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RadioGraphics

Best Cases from the AFIP

Osmotic Demyelination Syndrome[1]

Editor's Note.—Everyone who has taken the course in radiologic pathology at the Armed Forces Institute of Pathology (AFIP) remembers bringing beautifully illustrated cases for accession to the Institute. In recent years, the staff of the Department of Radiologic Pathology has judged the "best cases" by organ system, and recognition is given to the winners on the last day of the class. With each issue of *RadioGraphics*, one or more of these cases are published, written by the winning resident. Radiologic-pathologic correlation is emphasized, and the causes of the imaging signs of various diseases are illustrated.

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History

A 22-year-old woman with a history of drug abuse was found, by her mother, unconscious and unresponsive at a friend's house. It was reported that she had a 2-week history of unresponsiveness and vomiting. She was taken to a local hospital by emergency medical services.

Upon admission, the patient experienced a generalized tonic-clonic seizure and was intubated for airway protection. She was markedly hyponatremic, her urine toxicology results were negative, and computed tomographic (CT) images of the head were reportedly normal (images unavailable). Her sodium level was rapidly corrected over the course of 11 hours. The initial sodium level was 113 mmol/L. Five hours later it was 124 mmol/L, and 6 hours after that it was 136 mmol/L. For the first few days of hospitalization, the patient remained completely unresponsive. On the 5th day of hospitalization, she began to spontaneously open and close her eyes, but she did not follow commands or track movements. Serial electroencephalograms showed a polymorphic delta rhythm, a finding consistent with severe hypoxic encephalopathy. Magnetic resonance (MR) imaging performed 2 weeks later reportedly showed extensive restricted diffusion throughout the cerebral cortex, thalami, and pons (images unavailable). Her mental status remained unchanged for approximately 2 months, at which time she was transferred to a tertiary care center.

Upon admission to the tertiary care center, she was again noted to spontaneously open and close her eyes. Significant findings of neurologic examination were decerebrate posture, bilateral hypertonia in the upper limbs, Babinski reflex on the right side, and normal (downward) plantar reflex on the left.

Abbreviations: ADC = apparent diffusion coefficient, FLAIR = fluid-attenuated inversion recovery

