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Case Report

Paraneoplastic Cerebellar Degeneration Secondary to BRAF Mutant Melanoma Metastasis from an Occult Primary Cancer

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Keywords

Melanoma · Nervous system paraneoplastic syndrome · Occult primary neoplasm · Paraneoplastic cerebellar degeneration · Proto-oncogene protein B-Raf

Abstract

Melanoma metastasis from an unknown primary cancer has an incidence of 3.2% among melanoma patients. Furthermore, paraneoplastic neurological syndromes (PNS) are rare, occurring in 1–3% of patients with malignancies. Paraneoplastic cerebellar degeneration (PCD) is one of the classic PNS and is characterized by acute or subacute onset of ataxia and/or presence of onconeural antibodies. A 61-year-old male with ataxia, vertigo, and headache later developed dysarthria, multidirectional nystagmus, hyperactive delirium, auditory hallucinations, psychomotor agitation, and myoclonus. Toxicological, metabolic, infectious, and autoimmune etiologies were assessed and reported negative. An osteolytic lesion was observed in the right iliac crest via computed tomography (CT). A positron emission tomography-CT reported increased fluorodeoxyglucose uptake of a right iliac and right inguinal ganglion. After biopsy of the right inguinal ganglion, a BRAF mutation-positive melanoma metastasis from

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an occult primary cancer was diagnosed. Dermatologic, ophthalmologic, and endoscopic gastrointestinal assessment did not reveal a primary malignant melanoma. The patient's movement disorders and neuropsychiatric symptoms improved with quetiapine, prednisone, azathioprine, and cyclophosphamide. Oncological management was conducted with MAPK pathway inhibitors (i.e., dabrafenib and trametinib). Movement disorders associated with neuropsychiatric symptoms are complex to diagnose. PNS are rare and often associated with antibodies against neural antigens expressed by the tumor. The case presented above describes a patient with a BRAF-positive malignant melanoma metastasis from an occult primary associated with PCD – to the best of our knowledge, the first reported in the literature.

Introduction

Ataxia is a disorder of balance and coordination involving dysfunctions of the cerebellum and its afferent and efferent connections [1]. Ataxia is usually an initial manifestation of cerebellar disease [2]. Among the etiologies that manifest with ataxia are: (1) cerebrovascular disease; (2) neoplasia and paraneoplastic diseases; (3) metabolic diseases (e.g., hyponatremia, hypoglycemia, and hyperazotemia); (4) pharmacologic or alcohol intoxication; (5) head trauma; (6) autoimmune disease (e.g., multiple sclerosis and acute disseminated encephalomyelitis); (7) infectious disease (e.g., herpesvirus, HIV, and Epstein-Barr virus); and (8) polyradiculopathies (e.g., Miller Fisher syndrome and acute inflammatory demyelinating polyneuropathy) [2, 3].

Paraneoplastic neurological syndromes (PNS) occur in 1–3% of patients who have malignancies [4]. Cerebellar ataxia is the movement disorder most commonly associated with PNS and is associated with several antibodies such as anti-Hu, anti-Ri, and anti-Yo [5]. Lymphoma, thymoma, and endometrial, breast, testicular and ovarian cancer have been associated with PNS characterized by cerebellar ataxia [6, 7]. Paraneoplastic cerebellar degeneration (PCD) is among the classic PNS (i.e., paraneoplastic limbic encephalitis, subacute sensory neuropathy, paraneoplastic opsoclonus-myoclonus, and Lambert-Eaton myasthenic syndrome) and is characterized by subacute development of pancerebellar dysfunction [8].

We present the case of a male patient with ataxia and PCD associated with a metastatic melanoma tumor. The patient had a sudden onset, developing behavioral and more movement disorders associated with the PNS. While infectious, toxicological, autoimmune, and metabolic etiologies were excluded, a positive right inguinal ganglion biopsy revealed melanoma metastasis from an occult primary. This is the first case reported in the literature of PCD secondary to a BRAF-positive melanoma metastasis from an occult primary cancer and the second case of a PNS associated with a BRAF-mutant melanoma.

