CASE REPORT

Tacrolimus associated Guillain–Barre syndrome

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ABSTRACT

Guillain–Barré syndrome (GBS) is a rare but serious neuropathy in hematopoietic stem cell transplant recipients. Immunosuppressants, particularly tacrolimus, have been implicated as potential triggers. We present a 27-year-old man with BCR-ABL-positive acute myeloid leukemia who developed an acute demyelinating polyneuropathy possibly related to tacrolimus therapy post-transplantation, highlighting diagnostic challenges and management considerations. The patient developed progressive ascending weakness, areflexia, sensory loss, and bulbar symptoms 58 days after an allogeneic stem cell transplant from an HLA-matched sibling donor. Cerebrospinal fluid (CSF) analysis showed elevated protein (1,900 mg/L) with lymphocytic pleocytosis (51 cells/μL), an atypical finding for GBS. Magnetic resonance imaging revealed subtle nerve root enhancement, and nerve conduction studies demonstrated markedly slowed conduction velocities and prolonged distal latencies consistent with an acute inflammatory demyelinating polyneuropathy. Extensive infectious work-up (including viral PCR panels and cultures) was negative, and no leukemic cells were seen in CSF. Tacrolimus was discontinued (trough level 3.1 ng/mL, below therapeutic range) and intravenous immunoglobulin (2 g/kg total over five days) initiated. The patient's neurological deficits improved rapidly, with near-complete recovery within four weeks. Notably, withdrawal of tacrolimus immunosuppression did not precipitate graft-versus-host disease, and the patient's acute leukemia remained in remission on ponatinib monotherapy. This case illustrates an acute demyelinating polyneuropathy in a post-transplant patient, associated with tacrolimus. It underscores the importance of careful diagnostic assessment of GBS in transplant recipients, including consideration of atypical CSF findings and alternative diagnoses. Prompt recognition and management – including immunosuppressant adjustment and immunotherapy – can achieve full neurological recovery without compromising transplant outcomes.

KEYWORDS: Guillain–Barré syndrome (GBS); tacrolimus-associated neuropathy; hematopoietic stem cell transplantation (HSCT); acute myeloid leukemia (AML); graft-versus-host disease (GVHD)

INTRODUCTION

Guillain-Barré syndrome (GBS) is a rare neurological complication following hematopoietic stem cell transplantation (HSCT), with an annual incidence of 1.3 per 100,000 individuals [1]. While typically triggered by antecedent infections [2], GBS can also be induced by medications, particularly calcineurin inhibitors such as tacrolimus [3]. We report a case of tacrolimus-associated GBS in a young adult with BCR-ABL-positive acute myeloid leukaemia post-allogeneic transplantation, highlighting successful management without compromising disease control or graft integrity.

CASE PRESENTATION

A 27-year-old man with BCR-ABL-positive acute myeloid leukaemia (AML) presented with neurological symptoms 58 days after peripheral blood stem cell transplantation (PBSCT). His medical history included partial nephrectomy at age 1 year for a renal mass, bariatric surgery, and right cardiac thrombus managed with apixaban. Following myeloablative conditioning with etoposide and total body irradiation, he received PBSCT from an HLA-matched sibling donor.

The patient presented to the emergency department with a 4-day history of bilateral lower limb numbness, progressive weakness, and dysphagia predominantly affecting liquids, with associated choking and post-swallow cough. He reported a decreased urinary stream without fecal incontinence. Ten days before the presentation, he had contact with an individual with an upper respiratory tract infection but remained asymptomatic.

Clinical Findings

On examination, he was hemodynamically stable but mildly distressed. Cranial nerve function was intact (normal speech, comprehension, pupillary reflexes, and eye movements). Motor exam revealed symmetric weakness (Medical

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Research Council grade 4/5 in proximal upper limbs, 3–4/5 in distal lower limbs) with neck flexor weakness. Deep tendon reflexes were globally diminished (absent at ankles, 1 + at knees), and plantar responses were flexor. Sensory exam showed intact vibration and proprioception, but reduced pinprick in a stocking distribution. There were no signs of rash, organ dysfunction, or other GVHD manifestations. (Table 1).

