Neuropathy and Myopathy in Patients with Graft-Versus-Host Disease Treatment and Diagnostic Algorithm: Review of the Literature

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is an intractable complication associated with considerable morbidity and being a leading cause of non-relapse mortality: the average mortality is 26%. Though several investigational treatment options showed preliminary favourable outcomes including treatment with Rituximab, plasmapheresis, Sirolimus [1–3], as initially defined, resembled an autoimmune disorder occurring 100 days after allogeneic transplantation. The arbitrary day of onset, however, may not be as crucial in separating acute from chronic GVHD; rather, these two syndromes appear to result from different mechanisms [4, 5]. cGVHD is known to involve skin, gut, liver. Targeting of other organ systems is described; however overlapping symptoms caused by infections, autoimmune manifestations, drugs make the diagnosis challenging.

Summary. Vilnius University Hospital Center of Hematology, Oncology and Transfusion Medicine (HOTC) performs about 100–120 hematopoietic stem cell transplantations per year (HSCT). According to the number of hematopoietic stem cell transplantations Vilnius HOTC is very close to the number of patients at one of the biggest European Hematology and Bone Marrow Transplantation center at Innsbruck University Hospital in Austria. Hematopoietic stem cell transplantation (HSCT) is a method of treatment when potentially neurotoxic medications presss immune system and destroy tumor cells. Most frequently such as oncohematology diseases, aplastic anemia or metabolic disorders are treated. Nowadays the urgent topic that has been discussed is neurological complications after HSCT. It occurs from 37% to 91% and is the main cause of death accounting from 6% to 26%. The circumstance aggravating the overall condition of patients is autoimmune system activation against the transplantant. It is called graft-versus-host disease (GVHD). When immune system activation occurs more than 100 days after transplantation it is called chronic GVHD. Most often GVHD damages gastrointestinal tract, liver, skin, and lungs. So long there are few case reports of GVHD and neurological complications. It results from masked clinics and complicated diagnostics due to continuous immunosuppression and neurotoxic impact of chemotherapy.

This article focuses on the peripheral nervous system damage (chronic inflammatory demyelinating polyradiculoneuropathy, Guillain–Barre syndrome), neuromuscular disease (myasthenia gravis) and myopathy after hematopoietic stem cell transplantation and GVHD. Furthermore, we present Rituximab treatment recommendations to glucocorticoids refractory GVHD forms. To conclude, we recommend algorithms for diagnosis and treatment of possible peripheral nervous and muscular diseases and GVHD.

Keywords: hematopoietic stem cell transplantation, immunosuppression, graft-versus-host disease, Guillain–Barre syndrome, myasthenia, rituximab.
Research in the area of neurologic complications and its association with GVHD is limited with regard to allo-
genetic hematopoietic stem cell transplantation (allo-
HSCT). Most studies have been retrospective [6–11]. Pros-
spective evaluation of this complication has been rare [12,
13]. The incidence of neurologic complications has varied
from 37% to 91%, and such complications have been the
cause of death in 6% to 26% of patients [6].

Neurologic symptoms and signs which were mild and
sub-acute and predominantly affected the peripheral ner-
vous system after HSCT have been reported in 57% of
the patients. Signs indicated axonal sensory-motor poly-
neuropathy and proximal muscular atrophy. The risk fac-
tors of neurologic complications were, acute GVHD, chronic GVHD, liver dysfunction, total body irradiation,
use of steroids more than 3 months, previous chemotherapy
cycles [12]. In those patients who have got mild sen-
sory polyneuropathy because of cycles of chemother-
aphy before HSCT, it worsens after HSCT [14].
Neuromuscular system involvement in GVHD is under
attention in the past decade [15]. Peripheral neuropathy
has also been associated with either acute or chronic
GVHD after allo genetic HSCT. Most cases developed
 neuropathy as an acute Guillain–Barré syndrome (GBS)
or chronic recurrent form as chronic inflammatory
demyelinating polyneuropathy (CIDP). Although, in a
setting of stable GVHD, all peripheral nervous system
damages could be interpreted as GVHD induced neuropa-
athy or myopathy. There are some reports on polyneu-
ropathy in patients with GVHD after bone marrow trans-
plantation.

IMMUNE-MEDIATED NEUROPATHIES AND
MYOPATHIES

Chronic inflammatory demyelinating
polyradiculoneuropathy (CIDP)

CIDP is an unusual, but important complication of HSCT
[16, 17]. Inflammatory demyelinating polyradiculoneu-
ropathy (CIDP) as a manifestation of GVHD was first re-
ported in 1991 and was followed by eight further cases in
the following decade. Authors Werneck et al [19] have de-
scribed CIDP manifestation in chronic Graft-versus-host
disease. CIDP is a clinical syndrome based on a physiolo-
gical and pathological concept as followed: (1) clinical fea-
tures of chronic progressive or relapsing and remitting,
symmetrical, sensory and motor poly radiculoneuropathy
causing weakness of proximal and distal muscles; (2) CSF
protein concentration is almost always increased;
(3) electrophysiological evidence of demyelination is re-
quired for the diagnosis and axonal degeneration can oc-
curs in evolution; (4) histological examination reveals
demyelination with variable inflammatory infiltrates. The
CIDP also occurs after HSCT as a chronic progressive or
relapsing and remitting CIDP [15, 19].

