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Hodgkin lymphoma presenting as paraneoplastic cerebellar degeneration: A case report

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Abstract

A 49-year-old male presented with subacute onset of ataxia, dizziness, and dysarthria over a 4-week period. Laboratory workup and magnetic resonance imaging brain imaging were unremarkable, and no neurological etiology was identified. Anti-Tr antibodies were detected in serum and cerebrospinal fluid. A positron-emission tomography scan showed small nonspecific periaortic and aortocaval lymph nodes, which were not amenable for biopsy. He was treated with immunosuppressive treatment, and a CT scan showed resolution of the previous activity. A repeat positron-emission tomography scan 6 months after the original presentation showed reappearance with increased size and activity of the lymph nodes. An abdominal lymph node biopsy showed classical Hodgkin's lymphoma. The bone marrow biopsy was negative, placing him at Ann Arbor stage IIA. He was treated with two cycles of Adriamycin, Bleomycin, Vinblastine, and Dacarbazine followed by two cycles of Adriamycin, Brentuximab Vedotin, Vinblastine, and Dacarbazine due to a drop in diffusion capacity of the lungs for carbon monoxide from Bleomycin. He remains in remission from the lymphoma but with residual neurological symptoms. This case report suggests that patients with Hodgkin's and paraneoplastic neurological syndrome may demonstrate radiological improvement related to immunosuppressive treatment which can delay diagnosis and accurate treatment in patients with paraneoplastic cerebellar degeneration and underlying malignancy. The presence of anti-Tr antibody supports the diagnosis of Hodgkin lymphoma in the setting of paraneoplastic cerebellar symptoms.

Keywords

Hodgkin lymphoma, paraneoplastic neurological syndrome, paraneoplastic cerebellar degeneration, anti-Tr antibody

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Introduction

Paraneoplastic neurological syndromes (PNSs) can manifest as the initial symptom of a malignancy while the primary cancer remains occult. The constellation of such symptoms includes ataxia, tremors, rigidity, hypokinesis, or other movement disorders such as chorea or pseudo athetosis. The neurological manifestations are hypothesized to be secondary to immune mechanisms triggered by antigens normally present in the nervous system and ectopically expressed by the tumor, also known as onconeural antigens (Graus et al.[1]). PNS can be associated with specific autoantibodies directed against the tumor cells, normal cells, or both. An onconeural antibody is considered high-risk (associated with cancer in more than 70% of cases), intermediate-risk (associated with cancer in 30-70% of cases), or low-risk (associated with cancer in less than 30% of cases) (Jadoon et al.[2]). High-risk phenotype includes rapidly progressive paraneoplastic cerebellar degeneration (PCD), limbic encephalitis (LE), encephalomyelitis, opsoclonus–myoclonus, sensory neuropathy, and Lambert Eaton syndrome. Amongst the PNSs, PCD is a rare manifestation of solid tumors such as gynecologic, breast, small cell lung cancer, and lymphomas, specifically Hodgkin lymphoma (HL). PCD tends to occur before the diagnosis of HL in approximately 80% of cases.

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CRMP5, NR1, Ma2, GAD65, Yo (Purkinje cell antibody-1), and voltage-gated calcium channels (VGCCs) are some of the antibodies seen with solid tumors. Yo, Tr, and VGCC antibodies can preferentially cause cerebellar ataxia. Although anti-Tr antibodies are seen in lymphomas, either Hodgkin or non-Hodgkin, the anti-Tr antibodies are more specific to HL (Panzer and Dalmau Current Opinions Neurology 2011[3]). The association between PCD and HL was first described in 1976 when antibodies targeting the cerebellar Purkinje cells were discovered (Trotter et al.[4]). The anti-Tr antibody targets the antigen delta/notch-like epidermal growth factor-related receptor (DNER) transmembrane protein expressed in central nervous system Purkinje cells (Christensen et al.[5]).

The hallmark of PCD is extensive loss of Purkinje cells of the cerebellum and inflammatory infiltration in the cerebellar cortex, nuclei of the cerebellum, and medulla oblongata (Dalmau and Rosenfeld[6]). Anti-Tr antibodies target the DNER transmembrane protein and disrupt the DNER signaling resulting in loss of Purkinje cell neurons (Greene et al.[7]). The Purkinje cell antigens can cross-react with onconeural antibodies produced by the host's immune system.

Magnetic resonance imaging (MRI) is the gold standard modality for imaging and can show hyperintense T2 signals in the cerebellar hemispheres. Early on in the course of the presentation, MRI may be normal. Cerebellar atrophy may be noted later on in the clinical course. Cerebrospinal fluid (CSF) typically shows pleocytosis with elevated CSF protein levels. Onconeural antibodies may be detected in the serum or CSF.

