Reversible Paraneoplastic Encephalomyelitis Associated with a Benign Ovarian Teratoma

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ABSTRACT: Background: Paraneoplastic encephalomyelitis (PEM) is a well characterized, and typically irreversible, paraneoplastic syndrome, usually associated with small cell lung cancer or other malignancy. We describe a case of a young woman with a benign ovarian teratoma who presented with a reversible PEM. Case report: A 24-year-old woman presented with a three week history of memory impairment, unusual behavior, personality changes, auditory hallucinations, hypersomnolence and binocular diplopia. On admission she was disoriented and inattentive with impaired short term memory. Small doses of lorazepam (1 mg), given for episodic agitation, repeatedly induced multidirectional bilateral nystagmus and a skew deviation, but her neurological examination was otherwise normal. A left-sided pelvic mass was palpable. Brain MRI pre- and post-gadolinium was normal. There was a mild CSF pleocytosis and an EEG showed minimal bilateral background activity irregularities. There were no other laboratory abnormalities. Two weeks after admission, she clinically deteriorated developing central respiratory failure and a flaccid paraplegia. Repeat MRI showed an area of increased T2 weighted signal in the medulla and three similar areas in the spinal cord. Following removal of her tumor, treatment with high dose corticosteroids and intravenous immunoglobulin, she ultimately made a full recovery. Pathology revealed the tumor to be a benign ovarian cystic teratoma. Conclusions: This is the first report of a reversible PEM seen in association with a benign tumor, in this case a mature ovarian teratoma. Presumably, an immune response directed against neural elements of the teratoma cross-reacted with normal brain, brainstem and spinal cord antigens to cause neurologic symptoms. Tumor removal was followed by neurologic recovery.

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Paraneoplastic syndromes are remote effects of cancer that are not directly related to metastases, metabolic or nutritional derangements, or side effects of therapy. There is now increasing evidence that autoantibodies produced against the malignancy cross-react with normal brain antigens, though the pathogenesis of the paraneoplastic syndromes may actually be related to cell-mediated autoimmunity. A clinical approach to the paraneoplastic syndromes has been outlined by Dalmau, which requires that one of four criteria be met for diagnosis: (1) the presence of a typical paraneoplastic syndrome in a patient known to have an appropriate underlying cancer, (2) the presence of a
neurological disorder associated with a typical antineuronal antibody in serum or CSF, (3) the presence of a neurological disorder which resolves when the cancer is discovered and adequately treated, or (4) pathological findings typical of a paraneoplastic disorder.

Paraneoplastic encephalomyelitis (PEM) is a well characterized paraneoplastic syndrome, most commonly associated with small cell lung cancer. Its manifestations are variable, and PEM can present as a limbic encephalitis, which has also been reported in cases of Hodgkin’s disease, thymoma, uterine, breast, prostate, bladder, testicular, and colon cancers, as well as in several cases where no malignancy was found.

There have been two recent case reports of immature ovarian teratomas presenting in association with limbic encephalitis. In both cases, there was a mild CSF pleocytosis with no antineuronal antibodies detected. There was stabilization or some degree of recovery of each patient’s symptoms after tumor removal.

In addition, there has been one case report of a malignant mediastinal teratoma where autopsy revealed findings consistent with PEM. No other causative agents were detected, nor were autoantibodies to brain tissue found.

We describe here a case of a reversible PEM which occurred in a young woman with a benign ovarian teratoma.

**CASE REPORT:**

A 24-year-old right-handed woman of Chinese descent presented with a three week history of memory impairment, unusual behaviour, and personality changes. One week prior to admission, she developed hypersomnolence, delusional thinking and auditory hallucinations. She complained of forgetfulness and of binocular diplopia in all gazes of direction. Because of this, she tended to keep her left eye closed. She was never febrile but had suffered some symptoms of cough and was treated with an antibiotic one week prior to admission.

She was previously well but had had an asymptomatic pelvic mass detected on routine exam one month prior to admission which on an ultrasound performed at another centre was felt to be a dermoid cyst. She was awaiting gynecological consultation.

She had no history of smoking, alcohol or other drug use, no history of toxic exposures and no HIV risk factors. She was on no medications, had no known drug allergies, and had no recent immunizations.

A brain CT done one week prior to admission was normal but an EEG was reported to show intermittent bilateral temporal slow wave activity.

