

A case of Cerebellar Ataxia



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Presentation:

Mr X, a 66-year-old gentleman, presented to the emergency department with progressively worsening unsteadiness on his feet, double vision, nausea and vomiting.

Two months previously the patient noticed he was becoming unsteady on his feet. This progressed such that he was now struggling to walk unaided. Four days prior to his admission the patient developed persistent nausea and vomiting and noticed double vision. It was this that brought him to the emergency department.

The patient denied any headaches, vertigo, weakness, confusion, bowel or bladder dysfunction and the unsteadiness was independent of position. Bowel movements were normal and he reported no other symptoms of abdominal pathology. The patient drank on average 10 units of alcohol a week and reported no recent increase in consumption. He was a life-long non-smoker, and denied any recent symptoms of respiratory pathology. On further questioning it emerged that he had noticed weight loss of approx 10kg over the last 2 months. He had no past medical history of note and was currently taking no medications. His father had been diagnosed at 84 with a glioblastoma and a first-cousin, 63 years old, had recently been diagnosed with Parkinson's disease. There was no other family history of neurological or neoplastic disorders.

On examination Mr X was a fit, well kempt gentlemen of normal weight. He appeared alert and comfortable at rest. His blood pressure was 120/94mmHg, pulse rate 107bpm, respiratory rate 14 and temperature 37.4C. He was able to sit upright in the bed unsupported. Of note there was no clubbing of the fingernails, no signs of malnutrition and no slurring of speech. In depth neurological examination revealed a wide-based gait with inability to walk in tandem gait. Tone and power were normal; intention tremor with past pointing was present bilaterally. The patient reported diplopia at all eye positions with images displaced horizontally, there was no noticeable nystagmus.

Full blood count, urea and electrolytes, clotting studies, liver function tests, thyroid function tests and blood glucose revealed no abnormalities and the patient was admitted to await a CT head. This was performed the following day and showed normal appearance of the cerebellum, cortex and brain stem. Bloods were sent for autoantibody screening and the patient was booked in for an oesophagogastroduodenoscopy (OGD). OGD biopsy of the mucosa of the duodenum revealed normal villus structure with no signs of atrophy. However,

an incidental finding was the presence of gastritis and *Helicobacter pylori* infection; the patient was started on triple therapy. The autoantibody screen was negative. Lumbar puncture showed a raised CSF protein level of 1.3g/L. A MRI head and spine with gadolinium contrast was performed revealing normal anatomy of the head and spine. However, a number of enlarged paraspinal lymph nodes were observed. A further CT scan of the chest, abdomen and pelvis showed multiple enlarged para-aortic, aortocaval and iliac lymph nodes; a 6cm x 7cm lymph node mass in the pelvis and 3 peritoneal nodules in the paracolic gutter. CT guided biopsy of the paraspinal lymph nodes was undertaken. The biopsy showed Reed-Sternberg cells and the diagnosis of non-hodgkins lymphoma with associated paraneoplastic cerebellar ataxia was made.

Differential Diagnosis:

The patient presented with a 2-month history of worsening ataxia. Examination suggested the ataxia was cerebellar in origin with both midline and bilateral hemispheric symptoms suggesting that there was not a focal lesion, but rather diffuse involvement.

The causes of a chronic/subacute onset of cerebellar ataxia are numerous. They can be simply divided into hereditary and sporadic, with sporadic further divided into symptomatic or idiopathic. The age of onset and lack of family history make hereditary causes unlikely although do not completely rule them out. Seventy-five percent of male carriers of the FMR1 premutation gene (full mutation form leads to fragile-X-associated tremor ataxia syndrome, an X-linked disorder) over the age of 80 will have ataxia. The carrier frequency of this premutation is relatively high (1:810 males) and studies of sporadic cerebellar ataxia in older males the prevalence of FMR1 premutation has been seen to be as high as 5%. Sporadic mutations also cannot be excluded, though these represent a very rare cause of cerebellar ataxia.

The initial differential diagnosis for this patient was necessarily broad and included toxicity, primary neoplastic lesion of the cerebellum, metastatic disease, multiple system atrophy (MSA), post-viral cerebellar syndrome, paraneoplastic syndrome, gluten ataxia, demyelinating disease, toxicity, endocrine disorder (hypothyroidism, diabetes) and malnutrition.

The most informative initial test was imaging of the head. MRI is preferred over CT due to improved resolution of soft-tissue changes. CT though is much more readily available and the patient underwent a CT head on the day after admission. No structural changes were seen; in particular no metastatic deposits or primary tumours (medulloblastoma, hemangioblastoma), no evidence of multiple sclerosis or normal pressure hydrocephalus and no abscesses, nor was there any evidence of infarction, haemorrhage or cerebellar atrophy.

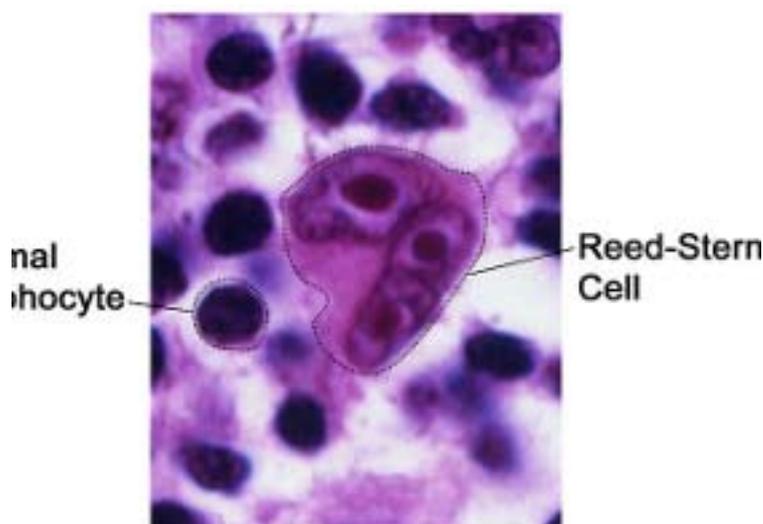
There was no history of exposure to toxic agents (alcohol, lead, solvents, medication e.g. phenytoin) and this was supported by normal findings from simple blood tests. Of note, liver function tests (LFTs) and full blood count (FBC) showed no indication of alcoholism or associated vitamin deficiencies, consistent with the history and examination. Thyroid function tests and blood glucose were both normal ruling out diabetes or hypothyroidism as causes of this gentleman's ataxia. At this point bloods were sent for autoantibody

