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OCCURRENCE OF THROMBOTIC MICROANGIOPATHY IN A PATIENT WITH GRANULOMATOSIS WITH POLYANGIITIS AFTER REMISSION INDUCTION THERAPY: A RARE PRESENTATION

GRANÜLOMATÖZ POLİANJİT TANILI BİR HASTADA REMİSYON İNDÜKSİYON TEDAVİSİ SONRASI TROMBOTİK MİKROANJİYOPATİ GELİŞMESİ: NADİR BİR PREZENTASYON

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ABSTRACT

In the literature thrombotic microangiopathy (TMA) associated with ANCA-associated vasculitis (AAV) has only been reported in isolated case reports. Here, we report a patient with granulomatosis with polyangiitis (GPA), who presented with TMA after initiation of remission induction therapy. A 36-year-old male patient presented with dyspnea and decreased urine output. Laboratory results demonstrated elevated creatinine, low albumin, low hemoglobin, normal leukocyte and platelet count, normal LDH, and elevated acute phase reactants. Urinalysis revealed proteinuria (1275 mg/day) and an active urine sediment. Serum complement levels were normal and proteinase 3 ANCA titer was> 200 IU/ml. Urinary ultrasound revealed normal kidney sizes and normal parenchymal thicknesses with increased renal parenchymal echogenicity. A kidney biopsy revealed pauci-immune crescentic glomerulonephritis. The diagnosis was GPA and an induction treatment of pulse steroid, intravenous cyclophosphamide, and plasma exchange was initiated. After two doses of cyclophosphamide, rituximab treatment was initiated. Fifteen days after the second dose of rituximab, thrombotic microangiopathy (TMA) was considered in the patient who had no increase in hemoglobin value (despite initiation of erythropoetin)

ÖZET

Literatürde ANCA ilişkili vaskülit (AİV) ile ilişkili trombotik mikroanjiyopati (TMA) sadece olgu sunumlarında bildirilmiştir. Burada remisyon indüksiyonu tedavisi sonrasında TMA tablosuyla başvuran granülomatöz polianjit (GPA) tanılı bir hastayı sunmayı amaçladık. Otuz altı yaşında erkek hasta nefes darlığı ve idrar çıkışında azalma şikayetleriyle başvurdu. Hastanın laboratuvar tetkiklerinde kreatinin ve akut faz reaktanı yüksekliği, albümin ve hemoglobin düşüklüğü, normal lökosit ve trombosit sayısı ve normal LDH düzeyi saptandı. İdrar tahlilinde 1275 mg/gün proteinüri ve aktif idrar sedimenti mevcuttu. Serum kompleman seviyeleri normaldi ancak proteinaz 3 ANCA titresi > 200 IU/ml olarak saptandı. Üriner ultrasonografide normal böbrek boyutları ve normal renal parankim kalınlığı ile artmış renal parankimal ekojenitesi tespit edildi. Böbrek biyopsisinde immün birikimden fakir kresentik glomerülonefrit saptandı. Hastaya GPA tanısı kondu ve yüksek doz steroid, intravenöz siklofosfamid ve plazma değişiminden oluşan güçlü bir indüksiyon tedavisi başlandı. İki doz siklofosfamid sonrası rituksimab tedavisi verildi Eritropoetin başlanmasına rağmen hemoglobin değerinde artış olmayan ve trombosit sayısında azalma olan hastada ikinci rituksimab dozundan 15 gün sonra trombotik mikroanjiyopati (TMA)

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and decreased platelet count. Peripheral blood smear revealed 5-9 schistocytes in each area. A corrected reticulocyte count was elevated, and haptoglobin was low. ADAMTS13 activity was normal. Plasma exchange was not reinitiated. The kidney biopsy was re-evaluated, but no histopathological changes consistent with TMA were found. The patient was under follow-up for TMA by checking his hematological parameters once a week. Two months later, at the third month of rituximab treatment, an increase in hemoglobin and platelet values was observed. Reticulocyte percent and haptoglobin were within normal limits. His follow-up as an outpatient is continuing. In most of the reported cases of TMA associated with ANCA-associated vasculitis, TMA appeared in the course of active vasculitis. Our case is noteworthy due to the fact that TMA developed after the active phase of GPA, even after the initiation of potent remission induction therapy.

