CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Stream of Consciousness

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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A 65-year-old man presented to an emergency room in New England in early summer with a 3-week history of progressive fatigue. He initially noted moderate fatigue and a mild headache that did not change with position, was worse in the morning and decreased in severity with the use of nonsteroidal antiinflammatory agents. He began to sleep most of the day. A few days before presentation, he had become forgetful and confused. He was unable to complete his usual tasks and had difficulty finding words. He reported no focal weakness or sensory deficits, fevers, chills, weight changes, blurry vision, neck stiffness, nausea, vomiting, back pain, change in bowel or bladder function, chest pain, or shortness of breath. He had felt completely well before the onset of symptoms, although he noted that he had recently received a diagnosis of hypertension from his primary care physician.

The described course of worsening fatigue and headache progressing to impaired cognition over a period of weeks is consistent with subacute encephalopathy, which can result from a broad range of intracranial or systemic processes. The time course of the patient's illness is less consistent with ischemic stroke or subarachnoid hemorrhage, but venous sinus thrombosis, chronic subdural hematoma, or hypertensive emergency could manifest in this manner. Hydrocephalus or an intracranial neoplasm should be considered. Metabolic causes, such as hepatic dysfunction, uremia, electrolyte abnormalities, thiamine deficiency, substance abuse, or a side effect of medication, should be ruled out. Intracranial abscess, syphilis, or mycobacterial disease are considerations in patients with relevant risk factors such as travel to regions in which infectious disease is endemic, impaired host response due to inherited or acquired conditions, or injection drug use. The time course, absence of fever, and absence of neck stiffness make bacterial or viral meningitis or encephalitis an unlikely diagnosis.

The patient's medical history was notable for paroxysmal supraventricular tachycardia, seasonal allergies, and hypertension. His prescribed medications were loratadine–pseudoephedrine and aspirin; both were long-standing prescriptions. He had no known drug allergies. He lived with his wife in a Boston suburb and worked as a school principal. He did not smoke and reported no illicit substance use. He consumed up to three glasses of wine each evening. His family history was notable for heavy tobacco use and lung cancer in his father and melanoma in his brother; both cancers were diagnosed in early adulthood. There was no family history of hypertension.

He has no clear risk factors for an immunocompromised state. Although pseudoephedrine can increase blood pressure, this seems unlikely to explain his presentation, given the history of long-term use. The family history of cancer warrants consideration. Primary cancer of the central nervous system or metastatic disease from primary lung cancer, melanoma, renal-cell carcinoma, or other less common cancers is possible. Long-term moderate alcohol use may contribute to cognitive decline, particularly if use is underreported. He is not receiving antihypertensive medications despite a recent diagnosis of hypertension. Lifestyle modification without initiation of pharmacologic therapy would be a reasonable initial management strategy for early-stage hypertension; it would be valuable to know his previous blood-pressure readings.

On physical examination, the patient was afebrile, alert, and oriented; his heart rate was 101 beats per minute, and his blood pressure 197/100 mm Hg. He had no abnormalities on cardiac, pulmonary, or abdominal examination. The results of cranial nerve, motor, and sensory examinations were reported to be normal. Gait evaluation and funduscopic examination were not documented. Laboratory studies revealed a serum sodium level of 140 mmol per liter, potassium level of 5.2 mmol per liter, chloride level of 105 mmol per liter, bicarbonate level of 22 mmol per liter, blood urea nitrogen level of 57 mg per deciliter (20 mmol per liter), serum creatinine level of 3.92 mg per deciliter (347 μmol per liter; level 1 year earlier: 1.12 mg per deciliter [99 μmol per liter]), and glucose level of 186 mg per deciliter (10 mmol per liter). The results of calcium, albumin, and liver function tests were within the normal ranges. Complete blood counts were unremarkable. An initial screening test for borrelia IgG and IgM was negative.