Guillain–Barre syndrome (GBS)

Guillain–Barre syndrome is a rare complication following
hematopoietic stem cell transplantation (HSCT). Only a
few cases of GBS during acute graft-versus-host disease
(acute GVHD) have been reported and its pathogenesis is
unclear. GBS in the early period post HSCT has been at-
tributed to the conditioning regimen, particularly cytosine
arabinoside [20]. In contrast, the etiology of GBS in the
late HSCT period remains unknown [21]. Some reports
suggest an association with antecedent infections such as
Campylobacter pylori and cytomegalovirus (CMV). GBS
is characterized by rapidly evolving limb weakness, loss of
deep tendon reflexes, absent or mild sensory deficits, and
variable autonomic dysfunction. Weakness can develop
acutely (days) or sub-acute (up to 4 weeks), and it may
progress with eventual resolution of paralysis [22, 23] (ta-
ble 1).

Myasthenia gravis

Myasthenia gravis is an autoimmune disease rarely diag-
nosed following HSCT. It may be a part of the spectrum of
chronic graft-versus-host disease (GVHD) [24] and is as-
sociated with discontinuation of immunosuppressants
[25]. Muscle weakness often involves the ocular muscles,
bulbar muscles and muscles innervated by other facial
nerves. It can be generalized and might involve the prox-
imal limb muscles as well. The diagnosis is made clinically
and supported by electro-diagnostic testing, elevated titers
of anti-AChR antibodies, and improvement in strength
with anticholinesterase therapy (table 2).

The analysis of reports supports the idea that GVHD is a
multi systemic organ system disease; obviously the pe-
ripheral nervous system could also be involved in the
pathogenesis of GVHD.

Myositis

Myositis as a complication of cGVHD has been reported in
up to 7.6% of patients [4]. Chronic GVHD-related poly-
myositis has been reported, usually with other manifesta-
tions of GVHD. Previous studies have described a hetero-
genous group of myositis-associated chronic GVHD
patients, most with either nonspecific muscle biopsy find-
ings [26, 27], or without muscle biopsy analysis [28, 29].

Muscle may be a target tissue for chronic GVHD. Among
1859 individuals who developed chronic GVHD, 12 de-
veloped myositis. It was first identified between 7 weeks
and 5 months after transplantation. In histopathology,
electromyography, laboratory values and response to
immunosuppressive therapy, the cases resembled idio-
pathic polymyositis. Autoantibodies were found in eight
cases [30]. The predominant clinical picture described is
one of proximal weakness and myalgia, often responding
to corticosteroids or other immunosuppressive treatment.

