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Proposal for Diagnostic Criteria for Manifestations of Chronic Graft-versus-Host Disease in Peripheral Nervous System and Muscles

Tim Steinberg[1], Klemens Angstwurm[1], Matthias A. Fante[2,3], Wolfgang Herr[2], Ernst Holler[2], Matthias Edinger[2], Ralf Linker[1], De-Hyung Lee[1], Daniel Wolff[2,*], Alexander Denk[2]

[1] *Department of Neurology, University Hospital Regensburg, Regensburg, Germany*
[2] *Department of Internal Medicine III, University Hospital Regensburg, Regensburg, Germany*
[3] *Department of Internal Medicine II, University Hospital Wuerzburg, Wuerzburg, Germany*

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A B S T R A C T

Atypical neurological graft-versus-host disease (cGVHD) is a rare complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). In addition to central nervous system (CNS) involvement, patients with cGVHD may also exhibit pathology of the peripheral nerves, muscles or neuromuscular junction. In this report, we propose more detailed diagnostic criteria for these manifestations and apply them in a case series of peripheral nervous system and muscles (PNSM) involvement of cGVHD. Based on an interdisciplinary evaluation applying the recent provisional criteria for atypical manifestations of cGVHD, we propose a scoring system to diagnose and classify the four distinct forms of atypical cGVHD affecting the PNSM: immune-mediated inflammatory polyneuropathy, small-fiber polyneuropathy, neuromuscular junction disorder, and myositis. The proposed scoring system was retrospectively applied to all patients who underwent allo-HSCT at the University Hospital of Regensburg between 2007 and 2022 and presented with suspected cGVHD involving the PNSM. The objective was to advance the understanding of neurological manifestations associated with cGVHD by systematically evaluating neurological symptoms, diagnostic findings, and the clinical trajectories of affected patients. Out of 770 patients who underwent allo-HSCT, 15 (1.9%) were identified with cGVHD affecting the PNSM. According to the proposed scoring system, six patients were classified as possible and nine patients as probable atypical cGVHD of the PNSM. 1st-line treatment comprised intravenous immunoglobulin for most cases (10/15). A clinical response to 1st-line therapy was observed in 11 patients. In total, 12 patients showed response to immunosuppressive treatment (IST) while two patients did not respond to IST and one patient did not receive IST, but was successfully treated with pyridostigmine. Nine patients suffered from long-term neurologic sequelae. The 6-months and 1-year overall survival following PNSM-cGVHD onset was 12/15 and 9/15 patients, respectively. Cause of death was at least partly

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*Correspondence and reprint requests: Daniel Wolff, MD, Department of Internal Medicine III, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg 93053, Germany.
E-mail address: daniel.wolff@ukr.de (D. Wolff).

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attributed to PNSM-cGVHD in three patients; up to last follow-up, non-relapse related mortality was 6/15 patients and relapse-related mortality 2/15 patients. With an incidence of 1.9%, PNSM-cGVHD is a rare but serious complication after allo-HSCT associated with long-term neurologic sequelae; early diagnosis and IST are mandatory. We propose a modified scoring system to diagnose this entity as a basis for larger multicenter studies.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a significant complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT), contributing to increased non-relapse mortality (NRM) and a decline in quality of life [1–3]. It affects roughly 30% to 50% of patients, typically developing between 3 months and 2 years after allo-HSCT [4–7]. The pathophysiology of cGVHD encompasses several mechanisms, such as sustained tissue injury with ongoing inflammation, disruption of central and peripheral immune tolerance, and abnormal tissue regeneration leading to fibrosis [8,9].

Classical, NIH-defined target organs of cGVHD are skin, mouth, eyes, lungs, musculoskeletal system, gastrointestinal tract, genitourinary tract and liver [10–12]. A variety of atypical manifestations and target organs were recently presented in the NIH Highly Morbid Forms Report 2020 and a NIH taskforce, including central and peripheral nervous system [13,14].

Cuvelier et al. [14] highlighted that based on several reports of immune-mediated diseases of the peripheral nervous system and muscles (PNSM), such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, radiculoplexus neuropathies, and myositis [15,16] - the PNSM is an atypical target of cGVHD with a reported incidence of 0.7% to 6.1% of patients [14,17–21]. Additionally, Cuvelier et al. [14] pointed out several critical gaps in the research on peripheral neuropathies and myositis associated with cGVHD. These include the absence of standardized diagnostic criteria and the need for reliable methods to assess the prevalence, diagnostic approaches, severity, treatment strategies, and patient outcomes related to these conditions.

We developed a scoring system to diagnose atypical presentations of cGVHD in the PNSM, and evaluated the neurological symptoms, diagnostic findings, and clinical course of 15 patients diagnosed with atypical PNSM-cGVHD at our center. The new diagnostic score for PNSM-cGVHD might be a basis for prospective studies and a better understanding of neurological manifestations of cGVHD and treatment.

