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Review article

Paraneoplastic cerebellar degeneration in platinum-responsive endometrial cancer: A case report and review of literature

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ABSTRACT

Paraneoplastic cerebellar ataxia is a rare immune-induced, non-metastatic neurologic syndrome, most frequently associated with gynecological cancers, which carries an abysmal prognosis. We report the case of a patient with advanced-stage uterine cancer, who developed severe pancerebellar ataxia, while in partial remission, after the completion of 3 cycles of neoadjuvant platinum-based chemotherapy. Swift initiation of immunosuppressive therapy with corticosteroids combined with plasmapheresis did not result in significant clinical benefit. Early recognition of this debilitating condition and standardization of its treatment strategy are prerequisites for both improved survival outcomes and quality of life in these patients. Further studies are warranted to clarify the immune-stimulating impact of effective cytotoxic chemotherapy and the occurence of autoimmune paraneoplastic neurological syndromes.

1. Introduction

Paraneoplastic neurological syndromes (PNS) affect less than 1% of oncological patients and represent neurological manifestations related to immune-mediated responses caused by the expression of onconeural antigens from the underlying solid tumor (Höftberger et al. 2015; Braik et al. 2010). PNS usually precede the diagnosis of neoplasia or its recurrence, whereas, treatment of the underlying malignancy is considered to be the pillar of their management (Hammack et al., 1990; Blaes et al., 1999). Paraneoplastic cerebellar ataxia (PCA), associated with Purkinje cell cytoplasmic antibody type 1 (PCA1) or Anti-Yo, is the most common among PNS (O'Brien et al., 1995), usually observed in gynecological cancers (Yan et al., 2018).

Herein, we present a rare case of an elderly female who developed rapidly progressive PCA during the course of effective platinum-based chemotherapy for locally advanced uterine carcinoma of serous histology. Despite the early introduction of both high dose corticosteroids and plasmapheresis her neurological symptoms deteriorated and rendered her bedridden.

2. Case presentation

A 70-year-old, ex-smoker female, of Caucasian origin, with multiple comorbidities, presented with postmenopausal vaginal bleeding of 1-year duration. An endometrial biopsy was performed and pathology revealed uterine serous carcinoma showing immunohistochemical expression of p16, estrogen receptor (ER), and WT1, absence of human epidermal growth factor receptor 2 (HER2)/neu overexpression, and wild-type pattern of p53 expression. Immunohistochemical analysis was also indicative of extensive lymphocytic infiltration (Fig. 1). By that time no further molecular analysis of the neoplasm was performed and was classified as serous uterine carcinoma based on the histopathological analysis only.

A subsequent abdominal magnetic resonance imaging (MRI)

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demonstrated the presence of a 6 × 4 cm bulky mass that distended the uterine cavity and enlarged iliac, femoral, and inguinal lymph nodes (Fig. 2A); thus, tumor was classified as FIGO stage IVB. The patient was not considered as candidate for surgical intervention and neoadjuvant chemotherapy with three-weekly regimen of carboplatin and paclitaxel was commenced.

Post 1st cycle of chemotherapy patient presented with symmetrical numbness in the lower extremities resulting in gait abnormality, attributed to taxane-associated neuropathy. Due to this adverse event dose of paclitaxel was initially reduced and subsequently permanently discontinued. After the completion of 3 cycles of treatment, the patient developed a rapidly progressive cerebellar syndrome with blurry vision, horizontal nystagmus, truncal ataxia, and pronounced dysarthria. Nevertheless, computed tomography (CT) scan of the chest and abdomen revealed partial response of the disease (Fig. 2B).

MRI of the brain excluded metastatic disease, structural abnormalities, ischemia, and hematomas (Fig. 3a), whereas cerebrospinal fluid (CSF) analysis showed mild lymphocytic pleocytosis (10 cells per mm^3), mild elevation of protein and glucose levels, and negative results on both cytology and culture. The presence of a positive titer of anti-Yo antibodies both in serum and CSF confirmed the diagnosis of PCA.

Within 15 days after the onset of neurological symptoms, intravenous followed by oral dexamethasone (24 mg daily at first followed by slow tapering schedule) was commenced. She also underwent three sessions of plasmapheresis without any clinical improvement.

Despite the early initiation of treatment, including intravenous corticosteroids and plasmapheresis, her neurological symptoms relentlessly progressed and no further therapeutic approaches had been attempted. Due to her disability, our patient relocated to her hometown whereas she received best supportive care. She eventually died 11 months after the diagnosis of her endometrial cancer and 8 months after the diagnosis of PCA, presumably due to liver metastatic disease after a brief hospitalization for abdominal pain.

