

Posterior reversible encephalopathy syndrome in a patient with paraneoplastic extralimbic encephalitis and small cell lung cancer

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ABSTRACT - Background: Paraneoplastic encephalomyelitis (PEM) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. **Case report:** We describe a 41-year-old female patient with subacute development of dysarthria, dysphagia, tetraparesis, ataxia, breathing difficulties and cognitive deterioration. Brain magnetic resonance imaging revealed multiple confluent hyperintense lesions in cortical and subcortical white matter consistent with the posterior reversible encephalopathy syndrome. Ultimately, she was diagnosed with anti-Hu positive paraneoplastic extralimbic encephalitis and small cell lung cancer. Treatment with intravenous corticosteroids and immunoglobulins led to minimal clinical improvement, while significant regression of bilateral symmetric cortical edema and edema of subcortical white matter was seen on follow up brain magnetic resonance imaging. **Conclusion:** The paraneoplastic extralimbic encephalitis and posterior reversible encephalopathy syndrome are rare first manifestations of small cell lung cancer.

Key words: posterior reversible encephalopathy syndrome, extralimbic paraneoplastic encephalomyelitis, small cell lung cancer

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INTRODUCTION

Paraneoplastic encephalomyelitis (PEM) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. The most frequently recognized focal paraneoplastic disorders of the CNS are limbic encephalitis, cerebellar degeneration and brainstem encephalitis. Although PEM can affect any part of CNS, involvement of extralimbic brain structures is not often reported in the literature (1). We describe a female patient who had reversible large T2 and FLAIR hyperintensities on magnetic resonance imaging (MRI) consistent with the diagnosis of posterior reversible encephalopathy syndrome (PRES) in a setting of PEM and small-cell lung carcinoma (SCLC).

CASE REPORT

A 41-year-old female presented with a ten-month history of nonspecific muscle pain in legs and hands, walk and speech difficulties accompanied with general weakness. She was seen by a neurologist in a local hospital, brain MRI was performed

and showed multiple small T2 and FLAIR hyperintensities in the deep white matter bilaterally (MRI not available). No further work up was taken.

However, the patient's condition worsened and she presented to our emergency department. On admission, neurological examination revealed dysarthria, facial myoclonic jerks, gaze apraxia, down-beat nystagmus, tetraparesis, limb and truncal ataxia, and short-term memory impairment. Cerebrospinal fluid (CSF) analysis showed mild pleocytosis, 13 white cells *per cubic millimeter*, a slightly elevated protein level of 0.51 g/L (normal values 0.17-0.37 g/L), positive oligoclonal bands and normal level of protein 14-3-3. Serologic analysis of serum and CSF for HIV, syphilis and neurotropic viruses was negative. Electroneurography showed axonal neuropathy. Although lung oncomarkers and chest x-ray were normal, chest computed tomography (CT) revealed enlarged mediastinal lymph nodes. Bronchoscopy and transthoracic biopsy of the lymph nodes verified SCLC. Paraneoplastic anti-Hu antibodies in serum were positive. The diagnosis of PEM was established.

The patient's clinical condition continued to deteriorate. During the first week after admission, par-