Distal weakness in patients following HSCT might also re-
fect the presence of a GVHD-associated polyneuropathy
or the toxic effects of chemotherapeutic agents [19].
<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>Age / Sex</th>
<th>Underlying disorder</th>
<th>Latency*</th>
<th>Neurological toxicity</th>
<th>CSF protein</th>
<th>Histology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato et al. (Amato, 1993)</td>
<td>1993</td>
<td>31/M</td>
<td>CML</td>
<td>6 months</td>
<td>CIDP</td>
<td>NP</td>
<td>No</td>
<td>PSL+AZP+CS+IVIg</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>44/M</td>
<td>CML</td>
<td>8 months</td>
<td>CIDP</td>
<td>?</td>
<td>No</td>
<td>PSL+CS+IVIg</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29/M</td>
<td>AA</td>
<td>2 weeks</td>
<td>CIDP</td>
<td>NP</td>
<td>No</td>
<td>PSL+CS+IVIg</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43/M</td>
<td>NHL</td>
<td>1 month</td>
<td>CIDP</td>
<td>?</td>
<td>No</td>
<td>PP+PSL</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Adams et al. (Adams, 1995)</td>
<td>1995</td>
<td>5/F</td>
<td>MOP</td>
<td>4 years</td>
<td>CIDP</td>
<td>NP</td>
<td>No</td>
<td>PP</td>
<td>R</td>
</tr>
<tr>
<td>Griggs et al. (Griggs, 1997)</td>
<td>1997</td>
<td>42/M</td>
<td>NHL</td>
<td>3 years</td>
<td>CIDP</td>
<td>?</td>
<td>No</td>
<td>PP</td>
<td>R</td>
</tr>
<tr>
<td>Nagashima et al. (Nagashima, 2002)</td>
<td>2002</td>
<td>32/M</td>
<td>NHL</td>
<td>5 years</td>
<td>CIDP</td>
<td>NL</td>
<td>The sural nerve showed a loss of myelinated nerve fibers with epineurial fibrosis and rare occurrence of T cells, but without obvious vasculitic changes.</td>
<td>MPS</td>
<td>PR</td>
</tr>
<tr>
<td>Openshaw et al. (Openshaw, 1991)</td>
<td>1991</td>
<td>36/M</td>
<td>CML</td>
<td>7 days</td>
<td>CIDP</td>
<td>?</td>
<td>Sections of multiple peripheral nerves sampled post mortem revealed prominent demyelination with heavy infiltration of macrophages and lymphocytes. Immunohistochemical studies demonstrated that most of the lymphocytes were of the CD8+, cytotoxic/suppressor cell class and that many of the Schwann cells expressed class II (HLA-DR) antigen.</td>
<td>P+CP+PP+IVIg</td>
<td>D</td>
</tr>
<tr>
<td>Peter et al. (Peters, 2005)</td>
<td>2005</td>
<td>62/M</td>
<td>MM</td>
<td>1 month</td>
<td>CIDP</td>
<td>NP</td>
<td>No</td>
<td>P+CP+PP+IVIg</td>
<td>R</td>
</tr>
<tr>
<td>Lorenzoni et al. (Lorenzoni, 2007)</td>
<td>2007</td>
<td>17/F</td>
<td>AML</td>
<td>10 months</td>
<td>CIDP</td>
<td>?</td>
<td>The nerve biopsy had mild inflammatory perivascular lymphomononuclear infiltration in the endoneurium and epineurium, a reduction in the number of large myelinated fibers in some sectors of the fascicles, asymmetrical axonal degeneration within fascicles, occasional presence of myelin ovoid, and compact and disarranged myelin sheath in most of the material.</td>
<td>IvIg+PP+P+MM</td>
<td>R</td>
</tr>
<tr>
<td>Wada et al. (Wada, 2008)</td>
<td>2008</td>
<td>54/M</td>
<td>ALL</td>
<td>1 year</td>
<td>CIDP</td>
<td>?</td>
<td>Peroneal nerve biopsy revealed demyelination.</td>
<td>IvIg</td>
<td>R</td>
</tr>
<tr>
<td>Gonzales et al. (Mi González, 2000)</td>
<td>2000</td>
<td>25/?</td>
<td>CML</td>
<td>7 days</td>
<td>GBS (toxoplasmosis)</td>
<td>NL</td>
<td>Axonal degeneration of nerve roots compatible with the axonal form of GBS.</td>
<td>?</td>
<td>D</td>
</tr>
<tr>
<td>Suzuki et al. (S Suzuki, 2007)</td>
<td>2007</td>
<td>58/F</td>
<td>ALL</td>
<td>6 months</td>
<td>GBS</td>
<td>?</td>
<td>No</td>
<td>IvIg+PSL+T</td>
<td>D</td>
</tr>
<tr>
<td>Rodriguez et al. (Krance RA, 2002)</td>
<td>2002</td>
<td>16/M</td>
<td>T cell leukemia</td>
<td>6 days</td>
<td>GBS</td>
<td>?</td>
<td>No</td>
<td>IvIg</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>17/M</td>
<td>T cell lymphoma</td>
<td>5 days</td>
<td>GBS</td>
<td>?</td>
<td>No</td>
<td>IvIg</td>
<td>D</td>
<td></td>
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<tr>
<td></td>
<td>18/M</td>
<td>ALL</td>
<td>2 days</td>
<td>GBS</td>
<td>?</td>
<td>No</td>
<td>IvIg</td>
<td>D</td>
<td></td>
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</table>
### Table 1. Reported cases of CIDP and GBS after HSCT (cont.)

<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>Age / Sex</th>
<th>Underlying disorder</th>
<th>Latency*</th>
<th>Neurological toxicity</th>
<th>CSF protein</th>
<th>Histology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al. (B Khan, 2005)</td>
<td>2005</td>
<td>?/F</td>
<td>Aplastic anaemia</td>
<td>?</td>
<td>GBS</td>
<td>?</td>
<td>?</td>
<td>IvIg</td>
<td>R</td>
</tr>
<tr>
<td>Zhang et al. (L Zhang, 2008)</td>
<td>2008</td>
<td>?/?</td>
<td>CML</td>
<td>2 days</td>
<td>GBS</td>
<td>?</td>
<td>?</td>
<td>PP</td>
<td>R</td>
</tr>
<tr>
<td>Mudad et al. (R Mudad, 1995)</td>
<td>1995</td>
<td>44/F</td>
<td>Breast cancer</td>
<td>2 days</td>
<td>GBS</td>
<td>?</td>
<td>?</td>
<td>PP</td>
<td>R</td>
</tr>
<tr>
<td>Zhang et al. (L Zhang, 2008)</td>
<td>2008</td>
<td>?/?</td>
<td>CML</td>
<td>2 days</td>
<td>GBS</td>
<td>?</td>
<td>?</td>
<td>PP</td>
<td>R</td>
</tr>
<tr>
<td>Thöne et al. (J Thöne 2010)</td>
<td>2010</td>
<td>?/F</td>
<td>CML</td>
<td>4 month</td>
<td>GBS</td>
<td>?</td>
<td>?</td>
<td>IvIg+PP</td>
<td>?</td>
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</tbody>
</table>