Diagnostic Assessment

Given the suspicion of GBS, a lumbar puncture was performed. CSF opening pressure was 110 mmH and the fluid was clear. Notably, CSF analysis showed 51 WBC/mm^3 (96% lymphocytes) with no blasts on cytology, alongside a protein of 1,900 mg/L and glucose of 3.7 mmol/L. This indicated a markedly elevated protein with lymphocytic pleocytosis rather than classic albuminocytologic dissociation. Complementary MRI scans of the brain and spinal cord showed minimal enhancement of the cranial nerves and the anterior nerve rootlets of the cauda equina (Figure 1). Nerve conduction studies demonstrated diffuse demyelinating features – markedly prolonged distal motor latencies, slowed conduction velocities (<40% of normal in affected nerves), absent F-waves in the lower extremities, and absent sural sensory responses – findings supportive of acute inflammatory demyelinating polyneuropathy. These electrodiagnostic results, together with the clinical presentation, fulfilled the key diagnostic criteria for GBS (progressive symmetric weakness with areflexia over <4 weeks, and electrophysiological evidence of demyelination).

Routine laboratory tests (CBC, metabolic panel) were unremarkable. An extensive infectious and neoplastic workup was negative: PCR panel for neurotropic viruses (including HSV1/2, VZV, CMV, EBV, HHV6, enterovirus, and others) in CSF was negative, as were blood and urine cultures. No malignant cells were identified in CSF or peripheral blood, and bone marrow chimerism showed 100% donor engraftment with continued molecular remission of leukemia (BCR-ABL undetectable). These findings supported the diagnosis of GBS over alternative etiologies (Table 2).

Table 1. Central Nervous System examination.

CNS Examination Component	Findings
Speech and Comprehension	Normal
Respiratory Count	Able to count to 26 in one breath
Pupil Reaction	Symmetric, reactive to light
Extraocular Movements (EOM)	Intact, no ptosis
Facial Sensation	Normal sensation over the face
Neck Flexion	4/5
Motor Examination	
Tone	Normal
Power	Distal > Proximal
Shoulder Abduction	4+
Shoulder Adduction	4+
Elbow Flexion	4+
Elbow Extension	4+
Hand Grip	4+
Dorsiflexion (DF)	3/5
Plantar Flexion (PF)	4/5
Knee Extension (KE)	4-/5
Knee Flexion (KF)	4-/5
Hip Flexion (HF)	4-
Hip Abduction	4+
Deep Tendon Reflexes (DTR)	
Ankle	Absent
Knee	Absent
Triceps	2+
Brachioradialis	Absent
Biceps	Absent
Sensory Examination	
Position Sense	Intact
Vibration Sense	Intact
Pinprick Sensation	Decreased in bilateral lower extremities

Therapeutic Intervention

Tacrolimus was promptly discontinued on suspicion of a drug-associated neuropathy, and methylprednisolone was added for GVHD prophylaxis. The patient was treated with high-dose intravenous immunoglobulin (IVIG) (0.4 g/kg/day for 5 days, total 2 g/kg), along with aggressive supportive care. IV hydrocortisone and diphenhydramine were given as pre-medications to IVIG. Over the ensuing days, the patient underwent intensive rehabilitation including daily physiotherapy and occupational therapy.

Follow-up and Outcomes

The patient's GBS resolved completely within 4 weeks following intensive rehabilitation, including physiotherapy and occupational therapy. Prior to symptom onset, he had contact with an individual with an upper respiratory tract infection, though remained asymptomatic himself. The successful management of GBS without tacrolimus

