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SHORT REPORTS

Paraneoplastic Cerebellar Degeneration in Nasopharyngeal Carcinoma: a Unique Association

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Abstract

Paraneoplastic cerebellar degeneration (PCD) is a rare disorder that is associated with lung or gynecological malignancies and Hodgkin lymphoma. Neurologic symptoms are commonly the initial presenting sign leading to the diagnosis of an underlying malignancy. We are presenting an Asian male with progressive lower extremity weakness with EBV-positive nasopharyngeal carcinoma (NPC) and anti-Yo antibodies. Peculiarly, transient diffuse leptomeningeal enhancement is seen on MR imaging. This is the first report of PCD associated with NPC and thus illustrates that PCD embodies a boarder set of disease than previously described.

Keywords Paraneoplastic · Cerebellum · Cerebellar · Nasopharyngeal · Cancer · Oncology · Neurology · Leptomeningeal · Anti-Yo · Autoimmune · Syndrome

Abbreviations

CD	Classification determinant
CSF	Cerebrospinal fluid
CT	Commuted tomography
PET	Positron emission tomography
EBV	Epstein-Barr virus
EBER-ISH	Epstein-Barr encoding region in situ hybridization
ER	Emergency room
FLAIR	Fluid attenuation inversion recovery
IgG	Immunoglobulin G
IV	Intravenous
NPC	Nasopharyngeal carcinoma
MRI	Magnetic resonance imaging
PCD	Paraneoplastic cerebellar degeneration
PCR	Polymerase chain reaction
RBC	Red blood cell
RNA	Ribonucleic acid
WBC	White blood cell
WHO	World Health Organization

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Introduction

Paraneoplastic cerebellar degeneration arises from immune-mediated responses to the cerebellum [1]. Symptoms include dizziness, ataxia, dysarthria/dysphagia, diplopia, and nystagmus of subacute onset, progressing towards inability to ambulate within months [2]. It is associated with gynecological or pulmonary malignancies and lymphoma and sometimes with esophageal and gastric adenocarcinoma [3–5]. Initial MRI is normal with later stages showing cerebellar atrophy [6]. We present a patient with newly diagnosed nasopharyngeal carcinoma and ataxia, with leptomeningeal enhancement on MRI and brain biopsy-proven, anti-Yo antibody-positive, PCD. This is the first reported instance of NPC associated with PCD [7].

Clinical Presentation

A middle-aged male with a 46 pack–year smoking history presented to the ER with left greater than right lower extremity weakness progressing over 4 months, difficulty with ambulation, and a 15-lb weight loss. He denied any pain, fever/chills, night sweats, headaches, dizziness, or blurry vision. There were no preceding illnesses, insect bites, or rash.

On examination, the patient had sustained gaze-evoked nystagmus with saccades beating into the direction of gaze. There was proximal muscle weakness with 4/5 power on hip flexion and decreased tone, as well as gait instability and symmetric truncal appendicular ataxia. Reflexes were mildly reduced but with intact sensation. An EMG showed small polyphasic myopathic motor units in the deltoid and biceps. Repetitive stimulation did not show an increment or a decrement of left median and accessory nerve compound motor action potentials.

Lumbar puncture revealed high protein (187) and normal glucose (79) with 38 white blood cells, predominant lymphocytosis to 92% and 8% monocytes, but no definitive infectious cause or malignant cells were seen. Serum anti-Yo antibodies were positive on immunofluorescence assay.

Imaging of the spine and bloodwork ruled out spinal cord compression, vitamin B_{12} deficiency, and diabetes as causes for the presenting neuropathy. MRI brain (see Figs. 1 and 2) showed leptomeningeal enhancement surrounding the cerebellum and oculomotor nerves and asymmetric soft tissue fullness in the left fossa of Rosenmuller with an adjacent enlarged lymph node. Three months later, follow-up MRI demonstrated resolution of enhancement with new areas of symmetric high signal-intensity surrounding the dentate nuclei (Fig. 3). No cerebellar atrophy was seen.

