Gynecologic Oncology Reports 35 (2021) 100695

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Paraneoplastic cerebellar degeneration associated with anti-Yo antibodies in an ovarian cancer case: A case report

Sandra Deac [a,*], Mihaela Marioara Stana [a], Andrei Dan Havasi [a], Calin Cainap [a,b], Anca-Raluca Popita [c], Ana Maria Bordeianu [d], Simona Cainap [e], Madalina Bota [e], Ovidiu Vasile Bochis [a]

[a] Oncology Institute "Ion Chiricuta", Medical Oncology Department, Cluj Napoca, Romania
[b] Department of Oncology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania
[c] Oncology Institute "Ion Chiricuta", Radiology and Medical Imaging Department, Cluj Napoca, Romania
[d] RoNEURO Institute, Cluj-Napoca, Romania
[e] Department of Mother and Child, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania

ARTICLE INFO

Keywords:
Paraneoplastic cerebellar degeneration
Paraneoplastic syndromes
Anti-Yo antibodies
Ovarian cancer
Gynecological cancer

ABSTRACT

Paraneoplastic neurologic syndromes (PNS) are a rare heterogeneous group of disorders associated with malignancy that can result in significant functional impairment. One syndrome in particular, paraneoplastic cerebellar degeneration (PCD), may be severely disabling. PCD is a rare neurological syndrome, associated with active or subclinical cancer, characterized by acute or subacute onset cerebellar ataxia due to tumor-induced autoimmunity against cerebellar antigens. Treatment of paraneoplastic syndromes is generally unsatisfactory, but early diagnosis and treatment of PCD, which includes neurological treatment, immunotherapy and oncological treatment of associated malignancy, may improve the neurological prognosis. We reported the case of a 59-year-old woman who presented PCD as the first sign of ovarian cancer. Laboratory investigations showed the presence of anti-Yo antibodies in the serum. The brain MRI revealed specific modifications for PCD. After oncological treatment, intravenous immunoglobulin therapy and corticosteroid therapy, the oncological response was satisfactory, but no improvement of the neurologic symptoms was achieved.

1. Introduction

Paraneoplastic neurologic syndromes (PNS) are a group of neurologic conditions that affect 0.5–1% of all cancer patients. Paraneoplastic cerebellar degeneration (PCD) is a rare and severely debilitating immune-mediated neurological syndrome that occurs in less than 1% of all cancer patients. PCD can be associated with any cancer, but the most commonly associated are gynecological and breast cancer, small cell lung cancer and Hodgkin lymphoma (Vogrig et al., 2019; Kannoth, 2012). To reach PCD diagnosis there is need to undergo clinical, laboratory and imagistic evaluations. Clinically, PCD is characterized by acute or subacute development of severe pancerebellar dysfunction. It is typically beginning with dizziness, nausea and gait unsteadiness progressing to ataxia, diplopia, often dysarthria, dysphagia and nystagmus (Dalmau and Rosenfeld, 2008; Vedeler et al., 2006; Mitoma et al., 2016). Serologically, multiple antibodies are highly specific for PCD, of which the most common are Anti-Yo antibodies [Table1]. Anti-Yo–mediated PCD tends to occur predominantly in women around the age of 60 and is mostly associated with gynecologic malignancy (ovary, uterus and breast). The anti-Yo antibody is the most common serological marker in PCD associated with ovarian cancer, although only 50% of these patients have positive serological findings (Kannoth, 2012; Shams'ili et al., 2003).

Early diagnosis and treatment of PCD are essential because any delay can result in progression and irreversible neurological damage (Kannoth, 2012). The PCD treatment includes immunoglobulins, corticosteroids, and chemotherapy in association with supportive therapy.

2. Case report

A 59-year-old, Caucasian, menopausal woman consulted a neurologist complaining of vertigo, dizziness, postural balance disorders, gait instability with a tendency to fall, bilateral plantar paresthesia and intermittent postural tremor of the cephalic extremity with intentional

* Corresponding author.

https://doi.org/10.1016/j.gore.2020.100695
Received 12 October 2020; Received in revised form 6 December 2020; Accepted 27 December 2020
Available online 31 December 2020

Table1
Main autoantibodies reported in paraneoplastic cerebellar degeneration (Dalmau and Rosenfeld, 2008; Yshii et al., 2020).