This degree of blood-pressure elevation arouses concern for hypertensive encephalopathy. Antihypertensive medications should be used to lower the mean arterial pressure by 20 to 25% in the first 2 to 3 hours; a more aggressive initial reduction could lead to secondary ischemic events. Thereafter, the blood pressure is typically lowered to the normal range over a period of 24 to 48 hours to avoid ongoing vasogenic edema, which could lead to mass effect, cerebral ischemia, and intracranial hemorrhage. For hypertensive encephalopathy, many experts recommend using intravenous dihydropyridine calcium-channel blockers (e.g., clevidipine or nicardipine) or a dopamine agonist (e.g., fenoldopam). Nitroprusside should be avoided because of its potential to increase intracranial pressure.

The elevation in creatinine level could be chronic or recent, and renal disease may be contributing to the encephalopathy through the effects of uremia or renally mediated hypertension. Acute renal dysfunction could be caused by a hypertensive emergency, glomerular disease, obstructive nephropathy, or use of nonsteroidal antiinflammatory drugs. Renal imaging, urinalysis, and urine sediment examination should be performed. Given the patient's symptoms on presentation, cerebrospinal fluid should be sampled after neuroimaging to rule out a space-occupying lesion.

Computed tomography (CT) of the head without contrast revealed extensive hypodensities in the right temporal lobe and in the left frontal lobe, the latter of which exerted a slight mass effect on the anterior falx. Additional hypodensities were found in the right frontal lobe and in the right and left parietal lobes (Fig. 1). The patient was transferred to our hospital for further evaluation.

The CT findings are suggestive of the posterior reversible encephalopathy syndrome (PRES) but do not exclude the possibility of malignant, infectious, or inflammatory processes. PRES is seen in patients with a hypertensive emergency but can also be seen with other conditions, such as sepsis and eclampsia. PRES derives its name from the altered mental status and reversible white-matter signal changes in posterior brain regions that characterize the syndrome, but other clinical manifestations and radiographic abnormalities are common.

On arrival at the emergency department, the patient was afebrile and had a heart rate of 92 beats per minute, blood pressure of 203/102 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 99% while he was breathing ambient air. On physical examination, he appeared well and was in no distress. He had no nuchal rigidity. The lungs were clear to auscultation and percussion. No rubs or gallops were heard. The findings from abdominal examina-

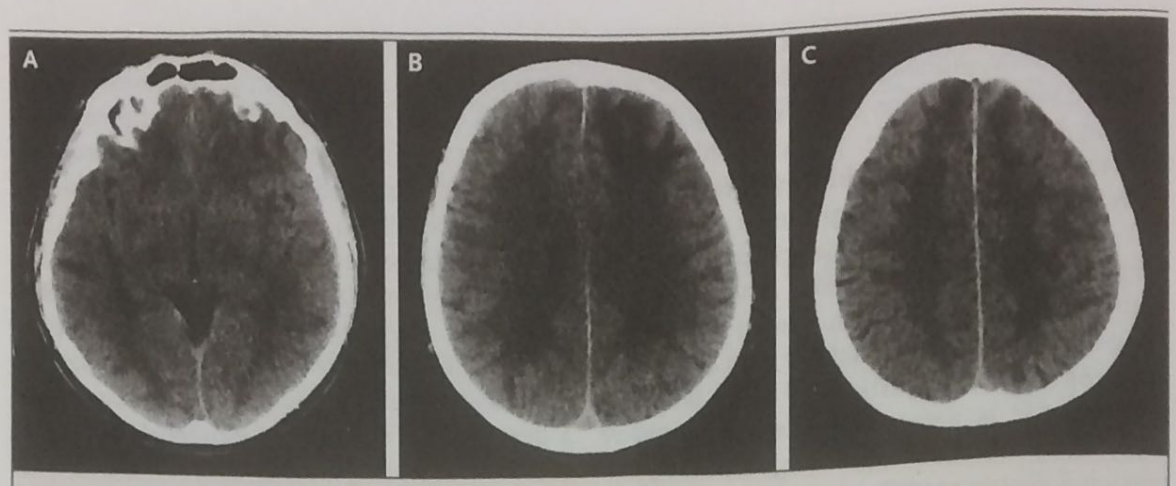

Figure 1. CT Scans of the Head at Presentation.
CT scans of the head obtained on the day of presentation show diffuse white-matter hypodensities that are most extensive in the right temporal lobe (Panel A), in the left frontal lobe (Panel B), and at the vertex (Panel C).