Biopsy of the nasopharyngeal mass in the fossa of Rosenmuller described on initial MRI confirmed NPC. Brain biopsy showed Purkinje cell loss, reactive gliosis and

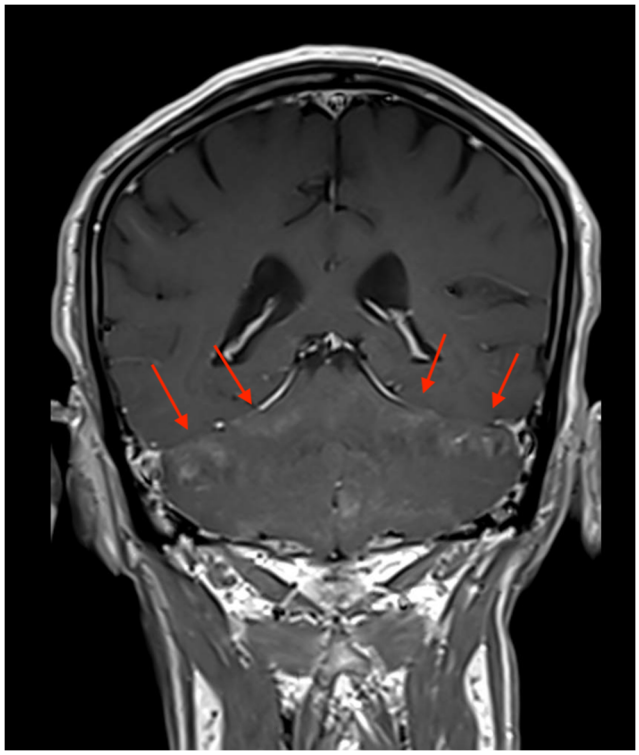

Fig. 1 Imaging at presentation. Coronal T1-weighted imaging after the intravenous administration of contrast demonstrates patchy enhancement of the cerebellar hemispheres peripherally (red arrows) corresponding with the subarachnoid space and leptomeningeal surfaces

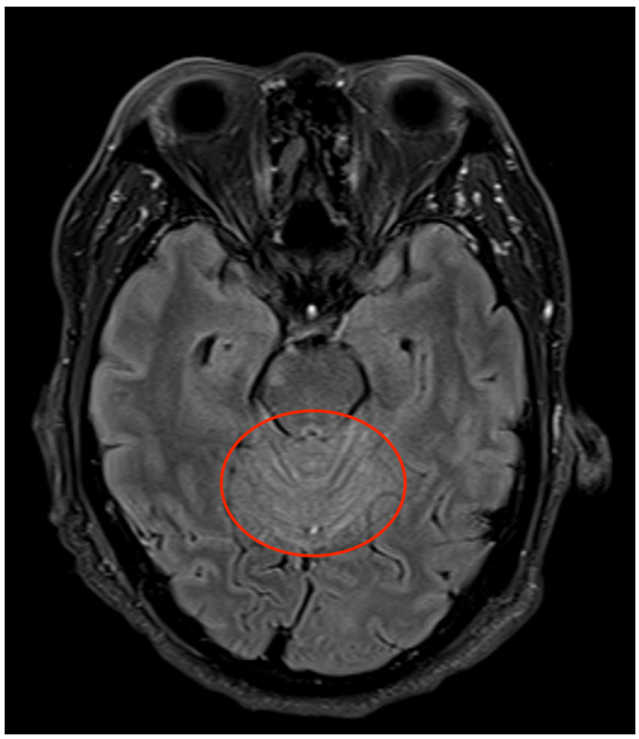

Fig. 2 Leptomeningeal enhancement. Axial contrast enhanced fluid-attenuated inversion recovery (FLAIR) prepared T2-weighted imaging reveals linear high signal intensity over the surface of the cerebellum (red circle) not present on the pre-contrast FLAIR (not shown) compatible with leptomeningeal enhancement

