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Case Report / Olgu Sunumu

Acquired Immune Deficiency Syndrome Showing Its First Symptom with Nervous System Involvement

İlk Semptomunu Sinir Sistemi Tutulumu ile Gösteren Edinilmiş Bağışıklık Yetmezliği Sendromu

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Abstract

Human immunodeficiency virus (HIV) infection is increasingly common today and the diversity of its clinical presentation makes the diagnosis difficult. The virus can cause neurologic involvement in the entire nervous system through direct action or opportunistic infections. HIV-associated neurocognitive disease, HIV encephalopathy, HIV-associated vacuolar myelopathy, and distal symmetric polyneuropathy are some of the neurologic involvements. The aim of this article was to present patients who were admitted to Pamukkale University Hospital, Neurology Clinic with neurologic symptoms as the first clinical evidence of HIV infection, and to compare their patterns of neurologic involvement with patterns in the literature.

Keywords: HIV encephalopathy, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy

Öz

İnsan immün yetmezlik virüsü (HIV) enfeksiyonu günümüzde artan sıklıkla görülmekte ve klinik prezentasyon çeşitliliği tanıyı güçleştirmektedir. Virüs direkt etki veya fırsatçı enfeksiyonlar yolu ile tüm sinir sisteminde nörolojik tutulum yapabilmektedir. HIV ilişkili nörokognitif hastalık, HIV ensefalopatisi, HIV ilişkili vakuoler miyelopati ve distal simetrik polinöropati nörolojik tutuluma bağlı tablolardan bazılarıdır. Bu makalede, Pamukkale Üniversitesi Hastanesi, Nöroloji Kliniği'ne başvuran, ilk semptomlarını nörolojik sistem tutulumu ile gösteren ve HIV tanısı alan hastaların sunulması ve nörolojik tutulum özelliklerinin detaylandırılarak, literatür ile karşılaştırılması amaçlanmıştır.

Anahtar Kelimeler: HIV ensefalopatisi, serebral toksoplazmoz, progresif multifokal lökoensefalopati

Introduction

Human immunodeficiency virus (HIV) is seen with increasing frequency today and the variety of clinical presentations makes diagnosis difficult. Neurologic complications occur in 40-50% of patients with Acquired Immune Deficiency syndrome (AIDS), and in 10% of patients, initial symptoms are associated with the nervous system. In an autopsy series, central nervous system involvement rates varied between 75-90% (1).

The virus can cause neurologic involvement in the entire nervous system through direct action or opportunistic infections. HIV-associated neurocognitive disease, HIV-associated neurocognitive disorder (HAND), HIV-associated vacuolar myelopathy and distal symmetric polyneuropathy are some of the disorders linked to neurologic involvement. Cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), cryptococcal infection, cytomegalovirus (CMV) infection, central nervous system tuberculosis, nocardia infection and central nervous system lymphoma are opportunistic infections and cancers seen in patients with HIV infections (2).

In this article, it was aimed to present the features of neurologic involvement in detail of patients who were admitted to Pamukkale University Hospital, whose first symptoms appeared due to neurologic system involvement, and were diagnosed as having HIV, and to compare them with the literature.

Case Reports

Patient 1

A 44-year-old male patient presented to the neurology outpatient clinic with symptoms of humming in the ears and confusion lasting for 5 seconds in the past three months after

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nephrolithiasis surgery. The patient had no history of hypoxia during the surgery. Impaired consciousness and blurred speech were added to his symptoms one week ago. The patient was hospitalized to the neurology ward to investigate the etiology of encephalopathy.

The patient had no fever, vital signs were stable, and no pathology was detected in the neurologic examination except apathy. The white blood cell count was normal at the beginning, but began to decrease in the follow-up and also lymphopenia emerged. Biochemical tests were within normal limits except for a mild increase in liver enzymes. An electroencephalography (EEG) examination was normal. Impairment in attention and memory was detected in the Neuropsychological Test Battery (NPT). In brain magnetic resonance imaging (MRI), hyperintense signal changes in the frontal and parietal regions, ranging from the periventricular area to the subcortical white matter with relatively protected posterior areas, were detected in T2A- and fluid-attenuated inversion recovery (FLAIR)-weighted images (Figure 1).

Lumbar puncture (LP) was performed. No pathology was detected in cerebrospinal fluid (CSF) direct microscopic examination, Gram and Giemsa-stained examinations, culture, biochemistry, and serology. The patient was started on 1 g/day methylprednisolone treatment. ANA, ANA profile, anti-dsDNA, antiphospholipid antibody, anticardiolipin antibody, anti-beta-2 glycoprotein, lupus anticoagulant, rheumatoid factor, C3, C4, direct and indirect Coombs, Brucella and Borrelia and Herpes antibodies, VDRL, HIV, and serologic markers of hepatitis were measured in the blood for the exclusion of possible vasculitic and infectious processes.

The patient, who was found positive in terms of antigen test and anti-HIV antibody, was transferred to the infectious diseases ward with a diagnosis of HIV-related neurocognitive disorder. The patient with HIV RNA 348.000 copies/ml and CD4 number of 2 cells/ml was started on antiretroviral therapy (ART) with emtricitabine and tenofovir disoproxil fumarate (TDF) 200/245 mg/day and dolutegravir 50 mg/day. Trimethoprim sulfamethoxazole (TMP-SXT) for prophylaxis against pneumocystis carini pneumonia (PCP) and *Toxoplasma gondii (T. gondii)* and azithromycin for prophylaxis against mycobacterium avium complex (MAC). CMV retinitis was not detected in the ophthalmic examination. The patient, whose antiretroviral treatment was administered and symptoms improved, was discharged to be followed up by the infectious diseases outpatient clinic.

