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# İç Hastalıkları Servisimizde Mikroanjiopatik Hemolitik Anemi (MAHA) Tanısı İle Yatırılarak Takip Ettiğimiz Hastaların Retrospektif Analizi

## Retrospective Analysis of Patients Hospitalized With The Diagnosis of Microangiopathic Hemolytic Anemia in Our Internal Medicine Clinic

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## ÖZ

**Giriş:** Mikroanjiopatik hemolitik anemiler (MAHA) oldukça nadir görülen ve tedavi edilmediğinde mortal seyreden bir grup hastalığa verilen isimdir.
**Amaç:** Bu çalışmadaki amacımız; trombositopeni saptanan ve özellikle de end-organ tutulumu olmayan hastalarda ayırıcı tanıda MAHA'nın hatırlanması gerekliliğini vurgulamaktır. Aynı zamanda erken tanı ve tedavide mortalite oranının düştüğünü gösterebilmektir.
**Gereç ve yöntem:** Eylül 2017- mayıs 2019 tarihlerinde arasında iç hastalıkları servisinde tanısı koyularak takip ve tedavi edilen vakaları retrospektif olarak inceledik. Tanı kriterlerine uyan toplam 15 hasta çalışmaya alındı. Hastalardan, ilk başvuruda; tam kan sayımı, sedimentasyon, periferik yayma, direkt coombs, CRP, koagülasyon testleri ve biyokimyasal tetkikler çalışıldı. Ayrıca her plazmaferez işleminden önce ve sonra; tam kan sayımı, üre, kreatin, LDH, indirek bilirubin düzeyleri bakıldı.
**Bulgular:** Hastaların E/K oranı 8 /7 (% 53.3/ 46.6) ve yaş ortalaması 46.8 (25-79) bulundu. Hastaların etyolojik sınıflandırılması sonucu; 8 hasta (%53.3) TTP(Trombotik trombositopenik purpura) olarak, 4 hasta (%26.6) vitamin B 12 eksikliğine bağlı, 1 hasta sistemik lupus eritamatozus (%6.6), 1 hasta (%6.6) atipik hemolitik üremik sendrom ve 1 hasta (%6.6) da ilaç ilişkili MAHA olarak değerlendirildi.
**Sonuç:** Çalışmaya alınan 15 hastadan 11 hastanın (%73.3) iyileşme, 4 hastanın (%20) izlemi esnasında exitus, 1 hastanın (%6.6) taburculuktan sonra, toplamda 5 (%33.3) hastanın exitus olduğu tespit edildi.
**Anahtar Kelimeler:** Anemi, hemolitik, retrospektif

## ABSTRACT

**Introduction:** Microangiopathic hemolytic anemia (MAHA) is a group of diseases rarely seen and having severe mortality rate if it doesn't treated.
**Aim:** Our aim is to emphasize the need to recall the MAHA in differential diagnosis of patients with thrombocytopenia, especially those without end-organ involvement, which are presented in this study. At the same time to show the rate of mortality decreases in early diagnosis and treatment.
**Materials and methods:** We retrospectively reviewed the cases that were diagnosed and examined and treated in the Internal Medicine Service between september 2017 and may 2019. A total of 15 patients were included in the study. Complete blood count, sedimentation, peripheral smear, direct coombs, CRP, coagulation tests and biochemical tests were performed as the first application. In addition, complete blood count, urea, creatinine, LDH, indirect bilirubin levels were measured both before and after each plasmapheresis.
**Findings:** Gender ratio of the patients was 8 / 7 (53.3 / 46.6) and the mean age was 46.8 (25-79). As a result of etiological classification of patients; 8 patients (53.3%) had TTP (Thrombotic thrombocytopenic purpura), 4 patients (%26.6 ) had vitamin B12 deficiency, 1 patient had systemic lupus erythematosus ( %6.6), 1 patient (%6.6) was associated with complement, 1 patient (%6.6) had drug-releated MAHA.
**Conclusion:** Of the 15 patients included in the study, 11 patients (73.3%) were recovered, 1 patient (6.6%) died after discharge, and 4 patients (20%) died during follow, totally 5 (%33.3) patients died.
**Keywords:** Anemia, hemolytic ,retrospective