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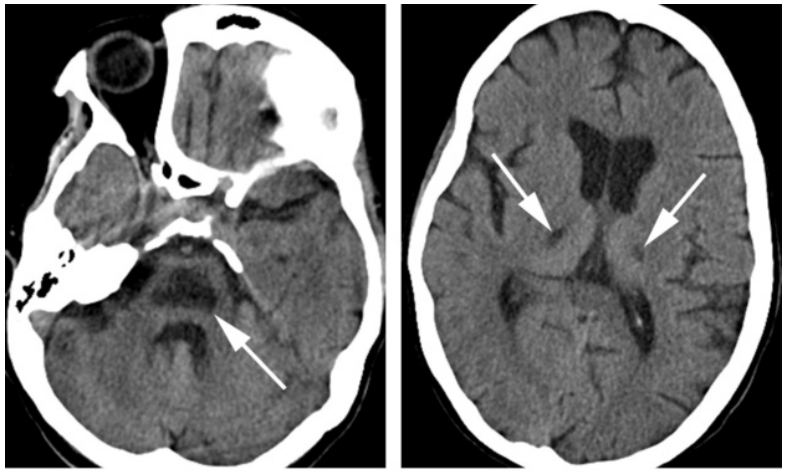
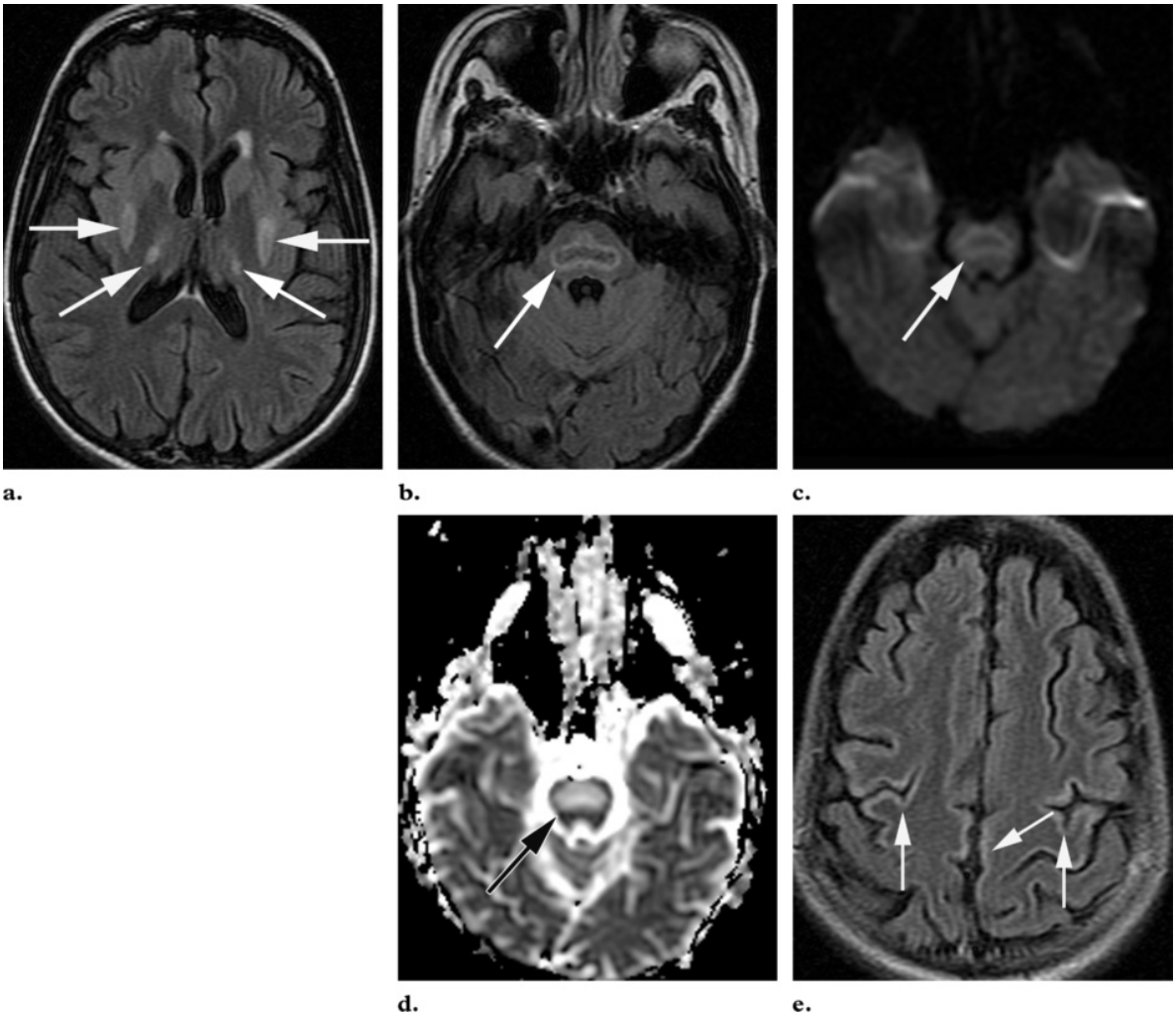


Figure 1. **(a)** Axial unenhanced CT image obtained at the level of the fourth ventricle shows a symmetric, centrally located region of low attenuation within the pons (arrow). **(b)** Axial unenhanced CT image obtained at the level of the lateral ventricles shows symmetric low-attenuation foci within the lateral thalami (arrows).

Figure 2. **(a, b)** Axial fluid-attenuated inversion recovery (FLAIR) MR images at the level of the lateral ventricles **(a)** and pons **(b)** show bilateral symmetric T2 prolongation in the basal ganglia and lateral thalami (arrows in **a**) and a trident-shaped area of T2 prolongation surrounding an area of encephalomalacia in the central pons (arrow in **b**). **(c, d)** Diffusion-weighted MR image **(c)** and apparent diffusion coefficient (ADC) map **(d)** at the level of the pons show a trident-shaped rimlike area of hyperintensity surrounding the central pons (arrow). On the ADC map, there is no signal dropout in the region of hyperintensity, a finding consistent with T2 shine-through. **(e)** Axial FLAIR MR image at the level of the convexities shows bilateral symmetric T2 hyperintensity predominantly involving the precentral and central sulci (arrows).



