Nonconvulsive Status Epilepticus in Patients With Cancer

Imaging Abnormalities

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Background: Convulsive status epilepticus may cause reversible neuroimaging abnormalities. These cortical changes have been reported rarely in association with nonconvulsive status epilepticus.

Objective: To describe patients with cancer who had reversible magnetic resonance (MR) imaging abnormalities from nonconvulsive status epilepticus and whose altered mental status and MR imaging findings were initially considered to result from a structural lesion related to their underlying tumor.

Design: Retrospective study.

Setting: Department of Neurology at Memorial Sloan-Kettering Cancer Center, New York, NY.

Patients: Eight patients with a diagnosis of nonconvulsive status epilepticus who underwent MR imaging.

Results: Enhancing cortical abnormalities were observed on MR images in 4 (50%) of 8 patients with cancer who had impaired mental status and an electroencephalogram demonstrating seizure activity. Follow-up MR images showed neuroimaging improvement or resolution in all patients.

Conclusions: Cortical enhancement on MR images in patients with cancer who have altered mental status may be due to nonconvulsive status epilepticus and not recurrent or metastatic tumor. If electroencephalography is not immediately available at initial evaluation, a trial of anticonvulsant therapy deserves consideration.

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ONCONVULSIVE STATUS epilepticus (NCSE) is sometimes an unrecognized cause of altered mental status. In patients with cancer who develop impaired mental status, imaging of the brain is the first test performed to exclude a structural lesion. We evaluated a patient with a brain tumor who presented with stupor; cranial magnetic resonance (MR) imaging showed cortical abnormalities identical to those associated with typical status epilepticus.1,2 Electroencephalography (EEG) confirmed the diagnosis of NCSE and the patient’s symptoms reversed with anticonvulsant therapy. We retrospectively studied MR images of patients with cancer who had NCSE and identified a total of 4 (including the index patient) who had radiographic abnormalities that could be attributed to seizures. Recognition of these NCSE-related changes should prompt immediate evaluation for and treatment of a seizure disorder.

METHODS

We reviewed the neurology departmental database for patients admitted to the Department of Neurology at Memorial Sloan-Kettering Cancer Center, New York, NY, because of confusion, seizures, status epilepticus, or unresponsiveness, from January 1, 2000, through December 31, 2002. We identified 9 patients whose final diagnosis was NCSE, and we reviewed their EEGs and cranial MR images. The criteria used for diagnosis of NCSE were impaired mental status of at least 30 minutes’ duration and no clinical signs of seizure activity with an EEG suggestive of electrographic seizure activity. One patient was excluded because MR imaging was not performed. For all other patients, MR imaging was performed on a 1.5-T imager (GE Medical Systems, Milwaukee, Wis). Diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR) imaging, T2-weighted imaging, and T1-weighted imaging after administration of gadolinium contrast material (gadopentetate dimeglumine) were performed in all patients; follow-up imaging was performed in all who had abnormalities identified on initial imaging.

RESULTS

The median age of the 8 patients was 62 years (range, 39-80 years); 4 were men. Seven patients had active or previous central nervous system tumor. Five patients had primary brain tumors (3 glioblas-
Clinical and Imaging Features of Patients With Transient MR Imaging Abnormalities

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Tumor Type and Location</th>
<th>Clinical Presentation</th>
<th>MR Imaging</th>
<th>Location</th>
<th>PET</th>
<th>EEG Findings</th>
<th>Clinical and Follow-up MR Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/62</td>
<td>Posterior fossa ependymoma (NED)</td>
<td>Unresponsive</td>
<td>NA</td>
<td>Cortical thickening</td>
<td>Leptomeningeal + cortical enhancement</td>
<td>R cerebral hemisphere</td>
<td>Not done</td>
</tr>
<tr>
<td>2/F/80</td>
<td>NSCLC</td>
<td>Unresponsive</td>
<td>Cortical hyper-intensity</td>
<td>NA</td>
<td>NA</td>
<td>L frontoparietal</td>
<td>Hypermetabolic L frontoparietal</td>
</tr>
<tr>
<td>3/M/39</td>
<td>L temporoparietal oligodendroglioma (NED)</td>
<td>Unresponsive</td>
<td>Cortical hyper-intensity</td>
<td>Cortical hyper-intensity</td>
<td>Leptomeningeal + cortical enhancement</td>
<td>R cerebral hemisphere</td>
<td>Hypermetabolic R temporal</td>
</tr>
<tr>
<td>4/M/62</td>
<td>R frontal GBM (NED)</td>
<td>Confusion</td>
<td>Cortical hyper-intensity</td>
<td>Cortical hyper-intensity</td>
<td>Leptomeningeal + cortical enhancement</td>
<td>R frontal</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Abbreviations: DWI, diffusion-weighted imaging; EEG, electroencephalogram; FDG, fludeoxyglucose F 18; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma multiforme; Gd, gadolinium; L, left; MR, magnetic resonance; MS, mental status; NA, no abnormality; NED, no evidence of active disease; NSCLC, non–small cell lung cancer; PET, positron emission tomography; PLEDs, periodic lateralizing epileptiform discharges; R, right.

toma multiforme, 1 posterior fossa ependymoma, and 1 oligodendroglioma); 3 had no evidence of active central nervous system tumor. One patient had a brain metastasis, and 1 had leptomeningeal metastases. Four patients were comatose and 4 were confused.

