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Management and outcomes of malignant posterior reversible encephalopathy syndrome

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ABSTRACT

Introduction: Recognition of severe forms of posterior reversible encephalopathy syndrome (PRES) has improved. Management of these patients remains challenging, particularly in patients with the combination of edema and hemorrhage.
Methods: A prospective inpatient neuro-intensive care database was queried for patients with PRES. Malignant PRES was diagnosed by clinical assessments (GCS less than 8 and clinical decline despite standard medical management for elevated intracranial pressure) and radiographic criteria (edema with associated mass effect; brain hemorrhage exerting mass effect; effacement of basal cisterns, transtentorial, tonsillar, or uncal herniation). Malignant PRES was defined as: radiology studies consistent with PRES; GCS less than 8; and clinical decline despite standard elevated intracranial pressure management.
Results: Five cases were identified over a 4 year interval. The following contributing conditions were also present: chemotherapy (1), systemic lupus erythematosis (2), pregnancy (1), and methamphetamines (1). Neurocritical care interventions included: hyperosmolar therapy (5), anticonvulsants (5), management of coagulopathy (5), and ventilatory support (5). Neurosurgical interventions included: craniectomy (5), hematoma evacuation (3), and external ventricular drain (4). Brain biopsy was performed in 5 patients and was negative for vasculitis, demyelinating disease, tumor, or infection. Cyclophosphamide was administered to the two patients with SLE. With long-term follow up, all patients achieved good functional outcomes (modified Rankin score 1–2).
Conclusion: In contrast to historical reports of high mortality rates (16–29%) for severe and hemorrhagic PRES variants, we had no fatalities and observed favorable functional outcomes with intracranial pressure monitoring and craniectomy for malignant PRES cases who fail medical ICP management.

1. Introduction

Neurocritical care is important for patients with advanced brain edema due to posterior reversible leukoencephalopathy (PRES). Recent reports have identified a hemorrhagic subtype of PRES [1–7]. Less is known about clinical management and outcome for patients with hemorrhagic PRES and PRES with malignant features.

PRES has been extensively described in the neurology, obstetrics, and radiology fields. In the original report [8], all patients resolved their neurologic deficits within two weeks. PRES is associated with diverse conditions including: pregnancy, renal failure, malignant hypertension, advanced liver disease, chemotherapy agents, autoimmune diseases, encephalitis, and certain transplant medications such as cyclosporine and tacrolimus [9]. Edema in the posterior cerebral hemispheres is a key finding, but the edema may occur in the cerebellum, brainstem, thalamus, basal ganglia, and other regions of cerebral cortex [7]. It is symmetric in some patients, yet asymmetric in others. Vascular caliber changes may also be present, when angiography is obtained. It has also been recently recognized that some systemic lupus erythematosis (SLE) patients have PRES rather than cerebritis [10–13]. In our experience, there can be considerable clinical and radiographic overlap when treating advanced forms of PRES, cerebritis, and acute disseminated encephalomyelitis (ADEM), particularly when brain biopsy is not available.

Although the initial description of PRES stated that 'clinical signs and abnormalities on imaging are always reversible [8], further experience has tempered this optimism. In fact, some authors

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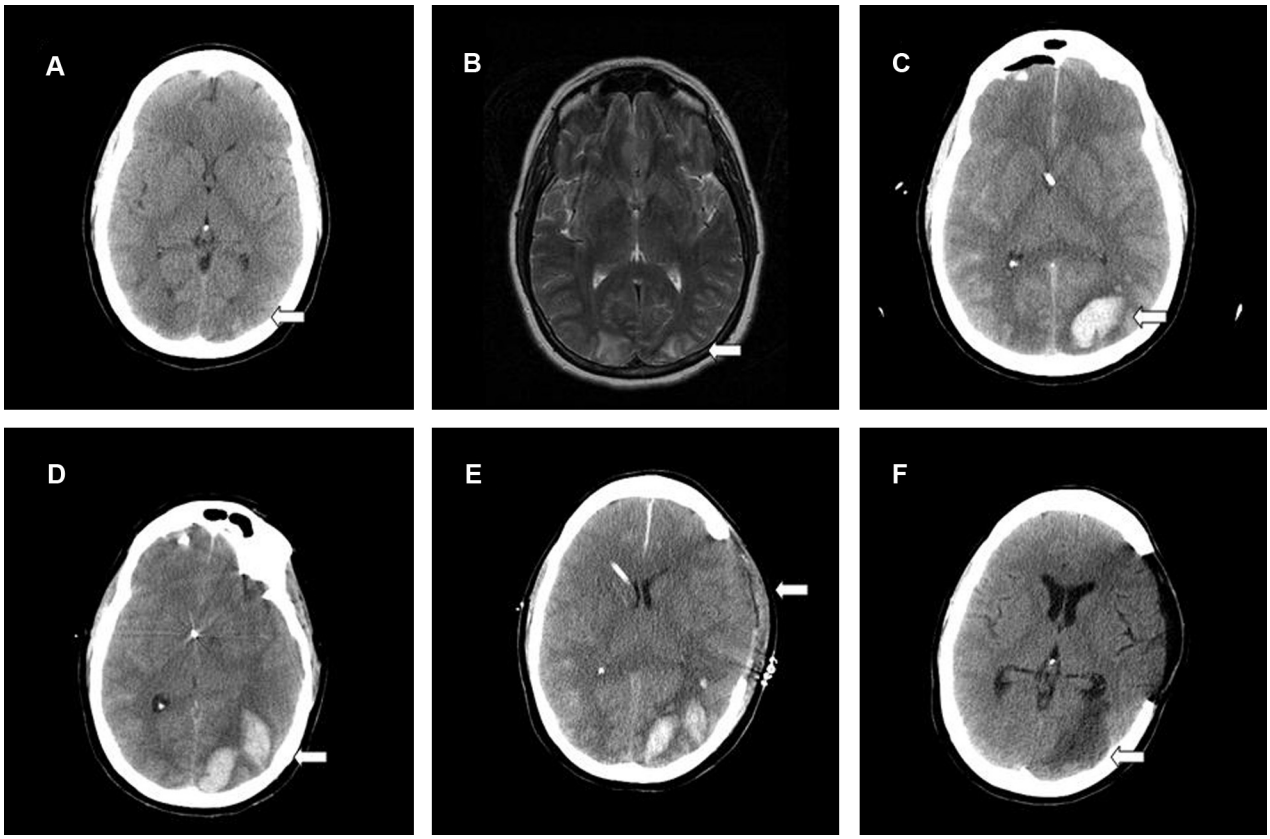

