Case Report

Paraneoplastic encephalitis with leukoencephalopathy in primary fallopian tube carcinoma

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A B S T R A C T

Previous reports of paraneoplastic encephalitis occurring in primary fallopian tube carcinoma have been exclusively classified as paraneoplastic cerebellar degeneration, with MR imaging either unremarkable or demonstrating cerebellar atrophy. We report a case of paraneoplastic encephalitis in a 64-year-old female with primary fallopian tube carcinoma, reminiscent of N-methyl D-aspartate receptor encephalitis, with MR imaging demonstrating bilateral subcortical and deep white matter T2-FLAIR hyperintensities sparing cerebellar and brainstem structures. To our knowledge, this represents the first reported case of noncerebellar paraneoplastic encephalitis related to primary fallopian tube carcinoma.

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Introduction

Paraneoplastic encephalitis is an immune-mediated inflammation of the brain occurring in the presence of malignancy. This syndrome is often associated with antibodies against neuronal antigens, and these antibodies are often correlated with the neoplastic origin [1,2]. Magnetic resonance (MR) imaging in paraneoplastic encephalitis classically demonstrates T2 fluid attenuated inversion recovery (FLAIR) hyperintense signal changes, especially within temporal or limbic structures [3]. However, neuroimaging findings in differing clinical or immunologic subtypes are variable, with some characteristically demonstrating “extralimbic” involvement [3].

Primary fallopian tube carcinoma (PFTC) is a rare disease accounting for only 0.3%-1.1% of gynecologic malignancies [4]. There are a few reports of paraneoplastic encephalitis conditions occurring in the presence of PFTC, classified almost exclusively as paraneoplastic cerebellar degeneration (PCD) [5–11]. Purkinje cell cytoplasmic autoantibody type 1, an antibody strongly associated with gynecologic malignancy commonly referred to as anti-Yo, was identified in the majority of these reports [12]. MR imaging findings included in these cases were mainly either unremarkable or demonstrated cerebellar

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atrophy [5–11]. We report a unique case of paraneoplastic encephalitis associated with PFTC.

Case presentation

A 64-year-old female presented to the emergency department for a 1-day history of disorientation and confusion, with past medical history significant for anxiety, depression, hypothyroidism, and type 2 diabetes mellitus. Two months prior, she had undergone a hysterectomy, with bilateral salpingo-oophorectomy and omentectomy for diffuse seeding of a serous carcinoma, which was subsequently classified as stage 3 PFTC originating from the right fallopian tube. She developed an altered mental status and difficulty walking on postoperative day 3 and was admitted to the intensive care unit, where she was subsequently intubated for a Glasgow Coma Scale (GCS) of 7. This encephalopathy of unclear etiology resolved spontaneously, and the patient was discharged on postoperative day 7 without persisting neurologic symptoms. The patient’s life-expectancy at this time was determined to be less than 1 year, due to the extensive peritoneal seeding observed during her surgery.

Upon this present visit to the emergency department, she was only oriented to person and had a GCS of 14 secondary to confusion, despite stable vital signs and an otherwise normal physical and neurological exam. Specifically, she did not demonstrate signs of cerebellar dysfunction. MR imaging of her brain at this time was unremarkable. Following admission to the neurology floor, the patient’s neurologic status steadily declined. Her verbal responses became increasingly limited and inappropriate. She also began exhibiting muscle rigidity, upper arm myoclonus, and automatisms including lip smacking and involuntary smiling. Electroencephalogram (EEG) recording during this period was indicative of nonconvulsive status epilepticus, which resolved after a couple days to reveal a baseline electroencephalogram suggestive of moderate to severe encephalopathy. The patient’s GCS decreased to 7 on hospital day 4 and she was transferred to the intensive care unit. Later this same day, the patient became unresponsive and exhibited autonomic instability with tachycardia, blood pressure fluctuations, and diaphoresis.

On hospital day 5, complete blood count revealed a serum leukocyte count of 12.1 × 10^9/L, with a neutrophilic predominance (77%), and hemoglobin of 89 g/L. Chemistry panel was unremarkable except for an elevated BUN of 9.28 mmol/L. Serum CA-125 was significantly elevated at 1021.6 kU/L. Procalcitonin and myelin basic protein were elevated as well, suggestive of an inflammatory process. Lumbar puncture showed no abnormalities, with negative results for common viral, bacterial, and fungal etiologies of meningitis or encephalitis. Extensive serum and cerebrospinal fluid autoantibody panels were all negative, including an absent anti-Yo. Repeat MRI brain at this time showed diffuse confluent T2-FLAIR hyperintensity throughout the supratentorial white matter, without involvement of the brainstem or posterior fossa structures (Fig. 1). This patient did not receive a PET scan.

