Subacute Paraneoplastic Cerebellar Degeneration in an Advanced Small Cell Lung Cancer Patient: Case Report and Literature Review

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Abstract: *Introduction*: Paraneoplastic Cerebellar Degeneration (PCD) is a rare paraneoplastic syndrome, and difficult to diagnose. PCD is associated with certain types of cancer such as ovarian cancer, uterus or its annexes, breast cancer, Hodgkin's lymphoma and small cell lung cancer (SCLC), however, this syndrome is not associated with metastatic dissemination. Here we report a case of a patient with advanced SCLC, which develop PCD.

Case Report: Female patient, 51-year-old, large smoker, with advanced SCLC with involvement of abdominal lymph nodes, presented muscle weakness, without spinal cord level, during second-line treatment with Cisplatin and Irinotecan, even with important clinical response to chemotherapy. The patient developed nystagmus and cerebellar ataxia. Cerebrospinal fluid analysis and brain magnetic resonance imaging without findings. The patient was assessed by neurologist, with clinical diagnosis of subacute PCD. Patient started pulse therapy with methylprednisolone, with significant remission of neurological symptoms.

Discussion and conclusion: PCD finding, although rare, usually precedes the detection of a tumor, and it is important to start early research and treatment of cancer because of better survival and patient´s quality of life. This case differs from usual descriptions found in the literature because the patient developed PCD during good clinical response in second-line treatment. PCD evolves with progression of the neurological condition in weeks to months and then stabilizes. The low incidence difficult to establish treatment strategies based on evidence for PCD, usually taking up aggressive immunotherapy, using intravenous immunoglobulin, plasmapheresis, steroids at high doses and/or immunosuppressive drugs.

Keywords: Paraneoplastic Cerebellar Degeneration, Small Cell Lung Cancer, Paraneoplastic Syndrome, Cerebellar ataxia, Nystagmus.

INTRODUCTION

Paraneoplastic cerebellar degeneration (PCD) is a rare neurological syndrome, difficult to diagnose and usually presents before diagnosis of a tumor. PCD is associated with certain types of cancer, however, this syndrome is not considered metastasis [1]. Approximately 1-3% of all cancer patients develop some type of paraneoplastic syndrome [2] and the prevalence between sexes in PCD varies widely, possibly depending on the underlying malignancy [3, 4]. PCD occurs predominantly in patients with ovarian cancer, uterus or its annexes, breast cancer, Hodgkin's lymphoma and small cell lung cancer (SCLC) [5, 6].

CASE REPORT

Female patient, 51-year-old, over 30 pack year smoking history, was diagnosed with SCLC in August 2012, staging investigation revealed advanced lung disease with extrapulmonary involvement (computed tomography findings: contour lobed nodule in left lower lobe, measuring about 5.7cm in the longest axis; irregular contours nodules in left perihilar region measuring 3.7cm and 1.4cm in longest axis; infracarinal lymph node increased measuring 2,7 x 1,9cm; involvement of abdominal lymph nodes). The patient underwent four cycles of first-line chemotherapy with Cisplatin and Etoposid until November 2012, with partial response. She also went through prophylactic central nervous system radiotherapy and remained under observation.

Seven months after first-line chemotherapy, the disease progressed and chemotherapy with Cisplatin and Irinotecan was indicated. During second-line treatment with good clinical response, the patient presented severe muscle weakness, evolving with cerebellar ataxia and nystagmus. Cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) of brain (Figure **1**) showed no pathological findings and computed tomographies of chest and abdomen evidenced important radiological response.

After specialized Neurology assessment, based on the clinical findings and complementary investigation,

