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Case Report

Multiple Paraneoplastic Neurological and Rheumatological Syndromes Revealing an Ovarian Cancer

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ABSTRACT

Multiple paraneoplastic syndromes are a rare clinical manifestation. We describe the case of an 82-year-old woman who presented with neurological (rapidly progressive cerebellar syndrome and combined sensory-motor neuronopathy) and rheumatological (palmar fasciitis and polyarthritis syndrome) paraneoplastic syndromes associated with two onconeural antibodies (anti-Yo and Zic4), that revealed an ovarian cancer. The involvement of multiple organ systems should be a clue to take into consideration a paraneoplastic etiology that could permit early detection of cancer. However, despite the existence of treatments, the prognosis of these conditions remains poor.

Introduction

Paraneoplastic syndromes are remote, immune-mediated effects of cancer on different organs and systems, not caused by the tumor and its metastasis, nor by infection, ischaemia, or metabolic disruptions [1]. Although rare, multiple paraneoplastic syndromes could be seen in the same patient and could lead to the detection of underlying cancer.

Case Description

An 82-year-old woman presented with a four-month history of gait disturbances, asymmetric painful tingling in her fingertips gradually extended to her toes. She reported pain and swelling in her hands and wrists and unintentional weight loss. Her background history includes atrial fibrillation and arterial hypertension. In addition to her cardiovascular treatment, she took Pregabalin which proved minimally effective on the sensory symptoms.

Neurological examination showed multidirectional nystagmus and hypermetric eye movements, mixed cerebellar and proprioceptive ataxia, hypopallesthesia, tactile and thermal hypoesthesia in a stocking-glove distribution, right hand pseudoathetotic movements, global areflexia, tetramelic minimal distal motor deficit with interosseous muscles atrophy (Figure 1). Hand examination also revealed flexion contractures and thickened palmar fascia.

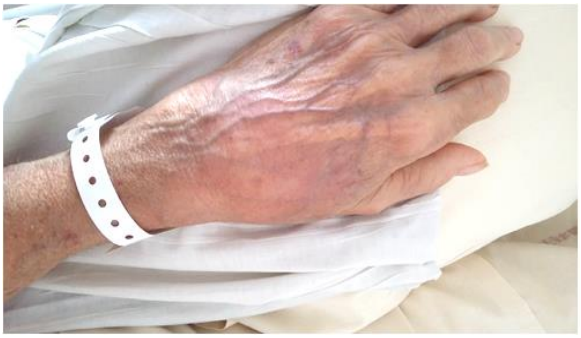

Figure 1: Left hand showing interosseous muscles atrophy and wrist swelling.

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Sensory neurography showed absent sensitive potentials in the left radial and medial cutaneous nerve and reduced amplitudes of the left median, left and right ulnar, bilateral sural, or superficial fibular nerves. The compound muscle action potential showed marked reduced amplitudes in the left upper limb. The myography was suggestive of widespread denervation of C6, C7, C8 left, and bilateral S1 myotomes. The spinal MRI showed cervical stenosis without contrast enhancement in the nerve roots. Ultrasound examination of hands and wrists soft tissue revealed bilateral and symmetric synovitis of radiocarpal and intercarpal joints, as well as thickening of the flexor tendon retinaculum and palmar fascia. Laboratory tests for prothrombotic, infectious, auto-immune, toxic aetiologies and protein immunofixation were all normal. Cerebrospinal fluid (CSF) analysis revealed 21 cells/mm^3 with 95% lymphocytes, normal glycorrhachia, hyperproteinorachia 0.79g/L (N<0,45g/L) and oligoclonal bands.

Anti-Yo and anti-Zic4 antibodies were present both in serum and CSF. Cerebral ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) was consistent with left cerebellar hemisphere hypo-metabolism (Figure 2A). Whole body ^{18}F-FDG-PET showed an increased metabolism of bilateral adnexal masses (left 28 × 33 mm, right 15×10mm in axial section) with sub- and supra-diaphragmatic lymphadenopathies and increased uptake at the level of wrist joints (Figures 2B-2D). The supraclavicular lymph nodes microbiopsies confirmed a metastatic high-grade serous carcinoma probably of ovarian origin (expressing CK7 +, PAX8 +, WT1 +, P16 +, RE+, RP +).

