Paraneoplastic Cerebellar Degeneration as Initial Presentation of Papillary Carcinoma of the Fallopian Tube: Evaluation and Usefulness of ^{18}F -FDG PET-CT. Case Report and Literature Review

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Abstract The acquisition of an ^{18}F -FDG PET-CT scan in patients with suspected paraneoplastic cerebellar syndrome can be helpful in determining the origin of a neoplasm because of its high sensitivity and also helps guide the neurological development course depending on the degree of incorporation of ^{18}F -FDG to the cerebellar parenchyma when compared with the rest of the brain.

Introduction

Paraneoplastic cerebellar degeneration (PCD) is a rare non-metastatic complication of a carcinoma caused by an immune-mediated mechanism other than a metastatic complication. This syndrome affects 1–3 % of all cancer patients, and it is mediated by antibodies generated against tumor antigens (proteins). Similar proteins are also expressed on Purkinje cells and possibly other cells within the cerebellum. The cancer-fighting antibodies mistakenly attack these normal protein cells in the cerebellum.

This immune activation in the central nervous system (CNS) results in cerebellar injury and dysfunction defined as paraneoplastic cerebellar degeneration. This syndrome occurs predominantly in patients with cancer of the ovary, uterus, or adnexa; breast cancer; small-cell carcinoma of the lung or kidney; or Hodgkin lymphoma.

The ^{18}F -FDG whole-body PET-CT (positron emission tomography and computed tomography) scan is a useful tool to determine the origin of a possible paraneoplastic cerebellar degeneration in patients suspected of having malignancy. In this case report, we describe the usefulness of the ^{18}F -fluorodeoxyglucose (FDG) PET-CT scan to evaluate the possible presence of PCD, determine the current status of the disease, and find its possible origin.

Case Report

A 64-year-old hispanic female reported a 2-month period of paresthesias in the lower limbs followed by the upper ones; subsequently occipital headache, unsteady walk, dysarthria, multidirectional nystagmus, and hypertension also developed a week prior to attending the emergency department of our hospital.

Her medical history included hormone replacement therapy. She denied a history of substance abuse, allergies, and/or transfusions and did not have diabetes mellitus or other diseases. She continued with neurological symptomatology and progressive cerebellar syndrome with dysarthria and ataxia, and her initial neurological examination showed nystagmus, diadochokinesis, dysarthria, and truncal ataxia. Her blood studies were normal.

Cranial magnetic resonance imaging (MRI) only showed multiple bilateral areas of gliosis in the frontal, parietal, and periventricular white matter (Fig. 1).

Because MRI showed no cerebellar pathology, a possible neoplastic entity was suspected by the neurologists

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Fig. 1 Initial MRI findings were normal. **a** Non-contrast-enhanced sagittal-slice T1-weighted image. **b**, **c**, and **d** Sagittal, coronal, and trans-axial T2-weighted image, respectively

and the general internist, so the patient underwent an abdominal pelvic ultrasound (USG) in which no evidence of malignancy was found. Subsequently, she was referred to the PET/CT unit, and a whole-body ^{18}F -FDG PET-CT was performed in search of a possible unknown primary tumor. It demonstrated diffuse and symmetrical abnormal increased metabolism on both cerebellar hemispheres with no evidence of structural damage (Fig. 2), two hypermetabolic lymph nodes in the right common femoral chain, a nodular lesion in the topography of the left internal iliac chain (adjacent to the ovary), and a hypermetabolic solid nodular splenic injury (Fig. 3).

Considering the imaging findings, she underwent a right inguinal lymph node biopsy with a histopathological report of papillary carcinoma of unknown primary. Therefore, another USG pelvic gynecological reassessment was requested, which only found thickened endometrium. As part of the study protocol, a thyroid biopsy was performed, which was negative for malignancy. Furthermore, given the findings of the PET-CT scan and biopsy, she underwent a pelvic examination, and a left salpingo-oophorectomy, hysterectomy, and bilateral pelvic lymphadenectomy were performed.

Meanwhile, cerebrospinal fluid (CSF) analysis was also performed during her hospital stay, showing a crystal-clear appearance, with 8 leukocytes/mm³ and 2 erythrocytes/mm³; the glucose level was 65 mg/dl and the protein level 59 mg/dl. Culture results were negative for gram stain, *Mycobacterium tuberculosis*, and antibody IgG and IgM to *Borrelia burgdorferi* and *Bartonella henselae*, cytomegalovirus (CMV), Epstein Barr DNA virus (EBV), and herpes virus. The Purkinje cellular (Yo) antibody LCR was not detected by immunofluorescence.

Intravenous immunoglobulin therapy was administered during the hospital stay.

The final pathology report described a well-circumscribed solid nodule, 1.3 cm in diameter, which caused a slight occlusion of the left fallopian tube compatible with poorly differentiated endometrioid type adenocarcinoma, arising in the fallopian tube and the ampullary region with metastatic disease in pelvic lymph (Fig. 4). Chemotherapy was given as part of the cancer treatment.

Four months later, the patient had no improvement in clinical neurological symptoms, so she returned for a PET-CT control study, which found a marked decrease of the cerebellar metabolism, probably secondary to the

Fig. 2 ^{18}F -FDG PET-CT brain scan. **a** 3D fused PET-CT sagittal slice and MIP reconstruction show increased metabolism in both cerebellar hemispheres. **b** 3D fused PET-CT axial slices. **c** Whole-brain axial slices

expected cellular damage and evolution time since the diagnosis was made (Fig. 5).