Clinical Presentation

A 61-year-old male arrived at the emergency department complaining of a headache with a frontal predominance that had progressively increased in 1 week to an 8/10 on the visual analog scale for pain at the time of admission. In the previous week, the patient reported an elevation in his blood pressure reaching 150/80 mm Hg. Meanwhile, the 24 h before seeking medical attention, the patient had had vertigo and ataxia without fever. The patient did not report any symptoms related to an acute infectious process (e.g., fever or malaise), nor alterations in his sleep-wake cycle or seizures. The patient's family history includes a mother with

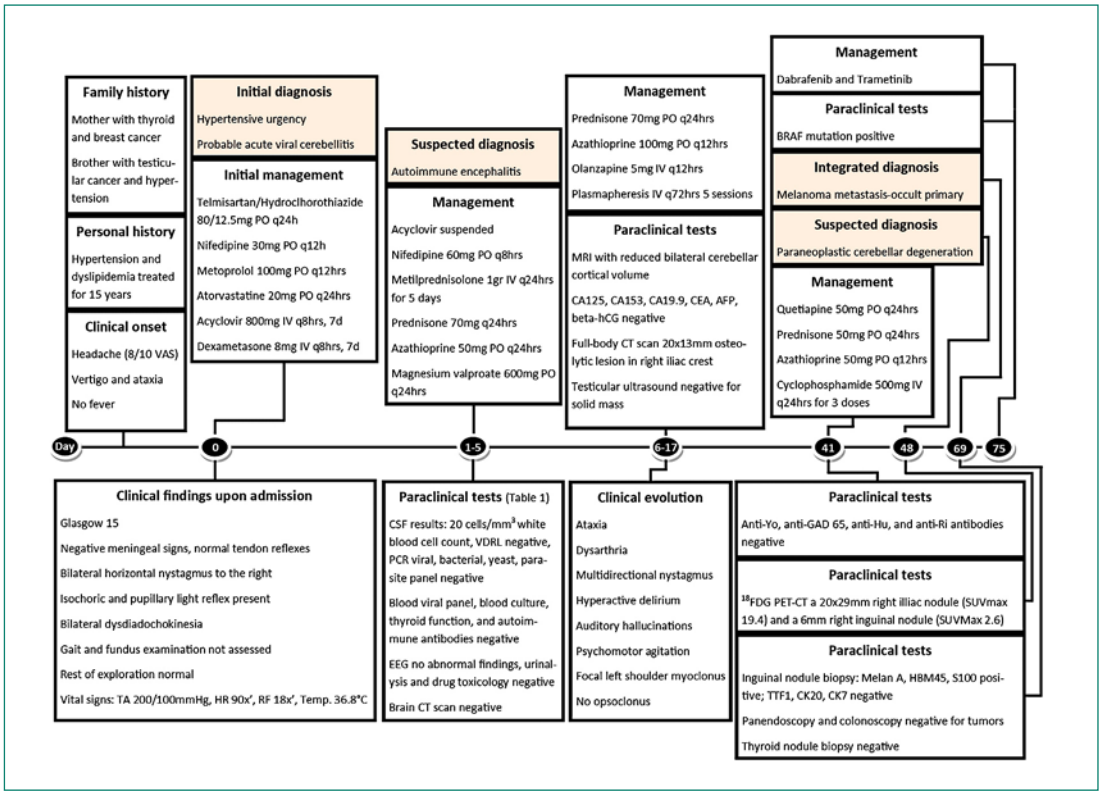

Fig. 1. Timeline of clinical presentation, clinical evolution, and clinical outcome. Summary of the clinical case with suspected diagnosis, laboratory and imaging workup, and management.

thyroid and breast cancer under treatment and a brother with testicular cancer in remission, as well as hypertension under treatment. The patient had a personal history of hypertension and dyslipidemia treated for 15 years. The patient denied the use of controlled substances, allergies, past blood transfusions, traveling to regions with endemic diseases within the last 3 months, tattoos, and body piercings.