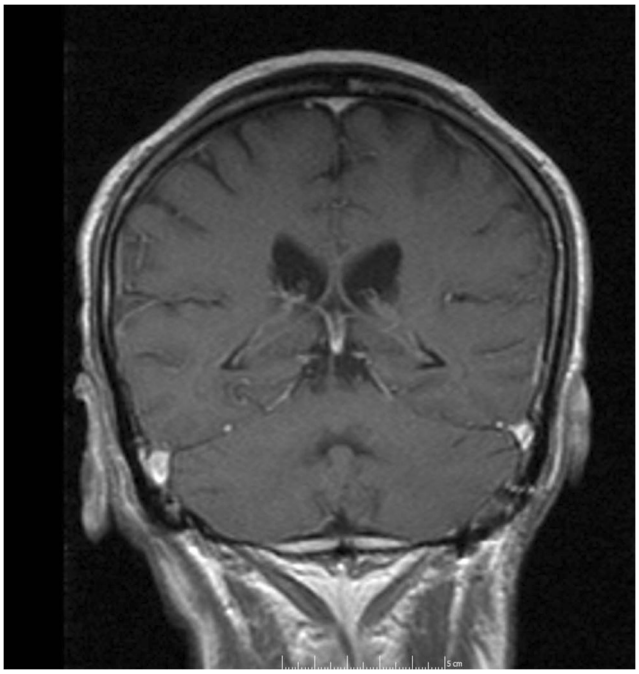

Fig. 3 Resolution of leptomeningeal enhancement. Imaging 3 months into treatment for nasopharyngeal carcinoma. Coronal T1-weighted imaging after the intravenous administration of contrast demonstrates resolution of the enhancement of the cerebellar hemisphere surfaces and the cranial nerves. Post-contrast FLAIR also revealed no leptomeningeal enhancement

lymphohistiocytic inflammation, and no evidence of metastatic carcinoma on cytology, CT, and PET imaging.

Patient received treatment for his NPC with chemoradiation and has been in remission. However, his disability deteriorated, plateauing to a modified-Rankin scale score of 4. High-dose intravenous steroids followed by IVIG resulted in no improvement. This treatment strategy was employed during the patient's second hospitalization after the diagnosis of NPC was made as the patient was exhibiting worsening ability to ambulate at that time.

Discussion

The anti-Yo antibody is one of the several types of antibodies found in the CSF or blood plasma in patients with paraneoplastic neurologic syndromes. Paraneoplastic syndromes occur when a malignancy expresses a protein antigen that is normally expressed only in the nervous system. The patient's immune response, mounted against the malignancy, inadvertently reacts against antigens of the nervous system. Often, these autoantibodies and their consequent symptoms appear prior to diagnosis of cancer. Anti-Yo antibodies are associated with paraneoplastic cerebellar degeneration (PCD), and, notably, recent studies have shown that anti-Yo antibodies may destroy Purkinje cells of the cerebellum. Symptoms of PCD include incoordination or ataxic gait, nystagmus, and dysarthria [8]. The ataxic syndrome associated with anti-Yo antibody accounts for 50% of all cases of paraneoplastic neurological syndromes and is thus the best studied. It is strongly associated with gynecological malignancies [7]. In Shams'ili et.al, 100% of patients (19) with anti-Yo antibodies had characteristic ataxia. Of these, 9/19 (47%) had gynecological cancer, 3/19 (16%) had breast cancer, and 4/19 (21%) patients did not demonstrate any evidence of tumor [3]. In one case, a parotid gland primary was found [9]. PCD has been associated with gastric adenocarcinoma in two instances (Debes J.D., et. al.; Meglic B., et.al) and esophageal adenocarcinoma in one instance (Sutton IJ., et. al.). However, there are no previously published reports of NPC associated with PCD (quote Toro C, et. al.).

Additionally, there have been no reports of leptomeningeal or cranial nerve enhancement associated with PCD [10, 11]. The etiology of this enhancement would be purely speculative as the oculomotor nerves were not biopsied. Additionally, biopsies of the cerebellum as well as repeated CSF analyses did not reveal metastatic malignant disease. Typically, early imaging in PCD is described as "remarkably unremarkable" with later stages showing cerebellar atrophy [12, 13]. Cerebellar enhancement was described by de Andrés et al. in a middle-aged woman who presented with gait instability, personality/mood changes, and a lung mass. Repeated MRI 2 months thereafter revealed marked atrophy of the cerebellar structures [14]. In our patient, the enhancement disappeared on later imaging whereas the patient's symptoms worsened. Additionally, imaging did not show correlative cerebellar atrophy although Purkinje cell loss was observed microscopically. It is also important to note that the initial leptomeningeal enhancement could easily have been attributed to metastatic disease; however, an unremarkable lumbar tap should provide a clinical clue for an alternative process such as PCD.

Therefore, when a paraneoplastic neurological syndrome such as PCD is recognized, a more extensive work up for underlying malignancy should be undertaken as it seems that PCD is associated with a broader set of malignancies than previously described. Furthermore, meningeal or cranial nerve enhancement on MR imaging may well be consistent with paraneoplastic disease.

