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A Case of Atypical Hemolytic Uremic Syndrome Superimposed on Behcet's Disease

T. Sakaci[1], E. Ahbap[1], M. Toprak[1], M. Sevinc[1], T. Basturk[1], Y. Koc[1], S. Akpinar[2], A. Ozagari[3], Y. C. Koksal[1], E. Kara[1], C. Akgol[1], Z. Atan Ucar[1], T. Sahutoglu[1], F. Bayraktar Caglayan[1] and A. Unsal[1]

[1]Department of Nephrology, Sisli Etfal Research and Educational Hospital, Istanbul, Turkey.
[2]Department of Hematology, Sisli Etfal Research and Educational Hospital, Istanbul, Turkey.
[3]Department of Pathology, Sisli Etfal Research and Educational Hospital, Istanbul, Turkey.

Authors' contributions

This work was carried out in collaboration between all authors. Author TS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author MT managed the literature searches. Author MS helped for language and wrote subsequent drafts. All authors read and approved the final manuscript.

Case Study

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ABSTRACT

Behcet's disease is a disorder that involves oral aphthous with genital ulcer, skin lesions, gastrointestinal, vascular, neurological diseases and systemic symptoms such as arthritis. Thrombophilia and vasculitis which may involve any vessel play a role in pathogenesis. aHUS is a syndrome which is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. We would like to report a case of aHUS in a patient with Behcet's Disease.

43 year old male patient was admitted to the emergency department with dyspnea for 3 days. In his medical history, 10 years ago Behcet's Disease was diagnosed and treated with colchicine. At presentation his blood pressure was 140/80mm Hg, heart rate 116/min, respiratory rate 16/min and body temperature 98.9ºF. Laboratory studies revealed microangiopathic hemolytic anemia, thrombocytopenia, acute renal insufficiency, increaded serum bilirubin and lactate dehydrogenase levels, decreased haptoglobulin level leading to suspicion of TMA. Peripheral blood smear was significant for common schistocytes, anisocytosis and thrombocytopenia which were also suggestive for

**Corresponding author: E-mail: musevinc@hotmail.com;*

thrombotic microangiopathy.
ADAMTS13 level was normal. Pathogenic bacteria in stool microscopy and culture were not available. The patient underwent kidney biopsy consistent with TMA. All symptoms were consistent with a diagnosis of aHUS; 1gr/d methylprednisolone was administered for 3 days with 40mg/d steroid maintenance afterwards. Plasmapheresis therapy was done for 15 times. On the 12th day of treatment, the response was dramatic. Dyspnea was disappeared, hemoglobin increased, platelet number and LDH level normalized, and creatinine was better.
aHUS is a disease with high mortality that response dramatically to plasmapheresis and immunsuppressive therapy. Without any other predisposing factor in Behcet's Disease, aHUS may develop de novo.

Keywords: Behcet's disease; atypical hemolytic uremic syndrome; acute renal failure; plasmaphresis.

1. INTRODUCTION

Behcet's disease is a disorder manifesting with oral aphthous with genital ulcer, skin lesions, gastrointestinal, vascular, neurological diseases and systemic symptoms such as arthritis. Thrombophilia and vasculitis which may involve any vessels play a role in its pathogenesis. Painful recurrent mucocutaneous lesions are common in clinical practice. The frequency of other findings show a difference in populations nevertheless renal disease is rare [1,2].

Hemolytic Uremic Syndrome (HUS) is a syndrome which is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. Generally it presents with a bloody diarrhea in childhood caused by E. Coli O157:H7 and also known as D(+) HUS. Atypical HUS (aHUS) is characterized by absence of diarrhea, lack of Shiga-like toxin in stool, ADAMTS13 negativity and is known as D(-) HUS. aHUS may be familial or sporadic. Familial aHUS reasons include mutations in complement factor H (FH), factor I (FI), C3 convertase proteins, thrombomodulin, membrane cofactor protein (MCP), von Willebrand factor washed metalloprotease activity failure (vWF-CP or ADAMTS13), complement FI failure and autoantibodies to FH. Secondary or sporadic aHUS may develop due to many reasons like Streptococcus Pneumoniae, HIV, H1N1 influenza A, malignancy, cancer chemotherapy, ionizing radiation, bone marrow or solid organ transplantation, calcineurin inhibitors, sirolimus, anti-VEGF (vascular endothelial growth factor) agents, pregnancy, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, malignant hypertension, glomerulopathies, systemic lupus erythematosus, antiphosholipid syndrome and scleroderma [3-5]. We would like to report a case of aHUS in a patient with Behcet's disease.

