Case Report
pISSN 1738-2637 / eISSN 2288-2928
J Korean Soc Radiol 2018;79(6):359-364
https://doi.org/10.3348/jksr.2018.79.6.359

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Paradoxical Cryptococcal Meningitis Immune Reconstitution Inflammatory Syndrome in a Patient with Human Immunodeficiency Virus Infection: Matching Clinical Findings with MRI Findings

인간면역결핍바이러스 감염환자에서 역설적 크립토코쿠스 수막염 면역재구성 염증증후군: 임상 소견들과 자기공명영상 소견들의 대조

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There are two forms of cryptococcal meningitis immune reconstitution inflammatory syndrome (CM-IRIS): paradoxical CM-IRIS and unmasking CM-IRIS. It is important to distinguish paradoxical CM-IRIS and CM relapse because mortality of CM-IRIS is higher than that of CM without IRIS, and paradoxical CM-IRIS and CM relapse requires different treatment. We report a case of paradoxical CM-IRIS that well matches the clinical findings with MR findings during three years follow-up of a HIV infected patient and new MRI finding is also introduced to help distinguish them.

Index terms
Human Immunodeficiency Virus
Acquired Immune Deficiency Syndrome
Antiretroviral Therapy, Highly Active
Cryptococcal Meningitis
Immune Reconstitution Inflammatory Syndrome

Received April 26, 2018
Revised July 10, 2018
Accepted July 25, 2018
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INTRODUCTION

According to International Network for the Study of HIV-associated IRIS (INSHI), there are two forms of cryptococcal meningitis immune reconstitution inflammatory syndrome (CM-IRIS): paradoxical CM-IRIS and unmasking CM-IRIS (1). Incidence of paradoxical CM-IRIS have been reported about 13–30% of patients with CM surviving to receive antiretroviral therapy (ART) (2). Mortality of CM-IRIS has been reported to be nearly twice that of patients with CM without IRIS (3).

Paradoxical CM-IRIS has been presumed as a result from vigorous immune responses to pathogen due to dysregulation of immune restoration. CM relapse is disease progression due to ongoing immunosuppression mimicking its symptoms. Therefore, it is important to distinguish paradoxical CM-IRIS and CM relapse because they may require different treatment. In the following section, we report a case of paradoxical CM-IRIS that well matches the clinical findings with MR findings during three years follow-up of a HIV infected patient and new MRI finding is also introduced to help distinguish them.

CASE REPORT

In April 2015, a 26-year-old man was admitted due to visual disturbance, left sided headache and mental change. Two years ago, he had been diagnosed with AIDS in another hospital, but had not taken any ART. On brain MRI and CT images, pathologic signal and density alteration was not detected. In cerebro-

spinal fluid (CSF) analysis, increased white blood cell (WBC) count (12 cells/mm^3), increased total protein (58 mg/dL) and decreased glucose concentration (11 mg/dL) were noted. Opening pressure was elevated (53 cm H_2O). Both CSF and serum cryptococcal antigens titers were 1:512. *Cryptococcus neoformans* was also cultured and stained by Indian ink. But JC virus, Tuberculosis, herpes simplex virus 1 and 2, cytomegalovirus, and varicellar zoster virus could not be detected by polymerase chain reaction. Also, latex agglutination tests that detect antigens of *Streptococcus pneumonia*, *Neisseria meningitides*, *Haemophilus influenza* type b, *Listeria monocytogenes*, Group B *Streptococcus* were all negative. In serum, the initial CD4+T-cell count was low (35 cells/μL) and HIV RNA load was high (59493 copies/mL). One week after on amphotericin B, ART was started although *Cryptococcus neoformans* was still cultured in CSF. Three months after ART initiation, CD4+T-cell count increased to 89 cells/μL and HIV RNA load decreased rapidly to 28 copies/mL. *Cryptococcus neoformans* was not cultured in blood but CSF study was not performed (Fig. 1A).

