Clinical/Scientific Notes

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ASYMPTOMATIC SPINAL CORD INVOLVEMENT IN POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES) is a reversible syndrome that presents with nausea and headache; altered consciousness; weakness; visual changes, including blurred vision or hemianopsia; seizures; and rarely coma.[1] MRI demonstrates vasogenic edema, generally bilateral, predominant in the posterior parietal, temporal, and occipital regions of the brain. Commonly associated with severe acute hypertension, PRES is associated with eclampsia, renal failure, electrolyte disorders, hypocholesterolemia, drug abuse, infections, autoimmune diseases, and immunosuppressive and chemotherapy.[1,2]

Case report. A 39-year-old woman with untreated hypertension was admitted with headache, nausea, and vomiting. Three months before admission she had received radiation therapy for a single metastatic lesion in the odontoid process of a peritoneal leiomyosarcoma; 20 days before, she had completed a chemotherapy cycle with gemcitabine. She was drowsy with blurred vision. Blood pressure was 220/120 mm Hg and examination of optic fundus disclosed signs of hypertensive retinopathy. The examination was otherwise unremarkable, with flexor plantar responses. Blood tests were normal. Spectral attenuated inversion recovery MRI sequences showed large, confluent, bilateral, mostly symmetric hyperintense regions in the white matter of parietal and occipital lobes, cerebellar hemispheres, and right frontal lobe (figure, A). Diffusion-weighted images demonstrated corresponding regions of increased water diffusivity; mild contrast enhancement was observed. MRI of the cervical spinal cord revealed a diffuse, central hyperintense signal on TSE T2-weighted sequences and mild swelling of the spinal cord; contrast enhancement was absent (figure, A). A diagnosis of PRES with spinal cord involvement was made.

Treatment with spironolactone 100 mg/day and lisinopril 10 mg/day was started, blood pressure was normalized, and the patient became asymptomatic within 2 days. An MRI at 2 weeks revealed that the spinal cord changes were completely reversed and the brain abnormalities reduced (figure, B). Neurologic examination was normal. At 4 weeks, there was an almost complete normalization of brain changes (figure, C).

Discussion. This case illustrates asymptomatic cervical spinal cord involvement in PRES, probably secondary to an acute hypertensive episode, an unusual finding.[3,4] Gemcitabine treatment may have been an etiologic factor, but we consider this less likely because of the prompt response to blood pressure normalization. Alternative etiologies accounting for the imaged abnormalities of the cervical cord include a compressive myelopathy secondary to the metastasis of the odontoid process or a radiation-induced myelopathy. That the patient did not show signs of spinal involvement and MRI abnormalities completely reversed after blood pressure normalization weigh against these hypotheses.

PRES is a disorder of cerebral blood autoregulation and endothelial function causing vasogenic edema, occurring by an uncertain mechanism.[2,5] Similar arterial regulatory mechanisms appear to occur in the spinal cord.[6] Due to the fact that the posterior regions of the brain and the cervical spinal cord have the same vertebrobasilar arterial supply, autoregulatory dysregulation could affect both vascular territories. Spinal cord blood vessels, unlike the rest of the vertebrobasilar vascular system, have dense sympathetic innervation, which may protect the cord if blood pressure exceeds the limits of autoregulation.[7] This could account for the lesser frequency of cervical cord involvement in PRES. Although in this instance symptoms and signs of spinal cord involvement were absent, despite evidence of extensive involvement by MRI, symptoms and signs can occur, such as paraparesis or Babinski signs.[3,4]

We suggest that imaging of the cord be considered in PRES if symptoms or signs are suggestive of a myelopathy.