tion were unremarkable, and there was no evidence of ascites. Rectal examination revealed normal tone and a smooth, symmetric, mildly enlarged prostate. There were no suspicious skin lesions. There was no peripheral edema. He was alert and oriented to person, place, and time; he had a mildly blunted affect and impaired ability to name uncommon objects. His optic disks appeared normal on funduscopic examination. There were no strength or sensory deficits. Deep-tendon reflexes were brisk at the biceps and brachioradialis in both arms and at both knees with contraction of neighboring muscle groups. There was a positive plantar reflex in the left foot. Coordination was intact, and the gait was narrow-based, although he was unable to perform a tandem walk.

Flame hemorrhages and papilledema can be seen on funduscopic examination in some patients with a hypertensive emergency, but their absence should not be considered reassuring. There is no evidence of melanoma. Mild enlargement of the prostate in a patient of this age is not an unexpected finding. However, because the assessment of prostate size by rectal examination is relatively inaccurate, the perceived "mild" enlargement may be an underestimate; in addition, the patient is receiving medications (loratadine and pseudoephedrine) that could exacerbate urinary retention. Urinary obstruction remains a possibility and could lead to secondary hypertension and subsequent PRES.

During an 8-hour period, 100 mg of intravenous labetalol and 300 mg of oral labetalol were administered, and the blood pressure declined to 180/100 mm Hg. The results of repeat laboratory tests were largely unchanged from the time of presentation. Troponin T was undetectable. A urinalysis showed no proteinuria, and an examination of urine sediment revealed no casts or dysmorphic red cells. An electrocardiogram was normal. Lumbar puncture revealed clear cerebrospinal fluid and an opening pressure of 29 cm of water. The cerebrospinal fluid glucose level was 87 mg per deciliter (5 mmol per liter), and the protein level was 210.8 mg per deciliter. The corresponding serum glucose level was 121 mg per deciliter (7 mmol per liter), and the albumin level was 3.4 g per deciliter. There were 70 red cells and 1 white cell per milliliter in the first tube of collected cerebrospinal fluid, and 32 red cells and 1 white cell per milliliter in the fourth tube. Specimens were sent to the laboratory for Gram's staining, culturing, and cytologic evaluation. Serum electrophoresis and cerebrospinal fluid did not show a monoclonal spike (M spike) or oligoclonal bands.

An elevated cerebrospinal fluid protein level with a low leukocyte count suggests a noninfectious cause but is otherwise nonspecific. An elevated protein level in cerebrospinal fluid is common in PRES, possibly because of the breakdown of the blood–brain barrier. Inflammatory causes, such as autoimmune encephalopathy, vasculitis, or inflammatory cerebral amyloid angiopathy, or paraneoplastic causes still cannot be ruled out. Demyelinating disease would be unlikely in a person in this age group, particularly in the absence of