Patient 2

A 42-year-old male patient, who underwent surgery due to intracranial mass in the outer center where he was admitted with speech impairment and loss of strength in the right arm, was referred to our hospital upon the appearance of *T. gondii* tachyzoites in a tissue sample, positive *T. gondii* polymerase chain reaction (PCR) and a positive HIV test.

In the neurologic examination of the patient, dysarthria and right central facial paralysis were detected, but there was no motor or sensory deficit. Routine laboratory examinations revealed no pathology other than mild C-reactive protein elevation. The patient was negative in terms of hepatitis markers and positive in terms of anti-Toxoplasma immunoglobulin (Ig)-G and anti-CMV IgG. In contrast-enhanced cranial MRI, the lesion at the right basal ganglia level associated with postoperative changes and the lesion at the right cerebellar peduncle level were thought to be compatible with Toxoplasma encephalitis. The first lesion was opening to the right lateral ventricle, showing peripheral faint contrast enhancement, causing peripheral pathologic diffusion constraint in the diffusion-weighted series. The second lesion extended to the right cerebellar peduncle, appearing hypointense in the central in T2A-weighted images and hyperintense in the peripheral in T2A- and FLAIR-weighted images, showed pathologic diffusion restriction in diffusion-weighted images but there was no contrast enhancement (Figure 2).

The patient with HIV RNA 72.500 copies/ml and CD4 number of 16 cells/ml was started on ART with emtricitabine and dolutegravir. TMP-SXT was started for the treatment of Toxoplasma encephalitis and prophylaxis against MAC was started.

The patient was discharged voluntarily and it was observed that his compliance with the treatment was not good. The patient was hospitalized again on the 11th day. During the follow-up, the patient's speech and general condition worsened. There was no growth in blood cultures and LP was performed. There were no cells in the CSF microscopic examination and there was no growth in the CSF culture. A viral meningitis panel measured with PCR (Epstein-Barr virus, CMV, Adenovirus, Herpes Simplex virus 1-2,

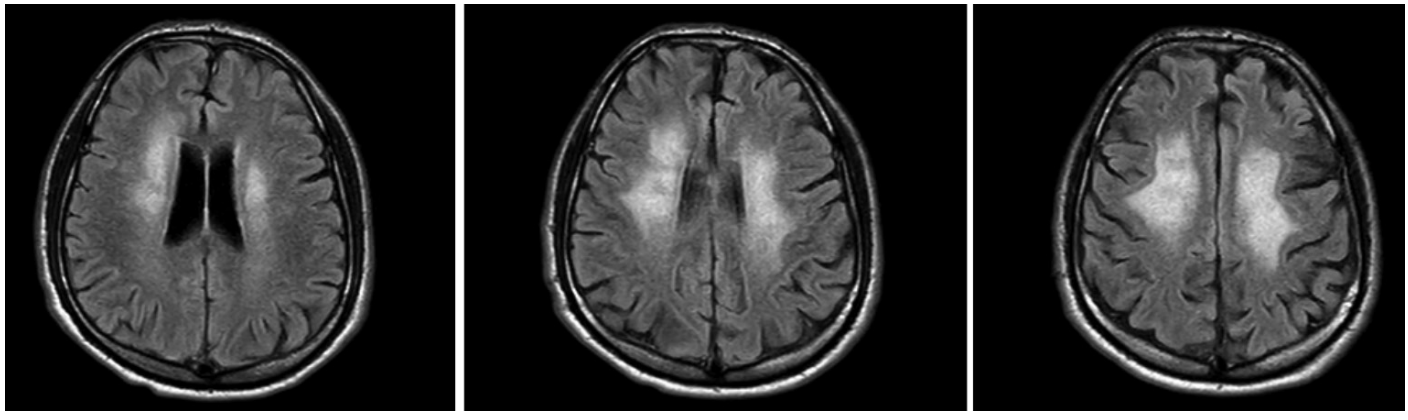

Figure 1. Patient 1; with HIV-associated neurocognitive disease, hyperintense signal changes in FLAIR-weighted images
HIV: Human immunodeficiency virus, FLAIR: Fluid-attenuated inversion recovery

Varicella Zoster virus, Enterovirus, Human Herpes virus 6-7) and bacterial meningitis panel *(Haemophilus influenzae, Neisseria meningitides, Streptococcus pneumoniae)* were negative. CSF glucose was 62 mg/dl and CSF protein was 153 mg/dl. Acid-resistant bacillus was not detected in CSF. Mycobacterium tuberculosis was also found negative in CSF PCR. No reproduction was detected in the tuberculosis culture. The patient developed paraparesis and contrast-enhanced cranial MRI was repeated. Electromyography (EMG) and spinal MRI were planned. As a result of a comparison with the previous MRI of the patient, it was understood that the hyperintense lesion observed in the right cerebellar hemisphere in T2A-weighted imaging had grown (Figure 3).

The patient had impaired consciousness and breathing and was intubated and transferred to the intensive care unit. Antibiotherapy and ART treatment were continued in the patient who was neutropenic and had hyponatremia. The patient, who was on a mechanical ventilator, died on the fifth day.