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## Introduction and purpose

Microangiopathic hemolytic anemias (MAHA) define a group of diseases characterized by destruction of the erythrocytes passing through the fibrin network in the microthrombus in the capillary system (1). They are progressing with thrombosis caused by platelets in systemic circulation, kidneys, and cerebral circulation and associated clinical symptoms. Thrombocytopenia are seen as a result of consumption-related thrombosis and schistocytes are seen as a result of mechanical damage to erythrocytes due to platelet plugs (2). We thought that the most important point in determining the treatment in patients with a diagnosed with MAHA was to determine the etiology. Our aim in this study is to emphasize the necessity of remembering MAHA in the differential diagnosis in patients with thrombocytopenia and especially in patients with or without end-organ involvement, and that rapid diagnosis and treatment can reduce mortality and morbidity.

## Materials and methods :

In our study; between September 2017 and May 2019, we retrospectively examined the cases that were followed up and treated in the internal medicine service with the diagnosis of MAHA. The etiology of MAHA was analyzed as primary MAHA (TTP, HUS) and secondary MAHA. Complaints, history of chronic illness, drug use, and family history of all patients at the time of admission were questioned. Daily physical examination findings, laboratory findings (complete blood count, CRP, erythrocyte sedimentation rate, direct coombs, prothrombin time, aPTT, INR, fibrinogen, ferritin, vitamin B12, urea, creatinine, AST, ALT, LDH, Indirect bilirubin, total protein, albumin, ADAM-TS-13 activator and inhibitor, peripheral blood analysis which was did by a hematology specialist was followed by us every day. Skin biopsy was performed from patients with skin lesions. The effects of corticosteroid, immunosuppressive and plasma infusion treatments applied to the patients were evaluated by monitoring their serum LDH levels and platelet levels, and the response differences of the patients to each treatment were made accordingly. This study was approved by the ethics committee of Bakırköy Training and Research Hospital in 2018.

## Exclusion criteria:

Patients with previous diagnosed of MAHA, women with pregnancy complications such as preeclampsia, eclampsia, hellps syndrome, and patients under 18 years of age were excluded. In the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov simirnov test. SPSS 22.0 program was used in the analyzes.

## Results

Fifteen patients were included in the study. 8 of the patients were male and 7 were female and the mean age was 46.8 ± 15.6 (25-79 years). 9 of the patients were considered to be primary MAHA (60%), 6 of them (40%) were evaluated based on secondary reasons. Demographic data of the cases including age, gender, marital status and smoking status are presented in a table (Table 1).

**Table 1.** Demographic characteristics of the cases

| | | Min – Max | Median | Average +- s.d | n-% |
|---|---|---|---|---|---|
| Age | | 25.0 – 79.0 | 43 | 46.8 +- 15.6 | |
| Gender | Female | | | 8 | 53.3% |
| | Male | | | 7 | 46.7% |
| Marital Status | Bachelor | | | 3 | 20.0% |
| | Widowed | | | 1 | 6.7% |
| | Married | | | 11 | 73.3% |
| Smoking | (-) | | | 10 | 66.7 % |
| | (+) | | | 5 | 33.3% |

The most common complaints of our patients were dizziness (31.0%) and headache (13.7%). Other complaints were nausea (10.2%), dyspepsia (3.4%), rash (3.4%), ocular findings (6.8%), altered consciousness (6.8%), bloody stools (3.4%), weakness (3.4%), fever ( 3.4%) and numbness in the fingers (3.4%). (Table.2).

**Table 2.** Evaluation of the age, gender and application complaints of the cases

| Case number | Age | Gender | Aplication complaints |
|---|---|---|---|
| 1 | 52 | Female | Headache, faint |
| 2 | 43 | Male | Dizziness, numbness in hands |
| 3 | 65 | Female | Clouding of consciousness |
| 4 | 31 | Female | Dizziness, vision loss |
| 5 | 30 | Female | Dizziness, nausia |
| 6 | 25 | Female | Headache, blurred vision, fever |
| 7 | 79 | Female | Dizziness, weakness |
| 8 | 30 | Male | Dizziness, nausia |
| 9 | 60 | Male | Prone to sleep, bloody stools |
| 10 | 40 | Male | Dizziness |
| 11 | 32 | Male | Weakness |
| 12 | 39 | Male | Dizziness |
| 13 | 64 | Male | Stomachache, bloody stools |
| 14 | 51 | Female | Headache, dizziness, nausia |
| 15 | 55 | Male | Headache, dizziness, rash |

Anemia and thrombocytopenia were detected in all patients and fragmentation findings were observed in their peripheral smears (100%). The vital signs of the patients at the time of admission were recorded. Two patients had high blood pressure and five patients had low blood pressure.

