Paraneoplastic cerebellar degeneration associated with ovarian cancer

ALESSIA ERIKA RUSSO[1,2], SIMONA SCALONE[2], GIULIA COSTANZA LEONARDI[1], AURORA SCALISI[3], GIORGIO GIORDA[4] and ROBERTO SORIO[2]

[1]Department of Biomedical Sciences, Section of Pathology and Oncology, Laboratory of Translational Oncology and Functional Genomics, University of Catania, Catania 95124; [2]Department of Medical Oncology C, National Cancer Institute, IRCCS, Aviano 33081; [3]Secondary Prevention and Screening Gynecological Unit, ASP, Catania 95100; [4]Unit of Gynecologic Oncology, National Cancer Institute, IRCCS, Aviano 33081, Italy

Received May 8, 2012; Accepted August 3, 2012

DOI: 10.3892/ol.2012.1016

Abstract. Paraneoplastic cerebellar degeneration (PCD) is a rare neurological disorder characterized by a widespread loss of Purkinje cells associated with a progressive pancerebellar dysfunction. PCD often precedes the cancer diagnosis by months to years. Here, we report the case of a 64-year-old woman who developed PCD symptoms, associated with high levels of anti-Yo antibodies, one year after a previous diagnosis of ovarian cancer. Clinical features, pathogenesis and treatment of PCD associated with cancer are discussed according to previous studies.

Introduction

Paraneoplastic neurological syndromes (PNSs) are a heterogeneous group of neurologic disorders caused by an immune response to a primary malignancy. It has been revealed that PNS may precede the diagnosis of cancer in 50-80% of cases (1). The exact incidence of PNS among those diagnosed with cancer remains uncertain, with estimates ranging from 1 in 10,000 to 1 in 100. Paraneoplastic sensory neuropathy (PSN) is probably the most common type of PNS (accounting for 3-7/1000 cancer diagnoses), followed closely by paraneoplastic encephalitis (PEM) (3/1000) and paraneoplastic cerebellar degeneration (PCD) (2/1000) (2).

PNS is initiated as a peripheral immune response directed against autoantigens expressed in tumors. A cancer-stimulated immune reaction that crossreacts with neural tissue, i.e., onconeural immunity, is considered to be the principal pathological mechanism for PNS. The oncoantigens that drive the immune response are normally restricted to the nervous system (3). The neurological attack may affect the central, peripheral somatic or autonomic nervous systems and presentations are commonly multifocal rather than 'classical' syndromes.

PCD is a rare but fatal neuronal syndrome associated with ovarian, breast and lung cancer patients (4-8). It is characterized by cerebellar atrophy with a diffuse loss of Purkinje cells, mediated by a cross-reaction of antibodies with tumor antigens and cerebellar tissue (3,9-12). PCD-related autoantibodies include: i) anti-Hu, ii) anti-Ri/Nova and iii) anti-Yo. Anti-Hu and anti-Ri/Nova are detected in patients with small cell lung and breast cancer, respectively (13). Anti-Yo, also called Purkinje cell cytoplasmic antibody type 1 (PCA-1), is usually associated with ovarian and other gynecologic cancers (14,15). It is an immunoglobulin (Ig) G directed against the cytoplasmic antigen cerebellar degeneration-related protein 2 (CDR2), detected in the central nervous system and tumor tissue. Intracellular antigens are not accessible to immune attack *in situ*, but peptides derived from intracellular proteins are displayed on upregulated major histocompatibility complex (MHC) class-I molecules in a proinflammatory cytokine milieu following proteasomal degradation, and are then accessible to peptide-specific cytotoxic T cells. Antibodies targeting nuclear or cytoplasmic antigens are serum markers of T cell effector-mediated injury. PCA-1 targeting these intracellular antigens is detected in serum and cerebrospinal fluid (CSF), but is not directly involved in the pathogenesis of neural tissue damage. In clinical practice, these antibodies serve as diagnostic markers of a T cell predominant effector process. CDR2 displayed in upregulated MHC class-I molecules is then accessible to peptide-specific cytotoxic T cells. Emigration of expanded populations of MHC class-I-restricted molecules and $CD8^+$ onconeural peptide-specific cytotoxic T lymphocytes from tumor-draining lymph nodes to the systemic circulation, and