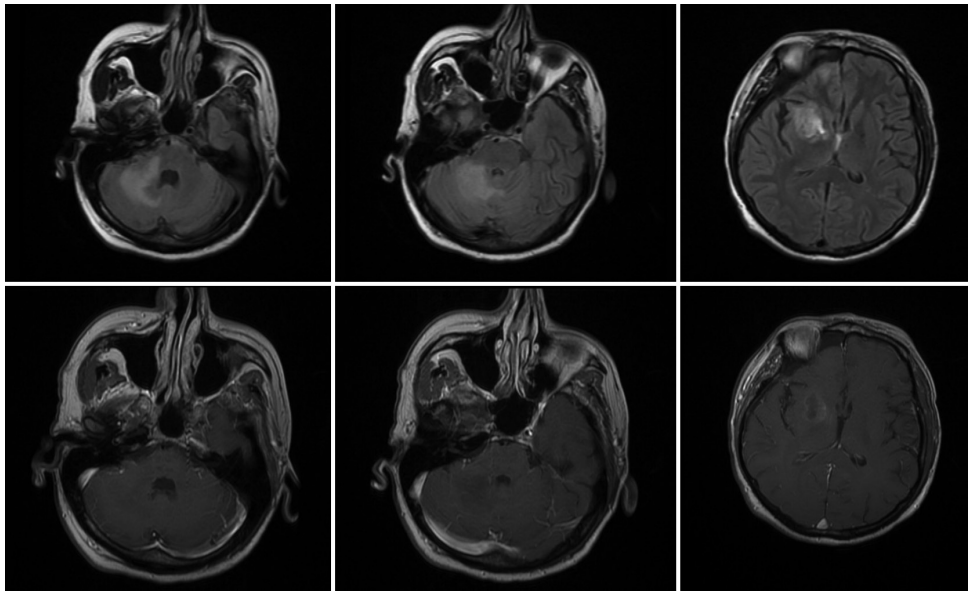

Figure 2. FLAIR-weighted images and contrast enhanced T1-weighted images of patient 2 who was HIV (+) and had Toxoplasma encephalitis
FLAIR: Fluid-attenuated inversion recovery, HIV: Human immunodeficiency virus

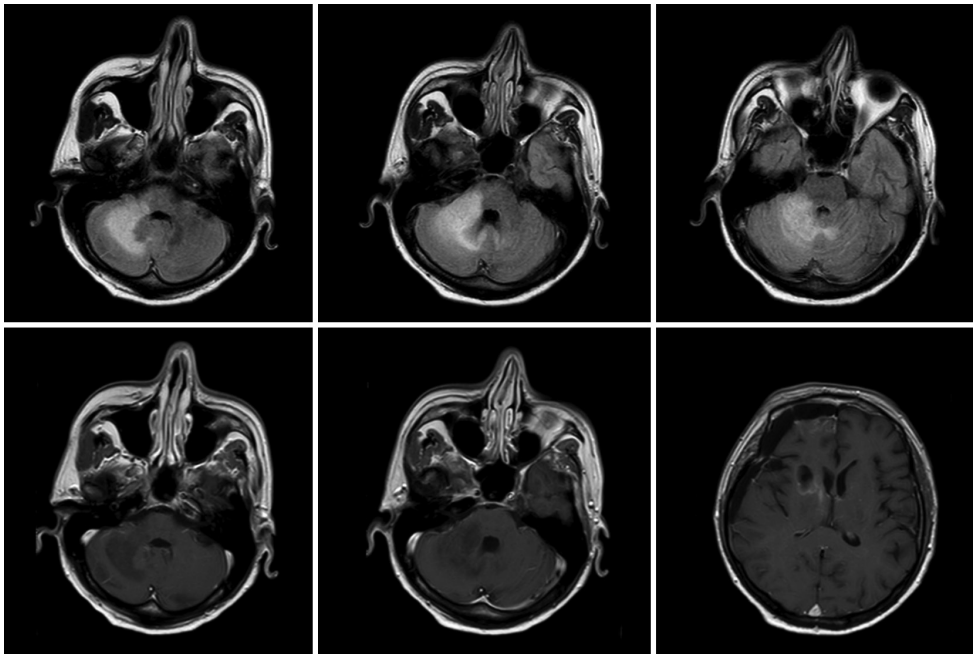

Figure 3. Growth in lesion size in the right cerebellar hemisphere in FLAIR-weighted images and contrast-enhanced T1-weighted images in patient 2
FLAIR: Fluid-attenuated inversion recovery

Patient 3

A 32-year-old male patient was admitted to the emergency department due to headache, dizziness, and weakness. His examination was normal, no pathology was detected in routine blood tests, and a cerebellar mass was detected in brain tomography, and the patient was hospitalized in the neurosurgery ward. Cranial MRI of the patient, whose HIV test was detected positive during the preoperative preparation period, showed a large number of lesions in bilateral cerebral hemispheres with cortical-subcortical location, in bilateral basal ganglia and thalami, and in both cerebellar hemispheres. The central parts of the lesions had hypointensity and the peripheral of the lesions had hyperintensity in T2A/FLAIR-weighted images suggesting edema (Figure 4). The lesions, showing diffusion restriction and ring-style contrast enhancement, were examined in more detail using MR spectroscopy, and neurotoxoplasmosis was considered primarily due to the increased lipid-lactate peak (Figure 5).

The patient was transferred to the infectious diseases ward with a diagnosis of AIDS and cerebral toxoplasmosis. HIV RNA was 1.109.000 copies/ml and the CD4 T lymphocyte count was 8/mm^3.

The quantiferon test and anti-Toxoplasma IgG were positive. TMP-SXT was started in the patient to treat toxoplasma encephalitis. Steroids and mannitol were also given for brain edema. ART, TDF + emtricitabine and dolutegravir were started. Treatment for tuberculosis was started due to the patient's lung findings. Ganciclovir was given due to the presence of CMV retinitis on ophthalmic examination. The patient, with a decrease in lesion sizes and vasogenic edema, was discharged on the 11th day of hospitalization to be followed up from the outpatient clinic (Figure 6).

