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## Case Report

# Haemolytic Uraemic Syndrome Associated with Docetaxel: A Case Report

Beshar Allos<sup>1\*</sup>, Verity Dunn<sup>2</sup>, Andrew Short<sup>3</sup>, Anton Borg<sup>4</sup> and Nawaz Walji<sup>5</sup>

<sup>1</sup>SpR Clinical Oncology, University Hospitals Coventry and Warwickshire NHS Trust, South Warwickshire Foundation NHS Trust, UK

<sup>2</sup>SHO Clinical Oncology, University Hospitals Coventry and Warwickshire NHS Trust, South Warwickshire Foundation NHS Trust, UK

<sup>3</sup>Consultant Renal Medicine, University Hospitals Coventry and Warwickshire NHS Trust, South Warwickshire Foundation NHS Trust, UK

<sup>4</sup>Consultant Haematologist, University Hospitals Coventry and Warwickshire NHS Trust, South Warwickshire Foundation NHS Trust, UK

<sup>5</sup>Consultant Clinical Oncologist, University Hospitals Coventry and Warwickshire NHS Trust, South Warwickshire Foundation NHS Trust, UK

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## ABSTRACT

Haemolytic uraemic syndrome (HUS) has no recognised association with single-agent docetaxel. We present the first documented case of HUS associated with docetaxel in a patient receiving adjuvant chemotherapy for early breast cancer. A previously fit 49-year-old presented nineteen days post final cycle of docetaxel (100 mg/m<sup>2</sup>) with general malaise, epistaxis and decreased urine output. Baseline bloods revealed haemoglobin (53 g/L), urea (45.2 mmol/L), creatinine (1706 µmol/L) and LDH (2140 IU/L). Tumor lysis syndrome was excluded on further biochemical analysis. Blood film analysis demonstrated evidence of acanthocytes, anisocytosis and red cell fragments. Septic, viral and autoimmune screens were negative. There was clear evidence of microangiopathic haemolysis alongside renal dysfunction. She required dialysis, plasma exchanges and blood transfusions. Renal function and blood counts normalised within two months post-admission due to prompt and aggressive management. HUS should be considered in any patient receiving docetaxel who develops simultaneous acute kidney injury and severe anemia.

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## Introduction

Haemolytic uraemic syndrome (HUS) is characterized by intravascular haemolysis, thrombocytopenia and acute kidney injury (AKI). Primary HUS results from genetic mutations which cause complement dysregulation [1]. Secondary HUS may be caused by infective agents (*Streptococcus pneumoniae* and shiga toxin-producing *Escherichia coli*) or drug toxicity [2]. Chemotherapy agents that have been associated with HUS include gemcitabine, mitomycin C, cisplatin, bleomycin and doxorubicin [3-5]. Docetaxel is a chemotherapy agent belonging to the taxane family whose mechanism of action is to inhibit microtubule formation. Docetaxel is used for the treatment of several different types of cancers including breast cancer. It is metabolized by the liver and excreted mainly via the faecal route. It is not known to cause HUS; there is only one previously published case report of HUS associated with docetaxel given in combination with trastuzumab [6].

We present the first case report of HUS associated with docetaxel as a single agent.

## Case Report

A previously fit and well pre-menopausal forty-nine-year-old woman with a diagnosis of left-sided breast cancer (grade 3 NST, pT2, pN0, ER positive, Her-2 negative) was commenced on adjuvant chemotherapy with 6 cycles of FEC-Docetaxel in June 2015 with growth factor support as primary prophylaxis. She negotiated five cycles of chemotherapy with minimal toxicity requiring no treatment delay or hospital admission. Her blood parameters prior to the sixth cycle of chemotherapy demonstrated normal renal and full blood count (FBC) parameters.

Nineteen days following the sixth cycle of chemotherapy (docetaxel 100 mg/m<sup>2</sup>) she presented to the acute medical unit with a short history of feeling generally unwell, epistaxis and decreased urine output. At

\*Correspondence to: Dr. Beshar Allos, SpR Clinical Oncology, University Hospitals Coventry and Warwickshire NHS Trust, South Warwickshire Foundation NHS Trust, UK; E-mail: [Beshar.allos@uhb.nhs.uk](mailto:Beshar.allos@uhb.nhs.uk)

admission, her baseline bloods were severely deranged. Haemoglobin was 53 g/L, platelet count  $123 \times 10^9/L$ , neutrophil count  $4.43 \times 10^9/L$ , sodium 124 mmol/L, potassium 5.5 mmol/L, urea 45.2 mmol/L, creatinine 1706  $\mu\text{mol/L}$ , lactate dehydrogenase (LDH) 2140 IU/L, haptoglobin  $< 0.1 \text{ g/L}$ . She was immediately transferred to the intensive care unit with a provisional diagnosis of tumor lysis syndrome (TLS). She was treated with rasburicase and omeprazole and received urgent blood transfusions as well as being commenced on hemofiltration and plasma exchange.

