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LETTER TO THE EDITOR

Malignant syndrome triggered by influenza A virus infection in a patient with Parkinson's disease with improvement after intravenous peramivir treatment

Kosuke Matsuzono[1,2] · Masamichi Baba[1] · Goro Imai[1] · Hiroaki Imai[1] · Shigeru Fujimoto[2]

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Introduction

Malignant syndrome, also called parkinsonism-hyperpyrexia syndrome, is a rare medical emergency in patients with Parkinson's disease (PD). The precipitating events that trigger malignant syndrome in patients with PD are anti-parkinsonian drug withdrawal and stress-related factors [1, 2]. Infection is a major cause of malignant syndrome, and fever is considered the trigger [1]. However, the relationship among malignant syndrome, influenza virus infection, and treatment for influenza virus remains unclear. We herein report a case involving a man with PD who developed malignant syndrome secondary to influenza A virus infection but improved after intravenous peramivir treatment without dantrolene.

Case presentation

A 71-year-old man had an 8-year history of Hoehn–Yahr stage III PD and lived at home with his wife. His gait was slightly unstable, but he was able to walk independently without a cane. His Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score was 70. He had been taking 400 mg/day of levodopa with 100 mg/day benserazide and 1.5 mg/day of pramipexole. Other than PD, he had hypertension for which he was taking 20 mg/day of telmisartan. His Parkinson's syndrome was stable and his medical compliance was good. However, he developed the flu with a high fever (39.4 °C) during the winter and was admitted to our hospital the day after symptom onset. A flu test revealed influenza A virus infection. His consciousness was stuporous on admission, and he became totally bedridden with an increase from Hoehn–Yahr stage III to V. His akinesia and rigidity became severe. Laboratory examination showed an elevated serum creatine kinase (CK) level of 3911 IU/L (reference range, 61–255 IU/L). In addition, mild anemia of serum hemoglobin level of 10.8 g/dl was present. Cranial and thoracoabdominal computed tomography images showed no abnormalities. He was admitted to the hospital and began treatment with 300 mg of intravenous peramivir.

The high fever disappeared and his consciousness became clear 3 days after symptom onset. At 5 days after onset, his serum CK level peaked at 7866 IU/L but then dramatically decreased without administration of dantrolene sodium (Table 1). Throughout the clinical course, the patient took all medications through an oral or nasogastric tube. Based on the modified Levenson's diagnostic criteria [3, 4], he was diagnosed with malignant syndrome. His Parkinson's syndrome, akinesia, and rigidity remained severe, and he could not walk even after the serum CK level became normal. Thus, the anti-parkinsonian drugs were gradually increased to 800 mg/day of levodopa, 200 mg/day benserazide, and 1.5 mg/day of pramipexole. Ninety days after rehabilitation in the hospital, he was able to walk independently without a cane and returned home with Hoehn–Yahr stage III PD. His MDS-UPDRS total score after the rehabilitation was 74. A summary of the

✉ Kosuke Matsuzono
kmatsuzono51@jichi.ac.jp

Masamichi Baba
mbaba@anz.or.jp

Goro Imai
goro-i@bf7.so-net.ne.jp

Hiroaki Imai
himai@anz.or.jp

Shigeru Fujimoto
shigeruf830@jichi.ac.jp

[1] Department of Internal Medicine, Imai Hospital, Tochigi, Japan

[2] Division of Neurology, Department of Internal Medicine, Jichi Medical University School of Medicine, Yakushiji 3311-1, Shimotsuke, Tochigi 329-0498, Japan