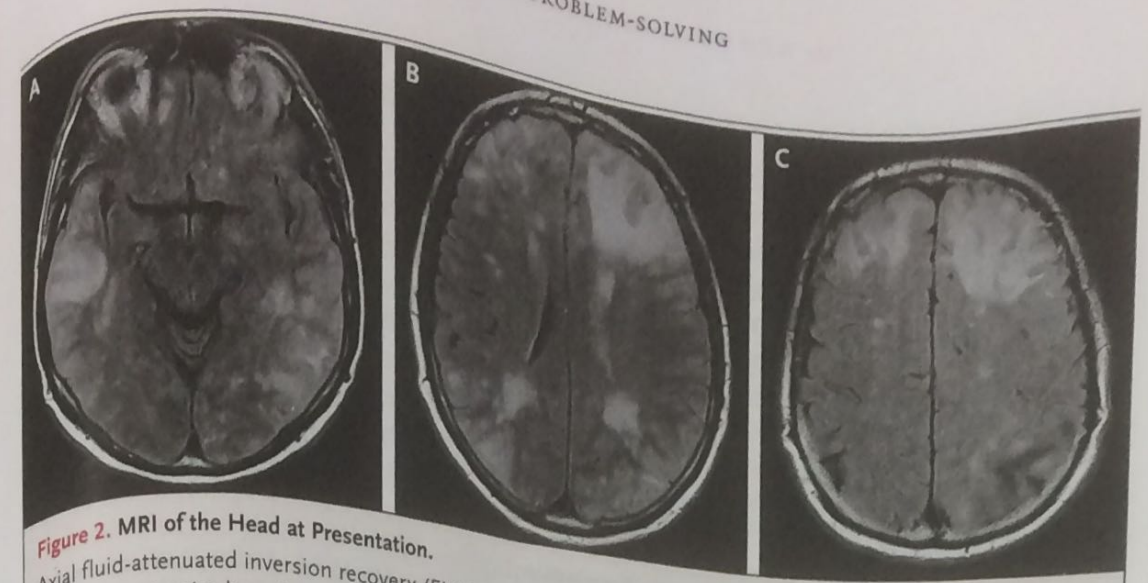

Figure 2. MRI of the Head at Presentation.

Axial fluid-attenuated inversion recovery (FLAIR) T_2-weighted sequences on MRI performed on the day of presentation show extensive hyperintensity consistent with cerebral edema affecting the subcortical white matter and, to a lesser degree, extending into the cortical gray matter at the levels of the midbrain (Panel A), the lateral ventricles (Panel B), and the vertex (Panel C).

oligoclonal bands. The findings from urinalysis and urine sediment examination are inconsistent with nephritis.

Magnetic resonance imaging (MRI) of the head without contrast showed patchy and confluent areas of edema involving the supratentorial subcortical white matter in the bifrontal lobes and in the right and left temporal lobes, as well as a suggestion of edema involving areas of the cortex (Fig. 2). Microhemorrhages in the edematous areas, innumerable punctate lesions elsewhere in the brain, and superficial siderosis overlying the left parietal cortex were observed. There was no evidence of infarction (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The patient's blood pressure was 198/80 mm Hg on the second hospital day; treatment included additional intravenous administration of 40 mg of labetalol, an increase in the oral dose of labetalol to 400 mg three times daily, and initiation of a nitroglycerin infusion at 25 μg per minute. Abdominal ultrasonography revealed hydroureteronephrosis in both kidneys, elevated resistive indexes of the intrarenal arteries with patent renal arteries and veins, and a markedly distended bladder with an estimated residual urine volume of 1785 ml after voiding. A urinary catheter was placed, and 2900 ml of clear urine was drained immediately.

The MRI findings are consistent with PRES and show changes extending beyond the characteristic posterior regions of the brain. Microhemorrhages, superficial siderosis, and vasogenic edema could also be seen in inflammatory cerebral amyloid angiopathy or a hemorrhagic neoplastic process. The bladder obstruction and obstructive uropathy provide a potential mechanism for the patient's renal failure and hypertension. Marked bladder enlargement without symptoms suggests chronic mechanical obstruction or neurologic dysfunction.

One hour after the urinary catheter was placed, the patient's blood pressure was 158/90 mm Hg. Nitroglycerin was gradually tapered off as his blood pressure normalized and his urine output exceeded 250 ml per hour. Amlodipine at a dose of 5 mg daily was initiated on the third hospital day, and the oral dose of labetalol was increased to 600 mg three times daily on the fourth hospital day. While the patient was receiving this regimen, his blood-pressure readings were consistently below 140/80 mm Hg. His creatinine level decreased to 1.77 mg per deciliter (156 μmol per liter), and his mental status returned to the baseline level (according to subjective assessment by the patient and his family). The prostate serum antigen level was 4.28 ng per milliliter (normal range, 0.00 to 4.00 ng per milliliter). Contrast-enhanced MRI of the head and cervical, thoracic, and lumbar spine revealed no clinically significant stenosis or cord abnormality. Labetalol was gradually tapered off. The patient was discharged home with a prescription for 10 mg of amlodipine and an indwelling Foley catheter.

