A malignancy phantom: a rare clinical case report of metastatic renal cell carcinoma with no evidence of a primary lesion presenting as cerebellar ataxia

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ABSTRACT

Background: Anti-Ma2 antibody-associated paraneoplastic syndrome (PNS) usually presents as limbic encephalitis in the context of testicular tumors. We report a rare case of anti-Ma2 positive PNS with deviation from the classic scenario, thus expanding the phenotype of anti-ma2 associated PNS.

Case Presentation: This is a 53-year-old male who presented with dizziness and visual changes and was later diagnosed with anti-Ma2 antibody-positive cerebellar ataxia. Further workup revealed retroperitoneal lymphadenopathy which, using biopsy, was identified as metastatic clear cell renal cell carcinoma. However, imaging did not reveal a primary renal lesion.

Conclusion: Physicians should be aware of non-classic presentations of PNSs, especially given that they commonly precede and point towards an underlying, many times undiagnosed, malignancy.

Keywords: Para-neoplastic syndrome, renal-cell carcinoma, cerebellar ataxia, tumor regression, case report.

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Background

Paraneoplastic syndromes (PNSs) are a group of clinical disorders involving non-metastatic systemic effects that accompany malignant tumors. Tumor-induced PNSs have been reported in about one-third of patients with renal cell carcinoma (RCC), with the classical triad of flank pain, hematuria, and palpable mass observed in only 15% of cases [1]. Given that RCC is one of the most lethal cancers worldwide, the ability of clinicians to recognize rare presentations is essential to ensure timely diagnosis and treatment of these patients [2].

Case Presentation

We present the case of a 53-year-old gentleman with a past medical history of hypertension, type II diabetes mellitus, and dyslipidemia who was completely independent when he visited the emergency room (ER) with complaints of dizziness and visual changes. Brain imaging and basic blood work at the time were unrevealing. The patient was discharged from the ER and referred to a neurologist. His physical examination at the time was overall normal, except for lateral nystagmus with a fast component towards the direction of the gaze and bilateral vertical nystagmus with a fast component directed upwards. He had normal sensory and motor function, intact extraocular movements and visual fields, and had normal gait. An initial workup was unrevealing, and the patient was diagnosed with atypical peripheral vestibulopathy with referral to occupational therapy. However, patient's symptoms continued to worsen until he became wheelchair-bound within less than a year due to severe ataxia. Eventually, upon further workup, the patient was found to have positive Ma2/Ta positive antibodies which was strongly suggestive of an anti-Ma2-associated PNS. As a result, the patient was referred to an oncologist and computed tomography imaging of his chest, abdomen, and pelvis revealed large retroperitoneal adenopathy, in addition to several spinal lesions. He also underwent a positron emission tomography scan which shows disease in the chest, skeleton, along with the bulky retroperitoneal adenopathy. Biopsy of the retroperitoneal lymph nodes indicated clear cell RCC. Immunohistochemical staining was positive for EMA, Pan-Keratin, PAX8, and RCC and negative for CD45 and S-100. Also, the following genomic alterations were detected: CDKN2A p16INK4a, MCL1 amplification, loss of exons 2-3 in PARK2, and microsatellite stability.

The patient was started on pazopanib (a tyrosine kinase inhibitor) at 800 mg daily, in addition to steroids. The dose was adjusted as he developed thrombocytopenia and

transaminitis after 2 weeks of therapy. He was also started on monthly intravenous immunoglobulin. Patient initially had significant improvement in his symptoms, and he was able to walk again with the help of a walker. Repeat imaging revealed improvement in areas of involvement. Unfortunately, his symptoms recurred 6 months later. He then went on to develop recurrent episodes of large volume aspirations and subsequent pneumonia requiring multiple hospital admissions, before he developed a myocardial infarction culminating in his death.