Keywords: Granulomatosis with polyangiitis, remission induction, thrombotic microangiopathy

düşünüldü. Periferik yaymada her alanda 5-9 şistosit görüldü. Düzeltilmiş retikülosit sayısı yüksek, haptoglobin düzeyi düşük, ADAMTS13 aktivitesi normaldi. TMA tablosu için plazmafereze tekrar başlanmadı. Böbrek biyopsisi tekrar değerlendirildi ancak TMA ile uyumlu histopatolojik değişiklik bulunamadı. Hasta TMA açısından haftalık olarak hematolojik parametrelerle takip edildi. İki ay sonra rituksimab tedavisinin üçüncü ayında hemoglobin ve trombosit değerleri arttı, retikülosit yüzdesi ile haptoglobin normal olarak saptandı. Hastanın poliklinik takibi devam etmektedir. Olgumuz, GPA'nın aktif fazından sonra, hatta güçlü remisyon indüksiyon tedavisi başlandıktan sonra TMA tablosunun gelişmesi nedeniyle dikkat çekicidir.

Anahtar Kelimeler: Granülomatöz polianjit, remisyon indüksiyonu, trombotik mikroanjiyopati

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is an anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) that most often affects the upper and lower respiratory tracts, and kidneys (1). Thrombotic microangiopathies (TMA) are a heterogeneous group of diseases characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage, often involving the kidneys (2). In the literature TMA associated with AAV has only been described in isolated case reports (3). Here, we aimed to describe the development of TMA in a 36-year-old patient with GPA after initiation of remission induction therapy and review the treatment options.

CASE PRESENTATION

A 36-year-old male patient presented to the emergency department with dyspnea and decreased urine output. Past medical history was unremarkable except for recent bilateral hearing loss. He did not regularly use any medications. His body temperature was 36.6 °C, blood pressure was 111/72 mmHg, pulse rate was 72/min, respiratory rate was 20/min, and blood oxygen saturation was 97% by pulse oximetry. Fine crackles were heard in the bases of both lungs on auscultation. Laboratory results were as follows: Urea: 97 mg/dl, creatinine: 8.32 mg/dl, eGFR: 7 ml/min/m^2, albumin: 24.2 g/L, total protein: 52 g/L, hemoglobin: 83 g/dl, mean corpuscular volume: 84 fl, platelet: 228000/µl, LDH: 236 U/L, CRP: 137.7 (0-5) mg/L, sedimentation: 39 mm/hour, microprotein in spot urine: 1275 mg/day, and urine microscopy showed 234 erythrocytes and 27 leukocytes. Initial peripheral blood smear revealed normochromic normocytic erythrocytes, a sufficient number of platelets, and no schistocytes. Proteinase3 (PR3) ANCA titer was> 200 IU/ml, myeloperoxidase (MPO) ANCA and anti-glomerular basement membrane antibodies were negative. Complement 3 was 0.95 g/L (0.9-1.8) and complement 4 was 0.15 (0.1-0.4). He was hospitalized with acute kidney injury. Urinary ultrasound revealed normal kidney sizes and normal parenchyma thicknesses with increased renal parenchymal echogenicity. A kidney biopsy revealed pauci-immune crescentic glomerulonephritis. Paranasal sinus computed tomography (CT) revealed bilaterally increased soft tissue density and decreased aeration in mastoid cells, in the mastoid antrum, and in both middle ear cavities. Thorax CT revealed bilateral pleural effusion, atelectatic changes in the lung areas neighboring the effusion, and two subpleural nodules in the right lung (one 11mm and the other 15 mm in diameter). He was also evaluated by the ear-nose-throat department for the etiology of his recent hearing loss, which turned out to be a sensorineural hearing loss. The patient was diagnosed with GPA. A potent induction treatment of pulse methylprednisolone (1000 mg/day for three days), intravenous cyclophosphamide was initiated and plasma exchange with fresh frozen plasma was performed for a total of eight cycles. During this period, the anuric patient underwent intermittent hemodialysis three times a week. After two doses of cyclophosphamide, which were administrated in doses of 750 mg/day within an interval of two weeks, the control PR3-ANCA titer was >200 IU/ml. Three weeks after the second cyclophosphamide infusion, rituximab treatment was initiated as 2x1000 mg intravenous infusion within an interval of two weeks. Two months after the initiation of induction treatment and 15 days after the second dose of rituximab, thrombotic microangiopathy (TMA) was considered a preliminary diagnosis in the patient who had no increase in hemoglobin value (despite initiation of erythropoetin) and decreased platelet count (116000/uL). Peripheral blood smear revealed a slightly decreased number of platelets, normochromic normocytic erythrocytes, and 5-9 schistocytes in each area. Corrected reticulocyte count was elevated (5.28%), haptoglobin was low, and red cell distribution width was slightly elevated. The ADAMTS13 activity was within normal range. Other potential causes

