American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e922342
DOI: 10.12659/AJCR.922342

Received: 2019.12.23
Accepted: 2020.02.19
Available online: 2020.04.20
Published: 2020.06.23

A Case of Paraneoplastic Cerebellar Degeneration that Preceded the Diagnosis of Classical Hodgkin's Lymphoma by 16 Months

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 44-year-old
Final Diagnosis: Hodgkin's lymphoma
Symptoms: Dizziness • dysarthria • unsteadiness
Medication: —
Clinical Procedure: Chemotherapy • CT scan • onconeuronal antibodies • PET-CT
Specialty: Hematology

Objective: Unknown ethiology

Background: Paraneoplastic cerebellar degeneration (PCD) is a rare condition that can present as an acute or subacute cerebellar syndrome. PCD is most commonly associated with gynecological and breast cancer, small-cell lung cancer, and classical Hodgkin's lymphoma. The symptoms of PCD can arise several months before tumor diagnosis. This report is of a case of a 44-year-old man with PCD that preceded the diagnosis of classical Hodgkin's lymphoma by 16 months.

Case Report: A 44-year-old man was admitted to hospital with a cerebellar syndrome that was initially diagnosed as vertebrobasilar insufficiency. Eight months later, cerebral magnetic resonance imaging (MRI) findings and serum anti-Tr antibodies supported the diagnosis of PCD, but no underlying malignancy was initially found. At 16 months after the initial diagnosis of PCD, the patient developed an enlarged inguinal lymph node. Histology of the excisional lymph node biopsy confirmed the diagnosis of classic mixed cellularity Hodgkin's lymphoma, Ann Arbor stage IIA. The patient responded to four cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy.

Conclusions: This case illustrates that in patients who present with PCD, an associated malignancy, such as classical Hodgkin's lymphoma, may emerge several months later, which supports long-term follow-up. The presence of anti-Tr antibodies may support a diagnosis of classical Hodgkin's lymphoma in a patient with a history of PCD who develops lymphadenopathy.

MeSH Keywords: Hodgkin Disease • Neurologic Manifestations • Paraneoplastic Cerebellar Degeneration

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/922342

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Background

Neurological paraneoplastic syndromes are rare and have been reported in less than 1% of patients with malignant neoplasms [1–3]. The causes of paraneoplastic syndromes remain unknown but are not directly due to metastases, nutritional deficiency, infections, coagulopathies, or toxicity associated with the treatment of malignancy.

Paraneoplastic cerebellar degeneration (PCD) presents as a severe and acute or subacute cerebellar syndrome and is diagnosed most commonly in patients with gynecological and breast cancers, small-cell lung cancer, and Hodgkin's lymphoma [1,2]. The detection of antineuronal autoantibodies against neuronal antigens may support the diagnosis of PCD, which prompts investigations for an underlying tumor.

The association between PCD and Hodgkin's lymphoma was first described by Trotter et al. in 1976 [4]. The delta/notch-like epidermal growth factor (EGFR)-related receptor (DNER) is the target antigen of the anti-Tr antibody response in paraneoplastic syndromes and is also present in the Purkinje cells of the central nervous system (CNS) [5,6]. PCD is associated with extensive loss of Purkinje cells [2,7,8] and is also associated with inflammatory infiltrates in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary nuclei of the medulla oblongata [2]. Although the symptoms of paraneoplastic syndromes can appear after or at the same time as the diagnosis of malignancy, they occur most commonly before the diagnosis of malignancy [1,9]. However, if the clinician is aware of the diagnosis of a paraneoplastic syndrome, such as PCD, malignancy such as Hodgkin's lymphoma may be diagnosed more rapidly. This report is of a case of a 44-year-old man with PCD that preceded the diagnosis of classical Hodgkin's lymphoma by 16 months.

Case Report

A 44-year-old man who worked as a farmer, with no prior significant medical history, was admitted to the emergency room with mild dysarthria, dizziness, unsteady gait, and sudden episodes of loss of consciousness. He spontaneously recovered after three days. He denied experiencing numbness, weakness, dysphagia, photophobia, clonus, rigidity, or anal sphincter relaxation. No accompanying fever, weight loss, or other systemic findings were reported. Laboratory investigations showed mild leukocytosis (11.87×10^3/μL) and neutrophilia (8.9×10^3/μL), and a cranial computed tomography (CT) was normal. He was discharged on 100 mg daily of oral acetylsalicylic acid.