2. CASE REPORT

43 year old male patient was admitted to the emergency department with dyspnea lasting for 3 days. In his past medical history, 10 years ago, mucocutaneous Behcet's disease was diagnosed because of oral aphthous and genital ulcers and treated with colchicine. His blood tests were normal 9 months ago. At presentation, blood pressure was 140/80mmHg, heart rate 116/min, respiratory rate 16/min, and body temperature 98.9ºF. Physical examination was remarkable for dyspnea, jaundice and decreased breath sounds bibasilarly. Chest X-ray was normal while sinus tachycardia was seen on ECG. Arterial pH, pCO_2, and HCO_3 was

7.44, 40, 26, respectively. D-dimer level was normal. Urea was 162mg/dl, creatinine 8.2mg/dl, LDH 2524 U/L, direct bilirubin 0.79 mg/dl, and indirect bilirubin 1.63mg/dl. Complete blood count revealed anemia (8.05g/dl), leukocytosis (12.666/L) and thrombocytopenia (50.000/uL). Haptoglobulin level was low (<10). Coagulation parameters were normal. Direct and indirect Coombs were negative. Peripheral blood smear was significant for common schistocytes, anisocytosis and thrombocytopenia which were suggestive for thrombotic microangiopathy (Fig. 1). All immunological tests (ANA, ANCA, C3, C4) and serological tests (HBsAg, Anti-HBs, Anti-HCV, Anti-HIV) were negative. Protein C, protein S and vWF levels were normal. Complement factor H, I, 3, B, CD46, membrane cofactor protein, and thrombomodulin gene mutations were not detected.

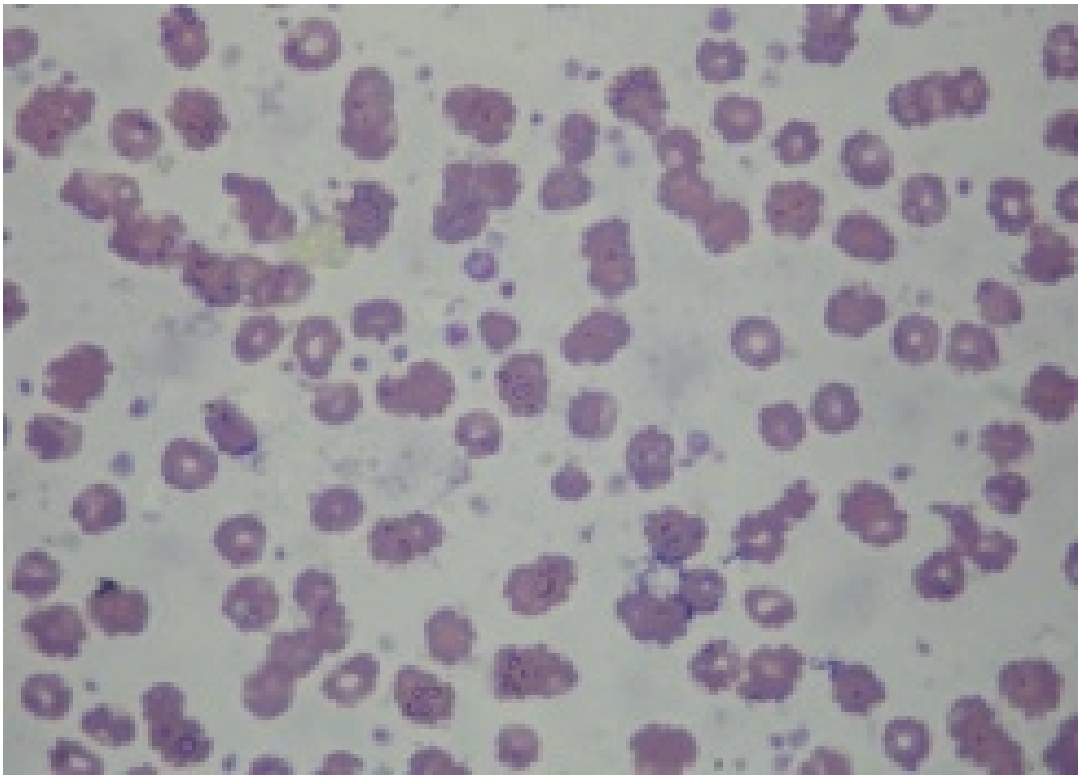

Fig. 1. Peripheral blood smear illustrated schistocytes with microhemolytic anemia and thrombocytopenia

ADAMTS13 level was normal. Stool microscopy and culture were negative for pathogenic bacteria. Brain MRI was reported as normal.

