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Case Report

Ataxia Following Allogenic Stem Cell Transplantation: No Stone Unturned

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Abstract

A thirty-one year-old Sri Lankan man presented with a two-month history of progressive pan-cerebellar syndrome, following allogeneic stem cell transplantation. This curative-intent therapy was performed in the context of an underlying acute myeloid leukemia. During the post-transplant period, patients are extremely vulnerable, especially due to the immunologic fluctuations. Reaching equilibrium is crucial, preventing complications of both extremes of the immunologic response, such as opportunistic infections or graft versus host disease. Numerous aetiologies were considered in the differential diagnosis of this pan-cerebellar syndrome. Most of those conditions mandate a prompt management, because of their reversible or lethal nature. Our thorough investigation process was a race against time. Excluding "Red Flags" remains the priority. Mindfulness and time will eventually lead to the proper diagnosis. We discuss our structured investigation process emphasizing on the key element: a "Systematic Approach".

Running Title: Ataxia post stem cell transplant

Keywords: ataxia; graft versus host disease; allogenic transplantation; anti-tr; anti-gad; opportunistic infections; neuroimmunology; pan-cerebellar syndrome; acute myeloid leukemia; clinical investigation

Clinical Scenario

A thirty-one year-old Sri Lankan man presented at the neuro-oncology clinic of Princess Margaret Cancer Centre for the investigation and management of a pan-cerebellar syndrome, progressively evolving for two months, following allogeneic stem cell transplantation. This curative-intent procedure was performed two years after a diagnosis of acute myeloid leukemia (AML). His initial therapy consisted of standard chemotherapy including: cyclophosphamide, cytarabine, doxorubicin and methotrexate. His family history was unremarkable for consanguinity, hereditary or metabolic conditions. Unfortunately, during the post-transplant period, this gentleman developed a multi-systemic graft versus host reaction (GVHD) involving his eyes, liver, skin and lungs. Reaching an immunologic equilibrium during this vulnerable period is challenging. The GVHD treatment induced an iatrogenic state of profound immunosuppression, leading to the development of multiple opportunistic Infections. The central nervous system (CNS) resides in a sanctuary, protected by the blood brain barrier (BBB); it remained unaffected throughout this period of fragility.

We were facing an extensive differential diagnosis [1] [Table 1], considering the presence of an underlying hematologic malignancy, the post-transplantation context associated with immunologic fluctuations, the coexistence of recent complications, namely multi-systemic GVHD and opportunistic infections. We also thought about any aetiology potentially responsible for the development of a pan-cerebellar syndrome in a young adult, manifesting as a sudden outburst in a state of extreme fragility.

Neoplastic infiltration	Neoplastic recurrence most concerning aetiology to exclude. History of AML. Brain MRI: limited sensitivity to detect leptomeningeal infiltration. [7] Four lumbar punctures performed: negative for presence of malignant cells. Despite tests mentioned above, neoplastic infiltration still remains a possibility.
Opportunistic infection	Context of recent immunosuppression. Progressive multifocal leukoencephalopathy may present as a pure cerebellar syndrome. Mycobacteria and mycoses could also have a predilection for the posterior fossa. Immunosuppressed individuals would not present usual systemic manifestations. CSF was unremarkable for the presence of bacteria, virus (including PML), mycobacteria, acid-fact bacilli and mycoses, but still doesn't exclude definitely this possibility.
Paraneoplastic Syndrome	Anti-Tr antibodies associated with hematologic malignancies would typically induce a characteristic pan-cerebellar syndrome [1]. Serum immunohistochemistry was performed twice on reliable samples; antibodies were absent.
GVHD	Multi-systemic GVHD documented previously + current ocular GVHD. Neurologic and ophthalmologic GVHD exacerbations correlate in time. Ocular and neurologic improvement after prednisone exposure. CFS results compatible with this entity, even if non-specific. No pathognomonic features at biopsy, remains an exclusion diagnosis.
Iron overload	Multiple blood transfusions lead to this complication (relevant to this case). Pan-cerebellar symptoms were unchanged despite the normalization of serum iron levels. Overall: evolution of the symptoms incompatible with this aetiology.
Chemotherapy	Cytarabine = chemotherapy renown to cause pan-cerebellar, but timing incompatible; ataxia worsened several months after the drug was discontinued. Cytarabine not renown for "coasting effect", implicating that neurologic symptoms could develop and become more prominent after the cessation of the drug.
Anti-GAD	This hypothesis was explored, but despite the presence of positive anti-GAD antibodies in our patient's serum, CSF level is more reliable. This etiology was discredited and serum + anti-GAD was attributed to false positive result, due to the presence of confounding factors.
Genetic Disorder	An underlying genetic disorder could be unmasked during a state of excessive metabolic demand or during the course of potent treatments leading to extreme fatigue. A work-up performed by a Movement Disorders specialist excluded most potential causes of genetic ataxia.
Metabolic	Vitamins deficiency – electrolytic imbalance – toxicology: thoroughly investigated and resulted in an overall negative work-up.

Table 1: Differential Diagnosis of Pan-Cerebellar Syndrome Investigated: Context of AML - Post Stem Cell Transplantation

After a thorough investigation as described in Table 1, GVHD became our main working diagnosis. The pan-cerebellar syndrome was characterized by the following findings at the clinical examination: symmetrical diffuse axial and appendicular ataxia impacting gait, symmetrical adiadochokinesia, bilateral dysmetria and dysrythmia involving upper and lower limbs, cerebellar dysarthria and downbeat nystagmus. Cranial nerves were otherwise within a normal range. The motor and sensory modalities were preserved.