Discussion

Ataxia is defined as impaired coordination and is a common symptom of several conditions. Defining the time frame within which ataxia develops can help narrow the differential diagnosis. In subacute ataxia (occurring over weeks), as was the case in our patient, the differential diagnosis includes atypical infections, chronic exposure to toxins or medications, alcohol abuse, vitamin deficiencies, autoimmune disorders, systemic metabolic disorders, and neoplasms [3]. With unrevealing workup, further testing for neuro-oncology antibodies (anti-Yo, anti-Ri, anti-Hu, anti-CV2, anti-amphiphysin, and anti-Ma2/TA) is appropriate.

PNSs are a diverse group of disorders that can affect any part of the nervous system in association with an underlying malignancy but are not the result of metastases or direct invasion. While PNS is a diagnosis of exclusion, the presence of specific anti-neuronal antibodies strongly supports this diagnosis and demands cancer screening. Since 2004, PNS's have been classified as classical vs non-classical according to the consensus of PNS experts. Classical cases, such as limbic encephalitis and Lambert-Eaton syndrome, have typical presentations and are easily recognized by the neurologist, whereas non-classical presentations, as the name implies, have diverse clinical presentations and can easily be missed, resulting in delay of crucial malignancy screening [4,5].

It is estimated that PNS's occur in ~0.01% of all cancer patients, most commonly in association with small-cell lung cancer, ovarian cancer, and breast cancer [5]. In RCC, more than 15 different PNSs have been described, with endocrine PNSs being the most common. PNS's in RCC patients have only been reported in a few cases of limbic encephalitis, cerebellar ataxia, bilateral phrenic nerve paralysis, stiff-person syndrome, and amyotrophic lateral sclerosis [6]. Ma2 antibodies in the context of RCC are extremely rare. In males younger than 45 years, Ma2 positivity is usually associated with testicular germ cell tumors, whereas in older men and women, it is usually associated with lung cancer and less frequently other solid tumors [4]. Also, there are only a few reported cases in the literature in which metastatic RCC was detected without evidence of a primary renal tumor [7-9]. In such cases, as in ours, immunohistochemistry and mutational analyses play a vital role in making the diagnosis. Negative S100 and CD45 rule out melanomas and lymphoid tumors, respectively. The specific markers for RCC are currently PAX2, PAX8, RCC marker, CD10, and a combination of vimentin and CK. RCC marker and CD10 have been shown to be useful for the diagnosis of metastatic RCC, however, their sensitivity is lower than that of PAX-2 and PAX-8 [10]. The PARK2 is usually downregulated in clear type RCC and has been linked to poor prognosis [11].

Spontaneous regression of tumors is exceedingly rare but is a well-known phenomenon and has been reported in all types of human cancers, most commonly RCC, lymphoma, leukemia, melanoma, and neuroblastoma [12]. Spontaneous regression of primary renal tumors is estimated to occur in ~1% of cases, but the percentage is slightly higher in a metastatic lesion after nephrectomy [13]. Possible mechanisms have been postulated and include auto-infarction or immunological and humoral mechanisms [14].

Conclusion

To the best of our knowledge, this is the first reported case of metastatic RCC with no evidence of a primary renal lesion which presented as Ma2-positive cerebellar ataxia. Neurologists and general practitioners should be aware of non-classical PNS's and their presentation, as they almost always antedate an underlying malignancy. In addition, our case highlights the diagnostic importance of immunohistochemistry and genetic mutation analyses in differentiating ambiguous cases.

What is new?

Anti-Ma2 positive PNS usually presents as limbic encephalitis in the context of testicular tumors. The authors report a rare case of anti-Ma2 positive PNS with deviation from the classic scenario, thus expanding the phenotype of anti-ma2 associated PNS. To the best of authors knowledge, this is the first reported case of metastatic RCC without evidence of a primary renal lesion presenting as Ma2-positive cerebellar ataxia.

Conflict of interest

Authors declare no conflict of interest related to this publication.

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Consent for publication

Written informed consent to publish this case was obtained from the patient's next of kin.

Ethical approval

No ethical approval from our institution is required for the publication of an anonymous case report.

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