Correspondence to: Dr Alessia Erika Russo, Department of Biomedical Sciences, Section of Pathology and Oncology, Laboratory of Translational Oncology and Functional Genomics, University of Catania, 83 Via Androne, Catania I-95124, Italy
E-mail: alessierikarusso@hotmail.it

Key words: paraneoplastic cerebellar degeneration, anti-Yo, ovarian cancer

thence to the CNS, is a plausible mechanism for neuronal degeneration in patients with PCA-1 autoimmunity (16-18).

Clinical manifestations of PCD are usually characterized by subacute onset but progressive pancerebellar dysfunction, including truncal and appendicular ataxia, dysarthria, vertigo, nystagmus and diplopia (19). These symptoms progress over weeks to months and then stabilize, leaving the patient severely disabled. It has also been observed that PCD precedes tumor occurrence by months or even years (8,20-22). In this report, we describe a case of a 64-year-old female patient developing PCD one year after the diagnosis of ovarian cancer. The study was approved by the ethics committee of the National Cancer Institute, IRCCS of Aviano and informed consent was obtained from the patient's family.

Case report

In June 2008, a 64-year-old female patient presented to the Department of Medical Oncology C at the National Cancer Institute (Aviano, Italy) with a two-month history of abdominal distension and pelvic pain, and markedly elevated levels of CA-125. Abdominal computed tomography (CT) identified large, bilateral, irregular and inhomogeneous ovarian masses inseparable from the uterus, as well as massive ascites and several small, confluent pelvic lymph nodes consistent with metastases. Total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, rectum-sigma resection, and bilateral pelvic and lombo-aortic lymphadenectomy were conducted. Histology revealed a high-grade ovarian serous papillary adenocarcinoma with rectal and appendicular involvement, as well as metastases in 23 out of 24 lymph nodes examined (FIGO stage IIIc). The patient achieved complete remission following six courses of treatment with paclitaxel (250 mg/m^2) and carboplatin (AUC 5), and since then has remained disease-free.

One year later, in June 2009, the patient was admitted to a neurology clinic for subacute onset of dysmetria with truncal and appendicular ataxia, dysgraphia, nystagmus, diplopia and mild dysphagia for liquids. A brain MRI did not reveal any mass lesion or signs of cerebellar atrophy, stroke or cerebellitis. The electromyogram and CA-125 levels were normal. A total body contrast-enhanced CT scan was negative for ovarian cancer recurrence. The detection of a high titer of anti-Yo onconeural antibodies in the CSF and blood, confirmed the clinical suspicion of PCD. High doses of intravenous Ig (400 mg/kg daily for 5 days) were administered in conjunction with corticosteroids without significant clinical improvement. One month later, the patient was referred again to our department. The neurological symptoms were significantly worse and the patient was unable to walk or talk, and developed severe dysphagia to both solids and liquids. We arranged a whole-body PET/CT scan to check for disease relapse but no evidence of abnormal hot spots was noted. The patient received other three cycles of intravenous Ig every 4-6 weeks and monthly boluses of cyclophosphamide (800 mg/m^2). No benefits were observed; therefore, a decision was made to terminate this immunosuppressive therapy. In October 2009, a new PET/CT scan was conducted. There was no evidence of recurrence, and a neurological follow-up at 3 months demonstrated stabilization in neurological status.

In June 2010, one year after the onset of neurological symptoms, the patient presented with an involuntary loss of fecal material and gas, as well as an intermittent discharge of mucus through the vagina. A CT scan of the abdomen, obtained two hours after administration of an oral contrast medium, revealed a fistulous communication between the vagina and a loop of sigmoid colon, as well as an accumulation of contrast material in the vaginal vault. For this purpose, the patient underwent laparoscopic surgery confirming the CT scan diagnosis. Due to the poor performance status, the patient was admitted to a Palliative and Supportive Care Unit.

