OLGU SUNUMU CASE REPORT

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Natalizumab Associated Progressive Multifocal Leukoencephalopathy-Immune Reconstitution Inflammatory Syndrome in a Patient with Multiple Sclerosis: Case Report

Natalizumab'a Bağlı Progresif Multifokal Lökoensefalopati-İmmün Rekonstitusyon İnflamatuar Sendromu Gelişen Bir Multipl Skleroz Olgusu

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ABSTRACT Aim of this study to describe the clinical and radiological features of a case of progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome (PML-IRIS) in a patient with multiple sclerosis treated with natalizumab. A 52 years old man with relapsing-remitting multiple sclerosis was switched disease-modifying therapy from glatiramer acetate to natalizumab because of two serious relapses. PML was developed after his 23rd infusion. Five cures of plasma exchange was given. On the follow up, the clinical picture of the patient was deteriorated. He was treated with 10 doses of intravenous methyprednisolone 1 g/day, followed by oral methyprednisolone treatment. He was partially improved and discharged from the hospital 4 months later with a sequel of left hemiplegia and right 4/5 hemiparesis. After 6 months, the patient died because of some systemic problems such as breath insufficiency secondary to aspiration pneumonia and gastric bleeding although there was not any suspicion of a new neurological attack. Natalizumab treated multiple sclerosis patients with any new magnetic resonance imaging (MRI) lesion, mainly subcortical white matter should suggest PML. Those patients should undergo carefull assessment, including serial clinical and MRI monitoring and cerebrospinal fluid analysis.

Keywords: Multiple sclerosis; natalizumab; leukoencephalopathy, progressive multifocal

ÖZET Bu yazıda natalizumab tedavisi sonrası progresif multifokal lökoensefalopati-immun rekonstitusyon inflamatuar sendromu (PML-İRİS) gelişen bir multipl skleroz olgusunun klinik ve radyolojik özellikleri anlatılmıştır. Yineleyici tipte multipl sklerozu olan 52 yaşındaki erkek hastada iki ciddi atak olması sebebiyle glatiramer asetat tedavisinden natalizumab tedavisine geçiş yapılmıştı. Hastada 23 aylık natalizumab tedavisi sonrası PML gelişti. Beş kür plazmaferez tedavisi uygulandı. Plazmaferez sonrası klinik takipte hastanın nörolojik tablosunda kötüleşme görüldü. 10 gün süre ile 1 g/gün intravenöz metilprednizolon uygulandıktan sonra oral metilprednizolon ile tedavisine devam edildi. Takipte kısmi düzelme görüldü ve hasta 4 ay sonra sol hemipleji ve sağ 4/5 hemiparezi ile taburcu edildi. Taburculuğundan 6 ay sonra aspirasyon pnömonisine bağlı solunum yetmezliği ve mide kanaması gelişen hasta, yeni gelişen bir nörolojik hadise olmamasına rağmen sistemik problemler sebebiyle kaybedildi. Natalizumab tedavisi altındaki bir multipl skleroz hastasında manyetik rezonans görüntülemede (MRG) özellikle subkortikal ak maddeyi etkileyen yeni bir lezyon görülmesi PML olasılığını akla getirmelidir. Bu olgularda PML açısından dikkatli bir değerlendirme, MRG takipleri ve beyin omurilik sıvı incelemesi yapılmalıdır.

Anahtar Kelimeler: Multipl skleroz; natalizumab; lökoensefalopati, progresif multifocal

Natalizumab is a monoclonal antibody against α4-integrin approved for the treatment of patients with multiple sclerosis (MS) who have failed other disease-modifying therapies or who have aggressive disease. However, one relatively rare but serious side effect of natalizumab is a risk of developing progressive multifocal leukoencephalopathy.[1,2] Progres-

sive multifocal leukoencephalopathy (PML) is a destructive demyelinating infection of the central nervous system (CNS) caused by JC virus (JCV) which usually occurs in immunocompromised individuals.[3,4] When a patient developed PML due to natalizumab treatment, plasma exchange (PLEX) or immunoabsorption (IA) is used to rapidly remove natalizumab and to re-establish immune surveillance of the CNS.[5] The effective removal of natalizumab and sudden restoration of cellular immunity may cause worsening of neurologic deficits, consistent with the development of immune reconstitution inflammatory syndrome (IRIS).[6]

Herein, we report the clinical and radiological features of a case of PML-IRIS in a patient with MS treated with natalizumab. Informed consent was obtained from the patient's family.