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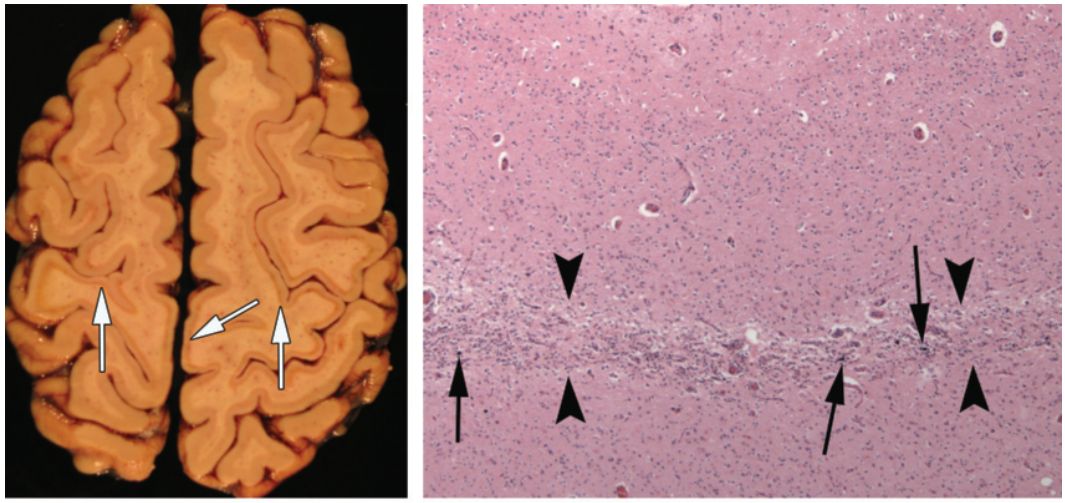


a. b.

Figure 3. **(a)** Photograph of both cerebral hemispheres shows a hyperemic band accentuating the gray matter–white matter junction and predominantly involving the parietal convexities (arrows). **(b)** Photomicrograph (original magnification, ×40; hematoxylin-eosin stain) shows cortical laminar necrosis and a linear area of neuronal dropout with foamy histiocytes (arrowheads) and small dystrophic calcifications (arrows).

Imaging Findings

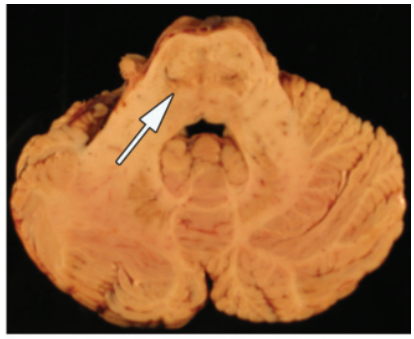
Unenhanced CT performed shortly after the patient was transferred to the tertiary care center revealed a large well-circumscribed area of hypoattenuation within the pons (Fig 1a) with bilateral symmetric foci of hypoattenuation in the thalami (Fig 1b), findings suggestive of osmotic demyelination syndrome.

Prominent signal abnormalities were seen within the basal ganglia, thalami, and pons on subsequent T2-weighted images, findings suggestive of osmotic demyelination syndrome (Fig 2a, 2b). Diffusion-weighted images showed increased signal intensity in the basal ganglia, thalami, and pons, with concordant increased ADC values, findings indicative of T2 shine-through (Fig 2c, 2d). On FLAIR and intermediate-weighted images, bilateral cortical T2 prolongation was seen at the convexities, with subtle associated diffusion abnormalities, findings suggestive of cortical laminar necrosis (Fig 2e).

Pathologic Evaluation

At sectioning, the cerebral cortical ribbon of the temporal and parietal lobes was normal in thickness, but soft and pale, with a hyperemic band accentuating the gray matter–white matter junction (Fig 3a). Microscopic examination of these areas of the temporal and parietal lobes revealed neuronal dropout, numerous histiocytes, and focal dystrophic calcifications (Fig 3b). These gross and histologic findings were suggestive of cortical laminar necrosis. In addition, although the cerebellum appeared normal at gross examination, near-complete loss of Purkinje cells with associated Bergmann gliosis was observed at histologic analysis. Like laminar necrosis, loss of Purkinje cells with Bergmann gliosis is associated with hypoxia or anoxia.