screening to exclude paraneoplastic neurological disorder (PND). Tests for all autoantibodies were negative, however this does not conclusively exclude paraneoplastic syndrome as in many cases antibodies cannot be detected³.

An OGD was requested to exclude coeliac disease (and therefore gluten ataxia) and Whipple's disease, a rare infective/inflammatory cause of cerebellar ataxia due to infection by the bacteria *Tropheryma whippelii*. However, Whipple's disease more commonly presents with diarrhoea and abdominal pain as well as weight loss and ataxia. Both coeliac and Whipple's can lead to villous atrophy in the small intestine. The biopsy showed normal villous architecture. Cerebellar ataxia can be secondary to coeliac disease and can occur without GI symptoms suggesting it is not related to malnutrition caused by malabsorption⁴. The exact cause is unclear, however there is evidence to support cross-reactivity of anti-gliadin antibodies (antibodies found in coeliac disease targeted against gliadin a protein found in gluten) with auto antigens on neuronal tissue¹.

A lumbar puncture was performed and showed raised CSF protein as the only abnormality. This is consistent with a diagnosis of paraneoplastic syndrome. However it is not a specific test as raised CSF protein can occur in other causes of ataxia e.g. viral meningitis or Creutzfeldt-Jakob Disease (CJD)

An MRI of the head and spine was also organized to investigate the possibility of multiple sclerosis and multiple system atrophy (MSA) as possible causes of the ataxia. MSA is estimated to account for 30% of cases of isolated late onset cerebellar ataxia⁷ and usually presents in the 6th decade. There was no structural change seen in this imaging study. However an incidental finding was multiple enlarged paraspinal lymph nodes. A CT scan of the chest and abdomen showed multiple enlarged para-aortic, aortocaval and iliac lymph nodes; a 6cm x 7cm lymph node mass in the pelvis and 3 peritoneal nodules in the paracolic gutter, this was highly suggestive of lymphoproliferative lesion.



CT guided biopsy was undertaken to collect samples for histology. Histology showed Reed-Sternberg cells (Figure 1). These are a clonal proliferation of B-cells and represent the malignant component of Hodgkin's lymphoma. They have a prominent cytoplasmic component with two or more nuclei containing eosinophilic nucleoli giving a classical "owl's eye" appearance. The presence of Reed-Sternberg cells is a requirement

for the diagnosis of Hodgkin's lymphoma but is not specific for the disease. However, other histological findings in the biopsy allowed the diagnosis of Hodgkin's lymphoma with paraneoplastic cerebellar degeneration to be made.

The patient was referred to Haematology for further management.

Paraneoplastic Syndromes:

Paraneoplastic syndromes are those caused not by the physical proximity of a tumour but indirectly by its presence. They can be classified by the systems they affect giving neurological, endocrine, dermatological, musculoskeletal and haematological groupings. Paraneoplastic syndromes are most commonly associated with small-cell lung cancer (SCLC), thymomas and B-/ Plasma cell malignancies, more rarely they are found in patients with Breast or ovarian cancer.

The neurological symptoms that characterize PNDs are the result of an immune response to neuronal antigens expressed on the surface of some tumours 6. The immune response can be either antibody mediated or T-cell mediated. Cerebellar ataxia is a symptom common to many PNDs. Those associated with the antibodies, anti-Yo, anti-Tr, anti-mGluR1-alpha and anti-Zic4 have cerebellar ataxia as their only symptom 2. Other significant onconeurological antibodies linked to cerebellar ataxia include anti-PCA2, anti-Hu, anti-Ri and anti Ma. The tumours most commonly associated with paraneoplastic cerebellar degeneration are SCLC, Breast cancer, Ovarian cancer and Hodgkin's lymphoma

To aid diagnosis of PND a set of recommended diagnostic criteria were proposed in 2004 (Table 1) 5. The presence of classical signs of paraneoplastic neurological disorder (subacute cerebellar degeneration) combined with the detection of a neoplastic lesion is sufficient to diagnose PND even in the absence of autoantibodies. More importantly, classical PND in the presence of well-characterised autoantibodies strongly suggests the presence of an undetected neoplastic lesion. PND can precede the detection of the associated cancer by months or even years and therefore can be a very effective tool for early diagnosis of neoplasia. In our patient, although the lymphoma was relatively advanced at the time of detection the paraneoplastic cerebellar degeneration was nonetheless the presenting symptom and allowed the diagnosis to be made.

Appendix

Diagnostic Criteria For PND

Diagnostic criteria for definite PND, from (5) , the presence of autoantibodies is not a requirement of the diagnosis of PND, but can be useful in the localisation of neoplasia.

1. A classical syndrome and cancer that develops within five years of the diagnosis of the neurological disorder

2. A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission.
3. A non-classical syndrome with onconeural antibodies (well characterised or not) and cancer that develops within five years of the diagnosis of the neurological disorder.
4. A neurological syndrome (classical or not) with well characterised onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin), and no cancer.

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