

***Enterococcus raffinosus* infection with atypical hemolytic uremic syndrome in a multiple myeloma patient after autologous stem cell transplant**

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Abstract

Autologous hematopoietic stem cell transplant (AHSCT) is the standard of care in the treatment of multiple myeloma worldwide. Infections are one of the most common complications of the chemotherapy regimen and AHSCT. Thrombotic microangiopathies are one of the rare but potentially life-threatening complications of infections associated with AHSCT. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (HUS) are two most common type of thrombotic microangiopathies. The HUS is classically related to diarrheal illness such as with *E.coli* strain O157: H7 that produce Shiga-like toxins. But it has never been described with *Enterococcus raffinosus* urinary tract infections (UTI). Here we are describing a case of atypical HUS associated with *Enterococcus raffinosus* UTI in a patient with multiple myeloma after AHSCT. The management of atypical HUS especially after AHSCT is challenging. Eculizumab, a humanized monoclonal antibody against complement protein C5, and thrombomodulin have emerging role in the management of some cases, but more studies are needed to define evidence-based management of this condition.

Introduction

Autologous hematopoietic stem cell transplant (AHSCT) is the standard of care in the treatment for multiple myeloma worldwide. Infections are commonly associated with the chemotherapy regimen and AHSCT. Thrombotic microangiopathies

such as atypical HUS are rare but potentially life-threatening complications of infections associated with AHSCT leading to increased morbidity and mortality after stem cell transplant. Atypical HUS is caused by endothelial toxicity related to chemotherapeutic agents and infections. The complement activation and dysregulation leads to the clinical hallmarks of hemolytic anemia and thrombocytopenia that are also seen in other thrombotic microangiopathies. Plasmapheresis, intravenous immunoglobulins (IVIg) and steroids have been used with variable success. The C5 complement antibody eculizumab, as well as thrombopoietin agonists, are new emerging agents which have been successfully used in some studies. Here we are describing a case of atypical HUS associated with *Enterococcus raffinosus* UTI in a multiple myeloma patient after AHSCT.

Case Report

The patient is a 62 y.o. Female, with past medical history of hypertension and gastroesophageal reflux disease, was diagnosed with Ig G-lambda multiple myeloma with initial presentation of acute renal insufficiency. Her bone marrow had 60% plasma cells on bone marrow aspirate at the time of diagnosis. She was treated with VDT-ACE (bortezomib, dexamethasone, thalidomide, adriamycin, cyclophosphamide, etoposide) induction chemotherapy and her renal function normalized. Repeat bone marrow showed 5% plasma cells on aspirate. The second induction chemotherapy cycle was done with VDT-PACE (bortezomib, dexamethasone, thalidomide, adriamycin, cyclophosphamide, etoposide, cisplatin) with stem cell mobilization collection. After the second induction cycle of chemotherapy, her bone marrow was negative for plasma cells. For consolidation phase, she received Melphalan 200 mg/m² based autologous stem cell transplant as an outpatient. Subsequently, she was admitted to the hospital for neutropenic fever with severe mucositis, diarrhea and *Enterococcus raffinosus* associated urinary tract infection.

The patient was admitted to the hospital. The testing for infectious causes including HHV6/HHV8, HSV1/2, EBV, CMV, adenovirus, parvovirus and stool for *C. difficile* was negative. The patient was started on broad-spectrum antibiotics and antifungals imipenem, vancomycin, and micafungin. Repeated blood cultures and urine cultures were negative, and antibiotics were

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stopped after completion their course of two weeks.

During her hospital course, she developed hypertension, acute renal insufficiency with elevated creatinine, LDH and liver enzymes including bilirubin (Figure 1). In the peripheral smear, she had features of microangiopathy including thrombocytopenia, hemolytic anemia with schistocytes >6/HPF. The patient became drowsy, though afebrile was transferred to intensive care unit for suspicion of thrombotic thrombocytopenic purpura (TTP). She was also started on plasmapheresis as the clinical features were suggestive of TTP. However her plasma ADAMTS 13 level was around 46%. Therefore classical TTP was excluded, and plasmapheresis after three sessions was stopped. The autoimmune profile including ANA, ds DNA was negative. The complements C3, C4 were within normal limits, but CH 50 levels were elevated.