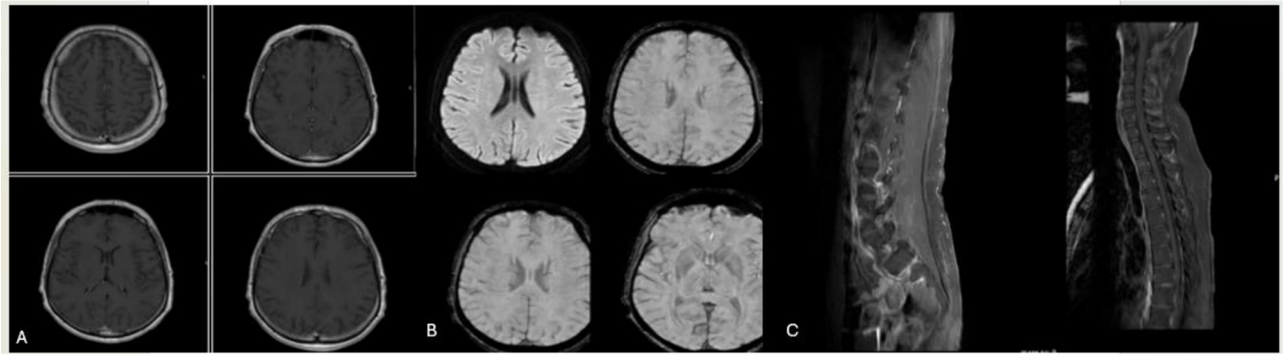

Fig.. 1. MRI brain, cervical, thoracic, lumber; Findings with contrast: MRI scans of the brain (A and B) and spinal cord (C) showed minimal enhancement of the cranial nerves and the anterior nerve rootlets of the cauda equina.

Table 2. Laboratory Findings.

Parameter	Result	Reference Range
WBC	4×10^9/L	4.5–11.0 $\times 10^9$/L
RBC	3.19 $\times 10^{12}$/L	4.3–5.9 $\times 10^{12}$/L
Hemoglobin	146 g/L	135–175 g/L
Hematocrit	0.390 L/L	0.41–0.53 L/L
MCV	78 fL	80–100 fL
Platelet count	152 $\times 10^9$/L	150–400 $\times 10^9$/L
Liver function test		
AST	16 U/L	8–48 U/L
ALT	27 U/L	7–55 U/L
Alkaline phosphatase	68 U/L	40–130 U/L
Albumin	4.0 g/dL	3.5–5.0 g/dL
Renal Function Tests		
Creatinine	79 μmol/L	62–106 μmol/L
Urea	2 mmol/L	2.76–8 mmol/L
Drug Level		
FK Level	3.1 ng/mL	5–20 ng/mL
Inflammatory Markers		
CRP	2 mg/L	<10 mg/L
Procalcitonin	0.10 ng/mL	<0.5 ng/mL
LDH	230 U/L	140–280 U/L
Infectious Workup		
Respiratory multiplex	Negative	Negative
CMV	Not detected	Not detected
EBV	Not detected	Not detected
Blood culture	Negative	Negative
CSF culture	Negative	Negative
Urine culture:	Negative	Negative
Molecular Studies		
BCR-ABL Quantitation	Not detected	Not detected
Chimerism		
Donor Myeloid cells Engraftment %	100	Target ~100%
Donor T-lymphocyte Engraftment %	95%	Target ~100%
CSF analysis		
Opening pressure	110 mL water	90–180 mL water
Appearance (clear)	Clear	Clear
WBC	51 cells/mm^3 (96% lymphocytes, mature/reactive, no blasts)	0–5 cells/mm^3
RBC	2 cells/mm^3	0 cells/mm^3
Protein	1900 mg/L	150–450 mg/L
Glucose	3.7 mmol/L	2.20–3.90 mmol/L
Rapid Multiplex PCR Meningitis	Result	Reference Range
Escherichia coli K1	Negative	Negative
Haemophilus influenzae	Negative	Negative
Listeria Monocytogenes	Negative	Negative
Neisseria meningitidis	Negative	Negative
Streptococcus agalactiae	Negative	Negative
Streptococcus pneumoniae	Negative	Negative
Cryptococcus neoformans/gattii	Negative	Negative
Enterovirus	Negative	Negative
Herpes simplex virus 1	Negative	Negative
Herpes simplex virus 2	Negative	Negative
Human herpesvirus 6	Negative	Negative
Human parechovirus	Negative	Negative
Varicella zoster virus	Negative	Negative
Streptococcus Pyogenes	Negative	Negative
Mycoplasma Pneumoniae	Negative	Negative
Paraneoplastic Autoantibody Panel which includes Amphiphysin, CV2, PNM2A (Ma2/Ta), Ri, Yo, Hu, Recoverin, SOX1, Titin, Zic4, GAD65, and Tr (DNER)	Negative	Negative