Fig. 1. Hemorrhagic PRES with malignant features following chemotherapy (Case 1). (A) CT head at the time of initial presentation for headache and seizures. (B) T2-weighted MRI brain at time of presentation with mild PRES (arrow). (C) CT head following neurologic worsening with hemorrhagic transformation of PRES (arrow). (D) CT head following ICP monitoring with an external ventricular drain. Hemorrhagic changes have increased (arrow). (E) CT head following craniectomy (arrow). The craniectomy extended to the middle cranial fossa but retained more parietal bone than usual due to concern for rebleeding with brain expansion. (F) CT head at 2 months. Chronic changes and resorption of blood posteriorly are visible (arrow).

observed that PRES is often neither posterior nor reversible [14–17]. Outcomes following PRES are variable and fatalities reach 30% with hemorrhagic PRES [4,6]. We report our treatment approach and outcomes for hemorrhagic and malignant PRES.

2. Methods

A prospective inpatient neurosurgery case registry is maintained with institutional review board approval. The database was reviewed over a 4-year period for patients admitted to the neuro-intensive care unit with PRES and atypical presentations of brain edema at a regional neuro-intensive care center (Kaiser Sacramento). During this time period, there were 4070 admissions to the neurointensive care unit. The medical records were retrieved using the electronic medical record database and reviewed systematically.

We diagnosed PRES when the patient had the following findings on radiographic studies: edema predominantly in the subcortical regions with a predilection for the posterior lobes (occipital, parietal, temporal), relative sparing of the cortex, no associated intracranial tumor, bacterial or fungal infection, or demyelination. We defined PRES with malignant features based on clinical assessments (GCS less than 8 and clinical decline despite standard medical management for elevated intracranial pressure) and radiographic criteria (edema with associated mass effect; brain hemorrhage exerting mass effect; effacement of basal cisterns, transtentorial, tonsillar, or uncal herniation). The term 'malignant' PRES was chosen to emphasize the similarity to malignant brain edema observed following other brain injuries such as malignant middle cerebral artery infarction. We relied on brain biopsy and microbiology studies to exclude acute demyelinating encephalomyelitis, vasculitis, and infection. Intracranial pressure monitoring was considered for patients with GCS of 8 or less; craniectomy was considered for patients with progressive neurologic decline despite aggressive multi-modal management of ICP and mass effect.

3. Results

For patients with malignant PRES, the initial management approach focused on the following objectives: (1) aggressive strategies to reduce mass effect and edema using steroids, hyperosmolar therapy, moderate BP control, and cerebral hematoma evacuation with associated craniectomy; (2) treatment of associated coagulopathy (usually platelet dysfunction and fresh frozen plasma transfusions); (3) seizure treatment and prevention; (4) management of associated medical co-morbidities including elective intubation for GCS <8; and (5) rigorous evaluations to exclude other diagnostic concerns. All patients were managed by a multi-disciplinary team with neurocritical care and neurosurgery guidance. Patients received support from additional specialists as clinically indicated.

Key features of the cases are presented in Table 1 and neuroimaging findings in Figs. 1–3. A detailed description of these cases is provided below. All patients received initial medical management with: hyperosmolar therapy; mechanical ventilation; sedation; rapid identification and reversal of coagulopathies; and steroids. These treatments were temporizing but not definitive. Patients with malignant PRES had further neurologic and