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Case Report
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Paraneoplastic Cerebellar Degeneration: A Rare but Important Consideration

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Abstract

Paraneoplastic cerebellar degeneration is an uncommon autoimmune disorder characterized clinically by progressive, ultimately incapacitating ataxia and pathologically by destruction of cerebellar Purkinje cells, with variable loss of other cell populations. The paraneoplastic cerebellar degeneration can antedate the recognition of malignancy and hence can be a warning sign for occult tumor. We are reporting two cases of paraneoplastic cerebellar degeneration that presented before any evidence of tumor and later developed advanced stage of malignancy not amenable for surgery.

Keywords: Paraneoplastic cerebellar degeneration; Purkinje cells; Ataxia; Paraneoplastic; Paraneoplastic syndrome

Introduction

Paraneoplastic Syndromes (PNS) are a rare heterogeneous group of disorders that are indicators of underlying occult malignancy. It is a primary neurological syndrome that is triggered by an erroneous immune-mediated attack on the nervous system antigens originally directed against the tumor itself [1]. Any part of the brain could be involved in PNS and isolated neurologic manifestations appear months or years before the detection of primary malignancy. It occurs before the presenting complaints of neoplasm in up to 65-80% of cases and so it can help in the early diagnosis of tumor [1-3]. When diagnosed earlier and in more favorable stages the tumor can be treated with more chances of cure in the patient. Prognosis of patients with cancer presenting with PNS is better compared to those without PNS due to detection of cancer at early stage although the prognosis may be bad due to severe neurological morbidity [4]. If the early warning signs are ignored or not taken care of with the seriousness that it warrants then it might progress to stages where nothing much can be done for the patients. Paraneoplastic cerebellar degeneration (PCD), most common subset of paraneoplastic neurological syndrome; is defined as a clinical syndrome of cerebellar manifestation due to non metastatic systemic effect of a neoplasm [5]. PCD was first described by Brower in 1919 and association between PCD and neoplasm was proposed by Brower and Biemond. It is commonly associated with small-cell lung cancer (SCLC), breast cancer, ovarian cancer, and Hodgkin lymphoma [5]. It is

characterized by rapid to subacute development of severe pancerebellar dysfunction over days to weeks due to extensive loss of Purkinje neurons with many patients stabilizing over months with significant disability in up to 90% [6]. Clinically it presents with appendicular and truncal ataxia, dysarthria, and nystagmus. The detection of culprit antibodies in a patient with subacute cerebellar syndrome helps both in confirming the paraneoplastic nature and in guiding the search of underlying tumor [1]. Here, we are discussing two interesting cases of sub acute progressive, symmetrical, cerebellar ataxia, which after intensive investigations proved to be cases of paraneoplastic cerebellar degeneration.

Case Presentation

Case 1

A 57 year old, non smoker, non alcoholic, female presented with one year history of unsteadiness of gait, tremulousness of both upper limbs and nine month history of dysarthria and dysphagia. There was no history suggestive of fever, headache, seizure, vomiting, altered sensorium, behaviour abnormality. Also there was no history of diplopia, vision impairment, hearing loss, tinnitus or fullness of ear. Neither there was any limb weakness, sensory complaints, extra pyramidal symptoms and significant drug intake or toxin exposure. Patient denied any history of sexual promiscuity and similar illness in family. On examination, she had bilateral gaze evoked nystagmus, bilateral symmetrical cerebellar signs, impaired tandem walking, along with normal pyramidal, extra pyramidal and sensory examinations.

She was approached as a case of gradually progressive, bilateral symmetrical cerebellar ataxia and was subjected to relevant respective investigations. Her preliminary investigations for acquired ataxias like blood sugar, thyroid profile, liver function test, serum vitamin B 12, vitamin E, folic acid, serum electrolytes, cerebrospinal fluid routine and microscopic examination, human immunodeficiency virus and VDRL serology were normal. Her Magnetic Resonance Imaging (MRI) brain showed diffuse cerebellar atrophy. After excluding common causes of cerebellar ataxia patient was further evaluated for sporadic and inherited spinocerebellar ataxias, but they proved to be negative. Paraneoplastic antibodies were tested in serum by immunoblot method and it revealed positive anti-Hu antibody (+++) (Figure 1a). The patient was diagnosed as a case of paraneoplastic cerebellar degeneration based on PNS diagnostic criteria [7]. However, her X-ray chest, ultrasonography abdomen, mammography, gynecological examination and colonoscopy were normal. Patient was planned for contrast enhanced computer tomography (CECT) chest and Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scan to search out for primary occult malignancy, but she was lost to follow-up.