Autoantibodies	Incidence in PCD	Main associated tumors
Anti-Yo(anti-PCA1)	38–50%	Ovarian tumor Breast cancer Other gynecological cancers Other adenocarcinomas
Anti-Hu	18–21%	SCLC Neuroendocrine tumors
Anti-CV2/CRMP5	13–27%	SCLC 5 Thymoma Colon cancer Breast cancer
Anti-Ma2	5%	Testicular germ cell tumors NSCLC NHL Cervical cancer
Anti-Tr	14%	Hodgkin disease
Anti-amphiphysin	17%	Breast cancer SCLC
Anti-Ri	12–32%	Breast cancer Gynecological cancer SCLC
Anti-GABAbR	unknown	SCLC Neuroendocrine tumor
Anti-Recoverin	unknown	SCLC Breast cancer
AGNA/Anti-SOX1	43–50%	Lung cancer
Anti-PCA2	unknown	SCLC
Anti-GluR1	unknown	SCLC
Anti-Zic4	12–29%	SCLC
Anti-Titin	80%	Thymoma

character and accentuated by emotions. Also, the patient was complaining of sad mood, insomnia, frontal-occipital headache with intermittent tension character, generalized pain in the spine and in the right abdominal flank, plus a significant weight loss of 7 kg in 2 months. Clinical onset was 4 months before presentation, accentuated in the last 2 months.

The patient's medical history, family and social history were insignificant for oncological pathology. Regarding the physiological history, the patient had menarche at the age of 14, G7P2 and menopause at the age of 45.

During the first hospitalization in the neurology department, several investigations were performed. Biological examinations showed mild hepatic cytolysis syndrome 2xULN.

The ECG, chest X-ray and native CT brain revealed no pathological changes. Carotid Doppler US revealed mild carotid atheromatosis and the EEG indicated diffuse irritant path. An abdominal US was performed, showing several round masses of 1.7–2 cm, hypoechoic, located paraaortic, in the hepatic hilum and between the stomach and the pancreas.

The patient was directed to a gastroenterology service where several investigations were carried out, as presented below.

Abdominal CECT scan revealed multiple lymphadenopathies located peritoneal, retroperitoneal and both on the lesser and greater curvatures of the stomach (max. of 2.5 cm in size). Also, there were discovered lymphadenopathies with tendence towards confluence in the splenic and superior polar spine and one supradiaphragmatic lymphadenopathy of 2.5 cm located in the left cardiophrenic angle. An upper digestive EUS with FNA was performed, showing one subepithelial lesion covered by the normal mucosa on the posterior antral wall, hypoechoic, homogeneous, hypervascularized of 1.7 cm. There were also identified multiple lymphadenopathies hypervascularized, located in the hepatic hilum, peripancreatic and perigastric of 2–3 cm in size. Gynecological examination with transvaginal US found out a mass of 43/32 mm, with vascular signal and intermediate echogenicity, located in the left ovary. The histopathological result of the biopsy was a high-grade ovarian serous carcinoma.

The patient consulted our oncology service with the result of the histopathological examination to establish the therapeutic strategy. Considering the neurological symptoms and the fact that the patient's condition worsened, we redirected the patient to the neurology service for a thorough investigation of the neurological syndrome in the context of oncological pathology.

The patient returned to the ER due to ongoing symptoms. In addition, she had severe headache with motor impairment to the upper and lower limbs, orthostatic and impossible gait, bilateral upper arm paresthesia, intolerance to light and noise, hearing loss of the right ear, severe dysarthria, diplopia and vomiting related to head mobilization. The patient was admitted to neurology department with suspected PNS based on clinical and imaging findings. The head CT result was without brain mass lesions or signs of stroke. Laboratory serum tests showed mild hepatic cytolysis syndrome (2xULN) and elevated IgG (1.3xULN). The CSF analysis results indicated pleocytosis, elevated level of glucose and proteins. The electromyogram and electroneurography revealed acute polyneuropathic asymmetric demyelination distal and proximal with secondary axonal damage. Serum antibody panel testing was positive for anti-Yo antibodies and negative for anti-Ri, anti-Hu, anti-Rcoverin, SOX1, Titin, Amphiphysin, CV2 and PNMA2.