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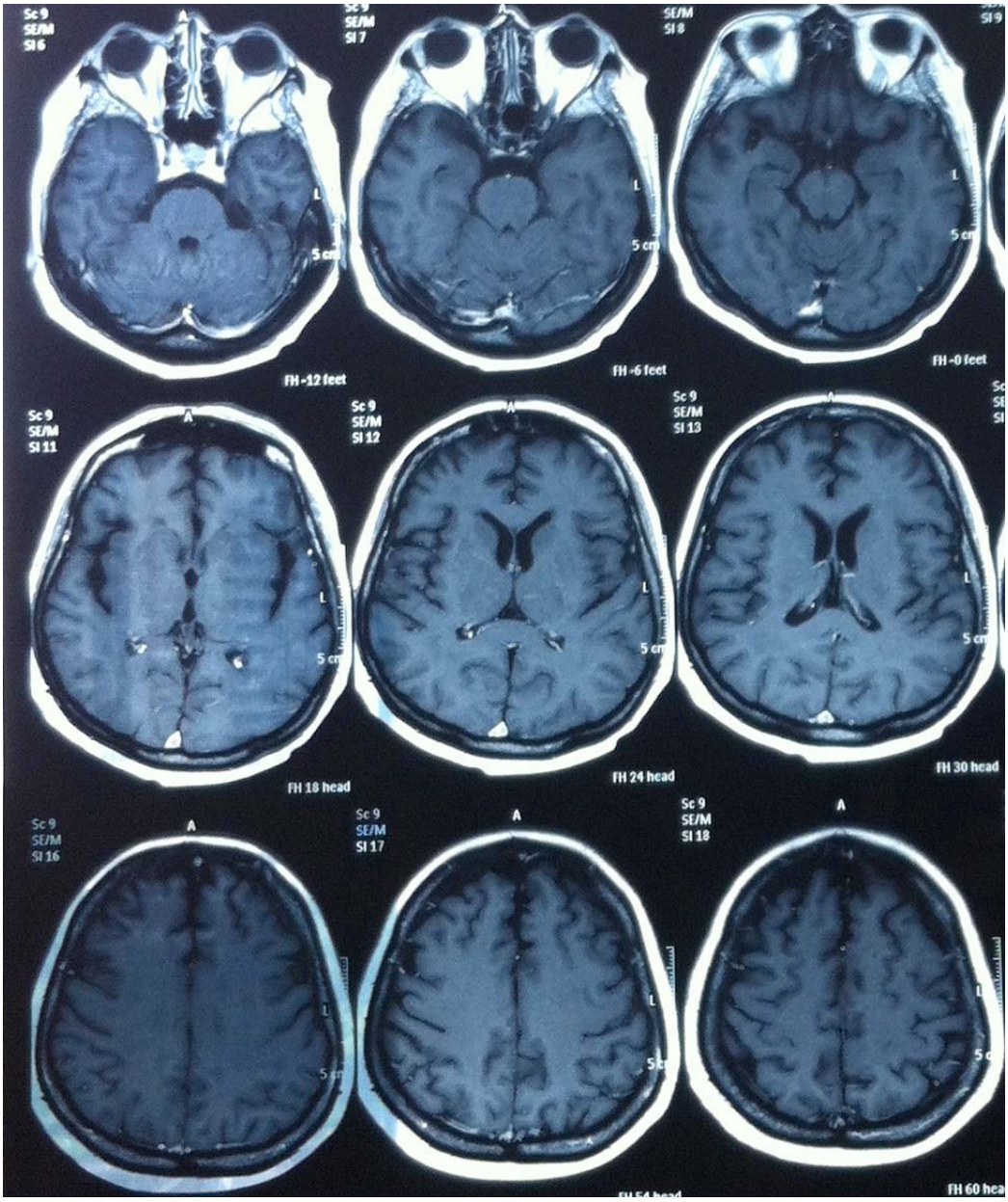

Figure 1: Patient´s brain Magnetic Resonance Imaging, without pathological alterations.

patient received clinical diagnosis of subacute PCD. She started in April 2013 methylprednisolone pulse therapy, with significant remission of neurological symptoms. She continued second-line chemotherapy, but in October 2013 developed extensive disease progression and decrease in performance status. It was then opted for palliative care and the patient died in December 2013.

DISCUSSION

1. Physiopathology

It is believed that PCD is caused by an immune-mediated mechanism in patients with malignant tumors that generally have not been detected [7]. PCD physiopathology is characterized by an immune response elicited by onconeural antigens produced by the tumor, which can cause antibody response against neuronal intracellular proteins or membrane antigens.

The apoptotic tumor cells are phagocytized by dendritic cells, which migrate to local lymph nodes where they activate antigen-specific B cells, TCD4+ and CD8+ cells by cross-presentation. The B cells differentiate into plasma cells that produces antibodies against tumor antigens (onconeural antibodies) capable of overcoming the blood-brain barrier, leading to inflammatory processes in areas of the nervous

system, with severe loss of Purkinge cells [8, 9], resulting in a pancerebellar syndrome [10].

These antibodies are present in patients with PCD that have some specific tumor types. The Anti-Tr antibody (PCA-Tr) is present in patients with Hodgkin's lymphoma, Anti-Yo (PCA-1) is commonly found in patients with PCD and ovarian and breast tumor and Anti-Hu (ANNA-1) is an antibody associated with SCLC [9]. In cases that the tumor has not been detected, Anti-Hu presence indicates a search for SCLC, but, according to a study, 56% of SCLC patient with PCD do not have Anti-Hu, which suggests that Anti-Hu absence does not exclude the possibility of SCLC diagnosis [11].

