Palliative and Supportive Care (2005), **3**, 51–53. Printed in the USA.

DOI: 10.1017/S147895150505008X

Neuroleptic malignant syndrome in cancer treatment

CHIAKI KAWANISHI, M.D., PH.D.,[1] HIDEKI ONISHI, M.D., PH.D.,[1,2] DAIJI KATO, M.D.,[1] TOMOKI YAMADA, M.D.,[1] MASANARI ONOSE, M.D.,[1] AND YOSHIO HIRAYASU, M.D., PH.D.[1]

[1]Department of Psychiatry, Yokohama City University School of Medicine, Kanazawa-ku, Yokohama, Japan
[2]Department of Psychiatry, Kanagawa Prefecture Cancer Center, Asahi-ku, Yokohama, Japan

(RECEIVED January 5, 2005; ACCEPTED February 24, 2005)

ABSTRACT

Objective: Neuroleptic malignant syndrome (NMS) is a life-threatening reaction to neuroleptics. Several prospective studies have reported NMS occurrence rates ranging from 0.07% to 2.2% of patients receiving neuroleptics. However, few occurrences of NMS have been reported in cancer patients despite frequent complications of cancer and its treatment by mental disorders managed with neuroleptic drugs. Exhaustion, dehydration, and malnutrition are considered risk factors for NMS, and cancer patients represent a high risk group for NMS.

Methods: We describe a patient with metastatic chondrosarcoma who had received frequent neuroleptic injections prior to brain surgery and developed NMS in the intensive care unit immediately after surgery. The patient showed delirium, hyperpyrexia, tachycardia, diaphoresis, and extrapyramidal symptoms. After a diagnosis of NMS was made, supportive care and careful monitoring were carried out, and the patient recovered over an interval of 11 days.

Results and significance of the research: Clinical NMS studies have been conducted mainly in psychiatric units, but NMS can occur wherever psychotropic drugs are administered. NMS can be difficult to diagnose due to multiple complicating factors in cancer treatment, but the diagnosis is highly important given the risk of death. Recognition of prodromal NMS symptoms can facilitate actions to decrease morbidity and mortality. It is suggested that special attention to cancer patients undergoing psychopharmacologic treatment is required in clinical oncologic practice.

KEYWORDS: Adverse drug reaction, Cancer, Neuroleptics, Neuroleptic malignant syndrome

INTRODUCTION

Neuroleptic malignant syndrome (NMS), a potentially lethal adverse reaction to neuroleptic administration, is characterized by hyperthermia, extrapyramidal signs, altered consciousness, autonomic dysfunction including fluctuation of blood pressure, arrhythmia, dyspnea, diaphoresis, and incontinence, elevated creatine phosphokinase in serum, and leukocytosis (Kawanishi, 2003). Several prospective studies have reported NMS occurrence rates ranging from 0.07% to 2.2% of patients receiving neuroleptics, and mortality in NMS is estimated to exceed 10%. In addition to neuroleptic drugs, NMS also can be caused by antidepressants, lithium carbonate, and other psychotropic agents. Clinical NMS studies have been conducted mainly

Corresponding author: Chiaki Kawanishi, M.D., Ph.D., Associate Professor, Department of Psychiatry, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. E-mail: chiaki@yokohama-cu.ac.jp

in psychiatric units, but occurrences in nonpsychiatric settings warrant consideration because NMS can occur anywhere psychotropic drugs are administered (Kawanishi, 2003).

In this report we describe a patient with metastatic chondrosarcoma who developed NMS. The patient had received frequent injections of a neuroleptic to treat psychiatric symptoms such as anxiety and agitation. NMS occurred in the intensive care unit immediately after a craniotomy. To date, only a few NMS occurrences have been reported in cancer patients. Although cancer patients represent at a high risk for NMS, NMS can be difficult to diagnose due to multiple complicating factors in cancer treatment, and clinical oncologists' unfamiliarity with NMS.

CASE PRESENTATION

A 42-year-old man with chondrosarcoma developed metastases to the brain, lung, and bones. In April 2003 he was referred to the Kanagawa Prefecture Cancer Center, where the brain metastasis was treated by stereotactic radiosurgery using the gamma knife. In June he was readmitted to the hospital because of sudden onset of aphasia and hemiparesis. Brain images disclosed growth of the tumor, intratumoral hemorrhage, and edema. Corticosteroids were given to reduce edema. The patient showed severe anxiety, agitation, irritation, and insomnia from hospital day 1, without abatement of symptoms. Ten milligrams of haloperidol were injected six times within 6 days after admission, and an additional 2.25 mg of haloperidol were given daily beginning on day 5. On day 7 tachycardia and diaphoresis were observed. On day 10 a craniotomy was performed to remove the tumor, attaining only incomplete removal. Immediately after surgery, psychiatric assessment was requested because of psychomotor excitement evident in the intensive care unit. The patient showed delirium, hyperpyrexia, tachycardia, "lead pipe" rigidity, tremor, dysarthria, and diaphoresis. Laboratory results included a high serum concentration of creatinine kinase (1413 IU/l; normal, 38 to 174). The peripheral white blood cell count was 13,800 mm^3 (normal, 3800 to 9800 mm^3). A diagnosis of NMS was made according to the criteria of Pope et al. (1986). Supportive care including hydration and careful monitoring was carried out, and the patient recovered over an interval of 11 days.

