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Anti-Yo Positive Paraneoplastic Cerebellar Degeneration Associated with Ovarian Cancer: A Case Report and a Review of the Literature

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ABSTRACT

Paraneoplastic cerebellar degeneration (PCD) is a rare n eurological disorder in cancer patients, characterized by a widespread loss of Purkinje cells associated with a progressive pancerebellar dysfunction. Furthermore, PCD is characterized by acute or subacute onset of neurological symptoms such as cerebellar ataxia, dysarthria and nystagmus due to tumor-induced autoimmunity against cerebellar antigens. It is believed that anti-Yo occurs usually in women and is most likely associated with gynecologic or breast cancers. PCD often precedes the cancer diagnosis by months to years.

Here, we present a case involving a 52-year-old woman who developed PCD symptoms two months before the diagnosis of ovarian cancer, which was associated with high levels of anti-Yo antibodies.

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Introduction

Paraneoplastic cerebellar degeneration (PCD) is a rare non-metastatic neurologic complication resulting from tumor-induced autoimmunity against cerebellar antigens [1]. The incidence of PCD is less than 1% of all cancer patients and the majority of the patients are middle-aged female, however there are very few reported cases in men [2]. In 50% of cases, PCD precedes the diagnosis of cancer by months or even years [3-5]. PCD can be associated with any cancer, but the most commonly associated cancers are gynecological, breast, small cell lung and Hodgkin lymphoma [6].

Clinical manifestations of PCD are usually characterized by acute or subacute onset but progressive pan cerebellar dysfunction. It typically begins with nausea, vertigo and dizziness progressing to ataxia, dysarthria, nystagmus, diplopia and dysphagia [7-9]. These symptoms progress over weeks to months and then stabilize, leaving the patient severely disabled. Graus et al. and Sidechain et al. described that between 90 and 98% of patients with cerebellar ataxia and anti-Yo antibodies have a cancer detected [10, 11].

Serologically there are nearly 30 different antibodies associated with PCD, from which anti –Yo antibodies are the most common type. Although the role of these antibodies in the mechanisms of PCD remains uncertain, the detection of these antibodies in serum of patients suspected of PCD often lead to a focused search for the underlying neoplasms [12, 13].

Brain MRI findings appear mostly normal early in the course of PCD but can show cerebellar atrophy as the diseases progresses. PCD may occur isolated or in association with symptoms of more widespread involvement of the central nervous system (CNS) [14].

Early diagnosis and treatment of PCD are very important because any delay can result in progression and irreversible neurological damage [15]. The PCD treatment includes operation (optimal debulking), chemotherapy, immunoglobulins, corticosteroids and supportive therapy.

This report describes a case of a 52year-old woman who developed PCD symptoms, associated with high-titer anti-Yo antibodies, two months before the diagnosis of ovarian cancer.

Case Presentation

In March 2021, a 52-year-old, premenopausal female patient, previously healthy, presented to the neurology department with progressive gait disorder in the last 4 weeks, which had increased markedly in the last days. In addition, the patient displayed inability to walk unaided. Paresthesia was not noticed, however, the patient had been noticing an increasingly incipient weakness in the hands for the last two days, in addition to a significant weight loss of eight to ten Kg in the past three months. The patient displayed dysphagia and a severe ataxia of the lower extremities, noticeably more in the right side. Deep tendon reflexes were brisk except for the patellar tendon reflex, which was markedly diminished.

It should be mentioned that in February 2021 the patient was infected with Covid-19, however with mild symptoms.

The patient's medical history, family and social history were insignificant for neurological pathology, based on physiological history, G3P3.

During the hospitalization at the neurology department, several investigations were performed:
The clinical findings of the legs showed suspicion of Thoracic Myelopathy; however, the thoracic and cervical spine MRI were concluded with normal results. Moreover, the cerebrospinal fluid (CSF) showed moderate pleocytosis with a moderate increase in protein. This result was compatible with both an inflammatory central nervous reaction and a tumor manifestation of the central nervous system. However, CMRT was also normal, therefore a cerebral tumor was excluded. As an attempt to cure the PCD, high doses of intravenous corticosteroids (1000 mg daily for 5 days) were administered, but there was no clinical improvement.

As a part of the extended CSF diagnosis, anti-Yo antibodies were then detected. Our patient's symptoms and the detection of anti-Yo antibodies met the diagnostic criteria of PCD. As a part of the tumor search a computed tomography (CT) thorax / abdomen / pelvis was performed. Abdominal CT showed large, irregular and inhomogeneous ovarian masses at the right side, as well as, confluent pelvic lymph nodes parailliakal consistent with metastases.

A month later, the patient was referred to our hospital. Based on the clinical findings and CT-results, we performed a diagnostic laparoscopy. The PCI (Peritoneal Cancer Index)-value, which was established to objectify the extend of peritoneal carcinomatosis and to predict operability in ovarian cancer, was very low (PCI=4) [16]. Due to macroscopic bilateral suspect ovaries, we performed a laparoscopic bilateral adnexectomy. A high-grade serous ovarian cancer was pathologically confirmed.