In May 2016, he re-admitted due to headache and seizure. CD4+T-cell counts tended to increase steadily to 98 cells/μL and HIV viral load was almost not detected (Fig. 1A). Lumbar puncture revealed the normal range of opening pressure. Not only CSF and serum cryptococcal antigen titers lowered to 1:16 and 1:128, respectively, but also *Cryptococcus neoformans* was not cultured and stained. In addition, no other opportunistic and community acquired infection pathogens are also detected. However, CSF inflammation indicators, CSF WBC counts and total proteins, increased to 32 cell/mm^3 and 256 mg/dL, respectively (Fig. 1A). T2/FLAIR imaging showed asymmetric high signal intensity in white matter of left occipital lobe without mass effect. Contrast enhanced MRI revealed prominent leptomeningeal enhancement at the left occipital convexity and perivascular enhancement in bilateral thalami and basal ganglia as well as bilateral choroid plexus enhancement. Prominent enhancement of deep medullary veins that seems like connecting

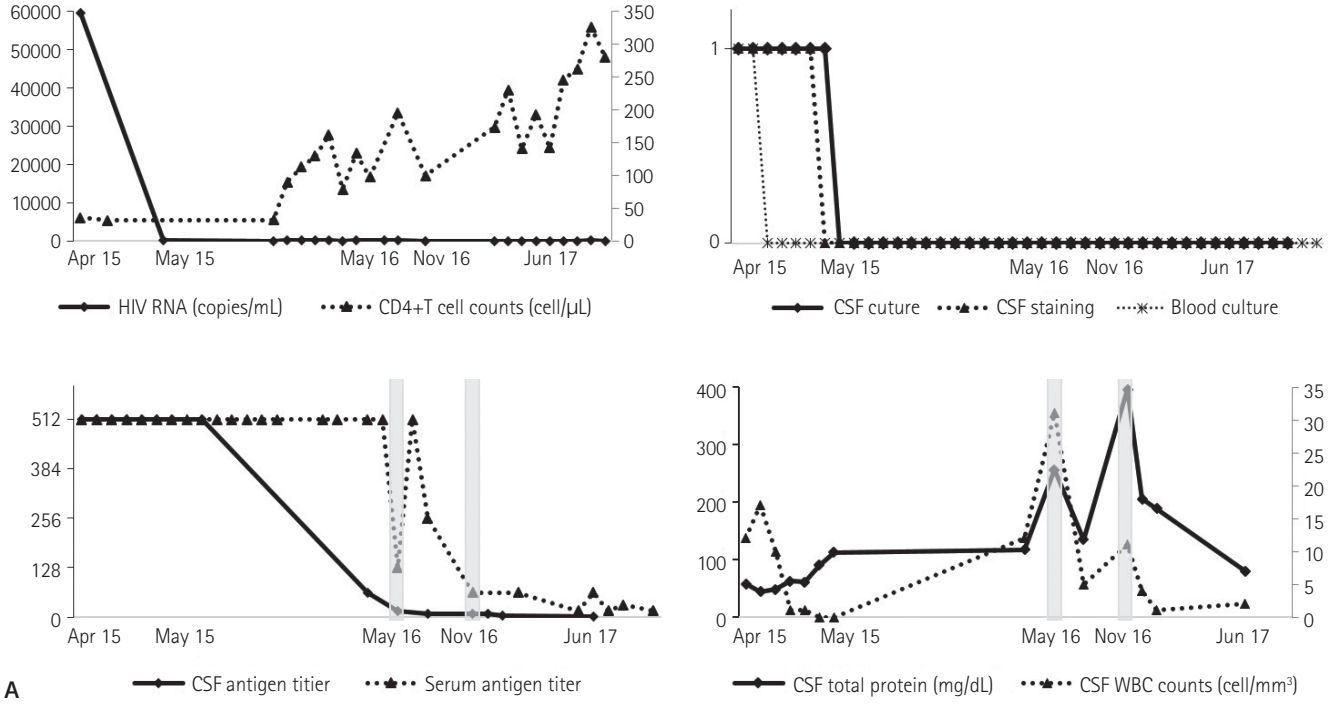
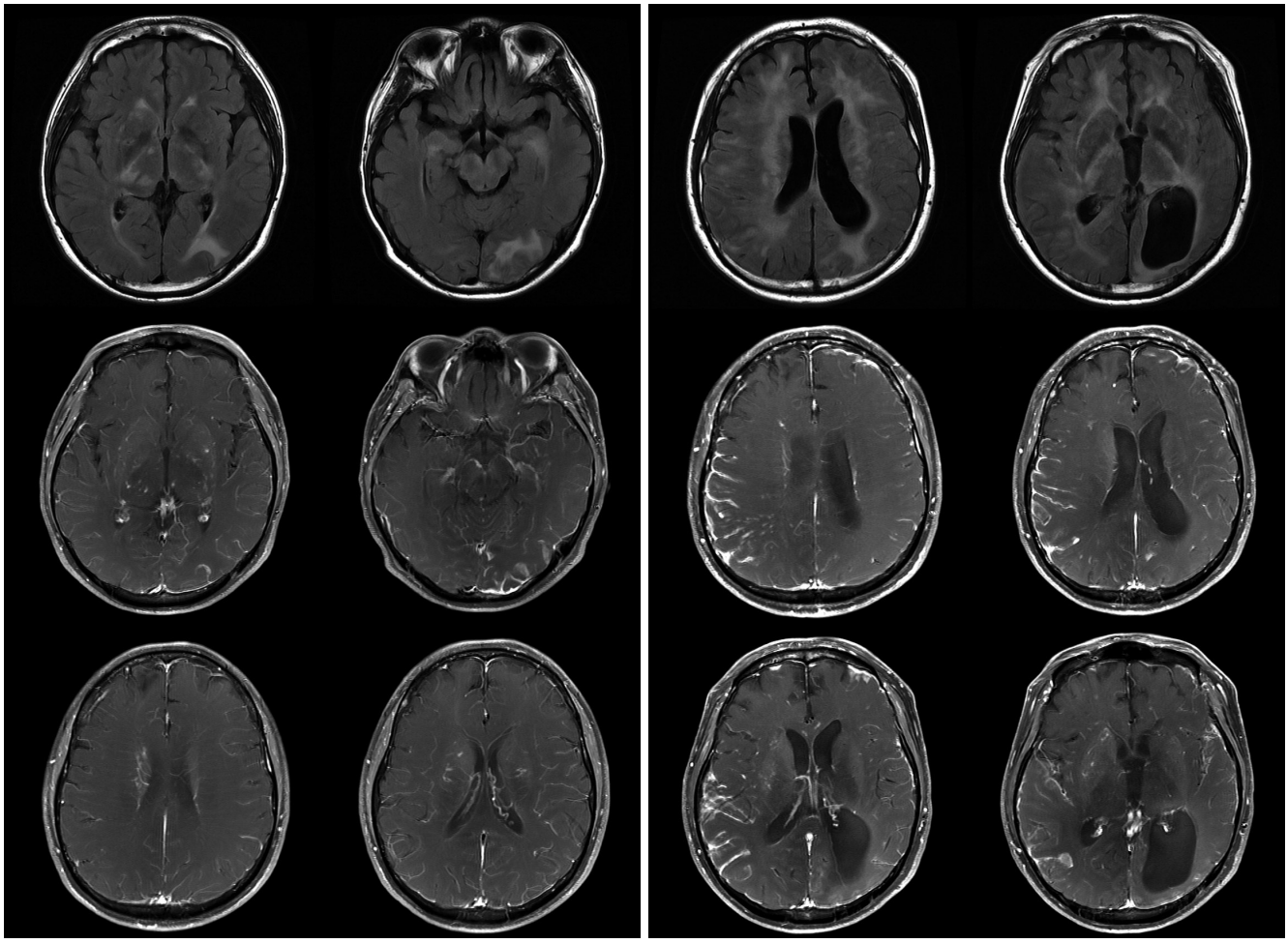


