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Review article

Lymphoma-associated dysimmune polyneuropathies

Joerg-Patrick Stübgen *

Department of Neurology, Weill Cornell Medical College/New York Presbyterian Hospital, New York, NY 10065-4885, USA

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ABSTRACT

Lymphoma consists of a variety of malignancies of lymphocyte origin. A spectrum of clinical peripheral neuropathy syndromes with different disease mechanisms occurs in about 5% of lymphoma patients. There exists a complex inter-relationship between lymphoproliferative malignancies and autoimmunity. An imbalance in the regulation of the immune system presumably underlies various immune-mediated neuropathies in patients with lymphoma. This article reviews lymphoma and more-or-less well-defined dysimmune neuropathy subgroups that are caused by humoral and/or cell-mediated immune disease mechanisms directed against known or undetermined peripheral nerve antigens.

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1. Introduction

Lymphoma is a group of lymphatic system malignancies. Many lymphoma classification systems were devised over the years; most hematologists/oncologists adopted the WHO International Classification of Diseases (ICD) system (presently ICD-10 version of 2010) (www.lymphomainfo.net). About 90% of lymphomas are of the non-Hodgkin type (NHL), a diverse group of diseases each distinguished by the specific characteristics of lymphocytes (85% B-cells, less commonly T- or NK-cells). About 10% of lymphomas are of the Hodgkin type (HL), characterized by the presence of germinal center B-lymphocyte-derived Reed–Sternberg cells. This review includes patients with chronic lymphocytic leukemia (CLL), because it is considered the same disease as small lymphocytic lymphoma (SLL), a NHL subtype, though with abnormal cells in the blood (www.lymphomas.org.uk).

A wide variety of peripheral nervous system abnormalities occur in 5% of patients with lymphoma [1]; however, electrophysiological evidence of mostly sub-clinical neuropathy was reported in as many

* Department of Neurology, Weill Cornell Medical College/New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065-4885, USA.
E-mail address: pstuebge@med.cornell.edu.

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as 35% of patients with various types of lymphoma [2]. Neuropathy can be the presenting feature of lymphoma or develop at any stage of disease, even during remission [3]. Lymphoma can involve any part of the peripheral nervous system. The mechanisms of lymphoma-associated neuropathy (i.e., excluding chemotherapy exposure, viral infections [e.g., HIV/*Herpes zoster*], and established nutritional disturbances) may entail [3–6]: (a) local or diffuse peripheral nerve lymphomatous (specifically NHL/T-) cell invasion i.e., neurolymphomatosis; (b) deposition in the endoneurium of circulating monoclonal antibodies (mostly IgM paraprotein) secreted by malignant or non-malignant lymphocytes/plasma cells; (c) autoantibodies directed against specific peripheral nerve antigens (e.g., myelin-associated glycoprotein or gangliosides) probably produced by non-lymphomatous clonal B-cell expansion due to immune "escape" mechanisms [1]; (d) lymphoma-induced (particularly HL) immune dysregulation that underlies immune-mediated inflammatory neuropathy; (e) ischemic neuropathy due to: (1) hematogenous metastases (angiotropic B-cell lymphoma) that occlude vessels by local intravascular proliferation, direct pressure, or tumor emboli; (2) cryoglobulin deposition (types I and II) [7–9], or (3) immune/"paraneoplastic" vasculitis; (f) focal amyloid deposition in the vasa nervorum, endoneurium and perineurium in the setting of monoclonal paraprotein (IgM-λ type) [10]; and (g) "other"/unclear explanation, possibly toxic/metabolic/nutritional.