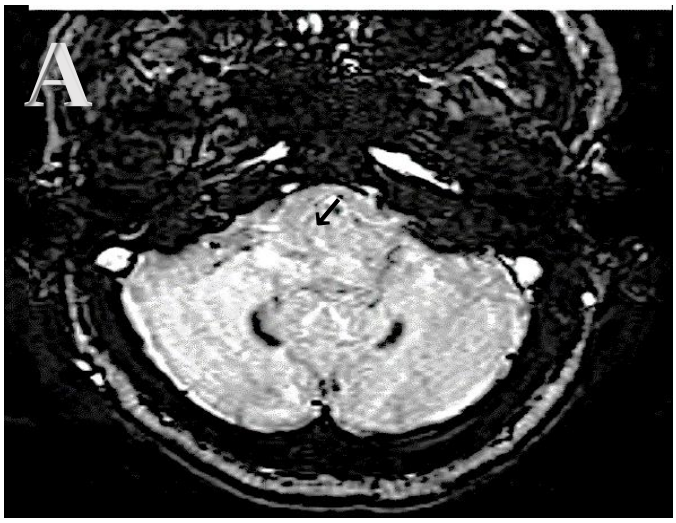
Reflexes were unaffected, except the presence of pendular reflexes at bilateral patellar sites. A subtle cerebellar intention tremor involved symmetrically bilateral upper limbs. There were superimposed ocular manifestations, such as keratosis, erythema and pruritus. After a specialized ophthalmologic investigation, those features were attributed to concomitant ocular GVHD. Moreover, a skew deviation was attributed to a contiguous brainstem involvement. Isolating the precise nature of each of ocular phenomenon was key in this investigation process. The parallel course of the ocular GVHD and the cerebellar/brainstem symptoms, flaring-up and improving at the exact same time, was the most important element suggesting the diagnosis of CNS GVHD, involving the posterior fossa. In addition, we noticed that administration of oral prednisone lead to an improvement of both neurologic and ocular manifestations. We would expect the opposite reaction in presence of opportunistic infection.

Our gentleman was prescribed azathioprine, 200 mg PO when GVHD became our main working hypothesis, and the presence of opportunistic infections was excluded. Azathioprine was selected aiming a long-term treatment, and a well-tolerated side-effect profile. However, we acknowledge that this drug could take up to nine months to show the first signs of improvement. Seven months later, the ataxia was still unchanged. The challenge is to be absolutely certain to have excluded without a doubt the presence of malignancy or opportunistic infections involving the posterior fossa. Those two reversible aetiologies remain untreated during the azathioprine trial, and warrant a prompt management, to avoid preventable lethality. The role of a brain biopsy was controversial and was discussed extensively during multidisciplinary tumor boards. It represents

the only modality to exclude without a doubt an infectious or neoplastic process undiagnosed by lumbar puncture. In this specific context, a brain biopsy is associated with high morbidity and could generate fatal complications. [2,3] The decision mainly relied on the patient's clinical status, permitting a biopsy in his current state, which could have deteriorated afterwards. We weighted thoroughly the risks and benefits of such a procedure, and finally ruled in favour of the biopsy.

The pathology analysis was finally compatible with a previous inflammatory process, currently in resolution. The presence of residual polyclonal lymphocytic infiltrates within the perivascular space suggested the presence of resolving inflammation. This description is compatible with GVHD, but it is not pathognomonic. The absence of infectious agents or neoplastic features was extremely reassuring and we proceeded by resuming azathioprine. We noted a clinical improvement after nine months of azathioprine treatment, which consolidated our diagnosis of CNS GVHD [4-6].

Numerous neurologic complications could arise from hematopoietic stem cell transplantation. The challenging aspect of this case is the definite exclusion of treatable conditions [3]. We presented this case to highlight a reality: every physician will face "unknown territories", and scenarios we never specifically learn to manage. We can't be wrong if we rely on our judgement, adopt a systematic approach, and remember that we are never alone, consultants are there for a reason. If the patient understands the reflection process, the logic standing behind every action, and ideally takes part to the discussion, the relationship patient-physician will be optimal and both parties will be reassured to crossing the "unknown territories" together.



Brain MRI performed 6 months following pan-cerebellar syndrome onse

Figure 1(a): Brain MRI, axial SWI sequence, showing prominent iron deposition in the dentate nuclei bilaterally (arrow).

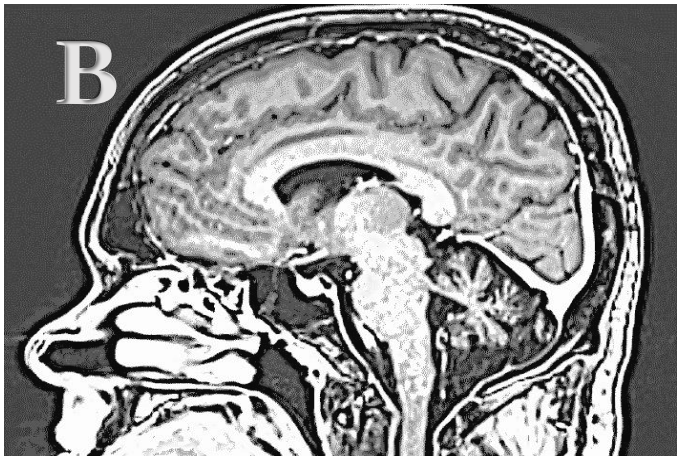


Figure 1(b): Brain MRI, sagittal T1 post-gadolinium sequence, showing volume loss of the overall posterior fossa, especially the cerebellar vermis, associated with ex vacuo ectasia at the level of the fourth ventricle.

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