Based on the subacute presentation of severe pancerebellar syndrome, clinical symptomatology and the paraclinical results, with ongoing ovarian carcinoma, the diagnosis of PCD with acute polyradiculoneuritis was established and the treatment with intravenous immunoglobulins (IV IgG) was decided. The therapeutic strategy was based on corticosteroid therapy and 5 days of intravenous immunoglobulins as a continuous infusion according to the next regimen: 2 g/kg of body weight with total dose calculated to 65 kg equal with 130 g administered in 5 days (day 1 total dose was 27.5 g with 25 ml/h, days 2–4 dose 25 g with 50 ml/h and day 5, 27.5 g with 100 ml/h).

After obtaining a slight improvement of the neurological symptomatology, the patient was directed to the oncology service to establish the oncological therapeutic strategy. Laboratory blood tests showed grade I normocytic normochromic anemia, minimal hepatic cytolysis syndrome (1.3xULN), CA125 tumor marker elevated (CA125 = 13,025 U/mL), and Anti-Yo antibodies detected positive.

Brain CEMRI revealed: Mild atrophy of the cerebellar hemispheres and vermis [Fig. 1a]. Signal changes (hyposignal in T2) were identified in the medial portions of the cerebellar hemispheres, slightly more pronounced in the right, suggestive for iron deposits [Fig. 1b]. Large fourth ventricle. A few scattered nonenhancing increased in T2 signal abnormalities in frontal lobes [Fig. 1c]. No acute vascular lesions or intracerebral lesions were detected.

BRCA1 and 2 germline mutations tests were performed showing BRCA1 germline mutation positive.

Considering the histopathological result correlated with the results of imaging examinations, with the presence of multiple centimetric peritoneal and retroperitoneal lymphadenopathies, we interpreted the case as being a high grade ovarian serous carcinoma stage IV FIGO. We decided to administer chemotherapy Taxol-Carboplatin(TC) protocol, weekly, after the informed consent signed by the patient was obtained.

After administration of chemotherapy 3 cycles TC Q1W regimen, Paclitaxel 80 mg/mp total dose 110 mg and Carboplatin 2 AUC total dose 200 mg, serum lab testing for CA125 was 4209 U/mL vs. 13,025 U/mL and Anti-Yo antibodies detected negative. After a good tolerance at weekly chemotherapy regimen, TC Q3W regimen was decided. After administration of 3 cycles TCQ3W Paclitaxel 175 mg/mp total dose 250 mg and Carboplatin 5 AUC total dose 500 mg, tumor marker CA125 value decreased significantly(CA125 = 247.8 U/mL), and a slightly improvement of symptomatology was achieved (disappearance of diplopia and vomiting), but neurological impairment worsened, causing the patient's death [Fig. 2].

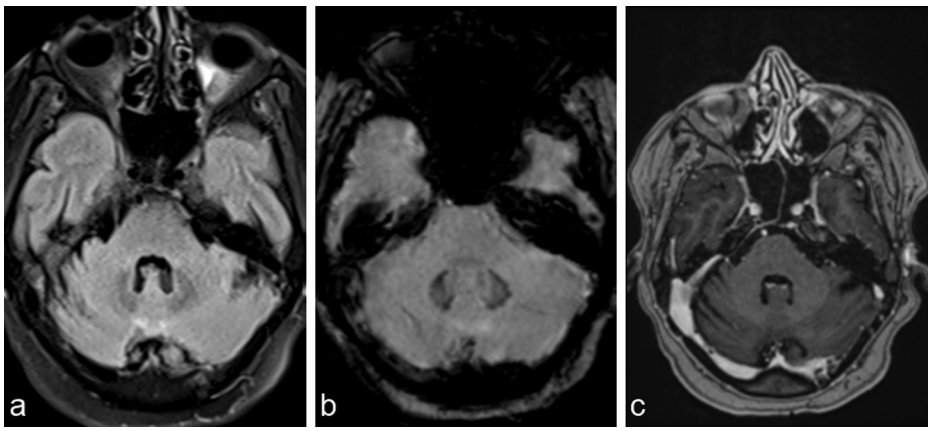

Fig. 1. Brain MRI with contrast. **(a)** Axial FLAIR - cerebellar atrophy. **(b)** Axial SWI - susceptibility artifact related to iron deposition in the median parts of the cerebellar hemispheres. **(c)** Sag T1-weighted + C - without cerebellar or dural enhancement.