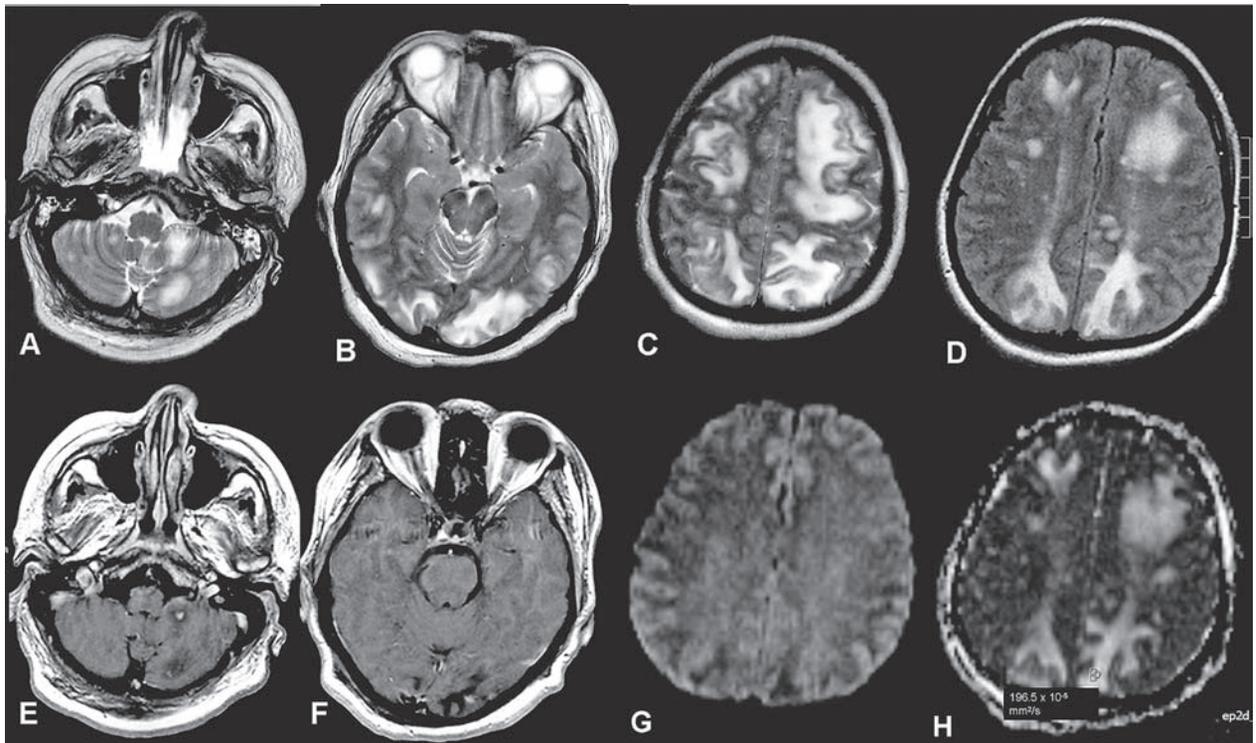


Fig. 1. Axial brain magnetic resonance images: T2-weighted images showing multiple confluent hyperintense lesions in the cerebellum, subcortical white matter, predominantly in posterior regions, but also present in frontal lobes (A-C); FLAIR image showing hyperintense lesions in deep and subcortical white matter in frontal and parietal lobes (D); several small foci in the cerebellum and left occipital lobe enhanced with contrast media (E, F); diffusion-weighted image with minimal T2 shine-through (G); lesions exhibit vasogenic edema, seen on the map of apparent diffusion coefficient, with ADC of $196.5 \times 10^{-5} \text{ mm}^2/\text{s}$ (H).

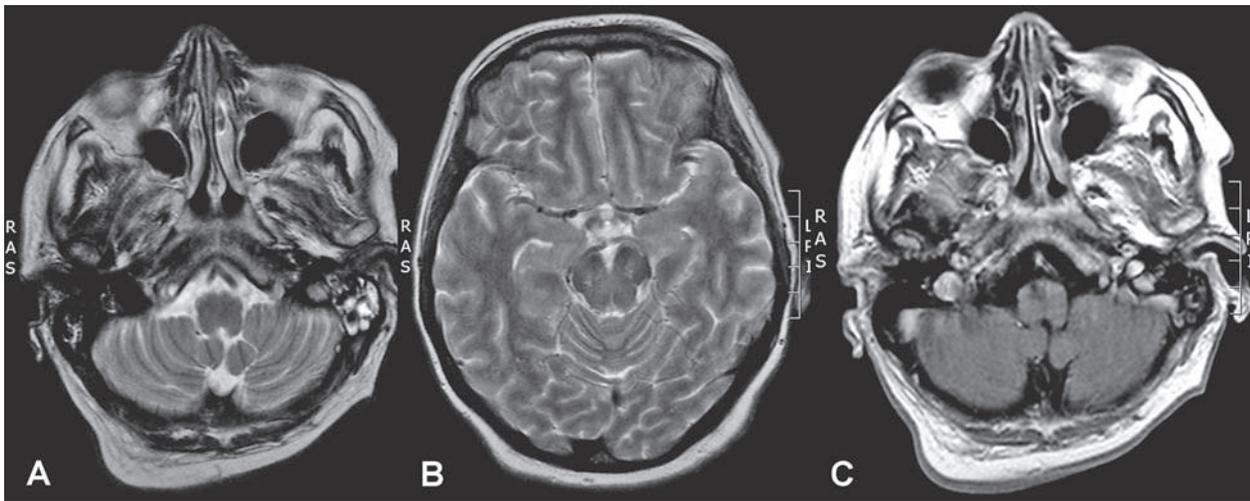


Fig. 2. Control magnetic resonance imaging (MRI): axial T2-weighted images (A, B) and post-contrast T1-weighted image 4 weeks after initial examination; complete resolution of previous T2-hyperintense lesions (A, B); no contrast enhancement on control T1-weighted MRI image (C).