**Table 3.** Vital signs of the patients at the time of admission.

| Case number | Systolic blood pressure | Diastolic blood pressure | Pulse | Fever |
|---|---|---|---|---|
| 1 | 100 | 65 | 82 | 37.5 |
| 2 | 120 | 70 | 80 | 36.5 |
| 3 | 130 | 85 | 96 | 36.7 |
| 4 | 170 | 95 | 90 | 36.5 |
| 5 | 90 | 50 | 100 | 36.5 |
| 6 | 135 | 90 | 88 | 36.5 |
| 7 | 100 | 60 | 95 | 37 |
| 8 | 90 | 60 | 55 | 36.5 |
| 9 | 90 | 50 | 100 | 36.5 |
| 10 | 110 | 70 | 100 | 37 |
| 11 | 90 | 50 | 102 | 36.5 |
| 12 | 100 | 60 | 68 | 36.6 |
| 13 | 100 | 60 | 76 | 36.4 |
| 14 | 90 | 50 | 80 | 37.5 |
| 15 | 180 | 110 | 94 | 37.7 |

The most common comorbid diseases in 15 patients were determined as hypertension, Type 2 diabetes, thyroid dysfunction, arrhythmia and hyperlipidemia.

**Table 4.** Smoking and comorbid diseases status of patients

| Case number | Smoking | Comorbid diseases |
|---|---|---|
| 1 | Yes | No |
| 2 | Yes | No |
| 3 | Unknown | Hypertension, Hypothyroidism |
| 4 | No | No |
| 5 | No | No |
| 6 | Unknown | No |
| 7 | Unknown | Arrhythmia |
| 8 | No | No |
| 9 | Unknown | Type-2 DM |
| 10 | Yes | No |
| 11 | Unknown | No |
| 12 | Yes | No |
| 13 | Former smoker | Type-2 DM, Hyperthyroidism |
| 14 | Unknown | Hypertension |
| 15 | Yes | Hypertension, Hyperlipidemia |

In the examinations of all patients at the time of diagnosis, high LDH levels, high indirect bilirubin, high reticulocyte, low thrombocyte, anemia, low haptoglobulin, and schistocytes in peripheral blood smear were found.

TTP in 8 patients, vitamin B12 deficiency in 4 (one of them had concurrent gastric adenocarcinoma, case 11), substance use in 1, SLE in 1, and atypical HUS in 1 were defined as etiological factors.

ADAMTS-13 activation and ADAMTS-13 inhibitor percentages of the cases are presented in Table 7. ADAMSTS-13 values were found within normal limits in 7 of the cases and therefore inhibition values were not calculated.

The treatments received and the final status of the cases are presented in a table. All cases except case 7 and case 12 evaluated as MAHA due to vitamin B12 deficiency were given corticosteroid treatment. Plasmapheresis treatments were not applied to Case 5 with drug-related MAHA due to refusal of treatment and to cases 7 and case 12 with B12 deficiency related MAHA because it was unneeded. Vincristine treatments were given to 2 cases who were resistant to plasmapheresis treatment, and 1 case was given rituximab. Eculizumab and hemodialysis treatments were applied to the case, which was evaluated as atypical HUS, due to severe renal dysfunction. 11 of the 15 patients were discharged with recovery. 1 patient died as a result of relapse 1 month after discharge. It is noteworthy that all 5 cases evaluated as exitus had TTP in their etiology. Also, these 5 cases also had comorbid diseases. The change of biochemical parameters at the time of diagnosis and in remission (the last value was taken if discharged or exitus) was examined. Peripheral blood smear findings, changes in PLT and LDH values were found to be significant ($p < 0.001$). It was determined that the mean basal LDH was 2101 U / L and regressed to the mean normal range (569 U / L) in remission, the mean platelet was $76.10^{3}$ / μL and increased to normal value $199.9\ 10^{3}$ / μL in remission. Duration of patients' hospitalization in the internal medicine service; the mean was determined as 20.25 days for cases with TTP, 14.25 days for cases with a diagnosis of vitamin B12 deficiency, 6 days for a drug-related cases, 20 days for a patient with SLE, and 46 days for atypical HUS.