The patient received a diagnosis of obstructive

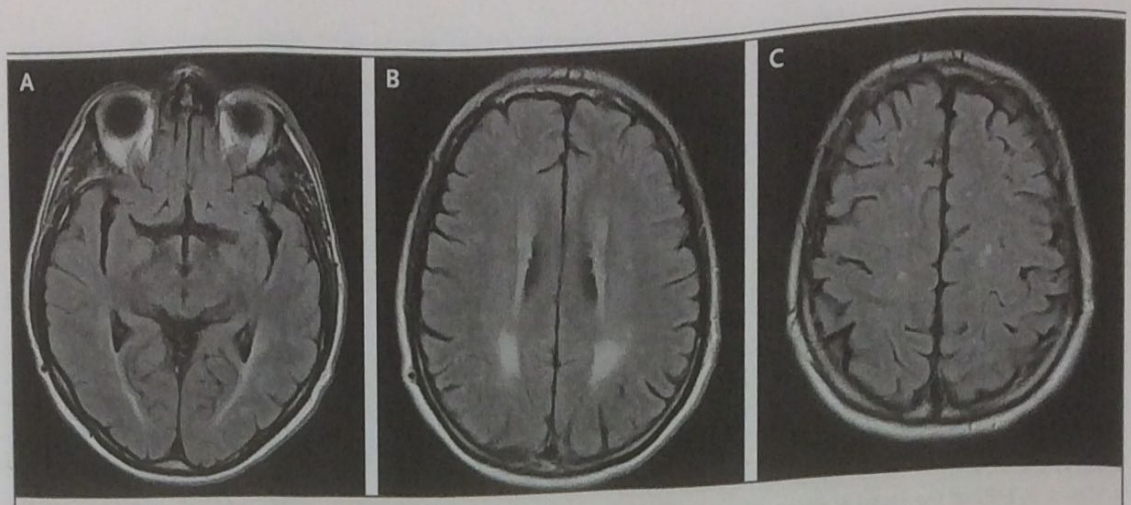

Figure 3. MRI of the Head at the 7-Week Follow-up Examination.

Axial FLAIR T_2-weighted MRI sequences show that near-complete resolution of the cerebral edema had occurred in the interval between the MRI performed at presentation and the current MRI, with persistence of mild-to-moderate white-matter disease (probably attributable to chronic underlying microvascular disease caused by untreated hypertension) at the levels of the midbrain (Panel A), the lateral ventricles (Panel B), and the vertex (Panel C).

nephropathy leading to a hypertensive emergency and PRES. At the 7-week follow-up examination, his systolic blood-pressure readings were in the range of 120 to 130 mm Hg. A repeat MRI showed near-complete resolution of the extensive white-matter changes (Fig. 3) and microhemorrhages (Fig. S2 in the Supplementary Appendix). Eight weeks after the initial presentation, the creatinine level had returned to the baseline value. The findings from urodynamic studies were suggestive of obstruction, and he required intermittent urinary catheterization despite tamsulosin therapy. Transurethral resection of the prostate confirmed a pathological diagnosis of benign prostatic hyperplasia and relieved the obstruction.

COMMENTARY

The most parsimonious explanation for this patient's presentation is obstructive nephropathy resulting in PRES. His blood pressure improved after the obstruction was relieved and was accompanied by a corresponding normalization of imaging abnormalities and neurologic symptoms. This pattern is consistent with the typically reversible nature of PRES.

PRES is characterized by alterations of mental status, posterior predominant radiographic white-matter changes, and, in most cases, reversibility of symptoms and imaging abnormalities with appropriate treatment.[1] The pathophysiological mechanism of PRES remains poorly understood but is thought to relate to cerebral autoregulatory and endothelial dysfunction leading to a breakdown of the blood–brain barrier, transudation of fluid and proteinaceous material, and petechial hemorrhages. In the clinical context of rapidly progressive hypertension, blood pressure exceeds the autoregulatory capacities of cerebral vasculature.[2-4] The preferential involvement of the posterior cerebrum has been attributed to a relative paucity of sympathetic innervation to the vasculature in this region, which renders posterior vessels less adaptable to hemodynamic stress.[5,6] The relative rise in blood pressure from a patient's baseline measurement appears to be a critical pathogenic factor; in cases of rapidly evolving hypertension, symptoms may be seen at blood pressures considered to be close to the normal range.

