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Case Report

Anti-*N*-methyl-D-aspartate receptor encephalitis in a patient with colon cancer

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1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is one of autoimmune disorders characterized by predominant neuropsychiatric symptoms such as a consciousness disturbance, memory disturbance, psychosis, hallucination, behavioral changes, and seizures. Anti-NMDAR encephalitis is the most common antibody-associated autoimmune encephalitis and generally affects young women with ovarian teratoma [1]. This encephalitis is rare in adult males, and only approximately 5% of affected adult male patients have a tumor, which is typically a testicular germ-cell tumor [1]. Herein, we report on a male patient with colon cancer who presented with anti-NMDAR encephalitis.

2. Case report

A 44-year-old male was referred to the emergency department due to abnormal behaviors and a confusion which lasted for 5 days. His family mentioned that he could not recognize them, and that he looked confused while making strange sentences such as an "alien told me something," "God talked to me," and so on. On the day of admission, he continued to exhibit odd behaviors. He put his underwear on his head to ease his stress and continuously grabbed the edges of objects within reach. He kept repeating himself and gave bizarre answers to questions. The patient had no recent symptoms of infection, including fever, chilling, and headaches. His past medical history included anorexia and a weight loss of 20 kg over 2 months. A prior esophagogastroduodenoscopy had revealed only mild gastritis.

His physical examination showed normal vital signs. He had no focal neurologic deficit upon neurologic examination. All blood analysis results were within a normal range. Cerebrospinal fluid (CSF) examination demonstrated a WBC count within normal limits of 2 cells / uL (100% lymphocytes), and an elevated protein level of 58 mg /dL (normal 15–45 mg /dL). Brain T2WI and FLAIR MRI images showed high signal intensities in the right mesial temporal lobes and insula, as well as a subtle enhancement of right mesial temporal lobe, suggesting limbic encephalitis (Fig. 1). EEG showed a generalized continuous slow pattern, predominantly on right frontotemporal area without epileptiform discharges.

Taking these findings together, we considered an autoimmune encephalopathy such as paraneoplastic encephalitis. The serum and CSF samples were collected for auto antibodies detection before the treatment. After comprehensive tumor screening, CT of the abdomen and pelvis showed an irregular wall thickening, suggesting cancer at the descending colon (Fig. 2). PET/CT scans also revealed an abnormal increase of fluorodeoxy glucose (FDG) uptake in the same area, but no evidence of metastasis. Steroid pulse therapy was initiated the next day and detailed autoimmune antibody examination were performed with CSF and serum.

His confusion, delusion, auditory hallucinations, and bizarre behavior continued after admission. The patient underwent a laparoscopic left hemicolectomy for tumor resection on hospital day 9. His mentality started to improve slowly from the second day after the surgery onward. He became able to communicate with other people, however

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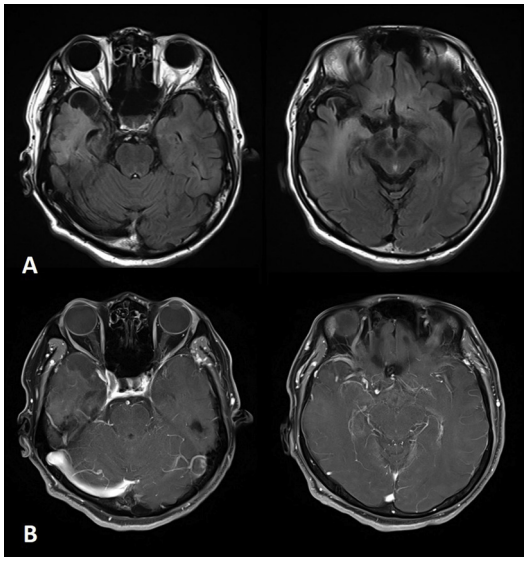

Fig. 1. Brain MRI images. Axial fluid-attenuated inversion-recovery (FLAIR) images show abnormal high signal intensities in right temporal lobe and insula (A). Subtle contrast enhancement is seen in right mesial temporal area on T1 contrast enhanced T1-weighted images (B).

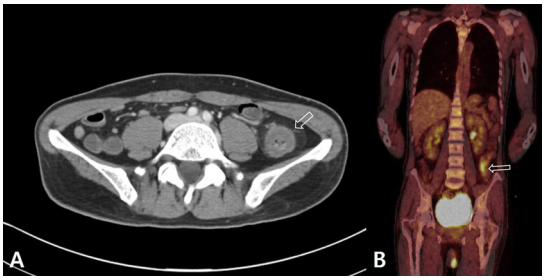

Fig. 2. CT abdomen & pelvis and PET-CT Images. CT study shows Irregular wall thickening (arrow) at the descending colon (A). PET-CT scan demonstrates focal uptake at the descending colon (arrow) without metastasis lesion in other body parts (B).

intermittent violent behaviors and recent memory problems remained.