**Table.5.** Laboratory values at the time of admission

| | Min-Mak | Medyan | Ort.±s.s |
|---|---|---|---|
| Creatinine (Mg/Dl) | 0,3-15,3 | 0,8 | 1,7 ±3,8 |
| AST (U/L) | 19,0-132,0 | 35,0 | 42,4 ±27,2 |
| ALT(U/L) | 15,0-116,0 | 28,0 | 37,4 ±28,9 |
| Hemoglobın (Gr/L) | 5,6-10,0 | 6,7 | 7,1 ±1,2 |
| HCT % | 15,0-31,0 | 19,0 | 20,1 ±4,5 |
| MCV (F/L) | 71,0-18,0 | 90,0 | 90,2 ±10,4 |
| White sphere (Mm3) | 2,5-20,4 | 6,6 | 7,3 ±4,6 |
| APTT (Sn) | 19,0-32,0 | 23,0 | 24,5 ±4,2 |
| PT (Sn) | 10,0-20,0 | 12,0 | 13,1 ±2,6 |
| INR | 0,8-1,2 | 0,9 | 0,9 ±0,1 |
| Sedimentation (Mm/H) | 26,0-81,0 | 56,0 | 52,5 ±14,4 |
| Urea (mg/dl) | 8,0-190,0 | 34,0 | 44,9 ±42,5 |
| LDH (U/L) | 357-5996 | 1300 | 2102 ±1861 |
| Last LDH (U/L) | 208-2251 | 269 | 569 ±665 |
| Platelet ($mm^3$) | 8,0-350,0 | 50,0 | 76,4 ±93,7 |
| Last Platelet ($mm^3$) | 9,0-338,0 | 240,0 | 199,9 ±94,0 |
| CRP (mg/dl) | 4,0-120,0 | 17,0 | 25,9 ±30,5 |
| Hospitalization | 1,0-46,0 | 20,0 | 19,4 ±13,8 |
| Calcium (Mg/Dl) | 7,8-9,4 | 8,6 | 8,5 ±0,5 |
| Indırect Bılırubın (Mg/Dl) | 0,4-2,3 | 1,4 | 1,3 ±0,6 |
| Haptoglobulin (Mg/Dl) | 0,0-3,0 | 0,0 | 0,4 ±0,9 |
| Retirulocyte index % | 0,6-13,2 | 5,0 | 5,6 ±3,5 |
| Vitamin B-12 (Pg/Ml) | 20,0-2000 | 306,0 | 403,1 ± 511,1 |

The patient having bad general condition in the admission has shortest hospital stay of 1 day and the longest-lasting case is atypical HUS with 46 days. Average length of hospital stay of patients diagnosed with primary MAHA is 26 days, and it is 23 days for secondary MAHA.

The number of patients with exitus was determined as 5 and the etiology of all of them was TTP. Hypertension, hypothyroidism, diabetes mellitus and hyperlipidemia were determined as co-morbid diagnoses, and 3 of them were male and 2 were female. All of them were found to have low ADAMTS-13 activator and high inhibitor. The gender distribution in patients diagnosed with primary MAHA according to etiology was determined as 4 females and 5 males. All patients with secondary MAHA (100%) were cured, 55.5% of the patients with primary MAHA were mortal.

## Discussion

Epidemiological data on TTP are quite scarce. Ethnic predisposition has not been deter mined. Familial predisposition may be present. It is more common in women and the ratio of M / F is 3/2 (3). According to CDC records in North America, it was reported that the incidence, which was stated around 0.5-1 / 1 million before 1990, gradually increased to 3.7 / 1 million (3). In our study, the mean age was 46.8 ± 15.6 (25-79 years). In our study, the female / male gender ratio was found to be 7/8.