Patient 4

A 42-year-old female patient was admitted to the neurology clinic due to progressive muscle weakness that started in the left leg one week ago and spread to the right leg and arm. In the neurologic examination of the patient, whose other physical examination findings were normal, right upper and lower limb muscle strength was 4/5, left lower limb muscle strength was 3/5, and left upper limb muscle strength was 5/5. Sensory examination was normal and deep tendon reflexes were normoactive. EMG revealed that distal latencies were prolonged and conduction velocities were slow in the tibial and ulnar motor nerves and tibial F-response latency was prolonged. Sural sensory nerves could not be bilaterally stimulated. The patient, with acute demyelinating sensorimotor polyneuropathy that affected the upper and lower extremities, was hospitalized in the neurology ward with a preliminary diagnosis of Guillain-Barre syndrome.

The patient underwent contrast-enhanced brain computed tomography (CT), and intravenous Ig treatment was started at a dose of 0.4 g/kg/day. LP could not be performed in the patient due to the risk of herniation. Contrast-enhanced cranial and spinal MRI was performed to evaluate multiple edematous lesions with peripheral contrast enhancing seen on CT. Spinal MRI was normal. There were multiple T2 hyperintense lesions in the cranial MRI. Lesions appeared cystic-necrotic centrally and showed contrast enhancement of the peripheral (Figure 7).

There was no pathology detected in routine blood tests. Infectious markers were investigated. The patient, with anti-Toxoplasma IgG, anti-HIV and CMV IgG positivities, was transferred to the infectious diseases ward with the pre-diagnosis of cerebral toxoplasmosis. Anti-edema treatment and ART were started. Other opportunistic infections were investigated. The CD4 T lymphocyte count was 169 cells/ml and HIV RNA was

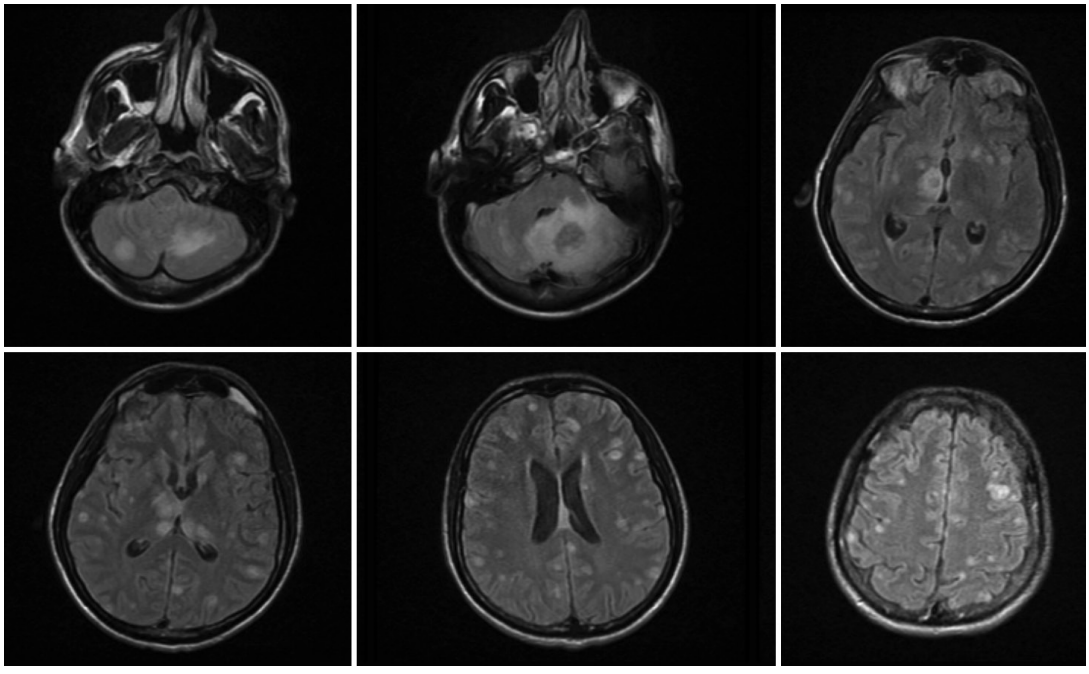

Figure 4. FLAIR-weighted images of patient 3 with cerebral toxoplasmosis
FLAIR: Fluid-attenuated inversion recovery

466.000 copies/ml. TMP-SXT was started in the patient to treat toxoplasma encephalitis. TDF + emtricitabine and dolutegravir were started as ART. The patient, with a regression in the lesions after treatment, was discharged to be followed up from the outpatient clinic (Figure 8).

Patient 5

A 28-year-old male patient was evaluated due to a decrease in vision in both eyes and weakness in the right arm and leg, which started 15 days before admission. His neurologic examination revealed right central facial paralysis and right hemiparesis. Right upper limb muscle strength was 1/5, right lower limb muscle strength was 3/5, and Babinski sign was positive on the right side. Direct and indirect light reflexes of the patient with low vision were positive and fundoscopic examination was normal. A visual acuity examination could not be performed due to the patient's poor cooperation and no sign of retinitis was observed. In cranial imaging, there were lesions in both hemispheres adjacent to lateral ventricles and at the level of the basal ganglia and left frontal lobe at the level of vertex, which were hypodense in CT and hyperintense in T2-weighted images without contrast enhancement (Figure 9). Lesions were compatible with PML. The