Four days later, he was readmitted and hospitalized following presentation with slurred speech, lack of balance on walking, and weakness of the lower extremities. Physical examination also showed bilateral vertical nystagmus and cerebellar ataxia. During this admission, supra-aortic angio-CT and cerebral magnetic resonance imaging (MRI) were performed, but no imaging abnormalities were found. Neurosonology imaging showed mild stenosis in the right cerebral artery and basilar artery. The patient was discharged with the provisional diagnosis of vertebrobasilar insufficiency.

The patient's clinical condition became worse, and he was unable to perform activities of daily living, but serial cranial CT scans showed no abnormality. He used a wheelchair. His modified Rankin score for neurological disability was 5 out of 6. Other symptoms included irritability, severe dysarthria, bilateral nystagmus, dysdiadochokinesia, a positive Holmes' sign, truncal ataxia, and an ataxic gait. A second MRI showed cerebellar atrophy. He had normal electromyography and a normal electroencephalogram. The detection of serum antibodies to Tr, the target antigen of delta/notch-like epidermal growth factor (EGFR)-related receptor (DNER), and cerebral MRI findings supported a diagnosis of paraneoplastic cerebellar degeneration (PCD), eight months after the onset of the neurological symptoms. He was treated with intravenous immunoglobulin (IVIG) (20 gm/24 h) for five days but without clinical improvement.

Following a diagnosis of PCD, the patient was investigated for an underlying malignancy. CT imaging of the neck, thorax, abdomen, and pelvis was negative. A combined positron emission tomography (PET) and CT scan identified a metabolically active subcranial lymph node measuring 2 cm in diameter, with a maximum standardized uptake value (SUV) of 4 (liver SUV of 2.6), and cerebellar hypoactivity. The histology of a transbronchial needle aspiration biopsy was nonspecific. The enlarged subcranial lymph was not visible in a second PET-CT investigation four months later. As no malignancy was identified, the patient continued to be treated with IVIG without chemotherapy.

Sixteen months after the initial diagnosis of PCD was made, the patient developed an enlarged left inguinal lymph node measuring 3 cm in diameter, which was identified by the patient's relatives. PET-CT imaging showed a single infradiaphragmatic lymph node in the left iliac and inguinal regions (SUVmax 16.64), with generalized mild lymphadenopathy. Histology of the excisional lymph node biopsy confirmed the diagnosis of classic mixed cellularity Hodgkin's lymphoma, Ann Arbor stage IIA.

The patient was treated with four cycles of chemotherapy consisting of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and achieved a complete metabolic response after the second cycle, which was confirmed by PET. At the last follow-up, two years after the diagnosis of Hodgkin's lymphoma, the patient had a complete response, and anti-Tr antibodies remained negative. However, the patient experienced minor

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improvements in his neurological symptoms, with residual dysarthria, dependency on the use of a wheelchair, and persistent mood disorder.

Discussion

Despite the presence of a tumor, neurologic syndromes of an unknown cause do not always represent a paraneoplastic syndrome. The detection of onconeural antibodies has been of great importance in indicating the presence of a tumor. However, a paraneoplastic syndrome is not always associated with onconeural antibodies, and a neurological syndrome may not exist despite detecting these antibodies [1,10].

In 2004, diagnostic criteria for paraneoplastic neurological syndromes were proposed to include definite and possible cases [10]. A set of diagnostic criteria was based on the presence or absence of malignancy for classical paraneoplastic syndrome with the use of well-characterized onconeural antibodies [10]. More recently, two onconeural antibodies have been added to the list of well-characterized onconeural antibodies, including antibodies to Sox1 and Tr [1,11].

Paraneoplastic syndromes are a rare association with lymphoma. The type and frequency of paraneoplastic syndromes are different between classical Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Limbic encephalitis (LE) and PCD are almost exclusively seen in patients with Hodgkin's lymphoma. Usually, lymphomas are associated with unique paraneoplastic syndromes, but the co-occurrence of paraneoplastic syndromes have also been reported [12,13]. Sensorimotor neuropathies and dermatomyositis are more common in Hodgkin's lymphoma, but the association between Hodgkin's lymphoma and acute motor and sensory axonal neuropathy (AMSAN) has also been recently reported [14].