**Table.6.** MAHA etiologies of the patients in our study

| Case Number | Etiology |
|---|---|
| 1 | TTP |
| 2 | TTP |
| 3 | TTP |
| 4 | Atypical HUS |
| 5 | Medication use (cannabinoid) |
| 6 | SLE |
| 7 | Vitamin B12 deficiency |
| 8 | TTP |
| 9 | TTP |
| 10 | Vitamin B12 deficiency |
| 11 | Vitamin B12 deficiency + gastric adenocarcinoma |
| 12 | Vitamin B12 deficiency |
| 13 | TTP |
| 14 | TTP |
| 15 | TTP |

**Table 7.** ADAMTS-13 levels of patients

| Case Number | ADAMTS-13 activation (%) | ADAMTS-inhibition (%) |
|---|---|---|
| 1 | 0.39 | 90 |
| 2 | 0.76 | 80 |
| 3 | 0.50 | 65 |
| 4 | 36 | - |
| 5 | 87 | - |
| 6 | 66 | - |
| 7 | 54 | - |
| 8 | 0.62 | 69 |
| 9 | 0.40 | 70 |
| 10 | 70 | - |
| 11 | 53 | - |
| 12 | 90 | - |
| 13 | 0.07 | 76 |
| 14 | 0.02 | 85 |
| 15 | 0.01 | 80 |

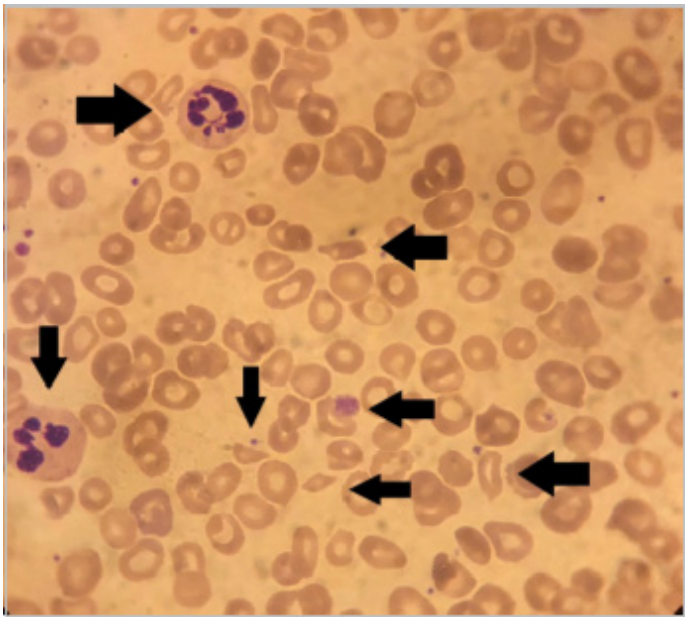
Many cases are idiopathic, moreover, it may occur in relation with the drug usage, postpartum pregnancy period, connective tissue diseases, autoimmune diseases, infective endocarditis or neoplasms (38). In our study, the rates for the etiology were determined as 60% for primary MAHA and 40% for secondary MAHA. Vitamin B12 deficiency causes hypersegmented neutrophils as peripheral smear finding. In severe deficiencies, thrombocytopenia, hemolysis and clinical findings are among the secondary causes of MAHA.

**Table 8.** Ethiological treatment

| | Min-Mak | Medyan | average.±s.s./n-% | | |
|---|---|---|---|---|---|
| diagnosis | TTP | | 8 | | 53,3% |
| | B12 deficiency | | 4 | | 26,7% |
| | drug releated | | 1 | | 6,7% |
| | compleman releated HUS | | 1 | | 6,7% |
| | Lupus releated MAHA | | 1 | | 6,7% |
| corticosteroid | (-) | | 3 | | 20,0% |
| | (+) | | 12 | | 80,0% |
| plasmepheresis treatment | (-) | | 5 | | 33,3% |
| | (+) | | 10 | | 66,7% |
| | | | 8,1 | ± | 8,9 |
| immunosuppressed therapy | (-) | | 11 | | 73,3% |
| | (+) | | 4 | | 26,7% |
| | Eculizumab | | 1 | | 6,7% |
| | Rituksimab | | 1 | | 6,7% |
| | Vincristine | | 2 | | 13,3% |
| prognosis | Exitus | | 5 | | 33,3% |
| | recovery | | 9 | | 60,0% |
| | Chemotherapy For Stomach Cancer | | 1 | | 6,7% |

