1. Introduction

Paraneoplastic neurological syndromes are a group of disorders which are postulated to occur due to tumor-mediated immune dysfunction of the nervous system. Paraneoplastic cerebellar degeneration (PCD) belongs to this category of rare disorders and can be difficult to diagnose as there is no confirmatory test or diagnostic criteria available. Presence of certain onco-neuronal antibodies either in cerebrospinal fluid (CSF) or plasma is an important clinical clue and can further elucidate the origin of an underlying malignancy. Regardless, the antibody testing also has limitations.

In addition, detection and treatment of the causative cancer is the cornerstone of PCD management. However, a malignancy cannot always be diagnosed in all patients with PCD who need aggressive immunotherapy and close cancer-surveillance.

We share an interesting case about a female patient who presented with symptoms of cerebellar dysfunction and was diagnosed to have PCD based on positive CSF anti-Ta antibodies. These antibodies are not usually seen in female population or patients who present with PCD. Furthermore, a malignancy could not be detected despite a thorough workup.

2. Case description

An 80-year old lady with history of hypertension, hypothyroidism and osteoporosis presented with slowly progressive dizziness, double vision, gait instability of 2-months duration. At the time of presentation, her vitals including orthostatics were unremarkable. Physical examination was unremarkable while a detailed neuro-ophthalmological exam showed vertical diplopia on right lateral gaze, bilateral up-beating nystagmus and ataxic gait concerning for a cerebellar/posterior fossa pathology. Initial results blood workup including thyroid profile, Vitamin-D, Vitamin-B12, Lyme serology and syphilis were unremarkable. Urinalysis, echocardiogram and EKG were also unremarkable. CT head and MRI/MRA brain/neck/cervical spine showed no acute pathology. As her symptoms remained unexplained, lumbar puncture was performed. CSF analysis was found to be normal apart from mildly elevated protein level while additional autoimmune and paraneoplastic results were awaited (Table 1). As patient remained stable, it was decided to transfer her to a rehabilitation facility after which she could follow with neurology/neuro-ophthalmology as outpatient.

However, the patient's current symptoms worsened over the next few days and she was admitted with new-onset dysarthria, dysphagia and respiratory failure secondary to aspiration. Repeat neuroimaging showed no acute abnormalities. She was immediately intubated and started on intravenous corticosteroids. Meanwhile, her results from the previous admission showed strongly positive anti-Ma, anti-Ta and weakly positive anti-amphiphysin antibodies confirming the diagnosis of paraneoplastic cerebellar dysfunction. This serology pattern was considered unusual as anti-Ta antibodies are usually found in young males with an underlying testicular cancer. Nonetheless, intravenous immunoglobulin therapy and workup for an underlying malignancy was commenced.

CT chest/abdomen/pelvis with contrast and tumor markers were unremarkable. A colonoscopy done few months prior to admission and a mammogram done within the year of admission didn’t show any abnormalities. A PET scan showed hypermetabolic uptake in gastro-esophageal junction. However, esophagogastroscopy revealed an area of gastritis with no signs of malignancy. Even though a malignancy was unable to be identified in our patient, she continued to improve slowly while receiving immunoglobulin therapy. Eventually, she was extubated and then discharged to a rehabilitation facility. She continues to follow closely with neurology as outpatient.

3. Discussion

Paraneoplastic cerebellar degeneration (PCD) is one of the paraneoplastic neurological syndromes (PNS) characterized by immune-mediated inflammation of the cerebellum. Although invariably associated with cancers of
different origin, the condition itself is not caused by direct cancer invasion or the metastatic process. The mechanism behind PCD is described to be a brain-specific immune phenomenon, either through antibodies or T-cells, in response to tumor antigens [1]. The actual prevalence of PCD varies from cancer to cancer but the overall estimated prevalence is approximately 1% in all patients with cancer. The onset is usually acute with PCD preceding the actual cancer diagnosis in almost 60% of the patients [2].

Making a timely diagnosis of PCD is a daunting task that requires a high index of clinical suspicion for individuals with a history of smoking, malignancy, or autoimmune who present with suggestive features of truncal/appendicular ataxia, vertigo, nystagmus and diplopia and in whom other common causes have been excluded. MRI with contrast showing mild cerebellar enhancement and CSF pleocytosis can be seen in some patients with PCD but are non-specific findings. Our patient presented with acute onset, rapidly progressive symptoms suggestive of cerebellar dysfunction which remained unexplained despite a detailed workup including toxicology, MRI brain/cervical spine, EEG and CSF analysis. Presence of anti-Ta antibodies (also known as anti-Ma 2) in CSF confirmed the diagnosis of a paraneoplastic neurological condition; however, the unusual points of this case are that patients with anti-Ta antibodies usually present with features suggestive of paraneoplastic limbic encephalitis such as mood/behavior changes, cognitive dysfunction and sleep disorders. PCD is an extremely rare disorder associated with these antibodies [5]. Furthermore, anti-Ta antibodies are classically detected in young males with an underlying testicular tumor [6].