tial motor epileptic seizures with secondary generalization were observed, for which she was treated with methylphenobarbital and levetiracetam. Electroencephalography (EEG) showed focal slowed activity in frontal and temporal regions. In the first 10 days of hospitalization, the patient's blood pressure fluctuated from hypotension to normotension (systolic min-max/diastolic min-max 77-132/33-79 mm Hg), measured by cuff-style, biceps monitor. Afterwards, hypertension occurred with blood pressure mostly 150-188/91-116 mm Hg. Only occasionally, blood pressure measurements were greater than 200/110 mm Hg. Angiotensin-converting-enzyme inhibitors and hydrochlorothiazides were introduced in therapy. These great fluctuations in blood pressure, with simultaneous fluctuations in cardiac rhythm and respiratory rate were considered a manifestation of autonomic nervous system dysfunction. Follow up brain MRI performed at that point (3 weeks after admission) revealed large multiple confluent hyperintense lesions in subcortical white matter, predominantly in posterior regions, but also present in frontal lobes, with minimal involvement of temporal lobes. Lesions exhibited vasogenic edema, seen on the map of apparent diffusion coefficient. Several small foci in the cerebellum and left occipital lobe showed post-contrast enhancement (Fig. 1). The patient developed bilateral pneumonia that eventually led to respiratory arrest for which she was intubated, mechanically ventilated for 5 days, and treated with intravenous antibiotics.

At that point, the patient's general condition was too poor for active cancer treatment, so she received treatment with 1000 mg of intravenous

methylprednisolone for 5 days, without any clinical improvement. In order to further improve the patient's condition, treatment with intravenous immunoglobulins was initiated (0.4 g/kg/day for five days). There were minimal clinical changes, although follow up brain MRI showed significant regression of earlier described lesions (Fig. 2). Despite intensive therapy, the patient died after two months without receiving specific cancer treatment.

Postmortem examination was not performed due to religious reasons.

DISCUSSION

We describe a patient with anti-Hu positive PEM and large reversible T2 and FLAIR hyperintensities on the MRI consistent with PRES. The patient was later diagnosed with SCLC. Rapid neurological deterioration, cognitive changes, mild pleocytosis, slightly elevated protein level and positive oligoclonal bands in the CSF, along with the detection of highly specific paraneoplastic anti-Hu antibodies in serum supported the diagnosis of PEM (2,3).

Positive paraneoplastic anti-Hu antibodies are present in 23% of patients with SCLC and their significance in patient outcome has not yet been completely clarified. Some studies show that SCLC patients with PEM have a more severe neurological deficit, are most refractory to treatment, and survival from the time of diagnosis is significantly worse (4-8). On the other hand, there are studies showing that SCLC patients with PEM have a higher probability of survival at 30 months compared

Table 1. *Paraneoplastic encephalomyelitis cases described in the literature*

<i>Patient sex/age (Ref. no.)</i>	<i>Brain MRI</i>	<i>Clinical presentation</i>	<i>Tumor</i>	<i>Therapy</i>	<i>Outcome</i>
M/66 (11)	T2 lesions in F and T lobes	Epilepsia partialis continua	SCLC	AED	Death
W/63 (10)	T2 extralimbic lesions	Hemiparesis, hemianopia	Brest adenocarcinoma	MPL, CP	Progressive dementia
W/79 (10)	F and PO lesions	Epilepsia partialis continua, monoparesis	Brest adenocarcinoma	DX	Improvement
M/65 (10)	Left hippocampus and amygdala	Sensory neuropathy, limbic encephalitis	Squamous cell lung carcinoma	PE, CP	Good
W/55 (12)	T2 lesions P and T lobes and insula	Seizures, aphasia	Thymoma	R, Th	Good
W/33 (13)	Multiple cortical and limbic T2 and DWI lesions with gadolinium enhancement	Seizures	Thymoma	Th, R, AED	Good
M/18 (14)	Bilateral F and T diffuse T2 lesions, brainstem involvement	Tetraparesis, seizures, coma	Hodgkin's lymphoma	PE, R, AED	Good

M = magnetic resonance imaging; M = man; W = woman; F = frontal; PO = parieto-occipital; T = temporal; AED = antiepileptic drugs; MPL = methylprednisolone; CP = cyclophosphamide; DX = dexamethasone; PE = plasma exchange; R = radiotherapy; Th = thymectomy.

with those without PEM (9). Low anti-Hu titers without PEM or sensory neuronopathy are associated with more indolent tumors (10).