The patient’s rapid clinical deterioration and MRI findings were suggestive of acute encephalitis. It was determined that paraneoplastic encephalitis was most consistent with the patient’s history and presentation, and a modified treatment was

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Fig. 1 – Brain MR images on hospital day 4. Axial FLAIR image (A) and coronal FLAIR image (B) demonstrate diffuse confluent T2-FLAIR hyperintensity involving the deep and subcortical supratentorial white matter (arrowheads). There is symmetric involvement of bilateral frontal, parietal, occipital and temporal lobes. The brainstem and posterior fossa structures were unremarkable. Diffusion-weighted imaging showed no evidence of infarction and there was no abnormal contrast enhancement.
initiated a high diagnostic suspicion. Although there is a notable lack of clinical trials for treatment of paraneoplastic neurologic syndromes, [13] the present standard treatment for paraneoplastic encephalitis is immunomodulation such as steroids, cyclophosphamide, intravenous immune globulin, or cyclophosphamide [14]. She had already received a 3 day course of high-dose steroids prior to this diagnosis, which was not associated with clinical improvement, and was therefore given plasma exchange as further immunomodulatory therapy. The patient’s condition failed to improve with 5 days of plasma exchange; she remained unresponsive and unable to protect her airway. Due to the patient’s poor prognosis, secondary to stage 3 PFTC, the medical team and patient’s family ultimately decided to proceed with palliative care. The patient expired within 3 days of transfer.

**Discussion**

The onset of progressive neurologic deterioration in the presence of advanced gynecologic malignancy is highly suggestive of paraneoplastic encephalitis. The patient’s serological and cerebrospinal fluid studies failed to demonstrate autoimmune antibodies typically seen in paraneoplastic encephalitis. However, lack of an identifiable antibody does not exclude the diagnosis of autoimmune encephalopathy [15,16]. Indeed, with the diagnostic criteria delineated by Graus et al, the present case would be classified as a “definite” paraneoplastic neurologic syndromes, due to her neurological findings and close association of malignancy and encephalitis onset [17]. The differential diagnosis also included infectious or toxic metabolic encephalitis, but the patient’s mainly unremarkable physical exam and labs, following an extensive work-up, are less consistent with either of these diagnoses.

As described in the introduction, PCD is the only paraneoplastic encephalitis reported in the literature to be associated with PFTC. However, this patient’s neurological findings and lack of anti-Yo were inconsistent with cerebellar dysfunction. Additionally, her MR imaging pattern of leukoencephalopathy is also not characteristic of PCD. Two case reports of PCD associated with PFTC did mention supratentorial T2-FLAIR hyperintensities, but these were both attributed to small vessel ischemic disease [5,10]. Considering that the present case involved development of FLAIR hyperintensity following initially unremarkable MR imaging, these findings are indicative of an acute process. One report of PCD associated with PFTC described a similar imaging course, with initial MR imaging at symptom onset followed by development of cerebellar atrophy after gynecologic surgery [11].

Considering the inconsistency with PCD, the lack of detectable autoantibody complicates diagnosis of which form of paraneoplastic encephalitis could be exhibited by the present case. We believe that the course of this patient’s disease and neurologic findings are most reminiscent of N-methyl D-aspartate receptor (NMDAR) encephalitis. NMDAR encephalitis is reported to have a characteristic course of psychiatric symptoms progressing to severe neurologic deficits, including encephalopathy, dyskinesias, language disturbances, and autonomic dysfunction [3,18]. This patient had similar neurologic findings as her encephalopathy progressed, and further review of her medical record revealed that she developed depressive symptoms and attempted suicide about 4 years before the encephalitis. MR imaging reported in NMDAR encephalitis is usually either normal or demonstrating T2-FLAIR hyperintensities, although the distribution and degree of these hyperintensities is highly variable [3]. The present case could be a NMDAR encephalitis in the presence of PFTC; however, without autoantibody detection (specifically to NR1 [18]), we are unable to determine with certainty if this is the diagnosis. Regardless, this case is a unique presentation of paraneoplastic encephalitis in the presence of PFTC.

**Conclusion**

Previous reports of paraneoplastic encephalitis in the presence of PFTC are classified as PCD, with MR imaging either unremarkable or demonstrating cerebellar atrophy. The MR imaging pattern in the present case of diffuse bilateral supratentorial T2-FLAIR white matter hyperintensities is therefore an unusual presentation of paraneoplastic encephalitis associated with PFTC. The clinical course had features similar to that of NMDAR encephalitis, suggesting that this could be a possible complication of PFTC. Further research is needed for stronger classification of paraneoplastic syndromes associated with this uncommon gynecologic malignancy.

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