Carcinomatous meningitis: Yet another cause for rapidly progressive dementia and triphasic waves in electroencephalograph!

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ABSTRACT

We report a 65-year-old woman who manifested with progressive cognitive impairment, abnormal behavior, slurred speech, inability to carry out activities with right upper limb, gait disturbances, emotional liability, and double incontinence that evolved progressively over the last 8 months. A clinical syndrome of “rapidly progressive dementia” was considered. The MRI of brain was unremarkable except for small para third ventricular enhancing lesion was detected in the left thalamic region. There was bi/tri-phasic sharp waves in the routine scalp EEG occurring at periodically 1.5–2.0 Hz, mimicking Creutzfeldt–Jakob disease (CJD). She was later diagnosed to have carcinomatous meningitis based on cerebrospinal fluid (CSF) cytology. This case is being discussed for rarity and interesting EEG observations in patients with carcinomatous meningitis and to highlight the importance of CSF cytology in an appropriate clinical setting. One needs to be careful in concluding CJD as possible diagnosis in such scenario.

Key words: Carcinomatous meningitis, dementia, triphasic waves

Introduction

Rapidly progressive dementia is often a diagnostic challenge and needs diligent search for potentially reversible conditions. Presence of periodic 1.0–2.0 Hz triphasic waves in scalp electroencephalograph (EEG) in a middle aged and old individual, manifesting with dementia, is considered as highly suggestive of Creutzfeldt–Jakob disease (CJD). However “similar EEG findings” have been reported in metabolic disorders, hepatic encephalopathy, hyperammonemia, thyrotoxic encephalopathy, lithium toxicity, carcinomatous meningitis among others. There are isolated reports of carcinomatous meningitis manifesting with rapid decline in cognitive function. However, often the diagnosis of carcinomatous meningitis with atypical presentation is established only at autopsy.

We discuss the EEG, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) features in an elderly woman presenting with dementia, who was clinically diagnosed as “possible CJD” and later detected to have carcinomatous meningitis.

Case Report

A 65-year-old woman was referred for evaluation of “rapidly progressive dementia.” She manifested with progressive cognitive impairment, abnormal behavior, slurred speech, inability to carry out activities with right upper limb, gait disturbances, emotional lability, and double incontinence that evolved over the last 8 months. There was no myoclonus or seizures. She was a non-vegetarian consuming egg, fish, and meat products. Many years ago, she underwent surgery for lipoma on the chest wall. She was detected to have hypertension five years ago and was on anti-hypertensive medications. Apart from this her past health was unremarkable and here was no family history of dementia.

Her vitals signs were normal. She was conscious, and cooperative but could but not verbalize, spontaneously...
or on commands. She had profound impairment of cognition and could not comprehend and communicate and therefore formal tests for mini mental state examination (MMSE) or detailed neuropsychological assessment could not be carried out. She also exhibited frequent unprovoked laughter. There was weakness of right hand as she was unable to grip the pen or hold glass properly. She had rigidity in all the four extremities, decreased blink rate, bradykinesia, and required one person support while walking. Other systemic examination and per vaginal and rectal examination were unremarkable. She was investigated for “rapidly progressive dementia.”

Routine urinary, hematological, biochemical (including liver and renal function) assays were normal. Serum levels of thyroid hormone, anti-thyroid globulin, ammonia, and vitamin B12 were within normal limits. Serological tests for vasculitis (RA factor, ANA), syphilis and HIV were negative. MRI of the brain revealed diffuse cerebral atrophy, pan-ventriculomegaly, and periventricular leucoariosis. Following gadolinium injection a small para third ventricular enhancing lesion was detected in the left thalamic region. Diffusion weighted imaging did not disclose any additional lesion in basal ganglionic or cortex [Figure 1a]. Carotid and vertebral artery Doppler study was normal. Scalp EEG revealed asymmetrical periodic biphasic and triphasic broad complex sharp waves occurring at 0.5–1.5 Hz frequency in both fronto-temporal leads (left > right) [Figure 1b]. Repeat EEG after 2 weeks revealed persistence of these abnormalities. The CSF was clear, colorless and had slightly raised protein of 58 mg/dl (normal ≤ 45.0 mg/dl), sugar of 47 mg/dl, and raised cell count of 14 cells/cu.mm (11 lymphocytes, 3 large cells). The cytoplasm stained with Leishman’s stain was moderately cellular with admixture of lymphohemocytotic series and clusters of large single and papillary epithelial component. These cells had amorphophilic cytoplasm, some of them vacuolated and large vesicular to hyperchromatic nuclei. These cells represent neoplastic adenocarcinoma, a carcinomatous meningitis [Figure 1d and e]. CSF-VDRL was non-reactive and negative for cryptococci. CSF could not be tested for 14-3-3 protein. Subsequent investigations for internal malignancy included serum CEA level, bone scan, X-ray chest, Ultrasound of abdomen and colonoscopy were normal. Her family could not afford total body PET CT.

