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CASE REPORT

A Rare Case of Anti-Caspr2 Autoimmune Encephalitis Associated with a Testicular Mixed Germ Cell Tumor

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Abstract

Paraneoplastic limbic encephalitis (PLE) is a poorly understood condition, thought to be caused by the cross-reacting of tumor antibodies with neurons in the brain, resulting in neuropsychiatric sequelae, such as personality and behavioral changes, psychosis, memory loss, and seizures. Anti-contactin-associated protein-like 2 (CASPR2) antibodies can cause PLE in patients with particular tumors, which in most cases can be identified as thymoma, lung cancer, or endometrial cancer. Some case reports show rare instances with other tumors, such as throat or sigmoid carcinoma. We present the first reported case of CASPR2-antibody encephalitis secondary to a testicular mixed germ cell tumor.

Keywords: Paraneoplastic limbic encephalitis, Testicular tumor, Mixed germ cell tumor, Tumor, Mixed germ cell, Encephalitis, Anti-CASPR2

1. Introduction

Paraneoplastic limbic encephalitis (PLE) is an uncommon immunological syndrome linked with specific types of cancer, where auto-antibodies are produced and exhibit immune cross-reactivity between the tumor cells and components of the nervous system.[1] Anti-contactin-associated protein-like 2 (CASPR2) antibodies are a subtype of auto-antibodies that can cause PLE by targeting CASPR2 proteins, leading to brain and peripheral neuropathy by destroying axon potassium current channels.[2] The symptoms associated with CASPR2 autoimmunity include diffuse pain, muscle twitching, irregular heart rate or blood pressure, memory problems, seizures, difficulty walking, and movement disorders.[3] Anti-CASPR2 autoantibody disease is a rare condition typically affecting older males (>50 years old). It progresses gradually, which complicates its early detection.[4] Only about 20% of individuals with anti-CASPR2 encephalitis experience it as a paraneoplastic syndrome associated with an underlying solid tumor commonly identified as thymoma, endometrial cancer, or lung cancer.[4] Cited cases show rare instances of PLE in squamous cell carcinoma of the throat and sigmoid carcinoma with positive anti-CASPR2 antibodies.[4,5] To our knowledge, this is the first case of CASPR2-associated PLE in the setting of a mixed germ cell tumor.

2. Case presentation

A 26-year-old male with no significant past medical history presented to the emergency department with the chief complaint of headache and abdominal pain. The patient reported four days of a worsening headache and abdominal pain that included nausea, vomiting, and diarrhea. He also reported testicular

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swelling but denied any hematuria or dysuria. Upon initial examination of the patient, there was concern for intermittent bizarre behavior along with paranoia, and the patient was alert to name and time. However neurological exam was unremarkable, there was no nuchal rigidity, or loss of sensation or weakness. Further physical exam showed an enlarged left scrotum with point tenderness and a negative transilllumination test. Initial labs were unremarkable except for an aspartate aminotransferase (AST) of 173 U/L and lactate dehydrogenase (LDH) of 667 U/L. An initial computed tomography (CT) scan of the abdomen and pelvis showed a scrotal mass measuring 9.4 × 0.4 cm along with left periaortic lymphadenopathy. These findings were suspicious for primary testicular neoplasm with lymphatic metastatic spread. The initial CT with contrast scan of the brain was negative for any hemorrhage, mass effect, or specific signs of acute infarct. A follow-up testicular ultrasound showed a large heterogeneous midline scrotal mass that appeared to arise from the inferior aspect of the testicles; this measured 7.9 × 7.4 × 10.9 cm. Oncology, psychiatry, neurology, and urology were all consulted.

Neurology started the patient on intravenous (IV) steroids along with IVIG and ordered a lumbar puncture (LP) to evaluate for suspected paraneoplastic limbic encephalitis. The patient's mentation did not improve while on IV steroids and IVIG; these medications were discontinued. Results of the LP came back negative for infection, including herpes virus, mumps virus, West Nile virus, Saint Louis encephalitis, Eastern equine encephalitis, and California encephalitis (Table 1). The patient was then tested for a series of autoantibodies due to the suspicion of paraneoplastic limbic encephalitis. Cerebral spinal fluid (CSF) samples were sent to test for Anti-MA2 antibodies and returned negative. Serum and CSF were sent for the Mayo paraneoplastic panel, and the results were positive only for the anti-CASPR2 antibody (Table 2).

Table 1. CSF results from LP.

CSF	Variable	Reference Range
Volume	16 mL	
Appearance	Clear	Clear
Color	Colorless	Colorless
WBC	<0.003 × 103	0.000–0.005
RBC	<0.002 × 106	0.000
Lymphocytes	Test not performed	40–80
Polynuclear WBC	Test not performed	0
Glucose	71	45–70
Total Protein	24	15–45

Table 2. Paraneoplastic autoantibody panel showing positive CASPR2-IgG in serum, tested by a cell-based assay (CBA).