After, one year she was brought in an altered state with complaints of fever, cough with intermittent hemoptysis, weight loss, decreased appetite, and worsening ataxia. She was bedridden for last one month. Patient was subjected to x-ray chest, which revealed well defined homogenous rounded opacity in left upper zone with multiple opacities in bilateral lung fields suggestive of primary lung cancer of left apical

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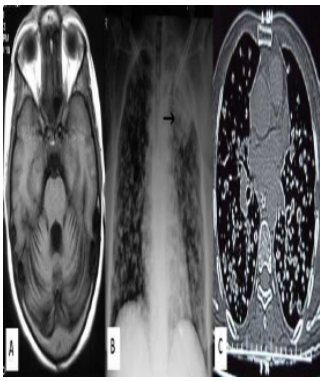

Figure 1: MRI brain T2 FLAIR axial section of case 1 showing diffuse cerebellar atrophy with prominent fourth ventricle (a). X-ray chest PA view of the patient showed well defined homogenous rounded opacity in left upper zone (arrow) with multiple opacities in bilateral lung fields suggestive of primary lung cancer of left apical zone and spreading extensively to both lung field (b). CT chest axial section showing multiple soft tissue opacities in both lung fields (c).

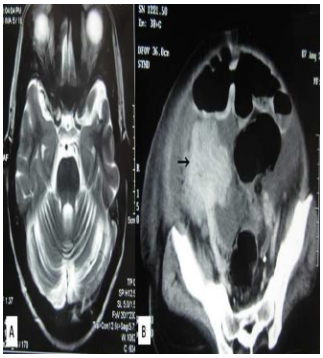

Figure 2: MRI brain T2 axial section of case 2 showing diffuse cerebellar atrophy (a) with CECT scan of abdomen showing left ovarian mass (arrow) infiltrating surrounding viscera with contrast uptake (b).

zone and spreading extensively to both lung fields (Figure 1b). Although her sputum examination for acid fast bacilli and malignant cell was negative, to confirm the diagnosis, CECT chest was done. CECT scan revealed a well defined soft tissue density lesion seen in apico-posterior segment of upper lobe of left lung with multiple opacities in bilateral lung fields, suggestive of primary lung cancer (Figure 1c). Despite all efforts the patient could not be revived and expired. Consent for post mortem examination was not given by the relatives.

Case 2

A 25 year old female patient presented with complaints of unsteadiness in walking for 6 months, slurring of speech since 5 months and tremulousness of hands since 3 months. The complaints were insidious in onset, progressive, symmetrical with no history suggestive of any motor weakness, sensory loss, sensation of walking on cotton wool, increased difficulty in night or ear symptoms like hearing impairment, vertigo, discharge, fullness and pain. There was also no history suggestive of higher mental function abnormality, diplopia, drooping of eyelids, blurring of vision, facial deviation, dysphagia, dysphonia, breathing difficulty. On examination the patient had dysarthria of scanning type, cerebellar function impairment in both upper and lower limbs with normal vestibular, sensory and motor examinations. The mental status examination, cranial nerves and extra pyramidal system were normal.

Preliminary investigations as in case 1 looking for common acquired causes were normal. MRI brain revealed pancerebellar atrophy. Then further investigations for hereditary ataxias and onconeural markers were planned but could not be done and patient was lost to follow up.

Four months later the patient presented again for further progression of ataxia along with new complaints of abdominal pain, weight loss and decreased appetite for one month duration. Ultrasound abdomen was done which revealed ill-defined solid, mix echogenic, 14-16 cm in size, right adnexal mass extending up to right hypochondrium and color Doppler showed increased vascularity (Figure 2a). CECT abdomen revealed left ovarian mass infiltrating to adjacent viscera with contrast uptake. Fine needle aspiration cytology of ovary showed adenocarcinoma of ovary. The patient was diagnosed as a case of PCD based on classical PNS in the presence of cancer [7]. Testing for onconeural marker was done using immunoblot method which came out to be anti-Yo positive (++). The malignancy was extensive hence it was not amenable for surgery. The patient was managed with palliative care (Figure 2b).

