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Paroxysmal Autonomic Dysregulation with Fever that was Controlled by Propranolol in a Brain Neoplasm Patient

Su Jin Oh, M.D. Yun Kyung Hong, M.D. and Eun-Kee Song, M.D.

Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, Korea

Intractable fever in cancer patients is problematic and the causes of this fever can be diverse. Paroxysmal persistent hyperthermia after sudden mental change or neurologic deficit can develop via autonomic dysregulation without infection or any other causes of fever. Paroxysmal hyperthermic autonomic dysregulation is a rare disease entity. It manifests as a form of paroxysmal hypertension, fever, tachycardia, tachypnea, pupillary dilation, agitation and extensor posturing after traumatic brain injury, hydrocephalus, brain hemorrhage or brain neoplasm. We recently experienced a case of paroxysmal hyperthermia following intracerebral hemorrhage along with brain neoplasm. Extensive fever workups failed to show an infectious or inflammatory source and/or hormonal abnormality. Empirical treatments with antibiotics, antipyretics, morphine, steroid and antiepileptic agents were also ineffective. However, Propranolol, a lipophilic beta-blocker, successfully controlled the fever and stabilized the patient. Fever in cancer patients is a common phenomenon, but a central origin should be considered when the fever is intractable. Propranolol is one of the most effective drugs for treating paroxysmal hyperthermia that is due to autonomic dysregulation.

Key Words : Paroxysmal autonomic dysregulation, Brain neoplasm, Propranolol

INTRODUCTION

Fever is one of the most frequently encountered problems during the management of cancer patients. The causes are usually infection, other inflammatory sources and/or hormonal imbalances such as thyroid storm and pheochromocytoma. Extensive workups for finding the origin of fever sometimes fail to reveal the problem and empirical treatment with antibiotics, antipyretics or steroid are tried for treating the undetermined infection or cancer fever.

If the paroxysmal hyperthermia is combined with acute mental change or neurologic deficit after brain injury, central fever should be considered. Studies on central fever have sometimes revealed infection of the central nervous system or septic cerebral embolism. According to some reports, paroxysmal hyperthermia after acute mental deterioration is due to traumatic brain injury and this is known as 'diencephalic syndrome' or 'paroxysmal hyperthermic autonomic dysregulation'; it presents with fever, tachycardia, hypertension and seizure.

Hyperthemia that's caused by autonomic dysregulation has usually been reported in cases after surgical or traumatic cerebral hemorrhage or hypothalamic damage. However, to the best of our knowledge, there have been no reports on paroxysmal hyperthermic autonomic dysregulation associated with brain tumor. We report here on a rare case of brain tumor that presented with intractable fever and this was successfully controlled by administering propranolol.

CASE REPORT

A 67-year old man was admitted to our hospital because of

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• Correspondence to : Eun Kee Song, M.D., Chonbuk National University Medical School, San 2-20 Geumam-dong, deokjin-gu, Jeonju 561-180, Korea
Tel : 82-63-250-1245, Fax : 82-63-254-1609, E-mail : eksong@chonbuk.ac.kr

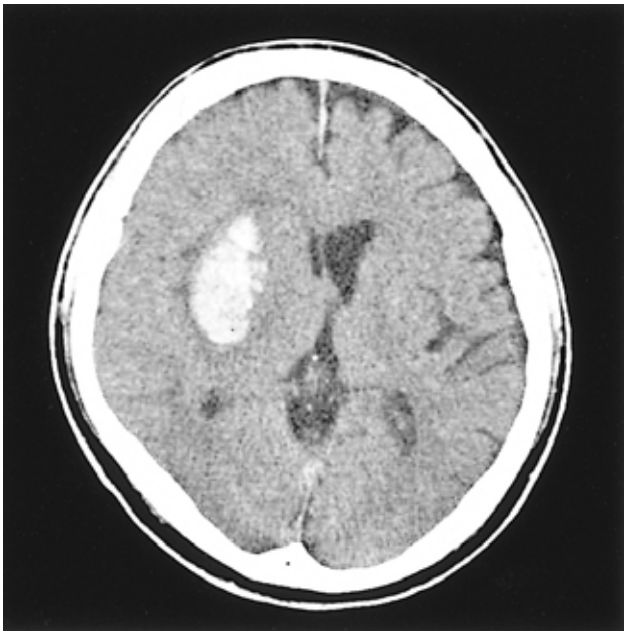

Figure 1. The brain CT shows the acute hemorrhage in the right basal ganglia.