of TMA such as systemic lupus erythematosus, antiphospholipid syndrome, malignant hypertension, and infective endocarditis were also excluded. A kidney biopsy specimen was re-evaluated, but no histopathological changes consistent with TMA were found. Re-biopsy was not performed because the patient was still anuric and the dialysis treatment was continued. The patient was under follow-up for TMA by checking his hematological parameters once a week. Since alternative causes of TMA were excluded and the patient had already received a potent immunosuppressive regimen (Three days of 1000 mg methylprednisolone pulses, eight cycles of plasmapheresis, two doses of 750 mg cyclophosphamide, and two doses of 1000 mg rituximab), no additional treatment was given for TMA. Prednisolone dose was maintained at 15 mg/day. Plasma exchange was not reinitiated. Two months later, at the third month of rituximab treatment, an increase in hemoglobin and platelet values was observed. Hemoglobin was 16.7 g/dl, platelet was $158x10^3$/uL, reticulocyte percent and haptoglobin were within normal limits. Meanwhile, the patient who had a fever during hemodialysis was hospitalized due to a catheter infection. Stenotrophomonas maltophilia growth was observed in the blood culture, the catheter was changed. PR3-ANCA titers persisted at >200 IU/ml. Due to the persistence of PR3-ANCA titers and the concomitant infection, intravenous immunoglobulin (IVIG) treatment was initiated at a dose of 2 g/kg/month, after rheumatology consultation. There was no finding in favor of infective endocarditis in the transthoracic echocardiography. Antibiotherapy was completed and acute phase reactants regressed. The patient's prednisolone dose was gradually tapered to 5 mg/day. The patient's hearing loss has completely recovered, and control CT images revealed normal mastoid cells, mastoid antrum, and middle ear as well as bilaterally normal lung parenchyma without any nodules or pleural effusion. He continued 3/7 hemodialysis program and his follow-up as an outpatient is continuing. His final PR3-ANCA titer is 53 IU/ml.

DISCUSSION

Thrombotic microangiopathies may rarely be observed in the course of AAV. Activation of the alternative pathway of complement and associated endothelial damage may trigger TMA in patients with AAV (4). The presence of histopathological signs of TMA in kidney biopsies of patients with AAV has been associated with poor renal prognosis in one study and increased all-cause mortality in another study (3, 5). The kidney biopsy of our patient did not demonstrate any signs of TMA.

A French nationwide retrospective case-control study and literature review of TMA in patients with AAV stated that TMA mainly occurred in patients with MPA, although cases with GPA have also been reported (6-8). In most of the reported cases, TMA appeared in the course of active vasculitis (6). Our case is noteworthy due to the fact that TMA was not present at the initial presentation of GPA, but it occurred after initiation of potent induction treatment, namely three doses of pulse methylprednisolone, 8 cycles of plasmapheresis, two doses of cyclophosphamide and two doses of rituximab. However, the treatment was not changed, considering that the therapeutic effect of rituximab would appear late. In addition, when the literature was evaluated, no additional treatment recommendations were found (9). Two months later, at the third month of rituximab treatment, the hematological findings of TMA completely disappeared.

In conclusion, TMA in a patient with AAV may also develop after the active phase of the disease, even after the initiation of potent remission induction therapy. However, it seems reasonable to wait for a while before changing therapy for TMA, especially in patients on remission induction therapy containing rituximab.

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