Discussion

The diagnostic criteria for PNS recommended by Graus et al divides patients of suspected PNS into definite and possible based on presence of 1) classical or non classical syndrome, 2) associated cancer within five years and 3) presence of well-characterized or partially-characterized paraneoplastic antibodie [7]. Well-characterized paraneoplastic antibody (anti-Hu antibody in case 1 and anti-Yo antibody in case 2) along with cancer (lung cancer in case 1 and ovarian cancer in case 2) in the presence of classical syndrome of subacute cerebellar syndrome suggested definite PCD in both of our cases. Around 50% of subacute cerebellar ataxia occurs due to non-paraneoplastic causes [1]. Subacute cerebellar syndrome can also occur due to vitamin deficiency (B1, B12, E or folic acid), in alcoholics, infectious causes (varicella zoster virus, Epstein-Barr virus, Whipple's disease, Creutzfeldt-Jacob disease), immune-mediated non-paraneoplastic (Gluten-sensitive enteropathy) or hereditary causes which need to be considered in differential diagnosis [6]. Since based on clinical features one cannot reliably distinguish between these causes, patients of subacute cerebellar ataxia of uncertain cause should be screened for onconeural antibodies. Paraneoplastic antibodies that are associated with PCD are anti-Yo, anti-Hu, anti-Tr, anti-Ri, anti-CV2, anti P/Q type voltage-gated calcium-channel (VGCC), amphiphysin, anti-Ma2 and anti-GluR1 [5-7]. These antibodies have great diagnostic as well as some prognostic value [8]. Presence of well characterized paraneoplastic antibodies like anti-Hu, anti-Yo or anti-Tr in a case of subacute cerebellar ataxia makes it definite case of PCD even in the absence of cancer [7]. It also helps in guiding the investigation of occult malignancy. Anti-Yo antibody which is most common antibody in patients of PCD is commonly associated with ovary, breast or other gynecological cancer. Likewise the second most common antibody in PCD, anti-Hu antibody is associated with SCLC in more than 85% cases [6]. Anti-Tr antibody is a marker of Hodgkin lymphoma when detected in a patient of PCD [1]. These antibodies also provide some information regarding prognosis. It has been seen that PCD with anti-Yo or anti-Hu antibodies have shorter survival compared to those with anti-Tr or anti-Ri antibodies [5]. Also patients with anti-Tr antibodies are more likely to improve after tumour removal than those with other antibodies [9]. The prognosis is worse in PCD patients with anti-Hu antibodies compared to those without onconeural antibodies in patients of SCLC [10]. Antibodies can also suggest presence of other neurological syndromes in a case of PCD. VGCC antibodies in patients of SCLC suggest presence of Lambert-

Eaton myasthenic syndrome while anti-CV2 antibodies in PCD are associated with neuropathy in 60% patients [10-12]. Pathophysiology of this syndrome is not entirely understood but onconeural antibodies suggest that it is an immune mediated state in which body may produce antibodies against tumor cells and these antibodies cross react with cerebellar tissue and destroy them [13]. Prognosis is largely poor, with treating the underlying neoplasm being the best way to at least stabilize the symptoms in PCD as in majority of patients the disability cannot be improved [5]. Improvement is rarely seen even on immunotherapy (plasma exchange, immunoglobulin, steroids, cyclophosphamide, rituximab) [5,14]. Immunoglobulin may be effective if given within three months of symptom onset [15]. As mentioned before, tumor removal in PCD patients with anti-Tr antibodies may show some improvement [9]. One more important point is to recognize the disorder promptly, in order to identify underlying primary tumor, because many times these malignancies are curable at the neurological stage [10]. Since in majority of patients PCD antedates the tumor diagnosis, systematic screening for occult tumor is indicated guided mainly by the antibody profile and partly by clinical features. Screening includes but is not limited to ultrasound abdomen and pelvis; CECT scan of chest, abdomen and pelvis; mammography and FDG-PET/CT are done as required. Majority of tumors are diagnosed in initial 3-6 months, up to 90% in first year and rarely beyond 4 years [1,4,16]. In patients in whom initial screening is negative, repeat screening is indicated in next 3-6 months and every 6 months thereafter up to 4 years [17]. Both patients of ours presented to us with subacute cerebellar syndrome, on initial evaluation case 1 was diagnosed as definite PCD but tumor screening could not be done while evaluation could not be completed in case 2 at initial presentation. Both patients later presented again with overt malignancy at advanced stage. Early and prompt recognition of underlying tumor could have lead to early diagnosis and treatment of tumor leading to arrest of cerebellar treatment.

Learning points

Cerebellar syndrome is a common disorder and sometimes the cause cannot be detected even after extensive investigation including genetic study for sporadic and inherited ataxias. PCD is a rare disorder which should be considered in patients presenting with gradually progressive, symmetrical, cerebellar ataxia after excluding other causes because it can be a warning sign for occult neoplasm. Failure to pick up the early warning signs of PCD due to various reasons can land the patients into more advanced stages that are not amenable to curative therapy.

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