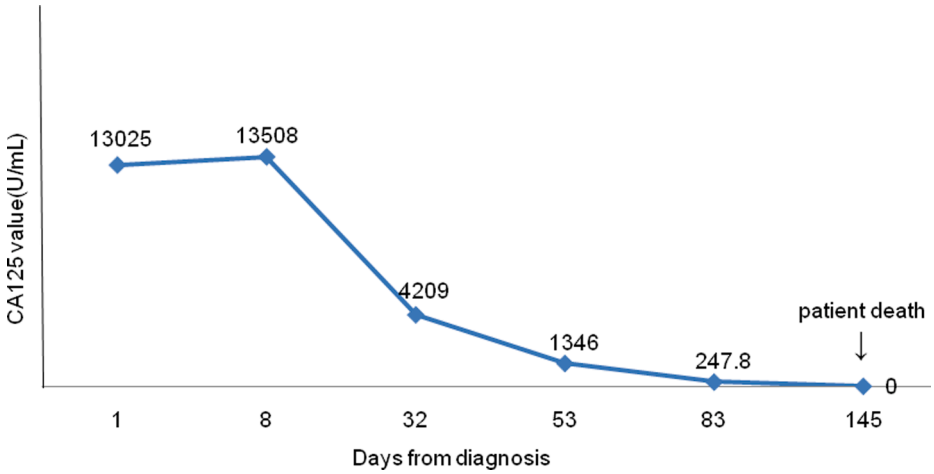

Fig. 2. CA125 Tumor's marker evolution.

3. Discussion

In cancer patients, the neurologic manifestations are mostly the consequence of direct tumor invasion of the nervous system or metastases. Other common causes of neurologic symptoms include infections, vascular or metabolic disorders and neurotoxicity from chemotherapy. In between 0.5 and 1% of cancer patients, an autoimmune response is developed that targets normal neuronal tissues, called PNS (Vogrig et al., 2019; Kannoth, 2012; Vedeler et al., 2006). The associated tumors express modified ectopic neuronal protein, called onconeural antigens, which may trigger the immune response against constitutional proteins at the neuronal level with the presence of highly specific antineuronal antibodies in the serum and cerebrospinal fluid (CSF). The absence of such antibodies cannot rule out the diagnosis of PCD (Dalmau and Rosenfeld, 2008). At least 12 onconeural antibodies are highly specific for PCD, including anti-Yo (PCA-1), anti-PCA2, anti-Hu, anti-Tr, anti-Ri, anti- mGluR1, anti-Zic4, anti-Ma, anti-CV2/CRMP5, anti-VGCC and anti-ANNA3 (Dalmau and Rosenfeld, 2008; Kannoth, 2012; Shams'ili et al., 2003) [Table1]. Our patient presented intense positive anti-Yo antibodies, but negative anti: -amphiphysin, -CV2, -PNMA2, -Ri, -Hu, -Recoverin, -SOX1, and -Titin serum antibodies.

From the clinical point of view, in the case of our patient, PCD has evolved over several months. In the literature, clinically, PCD is characterized by development of severe pancerebellar dysfunction. Onset is usually gradually (weeks/months), although acute forms have been rarely described (Vogrig et al., 2019).

Certain signs of degenerative neurological disease can also be identified by modern imaging techniques. Brain MRI findings appear normal early in the course of PCD but can show cerebellar atrophy in advanced cases (Vedeler et al., 2006). In our case, CT brain imaging did not found pathological points, instead the brain MRI showed cerebellar atrophy, large fourth ventricle and signal abnormalities in frontal lobes.

Given the small number of published cases worldwide of PCD associated with onconeural antibodies in solid tumors (<300 cases), an exact treatment protocol for PCD has not been established yet (Shams'ili et al., 2003; Russo et al., 2013; McKeon et al., 2011). It is known that in a small number of cases, the neurological symptoms of PCD have partially responded to administration of intravenous immunoglobulin therapy and the treatment of primary tumor, in combination with supportive therapy. There are no evidence-based recommendations available regarding the immunosuppressive therapy but it includes steroids, IV IgG, plasmapheresis, cyclophosphamide, azathioprine and rituximab (Kannoth, 2012). In the case we presented, after intravenous immunoglobulin administration in combination with corticosteroid therapy, supportive therapy and chemotherapy protocol TC, the anti-tumor therapeutic response was very good, proven by the decrease of the tumor marker. Although the presence of oncological positive response, the neurological benefit was still small, only managing to obtain a slightly neurological improvement, without stabilizing the progression of neurological degenerative disease.