Upon initial physical exploration, we found a recumbent patient with a freely chosen body position, a Glasgow Coma Scale score of 15 (i.e., eye-opening 4, verbal response 5, and motor response 6), without focal neurological deficits or meningeal signs, and aware of his environment. The patient's integumentary system was hydrated and without alterations. The patient had bilateral horizontal nystagmus to the right, with isochoric pupils and the pupillary light reflex present. A fundus examination was not performed due to excessive saccadic eye movements. A musculoskeletal exploration revealed stereotyped movements in all four extremities. A cerebellar examination revealed bilateral dysdiadochokinesia and a negative Romberg test result, but no alterations in the finger-to-nose and heel-to-shin tests; no resting tremor was observed, and no reduction in muscle tone of the upper limbs, but gait was not assessed due to the severity of the ataxia. The patient had normal plantar and other deep tendon reflexes. Upon inspection, palpation, auscultation, and percussion, the cardiorespiratory system had no abnormal findings. An abdominal examination yielded no alterations. Upon admission, the patient had the following vital signs: blood pressure of 200/100 mm Hg; a heart rate of 90 bpm; a respiratory rate of 18 breaths/min; a body temperature of 36.8°C; a body weight of 68.4 kg; a height of 172 cm; and a BMI of 22.2.

Table 1. Laboratory test results upon admission

Full blood count		**Meningitis/encephalitis PCR assay**	
Hemoglobin at admission	15.0 g/dL	*Bacteria*	
Hematocrit	46.0%	*Escherichia coli* K1	Not detected
Erythrocyte count	5,227/μL	*Haemophilus influenzae*	Not detected
Platelet count	378,000/μL	*Listeria monocytogenes*	Not detected
Mean corpuscular volume	91.5 fL	*Neisseria meningitides*	Not detected
Mean corpuscular hemoglobin	31.9 g/dL	*Streptococcus agalactiae*	Not detected
Leukocyte count	8,600/μL	*Streptococcus pneumoniae*	Not detected
Neutrophils	72.8%	*Mycobacterium tuberculosis*	Not detected
Lymphocytes	17.1%	*Viruses*	
Monocytes	8.3%	Cytomegalovirus	Not detected
Eosinophils	1.2%	Enterovirus	Not detected
Basophils	0.6%	Herpes simplex virus 1	Not detected
Blood chemistry		Herpes simplex virus 2	Not detected
Glucose	80 mg/dL	Human herpesvirus 6	Not detected
Albumin	3.8 g/dL	Human parechovirus	Not detected
Urea nitrogen	24.0 mg/dL	Varicella zoster virus	Not detected
Blood urea nitrogen	47.0 mg/dL	*Yeast*	
Uric acid	4.8 mg/dL	*Cryptococcus neoformans/gattii*	Not detected
Cholesterol	130 mg/dL	**Cerebrospinal fluid**	
Triglycerides	110 mg/dL	Aspect	Rock water
Liver function enzymes		Leukocytes	0
Aspartate transaminase	16.3 U/L	Erythrocytes	Scarce
Alanine transaminase	17.7 U/L	Protein	65.9 mg/dL
Lactate dehydrogenase	230 U/L	Glucose	74.4 mg/dL
Albumin	3.5 mg/dL	Light India ink staining	Negative
Alkaline phosphatase	50.8 U/L	Gram staining	No bacteria
Gamma-glutamyl transpeptidase	25 U/L	Culture	No development
Blood coagulation		**Thyroid function tests**	
Prothrombin time	15 s	Serum thyroxine (T_4)	9.16 μg/dL
Partial thromboplastin time	35 s	Free thyroxine (fT_4)	0.96 ng/dL
International normalized ratio	1.2	Serum triiodothyronine (T_3)	0.7 ng/mL
Electrolytes		T_3 resin uptake (T_3RU)	2.9 pg/mL
Sodium	139.0 mEq/dL	Serum thyrotropin (TSH)	2.43 μU/mL
Potassium	3.9 mEq/dL		
Chlorine	106.0 mEq/dL		
Calcium	8.7 mg/dL		
Phosphorus	3.0 mg/dL		
Magnesium	1.0 mEq/dL		

Clinical Evolution

An emergency computed tomography (CT) of the brain was performed to assess intra-axial lesions (e.g., hemorrhage, ischemia, and tumors), with normal findings. Management for the hypertensive urgency was initiated with antihypertensive drugs (Fig. 1). The patient was evaluated in the neurology department, initiating acyclovir and dexamethasone treatment, as a probable acute viral cerebellitis was suspected. A lumbar puncture was performed, yielding a cloudy aspect with mild pleocytosis (i.e., 20 cells/mm^3), normal protein (i.e., 65.9 mg/dL) and glucose (i.e., 74.4 mg/dL) levels; a meningoencephalitis PCR assay was performed, with no reported bacterial, viral, or yeast infection (Table 1), and a CSF culture resulted negative. The laboratory results at admission and the thyroid function test results are presented in Table 1. To exclude systemic viral infection or drug use, the following tests were requested: antibodies against hepatitis B virus, hepatitis C virus, and HIV, as well as urinalysis for benzodiazepines, barbiturates, cannabis, cocaine, methamphetamines, and opiates; all results were