Discussion

Cerebellar syndrome is a vascular disease caused by diverse etiologies: toxic, infectious, degenerative and paraneoplastic; the latter represents <1–3 % in patients with cancer [1, 3, 5, 8]. About 13 % of patients with paraneoplastic neurological syndrome (PNS) most often present neurological symptoms before the diagnosis of the tumor (more than 85 % of the time) [8].

Paraneoplastic neurological syndromes include many neurological disorders, including paraneoplastic cerebellar degeneration (PCD), which is caused by an immune-mediated mechanism other than a metastatic complication in patients with an underlying malignancy [10].

The presence of some antineuronal autoantibodies has been described. The most common are anti-Yo, anti-Tr, anti-Hu, and anti-Ri, which are considered to result from an immunological response to the tumor and may cross-react with cells of the nervous system, causing neuronal damage (a significant inflammatory reaction with lymphocytic infiltration and eventually a severe patchy loss of Purkinje cells,

especially in advanced cases). Atrophy of the granular and molecular layers is demonstrated, with microglial proliferation and astrocytosis but relative sparing of basket cells [3].

Not all patients presenting with paraneoplastic cerebellar degeneration and its clinical features have recognizable antineuronal antibodies. However, this does not exclude the likelihood of occult malignancy [5, 6]. In approximately 40 % of patients, no antibodies are identified.

PCD occurs predominantly in patients with gynecological carcinomas (ovarian and breast cancer), Hodgkin lymphoma, and small cell carcinoma of the kidney or lung [2, 9]. The related symptoms are usually ataxia, dysarthria, tremor, nystagmus, vertigo, and diplopia [3, 8]. Not all gynecological cancers present as paraneoplastic neurological syndrome; however, in a clinical presentation consistent with a paraneoplastic neurological syndrome, the chances of underlying malignancy are very high [9].

In our case, the etiology was a primary adenocarcinoma of the fallopian tube, which has a very low incidence among the gynecological tumors (0.3 to 1.8 %) [7]. It is considered even more rare if accompanied by PCD, being the acute or subacute form and the most predominant presentation in women over 50 years [4].

The pathophysiology of PCD, the time course of the disease (acute or chronic), and the size of the primary tumor

Fig. 3 ^{18}F -FDG whole body PET-CT. **a** and **b** MIP coronal reconstruction showing a focal hypermetabolism in the left pelvis, corresponding to the site of the primary tumor (Fallopian tube

topography) (arrowhead). **c** Right inguinal lymphadenopathy and a spleen focal lesion corresponding to metastatic disease (thick arrow)

lesion can influence and determine the findings in the different cranial imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), and can appear normal in the early course of PCD, whereas functional imaging (SPECT, PET, or MRI perfusion) has a high

sensitivity for the detection of abnormal vascular flow or metabolism, revealing increased perfusion/metabolism. In advanced cases, MRI may show cerebellar atrophy, while the SPECT or PET scan can reveal cerebellar hypometabolism [3] as in this case reported.

Fig. 4 Hematoxylin-eosin staining shows edema in the villi of the Fallopian tubes, semi-solid and papillary formation of neoplastic cells. **a** Normal tissue); **b** neoplastic tissue

Fig. 5 ^{18}F -FDG PET-CT brain scan after immunoglobulin and oncological therapy. **a** 3D fused PET-CT sagittal slice and **b** MIP reconstruction show decreased metabolism in both cerebellar hemispheres. **c** 3D fused PET-CT axial slices. **d** Whole brain axial slices

The diagnosis of an occult tumor or small lesions (<3 mm) based on the findings from the different conventional imaging studies may be negative; however, ^{18}F -FDG PET-CT can be a useful tool for detecting and localizing small primary tumors or metastatic lesions not seen by conventional studies. In a retrospective study, Rees et al. determined the sensibility of PET/CT in detecting occult primary tumors associated with PCD, which was about 37 % in cases where conventional imaging studies revealed no malignancy [4].

In addition to the imaging studies listed above, a thorough gynecological examination should be performed in patients with paraneoplastic cerebellar degeneration to identify the primary malignancy, as well as examination of CSF (cerebrospinal fluid) samples to identify mononuclear pleocytosis, elevated protein levels (immunoglobulin G), and oligoclonal bands.

Two approaches were used to treat the paraneoplastic neurological syndrome in our patient; the first treatment focused on the autoimmune disease and the second approach on the underlying tumor (total abdominal hysterectomy and bilateral salpingo-oophorectomy with adjuvant chemotherapy), with an unsatisfactory clinical course. Although in our case there was no evidence of antineural antibodies by immunofluorescence, poor response has been reported possibly to be related to the presence of anti-Yo/anti-GAD (anti-glutamic acid decarboxylase) antibodies in the serum and CSF, which may contribute to the aberrant immune response and the fulminating paraneoplastic cerebellar degeneration, identifying the

14-3-3 proteins in CSF, which are probably related to neuronal death [11].

Conclusion

Paraneoplastic syndromes are a rare clinical entity, especially in gynecological tumors secondary to fallopian tube carcinoma, so they become a therapeutic challenge for the neurologist, and their treatment is generally unsatisfactory. Early tumor detection and treatment should be the primary objective in these patients.

The degree of cerebellar metabolic abnormalities seen in PET is related to cell degeneration or loss of cells secondary to an inflammatory response or immunological reaction; in this report, we described an acute-subacute case of DCP where the whole-body ^{18}F -FDG PET-CT scan was demonstrated to be a useful tool to guide the biopsy for determining the primary tumor site, allowing the consequent staging of the disease, evaluating the current status of PCD and subsequently following up both diseases.

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