Paraneoplastic cerebellar degeneration in Hodgkin's lymphoma

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Abstract

Paraneoplastic cerebellar degeneration (PCD) is a rare disorder presenting typically with acute or subacute severe cerebellar ataxia. PCD is most commonly associated with small cell lung cancer followed by adenocarcinoma of breast and ovary, and Hogdkin's lymphoma. We report a case of a 54-year-old male with acute-onset pancerebellar syndrome with underlying Hodgkin's lymphoma. A high index of suspicion of PCD resulted in arriving at an early diagnosis of underlying Hodgkin's disease. The patient was managed with six cycles of chemotherapy, which resulted in clinical stabilization and reversal of magnetic resonance imaging abnormalities. Antitumor therapy appears to have a significant impact on reversing PCD and hence early diagnosis and intervention for the primary remains the corner stone in stabilizing the neurological condition.

Key Words

Anti-Tr antibody, cerebellar degeneration, Hodgkin's lymphoma, paraneoplastic syndrome

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Introduction

Paraneoplastic cerebellar degeneration (PCD) is most commonly associated with small cell lung cancer, adenocarcinoma breast and ovary and Hodgkin's lymphoma. Usually, PCD precedes the underlying disease posing a diagnostic challenge to the neurologist. A high index of suspicion in the appropriate setting is required and detection of antineural antibodies, anti-Hu (small cell lung cancer), anti-Yu (breast and ovarian cancer) and anti-Tr (Hodgkin's lymphoma) can be further helpful for the diagnosis. Early recognition is crucial as antitumor therapy is thought to help stabilize the neurological condition.

Case Report

A 54-year-old male recently diagnosed to be diabetic and hypertensive with a fair glycemic control on oral hypoglycemic agents developed pain in both knees while on a business trip abroad, followed by severe myalgia in both calves, with complete resolution of pain over 1 week. After a period of 3–4 days, he noticed progressively worsening unsteadiness with a tendency to reel to either side. No history of any headache, fever, vertigo, diplopia or limb motor or sensory deficits were observed. He gradually developed progressive truncal ataxia with ataxic dysarthria and intentional tremor, rapidly worsening over a period of 2 weeks. Although there was a history of psoriasis, this had remitted drug-free since 2005. Central nervous system examination revealed normal higher mental functions, bilateral 3 mm, isocoric pupils with normal reaction to light. Extraocular movements were full, with slow saccades. Fundi were normal. Prominent ataxic dysarthria, dysmetria of upper limbs more than lower limb, dysdiadochokinesia and intentional tremors were observed. No cranial neuropathy except for mild sensorineural hearing loss was identified. Upper and lower limb power was 5/5, with brisk tendon reflexes, hypotonia in the upper limbs and mild spasticity in the lower limbs. Marked truncal ataxia with inability to stand without support was observed. Gait however was narrow based with reeling to either side.

Routine hematological and biochemical investigations were within normal limits. Magnetic resonance imaging (MRI) brain (plain and contrast) with magnetic resonance venography (MRV) and magnetic resonance angiography (MRA) performed at 3 weeks of illness were within normal limits, except for bilateral periventricular old lacunes with normal MRA and MRV. Antinuclear antibody (ANA), anti-ds DNA, Anti neutrophil cytoplasmic antibodies (pr3-ANCA), mpo-ANCA and rheumatoid arthritis (RA) factor were negative. Serum protein electrophoresis was normal with no evidence of an M

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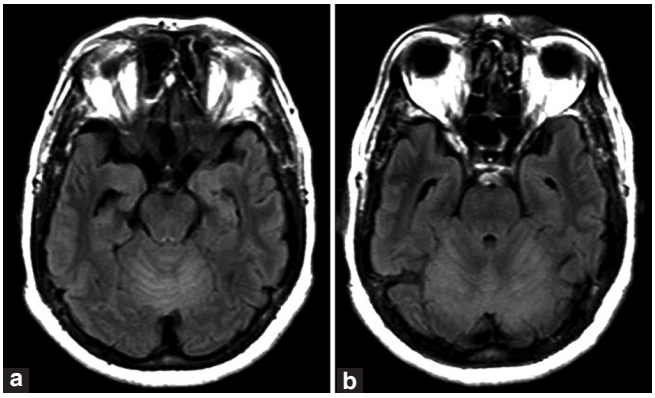

Figure 1: (a,b) FLAIR magnetic resonance imaging showing bilateral symmetrical cerebellar and vermian hyperintensities

