

Case report:**A CASE STUDY WITH BREAST CANCER AND BRAIN METASTASIS ENCOMPASSING ACUTE ONSET OF AMNESIA AND ALTERED MENTAL STATUS DUE TO LIMBIC ENCEPHALITIS – BIOCHEMICAL AND PROTEOMIC ASPECTS**

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ABSTRACT

A biochemical case study is reported on a 50-year old lady known to have breast cancer. The woman was treated by mastectomy and this was followed by unraveling brain metastases three years post-diagnosis of the cancer, which was treated by radiation and chemotherapy. Two months after ending her treatment, she exhibited acute changes in her mental status manifested by severe amnesia and fever. A generalized analytical and biochemical assessment revealed the presence of paraneoplastic limbic encephalitis.

Keywords: Cancer, encephalitis, mastectomy, metastasis

INTRODUCTION AND BACKGROUND

Paraneoplastic neurological syndromes (PNS) are regarded as remote offshoots of cancer that are not caused by invasion of the tumor or its metastases (Graus and Dalmau, 2007). Immunologic and biochemical factors implicated with the aforementioned are believed to be significant in the pathogenesis of PNS because antibodies (humoral) and T-cell mediated responses against nervous system antigens (onconeural) have been identified with several of those disorders (Graus and Dalmau, 2007;

Aznar et al., 2007; Storstein and Vedeler, 2007; Honnorat and Antoine, 2007).

At the onset of the neurologic symptoms, most patients may have not yet been diagnosed with cancer (Graus and Dalmau, 2007). On the other hand, in patients known to have established cancer, the presentation of a PNS condition may herald recurrence of a primary or secondary tumor (Graus and Dalmau, 2007). Rapid detection and immediate treatment of the underlying tumor appear to offer the best chance of stabilizing the patient and thus preventing further neurological deterioration (Aznar et al., 2007;

Storstein and Vedeler, 2007; Honnorat and Antoine, 2007).

CASE REPORT ASSESSMENT

A 50 year old lady known to have a history of cancer, and whose left breast tumor was treated by mastectomy, 3 years today, was diagnosed with brain metastasis, recently discovered, and presented as right hemiplegia that was treated by 30 cycles of radiotherapy and chemotherapy. Biochemically speaking, she was under a treatment regimen of phenytoin, prednisone, proton pump inhibitors, lovenox, xeloda, nevalbin (Graus and Dalmau, 2007).

Two months following the last course of radiotherapy, she was presented to the emergency room at Notre Dame de Secours, Byblos, Lebanon, with an acute onset of mental changes, severe amnesia and abnormal face movements.

On physical examination, she was considered as essentially stable hemodynamically, besides having a fever of 39 °C. Confused spatially and temporally, her Glasgow score was roughly 13. In addition, she was having clonic movement of the right lip and eyelid, and despite the fact that her cranial nerves were normal, her old right side exhibited conspicuous weakness and hyperreflexia, where cutaneo-planter reflexes were in flexion, sensitivity and gait; however, her coordination was difficult to assess (Graus and Dalmau, 2007). The physical exam, furthermore, was normal with no cleared site for any infections.

Technically, the biochemical ER differential diagnosis was the following according to manifestations:

- Hypoglycemia,
- Encephalitis: infectious- metabolic-neoplastic – radiation,
- Meningitis vs. meningoencephalitis,
- Cerebrovascular problems (hemorrhagic or ischemic),
- Mass lesions like metastasis,
- Subclinical status epilepticus,
- Hypothyroidism,
- Low vitamin B12 and
- Infections.

Furthermore, as initial management was undertaken for the aforementioned, the following were recognized: serum glucose was 100 mg/dl; CT scan of the brain did eliminate intracranial bleeding; EEG was normal; CSF analysis was insignificant; ECG and chest x-ray were normal; laboratory results were generally normal; and thyroid stimulating hormone (TSH) was relatively high with low free T₃ and T₄. Phenytoin level, in addition, was low, with low calcium concentration (Graus and Dalmau, 2007; Aznar et al., 2007; Storstein and Vedeler, 2007).