### Table 2. Reported cases of Myasthenia gravis after HSCT

<table>
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<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>AML</td>
<td>AML</td>
<td>CML</td>
<td>AA</td>
<td>AA</td>
<td>AA</td>
<td>AA</td>
<td>AA</td>
<td>AA</td>
<td>AML</td>
<td>T- ALL</td>
</tr>
<tr>
<td>Sex Mismatch</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Sicca</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Liver</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Lung</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Oral</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time of MG after HSCT (months)</td>
<td>100</td>
<td>46</td>
<td>29</td>
<td>60</td>
<td>19</td>
<td>27</td>
<td>35</td>
<td>33</td>
<td>25</td>
<td>26</td>
<td>46</td>
</tr>
<tr>
<td>Anti-AChr antibody elevation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thymoma</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>NR</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>NR</td>
<td>no</td>
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<tr>
<td>Associated with immunosuppression discontinuation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>+</td>
<td>+</td>
<td>NR</td>
</tr>
</tbody>
</table>

**HISTOLOGY**

All consideration whether CIDP manifests as an independent disease after HSCT or it occurs in terms of GVHD could be defined by histological confirmation which can be obtained in nerve or skin biopsy. The characteristic lesions of CIDP consist of patchy regions of demyelination and edema with variable inflammatory infiltrates, a reduction in the number of large myelinated fibers in some sectors of the fascicles, asymmetrical axonal degeneration within fascicles, occasional presence of myelin ovoid, and compact and disarranged myelin sheath in most of the material [31]. The inflammatory infiltrates are found in both the endoneurium and the epineurium but, in contrast to vasculitic neuropathy, are more abundant in the endoneurium made of mononuclear cells, mainly lymphocytes and macrophages cells. The histological analysis of the nerve showed perivascular inflammatory cells in 54.5% of the patients with CIPD [32].

Histopathological studies were performed in only three cases and immunohistochemical analysis was described in a single report and these have shown demyelization and vasculitis of the peripheral nerves. Biopsies taken from the left quadriceps femoris muscle, skin and sural nerve were fixed in formalin, embedded in paraffin and stained. For immunohistochemistry the sections were also stained for several lymphocyte markers including CD4, CD8 and UCHL-1, CD45RO, CD3 and CD68. In the muscle T-cell infiltration was detected around atrophied myocytes. The sural nerve showed a decreased number of myelinated fibers and marked nerve fiber depletion replaced by fibrosis and a slight intimal thickening with medial fibrosis of an accompanying arteriole [15]. There are no reports whether inflammatory infiltrate could be donors T, B lymphocytes, which could improve the GVHD and peripheral nervous system damage or myopathy diagnosis. Nevertheless, specific muscle findings can be similar to nerve findings varying according to the time and the severity of the disease [18]. American academy of neurology has reported evidence-based guidelines regarding the role of nerve biopsy and skin biopsy for assessment of polyneuropathy. Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, nononeuropathy multiplex due to vasculitis, or with atypical forms of chronic inflammatory demyelinating polyneuropathy (CIDP). Skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of distal symmetric polyneuropathy (DSP), particularly small fiber sensory polyneuropathy (SFNS). The most common technique involves a 3 mm punch biopsy of the skin from the leg. After sectioning by microtome, the tissue is immunostained with anti-protein-gene product 9.5 (PGP 9.5) antibodies and examined with immunohistochemical or immunofluorescent methods [33]. Skin biopsy could be less invasive, validated, technically possible diagnostic tool for patients with GVHD who are at high risk to develop infection and/or bleeding.

**cGVHD ANTIBODIES AND TREATMENT WITH RITUXIMAB**

The investigation of the immune pathophysiology of chronic GVHD is limited and just a few animal models have been developed that mimic the various clinical manifestations of this disease in humans [34]. The effective prevention of chronic GVHD by the depletion of T cells from the stem cell graft demonstrates that donor T cells play a critical role in this disease. When patients and donors are HLA-matched, minor histocompatibility antigens expressed in normal tissues of the recipient have been shown to elicit both CD4+ and CD8+ T-cell responses which result in either direct cell killing or cytokine-induced tissue injury. Thus, current therapies for chronic GVHD are targeted primarily and non-specifically against donor T-cell activity. Although donor T cells play a central role in the development of chronic GVHD, there is emerging evidence that donor B cells also contribute to the clinical manifestations of this disease [35].