The pons appeared markedly abnormal at both gross and microscopic examination. Within the center of the pons, there was a 2.3-cm, well-circumscribed, symmetric, rhomboid area that was soft and tan (Fig 4a). At histologic analysis, abundant foamy histiocytes, reactive neurons, and an absence of inflammation were observed (Fig 4b). Luxol fast blue staining of this area showed a loss of myelin (Fig 4c). Neurofilament protein staining showed preservation of the neuronal axons. These findings are suggestive of central pontine myelinolysis. In addition, bilateral myelinolysis of the external capsule was seen. The



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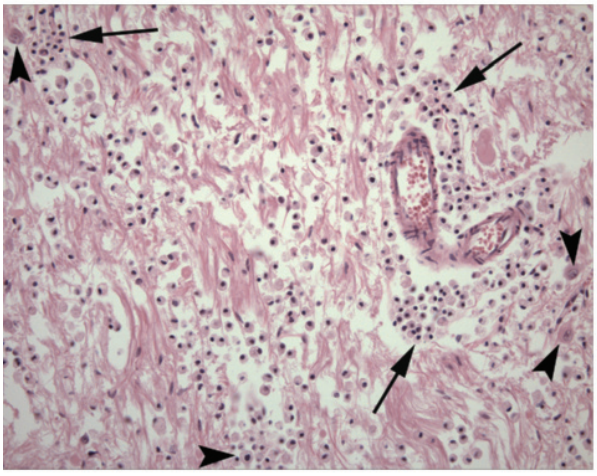

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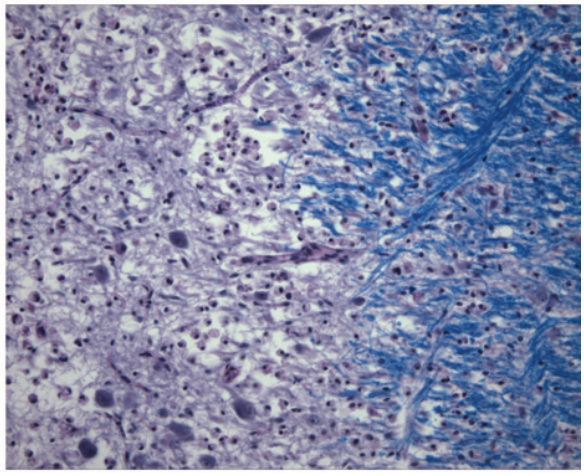

c.

Figure 4. **(a)** Photograph of a gross slice through the pons shows a symmetric, soft, tan lesion (arrow), findings indicative of central pontine myelinolysis. **(b)** Photomicrograph (original magnification, ×200; hematoxylin-eosin stain) shows central pontine myelinolysis, with numerous foamy histiocytes (arrows) and reactive neurons (arrowheads) but no associated inflammation. **(c)** Photomicrograph (original magnification, ×200; Luxol fast blue stain) shows the sharp demarcation of demyelinated (purple area on the left) and normal (royal blue region on the right) pontine tissue.

remainder of the cortical white matter was unremarkable. Finally, examination of the spinal cord showed pallor and degeneration of the corticospinal tracts, findings suggestive of insult to these tracts at the level of the pons.

Discussion

Central pontine myelinolysis was described in 1959 as a condition seen in alcoholic and malnourished patients (1). These patients developed spastic quadriplegia, pseudobulbar palsy (characterized by head and neck weakness, dysphagia, and dysarthria), or encephalopathy in association with noninflammatory demyelination centered within the pons. In 1962, it was noted that this myelinolysis syndrome could occur outside the pons, a condition that is referred to as extrapontine myelinolysis. Sites of extrapontine myelinolysis include the basal ganglia and cerebral white matter and, less commonly, the peripheral cortex, hippocampi, and lateral geniculate bodies (2). Extrapontine myelinolysis commonly occurs in conjunction with central pontine myelinolysis; however, it also may be seen in isolation (3). The term *osmotic demyelination syndrome* is used to encompass both entities.

Throughout the 1970s and 1980s, it became clear that the disease not only occurred in alcoholic or malnourished patients but also was commonly associated with rapid correction of hyponatremia, in which sodium level increases by more than 12 mmol/L/d (4). Patients with osmotic demyelination syndrome typically present with severe electrolyte disturbances, which lead to seizures or encephalopathy. As normonatremia is restored, mental status improves and may return to normal within 48–72 hours, only to rapidly deteriorate days later. Symptoms during the second period of mental deterioration include dysarthria, dysphagia, flaccid quadriparesis that later

becomes spastic, and horizontal gaze paralysis (3,5,6). Coma or delirium typically follows (3).