continuation did not precipitate GVHD. Post-transplant assessment demonstrated molecular remission of AML with undetectable minimal residual disease, enabling discontinuation of immunosuppression. Ponatinib was resumed as maintenance therapy to prevent disease relapses. At 6-month follow-up, he remained neurologically normal with sustained leukemia molecular remission and full donor chimerism.

DISCUSSION

HSCT recipients are at risk of neurological complication that might be caused from the primary disorder, infection due the immunocompromisation status pre, during and post the transplantation or as direct harm from the medication deployed during this the course of the illness [4,5].

One such complication is GBS, an acute immune-mediated polyneuropathy characterized by rapidly progressive, symmetrical flaccid paralysis. GBS has an annual incidence of 1.3 per 100,000, with a male predominance [1]. The majority of cases follow an infectious trigger, commonly a viral or bacterial illness affecting the respiratory or gastrointestinal tract [2]. The reminder of the cases is attributed to vaccine, medications, surgeries, and transplantation [3,6-8].

For transplant patients suspected of having GBS, the same clinical criteria used for postinfectious GBS are applied, clinical presentation, cerebrospinal fluid analysis, and nerve conduction studies. The cerebrospinal fluid typically shows elevated protein levels "albuminocytologic dissociation" with normal white blood cell count, while nerve conduction studies often reveal slowed or even blocked signal transmission [9].

However, a notable point of diagnostic uncertainty was the CSF pleocytosis. Typical GBS features albuminocytologic dissociation (elevated protein with $\leqslant$5 cells/μL); in this patient, the CSF white cell count of 51/μL was higher than usually expected. Mild lymphocytic pleocytosis (10–50 cells/μL) can be compatible with GBS, but counts exceeding 50/μL are atypical and should prompt evaluation for alternative diagnoses. Indeed, the presence of such pleocytosis in our case raised concern for conditions like leptomeningeal malignancy or infectious polyradiculitis rather than idiopathic GBS [2].

We undertook a thorough work-up to address this ambiguity. No evidence of leukemic meningitis was found (no blasts in CSF and sustained remission systemically), effectively ruling out neuroleukemiosis. Infectious etiologies were carefully considered: herpesviruses, enteroviruses, and Mycoplasma pneumoniae PCRs were negative, and cultures for bacteria and fungi were sterile.

Notably, HIV-associated GBS is known for causing CSF pleocytosis, but our patient had no risk factors and tested negative for HIV. Thus, after excluding other causes, we attributed the albuminocytologic dissociation with mild lymphocytic pleocytosis to an aberrant immune response related to GBS in this unique setting [10].

The pathophysiology of GBS is not fully understood, though molecular mimicry is central. This leads to an aberrant immune response targeting peripheral nerves, often mediated by T-lymphocytes [11].

Among the medications associated with GBS is tacrolimus, a calcineurin inhibitor (CNI) that suppresses T-cell proliferation by binding to the FK506 binding protein. Tacrolimus has well-recognized neurotoxic effects, most commonly manifesting as encephalopathy, seizures, or posterior reversible encephalopathy syndrome (PRES) in transplant patients [12]. It is believed that demyelination occurs due to changes in T-cell subsets, as tacrolimus disrupts intra-thymic T-cell development by blocking programmed cell death. This interference either enhances or fails to suppress T-cell activation in response to peripheral myelin [13].