3. Discussion

Direct invasion of the nervous system by malignancy, metastatic disease, cancer treatment-related toxicity, infections, metabolic and vascular disorders are among the common causes of neurological complications in cancer patients (Höftberger et al., 2015). PNS represent a rather rare, heterogeneous group of neurological syndromes characterized by cancer-stimulated immune responses, directed by specific antibodies, which cross-react with neural tissue, causing its damage (Braik et al., 2010). PCA, which accounts for 25% of PNS, is associated with breast, ovarian, and lung cancer, exhibits a strong preference for middle-aged female patients, and usually antedates tumor occurrence (Yan et al., 2018; Tanriverdi et al., 2013; Rojas et al., 2000). To the best of our knowledge, there have been published only 14 cases of PCA associated with endometrial cancer so far (Hammack et al., 1990; Peterson et al., 1992; Tsaukamoto et al., 1989; Brock et al., 2001; Lie et al., 2016; Karpathiou et al., 2016; Erez et al., 2007; Henry et al., 2005; Johns et al., 1999; Giometto et al., 1997; Petit et al., 1997; Rana et al., 2012), whilst our case is the first to be reported in a patient with chemotherapy-responsive uterine cancer.

Almost 50% of PCA cases correlate with Anti-Yo antibody, of IgG1 subtype (Amyes et al., 2001), which is synthesized in the central nervous system of the patients as an autoimmune response against an ectopically expressed neuronal antigen, the Yo antigen (Posner et al., 1989). This antigen is a cytoplasmic protein, called cerebellar degeneration-related protein 2 (CDR2), normally expressed in the Purkinje cells (PCs) of the cerebellum, but also in brain stem, spermatogonia, and ectopically in gynecological and breast tumors (Amyes et al., 2001; Aboul-Enein et al., 2008; Darnell et al., 2000).

It has been observed that CDR2 protein sequesters the transcription factor c-Myc, downregulating its activity, whereas the presence of anti-Yo antibodies disrupt this interaction, increasing c-Myc activity, thus leading to extensive PC apoptosis (Albert et al., 2000; Okano et al., 1999). It has also been postulated that the internalization of CDR2/CDR2-like (CDR2L) antibodies by Purkinje cells could lead to cells' impaired calcium homeostasis, thus neuronal destruction and excessive cell death (Schubert et al., 2014). Recently, Small et al. demonstrated that each PCA patient with anti-Yo antibodies carried at least one genetic alteration in CDR2 gene, suggesting that these somatic mutations in tumor cells might be sufficient to elicit an autoimmune response (Small et al., 2018).

Yet, the administration of anti-Yo antibodies in preclinical animal models may not always result in PCA (Verschuuren et al., 1996; Graus et al., 1991), whereas, both CDR2 and CDR2L antigens are widely expressed in ovarian cancers (Raspotnig et al., 2017; Darnell and Albert, 2000), hence seem to be inadequate to trigger autoimmunity. Accumulating evidence suggests that auto-reactive, cytotoxic, CDR2-specific CD8 T lymphocytes not only intensely infiltrate into gynecological tumors of anti-Yo positive patients with PCA (Vialatte de Pémille et al., 2018) but also appear to represent the final mediators of neuronal loss (Albert et al., 1998; Yshii et al., 2016). Indeed, the immunohistochemistry in our patient's diagnostic biopsy revealed prominent tumor lymphocytic infiltration.

Anti-Yo antibody was found to be present in some patients with paraneoplastic cerebellar degeneration (PCD), but it was very early documented that there is no evidence of its causal contribution in Purkinje cell loss (Tanaka and Tanaka, 1999). Instead, the interaction between peptide and Human Leucocyte Antigens (HLA) molecules had been demonstrated. Specifically, the HLA-class I restricted cytotoxic T cell (CTL) activity against autologous fibroblasts was shown, using a