Test	Result
CASPR 2 IgG Ab (CBA)	Positive
LGI1 IgG Ab (CBA)	Negative
Paraneoplastic Eval Com	Positive
Neuronal Nuc Ab Type 3	Negative
AGNA-1	Negative
Anti-Hu Antibody	Negative
Anti-RI Antibody	Negative
Anti-Yo Antibody	Negative
Purkinje Cell (PCA-2)	Negative
Purkinje Cytoplas Type Tr	Negative
CRMP-5 IgG Antibody	Negative

For the testicular mass, the patient was planned for an orchiectomy. The pathology for the testicular mass confirmed a mixed germ cell tumor (90% seminoma, 10% teratoma). After removing the testicular mass, the patient's mentation initially only slightly improved. Upon discharge, the patient was alert and oriented to person, place, and time. The patient also did not have any more bizarre behavior. The patient was instructed to follow up outpatient for chemotherapy after inpatient port placement was successfully achieved. He was also advised to follow up at the outpatient neurology clinic if he was not responding to chemotherapy treatment. At that time, plasma exchange therapy and rituximab would be considered for treatment.

3. Discussion

The significance of CASPR2 emerges as a pivotal player in the neurological symphony. CASPR2 is a membrane-bound protein ubiquitous throughout the central and peripheral nervous systems and orchestrates a myriad of neurodevelopmental processes, including the localization of voltage-gated potassium channels crucial for propagating neuronal action potentials. Moreover, CASPR2's role extends to synaptogenesis and the maintenance of synaptic integrity, underscoring its indispensability in neurological function. However, in the presence of anti-CASPR2 antibodies, the delicate equilibrium of neuronal homeostasis is disrupted, precipitating a cascade of neurologic manifestations.[2]

The pathogenesis of neurologic paraneoplastic disorders, such as PLE, is rooted in immune-mediated cross-reactivity between tumor cells and the nervous system. This immunological interplay is a poignant reminder of the intricate symbiosis between the immune system and tumorigenesis.[6] It is worth highlighting the protean nature of neuropsychiatric manifestations often precedes the overt clinical detection of malignancy in a substantial majority of cases, presenting providers with a

diagnostic problem of unearthing occult malignancies.[1] This problem was not present in our case, as our patient also had scrotal swelling on presentation, which was quickly discerned as a testicular tumor with ultrasonography and later confirmed to be a mixed germ cell tumor of the left testes after postoperative histopathological analysis of specimens from the resected testes.

Conventionally, imaging modalities and electroencephalography (EEG) serve as stalwart tools in unraveling the enigma of paraneoplastic neurological symptoms. Despite the diligent utilization of EEG showing normal results both in awake and sleep states and no concerning epileptic activity or seizures and magnetic resonance imaging (MRI) with and without contrast showing no acute infarct, abnormal enhancement, hemorrhage, or mass effect in our case, the results proved elusive, failing to yield a conclusive diagnosis. It was not until the emergence of a paraneoplastic serum panel bearing the signature of CASPR2 antibodies that the diagnostic fog began to lift, ultimately culminating in the identification of paraneoplastic limbic encephalitis secondary to a testicular mixed germ cell tumor.[7]

While anti-CASPR2 antibodies are less frequently associated with underlying malignancy, their presence bears significant prognostic implications. The incidence of anti-CASPR2 encephalitis varies depending on the related cancer type.[7] Notably, the malignancies commonly linked to anti-CASPR2 encephalitis include thymoma and lung cancer.[6] There are no previously documented cases of anti-CASPR2 encephalitis associated with testicular tumors. Conversely, anti-Ma2/Ta antibody is strongly associated with PLE in testicular tumors, and the presence of the antibody is almost always associated with testicular germ cell tumors.[8] However, our patient's paraneoplastic panel results were negative for anti-Ma2 antibodies and were unexpectedly positive for only anti-CASPR2 antibodies.

Regarding therapeutic intervention, the cornerstone lies in quelling the hyperactive immune response implicated in the pathogenesis of anti-CASPR2 encephalitis. A multifaceted armamentarium comprising surgery, chemotherapy, and immunosuppressive agents such as steroids, cyclophosphamide, intravenous immunoglobulin (IVIG), and plasma exchange forms the backbone of treatment.[9] However, the variability in patient responses and the evolving nature of the disease pose formidable challenges, precluding the formulation of a definitive treatment protocol. Our patient, initially treated with steroids and IVIG, did not show any improvement in symptoms. However, after undergoing a left orchiectomy and starting chemotherapy, his neuropsychiatric symptoms significantly improved. Our patient will continue chemotherapy and monitoring and will be started on rituximab if necessary later.

