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CASE REPORT

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Leukoencephalopathy during administration of etanercept for refractory rheumatoid arthritis

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Abstract A 74-year-old Japanese woman was diagnosed with rheumatoid arthritis due to polyarthralgia. She was prescribed various disease-modifying anti-rheumatic drugs, but most of them were discontinued because of side effects or poor effectiveness. She was referred to our hospital in 2004, and etanercept was administered from June 2005. This resulted in rapid improvement of polyarthritis; however, she developed disorientation from February 2006. She was admitted to our hospital because of convulsions and loss of consciousness. She was diagnosed with progressive multifocal leukoencephalopathy on the basis of clinical symptoms and magnetic resonance imaging of the brain. In this significant and important case, leukoencephalopathy occurred during etanercept administration, and we refer to the risk of anti-TNFα drugs.

Key words Elderly · Etanercept · Leukoencephalopathy · Rheumatoid arthritis

Introduction

Progressive multifocal leukoencephalopathy (PML) is a deadly demyelinating disorder secondary to central nervous system viral infection and is seen in patients who are immunodeficient, such as HIV-infected individuals and organ transplant recipients. The causative agent is mainly the JC virus, which belongs to the polyomavirus family. The virus is a common infecting agent in humans, but usually the infection is clinically silent, becoming reactivated with immunosuppression. Because of the lack of appropriate treatment for PML, it has become one of the deadliest opportunistic infections in immunodeficient patients. Here, we report a case of rheumatoid arthritis (RA) in a female patient who rapidly developed leukoencephalopathy during the administration of etanercept for treatment of RA.

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Case report

A 74-year-old Japanese woman suffered from pain in the right toes from July 1997. She visited an orthopedist and was diagnosed with RA. She was initially prescribed 5 mg/day of prednisolone and various disease-modifying anti-rheumatic drugs, such as auranofin, penicillamine, and 4-acetylaminophenylacetic acid. Methotrexate was also tried in 2003 but was discontinued because of the appearance of interstitial pneumonia. Leflunomide and cyclophosphamide were not effective. Several synovectomies were performed on the left knee, and the right knee was replaced. She was referred to our hospital in 2004 for control of the arthritis (Steinbrocker stage III) and was prescribed with 10 mg/day of prednisolone, but this did not improve her condition. Her ability to carry out the activities of daily life gradually worsened.

Consequently, she was admitted to our hospital and was administered 25 mg of etanercept twice a week from June 2005. Her chest X-ray on admission showed no shadow; however, she was also prescribed isoniazid (300 mg/day) to prevent tuberculosis because she recalled suffering from pleuritis and because of her age. This therapy resulted in rapid improvement of polyarthritis and she was discharged in 3 weeks.

The next month, she developed low-grade fever and petechiae on the limbs. We considered these to be side effects of isoniazid and switched to rifampicin (450 mg/day). Etanercept was subsequently continued; however, she was admitted to a related facility because of severe general malaise and loss of appetite in January 2006. Disorientation and

Table 1. Laboratory data on admission

WBC	16.2×10^3 μl	TP	5.6 g/dl	CRP	19.75 mg/dl
Neutro	95.5%	Alb	3.0 g/dl	RF	190 IU/l
Lymph	1.6%	T.bil	1.4 mg/dl	IgG	649 mg/dl
Mono	2.8%	D.bil	0.7 mg/dl	IgA	169 mg/dl
Eosino	0%	AST	28 IU/l	IgM	107 mg/dl
Baso	0.1%	ALT	33 IU/l	CH50	45.8 U/l
RBC	4.05×10^6 μl	ALP	168 IU/l	ANA	(–)
Hb	12.7 g/dl	LDH	271 IU/l	aDNA Ab	(–)
Plt	95×10^3 μl	γGTP	16 IU/l	aSS-A Ab	(–)
		BUN	27 mg/dl		
ESR	88 mm/h	Cr	0.8 mg/dl	β-D glucan	<5.0 pg/ml
		Na	133 mEq/l	CMV Ag	(–)
U-protein	(–)	K	3.9 mEq/l	HSV-1 IgM	<10×
U-glucose	(–)	Cl	103 mEq/l	HSV-1 IgG	40×
U-blood	(–)	Ca	8.3 mg/dl	VZV IgM	<10×
				VZV IgG	40×