In a study conducted in 2013 with 39 patients with SCLC and PCD, four types of antibodies were detected in association with PCD, SOX1 antiboby (in 49% of patients), VGCC antibody (in 44%), Anti-Hu antibody (in 31%) and ZIC4 antibody (in 13% of patients). At least one antibody was detected in 72% of patients [12].

2. Clinical Manifestations and Prognosis

PCD prodromal manifestations are dizziness, visual disorders, dysarthria, ataxia, oscillopsy and nystagmus with downbeat [13], of subacute onset and fast progression and may progress to severe and irreversible disability due to a pancerebellar syndrome [1]. It has also been described in the literature the association of chorea movements with PCD in patients with breast cancer [14]. Occasionally, PCD may occur in association with Lambert–Eaton Myasthenic Syndrome, paraneoplastic syndrome characterized by insidious muscle fatigue, coursing with atrophy, hyporeflexia, diplopia, ptosis and dysphagia [15].

SCLC patients may also evolve with other paraneoplastic syndromes, like neurological syndromes, as Lambert–Eaton Myasthenic Syndrome, Paraneoplastic Encephalomyelitis, Subacute Sensory Neuronopathy, and endocrine syndromes, the most frequent being Cushing's Syndrome and SIADH (Syndrome of Inappopriate Antidiuretic Hormone Secretion). One of tumor types most commonly associated with PCD is SCLC [12].

To define PCD as a classical syndrome, some criteria are required, as development in less than 12 weeks of severe pancerebellar syndrome, without evidence of other cerebellar atrophy type, unless atrophy expected for the age of the patient, and at least three symptoms that significantly affect the lifestyle of the patient, intervening on the patient's independence. The ataxic gait may be present in the early stages of the disease, but the absence of symptoms involving cerebellum is not uncommon and does not rule out the diagnosis [16].

PCD generally evolves with progression of the condition within weeks to months and then stabilizes [9]. However, some patients course with significant disability, requiring intensive care [11].

3. Investigation and Diagnosis

The diagnosis of PCD is usually done before tumor detection and recognition of this syndrome depends on a high degree of suspicion by the physician, knowing its symptoms and types of tumors that are associated with PCD. Because this paraneoplastic syndrome precede the detection of cancer, the diagnosis of PCD is very important for screening, identification and early treatment of the tumor, which is often still small and can not be detected even after repeated clinical evaluations [1]. The case in question differs from the usual descriptions found in the literature because the patient developed PCD during second-line treatment with good clinical response and MRI and CSF without pathological findings.

In the initial phase of PCD, MRI is normal, progressing with cerebellar atrophy not expected for the age of the patient [9]. MRI can also show cerebellar edema [10]. The differential diagnosis with other paraneoplastic syndromes can be made through the CSF study, electroencephalogram and antibodies research [1]. It is very important to carry out the investigation of the primary tumor site through radiography and chest tomography, ultrasound and tomography of the abdomen and pelvis, pelvic examination and mammography [1].

4. Treatment

The only therapy associated with stabilization of neurological paraneoplastic syndromes is tumor therapy itself, with or without immunomodulation [3, 17], which would already be performed despite the presence of the paraneoplastic disorder. Other therapies have been tried but literature presents only low quality evidence with conflicting results, none within a prospective trial or a standardized multi-center protocol. Difficulty lies above all on the scarce number of patients.

Based on plausible pathophysiological premises and analogy to similar immune-mediated disorders, usual care of PCD incorporates one or more classes of immunomodulatory drugs targeting the underlying autoimmune process. Main treatment options are corticosteroids, intravenous immunoglobulin G and cyclophosphamide, singly or in combination [18], but other option like plasmapheresis, tacrolimus and rituximab have also been tried [11, 18-21]. Immunosuppression therapy has, however, important side effects, which must be accounted for and, if possible, prevented - like disseminated strongyloidiasis [22].

Quality of life is an important issue to be addressed in these patients, especially considering their grim prognosis. Therefore, symptomatic treatment must be considered, although not many options arise as candidates. Clonazepam has been used effectively [4] and other antiepileptic drugs and propranolol have also shown modest additional gains [17].

Rehabilitation should be considered as soon as possible, as these patients may still retain a reasonable level of independence, since rehabilitation can bring significant improvements in functional neurological condition [23-25].

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