METHODS

Study Design and Patient Selection

All sequential patients who underwent allo-HSCT between June 15th, 2007, and December 31st, 2022, at the University Hospital Regensburg (Germany) surviving at least 3 months were screened in this retrospective analysis. All patients with suspected atypical cGVHD of the PNSM were reviewed individually through discussions between two neurologists (TS, KA) and two hematologists (AD, DW). Patients were excluded if there was insufficient supportive data to suspect PNSM-cGVHD such as preexisting peripheral neuropathy before transplantation.

GVHD and Endpoint Analysis

Diagnosis, assessment of organ involvement, and documentation of cGVHD were conducted as part of routine clinical practice using the NIH consensus criteria [11] either during inpatient therapy or at outpatient follow-up visits. GVHD was assessed using the Glucksberg criteria for acute GVHD (aGVHD) [22] and the NIH consensus criteria for NIH-defined cGVHD [11]. The last follow-up (LFU) was defined as either the date of death or October 23rd, 2024, whichever occurred first. Overall survival (OS) was measured from the date of allo-HSCT to the time of death. Relapse-related mortality (RRM) referred to death resulting from relapse of the underlying disease, while non-relapse mortality (NRM) encompassed death due to any other cause.

Development of the PNSM-cGVHD Score

Based on the NIH Report 2020 [14], the given literature and our experience, we developed a scoring system for the diagnosis of atypical cGVHD of the PNSM: immune-mediated inflammatory polyneuropathy, small-fiber polyneuropathy, neuromuscular junction disorder and myositis. The scores includes the recent findings regarding (1) clinical symptoms, (2)

electrophysiology (3) CSF findings, (4) manifestation of cGVHD at other NIH-defined organ sites, (5) onset after taper of immunosuppressive therapy (IST) at least 3 months after allo-HSCT or after donor lymphocyte infusion (DLI)/stem cell backup, (6) response to IST, (7) histological findings and (8) additional diagnostics (antibody diagnostic, radiological diagnostic, nerve ultrasound) (Table 1). The development of the score is based on the discussion between two neurologists (TS, KA) and two hematologists (AD, DW), as well as a review of current literature and standard diagnostic in similar autoimmune diseases in patients without allo-HSCT such as Myasthenia gravis and chronic inflammatory demyelinating polyneuropathy (CIDP). Furthermore, we subdivided our cohort into categories: unlikely cGVHD, possible cGVHD and probable cGVHD. We did not define a score value for definite PNSM-cGVHD, as there is currently no gold standard diagnostic for this condition.

Statistical Analyses

Absolute numbers, relative frequency (n, %), and median including interquartile range (IQR) are shown.

Ethical Approval

The ethics committee at the University of Regensburg approved the study (#23-3450-104). The analysis was conducted in accordance with the current Declaration of Helsinki.

Patient Consent

All patients alive at the time of data acquisition provided written informed consent and data were anonymized by removing potentially identifying characteristics, such as age and sex.

RESULTS

Diagnostic Criteria

Based on existing literature and diagnostic criteria for atypical cGVHD—particularly the 2020 NIH Consensus Statement on atypical cGVHD [14]—as well as our center's clinical experience, we have identified four distinct forms of PNSM involvement in cGVHD. Cuvelier et al. [14] characterized one such form as atypical cGVHD with a chronic inflammatory demyelinating polyneuropathy (CIDP)-like phenotype. We use the broader term cGVHD with immune-mediated inflammatory polyneuropathy, which we further subdivide into CIDP-like and Guillain-Barré syndrome (GBS)-like variants, based clinical course of disease progression. In contrast to Cuvelier et al. [14] we did not differentiate sensory and autonomic SFN, as these forms often present with overlapping symptoms [23]. In order to include other myasthenic syndromes, atypical cGVHD for Myasthenia gravis phenotype is defined as cGVHD with neuromuscular junction disorder. Lastly, Cuvelier et al. [14] added myositis as atypical cGVHD with affection of muscles, fascia and joints. As myositis syndromes are seen as diseases of the PNSM and usually treated by neurologists, we added this phenotype to our list of proposed criteria for the PNSM. In contrast, we did not add cGVHD with muscle cramps, as those may have several causes (eg, myopathies, neuropathies, metabolic disorders) [24].

Major requirement for the diagnosis of cGVHD is the exclusion of relevant differential diagnosis, most importantly therapy-associated toxicity. The criteria include clinical features, electrophysiology, CSF analysis, histology, other diagnostic measures, and correlation with other manifestations of cGVHD and IST (Table 1).