Osmotic demyelination syndrome affects men more often than women, and it is most common in middle-aged patients (2). The mechanism of myelinolysis is not fully understood; however, it is thought to be linked to intramyelinitic splitting, vacuolization, and rupture of myelin sheaths, which is presumably caused by osmotic effects in the setting of correction of sodium levels (5). Oligodendrocytes, which constitute the sheaths, are particularly sensitive to osmotic changes; therefore, the distribution of the changes that occur with osmotic demyelination syndrome parallels the distribution of oligodendroglial cells (5,6). Alcoholic and malnourished patients generally are deficient in organic osmolytes, a condition that may put them at greater risk for developing osmotic demyelination syndrome (6). Additional comorbid conditions that predispose patients to osmotic demyelination syndrome include prolonged use of diuretics; liver failure; organ transplantation, particularly liver transplantation with cyclosporine use; and extensive burns (6,7).

Imaging findings of osmotic demyelination syndrome typically lag behind clinical symptoms, and images acquired within 1–2 weeks after the onset of symptoms often show no features of the disease (5,8). Imaging performed after symptoms have been present for 2 weeks has been advocated to help confirm the diagnosis, although osmotic demyelination syndrome cannot be excluded with imaging alone (5,9). More recent studies have noted that restricted diffusion may be seen in areas of myelinolysis as soon as 24 hours after the onset of symptoms, and some authors therefore advocate performing diffusion-weighted imaging early in the course of disease (5).

CT is less sensitive than MR imaging in depicting osmotic demyelination syndrome (10). Areas of myelinolysis are hypoattenuating, usually located within the basilar part of the pons, and lack a mass effect. The pontine tegmentum often is spared. Areas of hypoattenuation also are often seen in areas other than the pons (eg, in the basal ganglia and thalamus); these findings are indicative of extrapontine myelinolysis (11).

A symmetric trident-shaped area in the central pons is a characteristic finding on T2-weighted and FLAIR MR images. The ventrolateral pons and the pontine portion of the corticospinal tracts typically are spared (2,5,12). Decreased signal intensity throughout affected areas, with no mass effect, is a classic finding on T1-weighted images. Less commonly, lesions appear isointense relative to surrounding brain tissue on T1-weighted images. Lesions typically do not enhance after the administration of contrast material (2,13). Case reports have suggested that restricted diffusion may be seen earlier than the classic findings in areas of osmotic demyelination on T2-weighted images (5,14). Because our images were obtained more than 2 months after the patient's hyponatremia was rapidly corrected, ADC values in the areas of demyelination were no longer decreased. Reports from the MR imaging evaluation performed at the outside hospital 2 weeks after the sodium level was corrected stated that restricted diffusion was identified.

Evidence of cortical laminar necrosis, which often occurs in the setting of hypoxia, also was seen at imaging and pathologic analysis. Although the patient was not hypoxic at the tertiary care center and transfer records from the outside hospital reported no episodes of hypoxia during her admission, prior to the initial hospitalization she had been unresponsive for approximately 2 weeks, during which time she vomited repeatedly and would have been at high risk for a hypoxic episode. The cause of the cortical lesions may have been hypoxia that occurred during those 2 weeks of unresponsiveness.

At gross examination, regions affected by osmotic myelinolysis appear as soft tan areas that are typically bilateral and symmetric (2). At histologic analysis, these regions are found to have abundant foamy histiocytes without an infiltrate of lymphocytes or neutrophils. Luxol fast blue staining demarcates the areas of demyelination, and neurofilament protein staining shows preservation of neuronal axons.

Because there have been no large clinical trials examining treatments for osmotic demyelination syndrome, treatment is largely supportive. Case reports have suggested that steroids, intravenous immunoglobulin, and thyrotropin-releasing hormone may be helpful; however, there are no findings from a large-scale trial to support the use of these therapies. Although results of animal studies

have suggested that reintroducing the hyponatremia may be beneficial, little research has been done in humans (3,15).

The prognosis for osmotic demyelination syndrome varies and has no apparent connection to clinical features or imaging findings (3). In a study of 34 patients with central pontine myelinolysis, two died; 10 survived but were left with significant neurologic sequelae, which rendered them unable to live unassisted; 11 had some deficits but were able to take care of themselves; and 11 recovered completely (16).

Our patient had clinical, radiologic, and pathologic findings that are typical of osmotic demyelination syndrome. After a 2-month hospitalization that included transfer to a tertiary care center, all but comfort care was withdrawn. The patient died shortly thereafter.

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