**B cells**

Twenty-four research groups have investigated the involvement of antibodies in the pathogenesis of cGVHD and found 35 different antibodies to be more prevalent in cGVHD [36]. Although not always analyzed, 8 autoantibodies and 5 alloantibodies seemed to be strongly associated with cGVHD (table 3).

Despite over 20 years of investigation, no studies have convincingly demonstrated that these antibodies contribute to the clinical manifestations of tissue injury in cGVHD. The location of most target antigens of these antibodies is intracellular and the antibodies do not have a direct cytolytic activity. In addition, tissue injury via immune complexes or vasculitis is not probable, as these are not prominent features of cGVHD.

Interesting data was published by Kim et all [37] who found higher levels of B cell activating factor (BAFF) in patients with active chronic GVHD at baseline than in normal controls [38]. Although not statistically significant, patients with lower pre-treatment BAFF levels tended to have better outcomes from therapy. Serum BAFF levels increased as B-cell numbers and immunoglobulin levels fell in response to rituximab therapy. This is consistent with the known function of BAFF as an important regulator of B-cell homeostasis and survival, and BAFF has previously been shown to play a critical role in B-cell reconstitution following myeloablative conditioning [38]. At normal basal levels, BAFF serves to promote survival of antigen-specific B cells; however, persistently high BAFF levels are also able to prevent apoptosis of auto-reactive B cells and promote the development of autoimmunity [39]. Earlier work from our laboratory showed that BAFF levels are higher in patients with chronic GVHD than in those without [40, 41]. Patients with chronic GVHD also have low numbers of B cells, and high BAFF/B cell ratios are, therefore, characteristic of active chronic GVHD. Patients who
do not develop chronic GVHD during the first year after hematopoietic stem cell transplantation have higher numbers of B cells at 6 and 9 months post-transplant than patients who do develop chronic GVHD. Further phenotypic analysis revealed that patients without chronic GVHD have higher proportions of naïve CD27– B cells whereas patients who develop chronic GVHD have higher proportions of activated CD27+ B cells. These findings suggest that persistent elevation of BAFF in the setting of delayed B cell reconstitution can support the survival of activated, allo-reactive B cells and, therefore, promote the development of chronic GVHD. BAFF is also produced by myeloid cells in the setting of inflammation, and this may be another factor driving ongoing BAFF production once B-cell numbers recover in patients with chronic GVHD [42]. Interestingly, high doses of steroids have been shown to lower BAFF levels, and this may represent one of the mechanisms by which these agents lead to improvements in chronic GVHD.

A recent study indicated that recipient B cells are not important initiators of GVHD, and that efforts to prevent GVHD by antigen presenting cells (APC) depletion should focus on other APC subsets [43].

**T cells**

Recently, T-regulatory cells (Tregs) have been investigated. Tregs can suppress proliferation and function of T cells, particularly of the Th1 type. They are also known to constitutively express CD25+. In a murine model it was demonstrated that the incidence and severity of cGVHD is higher in the absence of recipient CD4+ CD25+ T cells, and the subsequent repletion with recipient or host Tregs resulted in a protective effect. *De novo* generation of donor CD4+ T cells during acute GVHD is of importance for the progression to cGVHD. CD52+ and anti-CD25+ antibodies have been shown to be effective in preventing cGVHD. However, these were small, phase I and II, single center studies. Therefore, a prospective controlled randomized multicenter study is highly warranted to confirm these promising results.

**T and B cells collaboration**

Several studies have suggested a possible collaboration between B and T cells in the pathogenesis of cGVHD. In addition, various studies demonstrated B-cell responses to certain antigens in cGVHD patients, indicating the collaboration of B and T cells to produce specific antibodies against host antigens. Moreover, Zorn et al. demonstrated a coordinated B- and T-cell response in a male cGVHD patient after allogeneic HSCT with a female donor [44]. In this study, donor B cells were shown to mediate an alloimmune response and donor CD4+ T cells mediated an autoimmune response, via the development of anti-DBY antibodies. Furthermore, in cGVHD patients treated with rituximab, total lymphocytes decreased even more severely in number than B cells, suggesting that rituximab may somehow suppress T cells that interact with B cells.