CASE REPORT

A 52 years old man was diagnosed with relapsing-remitting MS in 1996 when he was 34 years old. He was treated with glatiramer acetate between 2004-2011 and remained relapse free for the last three years of this treatment, Expanded Disability Status Scale (EDSS) was 3.5 with a moderate disability as of 2011. He had two serious relapses in 2011 and EDSS was reached 5.0 although high-dose intravenous corticosteroids was given for the relapses. As of April 2012, he switched disease-modifying therapy to natalizumab, and he was free of relapses for 23 months. JC virus was positive with 0.7 titre in plasma before natalizumab tretament. In April 2014, after his 23rd infusion, he developed ataxia, left 3/5 hemiparesis, and right leg 3/5 paresis. Presumed to be having an MS attack, high-dose intravenous corticosteroid therapy was started. Then a brain magnetic resonance imaging (MRI) was performed. The brain MRI (April 30, 2014) demonstrated abnormal increased T2 and fluid-attenuated inversion recovery (FLAIR) signal involving the right posterior parietal region, right capsula externa and capsula extrema, right thalamus, and left anterior frontal subcortical white matter (Figure 1). We were suspected for a diagnosis of PML and cerebrospinal fluid (CSF) evaluation was performed. The time interval between beginning of corticosteroid therapy in contemplation of MS attack and suspicion of PML was 5 days. Results of JCV DNA polymerase chain reaction (PCR) testing in CSF was 10 000 copies/ml. The diagnosis of PML was established by evaluation of MRI scans and CSF analysis, and PLEX therapy was started. Five cures of PLEX was given. Three weeks after PLEX treatment, the patient's speech was slurred and slow, he had left 2/5 hemiparesis, right 4/5 upper limb and 2/5 lower limb paresis. The brain MRI was again performed at June 1, 2014. The FLAIR images demonstrated new increased signal changes, the lesions were extended, there was a partially mass effect on the right lateral ventricle, and also a partial involvement of the splenium of corpus callosum. Post-contrast images showed gadolinium enhancement in the right parietal subcortical white matter (Figure 2). We evaluated these findings consistent with IRIS. He was treated with 10 doses of high-dose intravenous corticosteroids, followed by oral steroid treatment. On the clinical follow up, about 7 weeks after PLEX, the patient's consciousness was impaired, dysphagia and triplegia was devel-

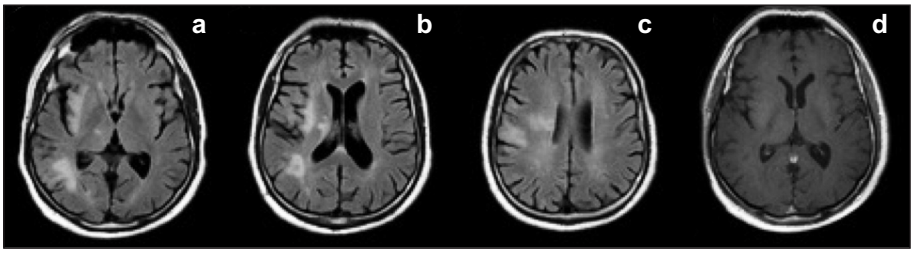

FIGURE 1: Magnetic resonance imaging (MRI) scans obtained at the onset of the symptoms (April 30, 2014); axial fluid-attenuated inversion recovery (FLAIR) images **(a,b,c)** demonstrate abnormal focus of increased T2 signal involving right posterior parietal region, right capsula externa and capsula extrema, right thalamus, and left anterior frontal subcortical white matter. Axial T1 postgadolinium image **(d)** showed no gadolinium enhancement.