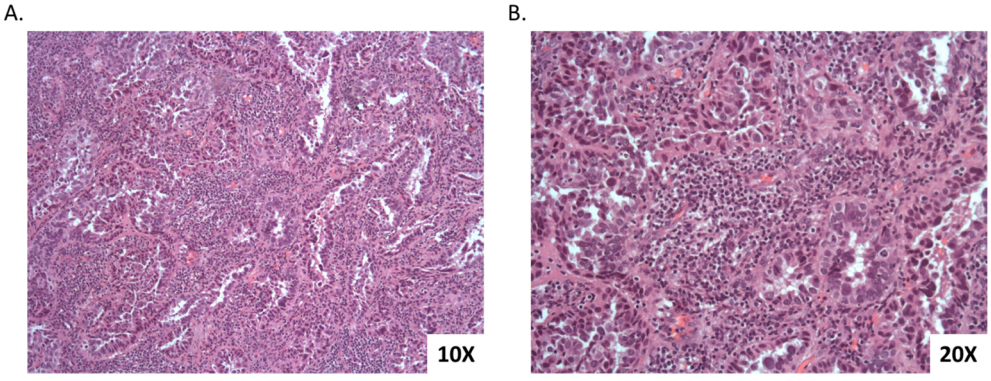

Fig. 1. Histopathological analysis of endometrial sampling tissue with 10× (A) and 20× (B) magnifications, respectively, indicative of extensive lymphocytic infiltration, immunohistochemical expression of p16, estrogen receptor (ER), and WT1, absence of human epidermal growth factor receptor 2 (HER2)/neu overexpression, and wild-type pattern of p53 expression.

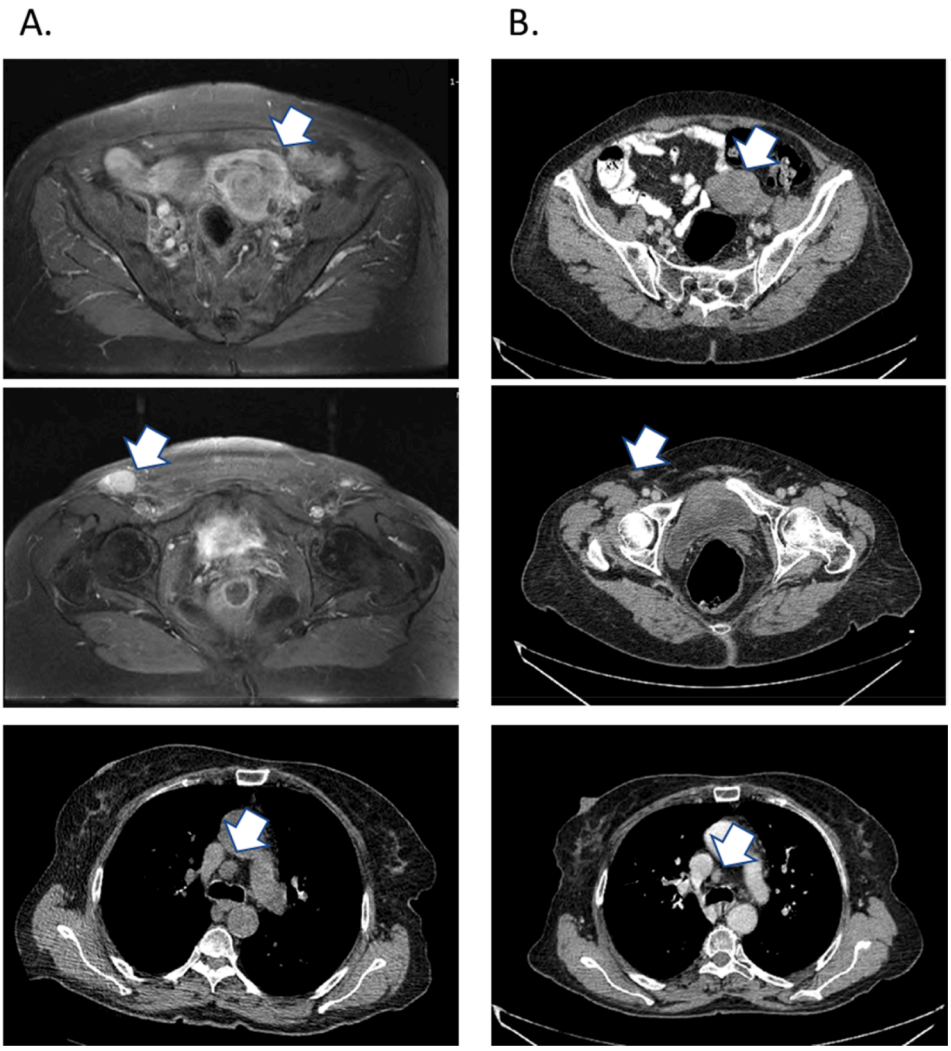

Fig. 2. Pre-treatment abdominal magnetic resonance imaging (MRI) (A) and post-treatment abdominal computed tomography (B), indicative of partial response.

peptide of the Yo protein with the HLA A24-specific allele. It was the first evidence of the presence of CTL reacting with a peptide of Yo protein in the peripheral venous blood from a patient with PCD (Tanaka and Tanaka, 1999). Furthermore, in another research paper, a complex HLA association in paraneoplastic cerebellar ataxia with anti-Yo antibodies was found, with protective or risk effect, mainly of the Class II domain (Hillary et al., 2018). This targeted HLA-driven autoimmunity was also documented in another case of a patient having multiple autoimmune disorders and malignancies, including gynecological tumors (Anagnostouli et al., 2014).

