Paraneoplastic Cerebellar Degeneration Associated with Anti-CV2/CRMP5 Antibodies in Ovarian Cancer: Case Report and Review of Literature.

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Case report

Keywords: Paraneoplastic neurological syndrome, Paraneoplastic cerebellar degeneration, ovarian cancer, onconeural antibodies, anti-CV2/CRMP5

Posted Date: August 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-789310/v1>

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Abstract

Background

Paraneoplastic neurological syndromes are rare presentations of an underlying oncological disease and even more unusual they can present during an oncological disease. These syndromes more likely present in small cell lung carcinomas and thymomas, but in less than 1% of the cases gynecological neoplasms have shown this paraneoplastic presentation, such as the case presented. Even though not completely understood yet, acknowledging the pathophysiology is essential for management, relate other types of neoplasms and explain its clinical presentation. We present a patient with an underlying gynecological cancer, that during her disease developed a paraneoplastic neurological syndrome with an unusual autoantibody (anti-CV2/CRMP5) mediating the disease.

Case Presentation

A 62-yo female diagnosed with ovarian cancer who in the course of her disease develops neurological symptoms associated with cerebellar degeneration. After ruling out differential diagnoses such as metastases, a neurological paraneoplastic syndrome was suspected and studied, in which anti-CV2/CRMP5 were positive. Putting together her clinical presentation, radiological features, auto-antibody positivity on CSF related with paraneoplastic neurological syndromes and an underlying oncological disease, cerebellar degeneration as a paraneoplastic syndrome was diagnosed.

Conclusion

The pathophysiology of neurological paraneoplastic syndromes is not fully understood; therefore, its diagnosis and management are complex. Diagnosis is based on clinical presentation and specific antibodies associated. Unfortunately, patients have a bad prognosis and diminished quality of life, therefore its management needs a multidisciplinary approach. It is important to mention that the presentation of paraneoplastic neurological syndromes do not mandatory appear before the diagnosis of cancer, multiple cases have been reported in which patients with an underlying oncological disease develop these syndromes. As medical oncologists and neurologists we must consider and study these syndromes as a possible etiology in cases with an underlying cancer who develop neurological symptoms in the course of their disease after ruling out differential diagnoses such as brain metastases.

Introduction

Paraneoplastic neurological syndromes (PNS) are a presentation of signs and symptoms mediated by an immune response associated with an underlying neoplasm and antineuronal antibodies. These syndromes commonly occur as the first sign of an underlying neoplasm leading to its detection and rarely occur during an oncologic disease. Its epidemiology is not well known but recent studies report an incidence of 3 cases per million person-years and a population-based study reported an incidence of 1/100,000 person years, a prevalence of 4/100,000, and an average of 68 years of age (1, 2). Tumors

associated commonly express neuroendocrine proteins such as small cell lung carcinoma (SLCL) (3–5%), being also the one commonly associated with other paraneoplastic syndromes (3, 4). Other cancers include, thymomas (15–20%), B-cells neoplasms (3–10%) and < 1% of cases gynecological neoplasms (5). The most common PNS is limbic encephalitis in 31% of cases, followed by paraneoplastic cerebellar degeneration (PCD) with 28% and encephalomyelitis with 20%. PNS presentation in gynecological tumors are extremely rare, understanding the pathophysiology and presentation is essential to guide management.

Case Presentation

A 62-year-old female presented in June 2018 with abdominal pain, increased abdominal circumference, 5-kg weight loss in the last month and asthenia. The diagnostic workup included a pelvic ultrasound, CT scan and CA-125 levels, which confirmed the presence of ascites, a pelvic mass with malignant characteristics in the left ovary and CA-125 levels of 2,400 U/ml (Fig. 1). A diagnostic laparoscopy with biopsy was performed, which confirmed a stage IIIC ovarian cancer, no germline BRCA mutation.

A total of six cycles of neoadjuvant chemotherapy with paclitaxel plus carboplatin and bevacizumab, were given. The patient showed partial response with CA-125 levels lowering to 120 U/ml, and underwent debulking surgery in January 2019, achieving suboptimal cytoreduction, with 3-month post-surgical CA-125 levels of 372 U/ml. She continued treatment with bevacizumab as maintenance therapy. Follow up test with PET-CT showed persistent disease in the right paracolic recesses, positive bilateral para-internal iliac lymph nodes, CA-125 levels of 180 U/ml and partial response by Response Evaluation Criteria on Solid Tumors (RECIST) criteria.

Two months after her last checkup the patient developed dysarthria, dizziness, right lateropulsion, tinnitus and gait instability, causing multiple falls from standing height. A brain MRI was performed, showing cortico-subcortical atrophy and PET-CT continued showing a partial response by RECIST (Figs. 2 and 3). Having a stable oncological disease on PET-CT and brain MRI findings unable to explain the sudden neurological symptoms, a PNS was suspected.