Criteria for Diagnosis of PNSM-cGVHD

Inclusion Criteria

1. Suspected PNSM-cGVHD
2. No other diagnosis is more likely (eg, drug toxicity, infectious (eg, CMV) or postinfectious diseases of the PNSM, paraneoplastic syndromes in case of active underlying malignancy, unrelated neurological diseases)

Patient Characteristics and Incidence of NIH-defined and Atypical cGVHD

All patients receiving an allo-HSCT at the University of Regensburg were screened as mentioned above. 30 patients requiring retransplantation were counted once only and 55 patients with treatment-related mortality (TRM) within the first 100 days including TRM due to aGVHD within the first 365 days ("patients not at risk") were excluded, resulting in a final cohort of 770 patients. 23 patients were considered to be potentially affected by PNSM-cGVHD. Four patients of this cohort were excluded because an alternative diagnosis seemed more likely (one each with diagnosis of (1) cytomegalovirus (CMV) radiculitis, (2) CMV myelitis, (3) radiculopathy after spondylodesis and diabetic polyneuropathy and (4) C8- and L4-syndrome and toxic polyneuropathy).

In our scoring system four patients were classified as unlikely PNSM-cGVHD and excluded from further statistics. Therefore, 15 patients

Table 1
Proposed diagnostic criteria for PNSM-cGVHD

cGVHD with immune-mediated inflammatory polyneuropathy (organ manifestation: PNS)	
Clinical signs indicative of progressive, sensory, motor, and/or autonomic polyneuropathy	1 point
Electrophysiological signs for demyelinating polyneuropathy	1 point
Cytalbuminologic dissociation in CSF	1 point
Nerve ultrasound and/or MRI indicative for inflammatory polyneuropathy	1 point
Prior or concomitant cGVHD outside the central nervous system and peripheral nervous system	1 point
Onset after the cessation or reduction of immunosuppression or after donor lymphocyte infusion (DLI)/stem cell backup, at least 3 months following allo-HSCT	1 point
Nerve biopsy showing immune-mediated inflammatory neuropathy	3 points
Clinical improvement with immunosuppressive therapy	1 point
Maximum count	10 points
Diagnosis of cGVHD with immune-mediated inflammatory polyneuropathy is unlikely (1-2 points), possible (3-4 points) or probable (≥ 5 points). In cases of monophasic disease and symptom progression for less than eight weeks, the disease is classified as GBS-like cGVHD. In cases with polyphasic diseases and/or disease progression for 8 weeks or more, CIDP-like cGVHD is diagnosed.	
cGVHD with small-fibre polyneuropathy (organ manifestation: PNS)	
Clinical signs of small fiber neuropathy (SFN), including allodynia, hypalgesia, analgesia, thermal hypesthesia, and thermal anesthesia	2 points
Electrophysiological signs of damage to Aδ- or C-fibers (for example: quantitative sensory testing)	2 points
Prior or concomitant cGVHD outside the central nervous system and peripheral nervous system	1 point
Onset after the cessation or reduction of immunosuppression or after donor lymphocyte infusion (DLI)/stem cell backup, at least 3 months following allo-HSCT	1 point
Skin biopsy showing small-fiber polyneuropathy	3 points
Clinical improvement with immunosuppressive therapy	1 point
Maximum count	10 points
Diagnosis of cGVHD with small-fiber polyneuropathy is unlikely (1-2 points), possible (3-4 points) or probable (≥ 5 points) cGVHD with small-fiber polyneuropathy.	
cGVHD with neuromuscular junction disorder (organ manifestation: PNS)	
Clinical signs of a myasthenic syndrome, especially load dependent ptosis, diplopia and/or paresis	2 points
Electrophysiological signs of affection of the neuromuscular junction, especially increment and/or decrement in repetitive stimulation	2 points
Clinical improvement with cholinergic therapy	2 points
Serum analysis showing antibodies against acetylcholine receptor, muscle-specific tyrosine kinase (MuSK), low density lipoprotein receptor-related protein 4 (LRP4) and/or voltage-gated calcium channel (VGCC)	1 point
Prior or concomitant cGVHD outside the central nervous system and peripheral nervous system	1 point
Onset after the cessation or reduction of immunosuppression or after donor lymphocyte infusion (DLI)/stem cell backup, at least 3 months following allo-HSCT	1 point
Clinical improvement with immunosuppressive therapy	1 point
Maximum count	10 points
Diagnosis of cGVHD with neuromuscular junction disorder is unlikely (1-2 points), possible (3-4 points) or probable (≥ 5 points).	
cGVHD with myositis (organ manifestation: muscle)	
Clinical signs indicative for myositis, especially paresis associated with muscle pain	1 point
Electromyography indicative for myositis, especially pathological spontaneous activity and/or myopathic patterns	1 point
Laboratory: elevated creatine kinase (>3 upper laboratory limit) and/or antibodies against muscle antigens	1 point
Muscle ultrasound or muscle MRI indicative for myositis	1 point
Prior or concomitant cGVHD outside the central nervous system and peripheral nervous system	1 point
Onset after the cessation or reduction of immunosuppression or after donor lymphocyte infusion (DLI)/stem cell backup, at least 3 months following allo-HSCT	1 point
Histological evidence of myositis in muscle biopsy	3 points

(*continued*)

Improvement with immunosuppressive therapy, seen clinically and/or in significant reduction of serum creatine kinase	1 point
Maximum count	10 points
Diagnosis of cGVHD with myositis is unlikely (1-2 points), possible (3-4 points) or probable (≥ 5 points).	

presenting with possible (n=6) or probable (n=9) PNSM-cGVHD were included in the final analysis (Figure 1).