Table 2. Evaluation of cerebrospinal fluid on admission

TP	84 mg/dl	Lymph	30/3 μl
Alb	46 mg/dl	IgG	6.2 mg/dl
Glucose	138 mg/dl	IgA	0.8 mg/dl
Cell	30/3 μl	IgM	<0.4 mg/dl
Neutro	0/3 μl		

incontinence were occasionally apparent from February 2006, and verbal communication gradually deteriorated, registering a score of 6 points on Hasegawa's dementia scale. The following month, she was transferred to our hospital after convulsions and loss of consciousness (Japanese Coma Scale: 200).

On this admission, the patient exhibited neck rigidity and Babinski's reflex. Laboratory investigations demonstrated leukocytosis and mild thrombocytopenia. C-reactive protein was 19.75 mg/dl (Table 1). The cerebrospinal fluid (CSF) revealed an elevated concentration of protein (84 mg/dl; normal range 10–40 mg/dl) and cell count (30/3 μl; normal range 0/3–10/3 μl), and glucose concentration was not reduced (Table 2). Contrast-enhanced fluid-attenuated inversion-recovery (FLAIR) magnetic resonance imaging (MRI) of the brain showed high-intensity lesions disseminated bilaterally throughout the white matter. We initially diagnosed encephalomeningitis and prescribed antibiotics, antimycotics, globulins, and acyclovir. Inflammation rapidly disappeared, but disorientation and abnormal reflexes continued and speech did not improve. In April 2006, CSF revealed further elevation of protein but was otherwise unchanged. Brain MRI revealed greater dissemination of white matter lesions (Fig. 1). After consultation by a neurologist, the patient was clinically diagnosed with PML. We tried to detect the JC virus in the CSF using polymerase chain reaction (PCR); however, the results of two tests were negative. The patient had a tendency to remain in bed, but with supportive therapy her condition temporarily improved enough to sit up for meals. She was transferred to a related sanatorium and continued to undergo rehabilitation (Fig. 2).

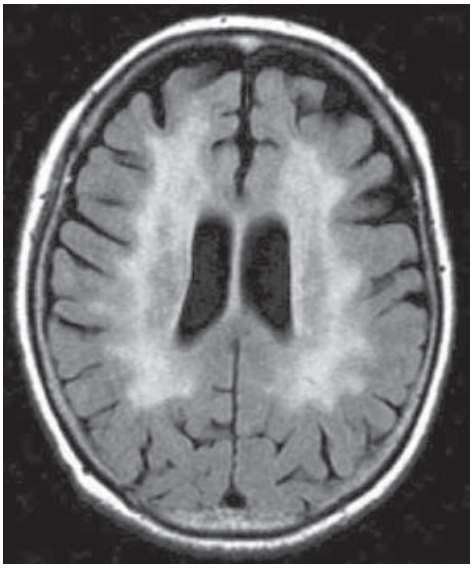

Fig. 1. Fluid-attenuated inversion-recovery (FLAIR) magnetic resonance imaging (MRI) of the brain revealed high-intensity lesions disseminated in the white matter

Discussion

There have been remarkable recent developments in biologic agents for RA. We can administer anti-tumor necrosis factor (TNF)-α treatment for RA. Etanercept has been one of the most anticipated of these agents; however, various side effects have been reported. It is known that age, complications of diabetes mellitus, and respiratory disease are risk factors leading to bacterial pneumonia when anti-TNFα drugs, including etanercept, are administered.[1] The risk factor of other opportunistic infections is considered to be similar.