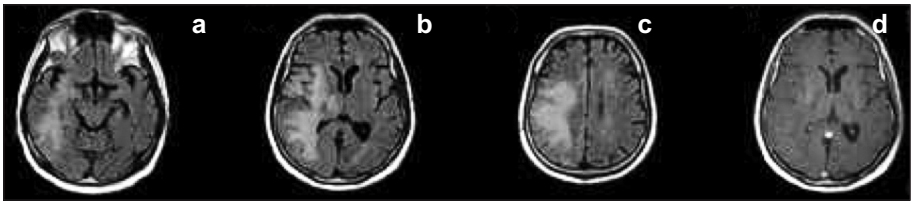

FIGURE 2: MRI scans obtained 3 weeks after PLEX (June 1, 2014); axial FLAIR images **(a, b, c)** showed significant increased in signal intensity in the right fronto-parietal subcortical white matter and periventricular area with involvement of corpus callosum splenium, and small hyperintense signal abnormality in the left anterior frontal subcortical white matter. There was minimum mass effect on the right lateral ventricle. Axial T1 postgadolinium image **(d)** showed gadolinium enhancement in the right parietal subcortical white matter.

oped. The brain MRI at June 30, 2014 demonstrated distinct progression of the lesions with an evident mass effect on the right lateral ventricle and involvement of the splenium of corpus callosum, and also involvement of the left occipital lobe. Gadolinium enhancement was existed in the right parietal lobe on postcontrast images (Figure 3). These findings were consistent with progression of IRIS. The patient was transferred to the medical intensive care unit. On the clinical follow up, the patient's consciousness, dysphagia, and triplegia were partially improved. The neurological status was stable with left hemiplegia, right 4/5 upper limb and 3/5 lower limb paresis. The patient was transferred to the Physical Therapy and Rehabilitation Clinic. The brain MRI obtained 2 months later (August 23, 2014) demonstrated regressing of the lesions with disappearing of mass effect on the right lateral ventricle (Figure 4). He was discharged from the hospital with a sequel of left hemiplegia and right 4/5 hemiparesis. At February 2015, he was admitted to our clinic with clinical signs of aspiration pneumonia. Respiration of the patient was impaired during his follow-up and he was transferred to the medical care unit because of to be in difficulty of respiration. During the follow-up period in medical care unit, gastric bleeding was occurred. The patient died 10 days into his medical care unit stay although there was not any suspicion of a new neurological attack.

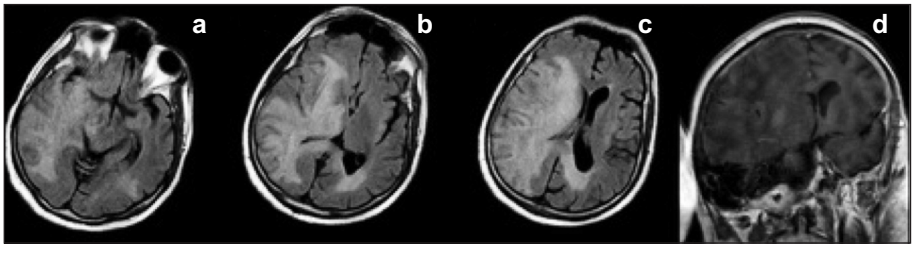

FIGURE 3: MRI scans obtained about 7 weeks after PLEX when obviously clinical impairment occurred (June 30, 2014); axial FLAIR images **(a, b, c)** demonstrate noticeably progression of the right fronto- parietal white matter and corpus callosum signal changes with involvement of the right basal ganglia and the left occipital area. Coronal T1 postgadolinium image **(d)** showed focal gadolinium enhancement in the right parietal subcortical white matter.

