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Case Report

Isolated ZIC4 Antibodies and Autoimmune Encephalitis in a Microsatellite-Instability-High Metastatic Uterine Carcinosarcoma during Immune Checkpoint Inhibitor Treatment

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Abstract

Paraneoplastic neurological disorders (PNDs) are a group of neurological disorders associated with neoplasm and are relatively rare, accounting for less than 1% of cancer cases. We present the case of a 58-year-old woman who was diagnosed with metastatic uterine carcinosarcoma and received the programmed cell death protein-1 inhibitor Pembrolizumab. The patient developed agitation, hallucinations and short-term memory loss, followed by seizures and progressive unresponsiveness. Intensive care support and ventilation were required. Given the high suspicion for autoimmune encephalitis, paraneoplastic antibody testing was requested that was strongly positive for ZIC4 antibodies solely. The unresponsiveness of our patient after immunosuppressive treatment inferred poor prognosis, and after a few days, the patient died. To the best of our knowledge, this is the first case of PND with multifocal neurologic deficits in a patient with isolated ZIC4 antibodies associated with uterine carcinosarcoma. Immunotherapy has been shown to precipitate underlying autoimmune diseases, leading to a wide variety of neurological symptoms including encephalitis. Our case highlights the importance of evaluating serum/CSF onconeural antibodies in patients presenting with complex neurological symptoms to determine the possibility of paraneoplastic disorder.

Keywords: Paraneoplastic neurological disorders; ZIC4 antibodies; Uterine carcinosarcoma Autoimmune encephalitis; Microsatellite instability, Immune checkpoint inhibitor; Pembrolizumab

1. Introduction

Paraneoplastic neurological disorders (PNDs) are a group of neurological disorders associated with neoplasm. These rare disorders account for less than 1% of cancer cases [1]. PNDs have a wide variety of clinical features and are usually diagnosed by the exclusion of other possible conditions like structural, vascular or inflammatory lesions [2]. The most common clinical manifestations of PNDs include Lambert-Eaton myasthenic syndrome (LEMS), limbic encephalitis, subacute cerebellar ataxia, and paraneoplastic cerebellar disease (PCD). The onset of neurological symptoms is dependent on the type of the lesion. Subacute onset with progressive disability is usually characteristic of PNDs often seen in cerebellar type lesions, whereas certain conditions like LEMS are gradual in onset [3]. PNDs are immune-mediated and often characterized by the detection of paraneoplastic autoantibodies such as anti-Purkinje cell antibody 1 (anti–*PCA-1* or anti-*Yo*), nuclear antigen antibody (*ANNA-1* or anti-*Hu*), anti-*ZIC* antibody, anti-Tr in serum and cerebrospinal fluid. Case reports of PND have shown that onconeural antibody anti-*Yo* is often associated with ovarian or breast cancer, *ZIC4* is associated with small cell lung cancer, and anti-*Tr* is associated with Hodgkin's lymphoma [2, 4, 5]. In this article, we report a case of PND with uterine carcinosarcoma and *ZIC4* auto antibody, possibly related to immunotherapy for treating uterine carcinosarcoma.

2. Case Report

A 58-year-old woman had an episode of significant vaginal bleeding. Biopsy revealed uterine carcinosarcoma, and she was then referred to our department. Bilateral, multiple enlarged pelvic and para-aortic lymph nodes were detected through abdominal contrast enhanced computed tomographic scan. Thoracic imaging demonstrated multiple bilateral mediastinal and left subclavian lymph node blocks. The patient received 4 cycles of chemotherapy with the combination of Carboplatin-Paclitaxel with near complete response and, after discussion at our multidisciplinary tumor board, underwent total abdominal hysterectomy and salpingo-oophorectomy with concomitant pelvic lymph node dissection. Unfortunately, the patient developed progressive disease post-operatively and was treated with second-line chemotherapy with the combination of Adriamycin and Ifosfamide/MESNA with subsequent disease-related acute renal failure.

The patient showed signs of disease progression after the second-line chemotherapy. The patient's uterine tissue was screened for microsatellite instability (MSI) using the immunohistochemical expression of mismatch repair proteins and the results showed loss of MLH1 and PMS2 protein expression implying a high level of MSI (MSI-H). The patient received the programmed cell death protein-1 inhibitor Pembrolizumab at 200 mg flat dose. The patient achieved a radiographic partial response, but after the sixth cycle, the patient developed agitation, hallucinations and short-term memory loss, followed by seizures and progressive unresponsiveness. Intensive care support and ventilation were required. Magnetic resonance imaging of the brain demonstrated nonspecific T2 hyperintensities in the basal ganglia. Electroencephalogram revealed epileptic activity from the temporal lobe. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis (white blood cells, 13/μL; 60% lymphocytes, 23% monocytes,

17% neutrophils), an elevated protein level (75 mg/dL), a normal glucose level and IgG index, matched oligoclonal bands in the CSF and serum, and no evidence of bacterial or viral infection. Cytological analysis of CSF did not show any evidence of malignant neoplasm.

Neurological immune-related adverse events (irAEs) like encephalitis have been reported in 0.2-0.5 % of patients with Pembrolizumab [6]. Thus, it was decided to treat the patient with high-dose intravenous methylprednisolone sodium succinate, equivalent to 1000 mg/d of methylprednisolone for 5 days. The patient did not show any improvement and remained stuporous. Paraneoplastic antibody screening analysis with Western blot and immunohistochemistry (cerebellar section) was subsequently performed for the following 10 antibodies in the serum and CSF of the patient: anti-*Amphiphysin*, anti-*CV2*, anti-*Hu*, anti-*PNMA2*, anti-*Recoverin*, anti-*Ri*, anti-*SOX1*, anti-*Yo*, anti-*ZIC4* and anti-*Tr*. All were negative, except for anti-*ZIC4* for which a strongly positive intensity signal (84 out of a maximum score of 150) was detected. Her neurological status was unresponsive to steroid treatment. The patient then received 0.4 mg/kg/d of intravenous immunoglobulin for 5 days, but her status remained unchanged. Symptomatic therapy was directed against epilepsy and psychiatric symptoms. No serological follow-up examination was performed. Two weeks later, the patient, while still in intensive care unit, and despite confirming a further radiographic partial response to her cancer, experienced gradual functional decline and died.