Patient Characteristics

Transplant-related characteristics of patients with possible or probable PNSM-cGVHD are summarized in Table 2. The median age at allo-HSCT was 54 years (range, 41-60 years) and sex was male in 11/15 patients. All patients were transplanted for hematologic malignancies. 11 patients had received peripheral blood stem cells with 8/15 of donors being related. Two patients received donor lymphocyte infusion (DLI) for relapse of hematologic malignancy. Prior acute GVHD grade II or higher, according to Glucksberg criteria, was observed in eight patients. Prior or active cGVHD at other organ sites (up to one month after onset of PNSM-cGVHD) was present in 11 patients. Median time between allo-HSCT and PNSM-cGVHD onset was 446 days (range, 237-700 days). The main characteristics related to extra-PNSM-cGVHD are displayed in Table 3. Three patients suffered from relapse of underlying hematologic disease, with one being in complete remission (CR) at last follow-up while two patients died due to relapse of hematologic malignancy.

Neurological characterization of cGVHD

Scoring. Of 15 patients, according to our score 11 were classified as cGVHD with immune-mediated inflammatory PNP (six possible and five probable), two patients with probable cGVHD with SFN and one patient each with probable cGVHD with neuromuscular junction disorder and probable cGVHD with myositis (Table 4).

Neurological Symptoms

All cases of cGVHD with immune-mediated inflammatory PNP presented with paresis of the lower extremities; 7/11 also showed paresis of the upper extremities, and 6/11 exhibited muscle atrophy. Common sensory symptoms included hyporeflexia/areflexia (8/11), pallhypesthesia (8/11), and sensory gait ataxia (9/11). Autonomic symptoms were observed in 3/11 patients, all presenting with orthostatic dysregulation. Interestingly, no patient showed involvement of the cranial nerves. Paresthesia, dysesthesia, and pain were reported in both patients with cGVHD with SFN. The clinical course of cGVHD with immune-mediated inflammatory PNP was chronic (disease progression >8 weeks) in all but two patients, who therefore were classified as GBS-like cGVHD with immune-mediated inflammatory polyneuropathy (Table 5).

Electrophysiological Characteristics

Electrophysiological investigations, particularly neurographies, were performed in all patients. Among the 11 cases of cGVHD with immune-mediated inflammatory PNP, eight showed axonal damage on neurography, while three exhibited indirect signs of axonal damage on electromyography. Demyelinating damage was observed in seven cases. F-wave abnormalities were noted in five, and conduction blocks in two patients. Overall, evidence of demyelinating damage was present in eight patients, leading to a diagnosis of

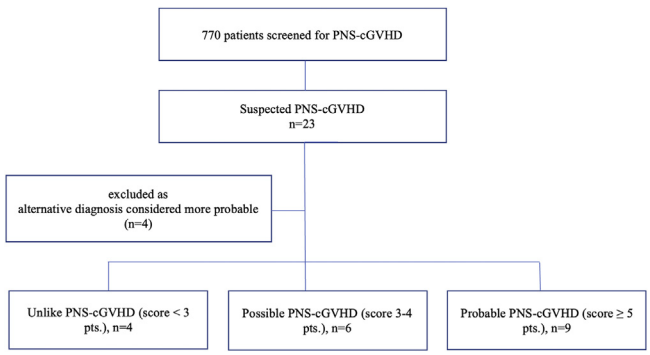

Figure 1. Flowchart regarding inclusion of patients. Pts.: points.