Fig. 1. Paradoxical CM-IRIS in a 26-year-old HIV-infected male patient.
A. Trend graph of patient's laboratory results. (Upper left) HIV RNA burden is rapidly decreased after ART initiation and CD4+ T cell counts tend to increase steadily. (Upper right) Before events of CM-IRIS, *Cryptococcus neoformans* was already eradicated in the order of blood culture, CSF indian ink staining and CSF culture. (Lower left) While baseline levels of CSF and serum cryptococcal antigen titer are as high as 1:512, these levels tend to be lower at the events of CM-IRIS (grey squares). (Lower right) Baseline levels of CSF WBC counts and total protein are low as 12 cells/μL and about 58 mg/dL respectively. Although in first event of CM-IRIS, both increased than baseline, in second events of CM-IRIS, total protein only increased than baseline. However, it closely coincides with period of events of CM-IRIS (grey squares).
CM-IRIS = cryptococcal meningitis immune reconstitution inflammatory syndrome, CSF = cerebrospinal fluid, WBC = white blood cell



B C

Fig. 1. Paradoxical CM-IRIS in a 26-year-old HIV-infected male patient.
B. Brain MRI in May 2016. (Upper row) FLAIR imaging shows high signal intensity at the bilateral basal ganglia and thalamus, white matter of left occipital lobe, left hippocampus and left cerebellum (not shown). (Middle row) Contrast enhanced MRI showed prominent leptomeningeal enhancement at the left occipital convexity, perivascular enhancement in bilateral thalamus and basal ganglia and bilateral choroid plexus enhancement. (Lower row) Prominent enhancement of deep medullary veins that seems like connecting with choroid plexus is shown and right side is predominant.
C. Brain MRI in November 2016. (Upper row) FLAIR imaging shows newly appeared extensive high signal confluence at the periventricular white matter and dilatation of occipital horn of left lateral ventricle due to adhesion associated with previous inflammation. (Middle and lower rows) Contrast enhanced MRI shows prominent perivascular enhancement in right parietal sulci and leptomeningeal enhancement at the new sites. Enhancement of deep medullary veins that seems like connecting with choroid plexus is shown again.
CM-IRIS = cryptococcal meningitis immune reconstitution inflammatory syndrome, FLAIR = fluid attenuated inversion recovery

with choroid plexus was also found (Fig. 1B). At this stage, clinicians considered the patient as CM relapse and antifungal medication was re-induced.

In November 2016, he re-admitted with same symptoms and his condition was almost similar to previous one. CSF cryptococcal antigen titers lowered to 1:4. *Cryptococcus neoformans* was not cultured and stained. No other opportunistic and community acquired infection pathogens are also detected. CSF WBC counts were degree of initial baseline whereas CSF total proteins were much higher than initial and previous one (Fig. 1A). Performed MRI revealed leptomeningeal and perivascular enhancement at the new regions and relatively symmetric T2/FLAIR high signal intensity without mass effect at the periventricular white matter. MR findings of entrapped occipital horn of left lateral ventricle due to adhesion associated with previous inflammation were also revealed. Enhancement of deep medullary veins that seems like connecting with choroid plexus was found again (Fig. 1C). Because of MRI findings of extensive en-

hancement despite immunosuppressed patient and clinical findings of negative culture results and CSF inflammation, we suggested recurrent CM-IRIS. However, clinicians were considered him as CM relapse again at that time and antifungal medication was maintained.

DISCUSSION

There are a few risk factors of paradoxical CM-IRIS. Baseline CSF antigen burden is not associated with its development whereas baseline serum antigen titer is suggested as its serum biomarker (3, 4). Especially, higher serum antigen burden prior to ART (≥ 1:512) is associated with it. One study reported that paucity of initial CSF inflammation is also risk factor of CM-IRIS (5). The study reported that its predictor is combination of baseline CSF WBC counts under 25 cells/μL and protein concentration under 50 mg/dL and elevation of these levels at its event was increased as compared to baseline. In our case, baseline serum antigen titer was as high as 1:512, CSF WBC counts were as low as 12 cells/μL and CSF total protein was a bit high as 58 mg/dL. Retrospectively, our patient already had some risk factors of development of paradoxical CM-IRIS at the time of CM diagnosis. As well, at its events, CSF inflammatory indicators, CSF WBC counts and total protein, almost increased than baseline level. Those clinical findings and abnormal MRI findings closely correlated with period of events of paradoxical CM-IRIS and recurrence (Fig. 1A).

CM-IRIS and CM relapse may require different treatment because the former presume results from vigorous immune responses due to dysregulation of immune restoration whereas the latter is disease progression due to ongoing immunosuppression. In cases of suspected paradoxical CM-IRIS, CSF fungal culture incubated for up to 14 days to exclude CM relapse (6). In case of mild symptoms, no definitive specific treatment is required because they will resolve spontaneously in days to weeks (6). In case of severe paradoxical CM-IRIS, corticosteroids are generally used to reduce the inflammatory response and raised intracranial pressure. Nonsteroidal anti-inflammatory drugs and thalidomide could be also used but data are too limited and small. ART stop is known to be unnecessary and uncertain benefit. Stopping ART is not recommended because HIV regrowth will cause aggravation of underlying opportunistic infection (2, 6). In confirmed case of CM relapse, antifungal therapy with the amphotericin should be re-induced to achieve CSF sterility. ART should be commenced 4–6 weeks after CM diagnosis and some strongly advises that ART not be delayed beyond 6 weeks after diagnosis (6, 7).