3. Discussion

We describe a patient with metastatic cancer who developed PND during therapy with an immune checkpoint inhibitor. High levels of MSI (MSI-H) in the primary tumor uterine carcinosarcoma made this case feasible for immunotherapy as MSI-H tumors show upregulation of immune checkpoint inhibitory molecules such as PD-1, PDL-1, and CTLA4 [7]. FDA has approved the use of Pembrolizumab in MSI-H solid tumors that have progressed following initial therapy [8].

The patient developed neurological symptoms following immunotherapy, and the timing of the onset of neurologic symptoms was suggestive of neurological irAEs related to immunotherapy [9]. Nonetheless, it is difficult to establish a direct causal association between immune checkpoint blockade and autoimmune encephalitis. PNDs are caused by an immunological reaction mediated by the underlying neoplasm and not due to the direct effect of the neoplasm [10]. In our case, it is possible that the neurological irAEs of Pembrolizumab are presenting as PND. The symptoms of PNDs either present as a focal disease such as PCD or as multifocal, diffuse lesions such as brainstem encephalitis [3, 5].

The identification of *ZIC4* anti-neuronal antibodies (ANAs) with uterine carcinosarcoma has not been described, to our knowledge. In our case, serum detection of *ZIC4* antibodies is considered as a marker for PND. The presence of onconeural antibodies is characteristic for the diagnosis of PND; at the same time, their absence cannot rule out the possibility of PND [3]. *ZIC* is a family of genes with minor variations between the subtypes, encoding proteins containing zinc finger domains. These proteins are important in the development of cerebellum [4]. Patients who had *ZIC4* antibodies (without anti-*Hu* or anti-*Yo*) were more likely to develop cerebellar lesions like PCD with

multifocal neurologic deficits characteristic of encephalomyelitis [2]. Also, PCD can manifest without ANAs and showed better prognosis than patients with *Hu* antibodies. Paraneoplastic encephalomyelitis or the 'anti-*Hu* syndrome' is one of the most common PNDs manifesting as paraneoplastic limbic encephalitis (PLE) [5, 11]. PLE without ANAs and those with *Ma2* antibodies have better response to immunosuppressive therapy, whereas immunosuppressive therapy is usually not effective in PCD [5].

Several studies have reported the association of *ZIC4* antibodies with PND and small cell lung cancer (SCLC) [1, 4]. Case reports of PND with SCLC reported serum cross reactivity between *ZIC1*, *ZIC2*, and *ZIC4* subtypes, indicating the conservation of zinc finger domains. Preclinical studies have demonstrated *ZIC2* mRNA in SCLC cell lines. LEMS is the most common manifestation of PND with underlying SCLC. In our case, interestingly, antibodies typically associated with gynecological tumors (such as anti-*Yo*) were not detected. Thus, to our knowledge, this is the first reported case of paraneoplastic encephalitis in a patient with isolated *ZIC4* antibodies and uterine carcinosarcoma.

The unresponsiveness of our patient after immunosuppressive treatment implies poor prognosis. An additional important poor prognostic indicator is hospitalization of ANA-positive neurological patients in an intensive care unit during the clinical course. Immunotherapy has been shown to precipitate underlying autoimmune diseases leading to a wide variety of neurological symptoms including encephalitis. The proposed mechanisms of neurological irAEs are due to increased stimulation of antibodies, cytokine-mediated inflammation, and neuronal damage by activated T-cells [6, 11]. The onset of neurological symptoms following immunotherapy and the presence of paraneoplastic antibodies are highly suggestive of PND following immunotherapy.

Based on our findings, we propose that our patient with isolated *ZIC4* antibodies, which did not respond to immunosuppressive therapy with corticosteroids and intravenous immunoglobulin, had concurrent immune activation after immune checkpoint inhibitor therapy. This was further implied from the confirmed radiographic partial response of her cancer to Pembrolizumab. This leads to widespread neurologic dysfunction, further underscoring the pathophysiological scenario in our patient. However, this possibility of autoimmune reactions to *ZIC4* antibodies following Pembrolizumab needs to be substantiated with more evidence from future studies.

4. Conclusion

To the best of our knowledge, this is the first case of PND with multifocal neurologic deficits in a patient with isolated *ZIC4* antibodies associated with uterine carcinosarcoma. Our case highlights the importance of evaluating serum/CSF onconeural antibodies in patients presenting with complex neurological symptoms to determine the possibility of paraneoplastic disorder. Accurate and early clinical diagnosis of PND guides the treatment plan, which might lead to early stabilization and improvement of the neurological symptoms, and results in a better prognosis. Also, PNDs occur frequently with SCLC, so the possibility of PND should be evaluated in a patient with history of smoking and complex neurological disorders. With the continuing increase in the use of immune checkpoint inhibitors for different types of solid tumors, it becomes crucial to consider PND in the differential diagnosis of

neurological immune-related adverse events. Further studies are needed to understand the optimal duration of immunotherapy to achieve tumor response with minimal neurological toxicity.

5. Disclosure

The authors have no conflicts of interest to disclose.

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