DISCUSSION

Since neuroleptic malignant syndrome was proposed as a clinical entity in the 1960s, various case descriptions and clinical studies have been reported from psychiatric and neurologic units. The pathophysiologic mechanisms of NMS still are unclear, but the dopaminergic system is thought to be pivotal in the etiology of NMS because all neuroleptics that can cause NMS act as antagonists at dopamine receptors in the central nervous system. Certain predisposing conditions such as dehydration, malnutrition, and exhaustion are risk factors for development of NMS. Psychomotor agitation, high or rapidly increasing neuroleptic doses, and frequent use of neuroleptic injections are other risk factors that tend to be interrelated (Kawanishi, 2003). Although minimizing risk factors could decrease NMS incidence to some extent, prediction and prevention of NMS still are difficult. On the other hand, a patient who has experienced NMS is at high risk for recurrence if neuroleptics are reintroduced. Thus, constitutional factors of NMS have been a focus of attention, and pharmacogenetic studies have suggested a genetic background for NMS occurrence (Kawanishi, 2003; Kishida et al., 2004).

Recent NMS cases reported from clinical settings apart from psychiatric and neurologic units underscore that NMS is possible wherever any neuroleptic drug is administered (Tenenbein, 1985; Zohar et al., 1992; Bakri et al., 1992; Tanaka et al., 1998; Russell et al., 2001; Onose et al., 2002). As diseases other than neuropsychiatric disorders could act as triggers if they significantly worsened the physical condition of the patient, individuals with advanced cancer could be considered at high risk. We recently reported development of NMS following neuroleptic treatment after bone marrow transplantation for acute myeloid leukemia; pretransplantation irradiation, chemotherapy, and graft-versus-host disease (GVHD) had resulted in both physical and mental stress (Onose et al., 2002). NMS in cancer patients has been reported only rarely despite frequent complications of cancer and its treatment by mental disorders managed with neuroleptic drugs. Tanaka et al. (1998) reported NMS occurrence complicating treatment of delirium that followed surgery for soft palate cancer, noting diagnostic difficulties arising from clinical oncologists' unfamiliarity with NMS and sometimes from the resemblance of NMS symptoms to those related to cancer itself, as we experienced in patients who underwent bone marrow transplantation (Onose et al., 2002).

We know of no previous reports of NMS occurrence in the intensive care unit on the day of surgery. In our patient, cerebral dysfunction might have triggered NMS after repeated haloperidol injections. Patients with organic brain diseases typically are naive to neuroleptics. Although organic

brain diseases themselves have been suggested as risk factors of NMS, this issue has not been fully assessed by a large-scale study (Shalev & Munitz, 1986). NMS and its prodromal symptoms also become more difficult to diagnose when neurologic symptoms from organic brain disease could mask NMS symptoms. Prodromal symptoms in our case were tachycardia and diaphoresis observed beginning on day 7.

NMS probably is less rare overall than initially thought, with incomplete forms being particularly likely to be overlooked in nonpsychiatric settings. Although NMS is potentially lethal, recognition of prodromal NMS symptoms can permit action to decrease morbidity and mortality. In clinical oncologic practice, patients undergoing psychopharmacologic treatment require vigilance against NMS.

ACKNOWLEDGMENT

This study was supported in part by a grant from Mitsubishi Pharma Research Foundation.

REFERENCES

Bakri, Y.N., Khan, R., Subhi, J., et al. (1992). Case report: Neuroleptic malignant syndrome associated with metoclopramide antiemeric therapy. *Gynecologic Oncology*, *44*, 189–190.

Kawanishi, C. (2003). Genetic predisposition to neuroleptic malignant syndrome: Implication for antipsychotic therapy. *American Journal of Pharmacogenomics*, *3*, 89–95.

Kishida, I., Kawanishi, C., Furuno, T., et al. (2004). Association in Japanese patients between neuroleptic malignant syndrome and functional polymorphisms of the dopamine D2 receptor gene. *Molecular Psychiatry*, *9*, 293–298.

Onose, M., Kawanishi, C., Onishi, H., et al. (2002). Neuroleptic malignant syndrome following bone marrow transplantation. *Bone Marrow Transplantation*, *29*, 803–804.

Pope, G.H., Keck, P.E., & McElroy, S.L. (1986). Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. *The American Journal of Psychiatry*, *143*, 1227–1233.

Russell, C.S., Lang, C., McCambridge, M., et al. (2001). Neuroleptic malignant syndrome in pregnancy. *Obstetrics & Gynecology*, *98*, 906–908.

Shalev, A. & Munitz, H. (1986). The neuroleptic malignant syndrome: Agent and host interaction. *Acta Psychiatrica Scandinavica*, *73*, 337–347.

Tanaka, K., Akechi, T., Yamazaki, M., et al. (1998). Neuroleptic malignant syndrome during haloperidol treatment in a cancer patient: A case report. *Supportive Care in Cancer*, *6*, 536–538.

Tenenbein, M. (1985). The neuroleptic malignant syndrome: Occurrence in a 15-year-old boy and recovery with bromocriptine therapy. *Pediatric Neuroscience*, *12*, 161–164.

Zohar, Y., Talmi, Y.P., Sabo, R., et al. (1992). Neuroleptic malignant syndrome during perphenazine treatment in a patient with head and neck cancer: A case report. *Otolaryngology-Head and Neck Surgery*, *106*, 206–208.