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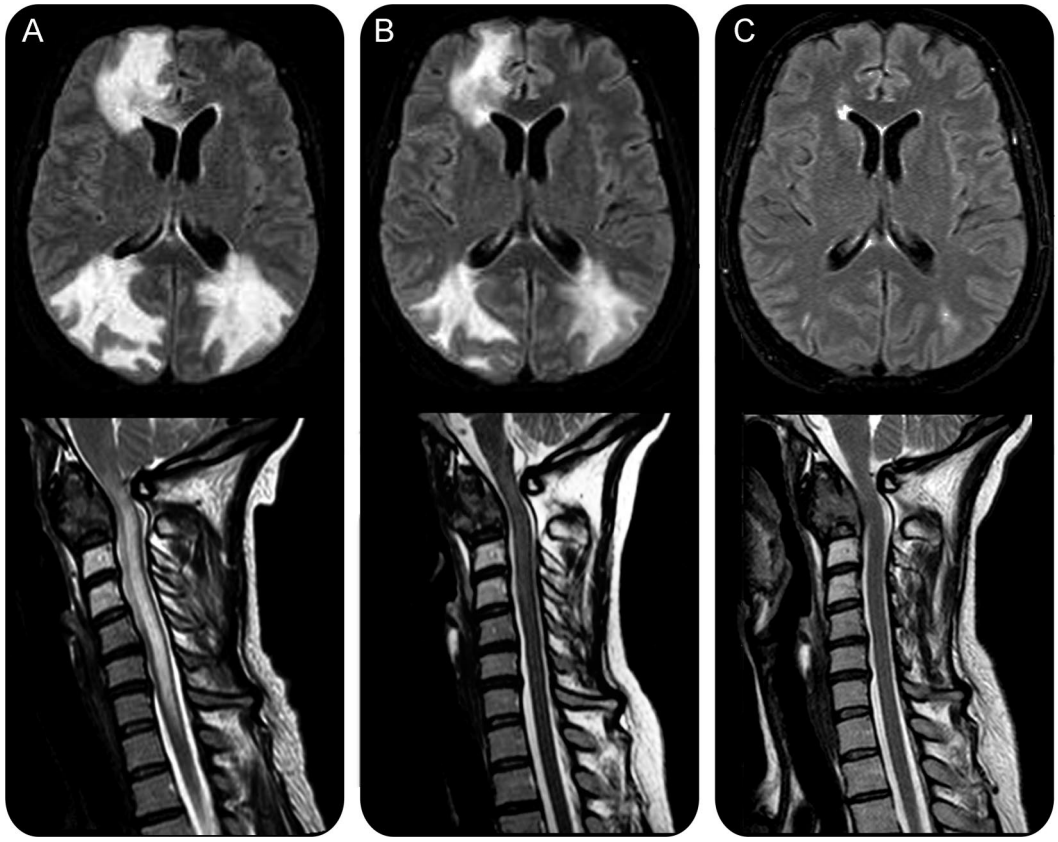
Figure Serial brain and spinal cord MRI studies



MRI studies at onset (A), 2-week (B), and 4-week (C) follow-up assessments. Axial spectral attenuated inversion recovery images (upper row) showed regions of hyperintense signal in the white matter of parietal and right frontal lobes (A). Signal changes were mildly decreased at the 2-week follow-up (B) and almost completely disappeared after 4 weeks (C). Sagittal TSE T2-weighted images (lower row) showed hyperintense signal and swelling of the cervical spinal cord (A), which completely reversed at the 2-week (B) and 4-week (C) follow-up assessments. The odontoid process was swollen and hypointense because of a metastatic lesion.

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MGMT METHYLATION IS A PROGNOSTIC BIOMARKER IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

In young patients with newly diagnosed glioblastoma (GBM), methylation of the *MGMT* (O-6-methylguanine-DNA methyltransferase) gene promoter has been associated with improved prognosis.[1] It is less clear if *MGMT* methylation is a prognostic biomarker in the elderly GBM patient population since patients >70 were excluded from the largest study documenting the association between methylation of *MGMT* and improved survival. Considering that the median age at diagnosis of GBM is 64, it is important to clarify the significance of *MGMT* methylation in elderly patients and determine whether it should influence treatment decisions in this large subset of patients.

Methylation of *MGMT* silences transcription of the enzyme MGMT which repairs DNA damage that would otherwise lead to cell death. MGMT is an important mediator of resistance to alkylating agents including temozolomide, a standard agent administered to newly diagnosed patients with GBM.[3-5] Consequently, this tissue biomarker is increasingly being incorporated into clinical trials and clinical practice. In order to assess the importance of *MGMT* methylation in elderly patients, we determined the association of *MGMT* methylation and survival in patients with GBM ≥70.