One week later the patient underwent exploratory laparotomy with hysterectomy, which consisted in a complete ureterolysis on the left, up to the entry of the bladder and en-bloc complete pelvic peritoneum inclusive complete removal of the peritoneal disseminated tumor seed in the pelvis. High separation of both adnexal vessel stumps bilateral pelvic lymphadenectomy par aortic lymphadenectomy peritonectomy of the right upper abdomen (diaphragm / Morrison pouch) multiple peritoneal biopsies (including right colon groove / left colon groove) were conducted. Upon completion of the operation, there was no intra-abdominal tumor left.

Histology exhibited a high-grade serous adenocarcinoma of both ovaries with peritoneal and lymphogenic metastasis, pT3b, pN1b (1/14), L0, V0, Pn0, G3 FIGO IIIB.

After an interdisciplinary postsurgical discussion, we decided to proceed with six courses of chemotherapy (Paclitaxel (250 mg/m^2) and Carboplatin (AUC 5)). After one month, our patient got the first chemo cycle. Between the second and the third chemo cycle, the patient was admitted to the hospital where she stayed for one week, due to a complicated urinary tract infection. After six months, she completed the chemotherapy courses. The therapy was well tolerated without serious side effects, but showed a lack of effectiveness on the neurological symptoms. Some of them worsened at the beginning (after the first course) and after a while the patient displayed a slightly improvement only in speech and swallowing. After the completion of the chemotherapy courses started the patient with Niraparib 200mg daily for 36 months and cyclophosphamide 750mg/m^2 every four to six weeks as an immunotherapy. Up to this day, all cancer follow up examinations revealed no evidence of any new tumor or metastasis.

Discussion

Neurologic manifestations in cancer patients are, in most of the cases, a result of a primary tumor of the nervous system or metastatic disease involving the nervous system. Other common causes of neurologic diagnosis include metabolic encephalopathy, infections, cerebrovascular disease, electrolyte imbalance and side effects of chemotherapy [17]. In <1% of patients with cancer, a tumor-induced autoimmune response is developed against normal neural antigens, called paraneoplastic neurologic syndrome (PNS) [6, 7, 15]. However, PNSs are very important because in 50% of cases they precede the cancer diagnosis by months to years [3, 5, 18], or may even predict the diagnosis of a recurrence [19]. One of the most common paraneoplastic neurologic syndromes is PCD. PCD is preferentially associated with ovarian cancer, breast cancer, small cell lung cancer (SCLC) or Hodgkin's disease.

PCD is arguably the best documented examples of naturally occurring tumor immunity in humans. PCD is an autoimmune process, mediated by the anti-Yo antibodies; these antibodies directed against antigens expressed physiologically by neural cells as well as by tumor cells, so-called "onconeuronal antigens" [20, 21]. This antigen is known as cerebellar degeneration-related protein 2 (cdr2 antigen, also called Yo protein), the cdr2 antigen is exclusively expressed on Purkinje cells within the cerebellum [22]. Highly specific anti-neuronal autoantibody PCA 1 (Purkinje Cell Cytoplasmic Autoantibody Type 1, also known as Anti-Yo antibody) targeting these intracellular onconeuronal antigens cdr2 is detected in serum and/or cerebrospinal fluid (CSF). The pathogenic immune response involves cellular immune mechanisms and irreversible neuronal death. This neuronal death leads to severe and irreversible neurological impairment resulting in the syndrome. In this way, the Purkinje cells of the cerebellar cortex are damaged secondary to an autoimmune process because of a tumor that has not metastasized to the central nervous system. However, the absence of such antibodies cannot rule out the diagnosis of PCD [8, 23, 24]. The complete immune-pathogenic mechanism is still uncertain. However, the importance of this humoral response in the path mechanism of the disease is unclear. Clinical manifestations of PCD are usually characterized by an acute or subacute onset of global cerebellar dysfunction, ataxia, vertigo, dysarthria, nystagmus and involuntary movements of the head and limbs [7-9]. The first case report was described in 1919 [25].

In clinical practice, these antibodies serve as diagnostic biomarkers of a T cell predominant effector process and are uttermost importance since the clinical presentation does not provide any conclusion of the type of the triggering antibody. The presence of this high titer antibody in patients provided the initial evidence of an immunologic basis for the disease pathogenesis [26, 27]. Initial CSF indices showing inflammation (increased WBC, increased protein, increased oligo clonal bands) with negative infection and negative malignancy while pending antibody results could suggest paraneoplastic syndrome [28]. Prior series have estimated that 93% of patients with PCD and other neurological disease will have abnormal CSF findings [29]. Presence of these autoantibodies, alone or in combination, helps to detect the tumor, as they are more tumor specific than for neurological syndrome. This can guide the search for the primary cancer. One retrospective analysis examined 557 breast and 253 ovarian cancer patients screened for PCA-1 and

found the rate of positivity to be 1.6% and 2.3%, respectively. In addition, of those with positive anti-PCA-1 antibodies, only 12% of patients actually had the clinical syndrome [30]. Furthermore, PCD is rare even though all ovarian cancer subtypes, regardless of their association with anti-Yo antibodies and PCD, express cdr2 [31-33]. Therefore, the mere expression of cdr2 by tumor cells is insufficient to trigger autoimmunity against Purkinje cells.