Discussion

PCD has been described prior to the appearance of a primary tumor (8,20-22). However, to our knowledge, only two cases of PCD have occurred in patients with a clinical history of cancer (23,24). In the present report, we described the case of a patient who developed PCD one year after a previous diagnosis of ovarian cancer. The patient presented with neurological symptoms and a high titer of anti-Yo antibodies in the CSF and peripheral venous blood.

In patients with ovarian cancer, only mild to moderate neurological improvements have been achieved following a combination of treatment, including plasmapheresis, intravenous Ig and chemotherapy, for the underlying neoplasm (25). There are no established protocols for the treatment of most paraneoplastic syndromes. The physician may employ either plasma exchange or a combination of intravenous Ig and immunosuppressive agents, including corticosteroids or cyclophosphamide. Although there have been occasional reports of improvement with these therapies, generally, there is a minimal effect since the antibodies are intrathecal and unaffected by plasmapheresis or intravenous Ig (3,25). Symptom relief is important in the management of patients with PCD. Intensive rehabilitation, speech therapy and psychological support are also vital in optimizing functional recovery (26). However, it has been demonstrated that early therapy of PCD may improve neurological status (27-32). Accordingly, we started immunomodulatory treatment regimes with high doses of intravenous Ig, corticosteroids and cyclophosphamide four weeks after the onset of PCD; however, our patient did not receive any benefit from this treatment. The failure of this therapy may be associated with neuronal loss, which was already high and irreversible prior to the diagnosis of PCD. A few cases with early diagnosis may have mild and reversible damage, thus responding favorably to treatment.

In conclusion, although the majority of cases of tumor occurrence are preceded months or even years by cerebellar signs, in this case report we observed that PCD may also emerge following the appearance of a primary tumor. Despite anecdotal case reports revealing neurological improvement with various combinations of treatment, there remains a requirement for greater efficacy in therapy for PCD. Further investigations on the pathogenesis of PCD are required to identify more effective therapies, which are able to stabilize or reverse the neurological symptoms.