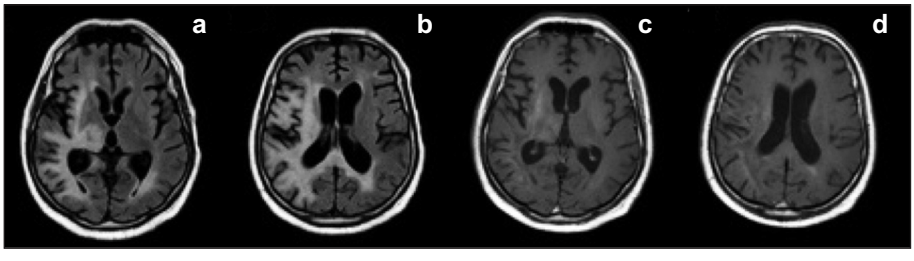

FIGURE 4: MRI scans obtained about 2.5 months after onset of IRIS (August 23, 2014); axial FLAIR images **(a, b)** demonstrate regressing of the lesions with disappearing of mass effect on the right lateral ventricle. Axial T1 postgadolinium images **(c, d)** showed indistinct gadolinium enhancement yet.

DISCUSSION

A risk-factor algorithm was developed to estimate the incidence of PML among patients treated with natalizumab. Prior use of immunosuppressive agents, positive anti-JCV-antibody status and treatment duration for more than 2 years have been independently identified as risk factors for the development of PML. Patients who were negative for anti-JCV antibodies represented at the lowest risk for PML with an estimated incidence of 0.09 cases per 1000 patients. Patients who had all three risk factors were at the highest risk for PML with an estimated incidence of 11.1 cases per 1000 patients.[7] Our patient had only one risk factor. In February 2013, JC virus was positive with 0.7 titre in plasma before natalizumab tretament. He has not been used immunosuppressive agents before natalizumab therapy and has not been used natalizumab treatment more than 24 months. During the natalizumab treatment, results of JC virus index values were 2.7 titre in February 2013, 3.6 titre in December 2013, and 3.3 titre in May 2014, respectively.

In some patients, initially a diagnosis of a new MS relapse was suspected and this delayed the proper diagnosis of PML, but generally only for a brief period. In our case, he developed ataxia, left 3/5 hemiparesis, and right leg 3/5 paresis after his 23rd natalizumab infusion. High-dose intravenous corticosteroid therapy was started, presumed to be having an MS attack. The brain MRI (April 30, 2014) was performed in a few days, and it led us for the diagnosis of PML (Figure 1).

New neurological symptoms and signs; especially neurobehavioural, motor, language, and visual symptoms, ataxia, and seizures should lead to careful evaluation for PML.[2,6,8] On MRI scans, new lesions are generally seen in areas mainly within subcortical white matter, not previously affected by MS. Gadolinium enhancement is usually minimum or absent.[2] The diagnosis of PML can be established by clinical history and evaluation, brain MRI scans, and detection of JC virus DNA in the CSF or by immunohistochemistry on brain tissue following biopsy.[2,6] It must be emphasised that undetectable JC virus by PCR testing can not rule out PML.[2] In our patient, results of JCV DNA PCR testing in CSF was 10 000 copies/ml. Plasma exchange was initiated and given for 5 cures.

Although there is no definite way to differentiate IRIS from PML progression,[2] extension of lesions without contrast enhancement or mass affect on neuroimaging was considered to be due to PML progression.[6] Worsening of neurological symptoms and signs within days to a few weeks following cessation of natalizumab or removal of natalizumab by PLEX/IA, and evidence of extension of lesions with contrast enhancement or mass effect on MRI in lesions should be considered for the development of IRIS. PML-IRIS patients can be taken into 2 subgroups. Early-PML-IRIS was defined by the contrast enhancement in the PML lesions at the time of PML diagnosis and before the withdrawal/removal of natalizumab. In late-PML-IRIS worsening of PML lesions or contrast enhancement observed only after withdrawal/removal of natalizumab. The time interval between PLEX/IA and the worsening of IRIS was 2.8 weeks in early-PML-IRIS and 4.3 weeks for development of IRIS in late-PML-IRIS.[6] In our case, four weeks later from the diagnosis of PML, the patient's speech was slurred and slow, he had left 2/5 hemiparesis, right 4/5 upper limb and 2/5 lower limb paresis. The brain MRI was again performed at June 1, 2014 (Figure 2). We considered the clinical and neuroimaging findings consistent with IRIS. But during the clinical follow-up, we observed an obviously clinical impairment about 7 weeks after PLEX. The new brain MRI which performed at June 30, 2014 was consistent with progression of IRIS (Figure 3). When we look at the interval between the PML diagnosis and clinical impairment after PLEX treatment, and also neuroimaging findings, late-PML-IRIS can be considered for our patient.