Table 2. Follow-up laboratory test results

Serum antibodies	
Cytoplasmic antineutrophil cytoplasmatic antibodies (cANCA)	0.1
Perinuclear antineutrophil cytoplasmatic antibodies (pANCA)	0.2
Anti-nuclear antibodies	0.5 IU/mL
Anti-double-stranded deoxyribonucleic acid	1.94 IU/mL
Anti-cardiolipin IgG	3.0 IU/mL
Anti-cardiolipin IgM antibody	3.0 IU/mL
Anti-*N*-methyl-D-aspartate (NMDA), IgG receptor	Negative
Anti-glutamic acid decarboxylase (anti-GAD 65)	Negative
Anti-Ri antibody	Negative
Anti-Hu antibody	Negative
Anti-Yo	Negative
Viral panel	
Hepatitis B virus	Negative
Hepatitis C virus	Negative
Human immunodeficiency virus	Negative
Tumor markers	
Alpha-fetoprotein	4.0 IU/mL
Human chorionic gonadotropin	0.93 mU/mL
CA125	27.0 IU/mL
CA153	3.1 IU/mL
CA19-9	4.5 IU/mL
Carcinoembryonic antigen	1.2 ng/mL
Urinalysis	
Appearance	Pale yellow
pH	7.0
Specific gravity	1.014
Proteins	20 mg/dL
Ketones, glucose, and nitrite	Negative
Leukocytes	3/HPF
Erythrocytes	4/HPF
Bacteria	Negative
Benzodiazepines	Negative
Barbiturates	Negative
Cannabis	Negative
Cocaine	Negative
Methamphetamines	Negative
Opiates	Negative

reported as negative (Table 2). The procalcitonin serum level was 0.19 ng/mL and the lactate dehydrogenase level 230 U/L. Ancillary paraclinical tests were performed to assess systemic infection and an autoimmune etiology (Table 2). After an infectious etiology had been excluded, antiviral and antibiotic therapy were suspended.

After 5 days of hospitalization, the patient had a blood pressure of 160/100 mm Hg and his management was adjusted (Fig. 1). An electroencephalogram was also performed, yielding no epileptogenic or abnormal activity. On the sixth day of hospitalization, the patient developed dysarthria, multidirectional nystagmus, hyperactive delirium, auditory hallucinations, psychomotor agitation, and focal left shoulder myoclonus but no opsoclonus. Olanzapine, prednisone, azathioprine, and plasmapheresis management were initiated to treat the suspected autoimmune encephalitis (Fig. 1). In search of an autoimmune etiology, the following serum tests were requested: cytoplasmic antineutrophil cytoplasmatic antibodies (cANCA), perinuclear antineutrophil cytoplasmatic antibodies (pANCA), anti-double-

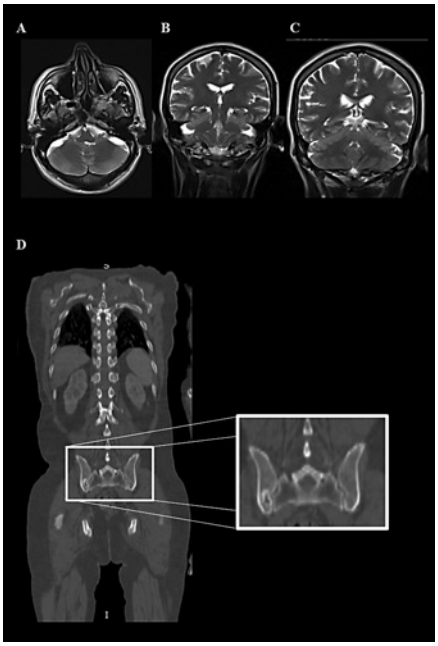

Fig. 2. Brain magnetic resonance imaging (MRI) and thoracic-abdominopelvic computed tomography (CT). **A** Axial T2-weighted MRI scan showing an increased subarachnoid space. **B**, **C** Coronal T2-weighted MRI scans showing reduced bilateral cortical volumes, an increased space bilaterally at the cerebellopontine angle, and an increased subarachnoid space at the posterior cranial fossa. **D** Coronal CT reconstruction with an osteolytic lesion (22 × 13 mm) at the right iliac crest.