### Table 3. Antibodies strongly associated with cGVHD

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Author</th>
<th>Years of publication</th>
<th>Prevalence in cGVHD patients after HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>Lister et al. (Lister, 1987)</td>
<td>1987</td>
<td>38% (n=26)</td>
</tr>
<tr>
<td>Anti-cytoskeletal intermediate filaments antibodies</td>
<td>Tazzari et al. (Tazzari, 1987)</td>
<td>1987</td>
<td>100% (n=16)</td>
</tr>
<tr>
<td>Anti-cytoplasmic squamous epithelium antibodies</td>
<td>Lortan et al. (Lortan, 1992)</td>
<td>1992</td>
<td>42% (n=36)</td>
</tr>
<tr>
<td>Anti-nucleolar B23 antibodies</td>
<td>Wiesierska-Gadek et al. (Wiesierska-Gadek, 1992)</td>
<td>1992; 1990</td>
<td>45% (n=22)</td>
</tr>
<tr>
<td>Anti-nucleolar C23 antibodies</td>
<td>Wiesierska-Gadek et al. (Wiesierska-Gadek, 1992)</td>
<td>1992; 1990</td>
<td>27% (n=22)</td>
</tr>
<tr>
<td>Anti-H1 hytotes antibodies</td>
<td>Wiesierska-Gadek et al. (Wiesierska-Gadek, 1992)</td>
<td>1992; 1990</td>
<td>18% (n=22)</td>
</tr>
<tr>
<td>Anti-nuclear lamins</td>
<td>Wiesierska-Gadek et al. (Wiesierska-Gadek, 1992)</td>
<td>1992; 1990</td>
<td>9% (n=22)</td>
</tr>
<tr>
<td>Anti-thyroid microsome antibodies</td>
<td>Lortan et al. (Lortan, 1992)</td>
<td>1992</td>
<td>43% (n=40)</td>
</tr>
<tr>
<td>Anti-PDGFR antibodies</td>
<td>Svegliati et al. (Svegliati, 2007)</td>
<td>2007</td>
<td>100% (n=22)</td>
</tr>
<tr>
<td>Anti-DBY antibodies</td>
<td>Miklos et al. (Miklos, 2004)</td>
<td>2004</td>
<td>50% (n=60)</td>
</tr>
<tr>
<td>Anti-UTY antibodies</td>
<td>Miklos et al. (DB Miklos, 2005)</td>
<td>2005</td>
<td>47% (n=75)</td>
</tr>
<tr>
<td>Anti-ZFY antibodies</td>
<td>Miklos et al. (DB Miklos, 2005)</td>
<td>2005</td>
<td>24% (n=75)</td>
</tr>
<tr>
<td>Anti-RPS4Y antibodies</td>
<td>Miklos et al. (DB Miklos, 2005)</td>
<td>2005</td>
<td>16% (n=75)</td>
</tr>
<tr>
<td>Anti-EIF1AY antibodies</td>
<td>Miklos et al. (DB Miklos, 2005)</td>
<td>2005</td>
<td>5% (n=75)</td>
</tr>
</tbody>
</table>

Adapted from Kapur, 2008.
MINOR HISTOCOMPATIBILITY ANTIGENS

Analysis of patients treated for post-transplantation relapse with donor lymphocytes has shown tumor regression to be correlated with expansion of cytotoxic T lymphocytes (CTLs) specific for hematopoiesis-restricted minor histocompatibility antigens (mHAs) [45, 46]. mHAs are peptides, presented by major histocompatibility complex (MHC) molecules, derived from intracellular proteins that differ between donor and recipient and due mostly to single nucleotide polymorphisms (SNPs) or copy number variations (CNVs) [47-49]. Identification and characterization of mHAs that are specifically expressed in hematopoietic but not in other normal tissues could contribute to graft-versus-leukemia/lymphoma (GVL) effects, while minimizing unfavorable graft-versus-host disease, one of the most serious complications of allo-HSCT [47, 48].

A recent study, which analyzed the mHAs alloreactivity from 24 donor/recipient pairs and correlated such alloreactivity with the development of GVHD or absence of relapse, provided a robust method to monitor mH antigens graft-versus-host reaction and suggest that current identified mHAs have predictive value on GVHD and GVL [50].

Although donor T cells play the main role in the development of chronic GVHD, there is evidence that donor B cells also act in the clinical manifestations of this disease [51, 52]. It was demonstrated a correlation between cGHVD and development of antibody responses to H-Y minor histocompatibility antigens in cases of sex-mismatched (male recipients with female donors) allo-HCT. These findings provided the scientific rationale for a number of studies exploring rituximab, which acts for profound B-cell depletion, to treat patients with steroid-refractory cGVHD.

The retrospective studies identified small numbers of patients who responded to rituximab [53, 54]. These findings were confirmed by larger studies [55]. The meta-analysis of published rituximab studies in patients with steroid-resistant chronic GVHD revealed an overall response rate of 66%, with responses observed for disease involving the skin, oral mucosa, liver, and lung [56, 57]. Summarized several potential mechanisms through which donor B cells can contribute to the clinical manifestations of chronic GVHD. In most of these mechanisms, B cells do not act independently but modulate immune responses of other cells, primarily CD4+ and CD8+ T cells. For example, alloantibodies can form immune complexes with recipient minor histocompatibility antigens and incorporation of these immune complexes by dendritic cells can stimulate donor T-cell responses specific for these minor histocompatibility antigens. Extensive depletion of all mature B cells with rituximab should interrupt all of the pathways in which B cells interact with T cells and suppress both antibody-dependent and antibody-independent B-cell mechanisms associated with chronic GVHD. Providing effective therapy for chronic GVHD without compromising normal immune functions and the graft-versus-leukemia effect remain important challenges and well-designed and adequately powered prospective studies to conclusively address this issue are needed.