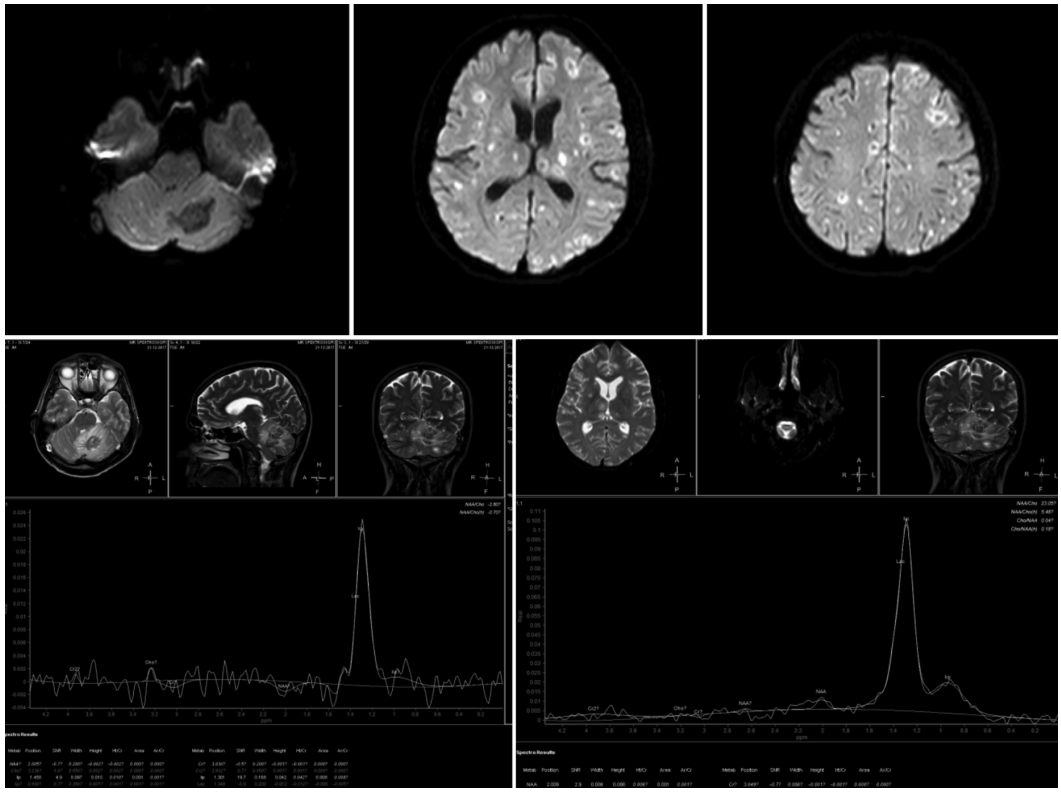

Figure 5. Diffusion MRI (top) and MR Spectroscopy (bottom) images of patient 3 with cerebral toxoplasmosis
MRI: Magnetic resonance imaging

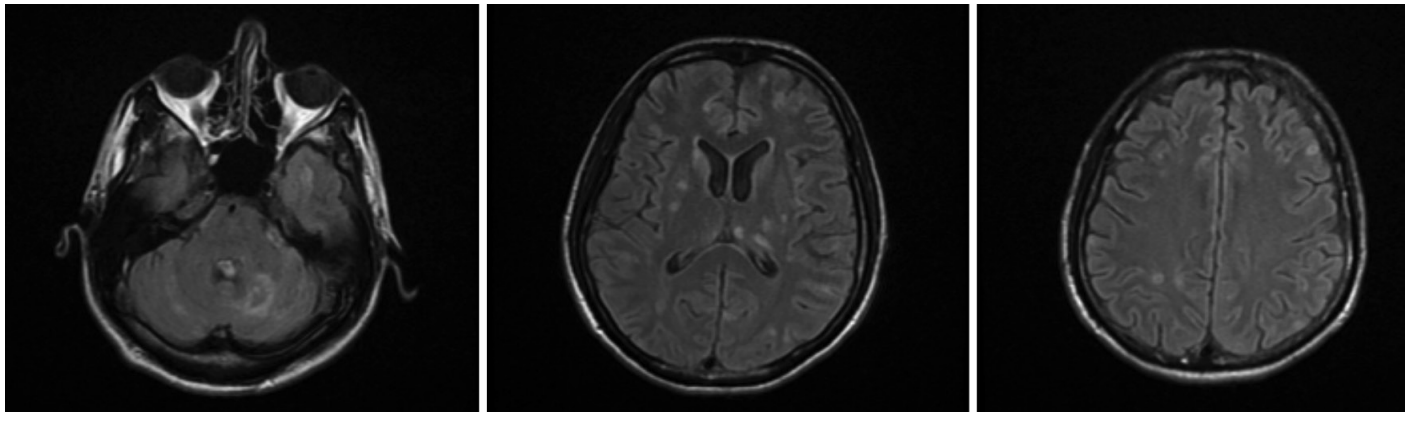

Figure 6. FLAIR-weighted images of patient 3 with cerebral toxoplasmosis after treatment
FLAIR: Fluid-attenuated inversion recovery

patient, with a positive HIV antibody test, was evaluated by an infectious diseases specialist. Routine blood tests were performed and blood, urine, and sputum cultures of the patient with fever were prepared. CD4 T lymphocyte count was 36 cells/ml and HIV RNA was 1.110.000 copies/ml. The patient was evaluated for tuberculosis. TDF + emtricitabine and dolutegravir were given as ART. After 5 days, antifungal therapy was initiated in the patient because he had candida esophagitis. PCP and *T. gondii* prophylaxis was given. CMV retinitis was not detected in the ophthalmic examination. Mirtazapine was started in the patient. HIV-RNA on the 20th day of treatment was 102 copies/ml and the CD4+ T-lymphocyte count was 5 cells/ml. With the current treatment, right limb strength improved and muscle strength was determined as 4/5. The patient recovered and was discharged. Due to the inability to use his medications regularly and decreased oral intake, the patient was admitted to the intensive care unit with a deterioration of general health condition approximately two weeks later, respiratory arrest developed, and the patient died.