References

1. Nath U and Grant R: Neurological paraneoplastic syndromes. J Clin Pathol 50: 975-980, 1997.
2. Bataller L and Dalmau J: Paraneoplastic neurologic syndromes. Neurol Clin 21: 221- 247, 2003.
3. Darnell RB and Posner JB: Paraneoplastic syndromes involving the nervous system. N Engl J Med 349: 1543-1554, 2003.
4. Tanaka Y, Suzuki N, Takao M, Ichikawa A, Susumu N and Aoki D: Paraneoplastic cerebellar degeneration with fallopian tube adenocarcinoma. Gynecol Oncol 99: 500-503, 2005.
5. Land R, Carter J, Houghton R, Atkinson K and Dalrymple C: Gynaecology meets neurology: paraneoplastic cerebellar degeneration. Aust N Z J Obstet Gynaecol 45: 79-81, 2005.
6. Brock S, Ellison D, Frankel J, Davis C and Illidge T: Anti-Yo antibody-positive cerebellar degeneration associated with endometrial carcinoma: case report and review of the literature. Clin Oncol (R Coll Radiol) 13: 476-479, 2001.
7. Peterson K, Rosenblum MK, Kotanides H and Posner JB: Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibodypositive patients. Neurology 42: 1931-1937, 1992.
8. De Beukelaar JW and Sillevis Smitt PA: Managing paraneoplastic neurological disorders. Oncologist 11: 292-305, 2006.
9. Ashour AA, Verschraegen CF, Kudelka AP and Kavanagh JJ: Paraneoplastic syndromes of gynecologic neoplasms. J Clin Oncol 15: 1272-1282, 1997.
10. Bolla L and Palmer RM: Paraneoplastic cerebellar degeneration. Case report and literature review. Arch Intern Med 157: 1258-1262, 1997.
11. Anderson NE, Rosenblum MK and Posner JB: Paraneoplastic cerebellar degeneration: clinical-immunological correlations. Ann Neurol 24: 559-567, 1988.
12. Verschuuren J, Chuang L, Rosenblum MK, Lieberman F, Pryor A, Posner JB and Dalmau J: Inflammatory infiltrates and complete absence of Purkinje cells in anti-Yo-associated paraneoplastic cerebellar degeneration. Acta Neuropathol 91: 519-525, 1996.
13. Lennon VA: The case for a descriptive generic nomenclature: clarification of immunostaining criteria for PCA-1, ANNA-1, and ANNA-2 autoantibodies. Neurology 44: 2412-2415, 1994.
14. Greenlee JE and Brashear HR: Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. Ann Neurol 14: 609-613, 1983.
15. Furneaux HM, Rosenblum MK, Dalmau J, Wong E, Woodruff P, Graus F and Posner JB: Selective expression of Purkinje-cell antigens in tumor tissue from patients with paraneoplastic cerebellar degeneration. N Engl J Med 322: 1844-1851, 1990.
16. Okano HJ, Park WY, Corradi JP and Darnell RB: The cytoplasmic Purkinje onconeural antigen cdr2 down-regulates c-Myc function: implications for neuronal and tumor cell survival. Genes Dev 13: 2087-2097, 1999.
17. McKeon A and Pittock SJ: Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol 122: 381-400, 2011.
18. Albert ML, Darnell JC, Bender A, Francisco LM, Bhardwaj N and Darnell RB: Tumor-specific killer cells in paraneoplastic cerebellar degeneration. Nat Med 4: 1321-1324, 1998.
19. Vedeler CA, Antoine JC, Giometto B, *et al*: Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol 13: 682-690, 2006.
20. Levite R, Fishman A, Kesler A, Altaras M and Gadoth N: Paraneoplastic cerebellar degeneration heralding fallopian tube adenocarcinoma. Int J Gynecol Cancer 11: 169-171, 2001.
21. Rojas I, Graus F, Keime-Guibert F, Reñé R, Delattre JY, Ramón JM, Dalmau J and Posner JB: Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology 55: 713-715, 2000.
22. Shams'ili S, Grefkens J, de Leeuw B, van den Bent M, Hooijkaas H, van der Holt B, Vecht C and Sillevis Smitt P: Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain 126: 1409-1418, 2003.
23. Greenberg HS: Paraneoplastic cerebellar degeneration. A clinical and CT study. J Neurooncol 2: 377-382, 1984.
24. Goldstein BH, Birk CL, Van Houten M, Veve R, Brown JV, Rettenmaier MA and Micha JP: Ovarian cancer and late onset paraneoplastic cerebellar degeneration. Arch Gynecol Obstet 280: 99-101, 2009.
25. Cao Y, Abbas J, Wu X, Dooley J and van Amburg AL: Anti-Yo-positive paraneoplastic cerebellar degeneration associated with ovarian carcinoma: case report and review of the literature. Gynecol Oncol 75: 178-183, 1999.
26. Perlmutter E and Gregory PC: Rehabilitation treatment options for a patient with paraneoplastic cerebellar degeneration. Am J Phys Med Rehabil 82: 158-162, 2003.
27. Moll JW, Henzen-Logmans SC, Van der Meché FG and Vecht CH: Early diagnosis and intravenous immune globulin therapy in paraneoplastic cerebellar degeneration. J Neurol Neurosurg Psychiatry 56: 112, 1993.
28. Counsell CE, McLeod M, Grant R. Reversal of subacute paraneoplastic cerebellar syndrome with intravenous immunoglobulin. Neurology 44: 1184-1185, 1994.
29. Blaes F, Strittmatter M, Merkelbach S, Jost V, Klotz M, Schimrigk K and Hamann GF: Intravenous immunoglobulins in the therapy of paraneoplastic neurological disorders. J Neurol 246: 299-303, 1999.
30. Widdess-Walsh P, Tavee JO, Schuele S and Stevens GH: Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: case report and review of the literature. J Neurooncol 63: 187-190, 2003.
31. Thöne J, Hohaus A, Lamprecht S, Bickel A and Erbguth F: Effective immunosuppressant therapy with cyclophosphamide and corticosteroids in paraneoplastic cerebellar degeneration. J Neurol Sci 272: 171-173, 2008.
32. Mowzoon N and Bradley WG: Successful immunosuppressant therapy of severe progressive cerebellar degeneration and sensory neuropathy: a case report. J Neurol Sci 178: 63-65, 2000.