PCD typically presents with rapid onset of ataxia, dizziness, vertigo, dysarthria, nystagmus, and diplopia. This may be preceded by headache, nausea, vomiting, and fever (Marsili et al.[8]). The symptoms can appear at the same time as the diagnosis of malignancy, or more commonly occur before the primary malignancy is even discovered. Symptoms can manifest as early as sixteen months preceding the diagnosis of classical HL(Arratbel et al.[9]). The largest published case series includes 28 patients with PCD who were positive for the anti-Tr antibodies, with 25 of them being diagnosed with HL. The diagnosis of PCD preceded the diagnosis of HL in 20 patients (Bernal et al.[10]). A second case series of 21 patients with HL had symptoms precede the diagnosis in 17 of them (Hammack et al.[11]). In another case series of classic HL, simultaneous diagnosis of PNSs and HL was seen in 42.2%. The diagnosis of HL antedated the diagnosis of PNSs in 33.6%, and the diagnosis of PNSs preceded that of HL in 16.4% (Fakih et al.[12]).

HL is a lymphoid neoplasm with two main variants: classical and nodular lymphocyte-predominant (NLP). Classical HL is further characterized into subtypes including nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted. Classical HL is more common and has a characteristic microscopic finding of multinucleated Reed–Sternberg cells. NLP HL has characteristic lymphocyte-predominant (LP) cells surrounded by either B or T lymphocytes.

We describe a case of HL presenting as PCD associated with anti-Tr antibodies. This case highlights that transient radiological improvement with immunosuppressive treatment can delay a diagnosis of lymphoma necessitating the need for tissue biopsy for early accurate treatment to prevent permanent neurological disability.

Case report

A 49-year-old Caucasian male with a history of bipolar disorder, depression, and migraines presented to an outside institution with subacute onset ataxia, dysarthria, and vertigo over 4 weeks. An MRI of the brain and spinal cord were unremarkable. The patient underwent a first lumbar puncture which revealed CSF pleocytosis with a white blood count (WBC) of 159 (78% lymphocytes, 18% monocytes, 3% neutrophils, and 1% basophils). There was evidence of CNS inflammation with elevated CSF protein and positive oligoclonal bands. Extensive infectious testing in the blood and CSF were negative.

He was initiated on intravenous steroids with concerns of autoimmune cerebellar syndrome with only minimal improvement after 5 days of treatment. Repeat CSF analysis showed continued pleocytosis with a CSF WBC of 40 (88% lymphocytes, 11% monocytes, and 1% neutrophils), and CSF cytology and lymphoma markers were negative. The autoimmune movement disorder panel was positive for anti-Tr antibodies in the CSF (1:128 titer) and glutamic acid decarboxylase (GAD) in the serum. GAD is an antibody that is typically seen in autoimmune disorders such as thyroiditis, pernicious anemia, and type I diabetes.

Malignancy screening was initiated for suspected lymphoma which has a strong association with anti-Tr antibody. A bone marrow biopsy with flow cytometry was negative, and a CT scan of the chest, abdomen, and pelvis showed no evidence of lymphoma. A testicular ultrasound was also negative. However, a whole-body positron-emission tomography (PET) scan revealed four small periaortic and aortocaval lymph nodes demonstrating radiopharmaceutical uptake. The largest lymph node in the anterior periaortic region measured 6 mm× 6 mm with a standardized uptake value (SUV) of 5.45. No other areas of abnormal radiopharmaceutical uptake were identified. The lymph node was deemed too small to biopsy, and a repeat PET scan was scheduled 6 months out. In the meanwhile, the patient received multiple immunosuppressive therapies including plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab which resulted in modest clinical improvement.

A repeat CT 3 months later showed resolution of the small lymph nodes noted earlier. A second serum movement disorder panel was positive for both GAD antibody and anti-Tr antibody. It was questioned if the negative CT scan reflected a radiologic improvement of a potential underlying malignancy secondary to the effect of steroids and other immunosuppressive treatments the patient