Discussion

HIV is a neurotropic virus that involves both the central nervous system and the peripheral nervous system. Neuropathology can be seen due to aseptic meningitis, a flu-like disorder in early period, polyneuropathy in the subacute period, coagulopathy in the late period, the toxic effect of drugs and/or opportunistic infections. The most common neurologic complications are focal mass effect (toxoplasma encephalitis, primary central nervous system lymphoma), PML-associated multifocal demyelination, encephalitis and meningitis (1,2). Cerebral toxoplasmosis was detected in three of the five patients who were followed up in

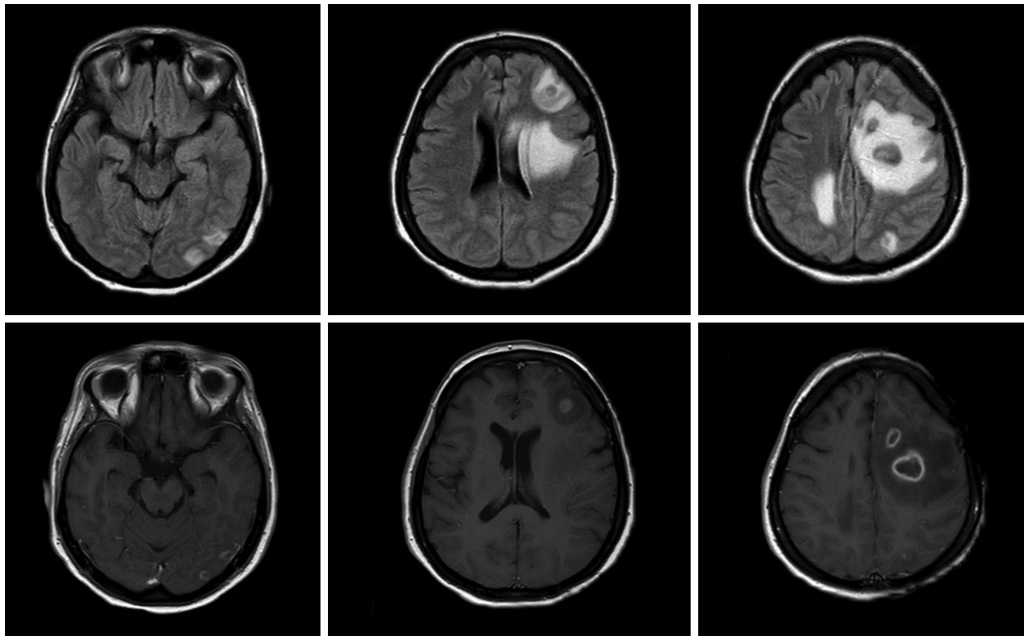

Figure 7. FLAIR-weighted (top) and postcontrast T1-weighted (bottom) images of patient 4 with cerebral toxoplasmosis
FLAIR: Fluid-attenuated inversion recovery

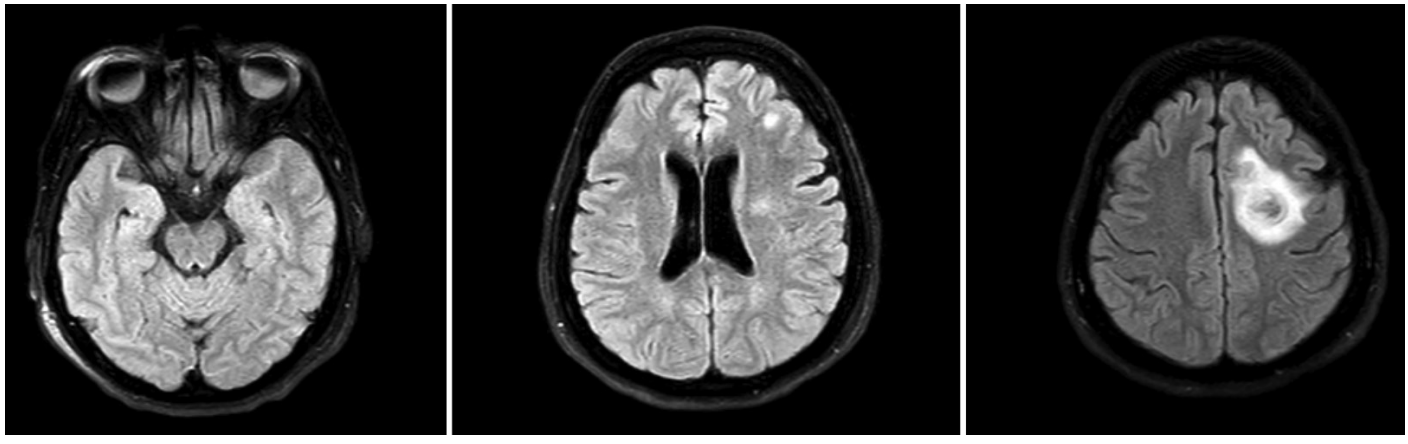

Figure 8. FLAIR-weighted images of patient 4 with cerebral toxoplasmosis after treatment
FLAIR: Fluid-attenuated inversion recovery