The patient engrafted, recovered WBC counts, but microangiopathic hemolytic anemia with thrombocytopenia persisted. We made a working diagnosis of atypical HUS associated with *Enterococcus raffinosus* UTI after AHSCT in a patient with multiple myeloma. The gene rearrangement for atypical HUS was negative though as mentioned in the discussion below, it is positive only in approximately 50% patients with atypical HUS. Among other coagulation parameters, direct coombs test was negative, coagulation profile PT/APTT, INR was within normal limits, however, d-

dimers were persistently high, and fibrinogen levels continue to be on lower limits of normal. Since atypical HUS has a complement mediated autoimmune pathology, it was decided to give her eculizumab. Meanwhile pending approval of this medication, we decided to give her high dose IVIG (0.5 g/kg × 3 days followed by 1 g/kg × 3 days) in combination with 1 mg/kg prednisone for the underlying autoimmune pathology of the disease. The liver function tests and LDH came down drastically after initiation of IVIG and prednisone, however, her thrombocytopenia and hemolytic anemia persisted. Subsequently, she was started on eculizumab. She received the meningococcal vaccine before starting eculizumab. She received three weekly doses of eculizumab, along with ciprofloxacin prophylaxis. Her hemolytic anemia improved after eculizumab but her thrombocytopenia persisted. The repeat bone marrow examination showed decreased megakaryocytes. She was started on eltrombopag. Her platelets levels stabilized and subsequently discharged home (Figure 2).

Discussion and Conclusions

Hemolytic uremic syndrome (HUS) is a rare thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal injury.¹ The typical HUS primarily affects children.² Approximately 90% of cases are preceded by an *Escherichia coli* infection, typically with *E.coli* strain O157:H7 that produce Shiga-like toxins and is thus classified as Shiga toxin-induced HUS (STEC-HUS).^{1,2} Typical HUS is generally associated with a good prognosis and low mortality. Atypical HUS also has features of microangiopathic hemolytic anemia, thrombocytopenia, and renal injury. Atypical HUS is associated with increased mortality, and about 50-60% of cases progress to end-stage renal disease.¹ The thrombotic microangiopathies occurring after hematopoietic stem cell transplant are particularly devastating and have very high mortality rates.^{2,3}

In our patient, clinical features were suggestive for atypical HUS with *Enterococcus raffinosus* UTI after AHST for multiple myeloma. The species *Enterococcus raffinosus* was first recognized in 1989,⁴ since then it has been associated with various infections in immunosuppressed patients especially in the acute care hospital settings.^{4,5} The natural habitat of *Enterococcus raffinosus* is unknown, but the organism has been found in the oropharyngeal flora of cats. It has been associated with wound infections, abscesses, urinary tract infections, vertebral osteomyelitis and endocarditis.⁴⁻⁹ However, microangiopathic hemolytic anemia has never been described in the literature with *Enterococcus* UTI. Though hemolytic uremic syndrome has been described with urinary tract infections with *E. coli*.^{10,11}

Chiurchiu *et al.*¹² first reported that

hemolytic uremic syndrome could be associated with non-diarrheal Shiga toxin producing *Escherichia coli* O157:H7 which causes bacteremia and urinary tract infection. Later, Park *et al.*¹³ studied the association between thrombotic microangiopathy and UTI. They found out that 23% of the visits for thrombotic thrombocytopenic purpura had UTI and concluded that occult bacterial infections could cause alterations

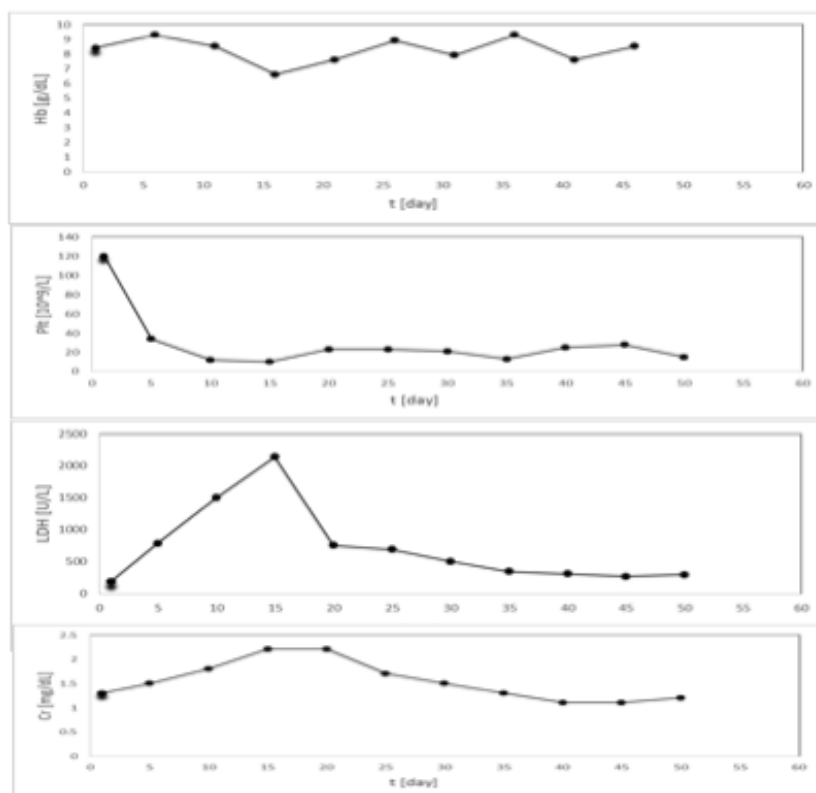


Figure 1. The graph showing the laboratory results in the patient with multiple myeloma with *Enterococcus raffinosus* infection