Methods. After receiving approval from our institutional review board, we reviewed *MGMT* methylation status and clinical characteristics of 64 patients ≥70 with newly diagnosed GBM who underwent resection at our institution from 1998 to 2009. Patients were included if they had enough tissue for MGMT analysis, so this excluded patients who only had a biopsy (consistent with the prior study in younger patients). MGMT analysis was performed by extracting tumor genomic DNA from fixed, paraffin-embedded sections for bisulfite conversion (EZ DNA Methylation-Gold Kit, Zymo Research, Orange, CA). *MGMT* methylation-specific PCR was performed using PCR primer sets specific for methylated and unmethylated *MGMT* promoter sequences.[6] Kaplan Meier curves and the log-rank test were used to compare median progression free (mPFS) and median overall survival (mOS) in patients who had methylated (ME) *MGMT* vs unmethylated (UN) *MGMT*.

Results. Of the 64 patients identified, 37 (57.8%) had ME *MGMT* and 27 (42.2%) did not (table). These results were slightly higher than the 44.7% of patients who had ME *MGMT* and the 55.3% who had UN *MGMT* in the Hegi et al.[1] study but similar to a small study in very elderly patients (≥80) where 13/22 patients (59%) had ME *MGMT*.[2] Potential explanations for this small discrepancy include age-related increase in genomic methylation that includes the MGMT promoter or the reduced ability to retrieve usable DNA from archived paraffin-embedded blocks.

Initial treatments for patients in our cohort included chemoradiation (35), radiation alone (16), or chemotherapy alone (3). In ME patients, 24/37 patients received an alkylating agent (temozolomide in 23, BCNU in 1) either as first-line therapy (21) or at recurrence (3). Sixteen of the 27 UN patients received an alkylating agent (all temozolomide): 15 as first-line therapy and 1 at recurrence. A total of 10 patients had no or unknown therapy (6 ME, 4 UN). In patients who received an alkylating agent, mOS in ME patients was 489 days vs 263 days in UN patients ($p = 0.0021$) and mPFS was 405 days vs 246 days ($p = 0.2742$) (figure e-1 on the *Neurology*® Web site at www.neurology.org). In an analysis including all 64 patients, mPFS in ME patients was 328 days vs 173 days in UN patients ($p = 0.0241$) and mOS was 345 days in ME patients and 223 days in UN patients ($p = 0.0178$). A univariate Cox proportional hazards model including all 64 patients showed that MGMT methylation was associated with reduced hazard for progression (hazard ratio [HR] 0.427, 95% confidence interval [CI] 0.199, 0.914, $p = 0.0283$) and death (HR 0.475, 95% CI 0.254, 0.890, $p = 0.0283$). In a multivariate Cox model including age, extent of resection, Karnofsky performance score, and alkylator use, *MGMT* methylation was significantly associated with a reduced hazard for progression (HR 0.374, 95% CI 0.138, 1.0, $p = 0.0521$) and death (HR 0.243, 95% CI 0.097, 0.608, $p = 0.0025$). These results suggest that MGMT methylation is a positive prognostic biomarker in the elderly GBM patient population independent of treatment received.

Discussion. Since *MGMT* methylation was previously thought to be a predictive marker associated with improved response to temozolomide, further work will need to be done to clarify if *MGMT* methylation is also a predictive marker in elderly patients. We were unable to address this question specifically in our study because of the small number of patients not treated with an alkylating agent.

Tumor tissue markers such as MGMT that may influence prognosis or clinical trial design are just as valid in the elderly population as in younger patients. Although our study was retrospective, it is the largest study of *MGMT* methylation status in this population. MGMT appears to be a useful prognostic marker in elderly GBM patients and its role in guid-

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Table Patient characteristics

	All	Methylated *MGMT* status	Unmethylated *MGMT* status
All patients	64	37	27
Extent of surgery	STR 40; GTR 24	STR 23; GTR 14	STR 17; GTR 10
Median KPS (range)	80 (50–100)	90 (60–100)	80 (50–80)
Median age, y (range)	74 (70–92)	74 (70–83)	74 (70–92)
Median MMSE (range)	28 (19–30)	28 (22–30)	28 (19–30)
mOS, d	319	345	223 ($p = 0.0178$)
mPFS, d	231	328	173 ($p = 0.0241$)
Treated with alkylating agent	40	24	16
Not treated with alkylating agent	14	7	7
Unknown/no treatment	10	6	4

STR = subtotal resection; GTR = gross total resection; KPS = Karnofsky performance score; MMSE = Mini-Mental Status Examination; mOS = median overall survival; mPFS = median progression-free survival.

ing treatment choices as a potential predictive biomarker should be explored in prospective studies.

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AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Elizabeth Gerstner.

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