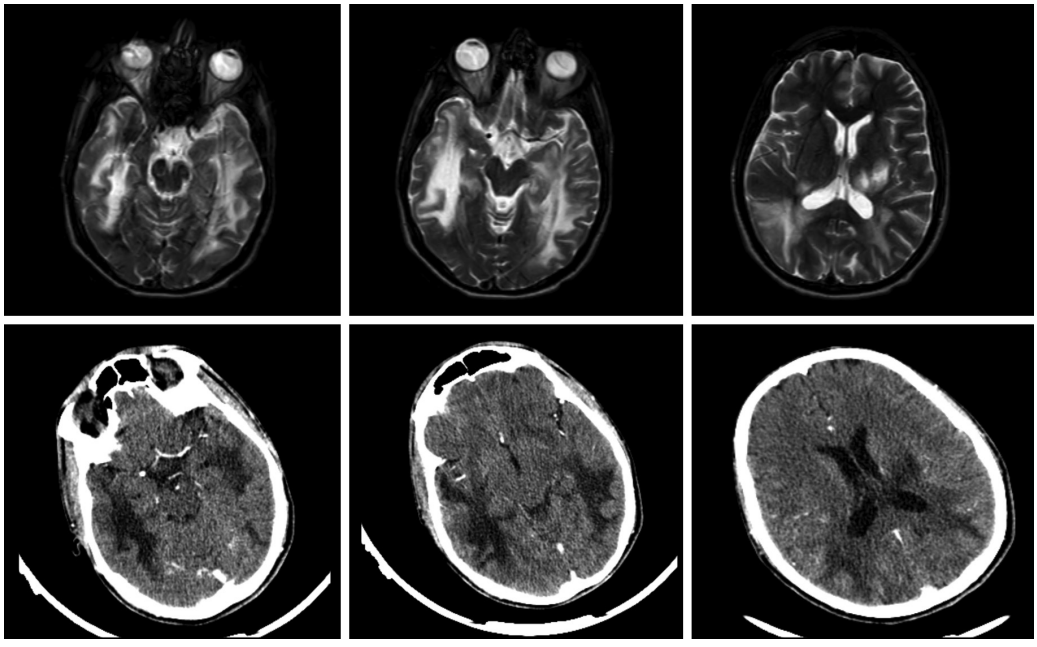

Figure 9. T2-weighted images (top) and cranial CT images (bottom) of patient 5 with progressive multifocal leukoencephalopathy
CT: Computed tomography

our clinic; HIV-related neurocognitive disorder was detected in one patient and PML was found in one patient. The first patient we presented was admitted because of confusion developing after nephrolithiasis surgery, the second patient was admitted because of speech disorder, the third patient was admitted because of headache and dizziness, the fourth patient was admitted due to polyneuropathy, and the fifth patient was admitted because of visual impairment and right hemiparesis. The first symptoms of all patients were neurological.

HIV-related neurocognitive disorders are increasing with the longevity of patients with HIV who are given highly active ART (HAART) (3). Although severe forms of HIV-related neurocognitive disorders have decreased with HAART, it is known that neurocognitive disorders, which are thought to be seen when the CD4 lymphocyte count is below 200 cells/ml during the pre-HAART period, are no longer associated with the CD4 lymphocyte count or CSF HIV RNA concentrations (4). Some patients have mild cognitive impairment due to the central nervous system involvement of HIV, and some patients have dementia. The prevalence of the disease is 7% and this rate can increase to 70% in autopsy series (5). Although the clinic is insidious, there are mild memory disorders, difficulty in concentrating, and psychomotor retardation in the early stages, and due to the addition of opportunistic infections in the late period, ataxia, paresis, and neuropathy are seen. Patients may be misdiagnosed as having depression because psychiatric symptoms frequently accompany (6). NPT must be performed for differential diagnosis.

In the first patient presented, although there were no neurologic examination findings other than apathy at the time of presentation, attention and memory impairment were detected in NPT. With the confusion emerging after the nephrolithiasis surgery, the patient was hospitalized with a preliminary diagnosis of uremic encephalopathy. Uremic and hepatic encephalopathies, the most common causes of metabolic encephalopathy, were investigated primarily. Other metabolic and infectious processes were investigated because laboratory tests and EEG were normal.

In addition to cerebral atrophy, symmetrical, hyperintense white matter lesions without sharp borders can be observed in the cranial MRI in HAND as in the first patient, because HAND has no pathognomonic MRI findings. Although a slight protein increase and lymphocytic pleocytosis could be seen in CSF, the findings were normal in our first patient (7). HIV causes HAND after it crosses the blood-brain barrier and reaches the central nervous system. For this reason, ART, which can cross the blood-brain barrier and reach the therapeutic level in the central nervous system, should be preferred in treatment (8,9).

Opportunistic infections of the central nervous system are caused by reactivation of a latent virus rather than being infected by a new virus. Toxoplasma encephalitis occurs in patients with HIV during the course of AIDS, at a rate of 7-15%. The earliest and most common symptom is headache, followed by confusion, lethargy, and fever. Focal neurologic findings such as speech disorder, paresis, and seizure can be seen in 65% of patients. Among the reported patients, the second patient presented with speech disorder, the third patient with headache, and the fourth with paresis.

In cranial imaging of cerebral toxoplasmosis, multiple lesions, especially located in the basal ganglia and corticomedullary junction are observed, which hold a ring-like contrast and often have edema effects around them. Cranial MRI is superior to CT in imaging the lesions (10). Although the definitive diagnosis is made by brain biopsy, the diagnosis is made based on the symptoms

specified in clinical practice accompanied by imaging findings and detection of microorganism or past infection in blood and/or CSF.