Anti-NMDAR antibodies test results from the CSF and serum returned positive. Unfortunately, only qualitative assay was possible, therefore, exact antibodies titer was unknown. Antibodies to AMPA1, AMPA, LGI1, CASPR2, GABA-B, Hu, Yo, Ri, Ma2, CV2/CRMP5, and amphiphysin were all negative. The pathologic results of the colon showed adenocarcinoma (signet ring cell carcinoma) at the descending colon, with a depth of invasion into the visceral peritoneum (T4a) and six lymph node metastases in 48 lymph nodes (pT4aN2aM0, pStageIIIC).

He was discharged after one month of steroid therapy. He received postoperative adjuvant chemotherapy with Capecitabine at our outpatient clinic. Two years later at a follow-up visit, we found his neurologic deficit had fully recovered and that he has not had cancer recurrence as well. We also recommended a follow-up test for antibodies, but the patient and his family refused because antibodies measurement are very expensive. Therefore, we couldn't do additional testing.

3. Discussion

Antibodies of anti-NMDAR encephalitis target synaptic NMDARs in the brain. This encephalitis was first described by Dalmau et al. in 2006. Since then, many studies and case reports have been published on the disorder. The most prominent features of this encephalitis are the psychiatric manifestations and its incidence in young women with ovarian teratomas. A large cohort study revealed that only 19% of the patients were male, and most of them were very young (below 12 years) or were old [2]. More than half of the patients reported are known to have concurrent tumors. Therefore, it is sometimes presented as one of the paraneoplastic syndromes. On the contrary, male patients tend to not have tumors. Only several cases with testicular tumors or small-cell lung cancer were reported. This report, to the best of our knowledge, is the first documented case of anti-NMDAR encephalitis related with colon cancer.

As far as we know, only three cases of paraneoplastic encephalitis associated with colon neoplasm have been reported. Tsukamoto et al. reported on a woman with paraneoplastic neurologic disorder of antineuronal antibody caused by sigmoid colon cancer [3]. The symptom started as cerebellar dysfunction, and developed to memory impairment and seizures. Her intelligence improved after complete removal of the tumor, but the cerebellar ataxia remained unchanged. Another patient with a tumor in the sigmoid colon presented with abdominal pain accompanied by an altered mental status. Her serum test showed increased levels of the anti-yo antibody [4]. Despite undergoing an emergent subtotal colectomy without immunotherapy, she remained in a permanent vegetative state. Sio et al. reported on a 53-year-old man with limbic encephalitis and sensory neuropathy concurrent with colonic adenocarcinoma with hepatic metastasis. Initial symptoms were abnormal sensations in the eyes and visual disturbance, and progressed to include urinary retention, numbness from the back to the toes, and confusion. He recovered well after being treated with methylprednisolone and receiving a hemicolectomy. However, autoantibodies, including the anti-NMDA antibody, were detected in neither CSF nor serum.

In the first two cases, autoantibodies against either neuronal cytoplasm or nuclear proteins were detected. These classes of paraneoplastic encephalitis are different from anti-NMDA encephalitis in that they are mediated by cytotoxic T-cells and tend to have focal neurological deficits which can leave behind some permanent clinical sequelae. Although the last case had no specific autoantibody found, the clinical symptoms suggested that it was encephalitis, but with unrecognized anti-neuronal or anti-nuclear antibodies. Our case, on the other hand, had the distinct psychiatric symptoms of anti-NMDA encephalitis and autoantibodies attacking NMDA receptors on cell surface, rather than at the nucleus or cytoplasm.

NMDAR in central nerve system has been known to participate in the pathogenesis of visceral hypersensitivity and pain, such as in irritable bowel syndrome. Furthermore, glutamate receptor GRIN2D (also known as NMDAR2D), which is a component of the NMDA receptor calcium channel, was shown to have vessel-restricted expression in colorectal cancer. Vascular and neuronal cells have a common embryonic stem cell lineage, and these cells have many similar mechanisms which control their vascular or neuronal architecture [5]. GRIN2D is also widely expressed within the brain. Therefore, this relationship could be one of the possible reasons why our patient with colorectal cancer also had NMDAR related encephalitis.

Even though the initial symptoms of anti-NMDAR encephalitis are severe, tumor removal and immunotherapy can improve neurological symptoms in approximately 81% of the patients after a follow up period of 24 months [2]. In particular, tumor removal is considered to be important for the prompt improvement of symptoms and for decreasing the risk of relapses. A large observational study found two predictors of a good outcome, which were the avoidance of admission to ICU care and prompt immunotherapy combined with tumor removal. For our patient, we started steroid therapy immediately and removed the tumor before the antibodies against NMDAR were identified, resulting in full recovery.

4. Conclusion

The present case indicates that anti-NMDAR encephalitis can occur

with colon cancer. In cases with acute cognitive alteration and behavioral changes without infection signs, paraneoplastic encephalitis should be suspected and prompt testing to identify the autoimmune antibodies should be done. Also, tumor screening should be performed to find a causative lesion along with immune therapy. We recommend performing an abdominal/ pelvic CT scan to search not only for teratoma, but also for colon cancer, especially in male patients. If a causative lesion is found, the tumor must be removed immediately.

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