In contrast to the autoregulatory failure associated with hypertension, sepsis and eclampsia are thought to induce PRES through endothelial dysfunction driven by systemic inflammatory factors (in the case of sepsis) and placental factors (in the case of eclampsia).[7-9] Cytotoxic and immunosuppressive medications, such as tacrolimus, cyclosporine, and bevacizumab, are known risk factors for PRES, but the mechanism of this relationship remains poorly understood. Tacrolimus and cyclosporine need not be at suprathrapeutic levels or recently introduced to cause

symptoms.[10,11] Autoimmunity has also been associated with PRES, although the mechanism is likewise poorly understood.

The neurologic symptoms of PRES vary across case series.[5] Encephalopathy occurs in 50 to 80% of patients; hypoactive symptoms may alternate with periods of agitation, and coma may occur in advanced cases.[5] Visual disturbances ranging from blurred vision to hemianopia and cortical blindness occur in roughly a third of cases.[5] A total of 60 to 75% of patients present with seizures, which may be preceded by vision loss[5]; in 5 to 15% of these patients, the seizures become generalized or progress to status epilepticus.[5] Constant holocephalic headache is reported in 50% of cases.[5] Deep-tendon reflexes are often diffusely brisk, and the Babinski sign may be positive.[5] Other than these findings, the neurologic examination is typically unrevealing, unless ischemia or hemorrhage gives rise to focal deficits, which occur in 10 to 15% of cases.[5]

The principal imaging methods used to identify PRES are CT and MRI. The parietal and occipital lobes are the most commonly affected regions of the brain, although edema can extend into the cerebellum and brainstem. As seen in the current case, interior white-matter, cortical, and deep gray-matter structures are sometimes involved in addition to the posterior brain structures. T_2-weighted fluid-attenuated inversion recovery sequences on MRI are the most sensitive method for detecting PRES and can help to differentiate this syndrome from other pathologic processes. Diffusion-weighted imaging is useful in distinguishing vasogenic edema from tissue infarction. Extensive vasogenic edema, tissue infarction, or hemorrhage (either intraparenchymal or subarachnoid) may occur in PRES and predicts poorer outcomes.[12]

Because data from randomized trials are lacking, management of PRES is guided by findings from case series and by clinical experience. Treatment is directed at the underlying process, but blood-pressure control is also key, particularly when the underlying cause cannot be determined or cannot be quickly treated. With appropriate treatment, patients often make rapid and complete recoveries.[1,5] In patients who present with seizures, anticonvulsant agents are indicated; these agents can generally be tapered off after durable clinical improvement is attained. In cases that are attributed to cytotoxic therapies, dose reduction is indicated in patients with supratherapeutic serum drug levels, and transition to alternative medications is indicated in patients with normal serum drug levels. Although most patients recover within 1 week after the initiation of treatment, a small number of cases require several weeks of treatment for a full recovery. A total of 3 to 6% of PRES cases are fatal, and 10 to 20% of patients have persistent neurologic sequelae.[5] In addition to poorer outcomes associated with the advanced radiographic features described here, a retrospective study showed that poorer outcomes were significantly more likely to occur among patients who were older, had undergone previous intracranial radiation, had sepsis, or had a history of autoimmune disease, diabetes, or smoking.[12] Hyperglycemia at presentation and longer time to treatment of the underlying cause may also be associated with a worse prognosis.[5]

In the current case, PRES resulted from renal dysfunction that was caused by obstructive uropathy attributable to benign prostatic hyperplasia, the effects of which may have been exacerbated by the patient's use of loratadine–pseudoephedrine. Benign prostatic hyperplasia is characterized by prostatic tissue enlargement and increased adrenergic tone in the stromal portion of the gland.[13] This common condition reaches a prevalence of 90% among men 80 to 90 years of age and can lead to bladder outlet obstruction.[14] Lower urinary tract symptoms are neither sensitive nor specific for diagnosing bladder outlet obstruction.[14] Decreased urinary flow in this clinical context can produce hypertension by up-regulation of the renin–angiotensin–aldosterone system and fluid retention.[15]

The presenting symptom complex of subacute encephalopathy has a broad differential diagnosis that can be challenging to navigate. In the present case, nothing in the patient's history suggested urinary obstruction; however, a careful diagnostic pursuit enabled expeditious diagnosis and treatment.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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