Table 1 Laboratory data of the patient

	Normal range	Day 1	Day 3	Day 5	Day 8	Day 13
WBC (cell/mm^3)	4000–8000	5500	5600	6800	6000	6200
RBC (cell/mm^3)	450–550	312	329	315	325	328
Hb (g/dl)	13.0–17.0	10.8	11.1	10.7	11.1	11.1
Platelet (cell/mm^3)	13.0–37.0	14.7	5.1	13.9	16.7	21.7
AST (IU/l)	8–38	64	128	149	54	14
ALT (IU/l)	4–44	17	40	48	35	16
LDH (IU/l)	106–211	314		520	397	266
CK (IU/l)	61–255	3911	6475	7866	2262	240
CK-BB (%)	0–2	0				
CK-MB (%)	0–3	2				
CK-MM (%)	96–100	98				
BUN (mg/dl)	8.0–20.0	22.4	20.3	23.5	16.4	23.1
Cr (mg/dl)	0.6–1.1	1.1	0.9	0.9	0.9	0.8
Sodium (mEq/l)	135–147	137	137	137	139	137
Potasium (mEq/l)	3.6–5.0	4.5	4.5	4.6	5.0	4.5
Chloride (mEq/l)	98–108	106	106	106	107	107
Calcium (mEq/l)	8.5–10.2	8.7		8.4		
BS (mg/dl)	70–109	104	107	106	101	92
CRP (mg/dl)	0.0–0.3	3.4	3.8	2.81		0.7
ESR (mm/1 h)	2–10	47				

WBC white blood cell, *RBC* red blood cell, *Hb* hemoglobin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *CK* creatine kinase, *CK-BB* creatine kinase isozyme found in brain, bladder, stomach, and colon, *CK-MB* creatine kinase isozyme found in cardiac tissue, *CK-MM* creatine kinase isozyme found in skeletal muscle, *BUN* blood urea nitrogen, *Cr* creatinine, *BS* blood sugar, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

patient's clinical course is shown in Fig. 1, and the laboratory examination changes are shown in Table 1.

Discussion

In this case, malignant syndrome was induced by influenza A virus infection in a patient with PD despite the fact that he was taking anti-parkinsonian drugs as prescribed. The patient's akinesia, rigidity, and serum CK level progressively worsened but then dramatically improved soon after treatment with intravenous peramivir and disappearance of the high fever. Although levodopa dosage increased up to 800 mg from 400 mg per day needed after the malignant syndrome, his ADL level maintained and the Hoehn–Yahr grade was same III. Takubo et al. reported that infection is the second most common cause of malignant syndrome in patients with PD and that in their study, 31.3% of patients failed to recover to their preclinical state [4]. Their report suggests the poor outcome of malignant syndrome, especially in patients with PD. The main treatment for malignant syndrome is administration of sufficient intravenous fluids, external cooling, administration of anti-parkinsonian drugs including levodopa and bromocriptine, and administration of dantrolene sodium. Subcutaneous apomorphine is also reported to be useful in some malignant syndrome cases [5]. In the initial stage of the present case, we considered transferring the patient to another hospital when we failed to suppress the malignant syndrome because no bromocriptine, dantrolene sodium, or apomorphine was available in our hospital. However, after treatment with intravenous peramivir, we succeeded in suppressing the malignant syndrome and the patient finally recovered.

Although infection is the second most common trigger of malignant syndrome, the pathology has not been completely elucidated. Cytokines might induce an inflammatory reaction in such patients [4]. In addition, the body temperature is associated with dopamine infusion to the anterior hypothalamus to a certain extent [6]. Peramivir is an intravenous neuraminidase inhibitor with potent antiviral activity against influenza A and B viruses, and it was approved for clinical treatment in 2010 in Japan [7]. Intravenous peramivir is reportedly effective based on the results of direct comparison with oral oseltamivir, and the median time to reach a body temperature of < 37 °C by intravenous peramivir is within 2 days in most patients [8]. In the present case, we speculate that the rapid suppression of cytokines and high fever by intravenous administration of peramivir for treatment of the influenza A virus infection resulted in steady recovery from the malignant syndrome.