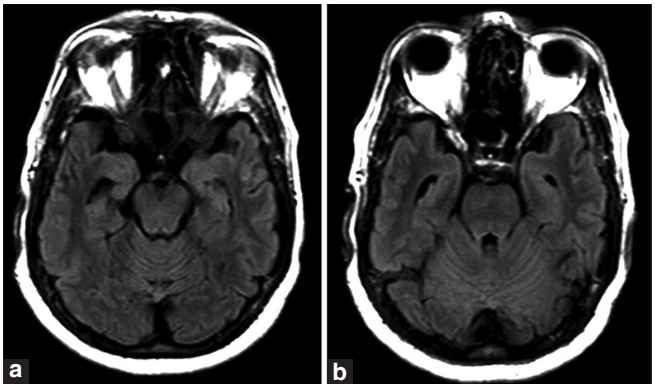

Figure 2 (a,b): Follow-up magnetic resonance imaging after six chemotherapy cycles showing significant resolution of cerebellar and vermian hyperintensities

band. Cerebrospinal fluid (CSF) examination did not reveal any abnormalities. CSF electrophoresis was negative for oligoclonal bands and cytospin was negative for malignant cells. CSF Cr Ag, PCR-TB, HSV I and II and arbovirus were negative.

In view of rapidly progressive pancerebellar syndrome and negative imaging, a possibility of PCD was considered and further evaluated accordingly. Contrast-enhanced computerized tomography of chest and abdomen revealed a 3 cm lymph node in the left axilla. Flurodeoxyglucose positron emission tomography scan was normal. Serum anti-Tr Ab was positive.

Repeat MRI plain and contrast in 1 week revealed T2 and FLAIR bilateral symmetrical cerebellar hyperintensities [Figures 1a and b] and old bilateral periventricular lacunes. Lymph node excision biopsy was performed and immunohistochemical staining was suggestive of nodular lymphocyte dominant Hodgkin's lymphoma.

The patient was managed with 12 cycles of chemotherapy (adriamycin, bleomycin, vinblastine and dacarbazine), which led to plateauing of neurological symptoms and signs following the third cycle of chemotherapy. Repeat MRI after six cycles of chemotherapy revealed regression of bilateral cerebellar hyperintensities [Figures 2a and b]. Subsequently, the patient showed moderate improvement in ataxic dysarthria, slow saccades and hemispherical cerebellar signs with marginal improvement in truncal ataxia.

Discussion

Small cell lung cancer, breast cancer, ovarian cancer and Hodgkin's lymphoma have been associated with PCD. The association between Hodgkin's lymphoma and cerebellar degeneration was noted by Rewcastle in the year 1963.[1] Although the pathogenesis of PCD is still not understood, the presence of antibody against the antigens of Purkinje cells, the intrathecal synthesis of these antibodies and presence of inflammatory infiltrate in the cerebellum strongly suggest an autoimmune process. Anti-Tr antibodies were identified by John L. Trotter, who described a patient with Hodgkin's and cerebellar ataxia.[2] Anti-Tr antibodies is identified by its immunohistochemical pattern on fixed cerebellar section and is associated with Hodgkin's and PCD. Anti-Tr antibodies can be detected in serum and the CSF, and serum suffices for the screening purpose. Serum anti-Tr antibody in our patient was positive, but CSF anti-Tr antibodies could not be performed.

A large series of 28 patients of anti-Tr–associated PCD revealed that in the majority, the diagnosis of PCD was made prior to the diagnosis of Hodgkin's, as also in our patient.[3] Majority of the patients of Hodgkin's lymphoma are males (80%). MRI flair and T2 hyperintensities in vermis and cerebellum in our patient with subsequent resolution following chemotherapy coinciding with clinical stabilization is an important observation. Treatment options are limited and are largely dependent on treating the underlying malignancy to lower antibody titers. Other therapeutic interventions such as intravenous immunoglobulins, plasmapheresis and immunosuppressive therapy (prednisolone, cyclosphosphamide) have been attempted with variable results.[4,5] The prognosis of PCD associated with Hodgkin's lymphoma is poor and, in one study, 86% of 28 patients suffered irreversible damage to the cerebellum.[3] In another large series, 50% patients with paraneoplastic syndrome with Hodgkin's lymphoma responded to chemotherapy with neurological improvement in 24%. Overall, 10 out of 53 patients eventually died, two of which were due to the paraneoplastic syndrome.[6] Favorable outcome was seen in patients who were relatively young (under 40 years). No correlation of the prognosis was seen with the type or stage of Hodgkin's lymphoma. With successful treatment of Hodgkin's lymphoma, the antibody titer disappeared in all patients, but reduction or disappearance of the titer did not correlate with a better outcome. Hence, it seems that the early diagnosis of PCD before major irreversible neuronal loss seem to be the only factor that can modify the prognosis in this condition.

Conclusion

PCD presents with an acute/subacute severe pancerebellar syndrome and should lead to prompt and extensive diagnostic workup. Early detection and management of the underlying malignancy is imperative to modify the prognosis of the condition.

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