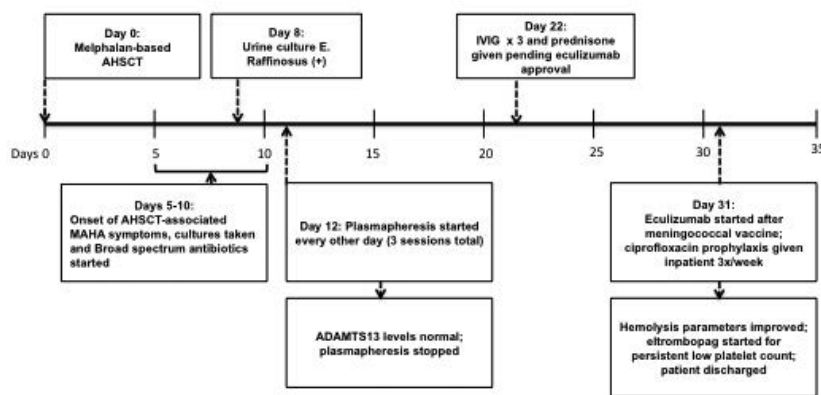


Figure 2. Timeline of the atypical HUS after *Enterococcus raffinosus* UTI infection after AHST in a multiple myeloma patient.

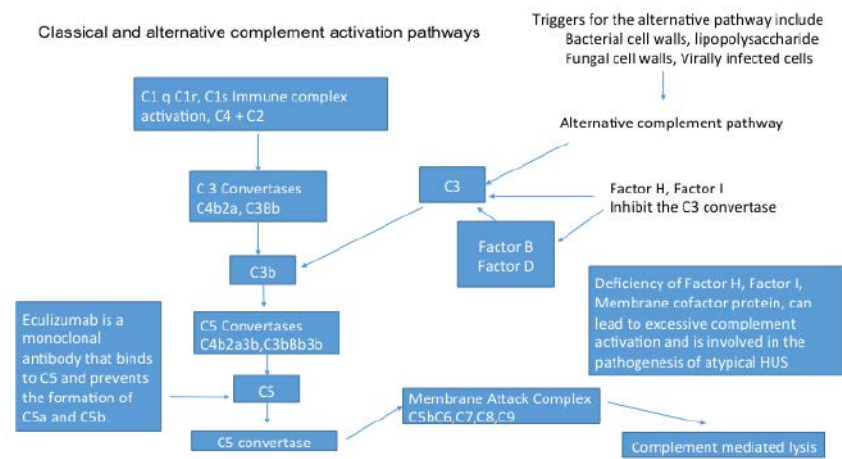


Figure 3. Classical and alternative pathways and role in pathogenesis of atypical HUS.

in the coagulation pathways probably resulting from the molecular mimicry between antibodies directed against infectious agents and the ADAMTS13 protein moiety.¹²⁻¹⁴

Over-activation of the complement system is the most common etiology of atypical HUS.¹⁴ The dysregulation of alternative complement pathway plays a central role in the pathogenesis of atypical HUS (Figure 3). The regulation of complement pathway is critical in preventing thrombosis from occurring, and genetic mutations have been described in up to 60% of adult aHUS case.^{14,15} The alteration in the alternative complement pathways especially mutations in complement factor I, complement factor H, and membrane cofactor protein are among the commonly seen abnormalities and account for approximately 50% of aHUS cases.^{14,15} Drugs such as calcineurin inhibitors and sirolimus have also been shown to cause endothelial injury and decrease VEGF expression leading to thrombotic microangiopathy.¹⁶ Sepsis may cause an alteration in ADAMTS13 activity most likely due to cleavage by circulating proteolytic enzymes.¹⁷

Until recently, treatment of aHUS was accomplished with plasma exchange although the efficacy of this treatment was variable and approximately 50% progressed to ESRD.¹⁸ Eculizumab, a monoclonal anti-C5 component antibody, is a promising new treatment option for aHUS.¹⁹ Eculizumab has also shown to be useful in treating typical HUS caused by STEC and thrombotic thrombocytopenic purpura (TTP) in which ADAMTS13 levels are below acceptable ranges.^{20,21}

Patients who develop atypical HUS or any thrombotic microangiopathy following

AHSCT have a high likelihood of succumbing to it and progression to multi-organ failure. This makes it especially important to identify candidates with the underlying genetic anomaly that predisposes them to this condition as well as the patients who will respond to eculizumab. Recently, recombinant human soluble thrombomodulin has also been used successfully to treat thrombotic microangiopathy after hematopoietic stem cell transplantation.²² Lastly, we need more studies to determine the exact pathophysiology of all these relatively uncommon disorders which can help proper diagnosis and management of these conditions especially in the setting of autologous stem cell transplants in hematological malignancies.

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