Leukoencephalopathy is known to be one of the serious adverse events associated with administering etanercept.[2,3] However we hardly experienced the cases with leukoencephalopathy even if we prescribed immunosuppressions as in the past. PML is a rare demyelinating cerebral disease, and was first reported by Astrom in 1958.[4] Padgett detected

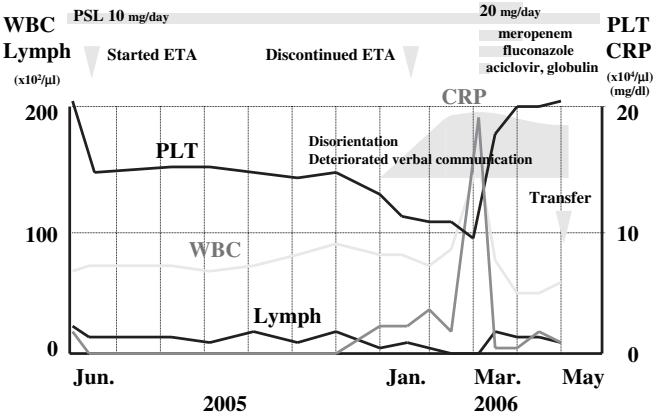

Fig. 2. Clinical course of the patient. Laboratory investigations on admission for leukoencephalopathy demonstrated lymphopenia and mild thrombocytopenia

the virus, which was named the JC virus, from PML patients in 1971,[5] following which PML was considered to be a viral infection. JC virus is widespread, found in at least 70% of the general population,[6] but usually remains latent, causing disease only when the immune system has been severely weakened. PML is reported to have occurred under immunosuppressive conditions such as adult T cell leukemia,[7] systemic lupus erythematosus,[8] and HIV infection.[9,10] Symptoms include weakness or paralysis, impaired speech, vision loss, and cognitive deterioration. PML is similar to another demyelinating disease, multiple sclerosis, but progresses much more quickly. There is no known cure, and most patients die within a year.

The CSF of PML patients usually shows only a slight increase of protein concentration, without an increase in lymphocytes and neutrophils cells or a decrease in the concentration of glucose. PML is diagnosed by testing for JC virus DNA in CSF; the sensitivity of JC virus-DNA PCR in CSF is reported to be 74%–92%.[11] Tests of CSF can help distinguish PML from other diseases such as multiple sclerosis and acute hemorrhagic leukoencephalopathy. Characteristic evidence of the damage caused by PML in the brain can also be detected on MRI images. This patient had most of the characteristic findings of PML in clinical conditions, whereas JC virus could be detected only in the CSF.

Recently, it has been reported that natalizumab therapy can predispose to JC virus infection resulting in PML.[12–14] Natalizumab, which blocks α4 integrins (including α4β1/VLA-4) and was anticipated to be a biological agent, has been used for the treatment of multiple sclerosis, Crohn's disease, and RA.[15] The 3417 patients were enrolled in a clinical trial and three patients in these cases were complicated to PML.[15] It is suggested that natalizumab-associated PML occurred as a result of the mobilization of JC virus-infected bone marrow cells, possibly in combination with reduced inflammatory and surveillance trafficking to the central nervous system.[16] On the other hand, a similar demyelination has already been reported during anti-TNFα therapy.[17] In that study, the participation of the JC virus in demyelination was not determined. However, the following possibilities need to be considered: (1) the sensitivity of JC virus DNA-PCR and (2) demyelination, which results in leukoencephalopathy, caused by the anti-TNFα drug itself. Although our patient was diagnosed with PML, we had the impression that it was different from the usual PML owing to the slow progression of the disease. We will have to resolve the problem from now on.

With the recent emphasis on various biologic agents for treatment of rheumatic diseases, we must recognize that leukoencephalopathy may appear as a complication of opportunistic infection or as a side effect of the biologic agents themselves.

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