Ultimately, the crux of therapeutic success hinges upon early detection and intervention, facilitating the expeditious eradication of the underlying tumor and antigenic source. By addressing the root cause of the disease, clinicians can optimize the prospects of neurological recovery and enhance overall prognosis. As our understanding of anti-CASPR2 encephalitis continues to evolve, ongoing research endeavors on the various presentations of this disease promise to elucidate novel therapeutic modalities to mitigate the devastating sequelae of this enigmatic condition.

4. Conclusion

Considering PLE as part of the differential diagnosis early on in ambiguous clinical scenarios with neuropsychiatric manifestations can increase the chances of positive outcomes both in terms of tumor detection and treating and preserving neurological health. Since the discovery of CASPR2 in 2011, testing for antibodies has significantly contributed to the diagnosis and treatment of numerous patients, including those who might have gone undiagnosed or received incorrect diagnoses without this biomarker.[10] Reports of paraneoplastic syndromes with positive anti-CASPR2 antibodies in different types of tumors are expanding. It is important to share findings of atypical cases to contribute to further knowledge in the evolving field of neuronal antibody-associated diseases.

Conflicts of interest

The above-listed authors, Dr. Haddadin, Dr. Aboujamra, Dr. Kapadia, Dr. Yoon, Dr. Zahlan, Dr. Buczek, and Dr. Riggio, have no conflicts of interest to declare.

Ethics section

We certify that this manuscript represents an accurate account of the research conducted and discusses its significance objectively. This work is original and has not been submitted elsewhere. All sources and prior work are appropriately cited, and the manuscript is not under consideration by any other journal. The corresponding author confirms that all contributors who meet the criteria for authorship are listed and have approved the final manuscript. Contributors not meeting authorship criteria are acknowledged appropriately.

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References

1. Almedallah D, Alsaffar G, Al-Shabeeb G, Baarmah A, Nassim E. *Paraneoplastic limbic encephalitis associated with testicular mixed germ cell tumor*. vol. 5. Neuroimmunology and Neuroinflammation; 2018:48. https://doi.org/10.20517/2347-8659.2018.55.
2. Wu L, Cai F, Zhuo Z, et al. CASPR2 antibody associated neurological syndromes in children. *Sci Rep*. 2023 Feb 6;13(1):2073. https://doi.org/10.1038/s41598-023-28268-x. PMID: 36747031; PMCID: PMC9902610.
3. Shivaram S, Nagappa M, Seshagiri DV, et al. Clinical profile and treatment response in patients with CASPR2 antibody-associated neurological disease. *Ann Indian Acad Neurol*. 2021 Mar-Apr;24(2):178–185. https://doi.org/10.4103/aian.AIAN_574_20. Epub 2021 Mar 31. PMID: 34220060; PMCID: PMC8232480.
4. Goovaerts S, Gens R, Seynaeve L, Engelborghs S, Vandervorst F. Anti-CASPR2 antibody-associated limbic encephalitis in a patient with a squamous cell carcinoma of the throat. *Acta Neurol Belg*. 2023 Jun;123(3):1205–1207. https://doi.org/10.1007/s13760-023-02272-4. Epub 2023 Apr 29. PMID: 37119470; PMCID: PMC10148571.
5. van Sonderen A, Ariño H, Petit-Pedrol M, et al. The clinical spectrum of Caspr2 antibody-associated disease. *Neurology*. 2016 Aug 2;87(5):521–528. https://doi.org/10.1212/WNL.0000000000002917. Epub 2016 Jul 1. PMID: 27371488; PMCID: PMC4970662.
6. Bataduwaarachchi VR, Tissera N. Paraneoplastic limbic encephalitis with associated hypothalamitis mimicking a hyperdense hypothalamic tumor: a case report. *BMC Med Imag*. 2016 Jan 18;16:8. https://doi.org/10.1186/s12880-016-0113-4. PMID: 26782815; PMCID: PMC4716643.
7. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain*. 2000 Jul;123(Pt 7):1481–1494. https://doi.org/10.1093/brain/123.7.1481. PMID: 10869059.
8. Chen C, Nadeem A, Karir B, Shohet HH, Babagbemi K. Paraneoplastic limbic encephalitis as initial presentation of testicular neoplasm: a case report. *Clin Imag*. 2021 Aug;76:61–64. https://doi.org/10.1016/j.clinimag.2021.01.032. Epub 2021 Feb 3. PMID: 33556762.
9. Newman MP, Blum S, Wong RCW, et al. Autoimmune encephalitis. *Intern Med J*. 2016;46:148–157. https://doi.org/10.1111/imj.12974.
10. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol*. 2011 Feb;69(2):303–311. https://doi.org/10.1002/ana.22297. PMID: 21387375; PMCID: PMC3059252.