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소세포폐암에서 Carboplatin 항암 치료 후 발생한 안구 진탕 1예 -증례 보고-

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A Case of Pathologic Nystagmus following Chemotherapy Using Carboplatin for Small Cell Lung Cancer -A Case Report-

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A quadriparetic 62-year-old male patient completely cured from small cell lung cancer was admitted to the hospital. The patient complained of dizziness and spontaneous horizontal nystagmus was present in both eyes. He was tolerable during the cancer treatment, but 4 months later he became bed ridden status and totally dependent on all of the daily living activities. Brain metastasis of primary cancer and paraneoplastic syndrome were suspected first, however the brain MRI and paraneoplastic antibody study revealed negative result. With reviewing his medical history, he took chemotherapy including carboplatin. We suspected the ototoxicity induced by carboplatin, as carboplatin has a unique side effect including ototoxicity affecting the balance function while preserving the hearing function. Clinicians should keep in mind this adverse effect in any patient with chemotherapy including carboplatin and who subsequently develops nystagmus and functional level impairment. In such, we present this case with the related literatures. **(Brain & NeuroRehabilitation 2013; 6: 82-85)**

Key Words: carboplatin, ototoxicity, pathologic nystagmus

Introduction

Cisplatin is the first-generation of platinum drugs approved in 1978 for testis cancer and ovarian cancer. Carboplatin, a second agent of platinum drugs, has equivalent activity for treatment of some type of cancers and is used in combination therapy for ovarian cancer and lung cancer.[1]

There is a report about adverse effect of carboplatin that carboplatin-induced ototoxicity affects cochlear inner hair cell and vestibular type-I hair cell selectively.[2] In such, this paper is a report of a patient with small cell lung cancer who showed nystagmus without hearing impairment after chemotherapy including carboplatin administration.

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Case Report

A quadriparetic 62-year-old male patient was admitted to our hospital. The patient was bed ridden status and totally dependent on all of the daily living activities. He, who took antihypertensive drugs, was diagnosed with small cell lung cancer, extensive stage. Chemotherapy including carboplatin was given in May 2011, for duration of about 5 months, and total cumulative dose was Irinotecan 780 mg/m^2 and Carboplatin 1,630.2 mg/m^2 (Irinotecan 1,443 mg and Carboplatin 3,016.08 mg). Prophylactic intracranial radiotherapy, for a total of 2,500 cGy, was performed for 3 weeks in November 2011. The

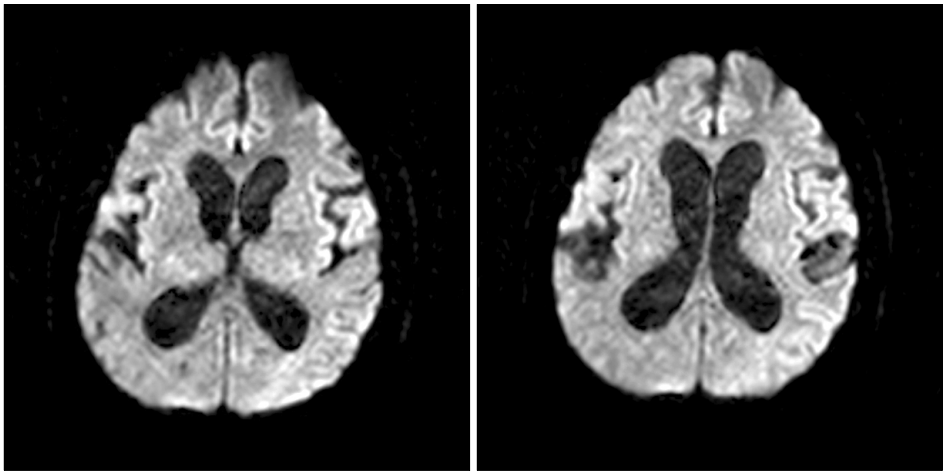

Fig. 1. There were no abnormal findings such as acute infarction or cortical atrophy, but communicating hydrocephalus was suspected in diffusion weighted brain MRI.

lung cancer showed complete remission in January 2012 on the chest PET-CT study. In February 2012, the patient was admitted to the neurology department with a complaint of nystagmus and tremors. Under medical records review, there was no history of prescription of other drugs except anti-cancer agent which can induce ototoxicity. The neurologist treated him with a high dose of steroid therapy, believing the symptoms to be due to radiation-induced encephalitis or paraneoplastic syndrome; however, the patient's symptoms were not improved. He was lying down most of time because of dizziness, nystagmus and tremors, and showed general weakness and functional level impairment.