DIFFERENTIAL DIAGNOSIS

The best-described polyneuropathies in the setting of HSCT are those associated with chemotherapeutic drugs: etoposide, cisplatin, paclitaxel, cytarabine (Ara-C), cyclosporine, tacrolimus, and interferon-a [58]. Severity of neuropathy increases with duration of treatment and progression usually stops once drug treatment is completed. An exception are platinum compounds where sensory loss may progress for several months after discontinuation of treatment (“coasting”). Pre-existent neuropathy may influence the development of toxic neuropathy. The neurologist managing cancer patients who develop neu-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical features</th>
<th>Electrophysiological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinca alkaloids</td>
<td>Symmetric sensomotor polyneuropathy; autonomic neuropathy, rarely cranial neuropathies</td>
<td>Axonal sensorimotor polyneuropathy; denervation in distal muscles</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Predominant sensory neuropathy; sensory ataxia; Lhermitte’s sign</td>
<td>Low-amplitude or unobtainable SNAPs; motor NCS and EMG usually normal</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Predominant sensory neuropathy; sensory ataxia; Lhermitte’s sign</td>
<td>Low-amplitude or unobtainable SNAPs; EMG with neuromyotonic discharges in acute cases</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Symmetric predominantly sensory polyneuropathy; rare autonomic symptoms</td>
<td>Axonal sensorimotor polyneuropathy; denervation in distal muscles</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Symmetric sensorimotor polyneuropathy; autonomic neuropathy; sensory ataxia and spasticity in severe cases</td>
<td>Axonal sensorimotor polyneuropathy; denervation in distal muscles</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Often, mild to moderate distal sensory loss, suppression of deep tendon reflexes, proprioception abnormalities. Mild to very severe pain, mainly at fingertips and toes. Usually, mild motor weakness in distal muscles of the lower limbs.</td>
<td>NCS; Reduction of a-SNAPs and CMAPs. Mild distal slowing of sensory and motor conduction velocities and increase in distal motor latencies. EMG: Active denervation changes with fibrillation potentials and increased size and complexity of motor unit potentials from distal muscles of the lower limbs.</td>
</tr>
</tbody>
</table>

SNAPs - sensory nerve action potentials; NCS – nerve conduction study; EMG – electromyography; CFS – cerebrospinal fluid
Another differential diagnosis is steroid myopathy which is evidently important, because polymyositis requires starting or increasing prednisone as opposed to discontinuation in the case of steroid myopathy. Electromyography (EMG) and occasionally muscle biopsy are very important tools for correct diagnosis [62].

Neurologic paraneoplastic syndromes are disorders associated with cancer but are not caused by local effects of the primary tumor mass. Instead, they are considered to be “remote effects” of cancer that result from autoimmunity—antibodies or inflammatory cells that are directed against neural antigens expressed by the tumor [63]. These syndromes can appear before any symptoms related to the cancer itself developed; sometimes, they may precede can-

...
Neuropathy and Myopathy in Patients with Graft-Versus-Host Disease Treatment and Diagnostic Algorithm: Review of the Literature

**Differential diagnosis and treatment algorithm of neuropathy after HSCT**

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<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>NCS/Needle EMG/RNS/brain MRI/CSF</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td><img src="image.png" alt="Diagram" /></td>
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</table>

**Fig. 2.** NCS – nerve conduction studies, RNS – repetitive nerve stimulation, EMG – electromyography, MRI – magnetic resonance imaging, CSF – cerebrospinal fluid, Abs – antibodies.

**Supportive treatment:** Plasma exchange, Steroids, Intravenous Immunoglobulin, Monoclonal antibody against CD20, symptomatic treatment.

Cancer diagnosis 2 years or more [64]. Paraneoplastic sensory neuronopathy most frequently is associated with the presence of anti-Hu antibodies, which also are known as antineuronal nuclear antibody type 1 (ANNA-1). Symptoms progress sub-acutely to involve the limbs, trunk, and face, causing severe sensory ataxia and pseudoathetosis. The CSF may show mild lymphocytic pleocytosis (20–40 lymphocytes/mm³), and moderate protein elevation [65]. Oligoclonal bands may be present [66]. The malignancy most commonly associated with sensory neuronopathy is small cell lung cancer (SCLC). Other malignancies encountered less frequently include cancers of the breasts, ovaries, prostate, adrenal gland, as well as neuroblastoma and Hodgkin’s lymphoma [66]. Discovery
Evaluation of lower motor neuron weakness in hematopoietic stem-cell transplantation patients

and treatment of the underlying cancer occasionally lead to improvement in the neurologic symptoms.

Peripheral neuropathy and myopathy are frequently associated with infections, particularly with HZV, EBV, CMV after HSCT [8, 67]. 13 from 19 with Guillain–Barre syndrome (GBS) had antecedent infections which significantly correlated with the disease p<0.0008 [68].