Table 2
Patient characteristics of patients with possible or probable PNSM-cGVHD

Parameter	Value
No. of patients	15
Male sex, n (%)	11 (73)
Age at allo-HSCT, yr, median (IQR)	54 (41-60)
Diagnosis, n (%)	
AML	7 (47)
Lymphoma	3 (20)
Myelodysplastic neoplasm	3 (20)
Multiple Myeloma	1 (7)
Myeloproliferative neoplasm	1 (7)
Comorbidity index, n (%)	
Sorror score 0	3 (20)
Sorror score 1-2	5 (33)
Sorror score $\geq$ 3	7 (57)
Conditioning regimen, n (%)	
Reduced intensity	13 (87)
Standard	2 (13)
Conditioning with TBI, n (%)	3 (20)
Graft source, n (%)	
PBSC	11 (73)
BM	4 (27)
Donor constellation, n (%)	
Matched	12 (80)
MRD	6 (40)
MUD	6 (40)
Mismatched	3 (20)
Haploidentical	2 (13)
MMUD	1 (7)
Female donor/male recipient, n (%)	1 (7)
History of DLI, n (%)	2 (13)
GVHD	
Prophylaxis, n (%)	
CNI + MMF	2 (13)
CNI + MTX	10 (67)
PTCy	3 (20)
Incidence of aGVHD, n (%)	14 (93)
Of those:	
Skin	11 (73)
Gut	5 (36)
Liver	2 (14)
Max. grade aGVHD	
I	6 (43)
II	5 (36)
III	2 (14)
IV	1 (7)
NRM, n (%)	6 (40)
RRM, n (%)	2 (13)

AML, acute myeloid leukemia; BM, bone marrow; CNI, calcineurin inhibitor; DLI, donor lymphocyte infusion; MRD, matched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; MMF, mycophenolate mofetil; MTX, methotrexate; PBSC, peripheral blood stem cells; NRM, non-relapse mortality; PTCy, post-transplantation cyclophosphamide; RRM, relapse-related mortality.

Table 3
Characteristics of extra-neurological cGVHD

Chronic GVHD (up to last follow-up)	
Incidence of NIH-defined cGVHD, n (%)	15 (100)
Of those:	
Skin	12 (80)
Mouth	8 (53)
Eyes	5 (33)
Gut	5 (33)
Liver	5 (33)
Lungs	4 (27)
Urogenital	1 (7)
Fascia	3 (20)
Other	Immune mediated thrombocytopenia 1 (7), pancreatitis 1 (7)
NIH-defined cGVHD, max. grade, n (%)	
I	3 (20)
II	6 (40)
III	6 (40)
History of cGVHD (both NIH-defined and atypical), n (%)	
De novo cGVHD	1 (7)
Quiescent cGVHD	12 (80)
Overlap syndrome	2 (14)
Onset NIH-defined cGVHD, day, median (range)	237 (161-456)
Onset PNSM-cGVHD, day, median (range)	446 (237-700)

demyelinating polyneuropathy in four cases. The diagnostic criteria for possible CIDP, as defined by Van der Bergh et al. [25], were met in only one case. A diagnosis of (additional) axonal polyneuropathy was made in eight patients. In 1/2 cases of cGVHD with SFN, both demyelinating damage and pathological findings on quantitative sensory testing were present, while the sympathetic skin response was normal. Repetitive nerve stimulation in the case of cGVHD with neuromuscular junction disorder yielded unremarkable results. In the case of myositis-like cGVHD, myopathic potentials were found in electromyography. For further details, refer to Supplementary Appendix S1 and Table S1.

Cerebrospinal Fluid Findings

Cerebrospinal fluid (CSF) results were available in eight cases, all of them had cGVHD with immune-mediated inflammatory PNP. Median CSF protein concentration was only mildly elevated (540 mg/l), five cases showed cytoalbuminologic dissociation. CSF pleocytosis was seen in two cases (6 cell/μl and 9 cells/μl). Oligoclonal bands (OCB) were assessed in four patients, none of them showed autochthone immunoglobulin synthesis (Table 6).

Other Diagnostics

Unfortunately, neither MRI / nerve ultrasound to assess nerve root swelling nor testing for

Table 4
Scoring values of our patients with possible or probable PNSM-cGVHD using the proposed score

Score Value	PNSM-cGVHD	Immune-mediated i nflammatory PNP	SFN	Neuromuscular j unction disorder	Myositis	Total
3 points	Possible	3	0	0	0	3
4 points	Possible	3	0	0	0	3
5 points	Probable	4	0	0	1	5
6 points	Probable	1	0	1	0	2
7 points	Probable	0	1	0	0	1
8 points	Probable	0	1	0	0	1
	Total	11	2	1	1	15

Table 5
Clinical manifestations of PNSM-cGVHD at initial presentation and during course of disease

	cGVHD with immune-mediated inflammatory PNP [11]	cGVHD with SFN [2]	cGVHD with neuromuscular junction disorder [1]	cGVHD with myositis [1]	Total
Peripheral nerve symptoms (negative sensory)					
Hyporeflexia, areflexia	8	1	0	1	10
Pallhypesthesia	8	2	1	1	12
Hypesthesia, anesthesia	6	1	1	1	9
Thermhypesthesia, -thermanesthesia	1	0	0	0	1
Hypalgesia, analgesia	1	1	0	0	2
Peripheral nerve symptoms (positive sensory)					
Dysesthesia	1	2	0	0	3
Paresthesia	4	2	0	0	6
Pain, hyperalgesia, allodynia	1	2	0	0	3
Peripheral nerve symptoms (motor)					
Paresis lower extremities	11	0	0	1	12
Paresis upper extremities	7	0	0	1	8
Muscle atrophy	6	0	0	1	7
Involvement of cranial nerves	0	0	0	0	0
Other peripheral nerve symptoms					
Tremor	1	0	0	0	1
Gait ataxia	9	0	0	1	10
Ataxia of extremities	2	0	0	0	2
Muscle cramps	3	1	0	1	5
Autonomic symptoms	3	0	0	0	3
Myasthenic symptoms					
Load-dependent diplopia	0	0	1	0	1
Load-dependent ptosis	0	0	0	0	0
Load-dependent dysarthria	0	0	0	0	0
Exertion-dependent weakness of extremities	0	0	1	0	1
Clinical course					
<8 weeks	2	0	0	0	2
>8 weeks	9	2	1	1	13