In the differential diagnosis of cerebral toxoplasmosis, primary central nervous system lymphoma must be considered. Although the imaging is highly similar to cerebral toxoplasmosis, the lesion in the primary central nervous system lymphoma is mostly single, relatively large, and solid. Despite this, lesions may be multicentric in central nervous system lymphomas developing in patients with AIDS, and even ring-like contrast enhancement may be observed, similar to toxoplasmosis. In such patients, MR spectroscopy will help diagnosis. As in the third patient who presented with cerebral toxoplasmosis, an increase in the lipid-lactate peak is observed in cerebral toxoplasmosis, whereas in lymphoma, a marked choline peak is accompanied by a mildly increased lipid-lactate peak.

The first option in treatment is pyrimethamine, and sulfadiazine and leucovorin are used in maintenance therapy (11). In some series, it is stated that good response is also obtained with TMP-SXT (12,13). We also gave TMP-SXT to our patients because other treatments were not available in our country and we obtained a good response in two patients with cerebral toxoplasmosis. However, patient 2 died because he was incompatible to treatment and he had mass resection before.

PML is observed in 4% of patients with AIDS due to reactivation of a human polyomavirus, John Cunningham virus (JCV). It is characterized by insidious, progressive focal neurologic findings such as hemiparesis, hemianopsia, dysmetria, and ataxia. Cranial MRI typically shows bilateral, asymmetrical, demyelinating lesions that do not retain contrast and have no edema effect. Although clinical findings and radiologic imaging findings are sufficient for diagnosis, the diagnosis is confirmed by JCV DNA positivity in CSF with PCR (14). Although various antivirals have been tried in treatment of PML, a clear consensus has not been reached and the average survival time is 1-6 months. The 5th patient was considered as having PML with clinical and imaging findings and treatment was initiated, but LP was not performed because the patient did not give permission for it and therefore the diagnosis could not be confirmed.

In patients with HIV, distal symmetric neuropathy, chronic inflammatory demyelinating polyneuropathy, and ganglioneuritis can sometimes be seen as the first symptoms. HIV-associated sensory neuropathy is painful. Sometimes it occurs due to ART. Demyelinating polyneuropathy develops subacutely and is similar to Guillain-Barre syndrome, as in our 4th patient. Although the diagnosis of Guillain-Barre syndrome is made with clinical examination, central nervous system pathologies and toxic, iatrogenic, and infectious causes should be investigated in patients with rapidly progressive limb weakness. In such patients, investigation of the presence of albuminocytologic dissociation by performing LP, electrophysiologic studies, and MRI will be supportive. Although EMG was supportive in our 4th patient, the lesions observed in cranial MRI led to the diagnosis.

Although there is no specific treatment for HIV-associated neuropathy, anticonvulsants, antidepressants, and analgesic drugs used in the treatment of neuropathic pain can be used (15).

As a result, HIV can involve both the central and peripheral nervous systems and mimic any neurologic disease. Patients can be admitted to clinics with a variety of symptoms such as headache, visual disturbances, paresis, ataxia, rapidly progressing dementia, and neuropathy. The first diagnosis can be made in neurology clinics because neurologic involvement is the first finding in approximately 10% of patients. HIV, the prevalence of which is gradually increasing, should be borne in mind in patients whose diagnosis cannot be clarified.

Ethics

Informed Consent: Informed consent was given by the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: S.S.K., Analysis or Interpretation: E.D., Literature Search: Z.Ü., Writing: Z.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Siddiqi OK, Agnihotri S, Koralnik IJ. Neurologic diseases caused by human immunodeficiency virus type 1 and opportunistic infections. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 2014:1690-1706.
2. Góngora-Rivera F, Santos-Zambrano J, Moreno-Andra de T, Calza daLópez P, SotoHernández JL. The clinical spectrum of neurological manifestations in AIDS patients inMexico. Arch Med Res 2000;31:393-398.
3. Wojna V, Skolasky RL, Hechavarria R, et al. Prevalence of human immunodeficiency virus-associated cognitive impairment in a group of Hispanic women at risk for neurological impairment. J Neurovirol 2006;12:356-364.
4. Dore GJ, McDonald A, Li Y, Kaldor JM, Brew BJ, National HIV Surveliillance Committee. Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS 2003;17:1539-1545.
5. Budka H. Human immunodeficiency virus (HIV)-induced disease of the central nervous system: pathology and implications for pathogenesis. Acta Neuropathol Berl 1989;77:225-236.
6. Portegies P, Enting RH, de Gans J, et al. Presentation and course of AIDS dementia complex: 10 years of follow-up in Amsterdam, The Netherlands. AIDS 1993;7:66-675.
7. Simpson DM, Berger JR. Neurologic manifestations of HIV infection. Med Clin North Am 1996;80:1363-1394.
8. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. Lancet Neurol 2005;4:543-555.
9. Ntshangase S, Mdanda S, Naicker T, Kruger HG, Govender T, Baijnath S. Rilpivirine as a potential candidate for the treatment of HIV-associated neurocognitive disorders (HAND). Journal of Molecular Histology 2019;50:295-303.
10. Levy RM, Mills CM, Posin JP, Moore SG, Rosenblum ML, Bredesen DE. The efficacy and clinical impact of brain imaging in neurologically symptomatic AIDS patients: a prospective CT/MRI study. J Acquir Immune Defic Syndr 1990;3:461-471.
11. Guideline for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents. 2016. Available from: URL: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf
12. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Antimicrob Agents Chemother 1998;42:1346-1349.
13. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. AIDS 2004;18:1342-1344.
14. Koralnik IJ. Neurology 1999;52:253-260 De Luca A. AIDS 2008;22:1759-1767.
15. Schütz S, Robinson-Papp J. HIV Related neurophaty- current perspectives. HIV-AIDS (Auckl) 2013;5:243-251.