The patient underwent kidney biopsy consistent with thrombotic microangiopathy (TMA). On biopsy specimen, 20 glomeruli were seen, one was globally sclerotic. Glomerular fibrin thrombi and fragmented erythrocytes in capillary lumens of glomeruli, arteriolar fibrinoid necrosis without any inflammatory changes were detected (Fig. 2). Arterial mucoid intimal thickening were seen as well (Fig. 3). Immunofluorescence staining for IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinojen were all negative.

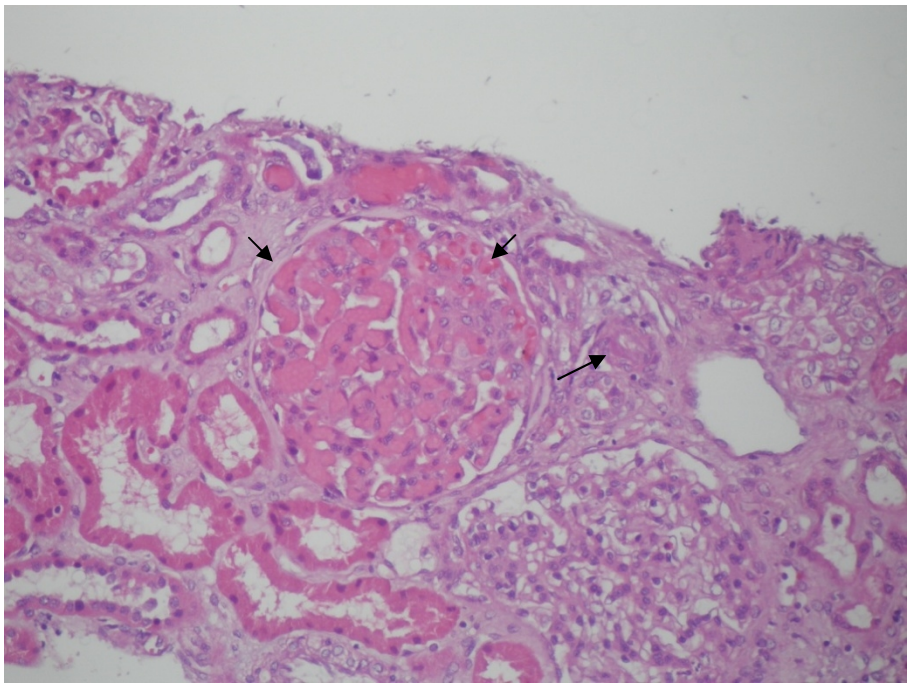

Fig. 2. There are numerous glomerular capillary thrombi (short arrows). The arteriole at the right of the glomerulus has fibrinoid necrosis (long arrow). (x20 obj. H&E)

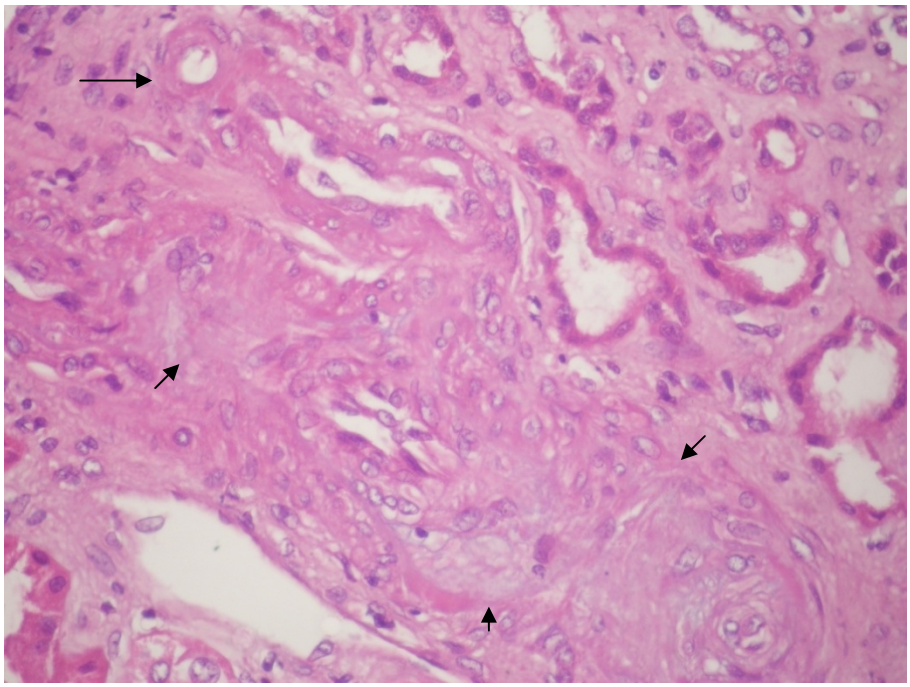

Fig. 3. The artery has mucoid intimal thickening (short arrows), and fibrinoid necrosis (long arrow). There is no associated inflammatory cells' infiltrate. (x40 obj. H&E)