The largest published case series included 28 patients with PCD who had anti-Tr antibodies, 25 of whom were diagnosed with classical Hodgkin's lymphoma [7]. The diagnosis of PCD preceded the diagnosis of Hodgkin's lymphoma in 20 patients with a median time between the development of paraneoplastic syndrome and tumor diagnosis of 3.5 months (range, 0–24 months) [7]. This finding has been supported by other studies [3,9,15]. The majority of patients with PCD and Hodgkin's lymphoma were male, and the most common histopathologic type was nodular sclerosing Hodgkin's lymphoma [7]. In another case series, the diagnosis of Hodgkin's lymphoma preceded the neurologic symptoms in 17/21 patients [16]. The reason for the different clinical presentations is unclear [7].

In this present report, a case was presented of a patient with PCD in with neurological symptoms diagnosed 16 months before the diagnosis of Hodgkin's lymphoma. This case report is unusual because 16 months is one of the longest periods between the onset of PCD and the diagnosis of Hodgkin's lymphoma. Chepovetsky et al. published a case report of an older man with PCD who was anti-Tr antibody-positive who presented without an initial detectable underlying neoplasm, in whom Hodgkin's lymphoma was diagnosed two years later [3].

It is possible that in cases of paraneoplastic syndrome with cerebellar manifestations, such as PCD, with anti-Tr antibodies, Hodgkin's lymphoma should be excluded during long-term follow-up. In this report, the diagnosis of Hodgkin's lymphoma was made after 16 months from the onset of cerebellar neurological symptoms, which meant that the effective treatment of the lymphoma did not improve the patient's neurological deficit. Earlier therapeutic intervention might have resulted in improved neurological outcome. Under such circumstances, the use of new methodologies, such as liquid biopsy, which can detect mutations associated with the disease, could improve diagnosis [17]. This patient had some unique clinical features. He developed dizziness, dysarthria, and ataxic gait early on, rather than prodromal symptoms, followed by progression to ataxia, diplopia, dysarthria, and dysphagia [2]. The initial cerebral magnetic resonance imaging (MRI) findings were normal, although some patients show minor abnormalities [2,9]. The only abnormality detected in this patient was the development of cerebellar atrophy, as shown by MRI (Figure 1), which was consistent with low fluorodeoxyglucose (FDG) uptake in positron emission tomography and computed tomography (PET-CT) imaging [2,8,18] (Figure 2).

The pathogenesis of PCD remains unclear, but it features extensive loss of cerebellar Purkinje cells, associated with inflammatory infiltrates in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary nuclei [1,6,7,8]. Neuronal loss is a result of the intrathecal synthesis of anti-Tr antibodies targeting the delta/notch-like epidermal growth factor (EGFR)-related receptor (DNER) transmembrane protein that is preferentially expressed in the Purkinje cell dendrites [1,6,19]. DNER has not yet been identified in tissue samples of Hodgkin's lymphoma, which suggests that the immune response is not controlled by ectopic tumor expression of the antigen [1].

The most useful diagnostic test for PCD is the detection of onconeuronal antibodies in serum or cerebrospinal fluid (CSF). As in this case, the Tr antibody is no longer present after the treatment of classical Hodgkin's lymphoma [7]. Early treatment of the underlying malignancy is essential for stabilizing or improving the patient's neurological symptoms in PCD [2,6,7,15,20]. Usually, plasma exchange, intravenous immunoglobulin (IVIG), or immunosuppressive treatment with corticosteroids or cyclophosphamide are ineffective. However, Gungor et al. described an 11-year-old boy in whom chemotherapy did not result in