**Table.9** Treatments applied and prognosis of the patients

| Case Number | Etiological factor | Treatments applied (1: Prednol 2: Plasmapheresis) | Prognosis |
|---|---|---|---|
| 1 | TTP | 1, 2, Rituximab | Discharge |
| 2 | TTP | 1, 2 | Post-discharge exitus |
| 3 | TTP | 1, 2, Vincristine | Exitus |
| 4 | Atypical HUS | 1, 2, Eculizumab, Hemodialysis | Discharge |
| 5 | Medication use (cannabinoid) | 1, fresh frozen plasma (plasmapheresis not done) | Discharge |
| 6 | SLE | 1, 2 | Discharge |
| 7 | Vitamin B12 deficiency | Vitamin B12 | Discharge |
| 8 | TTP | 1, 2 | Discharge |
| 9 | TTP | 1, 2 | Exitus |
| 10 | Vitamin B12 deficiency | 1, 2, Vitamin B12 | Discharge |
| 11 | Vitamin B12 deficiency + gastric adenocarcinoma | 1, 2, Vitamin B12, chemotherapeutic agent | Discharge |
| 12 | Vitamin B12 deficiency | Vitamin B12 | Discharge |
| 13 | TTP | 1, 2 | Discharge |
| 14 | TTP | 1, 2, Vincristine | Exitus |
| 15 | TTP | 1, 2 | |



**Picture.1** Peripheral smear findings of vitamin B12 deficiency

In the literature, we have not done a study determined by distinguishing between primary and secondary. With this result, we think we contribute to the literature. The most important treatment approach in this disease, which can result in 90% death if early diagnosis is not happen and treatment is not initiated, is plasma exchange (2). In our study, the mortality rate was found to be 33.3%. Compared to literature this is lower. The most common form is acquired idiopathic TTP characterized with one time acute attack (2). In our study, the most common form was found to be TTP. Neurological features seen in more than half of the cases are the most common findings. Frequent neurological findings; headache, organic brain syndromes, coma, blurred vision, paresis, aphasia, dysarthria, syncope, vertigo, ataxia, seizures, and cranial nerve paralysis (5). The most common complaints of our patients were dizziness 9 (31.0%), headache 4 (13.7%). Nausea 3 (10.2%), dyspepsia 1 (3.4%), rash 1 (3.4%), ocular finding 2 (6.8%), altered consciousness 2 (6.8%), bloody stool 1 (3.4%). ), weakness 1 (3.4%), fever 1 (3.4%), numbness in fingers 1 (3.4%) are also diagnosed. There is no specific rate in the literature, but the most common findings were determined to be neurological. Use of steroids combined with TPD; Rubia et al (1999) reported the results of 11

patients who were given combined steroids with fresh frozen plazma (FFP) to acute TTP patients in a publication from Spain. They found a complete response rate of 82% after FFP (6). 60% of the patients included in our study received FFP treatment and 70% of these patients were cured. This rate is similar to the literature. In cases where TTP cannot be ruled out, plasma infusion can be given until the initiation of FFP. Steroids, twice-daily FFP could be applied In the treatment of MAHA. Along with them in steroid and / or rituximab unresponsive cases, cyclosporine, cyclophosphamide, vincristine and rarely splenectomy may be a treatment option. When the diagnosis of atypical HUS is considered, eculizumab treatment should be started and the drug should be continued after the diagnosis is confirmed, because relapse may occur when the drug is discontinued. Hematological response is rapid, but recovery of renal functions takes months (7). 4 of our cases who did not respond to FFP and steroid were given immunosuppressed treatment. 1 of them was atypical HUS and received eculizimab treatment and cure was provided. 3 of them were TTP and 1 patient received rituximab treatment and cure was provided. 2 patients received vincristine treatment and death has been. Severe vitamin B12 deficiency in adults is among the secondary causes of MAHA (8). In our study, we encountered 4 cases with vitamin B 12 deficiency, we applied parenteral replacement therapy to all of them. 2 patients developed the need for plasmapheresis and all patients were cured. The need for plasmapheresis developed in 2 patients and all patients were cured. The gastroscopy of the patient revealed a mass in the stomach while investigating the etiology of the patient, and the biopsy resulted as gastric adenocarcinoma. Vitamin B 12 deficiency was considered due to lack of absorption. In the diagnosis, the lack of severe ADAMTS-13 activator together with the presence of anti-ADAMTS-13 autoantibodies, the need for respiratory support, neurological disorder and cardiac disorder and or high troponin are the most important factors associated with the severity of the disease (9). In our study ADAMTS-13 activator levels were reported to be low and ADAMTS-13 inhibitor levels were high, and a diagnosis of TTP was made. 5 (62.5%) of the patient diagnosed with TTP died. Polyarteritis nodosa, wegener granulomatosis, SLE, systemic sclerosis and antiphospholipid syndrome can cause MAHA and thrombocytopenia by immune and non-immune means (10). In our study, a SLE case with a MAHA clinic was detected. ANA, anti-dsDNA, coombs positivity were found in the case. Corticosteroids were added to their standard treatment. Various viral and bacterial infections may be transmitted due to plasma replacement (11).