Detailed anamnesis of past medical history for thrombosis was negative. All symptoms were consistent with a diagnosis of aHUS. For the treatment, 1gr/d methylprednisolone was administered for 3 days, with maintenance dose of 40mg/day thereafter. Plasmapheresis therapy was done for (0.3/kg) 15 times. On the 12th day of treatment, response was dramatic. Dyspnea was disappeared, hemoglobin was 10,6g/dl, platelet 402,000/uL, LDH 479 U/l, creatinine 4.31mg/dl (Table 1).

Table 1. The patient's biochemical analyzes chart

Date	28th Jan 2013	07th Oct 2013	06th Dec 2013
LDH	393	2524	479
Platelet	329.000	50.000	402.000
Creatinine	0.91	8.28	4.31

3. DISCUSSION

Behcet's disease is a disorder manifesting with oral aphthous, genital ulcer, skin lesions, gastrointestinal, vascular, neurological diseases and systemic symptoms. It is seen more frequently and more severely between East Asia and Mediterranean Sea. In the Eastern Mediterranean region, Behcet's disease is slightly more common in females than males and usually affects young adults between the ages of 20 and 40 [2]. It's also commonly diagnosed in Turkey (80-370 cases/100.000), Japan, Korea, China, Iran and Saudi Arabia [2]. The underlying cause is unknown. As with other autoimmune diseases, presence of an agent triggering an exaggerated autoimmune response, infectious pathology or genetic predisposition can result to the development of the disease.

Cause of thrombotic events has not been elucidated in Behcet's disease but microscopic examination of arteries and veins revealed vasculitis. Vascular involvement was reported in 7.7-60.6% of Behcet's disease. Venous system is affected most of the time even though arterial or combined involvement may be seen. Vessels become thrombotic or aneurysms may develop when vasculature is affected [2].

HUS is an acute syndrome which is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. 90% of cases diagnosed as HUS has been associated with diarrhea and also known as D(+) HUS. %10 of HUS cases is associated with complement over reactivity and diarrhea (Shiga toxin) is not available. In adult patients, aHUS term were defined together with presence of HUS and ADAMTS13 negativity (activity>%10). Familial or sporadic complement mutations have been found in many aHUS patients. aHUS may develop secondary to some triggering factors as well. However, despite all these developments, 30-40% of cases have not any defect in the complement system [3-5]. aHUS is a syndrome with a high mortality rate. After diagnosis, plasmapheresis should be started without delay to clear antibodies from the circulation, immunsuppressive therapy should be initiated to prevent renal damage.

In our patient, increased LDH levels, microangiopathic hemolytic anemia, thrombocytopenia and, kidney failure led to the suspicion of TMA. TTP was excluded by normal ADAMTS13 activity. Kidney biopsy was performed. No complement mutation was found so aHUS thought as idiopathic.

Association between TMA and some collagen vascular diseases such as SLE [1,2,6] may be possible. In the literature, there is a case of thrombotic microangiopathy (HUS/TTP) related to Behcet's disease has been investigated but the results are conflicting [4,7].

Kwon et al. [7] reported a case with thrombotic thrombocytic purpura diagnosed as Behcet's disease later on. ADAMTS13 level was not reported and the patient's renal function was recovered by steroid therapy alone, without plasmaphresis. As a result, one cannot regard this patient as aHUS.

Docci et al. [8] reported another case of a patient with Behcet's disease in whom HUS/TTP developed during treatment with cyclosporine. The mechanism was possibly endothelial damage by direct toxic effect of the drug [3,9].

Jabr et al. [10] reported a case with thrombotic thrombocytopenic purpura (TTP) in Behcet's Disease [9]. This case has some differences and similarities from our one. The most discriminative ones are lower thrombocyte and normal creatinine level in patient with TTP. They did not report the ADAMTS13 level.

Reports in the past could not diagnose patients as aHUS clearly, no one declared ADAMTS13 level. To our knowledge, this is the first case of aHUS in a patient with Behcet's disease. In our case, the patient's past medical drug history was not significant except colchicine.

According to the literature [10] absence of known risk factors for aHUS would support the hypothesized causal relationship between Behcet's disease and aHUS. In this case it is reported that we have explained to illuminate the cause of aHUS, we couldn't find any reason except Behcet's Disease.

4. CONCLUSION

aHUS is a disease with high mortality that response dramatically to plasmapheresis and immunosuppressive therapy. aHUS may be seen in Behcet's Disease even no other predisposing factor is present

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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