To our knowledge, the study about differences MRI findings between CM-IRIS and CM relapse has been not reported and differentiation in terms of clinical symptoms is impossible because of its similarity. A few articles reported that culture results may help to critically distinguish them (1, 7). However, because timing of CSF negative culture results is variable due to initial fungal burdens or antifungal regimen, it should be considered that a negative cryptococcal culture is not absolute for the diagnosis of paradoxical CM-IRIS (1). Boulware et al. (5) identified a distinct difference in CSF inflammatory profiles between cases of CM relapse and CM-IRIS. CM relapse was associated with persistent viable organisms and a lack of inflammation in CSF whereas CM-IRIS showed no organisms but a more robust inflammatory profile. In fact, as two entities of CM relapse and CM-IRIS are not always mutually exclusive but overlap, diagnosis can be made considering which one is supported more between two entities in terms of culture results and CSF inflammation.

Katchanov et al. (8) reported that MR lesions suggestive of focal leptomeningitis or meningoencephalitis were detected in all ART treated HIV-infected patients with cryptococcal infection. These differences were known that in ART naïve HIV-infected patients with cryptococcal infection, host immune function was not restored to make intense inflammation. However, it requires caution because high portions of HIV-infected patients with CM are likely to be a negative MRI (8). MRI findings of linear perivascular enhancement in the sulci and new meningeal or choroid plexus enhancement may be as imaging indicators of CM-IRIS (9). In presented case report, MRI revealed that leptomeningeal and perivascular enhancement at *de-novo* lesion with relapsing patterns as well as enhancement of deep medullary veins that seems like connecting with choroid plexus. This MRI finding of the enhancement of deep medullary vein has been not reported, to our knowledge. Considering pathogenesis of CM-IRIS that characterize the CSF inflammation due to exaggerated response to cryptococcal antigens, we presume that one of spread course of CSF inflammation is through CSF-blood barrier. But further studies are required.

Presented case report showed well matching the clinical data with MRI findings at two events of CM-IRIS and recurrence during 3 years follow-up in a HIV-patient with cryptococcal infection. Clinical findings of CSF culture result and CSF inflammation degree in immunosuppressed patients may help to distinguish CM-IRIS and CM relapse. Also, this case showed the new finding of enhancement of bilateral deep medullary veins that seems like connecting with choroid plexus. Although it represents one of spread course of CSF inflammatory change through CSF-blood barrier, further deep studies are required.

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인간면역결핍바이러스 감염환자에서 역설적 크립토코쿠스 수막염 면역재구성 염증증후군: 임상 소견들과 자기공명영상 소견들의 대조

문성준[1] · 함명훈[2]*

크립토코쿠스 수막염 면역재구성 염증증후군은 역설적 크립토코쿠스 수막염 면역재구성 염증증후군과 증상이 드러나는 크립토코쿠스 수막염 면역재구성 염증증후군의 두 가지 형태가 있다. 역설적 크립토코쿠스 수막염 면역재구성 염증증후군과 크립토코쿠스 수막염 재발을 구별하는 것은 중요하다. 왜냐하면 면역재구성 염증증후군 없는 크립토코쿠스 수막염보다 면역재구성 염증증후군이 있는 크립토 코쿠스 수막염의 사망율이 더 높고, 역설적 크립토코쿠스 수막염 면역재구성 염증증후군과 크립토코쿠스 수막염 재발은 다른 치료를 요구하기 때문이다. 우리는 인간면역결핍바이러스 감염환자의 3년의 추적기간 동안 임상 소견과 자기공명영상 소견이 잘 대조된 역설적 크립토코쿠스 수막염 면역재구성 염증증후군의 사례와 감별에 도움이 되는 새로운 자기공명영상 소견을 보고하고자 한다.

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