Table 6
Cerebrospinal fluid results of all patients

CSF results available	8
Of those: CSF WBC (maximum, cells/μl)	Median 3, Interquartile ration (IQR) 5, Mean 3
CSF protein available	8
Of those: cytalbuminological dissociation	5
Of those: CSF Protein (maximum, mg/l)	Median 540, IQR 490, Mean 716
CSF OCB available	4
Of those: CSF OCB showing intrathecal immunoglobulin G synthesis	0

antineuronal antibodies against the PNS (eg, ganglioside antibodies, antibodies against paranodal proteins) were performed in any case with cGVHD with immune-mediated inflammatory PNP. In the case of cGVHD with neuromuscular junction disorder, antibodies against the acetylcholine receptor were tested twice and returned negative results. In the case of cGVHD with myositis, MRI and CT of the muscles showed muscle edema.

Treatment

IST was administered to all but one patient. The latter patient suffered from cGVHD with neuromuscular junction disorder and was not treated with IST due to mild clinical symptoms and active high-risk human papillomavirus (HPV) infection. This patients' symptoms were successfully treated with pyridostigmine. Drugs prescribed as part of the 1st-line regimen (described in Table 7) comprised intravenous immunoglobulin (IVIG) for most cases (10/15 treated patients [67%]). Of note, 11/15 patients were already on therapy with steroids at onset of PNSM-cGVHD with a median dose of 0.2 mg/kg (range 0.04 mg/kg to 0.24 mg/kg), and only one patient was treated with high-dose steroids specifically for PNSM-cGVHD.

A clinical response to 1st-line therapy was observed in 11/15 patients (73%) (four patients with complete and seven patients with partial remission). In one patient, clinical relapse of symptoms required another administration of IVIG 1137 days after first successful treatment of PNSM-cGVHD, which again led to CR. Additional lines of treatment were administered to three patients due to insufficient response to 1st-line therapy (Supplementary Appendix S2). Therapies beyond 1st-line treatment comprised use of plasmapheresis, ibrutinib, abatacept, tocilizumab and belumosudil (each n=1). In total, all but two patients showed response to administered therapy. Regarding response of PNSM manifestations of cGVHD to steroid therapy, it can be noted that three patients were steroid refractory, while four patients were not treated with steroids for this purpose, and the remaining eight patients received steroids <0.5 mg/kg in combination with another IST, preventing assessment of steroid response in these patients.

Table 7
Treatment Administered as 1st-line regimen

First-line therapy	All Cases
Glucocorticosteroids	n = 1
Intravenous immunoglobulin	n = 10
Ruxolitinib	n = 2
Mycophenolate mofetil	n = 1
Pyridostigmine	n = 1

Sequential neurography was performed in five cases. Among those, three patients exhibited progressive electrophysiological deterioration despite clinical improvement and two demonstrated an improvement in both clinical status and electrophysiological results.

Outcome and neurological sequelae

Median follow-up after onset of PNSM-cGVHD was 751 days (range, 211-1464 days). 1-year follow-up was available for nine patients (one patient had not reached 6-months follow-up at LFU, while five patients died before 1-year follow-up on days 56, 78, 182, 239 and 351 after onset of PNSM-cGVHD). Therefore, 6-months OS was 12/15 and 1-year OS following PNSM-cGVHD onset was 9/15 patients.

Regarding PNSM-cGVHD, three patients achieved CR without neurological sequelae. Another patient who developed PNSM-cGVHD while being on treatment with interferon gamma due to severe pulmonary aspergillosis, showed CR with treatment of IVIG but flared 3 years later in the absence of immunomodulatory treatment requiring another successful course of IVIG.

Eight patients experienced persistent neurological impairments lasting longer than 6 months. Of those, seven patients showed partial remission (PR) under IST, though symptoms did not ameliorate completely; one patient experienced progressive deterioration despite treatment. Another patient is in PR on treatment with IVIG for PNSM-cGVHD and has not reached 6-months follow-up after onset of PNSM-cGVHD. Two patients died within 6 months after PNSM-cGVHD onset.