Cerebellar degeneration is the dominant presentation but neocortex, limbic system, basal ganglia, spinal cord and the peripheral nervous system can be involved [34]. However, symptoms suggestive of brainstem and cortex involvement are not uncommon but typically present later in the disease course [35]. The clinical presentation is partially correlated to the pattern of expression of the target autoantigen in the CNS, PNS can present with multiple clinical manifestations rather than 'classical' syndromes.

In the cerebellum of PCD patients, the inflammatory infiltrates are composed of CD8 T cells, macrophages, and activated microglia that can form nodules [36-38]. CD4 T cells and B cells are either absent or found in small numbers around blood vessels [36]. No IgG deposition or complement activation is found in relation to the Purkinje cells [37, 38]. The identification of cdr2 antigen-specific CD8 T cells in the blood and CSF of PCD patients favors the hypothesis that these T cells arise as a consequence of anti-tumor immunity [39, 40].

Diagnosis of PCD should always be associated with a search for the origin of a primary malignancy. It is rather the antigenic specificity than a particular neurologic syndrome that is more indicative for the tumor location [41]. Nevertheless, the most specific diagnosis is made with the combination of both. Generally, in PCDs, tumors expressing onconeural antigens elicit an immune response that successfully suppresses growth of the tumor. This immune response is so effective that tumors in PCD patients are only rarely found to be present when patients develop their neurologic symptoms. When identified, PCD tumors are typically very small and often found in regional lymph nodes [42, 43]. Therefore, the tumor needs extensive imaging for detection. Positron emission tomography (PET)/computed tomography (CT) is useful when the cancer is not detected by any other imaging modality. Even if the patient is tumor free in the initial evaluation, she has to be followed-up for a significant period, perhaps up to 4 years [41]. Furthermore, in PNS, 15% of the patients can have an unrelated additional neoplasm [44].Therefore, if there is an obvious neoplasm, but not the one predicted by the onconeural antibodies, search should be continued for the tumor that is predicted by the antibodies.

History or family history of cancer should alert the clinician regarding this diagnostic possibility. Medical history or family history of autoimmune diseases can be a clue to paraneoplastic neurologic autoimmunity.

In the present report, we described the case of a patient who developed PCD symptoms two months before the diagnosis of ovarian cancer. She was presented with neurological symptoms and high titer of anti-Yo antibodies in the CSF. PCD develops as a result of the malignancy [24]. Thus, it is not surprising that many studies report that the neurological outcome may improve after tumor excision [7, 45]. Anyway, in our case the neurological benefit was quite small, the patient showed a slightly improvement only in speech and swallowing. This can be explained with the theory that anti-Yo antibodies can persist indefinitely even after cure of the underlying cancer. There are occasional reports of improvement with plasmapheresis, immunoglobulins, or steroids but generally there is only mild to moderate effect because the antibodies are intrathecal and unaffected by plasmapheresis or intravenous immunoglobulin [46, 47].

Another study has revealed that the overall prognosis of the cancer by patients with PCD and anti-Yo antibodies is rather poor, particularly for patients with gynecologic tumors. However, it can be hard to estimate an effect of anti-tumor response on overall survival as nearly half of the patients with PCD die from the neurologic pathology [48]. Patients can be cured of their tumor but remain severely disabled by their cerebellar dysfunction.

The nature of antitumor reaction in ovarian cancer coexistent with PCD requires more research. Still, there are no established protocols for the treatment of such cases. However, symptom relief is extremely important in the management of patients with PCD. Intensive rehabilitation, speech therapy and psychological support are also vital to reach maximal functional recovery [49].

The cause of tumor disappearance in our case would generally be attributed to the effect of surgery and chemotherapy.

Keeping an open mind in situations of unusual presenting symptoms is important with many of the paraneoplastic phenomena. Awareness of PCD is important for all gynaecologists to avoid diagnostic delay and potential medicolegal pitfalls, as the neural damage is most often permanent and irreversible. A multidisciplinary team approach is also strongly advisable incorporating medical oncologists, gynaecological oncologists, physiotherapists, speech pathologists, occupational therapists, neurologists, and nursing staff.

Still, because of its rarity, the majority of the clinical literature on this topic remains in the form of case series and reports. Further investigations on the pathogenesis of PCD are required to identify more effective therapies, which are able to stabilize or reverse the neurological symptoms.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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