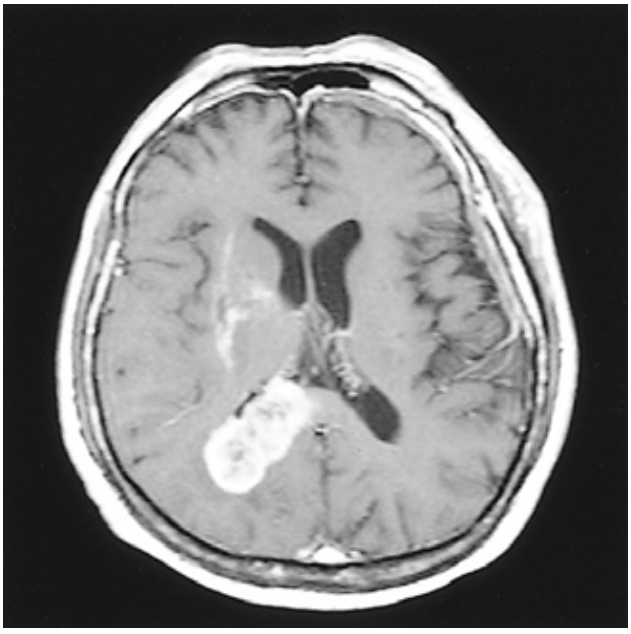

Figure 2. The brain MRI shows residual hematoma in the right basal ganglia and an additional mass lesion in the splenium portion of the right corpus callosum.

his acute altered mental status and left hemiparesis. He had a 10 year history of hypertension and he was taking antihypertensive drugs. There was a history 8 years ago of hypertensive cerebral hemorrhage, but no sequelae remained after conservative treatment. The family history and social history were nonspecific. On admission, the body temperature of the patient was 36.6℃, the blood pressure was well controlled at 120/80 mmHg, the pulse rate was 60 beats per minute and the respiratory rate was 20 times per minute. The patient appeared to be acutely ill, and he presented with a comatous mental status (Glasgow Coma Scale 4). His corneal reflex was intact, but the pupil was anisocoric. The motor strength of the left upper and lower extremities was decreased and an abnormal deep tendon reflex was present, but Babinski's sign was not detected. The brain computed tomography (CT) showed acute hemorrhage in the right basal ganglia and the right lateral ventricle was displaced because of a mass effect (Figure 1). Trephination was performed to remove the hematoma and to decompress the brain. After trephination, the Glasgow Coma Scale was improved to 6 from 4 on admission. Follow-up brain MRI revealed residual hematoma in the right basal ganglia and an additional mass lesion in the splenium portion of the right corpus callosum (Figure 2). The tumor seemed to be a malignant lesion such as gliomatosis cerebri. The diagnosis of glioblastoma multiforme was finally confirmed by stererotactic biopsy.

The laboratory investigations revealed a normal peripheral blood cell count with a leukocyte count of 6,050/mm^3, a hemoglobin level of 14.0 g/dL and a platelet count of 145.000/mm^3. The blood chemistry findings, including the liver function tests and electrolytes, were also within the normal ranges.

There was no fever at the time of admission, but paroxysmal fever developed at the recovery phase after stereotactic brain biopsy. Extensive fever workups were done. The repeated blood and cerebral spinal fluid cultures were all negative for bacterial growth. The chest X-ray was normal and the urinalysis was also normal. Follow up brain CT could not detect any inflammatory focus, including abscess formation. Several viral studies, including antibody tests for HIV, hepatitis A, B and C, cytomegalovirus and EB virus, were all negative. On the electroencephalogram, there was no epileptic discharge or spike-and-wave complex.