Tacrolimus-related neuropathies often resemble GBS or chronic inflammatory demyelinating polyneuropathy (CIDP) in their electrophysiological and pathological features [13]. Its mechanism—calcineurin inhibition—can impair regulatory T-cell pathways, possibly triggering autoimmune demyelination. Supporting this, prior case reports have described demyelinating polyneuropathies temporally associated with tacrolimus in both solid organ and stem cell transplant recipients. For example, Labate *et al.* reported a severe polyneuropathy after heart transplantation attributed to tacrolimus, which improved upon drug withdrawal [14]. Similarly, a 1994 series by Wilson *et al.* detailed patients on FK506 (tacrolimus) developing a CIDP-like sensorimotor neuropathy [13]. A literature review identified at least a dozen similar cases, with neuropathy onset ranging from days to several months post-transplant, and improvement frequently observed following tacrolimus dose reduction or discontinuation—sometimes in combination with immunotherapy [15].

Our case adds to this growing body of evidence linking tacrolimus to GBS. The symptom onset occurred around two months into tacrolimus therapy, and full recovery followed drug withdrawal and IVIG administration. This strongly suggests a causal role for tacrolimus, especially in a patient likely immunologically primed by the transplant and possibly an unrecognized viral trigger.

This case illustrates the complexity of diagnosing GBS in an immunocompromised post-transplant patient receiving multiple therapies, making thorough history-taking, physical examinations, and laboratory investigations crucial to pinpoint the trigger. The patient's presentation (rapidly progressive flaccid paralysis with areflexia and cranial nerve involvement) was characteristic of GBS, and nerve conduction studies confirmed a demyelinating polyneuropathy consistent with the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) variant. According to the 2023 EAN/PNS guidelines, the combination of progressive limb weakness, loss of reflexes, and supportive investigations (nerve conduction abnormalities and elevated CSF protein) strongly suggests GBS [16].

It is particularly important to exclude any infectious processes, signs, and symptoms of Graft versus Host Disease, and to monitor drug levels, as CNIs can cause neurotoxicity that is dependent on their concentration [14,17].

Prognosis in GBS is generally favorable, with around 80% of patients making a full recovery. Effective management heavily focuses on intensive support for respiratory and cardiovascular functions. In CNI-related neurotoxicity, adjustment of immunosuppression is also a key step. We elected to discontinue tacrolimus in favor of continuing corticosteroid prophylaxis; this decision was made collaboratively with the transplant team, weighing the risk of GVHD against the severity of the neuropathy. Fortunately, our patient did not develop any GVHD flare after stopping tacrolimus. This aligns with other reports where alternative immunosuppression (e.g. steroids or mycophenolate) covered the gap during CNI withdrawal [8]. Each case must be individualized – in some situations, reducing the tacrolimus dose (rather than full cessation) might be attempted if neuropathy is milder, but for our patient with significant motor impairment, we prioritized drug cessation. Finally, our patient's continued remission of AML on ponatinib alone is an encouraging sign that targeting the leukemia and managing GVHD can be balanced even when neurotoxic immunosuppressants are withdrawn [18].

Therapeutic interventions typically include IVIG and plasma exchange (plasmapheresis), which are pivotal in managing this condition. Additionally, it's vital to implement strategies to prevent complications from reduced mobility, such as pneumonia and thromboembolism, which are critical for enhancing patient outcomes and quality of life [19].

CONCLUSIONS

This case underscores the importance of maintaining a high index of suspicion for GBS in patients on calcineurin inhibitors who develop new-onset weakness, while also rigorously evaluating for atypical features such as CSF pleocytosis. By exercising diagnostic caution and promptly addressing potential causes, clinicians can achieve favorable neurological outcomes. Our patient's recovery without relapse of leukemia or GVHD demonstrates that timely intervention – including immunotherapy and tailored adjustments in immunosuppression – can lead to full neurological recovery without jeopardizing transplant success. Ongoing vigilance and further research are warranted to better understand the interplay between immunosuppressive drugs and post-transplant immune-mediated complications.

Ethics approval and consent to participate:

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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