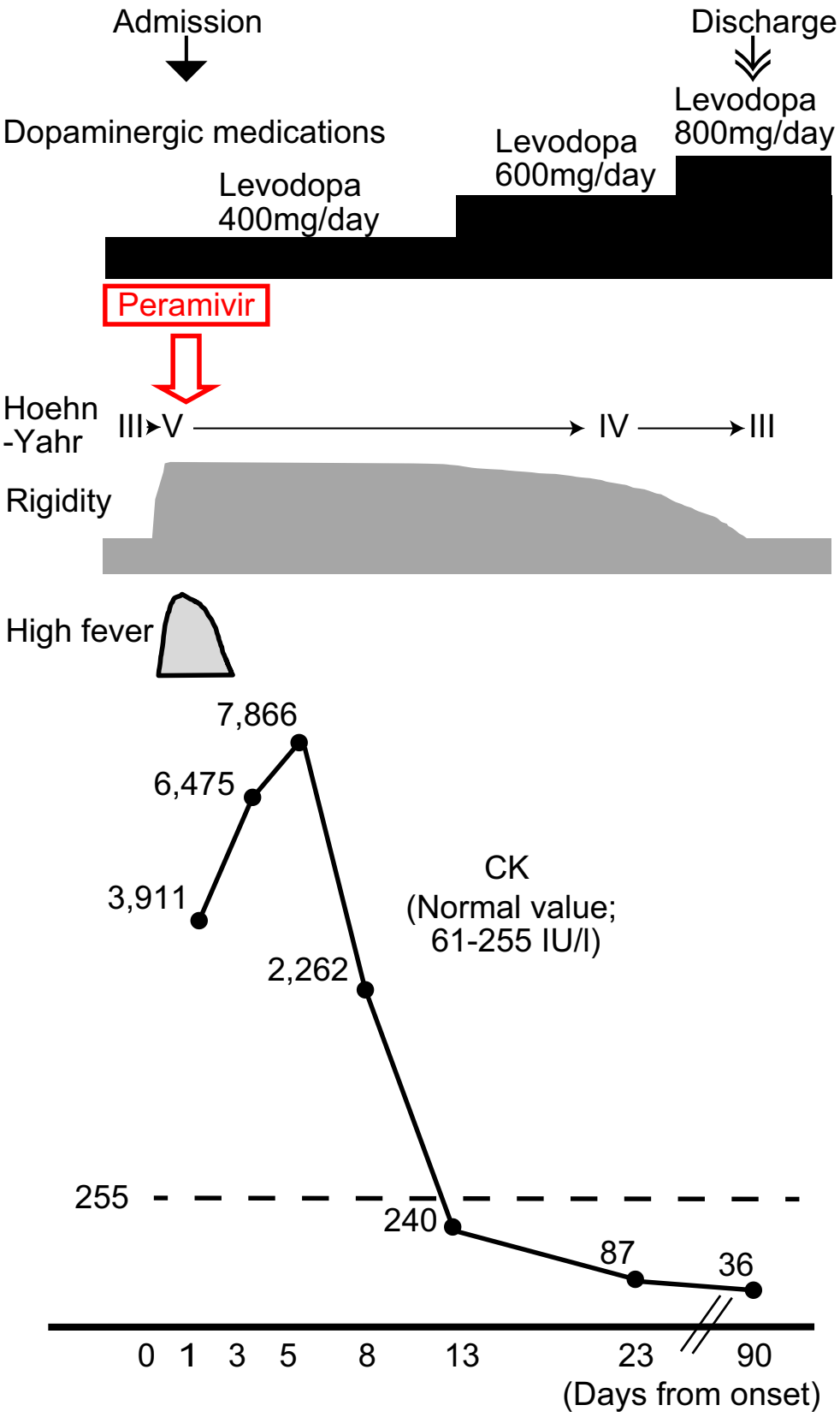

Fig. 1 Patient's clinical course. Intravenous peramivir (300 g) was initiated 1 day after symptom onset. The high fever (> 37 °C) disappeared 3 days after symptom onset. The serum creatine kinase level peaked at 7866 IU/L at 5 days after symptom onset

In summary, the present case suggests that in patients with PD, influenza A virus infection can induce malignant syndrome but that intravenous peramivir is a useful option for treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical standards Informed consent was obtained from the patient described in this article.

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