On a detailed review of literature, we were able to find rare case reports of anti-Ta associated PNS in older males and females. The malignancies detected in these patients were lung cancer, breast cancer, parotid gland cancer and non-Hodgkin’s lymphoma [6,7]. Interestingly, our patient was also found to have anti-Ma1 antibodies. A study done by Rosenfeld et al. showed that coexisting anti-Ma1 antibodies are more commonly detected in PCD/PNS with tumors other than testicular cancer [6].

After the diagnosis of PCD is confirmed, management should be directed towards the known malignancy as the treatment of malignancy itself resolves the neurological symptoms. In patients with no known cancer, a thorough workup should be done with the help of tumor markers, detailed imaging (MRI, PET scan) and exploratory procedures (colonoscopy, exploratory laparotomy). However, cancer may not be detected even with extensive investigations in some patients with PCD. In such cases, immunotherapy (corticosteroids, IVIG, plasmapheresis, Rituximab) should be initiated in addition to serial cancer-surveillance [5]. The clinical response in these patients is usually poor leading to significant debility [8]. Interestingly, we encountered the exact opposite in our patient. An extensive malignancy workup was unrevealing but patient demonstrated surface antibodies associated with non-paraneoplastic autoimmune neurological syndromes.

However, it should be kept in mind that only 60–70% of patients with PCD have detectable onconeural antibodies while not all cancer patients with onconeural antibodies develop PCD [3]. This is because these antibodies are tumor-specific only and while facilitating a diagnosis, are used mainly for the detection of an underlying malignancy.

Our patient was an 80-year old female who presented with acute onset, rapidly progressive symptoms suggestive of cerebellar dysfunction which remained unexplained despite a detailed workup including toxicology, MRI brain/cervical spine, EEG and CSF analysis. Presence of anti-Ta antibodies (also known as anti-Ma2) in CSF confirmed the diagnosis of a paraneoplastic neurological condition; however, the unusual points of this case are that patients with anti-Ta antibodies usually present with features suggestive of paraneoplastic limbic encephalitis such as mood/behavior changes, cognitive dysfunction and sleep disorders. PCD is an extremely rare disorder associated with these antibodies [5]. Furthermore, anti-Ta antibodies are classically detected in young males with an underlying testicular tumor [6].

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Table 1. Investigations performed for our patient.

| Investigations                        |          |
|---------------------------------------|----------|
| CSF analysis:                         |          |
| ● Specific gravity: 1.005              |          |
| ● WBC: 2/mm³                          |          |
| ● RBC: 1000/mm³                       |          |
| ● Glucose: 57 mg/dl                   |          |
| ● Protein: 51 mg/dl                   |          |
| ● Gram stain and culture: Negative    |          |
| ● Fungal culture: Negative            |          |
| ● Cryptococcal antigen: Negative      |          |
| ● VDRL: Negative                      |          |
| ● Viral panel: Negative               |          |
| ● Lyme serology: Negative             |          |
| CSF immunology:                       |          |
| ● Anti-Hu: Negative                   |          |
| ● Anti-Ri: Negative                   |          |
| ● Anti-Yo: Negative                   |          |
| ● Anti-CV2: Negative                  |          |
| ● Anti-ampiphysin: 1/4 (Normal 1:1)   |          |
| ● Anti-Ma1: 1:32 (Normal 1:1)         |          |
| ● Anti-Ma2/Anti-Ta: 1:32 (Normal 1:1) |          |
| Serum immunology:                     |          |
| ● Acetylcholine receptor blocking/modulating Ab: Negative |          |
| ● GAD65 Ab: Negative                  |          |
| ● Ampiphysin Ab: Negative             |          |
| ● ANNA1 (Hu) Ab: Negative             |          |
| ● ANNA2 (Ru) Ab: Negative             |          |
| ● ANNA3 Ab: Negative                  |          |
| ● PCA1 (Yo) Ab: Negative              |          |
| ● PCA2 Ab: Negative                   |          |
| ● PCA-Tr Ab: Negative                 |          |
| ● CRMP5/O2 Ab: Negative               |          |
| ● AGNA/SOX1 Ab: Negative              |          |
| ● VGCC Ab: Negative                   |          |
| ● VGKC Ab: Negative                   |          |
| ● Striated muscle Ab: Negative        |          |

Table 2. Onconeural antibodies associated with paraneoplastic cerebellar degeneration [4].

| Antibodies | Underlying malignancy |
|------------|-----------------------|
| ● Anti-Hu  | Lung cancer, thymoma, neuroblastoma |
| ● Anti-Yo  | Ovarian, endometrial, breast cancer |
| ● Anti-Ri  | Lung and breast cancer |
| ● Anti-Tr  | Hodgkin’s lymphoma |
| ● Anti-CRMP5 | Lung cancer, thymoma |
significant improvement with eventual recovery after being treated with IVIG.

4. Conclusion

This case highlights the clinical scenario when a rare disorder presents with unusual manifestations. Paraneoplastic cerebellar degeneration is a clinical condition which can be difficult to diagnose due to its rare occurrence. In addition, our patient had clinical and serological features uncharacteristic of PCD such as an elderly female, positive anti-Ta antibodies and an excellent response to immunotherapy in the absence of an underlying malignancy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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