stranded deoxyribonucleic acid, anti-cardiolipin IgG, anti-cardiolipin IgM antibody, and anti-*N*-methyl-D-aspartate (NMDAR) IgG antibody; all were reported as negative (Table 2). The following tumor markers were screened, and all were reported negative: α-fetoprotein, human chorionic gonadotropin, CA125, CA153, CA19-9, and carcinoembryonic antigen (Table 2).

Clinical Outcome

In order to screen for a neoplastic process in the brain, simple and contrast MRI scans were performed, while simple and contrast thoracic, abdominal, and pelvic CT scans were also performed to noninvasively assess tumor presence or apparent lymphadenopathy. The brain MRI displayed reduced bilateral cortical volumes and an increased space bilaterally at the cerebellopontine angle (Fig. 2A–C); meanwhile, a 20 × 13 mm osteolytic lesion was observed in the right iliac crest in the pelvic portion of the whole-body CT (Fig. 2D). A testicular ultrasound (USG) was performed, but no solid mass was observed. To further explore the etiology of the PCD, the following serum onconeural biomarkers were assessed and reported negative: anti-Yo, anti-glutamic acid decarboxylase (GAD) 65, anti-Hu, and anti-Ri (Table 2). A positron emission tomography-CT was performed with fluorodeoxyglucose (^{18}FDG), yielding cortical atrophy, a hypermetabolic thyroid nodule (i.e., 14 mm in diameter), a 20 × 29 mm external right iliac nodule (Fig. 3) with an SUV_{max} of 19.4, and a right inguinal nodule with a 6-mm diameter and an SUV_{max} of 2.6. The patient continued having dysarthria, nystagmus, and ataxia; accordingly, the management was changed to quetiapine, prednisone, azathioprine, and cyclophosphamide (Fig. 1), with clinical improvement except for mild ataxia and dysarthria.

Percutaneous USG-guided biopsies of the inguinal ganglion (i.e., 32 × 17 mm by USG) and the thyroid nodule were performed. The thyroid biopsy resulted normal; meanwhile, the histological sections of the inguinal lymph node showed a poorly differentiated malignant neoplastic lesion constituted by pleomorphic cells and atypical large hyperchromic nuclei with prominent nucleoli (Fig. 4A). Immunohistochemical staining was performed, and antibodies against HMB-45, melan-A, and S100 (Fig. 4B–D) were positive, while TTF1, CK20, and

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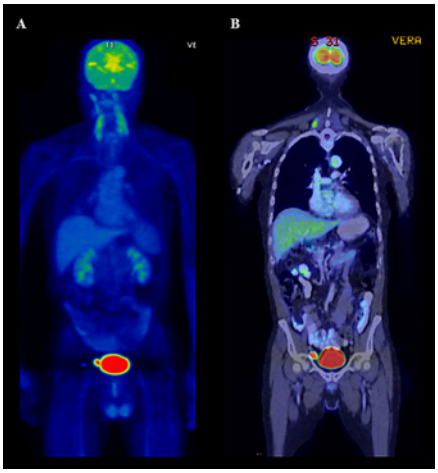

Fig. 3. Whole-body positron emission tomography-computed tomography. **A**, **B** Coronal reconstruction with an increased fluorodeoxyglucose uptake (i.e., an SUV_{max} of 19.4) of a right iliac nodule (i.e., 20 × 29 mm) in the pelvic region. A right thyroid hypermetabolic nodule is also visible.