After he was first admitted to our hospital, a physical examination was done. On the manual muscle test, both arms and legs showed Medical Research Council Grade III. Spasticity and upper motor neuron signs were not observed. The patient had no complaint of sensory change and there were no abnormal findings in sensory examinations. In the cerebellar function test, spontaneous horizontal nystagmus was present in both eyes, while resting and active tremors were also observed. Examination of the eyes in primary position revealed intermittent bursts of conjugate, rapid and horizontal movements, consistent with ocular flutter. The frequency and amplitude of nystagmus became significantly depressed by cold caloric stimulation. The nystagmus showed low amplitude and low frequency at 3～4 Hz. in the supine position, but the frequency was increased up to 8～9 Hz. in the sitting position, so the patient could not maintain a sitting posture. In laboratory tests, values were within normal limits. The audiometric tests including pure tone audiometry and speech tone audiometry were within normal limits.

A brain MRI was performed for evaluating the brain metastasis of primary small cell lung cancer; communicating hydrocephalus was suspected so cerebrospinal fluid drainage was performed but there was no improvement in tremors after the drainage (Fig. 1).

After 3 months, the patient was admitted for the second time; the patient reported improvement in dizziness and the frequency of nystagmus was decreased to less than 1 Hz. During the 3 months, he received comprehensive rehabilitation therapy including conventional neurodevelopmental treatment. As he didn't achieve motor power improvement as expected, a lumbar spine MRI study was done for evaluating other possible underlying causes, but the study showed no abnormal findings except a mild bulging disc. The Korean modified Barthel index score was 0 points in the data from the patient's first admission and 14 points in the data from the patient's second admission, with little improvement shown in the patient's functional level. He had been taking comprehensive rehabilitation with physical therapy and occupational therapy. A year after he could stand alone and walk with moderate assist and the Korean modified Barthel index score was improved to 21 points.

Discussion

Carboplatin has less adverse effect compared with other platinum drugs, such as cisplatin. Cisplatin can cause

peripheral neuropathy as neurotoxicity[3] and there is a case report of reversible posterior leukoencephalopathy syndrome, which shows brain white matter angiogenic edema in a brain MRI study with symptoms that include headache, visual disturbance, change in mental status and seizure attacks.[4] The ototoxicity caused by other drugs was reported as affecting the cochlear outer hair cell first. However, the mechanism of ototoxicity of carboplatin is somewhat different, as the initial targets of carboplatin are the type-I hair cells in the vestibular end organs and inner hair cells in the cochlea while sparing the cochlear outer hair cells.[2,5] In an animal trial using Chinchillas,[2] swollen afferent dendrites surrounding the vestibular type-I hair cell and several vacuole formations was observed after administration of carboplatin, and metabolism of remaining cochlear inner hair cell was decreased. Mizutari et al.[6] reported that inner ear energy failure causes balance dysfunction mainly by damaging the hair cells in the vestibule. They concluded that such a difference was derived from the different sensitivities for ototoxicity between cochlear and vestibular hair cells. Vacuolization and the loss of the hair cells in saccular maculae and cristae of the lateral semicircular were confirmed by electron microscopy and the results was similar with that of other studies.[2,5] In general, damages in the hair cell can affect hearing and balance function, but nystagmus was predominant while preserving the hearing function in the patient. This prevalence of nystagmus can account for the carboplatin damages of the cochlear inner hair cell and vestibular type-I hair cell selectively preserving the cochlear outer hair cell.

Radiation-induced encephalitis, brain metastasis of primary small cell lung cancer, paraneoplastic syndrome and chemotherapy-induced parkinsonism can be thought of as differential diagnosis. It is reported that the risk of sensorineural hearing loss is increased in the patients who received more than 45~50 Gy radiation,[7,8] but this patient received 25 Gy of radiation and the characteristics of toxicity was vestibular system damage instead of sensorineural hearing loss. Paraneoplastic antibody was all negative and there was no definite improvement after high dose steroid therapy treated in the neurology department with impression of paraneoplastic syndrome or radiation-induced encephalitis, so the possibility of paraneoplastic syndrome or radiation-induced ototoxicity could be ruled out. The brain MRI showed no metastatic lesion of the primary small cell lung cancer. There was a case report about secondary parkinsonism occurring after the chemotherapy,[9] but tremors were predominant in the child, while in the adult, the main feature was rigidity and bradykinesia. In this patient, rigidity and bradykinesia were not observed and the brain MRI showed no abnormal finding in the basal ganglia; whereas, signal changes in the basal ganglia was reported in the previous case. It could be thought that pathologic nystagmus induced by carboplatin was accompanied by physical deconditioning and the functional level of the patient was not fully recovered a year later.

In conclusion, carboplatin can induce ototoxicity mainly affects balance function while preserving hearing function. Clinicians should suspect this adverse effect in any patient with chemotherapy including carboplatin and who subsequently develops nystagmus and functional level impairment. Our study provides information as to the clinical features of carboplatin induced ototoxicity seen in our case and provides a literature review.

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