It is controversial whether anti-tumor treatment improves overall survival and morbidity in anti-Yo PCD. Our patient had no neurologic improvement despite remission of NPC, perhaps due to structural parenchymal injury, as evidenced by later enhancement of the dentate nuclei on imaging. In contrast, anti-tumor treatment in anti-Hu-positive patients has better outcomes [7].

No evidence-based guidelines for the treatment of PCD exist. Several case series employed plasma exchange, IVIG, and immunosuppressive therapy. With steroids, 1 in 17 patients showed a minimal and unsustained response. With cyclophosphamide, four patients showed no clinical benefit [3].

One study showed sustained improvement in three patients with IVIG. In one patient with anti-Yo-associated PCD, rituximab, which targets pre-B cells, showed improved ambulation, although cytotoxic T-lymphocytes have also been implicated in PCD [2]. Early intervention within a month of symptom onset is optimal, resulting in preservation of Purkinje cells [15].

Prognosis of anti-Yo-positive PCD is grim. In Shams'ili et.al, only 4 of 19 patients remained ambulatory at the end of the study, with about 75% becoming bedridden thereafter. Compared with anti-Tr and anti-Ri antibody-associated PCD, median survival time was worse with anti-Yo (113 vs. 13 months) [3]. In Venkatraman, A. et.al., < 10% ambulated without assistance and long-term survival rates were < 25% [7].

Conclusion

PCD is an immune-mediated syndrome commonly associated with anti-Yo antibody. The diagnosis, although supported by antibody-positive serum/CSF, is made clinically, based on symptoms, imaging, and diagnosis of a malignancy [1]. This report describes a male patient with subacute pancerebellar signs, NPC, and serum-positive immunofluorescence for anti-Yo. Although symptomatology was typical for PCD, the patient's gender, type of malignancy, and imaging findings are atypical, highlighting that PCD is a culprit for a wider variety of syndromes.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Dalmau, J., Rosenfeld, M. Paraneoplastic cerebellar degeneration. www.uptodate.com, Topic 15822 Version 13.0, Dec 12, 2017.
2. Rojas I, Graus F, Keime-Guibert F, et al. Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology. 2000;55:713–5.
3. Shams'ili S. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. Brain. 2003;126:1409–18.
4. Debes JD, et al. Anti-Yo-associated paraneoplastic cerebellar degeneration in a man with adenocarcinoma of the gastroesophageal junction. Dig Surg. 2007;24:395–7. https://doi.org/10.1159/000107782.
5. Meglic B, Graus F, Grad A. Anti-Yo associated paraneoplastic cerebellar degeneration in a man with gastric adenocarcinoma. J Neurol Sci. 2001;185:135–8.
6. Sutton IJ, Fursdon Davis CJ, Esiri MM, et al. Anti-Yo antibodies and cerebellar degeneration in a man with adenocarcinoma of the esophagus. Ann Neurol. 2001;49:253–7.
7. Venkatraman and Opal. Paraneoplastic cerebellar degeneration with anti-Yo antibodies – a review. Ann Clin Transl Neurol. 2016 Jun;3(8):655–63.
8. al Posner J e. Anti-Yo and anti-Hu. Laboratory Medicine. 1999;30(12):770.
9. Krakauer J e a. Anti Yo-associated paraneoplastic cerebellar degeneration in a man with adenocarcinoma of unknown origin. Neurology. 1996 May;46(5):1486–7.
10. McHugh JC, Tubridy N, Collins CD, Hutchinson M. Unusual MRI abnormalities in anti-Yo positive "pure" paraneoplastic cerebellar degeneration. J Neurol. 2008;255:138–9.
11. Toro C, Rinaldo A e a. Paraneoplastic syndromes in patients with nasopharyngeal cancer. Auris Nasus Larynx. 2009;36(5):513–20.
12. Dalmau and Rosenfeld. Paraneoplastic syndromes of the CNS. Lancet Neurol. 2008;7(4):327–40.
13. Gilmore CP, Elliot I, Auer D, Maddison P. Diffuse cerebellar MR imaging changes in anti-Yo positive paraneoplastic cerebellar degeneration. J Neurol. 2010;257:490–1.
14. Andrés d, et al. Unusual magnetic resonance imaging and cerebrospinal fluid findings in paraneoplastic cerebellar degeneration. J Neurol Neurosurg Psychiatry. 2006;77:562–8.
15. Widdess-Walsh P, Tavee JO, Schuele S, Stevens GH. Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: case report and review of the literature. J Neurooncol. 2003;63:187–90.