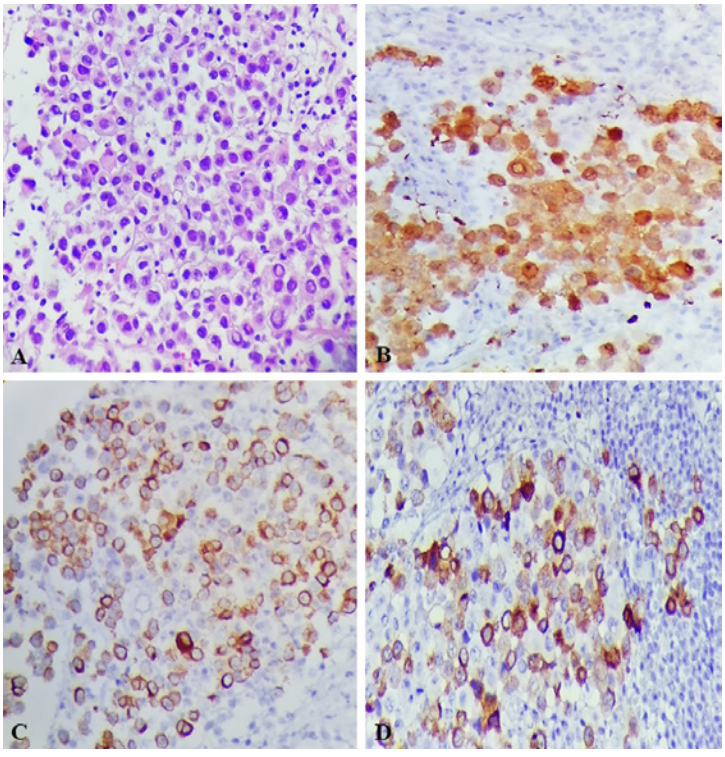

Fig. 4. Histopathology. **A** Inguinal lymph node ganglion, ×40, hematoxylin and eosin staining. There is a neoplasm composed of atypical dyscohesive cells that shows large and hyperchromatic nuclei, with pseudo-inclusions and eosinophilic nucleoli. The cytoplasm is abundant and finely granular. **B** Immunohistochemistry, ×40, S100 staining. Strong and diffuse nuclear and cytoplasmic positivity for S100. **C** Immunohistochemistry, ×40, melan-A staining. Strong and diffuse cytoplasmic positivity for melan-A. **D** Immunohistochemistry, ×40, HMB-45 staining. Strong and diffuse cytoplasmic positivity but weak nuclear positivity for HMB-45.

CK7 antibody staining was negative. The integrated diagnosis was melanoma metastasis from an occult primary cancer (i.e., T0, N2b, M1c; clinical stage IV). The patient was assessed clinically for neoplastic lesions at the dermatology and ophthalmology departments, without finding any primary tumors. In search of the primary melanoma site, colonoscopy and endoscopic assessment were performed, reporting no tumors. The oncology department requested PCR detection of the BRAF oncogene, with a positive result for V600E/Ec. Targeted therapy with selective inhibition of the MAPK pathway with dabrafenib and trametinib was initiated to treat the malignant melanoma metastasis.

Discussion

To the best of our knowledge, this is the first case reported in the literature of a PNS with PCD secondary to a BRAF-positive malignant melanoma metastasis from an occult primary cancer. A melanoma metastasis from an unknown primary cancer is rare, with an incidence of 3.2% [9]. Furthermore, only 5 cases of PNS secondary to melanoma metastasis and only 1 case involving a melanoma metastasis from an occult primary have previously been reported [10].

Our patient underwent whole-body CT, where an osteolytic lesion was observed; additionally, a positron emission tomography-CT with two positive ganglia (i.e., right iliac and inguinal) for FDG uptake were observed. The patient also had negative onconeural serum biomarkers (anti-Yo, anti-GAD 65, anti-Hu, and anti-Ri). After a biopsy of the ganglion, melanoma metastasis was diagnosed through immunohistochemistry. In search of the primary cancer site, the patient underwent endoscopic assessment of the entire gastrointestinal tract mucosa, as well as dermatologic and ophthalmologic clinical assessment, without yielding any tumors. After a positive result for the BRAF V600E/Ec oncogene, chemotherapy with dabrafenib and trametinib was initiated to treat the malignant melanoma metastasis.