Clinically, PCA is usually characterized by pancerebellar dysfunction (ataxia, diplopia, nystagmus, dysphagia, dysarthria) with subacute onset and rapid progression (Dalmau and Rosenfeld, 2008). Dedicated neuroimaging techniques of the cerebellum, including CT scan, MRI, and or functional MRI (fMRI), are usually normal, especially at the initial stages of the disease, thus of limited value. Yet, fluorodeoxyglucose positron emission tomography (FDG-PET) could reveal hypermetabolism due to the inflammatory responses at first, followed by abnormal decreased metabolism related to the undergoing neuronal cell degeneration (Dalmau and Rosenfeld, 2008).

CSF analysis reveals nonspecific abnormalities (Dalmau and Rosenfeld, 2008; Hasadsri et al., 2013). Among the well-characterized paraneoplastic antibodies, which could be present in both patient's CSF and/or sera and include the anti-Yo (PCA-1), anti-Tr, anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti-CRMP5 (CV2), anti-Ma1, anti-Ma2 (Ta), anti-Recoverin, anti-Amphiphysin, and anti-SOX1, the first three are the main, highly specific antibodies related to PCA, with anti-Yo being the most common, strongly related to gynecological cancers (Tanriverdi et al., 2013; Graus et al., 2004). Nevertheless, it has been suggested to test the entire range of these 10 onconeural autoantibodies, despite that almost 40% of PNS cases have undetectable antibodies (Giometto et al, 2010). Histopathologic examination reveals cerebellar atrophy, inflammatory infiltrates especially at the early stages of PCA, and gliosis (Giometto et al., 1997; Small et al., 2018).

Given its rarity, there are not established evidence-based therapeutic protocols. Yet, PCA stabilization is primarily associated with the treatment of the underlying malignancy (Dalmau and Rosenfeld, 2008). Immunosuppressive therapy consisting of corticosteroids, cyclophosphamide, azathioprine, and rituximab, with intravenous immunoglobulin (IVIG) and/or plasma exchanges most often have poor results (Kannoth, 2012). Accurate and timely diagnosis is needed, considering that treatment initiation within 1 month seem to correlate with better outcomes; breast cancer and young age have also been described as prognostic factors (Rojas et al., 2000; Widdess-Walsh et al., 2003; Vedeler et al., 2006). Overall, disease progression is the leading cause of death in PCA patients, despite PCA itself deteriorates patients' quality of life more than the underlying cancer (Hasadsri et al., 2013; Noorani et al., 2008).

In our uncommon case, the ataxic symptoms occurred while our patient's uterine cancer was in partial response, after the initiation of