Workup for diagnosis included corticospinal fluid (CSF) analysis for multiple onconeural and neuronal cell surface antibodies including anti-Zic 4, anti-NMDAR-D, anti-mGluR1, anti-PCA-1, anti-PCA-2, anti-TR, delta-notch-like, ANNA-1, ANNA-2, ANNA-3 and anti-CV2. The only positive antibody found was anti-CV2. Based on these antibodies, the characteristic cerebellar symptoms and her known oncological disease, we diagnosed the patient with paraneoplastic cerebellar degeneration secondary to an ovarian carcinoma.

Oncology and Neurology medical services proposed continuing oncological treatment, with the goal of maintaining a stable disease and reducing neurological symptoms. Also, treatment was focused on PNS management with high-dose methylprednisolone, plasmapheresis and rehabilitation.

Discussion And Review Of Literature

Pathophysiology:

PNS pathophysiology is immune mediated, these syndromes damage the nervous system via antineuronal antibodies via onconeural antibodies or neuronal cell surface antibodies. Antibody positivity isn't always present, in fact 60% of PNS affecting the central nervous system (CNS) and 20% affecting peripheral nervous system are antibody positive (6, 7). However, the presence of antibodies helps make a more specific diagnosis, identify the course and prognosis.

Onconeural antibodies indicate that the disorder is paraneoplastic and mediate damage via cytotoxic T-cells, making neuronal damage almost always irreversible (8–10). PNS that present these types of antibodies have the worse prognosis. Some examples include anti-Hu, anti-CV2/CRMP5, anti-Yo, anti-Ri, anti-Tr and anti-Ma. Contrastingly, neuronal surface antibodies cannot differentiate between cases that are paraneoplastic or not and the mediated damage is via antibodies targeting specific antigens in the CNS (11, 12). Examples include anti-NMDAR, anti-AMPA, anti-GABA, anti-mGluR1, anti-mGluR5 and anti-Zic4.

Paraneoplastic cerebellar degeneration (PCD):

Generally, presents before the diagnosis of a neoplasm, and rarely during an oncological disease. The tumors commonly involved are ovarian, breast, SCLC and Hodgkin's lymphoma (13, 14). PCD is predominantly associated with anti-Yo antibodies being the main antibody mediating the disease, especially in gynecological neoplasms (15). Other antibodies associated include anti-Ri antibodies in gynecological neoplasms and SCLC, anti-Tr antibodies in Hodgkin's lymphoma and anti CV2/CRMP5 in thymoma and SCLC (16, 17). All previously mentioned antibodies are onconeural and therefore have high syndrome specificity. Comparatively, anti-mGluR1 and anti-Zic4 antibodies have been associated with PCD in Hodgkin's lymphoma and SCLC respectively, these two are partly characterized paraneoplastic antibodies (18).

- Clinical presentation and diagnosis

PCD begins with dizziness, positional vertigo, and nausea. Shortly after, patients develop subacute onset of symmetric truncal and limb ataxia, dysarthria, and nystagmus; CSF cytology shows signs of an inflammatory process (19). Imaging studies in the acute phase show a normal MRI or increased T2 signal within the cerebellar hemispheres and FDG-PET may show signs of cerebellar hyper-metabolism (20, 21). MRI in the chronic phase will show T2 hyperintensity improvement, cerebellar atrophy and FDG-PET shows cerebellar hypometabolism (20).

Based on the Diagnostic Criteria for PNS by the Paraneoplastic Neurological Syndrome Euronetwork, our case is considered a definite diagnosis which includes a classical presentation, a tumor present and onconeural antibody positivity (7). The absence of onconeural antibodies does not rule out a PNS, but

their presence helps the diagnosis. Differential diagnosis to keep in mind include, cerebellar metastases, chronic degenerative diseases, Creutzfeldt-Jakob disease, infections, leptomeningeal disease, vitamin deficiencies and alcohol damage.

- Prognosis and management

PCD progresses fast, usually causing irreversible damage and poor prognosis since it is associated with onconeural antibodies, which cause neuronal damage and loss of Purkinje cells via cytotoxic T-cells leading to pancerebellar dysfunction. Comparing disability between different antibodies, those with anti-Tr antibodies have less disability compared with anti-Yo antibodies. Due to its poor prognosis, treatment is based on removing the primary tumor if possible and managing symptoms with rehabilitation, with the goal of offering a better life quality.