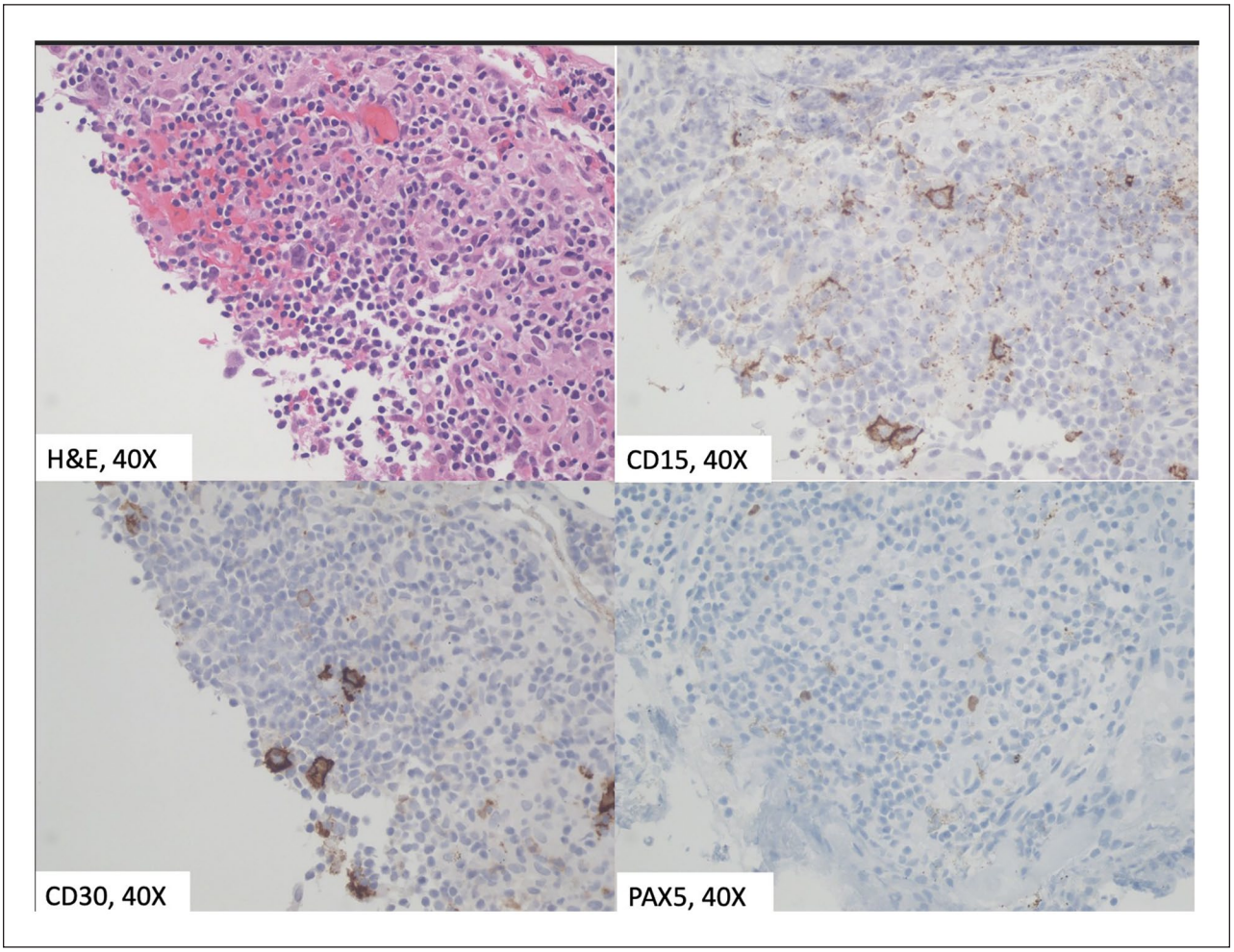

Figure 1. Hematoxylin and Eosin-stained slides show scattered large cells, a single prominent nucleolus in a background of small lymphocytes, scattered eosinophils, and occasional neutrophils. The large mononuclear cells are positive for CD15, CD30, and appear to express dim PAX5. Scale and magnification is 200 μm and 40×, respectively.

received. He continued to have persistent symptoms with dysarthria, ataxia, and swallowing problems, which required a gastric tube for nutrition.

A second PET scan 6 months after the first showed two non-enlarged periaortic lymph nodes at 7 mm with an SUV of 5.5. A left periaortic lymph node biopsy by interventional radiology revealed atypical CD30-positive large cells (Figure 1) consistent with classical HL. A bone marrow biopsy showed no evidence of lymphoma resulting in a stage IIA Hodgkin diagnosis. The patient received systemic chemotherapy with Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD). Bleomycin was stopped due to a drop in diffusion capacity for carbon monoxide (DLCO) after two cycles. He received AVD with Brentuximab Vedotin for two further cycles. A post-treatment PET scan was negative. The patient remains clinically in remission 2 years after completion of treatment. Unfortunately, he had minimal improvement of his cerebellar syndrome, continues to have significant neurological disability, and remains in a long-term care facility.