PNS include PCD, paraneoplastic limbic encephalitis, subacute sensory neuropathy, paraneoplastic opsoclonus-myoclonus, and Lambert-Eaton myasthenic syndrome [8]. Paraneoplastic degenerative cerebellar ataxia is defined as acute or subacute ataxia in a patient with cancer, diagnosed within 5 years, or with positive specific onconeural antibodies [11]. The association between PCD and malignant melanoma has previously been associated with carbonic anhydrase-related protein VIII [12]. A previous case of PCD revealed edema of the cerebellar cortex and a bilateral hyperintense signal at the caudate nuclei [13]. In the case presented here, the PCD was associated with an increased bilateral subarachnoid space at the pontocerebellar angle. PCD is characterized clinically by progressive ataxia associated with nausea and vertigo; meanwhile, this PNS has been linked to gynecological and breast carcinomas, small cell carcinoma of the lung, and Hodgkin's disease [14]. Among the onconeural antibodies associated with PCD are anti-Yo, anti-Hu, anti-Ri, anti-mGluR1, anti-AMPA, anti-GAD, and P/Q- and N-type calcium channel antibodies [14]. In the case presented here, the anti-Yo, anti-GAD 65, anti-Hu, and anti-Ri onconeural antibodies were negative. A case of a PNS associated with progressive ataxia and dysdiadochokinesia secondary to a BRAF-positive cutaneous malignant melanoma (note: also negative for onconeural antibodies) was treated with high-dose corticosteroids for symptomatic treatment and with dabrafenib and trametinib for the malignancy, with an adequate response [15].

Management of PNS centers on treatment of the underlying tumor and symptomatic treatment [8]. PCD rarely responds to immunotherapy and weakly to intravenous immunoglobulin, steroids, or plasmapheresis [8]. Administration of intravenous rituximab or cyclophosphamide pulses should be considered in refractory cases (i.e., no response or partial response) [5]. Our patient improved clinically after cyclophosphamide infusion (i.e., reduced ataxia and myoclonus). Treatment for the melanoma metastasis from an occult primary was with BRAF and MEK protein inhibitors (i.e., dabrafenib and trametinib).

Limitations

Other onconeural antibodies (e.g., voltage-gated calcium channel antibodies, anti-ANNA1, anti-ANNA2, anti-Tr, anti-amphiphysin, anti-Zic4, and anti-Purkinje cell antibody 2) could not be tested due to the out-of-pocket cost for the patient; furthermore, as the malignancy was immunohistochemically identified and was positive for BRAF oncogene mutation, our limited resources were allocated to the patient's management and disease monitoring. An electromy-

ography was not performed due to the patient's refusal. Other treatments (e.g., intravenous immunoglobulin, plasma exchange, and rituximab) were not used initially to treat the PNS before the identification of the malignant melanoma.

Conclusions

This case is the first presenting with an occult primary BRAF-mutant malignant melanoma with PCD and the second case of a BRAF-mutant melanoma described in the literature. Movement disorders associated with neuropsychiatric symptoms are complex to diagnose. Infectious, metabolic, autoimmune, and paraneoplastic etiologies must be considered and explored. PNS are rare and often associated with antibodies against neural antigens expressed by the tumor. The case presented above describes a patient with a BRAF-positive malignant melanoma metastasis from an occult primary associated with PCD. The patient was successfully treated for the movement and neuropsychiatric symptoms with prednisone, azathioprine, olanzapine, and quetiapine, while the targeted treatment for metastasis from the malignant melanoma was with BRAF and MEK protein inhibitors.

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Statement of Ethics

Approval from the ethics committee was not required due to the nature of this case report. Abiding by the Declaration of Helsinki, patient anonymity was guaranteed. Upon hospital admission, the patient signed an informed consent form permitting the use of his clinical file information, including publication of images, for didactic, research, and publication purposes.

Disclosure Statement

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Author Contributions

O. Jiménez-Zarazúa: project development, data collection, data analysis, and manuscript writing. L.N. Vélez-Ramírez: data collection, data analysis, and manuscript editing: M. Alcocer-León: data collection and manuscript editing. D.A. Hernández-Domínguez: project development, data collection, data analysis, and manuscript editing. J.E. Tadeo-González: data collection and data analysis. M.A. Martínez-Rivera: data collection, data analysis, and manuscript writing. M.D.A. López-González: project development, data analysis, and manuscript editing. S.X.L. Tafoya-Rojas: data collection and data analysis. J.D. Mondragón: project development, data analysis, manuscript writing, and manuscript editing.

Availability of the Data

The clinical data supporting the conclusions of this article are included in the article; the data can be provided on an as-needed basis.

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