In total, eight patients died during the follow-up period ending on October 23rd, 2024. In three cases, cGVHD of the PNSM was at least partially responsible for the patients' death (Supplementary Appendix S3, patients 1, 7 and 15). The remaining causes of death included relapse of hematologic malignancy (n=2), sepsis, multiple spinocellular carcinomas, and progressive multifocal leukoencephalopathy (PML) due to human polyomavirus 2 (JC virus) infection. Accordingly, as of the last follow-up, NRM was observed in 6/15 patients, while RRM occurred in 2/15 patients. A more detailed overview of outcomes and neurologic sequelae is provided in Supplementary Appendix S3.

One illustrative case of a patient with PNSM-cGVHD is shown in Supplementary Appendix S4.

DISCUSSION

Non-infectious neurologic complications are frequently reported after allo-HSCT (15%-65%) [26,27], but little is known about the incidence of neurologic cGVHD. To date, reports about PNSM-cGVHD are limited [17–19,21].

We assume that PNSM-cGVHD is underreported due to the lack of diagnostic criteria, lack of awareness and infrequent consultation of neurologists. Within our single-center cohort of 770 patients, 15 patients developed atypical PNSM-cGVHD, representing 1.9% of all patients "at risk". Worth mentioning, other atypical manifestations were detected in two patients with pancreatitis (n=1) and immune-mediated cytopenia (n=1). cGVHD can occur at different levels of the PNSM and involve the peripheral nerve, the neuromuscular junction or the muscle [28]. Identifying symptoms as a result of cGVHD can be quite complex, since generalized muscle weakness may also be caused by more frequentcly occurring systemic infections, use of corticosteroids, metabolic or nutritional issues, or side effects from other medications [28–30].

The 2005 and 2020 NIH consensus criteria for cGVHD described myositis, polymyositis, peripheral neuropathies and myasthenia gravis as features of PNSM-cGVHD [10,14]. While diagnostic criteria for CNS-cGVHD have been proposed [28], diagnostic criteria for PNSM-cGVHD are missing. To date, cGVHD of the CNS and PNSM can be only diagnosed in presence of NIH-defined cGVHD. However, Lambert et al. [1], referring to case reports [31,32] and their own findings, recently questioned the mandatory presence of NIH-defined cGVHD affecting other organs in cases of CNS-cGVHD, as CNS-cGVHD seems to occur also in patients without other signs of cGVHD. In addition, we recently published our findings regarding the identification of 34 patients (5.5% of all allo-HSCT patients) developing either only atypical cGVHD (n = 14) or atypical manifestations prior to NIH-defined cGVHD (n = 20) [33]. In line with this, prior or active NIH-defined cGVHD was only described in 11/15 patients of our cohort. In our newly proposed diagnostic criteria, we therefore still recognize the possible relation between NIH-defined cGVHD and atypical GVHD of the PNSM, but do not see the former mandatory for the diagnosis of the latter.

We propose diagnostic criteria for unlikely, possible and probable cGVHD of the PNSM. We deliberately included affection of two organ systems—the peripheral nervous system (including neuromuscular junction) and muscle—in this study, as (i) these conditions may present with similar symptoms and are often difficult to differentiate in the early stages of disease, and (ii) both organ systems should be evaluated by a neurologist. Nevertheless, with regard to overall GVHD grading, the three forms of peripheral nervous system affection (polyneuropathy, small-fiber polyneuropathy, and neuromuscular junction disorder) and myositis represent involvement of two distinct organ systems. In the case of cGVHD with immune-mediated inflammatory polyneuropathy (organ manifestation: PNS) discussed here, we considered whether antibodies against gangliosids and paranodal proteins should be included in the diagnostic criteria. Currently, data on antibody testing in this specific context are very limited. Moreover, in CIDP, the presence of such antibodies may support the diagnosis, but they are not part of the core diagnostic criteria [25]. Future studies may improve our understanding of their diagnostic value and could ultimately lead to modifications of the proposed criteria.

Meeting the expert opinion of two hematologists and two neurologists, all 15 patients of our cohort diagnosed with cGVHD of the PNSM achieved a score $\geq$3 and therefore had possible or probable PNSM-cGVHD. It is worth noting that eight more patients in our overall cohort were initially considered having cGVHD of the PNSM. However, applying the proposed scoring system, four of these cases had to be excluded due to more likely differential diagnoses and four were excluded because of low score values. In these cases, PNP was most often attributed to toxicity. Given the absence of a diagnostic gold standard and the frequent difficulties in distinguishing drug-induced toxicity from cGVHD, we emphasize that the proposed score may also aid in differentiating between these conditions.