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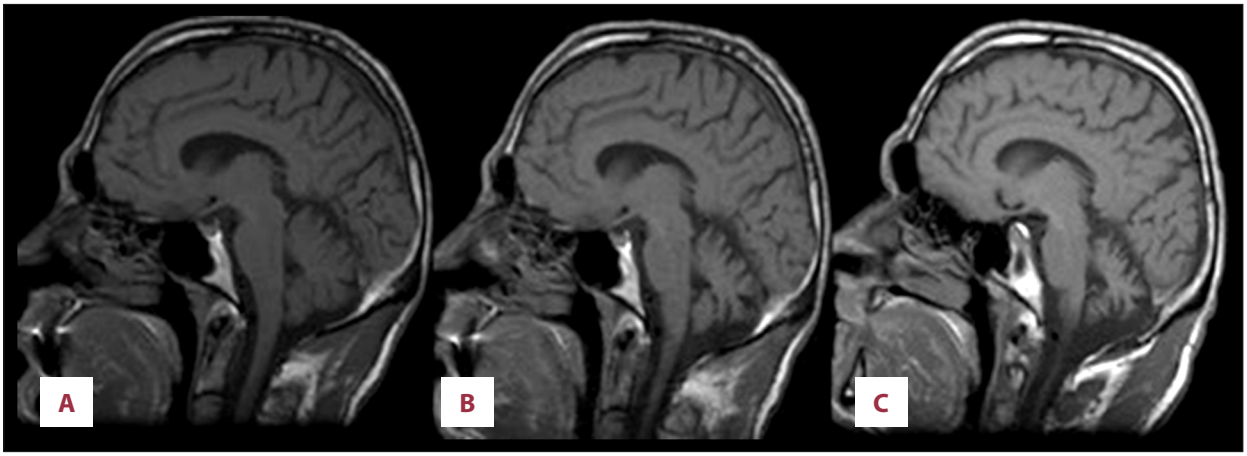

Figure 1. Sagittal cerebral T1-weighted magnetic resonance imaging (MRI) sequences in a 44-year-old man with paraneoplastic cerebellar degeneration (PCD) who developed classical mixed cellularity Hodgkin's lymphoma 16 months later. (**A**) Sagittal cerebral T1-weighted MRI at one month (**B**), two months, and (**C**) at sixth months after clinical onset. Cerebral MRI shows cortical and subcortical atrophy at the supratentorial and infratentorial levels and marked cerebellar atrophy.

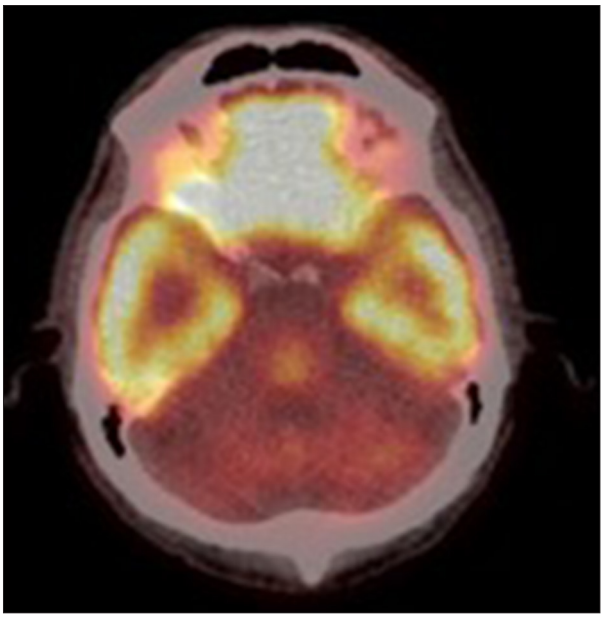

Figure 2. Axial cerebral imaging with 18-fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET-CT) shows a reduction of metabolic activity in the cerebellum in a 44-year-old man with paraneoplastic cerebellar degeneration (PCD) who developed classical mixed cellularity Hodgkin's lymphoma 16 months later.

any neurological recovery, but subsequent plasmapheresis with immunoadsorption and immunoglobulin was followed by improvement of neurological symptoms [15]. The prognosis of PCD can be poor, even in cases where antitumor therapy is started promptly and the antibodies are removed. It has been estimated that only 14% of patients recover or experience improvement in their neurological changes [1,7,16]. New strategies, such as non-invasive detection of genomic imbalances in early and advanced stages of Hodgkin's lymphoma by sequencing of circulating cell-free DNA, could enable earlier diagnosis of Hodgkin's lymphoma [17].

Conclusions

Paraneoplastic cerebellar degeneration (PCD) is a rare condition that can present as an acute or subacute cerebellar syndrome. This case illustrates that in patients who present with PCD, an associated malignancy, such as classical Hodgkin's lymphoma, may emerge several months later, which supports the need for long-term follow-up. The presence of anti-Tr antibodies may support a diagnosis of classical Hodgkin's lymphoma in a patient with a history of PCD who develops lymphadenopathy. Rapid diagnosis and treatment of Hodgkin's lymphoma in patients with PCD may prevent the development of irreversible cerebellar symptoms due to neuronal loss.

Conflict of interest

None.

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