On admission, her blood pressure was 120/80, heart rate 84 and regular, and temperature 37.6°C. Her general medical examination was unremarkable apart from a large palpable left-sided pelvic mass. She appeared lethargic but was easily roused. There was no meningismus. She was disoriented to time and place. 5-minute recall was impaired although long-term memory was intact. She had decreased concentration and attention with difficulty following 2 or 3 step commands. Language function was normal. Pupils and fundi were normal. After a small dose of lorazepam (1mg sublingual) for agitation, she had prominent gaze-evoked nystagmus and decreased concentration.

On day 17, an EEG was mildly abnormal with rare bilateral synchronous slow wave discharges anteriorly. A repeat EEG on day 4 was within normal limits. A brain MRI scan pre- and post-gadolinium administration was normal. CSF examination showed 8 million WBC/L (87% lymphocytes, 13% monocytes), 1 million RBC/L, glucose 4.3 mmol/L, and protein 0.31 g/L. Cryptococcal antigen, India Ink, bacterial, fungal and viral cultures were all negative. PCR for CMV, HSV and EBV, and IFA for CMV were negative. CSF cytology was negative for malignant cells. Serum and CSF VDRL were non-reactive. Serum was negative for HIV1 and 2. Pelvic ultrasound and CT scan of the abdomen and pelvis revealed a 14x10x10cm complex cystic pelvic mass arising from the left adnexa with a 4 cm mural nodule of variable attenuation with foci of calcification felt to be most likely an ovarian dermoid. No ascites or omental cake was seen. Her beta HCG was negative. AFP tumor marker <5 µg/L and Ca125 was normal. FSH, LH, HGH, prolactin, ACTH and cortisol levels were also normal.

On day 15, she developed dysphagia and subsequently had a respiratory arrest requiring intubation and mechanical ventilation. CXR revealed no pulmonary disease. She was not breathing spontaneously but would trigger the ventilator to command suggesting central hypoventilation. She was awake, alert and would follow commands. She had vertical and horizontal gaze-evoked nystagmus. Her cough and gag reflexes were decreased. There were no other cranial nerve abnormalities and no motor or sensory deficits. Her nystagmus decreased over the next few days but she developed restricted vertical gaze, more so in upgaze than downgaze. She began breathing spontaneously the following day.

The tentative working diagnosis had been, from early after her admission, a paraneoplastic rhombencephalitis/limbic encephalitis, given the normal MRI scan and normal laboratory results, apart from the minimal CSF pleocytosis and EEG changes. The initial gynecological opinion obtained in hospital recommended postponement of surgical excision of the patient’s pelvic mass until her neurologic/psychiatric symptomatology had resolved. After the neurologic deterioration and respiratory arrest, repeat gynecological consultation was obtained and the patient underwent a right salpingo-oophorectomy and omental biopsy on day 17.

The surgical pathology revealed a unilocular cystic ovary with a multiloculated mammillary pole measuring 5.5cm in diameter, which contained black hairs. Serial sectioning of the mammillary pole revealed multiple cystic spaces ranging from 1 to 7 mm in diameter. There were a variety of tissue types identified and the mesenchymal tissue was cellular but there were no areas of immaturity seen. There were no abnormalities of the fallopian tube or omentum and the ovarian tumor was diagnosed as a mature cystic teratoma. Peritoneal fluid cytology was negative for malignant cells.

Her neurological status remained stable until day 20 when she became more drowsy and developed a flaccid paraplegia with a T5 sensory level. Repeat brain and spinal cord MRI showed one area of increased T2-weighted signal in the dorsal aspect of the medulla measuring 8mm, and three areas of similar signal intensity in the spinal cord: one at C4-5, the second at T3 and the third at T8-9. The remaining neural structures were entirely normal.

She was started on methyl-prednisolone 1g IV daily for five days followed by a gradual taper of oral prednisone starting at 60mg daily. Her clinical status continued to deteriorate. By day 28, she was comatose with no motor response to pain and no eye opening. She had intact brainstem reflexes except for absent cough and gag reflexes and she required tracheostomy for continued ventilatory support.
Serial CSF studies showed a range of 8 to 23 WBCs per cubic millimeter with a lymphocytic predominance between 87 and 98%; 0 to 25 RBCs; glucose 3.1 to 4.2 mmol/L (2.2-4.4) and protein 0.31 to 0.61 g/L (0.15-0.45). CSF albumin was 100 mg/L (134-237 mg/L) and IgG was 19 (4-51).