Discussion

This patient had features of rapidly progressive dementia with pyramidal, extrapyramidal involvement and short interval biphasic/triphasic complexes in EEG and therefore a provisional diagnosis of probable sporadic CJD was considered. However, CSF analysis revealed abnormal cells leading to the diagnosis of carcinomatous meningitis. Whether our patient had coexistent CJD, is speculative as it could not be excluded for the want of facility to analyze the CSF 14-3-3 or prion protein mutation. However, absence of myoclonus, and MRI changes characteristic of CJD at this stage of illness, and presence of unilateral focal thalamic lesion, possibly metastasis would make the diagnosis of CJD...
unlikely. The MRI signal changes observed in thalami (pulvinar sign), basal ganglia and cortex (cortical-ribbon sign) have a high sensitivity (61%–90%) and specificity (94%) and are increasingly used to differentiate CJD from other dementia.[9] Dementia and delirium as the presenting manifestation of carcinomatous meningitis is uncommon.[6–8] Sugita et al. reported a 64-year-old woman with lymphomatous meningitis who died one year after the onset of progressive gait disturbance and dementia. [4] Vas et al. described a 56-year-old woman with rapidly evolving dementia, ataxia, and myoclonus. A diagnosis CJD was suspected although there were no periodic complexes in EEG. Her autopsy revealed features of carcinomatous meningitis.[3] It is noteworthy that the ante-mortem CSF analysis did not show malignant cells. Presence of low CSF sugar can be detected in patients with carcinomatous meningitis, which often provides clue to the diagnosis.[10]

Solid tumors commonly manifests as parenchymal lesions in the nervous system. Clinical evidence of leptomeningeal metastasis is recorded in 8% of patients with metastatic solid tumors.[10] However, at autopsy the prevalence might be as high as 19%. Among the solid tumors, adenocarcinomas of breast, lung, GIT and melanoma are among the common causes of leptomeningeal metastasis.[11] Though solid tumors like melanomas have greater propensity for leptomeningeal spread, but cancer of breast and lung are observed more frequently because of higher prevalence.[12] Patients with metastasis in the posterior fossa have higher incidence of leptomeningeal involvement. The hallmark of the carcinomatous meningitis is multifocal neurological involvement that involves different levels of neuraxis. Median survival is 4 to 6 weeks if left untreated, and 2 to 3 months if treated. However there are reports of longer periods of survival even up to 82 weeks, as in this patient.[13]

Our patient had periodic triphasic sharp waves in EEG. This observation in the setting of rapidly progressive dementia is highly suggestive of CJD and has been reported in meningeal carcinomatosis, diagnosed only at autopsy.[1,14]

Exact frequency of such EEG findings in patients with carcinomatous meningitis may not be not available, because EEG is not routinely carried out when the diagnosis of carcinomatous meningitis is confirmed by CSF analysis. Meningeal carcinomatosis should therefore be included as a differential diagnosis of such an EEG pattern. Diffuse carcinomatous meningitis and multiple cortical tumor nodules might alter CSF dynamics and derange the cortical activity. The periodic triphasic waves could have been due to disruption of synaptic connectivity in cortex by tumor deposit.[15] The role of thalamic lesion noted in our patient in the generation of periodic complexes could be speculative.

Our patient is unique since this is the first report of ante-mortem diagnosis of carcinomatous meningitis in a patient with rapidly progressive dementia and triphasic waves in EEG leading to clinical diagnosis of CJD. Our study also reiterates need for high index of suspicion and importance and CSF cytospin.

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