The use of corticosteroids, intravenous immunoglobulin, cyclophosphamide, or tacrolimus have not shown significant improvement in most cases (22–24). These agents must be a personalized treatment with a multidisciplinary group including neuro-oncologists and associated physicians treating the primary neoplasm. Symptomatic treatment is focused on rehabilitation, and some reports have shown improvement with clonazepam (25, 26). Immunotherapy treatment uses corticosteroids, intravenous immunoglobulin, and/or cyclophosphamide. A commonly used method is I.V methylprednisolone given 1gr daily for 3–5 days and prednisone 70mg daily (26). Contrastingly, immunoglobulin G and cyclophosphamide help by reducing T cell proliferation suppressing proinflammatory cytokines (27, 28). Plasma exchange patients might not respond as expected because it doesn't remove immunoglobulins from the CSF (29, 30). Unfortunately, most patients become wheelchair bound. Thus, new therapies focused on mediating immune response at the CNS level are needed.

Patients with anti-Yo, anti-Hu and anti-CV2/CRMP5 are the most refractory to treatment and have the worst prognosis. PCD with anti-Hu have an average survival of 7 months, followed by anti-Yo antibodies with 13 months, anti-Ri with 69 months and anti-Tr with 113 months. Survival and prognosis also depend on location and stage of the cancer.

Anti-CV2/CRMP5 antibody and PCD

Antibodies against collapsin-response-mediator-protein-5 (CRMP5 or CV2) a 66kDa cytoplasmic proteins member of the CRMP family participates in dendrite and axon formation and regeneration (31, 32, 33). CV2/CRMP5 is involved in brain development via the semaphorin-3A signaling, is mainly located in dendrites of pyramidal neurons, hippocampal pyramidal cells, Purkinje cells and oligodendrocytes (34–36). Anti-CV2/CRMP5 is mainly associated with PCD. Other syndromes include encephalomyelitis, optic neuritis, uveo-retinal symptoms and myasthenic syndromes (37). The most common tumors associated with these antibodies are SCLC and thymoma. However, cases in prostate, head and neck and uterine cancer have been reported (38–40). A summary of PCD with anti-CV2/CRMP5 cases and an underlying cancer, including the case presented, are represented on Table 1. In this table, cases with thymoma or SCLC are excluded since the association between anti-CV2/CRMP5 and PCD is well documented. Survival

of patients with anti-CV2/CRMP5 antibodies compared with anti-Hu was longer despite the type of tumor (34).

Table 1

PCD and anti-CV2 reported cases with an underlying cancer diagnosis (SCLC and thymoma not included):

Age	Gender	Type of tumor	Reference
62	Female	High grade ovarian serous carcinoma	Juárez VW, J.
70	Female	Uterine sarcoma.	Rogemond V and Honnorat J et. al (31,34).
72	Female	Uterine sarcoma.	Rogemond V and Honnorat J et. al (31,34).
60	Female	Squamous cell carcinoma of the tongue.	Saloustros E et. al (39).
80	Male	Prostate adenocarcinoma.	Aliprandi A et. al (40).
50	Female	Ovarian adenocarcinoma	Hezer S (41).

Conclusion

PNS are unfortunate clinical situations, where patients having an oncological disease, develop significant clinical deterioration, mostly irreversible.

In addition to having little evidence of PNS associated with gynecological tumors, it is relevant to present this case because it developed during a previously diagnosed cancer, while responding to oncological treatment and the uncommon relationship with anti-CV2 antibodies. A multidisciplinary team for management is essential, as well as ruling out differential diagnoses, mainly metastases but not losing sight of possible chronic degenerative diseases.

It is of great importance to share clinical cases, because these patients have unmet needs. Sharing information can be relevant to change the approach, outcome and improve their quality of life.

Abbreviations

PNS: Paraneoplastic neurological syndromes.

SCLC: Small cell lung carcinoma.

PCD: Paraneoplastic cerebellar degeneration.

RECIST: Response Evaluation Criteria on Solid Tumors.

FDG-PET: fluorodeoxyglucose-PET.

Declarations

1. Ethics approval and consent to participate.

2. Consent for publication.

Written, informed consent for publication of this report has been obtained from the patient. All identifying information has been removed to preserve confidentiality.

3. Availability of data and material.

Not applicable.

4. Competing interests.

Not applicable.

5. Funding.

Not applicable / non received.

6. Author's contributions.

JJJVW helped on conception, design, writing and proofreading of the manuscript.

KGHG helped on translation and writing of the manuscript.

JRRC helped on writing of the manuscript.

MEOC helped on a neurological approach of the case and review of medical file.

VGM and ACM helped on proofreading, review of medical file, obtaining informed consent and provision of imaging.

7. Acknowledgements.

We would like to thank our patient and her family for allowing us to use her medical information for their contribution to this article.

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Figures

Figure 1

Abdomen and pelvis CT scan at the time of diagnosis, showed peritoneal disease “omental cake”.

Figure 2

Brain MRI cortico-subcortical atrophy, no evidence of brain metastasis or leptomeningeal disease.

Figure 3

PET-CT continued showing partial response by RECIST criteria when developed sudden neurological symptoms.