A repeat EEG on day 30 showed a mild generalized disturbance of background activity. EMG and NCS done on day 31 showed no evidence of peripheral nerve involvement.

Because of the lack of response to high dose intravenous steroids and the patient’s poor clinical status, intravenous immune globulin (IVIG) was given at a dose of 400mg/kg/day for five days (days 30-35). By day 36 she had improved significantly, was awake and alert, and following commands. Extraocular eye movements were full and there was no nystagmus. She continued to have a poor cough and gag but cranial nerves were otherwise normal. Over the following two and a half weeks, she continued to progressively improve and was discharged from the ICU on day 55. She was never administered acyclovir.

A repeat brain and spinal cord MRI on day 42 pre- and post-gadolinium was unchanged from the study done on day 21.

Serum and CSF samples, along with the pathology specimen, were sent for further analysis for antineuronal antibodies (Dr. Jerome Posner; Memorial Sloan-Kettering Cancer Center, New York, NY). Using Western blot analysis, no antineuronal antibodies were detected when tested against normal human brain.

During the remainder of her hospital stay, the patient received extensive physiotherapy and was discharged on day 79, ambulating with a walker, to a rehabilitation facility. At that time, she remained entirely amnestic of the events which had occurred between the time she was admitted until shortly before she was transferred out of the ICU.

At six month follow-up, she had fully recovered apart from a mild burning truncal dysesthesia which was gradually improving. An MRI with gadolinium showed a decrease in the size of her previous lesions with no enhancement.

**DISCUSSION**

The clinical presentation of our patient was very similar to the cases described by Aydiner et al.\(^1\) and Nokura et al.\(^2\) with, initially, a pure limbic encephalopathy with features of impaired memory and judgement, behavioural changes, emotional outbursts and delusional thinking. In all three cases, CSF revealed a mild lymphocytosis, there was no evidence of underlying infection, and no antineuronal antibodies were detected.

The main difference in the present case is that the tumor was benign, i.e., no immature components were identified at pathology. It is not impossible that a microscopic malignant component of this tumor could have been missed on pathological examination, and there have been cases of paraneoplastic syndromes where the carcinoma was only detectable microscopically.\(^3\) However, careful review of our tumor did not show any immature features and we feel this is unlikely the case. It is also conceivable that the tumour was a coincidental finding and that the neurological syndrome was due to another disease process. However, we were unable to demonstrate any infectious etiology and serological studies for a systemic vasculitis were negative. The initial normal brain MRI, three and a half weeks after onset of symptoms, excludes from diagnostic consideration a para- or postinfectious acute disseminated encephalomyelitis.\(^7\) In combination, her clinical presentation, CSF profile, EEG, neuroimaging studies, and improvement following treatment by tumor resection argues strongly in favour of a paraneoplastic etiology.

Our patient initially continued to deteriorate despite resection of her tumor and she did not appreciably respond to high dose steroids. However, she began to show dramatic and sustained clinical improvement six days following institution of IVIG, a total of 19 days following removal of the teratoma. The relative contribution of our interventions is impossible to determine but the timing of her improvement suggests that IVIG may have hastened her recovery. Whether or not resection of her tumor contributed to the sustained benefit remains speculative, albeit plausible. Spontaneous improvement has been reported in rare cases of paraneoplastic limbic encephalitis, with or without positive anti-Hu antibodies;\(^10\) this confounding factor will limit definitive evaluation of treatment responses in any paraneoplastic syndrome.

In summary, this is the first reported case of a patient with a benign ovarian teratoma with clinical features of an encephalomyelitis including limbic encephalitis, brainstem involvement and a multifocal myelitis. Presumably, an immune response directed against non-malignant neural elements of the teratoma cross-reacted with normal brain, brainstem and spinal cord antigens to cause the neurologic symptoms. Resolution of the neurologic symptomatology ultimately followed removal of the underlying tumor in conjunction with steroid therapy and IVIG administration.

**REFERENCES**


11. Tsukamoto T, Mochizuki R, Mochizuki H, et al. Paraneoplastic...