In a recently report, it was emphasized that there was no evidence of beneficial effects of PLEX in natalizumab-associated PML (NTZ-PML). They examined retrospectively the effects of PLEX on the survival and clinical outcomes of patients with MS and NTZ-PML by searching the literature. They analyzed 219 NTZ-PML cases, and 184 of 219

cases (84%) had been treated with PLEX. They did not find improvement in mortality or residual disability in patients treated with PLEX compared to the untreated patients. According to these findings, they suggested that the spontaneous recovery of immunocompetence after natalizumab withdrawal might counteract the spread of PML and therefore not require any additional intervention.[9] In a case report, plasmapheresis was not performed due to lesion being asymptomatic and of a small size. The consequent IRIS was quite limited in time and space.[10] Lalive et al. described a similar case in which natalizumab withdrawal after early detection of PML was managed without plasmapheresis or corticosteroid treatment, with a good clinical outcome.[11]

PLEX was given for 5 cures in our patient. The possibility of development and progression to IRIS in our patient could not be denied if we have not used PLEX or used only for a short period.

When IRIS developed, high-dose corticosteroid therapy, typically 1 g intravenous methylprednisolone daily for 5 days followed by tapered doses of oral steroids variably over 2-6 weeks has been used to treat IRIS and often results in clinical improvement.[2,6] The overall outcome was worse in those who developed early-PML-IRIS compared to those with late-PML-IRIS.[6] The duration of IRIS is uncertain, but in many cases IRIS can persist for at least several months.[2] Younger age at PML diagnosis, less disability (lower EDSS scores pre-PML), shorter time between symptoms onset and PML diagnosis, more localised MRI lesions and lower JCV load in CSF at PML diagnosis were described to be associated with a better outcome in natalizumab-associated PML patients.[12] The patient was treated with 10 doses of high-dose intravenous corticosteroids, followed by tapered doses of oral steroid treatment about 3 months. The brain MRI obtained 2 month later (August 23, 2014) demonstrated regressing of the lesions with disappearing of mass effect on the right lateral ventricle (Figure 4).

Mefloquine, an antimalarial agent, and mirtazapine, a 5-hydroxy 2a (5-HT2a)-receptor inhibitor, had shown in vitro inhibitory effects of JC virus replication.[13,14] Supportive therapy with mefloquine and mirtazapine were prescribed for some patients at the diagnosis of PML, but there was no difference between the treated and non-treated groups in the use of either mefloquine or mirtazapine.[6] There was no clear evidence for mefloquine that this drug led to improved outcomes.[13] Also there was not shown clinical confirmation with mirtazapine.[15] In our patient, mefloquine and mirtazapine were not given for the supportive therapy of PML.

He was discharged from the hospital with a sequel of left hemiplegia and right 4/5 hemiparesis (EDSS:8.5) in August 2014. Six months later (February 2015), the patient died because of some systemic problems such as breath insufficiency secondary to aspiration pneumonia and gastric bleeding.

We can not say that the patient has directly died on account of PML-IRIS, but it is also a reality that the patient had a severe morbidity due to PML-IRIS, and similar complications could be inevitably seen in the patients who had severe morbidity.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea, Supervision, Interpretation, Writing the Article: *Mehmet Gencer;* ***Materials, Design of Figures:*** *Gizem Gürsoy;* ***Patient Follow-up, Critical Review:*** *Recai Türkoğlu;* ***Literature Review:*** *Yılmaz Çetinkaya;* ***Design of Article:*** *Hülya Tireli.*

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