We could not find any source of infection even though the patient exhibited persistent paroxysmal fever, so we presumed this was a cancer fever at first. We started high dose steroid therapy to control the cancer fever and empirical antibiotic treatment was administered to cover any undetected bacterial infection. Alas, all the presumptive treatments were in vain. We finally thought that the central fever was due to autonomic dysregulation, and the combined clinical patterns such as paroxysmal hyperthermia and the abrupt blood pressure elevation were relevant to the central origin. The first choice of drug was morphine, but it was useless. The next drug was propranolol, which is sympathetic blocking agent that is able to

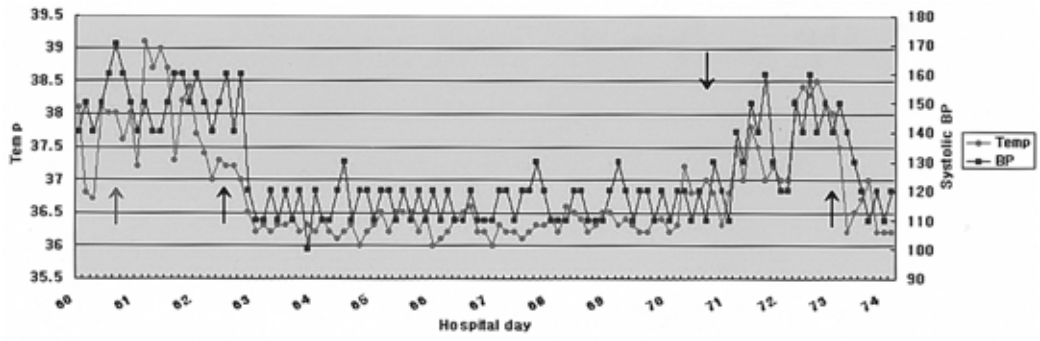

Figure 3. The graph represents the daily body temperatures and systolic blood pressures after initiation, withdrawal and reinitiation of administering propranolol. The upward pointing green arrow reflects the point of time for dexamethasone and morphine administration. The upward pointing black arrows reflect the point of time for administration and readministration of propranolol. The downward pointing black arrow reflects the point of time for withdrawal of propranolol.

pass the blood-brain-barrier. Propranolol successfully controlled the paroxysmal hyperthermia (Figure 3). After one week of propranolol treatment, we tried tapering the propranolol, but the fever developed again. Therefore, we continuously maintained the dose of the drug.

Even though the fever and blood pressure were stably controlled thereafter, his mental status didn't improve. Sadly, the patient succumbed to aspiration pneumonia one month later.

DISCUSSION

Paroxysmal hyperthermic autonomic dysregulation is a syndrome that occurs spontaneously and it arrives from an unknown cause. It is commonly associated with closed head injury and hydrocephalus. Typically, there are nonsustained episodes of hyperpyrexia, tachycardia, tachypnea, increased blood pressure, increased extensor tone, pupil dilation and diaphoresis[1-4]. The theories regarding the cause of this syndrome include several neuroimmunologic mechanisms. One theory is the initial release of several cytokines (IL-1, IL-6, TNF-α and IFN-ɣ) that is secondary to the direct trauma, infection of the brain, the inflammatory stimulation and the increased intracranial pressure after acute brain injury via the activate cyclooxygenase-2 pathways in the periventricular cells and the production of prostaglandin E2[5, 6]. Another theory is the stressed cells after brain injury synthesize heat shock proteins in a coordinated response to tissue injury. Hilaire et al. have described that this hyperthermia is associated with glutamate and nitric oxide release, which is caused by autonomic dysregulation of the brain stem[7-9].

Because this syndrome is diagnosed from clinical impressions, the differential diagnosis from infection, epileptic disorders, pheochromocytoma, neuroleptic malignant syndrome, increased intracranial pressure, hydrocephalus, Cushing's syndrome, thyrotoxicosis and deep vein thrombosis is essential and multidisciplinary approaches with other specialists are usually necessary[1, 4, 9].

Administering pharmacological agents that control the neurotransmitters in the complex autonomic nervous systems that are associated with autonomic regulation can be considered for treating hyperthermia, increased blood pressure, seizure and the secondary complications[10-14]. The current effective drugs are propranolol (β-blockers), opioid, clonidine (α2-agonist), bromocriptine (dopamine agonists), chlorpromazine (phenothiazine), dantrolene (muscle relaxants) and etc[15-18]. Stereotactic surgery is sometimes considered when these drugs are ineffective[19].

This present case demonstrates that uncontrolled fever in the patients suffering with brain injury by any causes should be viewed as possible paroxysmal hyperthermic autonomic dysregulation. Pharmacologic treatment that can control the hypothalamic thermoregulatory dysfunction should be considered.

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