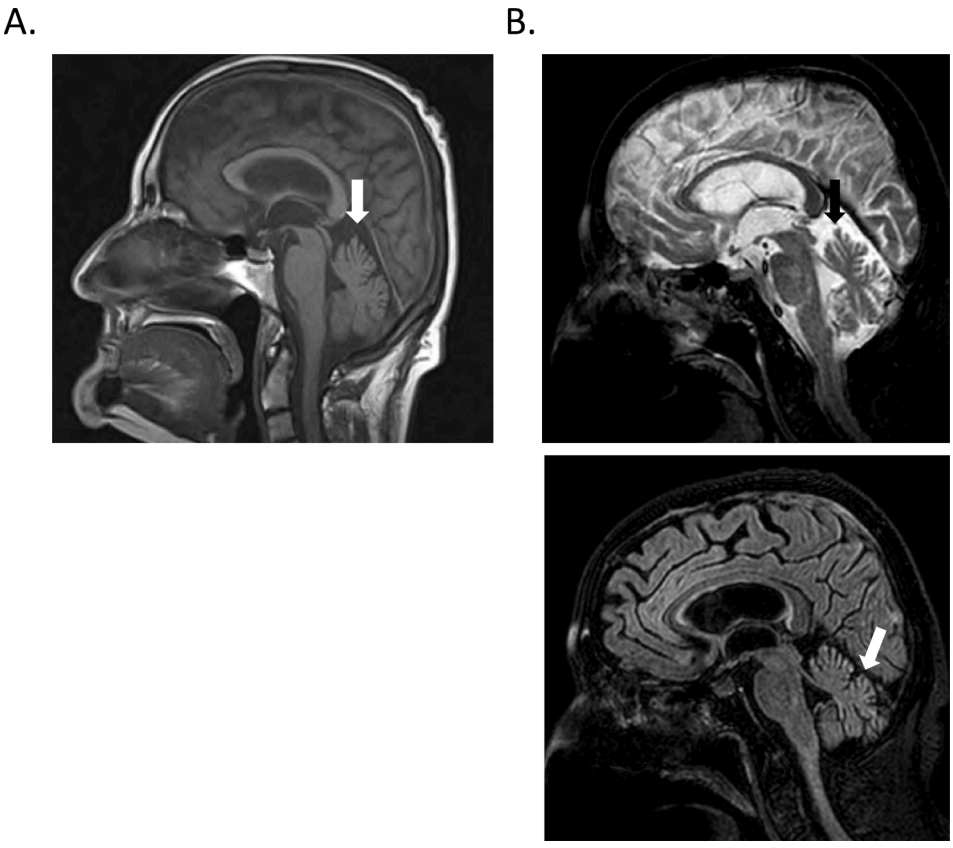

Fig. 3. Magnetic resonance imaging (MRI) of the brain (A) at initial diagnosis of paraneoplastic cerebellar ataxia (T1-weighted) and (B) 3 months later (T2-weighted and flair sequences) revealing evolving cerebellar atrophy (black and white arrows).

platinum-based chemotherapy. As our knowledge of the immunomodulating effects of chemotherapy deepens in relation to the well-described immunological basis of PCA pathogenesis, the hypothesis of accelerated immune responses to tumor antigens, expressed by the rapidly apoptotic cancer cells, seems appealing.

Indeed, cytotoxic chemotherapeutic agents have been the mainstay of treatment in cancer patients for over 70 years (Farber and Diamond, 1948). Despite their mechanism of action relies on impairment of mitosis (Opzoomer et al., 2019), however, accumulating evidence recognizes their potential immunomodulatory properties (Kroemer et al., 2013; Bracci et al., 2014; Pfirschke et al., 2016; Sakai et al., 2013; Pol et al., 2015). A few years ago, Kroemer et al. first characterized the immunogenic cell death (ICD), an immunostimulatory type of apoptosis, initiated by some chemotherapeutic agents (most commonly anthracyclines, alkylating agents, and platinum compounds), whereas the release of antigenic material expressed by dying tumor cells triggers an adaptive immune response, improving the overall antineoplastic efficacy (Dudek et al., 2013; Ghiringhelli et al., 2009; Schiavoni et al., 2011; McGranahan et al., 2016). Finally, it has also been described that apoptotic tumor cells yield a potent mean of antigen transfer to dendritic cells, which migrate to local draining lymph nodes and activate cytotoxic, CDR2-specific CD8 T lymphocytes, thus generating an antigen-specific immunity (Albert et al., 2000; Darnell, 2004).

Further studies are warranted to deepen the understanding of the exact pathogenetic mechanisms of PCA, and how the innate immune responses to immunomodulating effects of chemotherapy may precipitate autoimmune neurologic disease in particular.

4. Conclusion

PCA is a rare, devastating neurological disorder induced by paraneoplastic autoimmunity against the cerebellum, posing both a diagnostic and therapeutic challenge. The precise pathogenetic pathways promoting the breakdown of immune tolerance in PCA awaits to be fully deciphered, in order to provide the biological rationale for advancing its treatment in the near future.

CRediT authorship contribution statement

Michalis Liontos: Conceptualization, Data curation, Writing - review & editing, Project administration. **Oraianthi Fiste:** Data curation, Writing - original draft, Writing - review & editing. **Danai Drakopoulou:** Data curation, Writing - review & editing. **Nikolaos Thomakos:** Data curation, Writing - review & editing. **Kalliroi Goula:** Data curation, Writing - review & editing. **Flora Zagouri:** Writing - review & editing, Supervision, Project administration. **Maria Anagnostouli:** Conceptualization, Data curation, Writing - review & editing, Project administration. **Meletios-Athanasios Dimopoulos:** Writing - review & editing, Supervision, Project administration.

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.

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Ethics

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Patient consent for publication

Written informed consent has been obtained from the patient to publish this paper.

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