Intravenous (IV) calcium and IV antiepileptic drugs regimens ensued with scrutinized clinical observation. On the second day following admission, neurological reassessment demonstrated the presence of disorientation, severe amnesia (anterograde > retrograde), and no more clonic movement. Brain MRI was performed to show the presence of old metastasis lesion in the left temporo-parietal region with decreased severity of the surrounding edema (by comparison with the last MRI done when brain metastasis has been diagnosed) (Figures 1, 2 and 3).

The patient started taking L-thyroxin, calcium, phenytoin, decadron and valproic acid. Few days after, she still was amnesic with wax and wane mental status but with no more fever or any abnormal jerks. They gave her the usually scheduled chemotherapy (one course every 2 weeks).

Two days after, she recurred to have fever of 38.5 – 39 °C, with no alarming sign of infections. CBCD revealed neutropenia and the diagnosis of neutropenic fever was taken further into consideration (Graus and Dalmau, 2007). Another CSF was examined for analysis, culture, Gram stain and PCR of herpes, and MRI of the brain was done (Figures 4 and 5) with a full coverage of the patient with broad spectrum antibiotics (Targocid, amikin, tazocin) and zovirax.

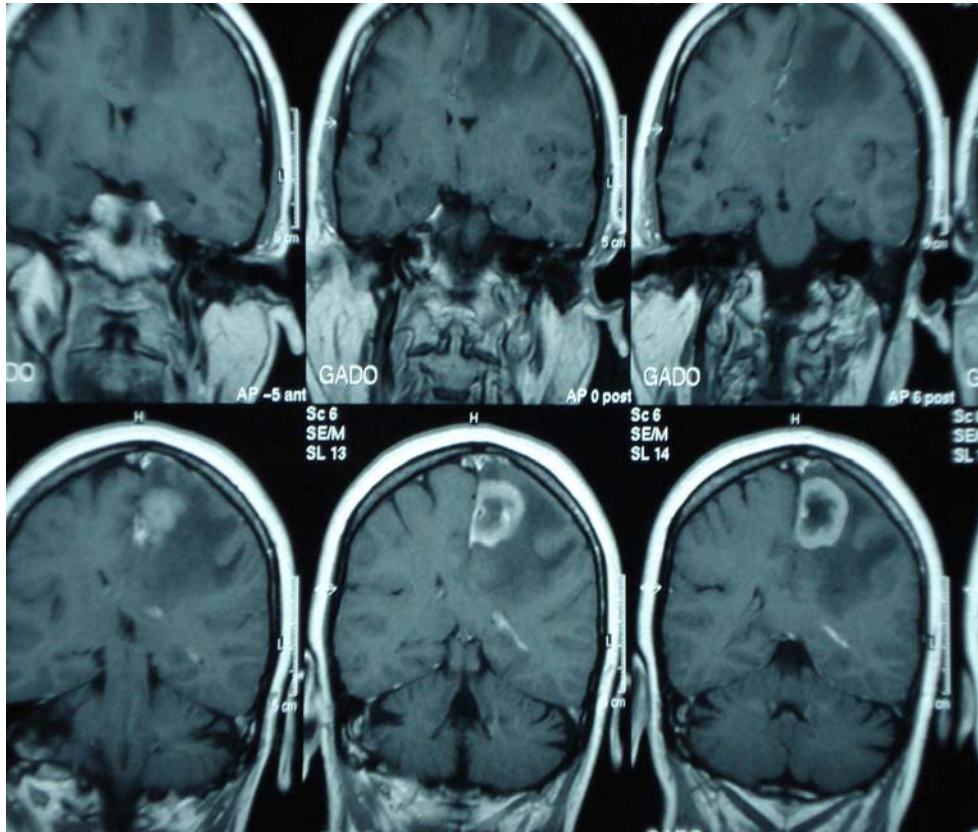


Figure 1: MRI showing the metastatic lesion with the surrounding edema

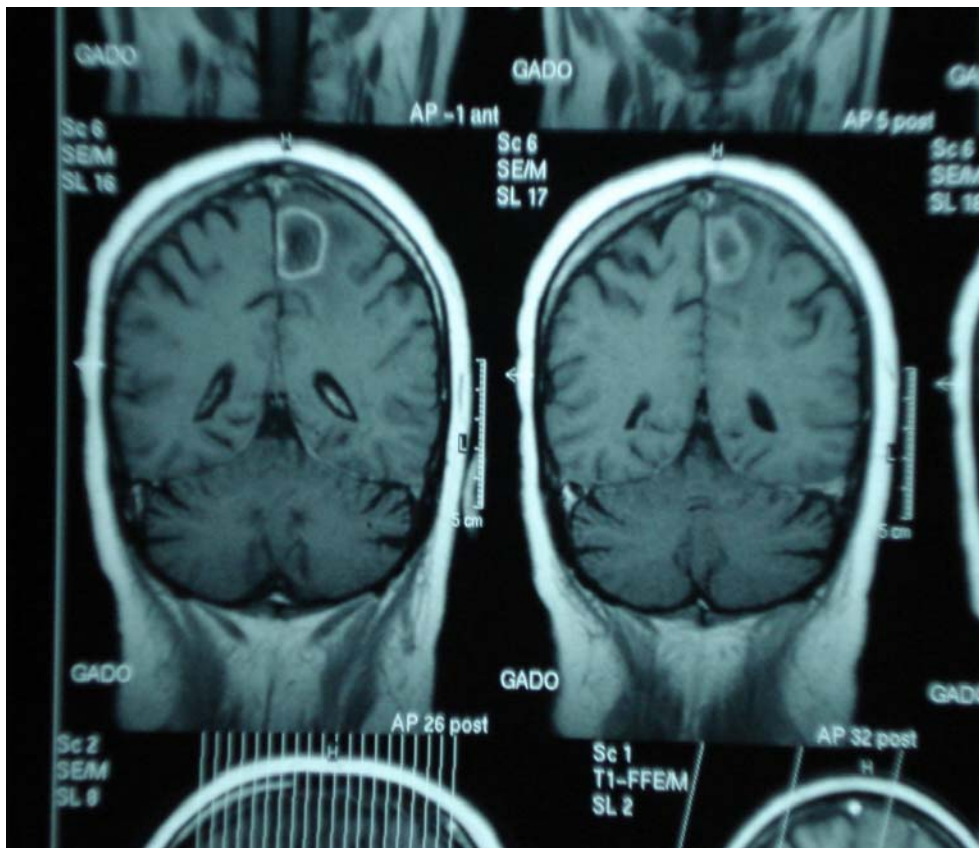


Figure 2: MRI with Gadolinium

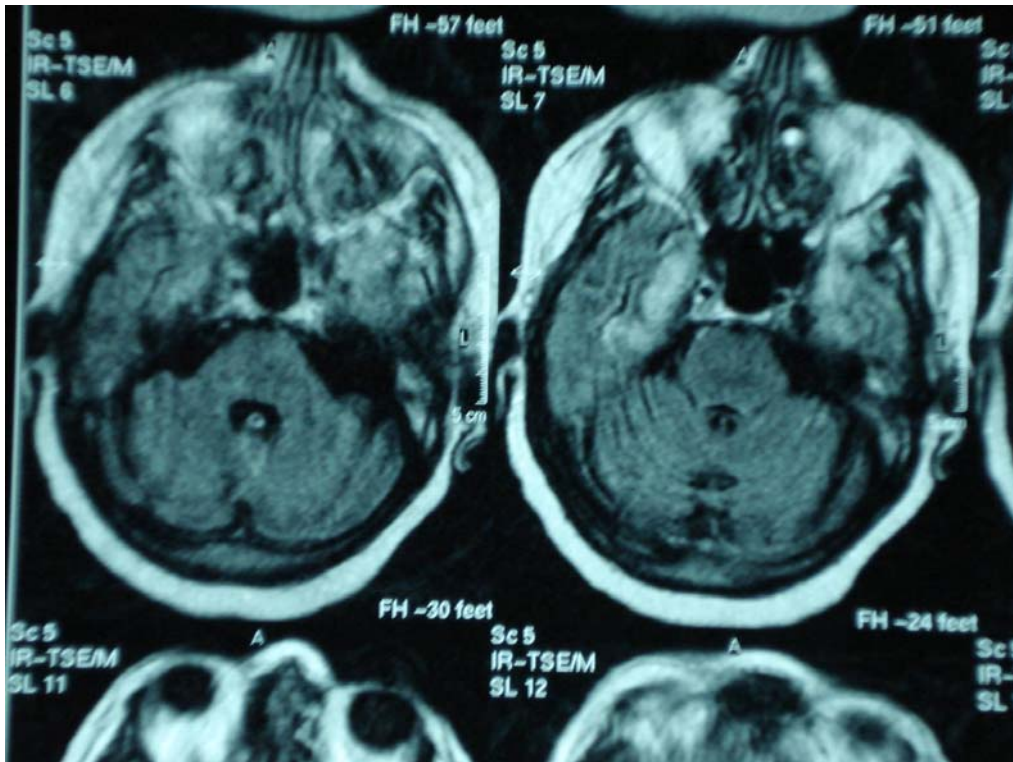


Figure 3: MRI with Gadolinium, continued

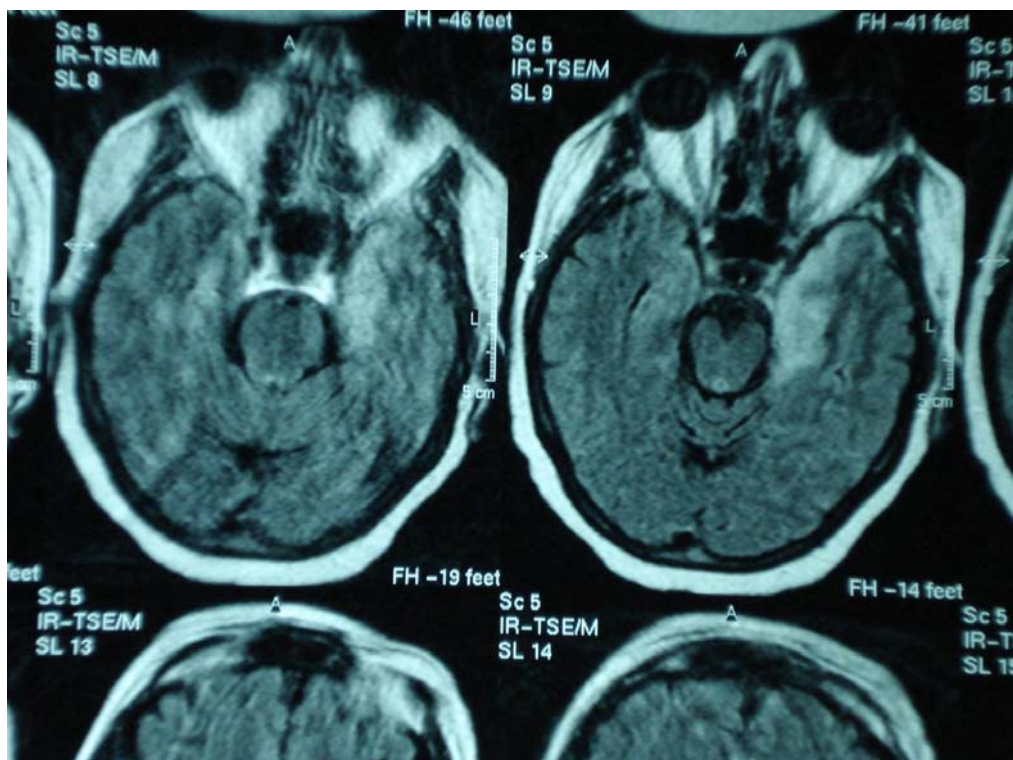


Figure 4: MRI with Gadolinium, continued

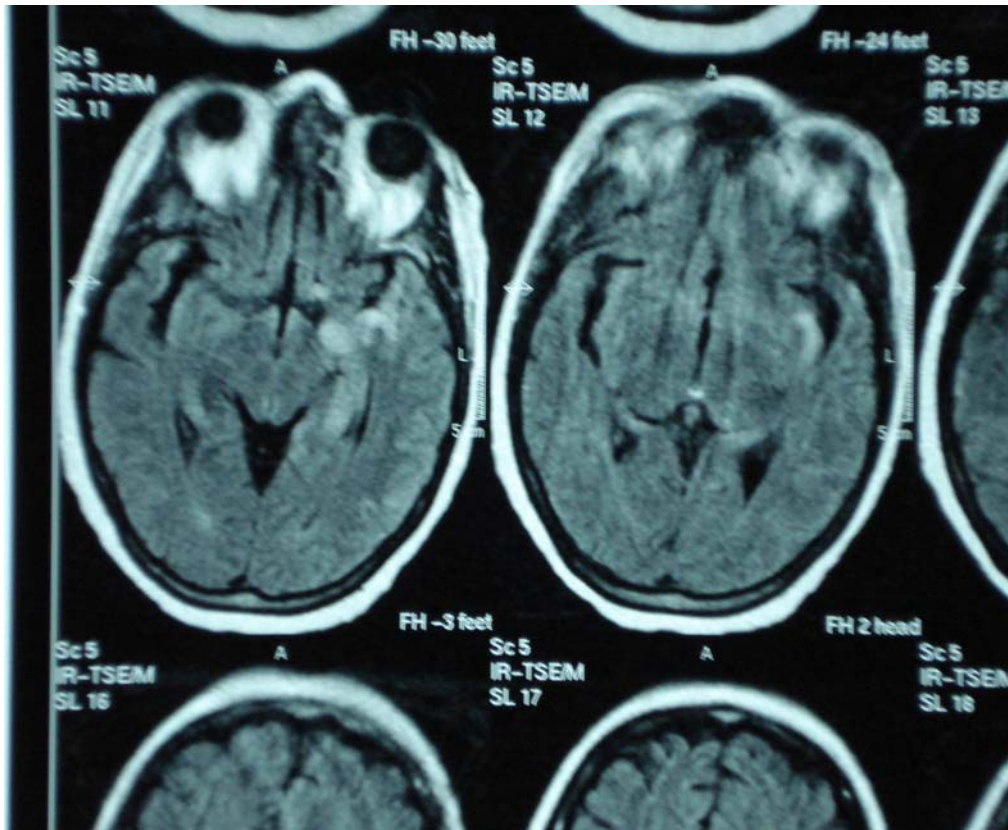


Figure 5: MRI with Gadolinium, continued

CSF tests were negative all over, and MRI showed the presence of hyper signal temporal lobe in the left side more than in the right one. The differential diagnosis changed at that point and it was directed toward the diseases (syndromes) causing hyper signal lesions on MRI of the brain, which were as follows:

- Herpes encephalitis: there was elimination by negative PCR and CSF tests;
- Infiltrating neoplasm: there was no mass lesion other than the old metastasis away from the new one;
- Ischemia: which indicated against this diagnosis the absence of specific vascular distribution;
- Post-ictal lesion: the patient was asymptomatic, clinically, and the EEG was normal; and
- Limbic encephalitis was considered as the most probable case.