A diagnosis of TLS was subsequently excluded (blood urate levels were low and blood calcium, phosphate and potassium levels were not elevated). Blood film analysis demonstrated evidence of acanthocytes, anisocytosis and red cell fragments. CT chest, abdomen and pelvis and ultrasound abdominal scanning showed no obstructive uropathy or evidence of malignancy. A working diagnosis of HUS was made, and the patient was transferred to a regional dialysis centre where she continued to require blood transfusions, hemodialysis via a femoral line and plasma exchange.

Further investigations including blood cultures, hepatitis screen and HIV testing were negative. Viral screen revealed coronavirus RNA positivity which was deemed not to be clinically significant. Autoimmune screen was negative, immunoglobulin levels and serum electrophoresis were normal. C3 and C4 were marginally decreased. The patient became pancytopenia within a week of admission and was commenced on prophylactic antibiotic treatment. She was commenced on amlodipine to treat her elevated blood pressure. Other observations, however, were normal.

A renal biopsy was not performed in light of the clinical evidence supporting a diagnosis of HUS. There was clear evidence of microangiopathic haemolysis with persistent anemia despite blood transfusions, low haptoglobin, abnormal blood films and AKI. Clinically, she remained well throughout her admission. Her urine output improved gradually and there was no further bleeding post admission. Dialysis continued as an in-patient over 17 days and she received seven plasma exchanges in total. Her renal function returned to normal one month after admission. The FBC returned to normal two months post-admission. She completed adjuvant radiotherapy following discharge from hospital and was commenced on adjuvant tamoxifen following normalization of renal function.

## Discussion

HUS is a serious condition that can be fatal. Recovery can be slow and incomplete with older data giving a two-month mortality rate of 50% [7]. It is characterized by microangiopathic haemolytic anemia, thrombocytopenia and AKI. There is a clinical overlap with thrombotic thrombocytopenic purpura (TTP) in which neurological symptoms (confusion, TIA-like features) and fevers can occur in addition to HUS features [8]. HUS and TTP are thrombotic microangiopathies with infection and drug toxicity being the commonest secondary causes. Malignancy itself is also a cause and, rarely, it can be secondary to autoimmune conditions and pregnancy [9]. In our patient there was clear evidence for a diagnosis of HUS and a causative link to docetaxel. Biochemically the presentation was consistent with a diagnosis of HUS

with AKI, thrombocytopenia and refractory anemia with evidence of haemolysis. TLS is rarely seen in solid tumors and non-hematological malignancies, especially in the adjuvant setting where the tumor has been surgically resected.

Several features help to corroborate docetaxel-induced HUS as the final diagnosis. Radiological imaging revealed no residual malignancy. Blood cultures and viral screen revealed no obvious infective cause and the patient did not demonstrate clinical features of sepsis. Whilst she did become neutropenic, this occurred after admission once severe renal failure and anemia were already established, and so any possible infection at this point is unlikely to have led to the development of HUS. Again, cultures were negative at this point and antibiotics were given empirically. She received no additional drug treatment during the time period between her third cycle of docetaxel and presentation, with the exception of anti-emetics and growth-factor support, which could account for her clinical presentation. She had received two previous cycles of docetaxel without significant toxicity. The development of HUS has been shown to occur post-chemotherapy in a dose-dependent fashion, i.e. due to cumulative dose, in which case there can be a gradual development of renal failure [7, 10].

There are no guidelines for the management of chemotherapy-related HUS as this is a rare occurrence, even with agents known to be associated with HUS. The most important factor is withdrawal of the suspected causative agent. Supportive care with blood transfusions, intravenous fluids, dialysis with or without plasma exchange and careful follow-up form the mainstay of treatment in severe cases. Our patient made a full recovery with return of normal renal function and FBC parameters with aggressive treatment.

## Conclusion

We present the first documented case of HUS associated with single-agent docetaxel. Prompt diagnosis and aggressive treatment resulted in the patient making a satisfactory recovery and the patient was able to complete her adjuvant treatment for early breast cancer.

## Competing Interests

None.

## Abbreviations

**AKI:** Acute Kidney Injury  
**C3:** Complement Component 3  
**C4:** Complement Component 4  
**CT:** Computerised Tomography  
**ER:** Oestrogen Receptor  
**FBC:** Full Blood Count  
**FEC:** Fluorouracil/Epirubicin/Cyclophosphamide  
**HER-2:** Her-2/neu-2 receptor  
**HIV:** Human Immunodeficiency Virus  
**HUS:** Haemolytic Uraemic Syndrome  
**LDH:** Lactate Dehydrogenase  
**NST:** No Special Type  
**RNA:** Ribonucleic Acid

**TIA:** Transient Ischaemic Attack

**TLS:** Tumor Lysis Syndrome

**TTP:** Thrombotic Thrombocytopenic Purpura

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