Vasculitic neuropathy (VN) can be a part of systemic vasculitis which occurs in 60–70% of patients. It also can be as a nonsystemic vasculitic neuropathy. VN presents either typically as mononeuritis multiplex, an asymmetric sensorimotor neuropathy or, less frequently, as a distal symmetric neuropathy (“small vessels vasculopathy”) [69]. Neuropathies are painful in more than 80% of patients. Histological studies show multiple focal lesions, with T and B cells involvement.

Openshaw et al suggest the algorithm to evaluate the lower motor neuron weakness in patients after HSCT [70] (Fig. 3).

We believe that immunologically mediated neuropathies may occur after autologous and allogeneic HSCT, and frequently lead to severe motor more than sensory symptoms and signs. Acute Guillain-Barre syndromes (GBS) and more protracted chronic forms (chronic inflammatory demyelinating polyneuropathies) (CIDP), myasthenia gravis (MG) or polymyositis (PM), have been described, almost all as case reports. The evidence for immune-associated mechanisms was circumstantial, based on the presence of multisystemic organ GVHD, response to plasmapheresis or corticosteroids [71].

To summarize all analyzed publications we recommend the algorithms for diagnostic and treatment purpose (Fig. 1, 2).

CONCLUSION

Establishing whether histopathological findings dominate in peripheral neuropathies or myopathies would help to evaluate proper treatment. Reduction or increasing drug doses may precede the onset, thus supporting the immune-mediated or steroid induced hypothesis.

Better outcomes of neurological complications would improve quality of life and decrease morbidity and mortality after HSCT. Prospective studies in this area focussing on complex clinical neurological syndromes, neuropathology, neurophysiologic tests and neuroradiologic imaging studies in large transplantation centers using clinical registries and strategies are strongly needed.

Gauta: 2011 01 10
Priimta spaudai: 2011 02 23
References


NEUROPATIJOS IR MIOPATIJOS
ONKOHEMATOLOGINIŲ LIGŲ ATVEJU PO
KAMIENINIŲ KRAUJO LASTELIŲ
TRANSPLANTACIJOS, KAI PASIREIŠKIA
TRANSPLANTANTO PRIEŠ ŠEIMININKĄ LIGA:
LITERATŪROS APŽVALGA

Santrauka

VULSK hematologijos, onkologijos, transfuzologijos centre kasmet atliekama apte 100–120 kamieninių kraujo lastelių transplantacijų. Pagal transplantuojamų ligonių skaičių šis centras prilygsta Universitetinės Insubruko ligoninės hematologijos ir kaulų įšūlynų transplantacijos centrui Austrijoje. Kamieninių kraujo lastelių transplantacija (KKLT) – tai gydymo metodas, kai, skiriand potencialiai neurotoksinus vaistus, supresuojama imüninė sistema ir susaikinamos navikinės lastelės. KKLT gydomos onkohematologinės ligos, aplastinė anemija ir metabolinai sutrikimai.

Šių dienų aktuali potransplantacinė problema – neurologinės komplikacijos, pasitaikančios nuo 37 iki 91%, sudarant nuo 6 iki 26% pagrindinių mirties priežasčių. Bendrą pacientų būklę sunkinant aplinkybė - autoimüninės sistemos suktyvėjimas prieš transplantantą, vadinama transplantanto prieš šeimininką liga (TPŠL). Kai ši imüninės sistemos aktyvacija pasireiškia po transplantacijos praėjus 100 d., ji vadinama létine TPŠL. Dažniausiai létinės TPŠL pažeidžiami organai taikiniai yra virškinimo trakto organai, kepenys, oda, plaučiai. Kol kas nėra daug duomenų apie nervų sistemos pažeidimą, esant TPŠL.

Šiame straipsnyje pagrindinis dėmesys skiriamas periferinės nervų sistemos pažeidimams (létinė uždegiminė demielinizuojujant poliradikuloneuripatija, Guillain-Barre syndromas), nervoraumens jungties ligoms (miastenija) ir miopatijų pasireiškimui po kamieninių kraujo lastelių transplantacijos, esant TPŠL. Dėl nuolatinės imunosupresijos bei chemopreparatų neurotoksinių poveikio TPŠL, kai pažeidžiama periferinė nervų sistema, klinika yra maskuota, o diagnostika sudėtinga. Straipsnyje aprašomos refrakterinių glukokortikoidams TPŠL formų gydymo rekomendacijos rituksima buo bei odos biopsijos histologinio tyrimo alternatyvos. Pateikiami apibendrintos diagnostikos ir gydymo rekomendacijos visoms tikėtinoms periferinės nervų sistemos pažeidimo ir raumens ligoms, esant TPŠL, nustatytų.

Raktąžodžiai: kamieninių kraujo lastelių transplantacijos, imunosupresija, transplantanto prieš šeimininką liga, Guillain-Barre syndromas, miastenija, rituksimasis.