The diagnosis of limbic encephalitis was based on the clinical assessment, risk factor (breast cancer), and the MRI lesion

(Anderson and Barber, 2008; Graus and Saiz, 2008). The patient took solumedrol in high dose for 5 days, zovirax was stopped, and antibiotics were continued till the 14th day with clinical follow up on daily basis. Ten days after embarking on the diagnosis of limbic encephalitis, the patient was transferred home with stable mental status, mild amnesia, old right hemiplegia, and no more fever or jerks. On the other hand, WBC increased to normal levels on the day of discharge. Two weeks after, she was admitted at the clinic for follow up and she was manifesting the same status (Lucas-Ramadan et al., 2008).

DISCUSSION

Paraneoplastic limbic encephalitis (PLE) is one of the rare PNS characterized by subacute onset (in days to a few months) of the short-term memory loss, seizures, confusion, and psychiatric symptoms, suggesting involvement of the limbic system (Graus and Dalmau, 2007). Hypothalamic dysfunction may occur with somnolence,

hyperthermia, and endocrine abnormalities. Also, it is part of paraneoplastic encephalomyelitis, with involvement of other areas outside the limbic system and brainstem.

Selective impairment of reception memory is the hallmark of the disease but may not be evident in patients presented with severe confusion or multiple seizures (Graus and Dalmau, 2007; Lucas-Ramadan et al., 2008). More than half of the patients admitted with limbic encephalitis may have an underlying neoplasm. Lung tumor may occur in 50-60 % (usually SCLC), testicular germ cell tumor in 20 %, and others may include breast cancer, similar to the aforementioned case, thymoma, Hodgkin's disease, and immature teratomas.

Clinically, PLE is divided into several groups, the most important of which are the following:

- Patients with anti-Hu antibodies and lung cancer (older, median age 62 years, female, smokers);
- Patients with anti-Ma2 antibodies and testicular cancer (younger, median age 34 years, male); and
- Patients with no anti-neuronal antibodies (40 % of cases).

The diagnosis of limbic encephalitis is often difficult because there are no specific clinical markers and symptoms (Ghosh et al., 2007). MRI and CT scans have shown abnormalities in 65-80 % of patients consisting of increased signal on T2-weighted and fluid-attenuated inversion-recovery images of one or both medial temporal lobes, hypothalamus, and brainstem. Co-registration of FDG-PET may further improve the sensitivity of imaging.

Moreover, CSF examination is abnormal in approximately 80 % of patients, showing transient mild lymphocytic pleocytosis with elevated protein, IgG, or oligoclonal bands. The detection of paraneoplastic antibodies may help establish diagnostic criteria and direct a tumor search that includes the lung, breasts, and testicles in the absence of paraneoplastic antibodies (Storstein and Vedeler, 2007; Honnorat and Antoine, 2007; Anderson and Barber, 2008).

Antineuronal antibodies are also found in approximately 60 % of cases. The most frequent related paraneoplastic antibodies are:

- Anti-Hu associated with limbic system lesions and lung cancer;
- Anti-Ma2 (also called anti-Ta) ± Ma1 associated alone with testicular cancers;
- Anti-CV2/CRMP5 associated with SCLC or thymoma;
- Anti-amphysin antibodies; and
- Anti-VGKC antibodies can exist with thymoma or non-paraneoplastic limbic encephalitis.

The treatment of PLE is non-specific; however, spontaneous recovery has been described in 30-64% of cases depending on the presence/absence and type of antibodies. Immunotherapy, in addition, is largely ineffective (Graus and Dalmau, 2007; Ghosh et al., 2007). Many cases were benefiting from antitumor therapy and high dose steroids for approximately 5 days.

Therefore, all efforts should be directed at identifying and treating the underlying tumor. If no tumor is established, the diagnostic and prognostic search should be repeated every 3-6 months for a period of 2-3 years. As a prognosis, approximately 64 % of cases of patients without antibodies had partial neurological recovery (Graus and Dalmau, 2007).

In getting back to our case, the patient took high dose of steroids and she received the treatment of her underlying breast cancer; she was clinically improving, at least partially, but the detection of neuronal antibodies hasn't been undertaken, which necessitates further analytical testing and follow-up.

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