Discussion

An international panel of neurologists established guidelines in November 2002 for the diagnostic criteria for PNS (Graus et al.[13]). The panel concluded that the diagnostic criteria for PNS should be based on the presence or absence of cancer, the definition of classical syndrome, and a well-characterized onconeural antibody. Based on the clinical symptoms, antibody type, and presence or absence of underlying cancer, two levels of evidence of PNS have been suggested: definite and possible. The diagnostic criteria were updated by the PNS-Care panel in 2021 with the term "high-risk phenotype" for classical syndrome and rapidly progressive cerebellar syndrome for subacute cerebellar

degeneration (Graus et al.[14]). Onconeural antibodies have been replaced by the term "high-risk antibodies."

A thorough medical history is crucial. Toxins that cause cerebellar damage such as carbon tetrachloride, heavy metals, phencyclidine, gallium, and toluene should be excluded from the differential diagnosis. Medications associated with cerebellar ataxia include antibiotics, antivirals, antihelminthics (metronidazole, piperazine, zidovudine), antiepileptics (phenytoin), sedative drugs (barbiturates, benzodiazepine, bromides), chemotherapeutic agents/immunosuppressive drugs (asparaginase, cyclosporine, cytarabine, fluorouracil, tacrolimus), and others (amiodarone, bismuth, glucocorticoids, lithium) (Adams et al.[15]). Laboratory testing should include vitamin levels, thyroid function tests, HIV serology, anti-gliadin and anti-GAD antibody tests, and CSF analysis to establish the diagnosis of PCD. Differential diagnosis for PNS includes malignancy, stroke, demyelinating disease, vitamin deficiency, hypothyroidism, infection/post-infection such as HIV, SARS-COVID, primary autoimmune cerebellar ataxia (PACA), and other degenerative etiologies (Höftberger et al.[16]). Radiological imaging plays a pivotal role in diagnosis. Symptoms should guide imaging for tumor screening. The European Federation of Neurological Societies (EFNS) Task Force published guidelines for cancer search when PCD is suspected. CT thorax and abdomen, ultrasound pelvis, and mammogram with or without breast MRI is recommended. A whole-body 18F-fluorodeoxyglucose PET (FDG-PET) scan should be considered if preliminary imaging is negative (Titulaer et al.[17]). If cancer is not detected at the baseline assessment despite the presence of neurological symptoms and identification of high-risk antibodies, repeat cancer screening should be considered every 4–6 months over a period of 2 years (Loehrer et al.[18]).

In our case report, anti-Tr antibody in the CSF raised the concern for HL but because the lymph nodes in the abdomen were very small, a diagnostic biopsy could not be attempted. The presence of GAD antibody in the serum indicated an autoimmune neurological process; thus, an empiric trial of immunosuppressive treatment was attempted. The follow-up PET scan showed resolution of the previously noted lymph nodes, demonstrating that even with repeat cancer screening imaging, diagnosis can be delayed due to limitation of tissue sample as a result of immunosuppressive drugs. In the presence of anti-Tr (DNER) antibody, the frequency of HL is up to 90% (Roszkowska et al.[19]). Thus, a high index of suspicion and workup for HL is warranted if anti-Tr antibody is detected.

After completion of treatment, only a proportion of patients who are in remission from a lymphoma seem to recover from the PCD-related symptoms. PCD related to antibodies against the DNER antigen do not seem to respond to treatment as well as disorders related to antibodies against other cell surface antigens. In two larger series of PCD and HL, only 14% showed a partial to full neurological recovery. The prognosis of Hodgkin's with PCD is considered to be better than PCD associated with solid tumor cancers. Patients with PCD had a median survival of approximately 113 months for anti-Tr antibodies compared to 69 months for anti-Ri, 13 months with anti-Yo, and 7 months for anti-Hu (Shams'ili et al.[20]). Corticosteroids or other immunosuppressive treatments do not seem to help as much, and most patients with PCD seem to remain in a disabled state after treatment (Hammack et al.[11]). Therapy directed against underlying cancer seems to be of fundamental importance as opposed to immunosuppressive treatment (Candler et al.[21]). A recent systematic literature review of 128 patients with PNS and classic HL showed that the complete response rate of lymphoma with treatment was 77% and resolution of the PNS was only 54% (Fakih et al.[12]).

Conclusion

PNSs, although rare, can be the first presentation of a lymphoma. A high index of suspicion in the setting of unexplained movement disorders can help initiate a malignancy workup. Detection of anti-Tr antibodies supports the diagnosis. Thus, recognition of these symptoms earlier in the course of the illness is critical. A thorough workup for a suspected HL with imaging, testing for onconeural antibodies, and excluding other causes can lead to early detection and treatment thus preventing further neurological deterioration.

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Statements and Declarations

Consent for publication

Written informed consent was acquired from the patient for clinical information and medical images to be published.

Author contributions/CRediT

A.K. conceptualization, formal analysis, investigation, methodology, writing—original draft, review and editing; L.A.J. writing, review and editing; M.M. review and editing.

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Informed consent

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