Histology showed extensive intra-alveolar haemorrhage on a background of diffuse interstitial fibrosis. This finding was consistent with primary pulmonary fibrosis, such as in bleomycin toxicity.

*Discussion*. Haemolytic uraemic syndrome is a rare disorder which may be primary or secondary to infectious diseases, pregnancy, autoimmune disorders, use of oral contraceptives and cytotoxic agents. The clinical features are characteristic of renal microangiopathy involving small arterioles and glomerular capillaries, microangiopathic haemolytic anaemia (MAHA) and platelet destruction leading to varying degrees of thrombocytopenia. The blood film contains fragmented erythrocytes, burr cells and some microspherocytes. Usually the plasma levels of factors V, VIII and fibrinogen are normal or increased. The basic pathology consists of fibrin deposition on the walls of capillaries and arterioles as well as intraluminal thrombi containing fibrin and platelets (5).

Chemotherapy-induced HUS differs from the classic form. The clinical syndrome is characterized by the triad of MAHA, thrombocytopenia and renal failure. Severe dyspnoea and hypoxaemia attributable to non-cardiogenic pulmonary oedema is considered characteristic of chemotherapy-related HUS. Neurologic abnormalities are not found consistently and fever is uncommon. The onset is usually within 4 to 8 weeks after the last dose of chemotherapy, but has been reported to vary from 1 week to 15 months. Most cancer patients who develop this syndrome are in clinical remission. The mortality (mostly due to renal or pulmonary failure) is also much higher than the classic syndrome; almost 75% of patients die despite all therapy (4, 6, 7).

The laboratory tests are typical of moderate MAHA, with evidence of intravascular haemolysis: schistocytes in the blood film, reticulocytosis and decreased plasma haptoglobin levels. The Coomb's antiglobulin test is negative and platelets are usually decreased. In general, there is no evidence of disseminated intravascular coagulation (DIC) as measured by elevated XDPs; the serum creatinine is elevated and urinalysis shows haematuria, proteinuria and sometimes hyaline casts.

Our patient displayed many of the classical features of chemotherapy-induced HUS, although the diagnosis was obscured by severe myelosuppression and renal dysfunction, presumed to be due to chemotherapy. Nevertheless, there was evidence of extensive intravascular haemolysis one week after cycle 3 of chemotherapy, with otherwise unexplained renal failure, and a degree of thrombocytopenia not seen in cycle 1 of chemotherapy, thereby suggesting platelet destruction. The coagulation profile showed no evidence of DIC. Interestingly, there was a paucity of microscopic autopsy findings in the kidneys or lungs consistent with microangiopathy, which may possibly be explained by a short duration of the syndrome. In retrospect, the patient had evidence of a milder reversible haemolytic uraemic syndrome after cycle 2 of chemotherapy, manifest as profound anaemia and thrombocytopenia, and fragmented red cells on the blood film, but this diagnosis was not considered at that time.

Almost all cases of HUS are associated with mitomycin-C (5, 6, 8). Haemolytic uraemic syndrome after chemotherapy with bleomycin and cisplatin is unusual; only 12 cases have been reported to date (6, 7, 9–13). In a retrospective study 85 cases of cancer-associated HUS were found of which 84 patients had mitomycin-C, and only one patient had cisplatin with bleomycin (6). It is interesting to note that there are no reports in the literature attributed to cisplatin without bleomycin and only two cases involving bleomycin without cisplatin (8, 14), suggesting that the combination of these agents may be causative. There are no reports of HUS attributed to anthracyclines. From the 85 cases, 89% had a diagnosis of adenocarcinoma and 26% had gastric carcinoma. None of the patients had carcinoma of the nasopharynx (3).

The pathogenesis of chemotherapy-induced HUS is unclear. A primary pathogenic mechanism may involve direct drug-induced damage to the endothelium with the subsequent activation of the clotting system. Both bleomycin and cisplatin are known to cause syndromes associated with vascular injury, such as cerebral vascular events, myocardial infarction and Raynaud's phenomenon (15). It has been reported that Raynaud's phenomenon is more common in patients treated with cisplatin vinblastine and bleomycin, suggesting that cisplatin may enhance bleomycin vascular effects (16). Furthermore, renal insufficiency induced by cisplatin may increase bleomycin pulmonary toxicity by reducing the renal excretion of bleomycin (3). Another theory suggests that circulating immune complexes containing tumour antigen trigger local intravascular coagulation at sites of their deposition, but this does not explain those cases occurring in patients with no evidence of cancer. A suggested mechanism for bleomycin in combination with either cisplatin or a vinca alkaloid is that such combination chemotherapy can cause endothelial injury and vasospasm leading to further damage (12). The injured endothelial

cells then release large amounts of von Willebrand factor multimers, which lead to focal platelet aggregation and fibrin deposition resulting in thrombotic microangiopathy.

When drug-induced HUS is suspected, the drug should be discontinued immediately. Transfusions are felt possibly to exacerbate the syndrome (5). Heparin has no proven value in the treatment and steroids are usually not beneficial. Cytotoxic drugs such as azathioprine, cyclophosphamide and vincristine may be useful. Antiplatelet drugs such as aspirin and dipyridamole are also not successful. Plasmapheresis and immunoperfusion have been used to clear the circulation of immune complexes (6). These treatments can reverse the haematological abnormalities and the thrombocytopenia but renal failure will usually persist. In the case of our patient, the rapid progression did not allow sufficient time for any effective therapy.

The respiratory problem presenting in the two days prior to death was presumably a result of pneumonitis. However the classical prodrome for bleomycin-induced pneumonitis of dry cough and fever was absent, and intra-alveolar haemorrhage as a result of thrombocytopenia and endothelial injury in pulmonary vessels secondary to haemolytic uraemic syndrome could have contributed. This association has been reported previously in a patient treated with mitomycin C (8). The clinical features were not consistent with non-cardiogenic pulmonary oedema as described in association with chemotherapy-induced HUS. It is feasible that pulmonary vascular injury caused some of the features of HUS as well as haemoptysis and the apparent fibrosis seen at autopsy, although there was no clear pathologic evidence of microangiopathy at autopsy.

Although the prognosis for chemotherapy-induced HUS is poor, the outcome may have been different in our patient had the diagnosis been made earlier, by paying more attention to the blood film abnormalities. Our case illustrates how early manifestations can be overlooked, and how their recognition could avert the disastrous consequences of the full-blown syndrome.

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