The MR images showed cortical changes in 4 patients, consisting of hyperintensity on FLAIR images, T2-weighted images, or DWI, with or without leptomeningeal enhancement on gadolinium T1-weighted images (Table) (Figure 1 and Figure 2). In 2 of these patients (patients 2 and 3), fludeoxyglucose F 18 (18F) positron emission tomography showed hypermetabolic activity in the new cortical abnormalities on MR imaging (Figure 1). Of the other 4 patients, 2 had normal MR images and 2 had mass lesions consistent with their known glioblastoma multiforme. A lumbar puncture showed normal cerebrospinal fluid.

All 8 patients had EEGs that demonstrated epileptiform discharges consisting of runs or continuous spikes, periodic lateralizing epileptiform discharges, or sharp and slow waves; these abnormalities were localized to the area of cortical hyperintensity or enhancement on the MR images of the 4 patients whose images were abnormal. Patients had been intermittently confused or unresponsive for 1 to 7 days before MR imaging was performed. The NCSE was attributed to new leptomeningeal metastasis in 1 patient, increasing brain tumor in 3, intracranial hemorrhage in 1 (patient 4), and fever in 1 with a seizure history (patient 3). In the remaining 2 patients (patients 1 and 2), no cause of the seizures was identified. All patients with cortical abnormalities had no evidence of tumor at the site of abnormality. All 8 patients received anticonvulsants and their mental status returned to baseline, except patient 2, who remained in a stupor and died 4 weeks later.

Follow-up cranial MR images were obtained 1 to 5 weeks later in the 4 patients with cortical changes; 3 had complete resolution of the abnormalities (patients 1, 3,
The presence of NCSE was identified in 8% of 236 comatose patients admitted to an intensive care unit and was found in 6% of patients with cancer who had altered mental status. In another study, it was estimated that the incidence of seizures in encephalopathic patients with cancer was 9%, but EEG was not routinely performed. However, none of these studies included patients with brain tumors.

Repeat positron emission tomography was not performed in patients 2 and 3. Patients 3 and 4 were alive at 2-year follow-up without evidence of recurrent brain tumor; patient 1 died 3 months later of recurrent posterior fossa ependymoma. Two of the other 4 patients died of progression of glioblastoma multiforme.

Abnormalities on DWI have been reported in NCSE and after 1 or several seizures. During a 3-year period, 50% of patients with NCSE had reversible abnormalities on MR images, 3 of whom had prior structural disease of the brain. Transient focal abnormalities appearing on cranial CT scans of patients in partial status epilepticus were recognized 19 years ago. Increased signal intensity on T2-weighted MR images during focal status epilepticus that resolved with seizure control was reported in one patient. Subsequently, investigators have shown focal cortical hyperintensity on T2-weighted images, FLAIR images, and DWI and leptomeningeal enhancement in patients with partial status epilepticus. Similar MR imaging abnormalities localized to the region of a previously resected glioblastoma, in the absence of recurrent tumor, were reported in a patient with persistent seizures. Localized breakdown of the blood-brain barrier with increased permeability due to prolonged seizure discharge, development of vasogenic or cytotoxic edema, and hyperperfusion of the epileptic region may contribute to these radiographic changes. Given the transient nature of these abnormalities, neuronal cell death is an unlikely explanation. These changes can be differentiated from other processes on MR images because they are reversible, do not respect vascular territories, and lack mass effect.

We described 8 patients with cancer who presented with stupor or confusion secondary to prolonged seizures. None had evidence of metabolic abnormality or drug toxicity. Neuroimaging was the first test performed to exclude structural brain disease that explained their mental status.

On the MR images of 4 patients, cortical hyperintensity was seen in a gyriform pattern not restricted to a vascular distribution, without edema or mass effect. These features made a stroke or recurrent tumor unlikely. In 3 patients, leptomeningeal enhancement was present but metastatic tumor does not resolve in several weeks; the results of cerebrospinal fluid studies were negative in all patients. In 2 patients with primary brain tumors, MR imaging abnormalities were in a different location from the original tumor, but they correlated with the focal EEG findings. None of our patients was receiving active cancer therapy, which makes treatment-related toxicity an unlikely cause of the seizures or imaging abnormalities, although acute chemotherapy toxicity may contribute to NCSE in patients with cancer.

In 2 patients, [18F] positron emission tomography showed hypermetabolic activity corresponding to the seizure focus. Increased metabolism is seen in high-grade brain tumors, but the resolution of cortical changes and the patients’ full clinical recovery indicate a functional process such as seizures as the cause of imaging abnormalities. The hypermetabolism likely represents active seizures during the positron emission tomography. Glucose metabolism is complex in seizures, and both ictal increase and decrease in cerebral metabolism have been documented; this may represent either enhanced excitatory or inhibitory neuronal activity or both.

In unresponsive patients with cancer, the finding of cortical ribbon hyperintensity on DWI, T2-weighted images, and FLAIR images may be a consequence of NCSE.
An EEG should be obtained immediately, and if confirmatory EEG is not promptly available, intravenous lorazepam may be tried to reverse possible NCSE. Lorazepam is unlikely to seriously worsen the patient’s condition and may prevent secondary central nervous system damage. Subsequent EEG can be performed to confirm the initial diagnostic impression, and follow-up MR imaging is warranted to confirm reversibility of the lesions.

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REFERENCES