Although several case reports of PCD are published, we consider the case presented by us to be interesting because a young woman who

developed subacute cerebellar degeneration, a disease that requires rapid diagnosis and urgent treatment, has been shown to have the main cause an ovarian cancer. The diagnosis of PCD was supported by the presence of anti-Yo antibodies and the presence of brain MRI changes. The response to chemotherapy was favorable, which leads us to think that if the gynecological tumor had been diagnosed earlier, the neurological prognosis would have been better and the survival time longer."

4. Conclusion

PCD, a rare pathology, should be suspected in cancer patients with degenerative neurological symptoms, especially in cases of women with gynecological cancers.

In the case we presented, PCD was the first clinical manifestation of the underlying cancer and the diagnosis was established by clinical manifestation of cerebellar ataxia, anti-Yo antibodies raised in the serum and the brain imaging with cerebellar atrophy.

Even if the diagnosis was delayed, after the clinical picture of cerebellar ataxia was quite advanced, treatment with immunoglobulins, corticosteroids and chemotherapy in association with supportive therapy brought an anti-tumor response, with slight improvement of the symptoms but with progression of degenerative neurological disease.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Sandra Deac: Writing - original draft, Writing - review & editing. **Mihaela Marioara Stana:** Writing - review & editing. **Andrei Dan Havasi:** Writing - review & editing. **Cainap Calin:** Writing - review & editing. **Anca-Raluca Popita:** . **Ana Maria Bordeianu:** Writing - review & editing. **Simona Cainap:** Writing - review & editing. **Madalina Bota:** Writing - review & editing. **Ovidiu Vasile Bochis:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2020.100695.

References

Dalmau, J., Rosenfeld, M.R., 2008. Paraneoplastic syndromes of the CNS. Lancet Neurol. 7 (4), 327–340. https://doi.org/10.1016/S1474-4422(08)70060-7.

Kannoth, S., 2012. Paraneoplastic neurologic syndrome: A practical approach. Ann. Indian Acad. Neurol. 15 (1), 6–12. https://doi.org/10.4103/0972-2327.93267.

McKeon, A., Tracy, J.A., Pittock, S.J., Parisi, J.E., Klein, C.J., Lennon, V.A., 2011. Purkinje Cell Cytoplasmic Autoantibody Type 1 Accompaniments: The Cerebellum and Beyond. Arch. Neurol. 68 (10), 1282–1289. https://doi.org/10.1001/archneurol.2011.128.

Mitoma, H., Adhikari, K., Aeschlimann, D., Chattopadhyay, P., Hadjivassiliou, M., Hampe, C.S., et al., 2016. Consensus paper: neuroimmune mechanisms of cerebellar ataxias. Cerebellum 15, 213–232.

Russo, A.E., Scalone, S., Leonardi, G.C., Scalisi, A., Giorda, G., Sorio, R., 2013. Paraneoplastic cerebellar degeneration associated with ovarian cancer. Oncol. Lett. 5 (2), 681–683. https://doi.org/10.3892/ol.2012.1016.

Shams'ili, S., Grefkens, J., de Leeuw, B., van den Bent, M., Hooijkaas, H., van der Holt, B., Vecht, C., Sillevis Smitt, P., 2003 Jun. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain 126 (Pt 6), 1409–1418. https://doi.org/10.1093/brain/awg133. PMID: 12764061.

Vedeler, C.A., Antoine, J.C., Giometto, B., Graus, F., Grisold, W., Hart, I.K., Honnorat, J., Sillevis Smitt, P.A., Verschuuren, J.J., Voltz, R., 2006 Jul. Paraneoplastic Neurological Syndrome Euronetwork. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur. J. Neurol. 13 (7), 682–690. https://doi.org/10.1111/j.1468-1331.2006.01266.x. PMID: 16834698.

Vogrig, A., Bernardini, A., Gigli, G.L., Corazza, E., Marini, A., Segatti, S., Fabris, M., Honnorat, J., Valente, M., 2019. Stroke-Like Presentation of Paraneoplastic Cerebellar Degeneration: a Single-Center Experience and Review of the Literature. Cerebellum 18 (5), 976–982. https://doi.org/10.1007/s12311-019-01075-9.

Yshii, L., Bost, C., Liblau, R., 2020. Immunological Bases of Paraneoplastic Cerebellar Degeneration and Therapeutic Implications. Front. Immunol. 11, 991. https://doi.org/10.3389/fimmu.2020.00991.