In our study, hepatitis markers and HIV were examined routinely in 10 patients who underwent plasmapheresis, none of the patients were found positive for hepatitis or HIV. No positivity was found in their follow-up. Relapse is seen in 21-64% of the patients. Especially in patients with severe ADAMTS 13 enzyme deficiency, relapse is more frequent. (9) Our study lasted about 2 years, during which time 1 of our patients died due to intracranial hemorrhage after discharge and thrombocytopenia was detected in the examinations performed in the emergency department. Thought as relapse but enough time didn't exist for examination and treatment. In a study conducted by Loan Nguyen et al. in the Oklahoma region in 2008, they evaluated 27 patients with MAHA with rephracter TTP in the etiology. Loan Nguyen et al. changed the immunosuppressive treatment with FFP once a day to immunosuppressive treatment with FFP twice a day and followed the number of attacks. Complete response was present in 3 of 27 patients, moderate-to-advanced response in 23 patients, and no response in one patient. The treatment of vincristine, eculizimab, rituximab is included in various publications for treatment of MAHA. Rituximab is an anti CD20 monoclonal antibody. Its addition to the standard treatment in relapse or refractory TTP with antibody-associated ADAMTS 13 deficiency has become a new treatment modality. In more than 50% of cases clinical remission and improvement in ADAMTS 13 activity reported. Rituximab is recommended as an alternative treatment method to be considered in the treatment of refractory TTP (12). In our cases, rituximab was used in one case and a positive response was obtained, and vincristine, which binds the microtubules during mitotic division, were used for treatment of two cases and negative response was obtained. Vincristine is recommended to use 1 mg twice a week and totally 4 doses. In our atypical HUS case, eculizimab, which binds to complement C5 was used and no response was obtained.

## Conclusion

The process until the diagnosis of MAHA in the internal medicine clinic of the University of Health Sciences, Istanbul Kanuni Sultan Suleyman Training and Research Hospital, the clinic, test results, treatment and prognosis of the patients were retrospectively analyzed. The most common reason for presenting the patients was neurological and dizziness. The most common positive examination finding was petechiae-purpura. Hypertension was the most common in the chronic disease history of the patients. Thrombocytopenia and schistocysts were observed in peripheral blood smears of all patients, and hypersegmented neutrophils were observed in patients with vitamin B 12

deficiency. Female-male ratio was observed to be close to each other (53% versus 46%). ADAMTS-13 activator and inhibitor was considered an indisputable marker in the diagnosis of TTP. Biochemical markers of hemolysis in patients were indirect hyper bilirubinemia, increased LDH, anemia and thrombocytopenia. in electrolytes and Coagulation parameters, no significant pathology was detected. Primary MAHA and secondary MAHA rates were found to be close to each other (60% versus 40%). While the prognosis of secondary MAHA cases was good, the rate of mortality in primary MAHA cases was higher (55%). Fatality rate (33.3%) was found to be similar to the literature. Mortality rate was 75% in primary MAHA cases with a refractory course. Early diagnosis and treatment of MAHA significantly reduces mortality rates. Results of our study, it supports the need to start plasmapheresis immediately when the primary MAHA diagnosis is considered.

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**Author Contributions:** Conception/Design of Study-Dİ.; Data Acquisition- Dİ.; Drafting Manuscript- Dİ.; Critical Revision of Manuscript- Dİ.; Final Approval and Accountability- Dİ.; Supervision- MS,AK.ÖT

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