However, paraneoplastic antibodies are not always present in a patient with paraneoplastic neurologic syndrome, and their absence should not repel the diagnosis (11).

As our patient's condition deteriorated, follow up brain MRI showed large lobar T2 and FLAIR hyperintensities bilaterally in the frontal, parietal and occipital lobes and cerebellum with minor involvement of the temporal regions. Brain MRI in PEM usually shows changes in temporal lobes, limbic part of the CNS and cerebellum. Abnormal MRI contrast enhancement is not a typical feature of PEM but it can be present (12). The extralimbic abnormalities in MRI are rarely reported and there are only few described cases in the literature (12-16) (Table). The PRES is exceptionally associated with SCLC; when present, it is usually associated with chemotherapy (17). Its occurrence is well described in hypertensive patients where it is postulated that failure of cerebral blood flow autoregulation and hyperperfusion leads to cerebral edema. The appearance of PRES in normotensive patients

as its absence in many hypertensive patients suggests a more complex underlying mechanism besides blood pressure autoregulation failure (18,19). In a patient like ours who had high blood pressure in the third week of hospitalization, merely a coincidence of PRES in a setting of PEM has to be considered. Besides hypertension, the clinical conditions usually associated with PRES are preeclampsia/eclampsia, infection, sepsis, shock, autoimmune diseases, cancer chemotherapy and organ transplantation. A similar immune process in these conditions with T-cell activation, production of inflammatory cytokines, endothelial activation could lead to endothelial injury (20). Although histologic studies in PRES are rare, there are data describing chronic vessel injury (21). This would be in concordance with brain MRI and CT studies in PRES that show involvement of watershed zones and this could explain involvement of other brain regions besides the posterior one (18). In our patient, watershed zones were seen in the cerebellum (Fig. 1A) and semioval center bilaterally (Fig. 1D).

As the name PRES implies, the lesions are predominantly occipital, however, extraoccipital lesions should not exclude this diagnostic possibility. Lesions in the frontal lobe, basal ganglia, cerebellum

or brainstem can be found in about one-third of cases, but there are only a few case reports with isolated atypically located lesions (22). Patients with extensive lesions on T2 weighted imaging tend to have a worse prognosis (23).

Paraneoplastic encephalomyelitis is a rare first manifestation of SCLC and there are no established protocols for its treatment. Removal of the underlying tumor and suppression of the immune response are two usual approaches (24,25). Immunotherapy can be helpful in PEM treatment, but improvement is mild or not sustained unless the underlying tumor is controlled (26). Our patient received immunosuppressive therapy with steroids and intravenous immunoglobulins for PEM treatment with minimal clinical improvement, while there was almost complete regression of MRI lesions, supporting the diagnosis of PRES in the setting of PEM.

CONCLUSION

The PEM and PRES are rare first manifestation of SCLC. In the absence of known malignancy the right diagnosis is very difficult to make, especially when clinical picture and radiological findings are not typical.

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Sindrom posteriorne reverzibilne encefalopatije u bolesnice s paraneoplastičnim ekstralimbičnim encefalitisom i malostaničnim karcinomom pluća

SAŽETAK – Cilj: Pokazati kako raznovrsna klinička prezentacija i tijek bolesti mogu otežati postavljanje dijagnoze i liječenje paraneoplastičnog sindroma. **Prikaz slučaja:** Opisujemo slučaj 41-godišnje bolesnice s postupnim razvojem dizatrije, disfagije, tetrapareze, ataksije, otežanog disanja i kognitivnih smetnji. Magnetska rezonancija mozga pokazala je multiple konfluirajuće hiperintenzivne lezije kortikalne i subkortikalne bijele tvari koje upućuju na sindrom posteriorne reverzibilne encefalopatije. Bolesnici je dijagnosticiran anti-Hu pozitivan paraneoplastični ekstralimbični encefalitis i malostanični karcinom pluća. Liječenje intravenskom primjenom kortikosteroida i imunoglobulina rezultiralo je tek minimalnim kliničkim oporavkom, dok je kontrolna magnetska rezonancija mozga pokazala značajnu regresiju ranijeg simetričnog bilateralnog kortikalnog edema i edema subkortikalne bijele tvari. **Zaključak:** Paraneoplastični ekstralimbični encefalitis i sindrom posteriorne reverzibilne encefalopatije rijetka su prva manifestacija malostaničnog karcinoma pluća.

Ključne riječi: sindrom posteriorne reverzibilne encefalopatije, ekstralimbični paraneoplastični encefalomijelitis, malostanični karcinom pluća