Patients with atypical cGVHD with immune-mediated inflammatory polyneuropathy exhibited not only sensory symptoms such as hyporeflexia/areflexia, hypesthesia, and pallhypesthesia, but also consistent motor impairment (11/11 patients) and muscle atrophy (6/10 patients), typical for classical CIPD [25]. Several individuals experienced severe gait disturbances or were bedridden, and in these cases, the response to IST was poor. Apart from two cases with GBS-like cGVHD, all patients showed disease progression for more than eight weeks and therefore had CIDP-like cGVHD. Notably, no signs of cranial nerve

involvement or tremor—features associated with other autoimmune polyneuropathies such as Miller-Fisher syndrome or paranodopathies—were observed [34]. The two patients of our cohort with cGVHD with SFN, as well as the patients with cGVHD with neuromuscular junction disorder and cGVHD with myositis, did not show any clinical features distinguishing them from classical SFN, ocular myasthenia gravis or classical myositis, respectively. Remarkably, one patient developed GVHD of the PNSM on day +51 after allo-HSCT, exhibiting a GBS-like phenotype of GVHD with immune-mediated inflammatory PNP. This might reflect an unusual early onset of cGVHD and has also been described by others [28,35,36].

Only one case of cGVHD with immune-mediated inflammatory polyneuropathy fulfilled the van der Bergh et al. criteria [25] for possible CIDP; however, demyelinating damage was observed in 4/11 patients. Predominantly, axonal damage was detected in 8/11 patients. This suggests that in cGVHD with immune-mediated inflammatory polyneuropathy, axonal involvement may represent the predominant pattern of nerve injury. As a result, differentiation from toxic polyneuropathy becomes more challenging and highlights the importance of additional diagnostic tools, such as nerve biopsy or nerve ultrasound. The latter is an emerging diagnostic tool for autoimmune polyneuropathies and can even help distinguish subtypes such as CIDP and multifocal motor neuropathy [37,38]. We, therefore, recommend considering this method into the diagnostic workup of cGVHD of the PNSM, including its potential to aid in differentiating treatment-associated polyneuropathy from cGVHD. According to the scoring system, two patients (both SFN) reached a score of more than six points. In the remaining cases—particularly those involving cGVHD with immune-mediated inflammatory polyneuropathy—no patient scored more than six points, primarily due to the absence of nerve biopsies. In the case of cGVHD with myositis, muscle biopsy was done at a late stage of the disease, showing atrophy, but no signs of florid inflammation. As with CNS-cGVHD, our understanding of the pathophysiology of cGVHD affecting the PNSM remains limited. As previously noted, nerve biopsy should be performed in cases of suspected cGVHD with immune-mediated inflammatory PNP, cGVHD with SFN, and cGVHD with myositis. In the latter two conditions, biopsy represents the diagnostic gold standard in routine evaluations unrelated to cGVHD [39,40]. It is worth noting that our cohort did only include one case of cGVHD with myositis. In other cohorts, myositis has also been reported less frequently than cGVHD with immune-mediated inflammatory PNP [19].

Cytalbuminologic dissociation was observed in 5/8 cases of cGVHD with immune-mediated inflammatory polyneuropathy and available CSF results. This finding may reflect a delay between the peak of disease activity and the timing of the lumbar puncture.

Our study shows that PNSM-cGVHD can contribute to severe neurologic sequelae. 9/15 patients suffered from long-term neurologic symptoms and 3/15 patients died in association with PNSM-cGVHD. In light of an incidence of 1.9%, which for most physicians might be higher as suspected, early diagnosis is crucial. As the majority of our study (13/15, 87%) showed response to administered therapy, early administration of IST is mandatory. A commonly used treatment strategy for CIDP outside the transplantation setting involves IVIG [33,41], which also appeared to be effective in patients with cGVHD with immune-mediated inflammatory PNP.

With 6/15 patients, NRM was comparably high in our cohort; however, there were only two patients with RRM in our cohort. The compared to existing literature [42]—high NRM of our cohort might reflect the severity of PNSM-cGVHD and vulnerability of patients suffering from this entity, while the low RRM is in line with published literature suggesting a graft-versus leukemia effect [43]. 6-months OS was 12/15 and 1-year OS following PNSM-cGVHD onset was 9/15 patients.

The retrospective design and the small number of patients with atypical PNSM-cGVHD are major limitations of our study. Due to the limited sample size, no statistical analysis was conducted, as this would imply a level of certainty that is not warranted. However, to the best of our knowledge, this represents the largest analysis of patients with atypical cGVHD of the PNSM addressing the diagnostic challenge of atypical manifestations of the PNSM.

The proposed criteria for the various atypical manifestations of PNSM-cGVHD should be validated in larger, multicenter cohorts and could therefore be applied in registries. This may provide a foundation for advancing our understanding of the pathophysiology of PNSM-cGVHD. Given the potentially distinct underlying mechanisms in each subgroup, gaining deeper insight into these conditions could facilitate the

development of more targeted therapies for PNSM-cGVHD.

DATA AVAILABILITY

Data will be shared upon reasonable request.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2026.01.038.

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