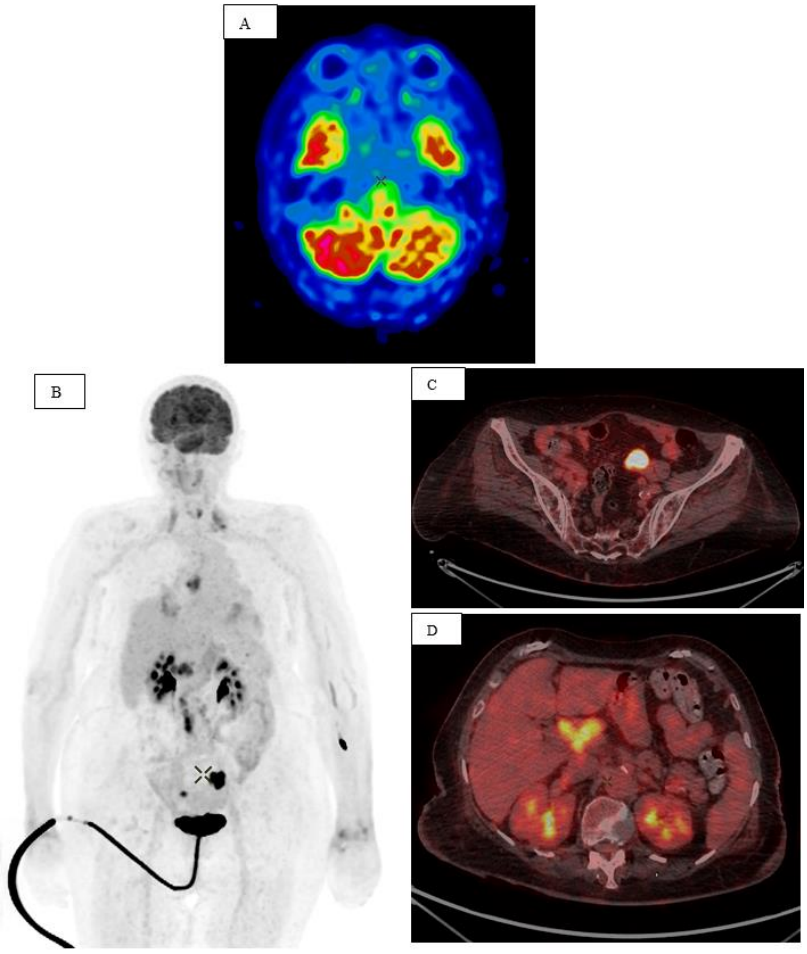

Figure 2: A) PET-CT ^{18}F-FDG brain imaging showing left cerebellar hemisphere hypometabolism; **B)** Whole body PET-CT ^{18}F-FDG showing bilateral adnexal tissue masses hypermetabolism, **(C)** left ovary showed in axial section) along with retroperitoneal, hepatic hilar, **(D)** also showed in upper abdominal axial section), mediastinal and bilateral supraclavicular lymphadenopathies; of note, increased uptake at the level of the writs suggestive of inflammation.

A diagnosis of paraneoplastic combined sensory and motor neuronopathy, rapidly progressive cerebellar syndrome and palmar fasciitis and polyarthritis syndrome were retained as remote effects of an ovarian cancer. A treatment with intravenous immunoglobulins (2g/kg for 5 days/ month) was initiated. In front of medical comorbidities, poor performance status, and old age, neoadjuvant platinum-based chemotherapy was preferred. However, after three months she deteriorated clinically with global motor weakness that confined her to bed and the patient along with the family opted for palliative care.

Discussion

This case presents a rare simultaneous combination of multiple paraneoplastic syndromes involving both the peripheral and central nervous system, as well as the skeletal system. The diagnosis of a

definite paraneoplastic neurologic syndrome (PNS) was made on the presence of high-risk phenotypes (subacute sensory neuronopathy (SNN), rapidly progressive cerebellar syndrome) along with a high-risk antibody (anti-Yo), and the presence of an ovarian cancer consistent with the phenotype and the antibodies [1].

SNN as a PNS is commonly encountered in small-cell lung cancer (SCLC) and in the presence of Hu, CV2/CRMP5 and amphiphysin antibodies. An infraclinical motor involvement is possible in association with a paraneoplastic SNN [1]. However, a subacute motor neuronopathy was depicted as a distinct rare PNS emerging in the presence of well-characterized onconeural antibodies (Hu, Ri, Yo, Ma2/Ta, and CV2), inflammatory CSF and diverse neoplasms (breast, renal cell, lung, ovarian, testicular, gall bladder, duodenal cancer, and thymoma) [2].

In the 2018 update on PNS, Zic4 antibodies were presented as partially characterized onconeural antibodies, significant for SCLC and Subacute Cerebellar Degeneration [3]. To the best of our knowledge, a single case of anti-Zic4 antibodies related to an ovarian cancer was reported in the literature [4]. Their association with sensory and/or motor neuronopathy is unusual.

Association with anti-Yo antibodies was reported in a pure monomelic sensory neuronopathy related to breast cancer and three motor neuronopathies associated with prostatic, ovarian and breast cancer, one of which also had a proprioceptive deficit and cerebellar ataxia [2, 5]. Palmar fasciitis and polyarthritis syndrome is one of the paraneoplastic arthritides, ovarian cancer being the main malignancy linked to this condition. No biological test or imagistic examination proved to be specific in this condition [6].

Multiple paraneoplastic disorders could emerge simultaneously in the same patient, although rare. A patient with anti-Hu antibodies subacute cerebellar degeneration and sensory neuronopathy was previously reported [7]. However, an association of combined motor and sensory neuronopathy, subacute cerebellar syndrome and a rheumatologic paraneoplastic syndrome in the presence of both anti-Yo and anti-Zic4 antibodies is uncommon. Whether the individual presence of these antibodies or their combination could predispose to developing multiple PNS or mixed neuronopathy is a question that requires further studies.

Conclusion

In the presence of rapidly progressive neurologic and rheumatic symptoms, a detailed diagnostic workup including onconeural antibodies and whole-body scan should be performed to detect a paraneoplastic etiology and for an early identification of underlying neoplasm. Given the fact that many paraneoplastic syndromes coexist with advanced cancer the response to therapeutic intervention remains poor.

Conflicts of Interest

None.

Funding

None.

Abbreviation

CSF: Cerebro-Spinal Fluid
MRI: Magnetic Resonance Imaging
^{18}F-FDG-PET: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography
PNS: Paraneoplastic Neurologic Syndrome
SCLC: Small-Cell Lung Cancer
SNN: Subacute Sensory Neuronopathy

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