This article reviews lymphoma-associated peripheral nerve disorders with presumed immune-mediated pathogeneses. Specifically, this review concentrates on lymphoma and more-or-less well-defined immune neuropathy subgroups that are caused by humoral and/or cell-mediated immune attacks against either known or undetermined peripheral nerve antigens. The selective approach to this topic entailed careful screening of the literature and the exclusion of reports with variables that interfered with the interpretation of chosen, defined neuropathy subgroups: (a) cryoglobulinemic neuropathy (mechanism is vasculitic ischemic damage to nerves); (b) plasma cell dyscrasias that are not usually classified with the lymphomas [1] e.g., Waldenström's macroglobulinemia/IgM-secreting lymphoplasmacytic lymphoma (although deposits of endoneurial monoclonal IgM secreted by plasma cells may lead to immune-mediated neuropathy) [11–13]; (c) "paraneoplastic" primarily sensory [14–16] or motor [17–19] neuronopathies (immune attack presumably directed at nerve cell body antigens); (d) initial presentation as, or exacerbation of, an acquired inflammatory demyelinating neuropathy but: (1) biological treatment likely contributed significantly to immune dysregulation e.g., rituximab introduction [20] or maintenance therapy [21], or recent completion of a course of alemtuzumab [22]; (2) effects of therapy resulted in severe superimposed immune disturbance e.g., acute tumor lysis syndrome [23], mobilization therapy with "pyrexia of unknown origin" [24], or after autologous bone marrow transplantation [25,26]; (3) preceded by virus infection/reactivation e.g., *Varicella zoster* reactivation [27], or (4) eventual evidence was found of malignant lymphocytic spread to CSF/nerve roots [28–30] or peripheral nerves [31]. A systematic search was conducted of relevant publications using databases such as MEDLINE [PubMed], EMBASE and DynaMed, and included case reports and series, retrospective studies, and reviews. Search terms included "neuropathy", "immune-mediated", "autoantibody", "autoimmune", and "lymphoma". Publications were retrieved and scrutinized, and article bibliographies were cross-referenced to ensure that this review is accurate and comprehensive.

2. Immune-mediated polyneuropathies

2.1. Pathogenesis

Reviews exist on the presumed immunopathogenesis of the acquired inflammatory demyelinating polyneuropathies [32–37] and autoantibody-mediated polyneuropathies [38–42], and will not be discussed in detail here. To summarize, in inflammatory demyelinating polyneuropathies, cellular and humoral immune responses both participate in the disease mechanism (Figs. 1 and 2). This immune response is directed against the myelin or axon of the peripheral nerve; no specific antigen has been consistently identified. Cellular immunity participation is supported by evidence of T-cell activation, crossing of the blood–nerve barrier by activated T-cells followed by macrophage-mediated demyelination, and by expression of cytokines, tumor necrosis factor, interferons, and interleukins. Humoral immunity is implicated by the demonstration of immunoglobulin and complement deposition on Schwann cells and myelinated nerve fibers, and by passive transfer experiments that induce conduction block and demyelination (by injecting serum or purified IgG from patients into rodent nerves).

Anti-MAG antibodies have been implicated in a chronic demyelinating peripheral neuropathy. There is compelling evidence that anti-MAG antibodies play a causative role in the pathogenesis of neuropathy e.g., intraneural injection of serum from patients with demyelinating neuropathy and anti-MAG antibodies induced nerve demyelination in animal models. Studies of nerve biopsy specimens showed loss of myelinated fibers, thinned myelin sheaths, segmental demyelination, and occasionally tomacula and onion bulbs. Antibodies bind to an oligosaccharide determinant that is shared by MAG and the glycolipid sulfoglucuronyl paragloboside (SGPG).

Anti-GM1 IgM antibodies are presumed to be pathogenic in the development of MMNCB, but it is not absolutely established whether antibodies are disease causative or merely an associated abnormality.

2.2. Autoantibody-mediated polyneuropathies

In this literature search 23 cases were retrieved of polyneuropathy associated with autoantibodies directed against specific peripheral nerve antigens in patients with various types of lymphoma (Table 1a and b). The temporal association between neuropathy onset and lymphoma diagnosis varied: (1) In most patients, onset of neuropathy preceded by variable periods the diagnosis of lymphoma: (a) lymphoma was diagnosed only at autopsy in a patient with a 3-year history of polyradiculoneuropathy [43,44]; (b) a patient with a 6-year progressive sensory demyelinating polyneuropathy associated with MGUS (? undetected lymphoma) developed fatal EBV + intracerebral lymphoma after treatment with various courses of immunotherapy [46]; analyses of intrathecal and peripheral M-protein as well as brain immunocytochemical studies suggested a common clonal origin of both immunoblastic cerebral proliferation and the serum paraprotein-secreting cells. Presumably, immune deficiency due to monoclonal B-cell proliferation and/or immunosuppressive therapy resulted in EBV-reactivation and dysregulation of CNS-restricted T-cell control of B-cell proliferation; autopsy did not include search for systemic lymphoma; (c) chronic (up to 3-year duration), slowly progressive [8,56,60] or relapsing–remitting [54] neuropathies preceded diagnoses of either indolent/low grade or diffuse large cell lymphoma, respectively; (d) a patient with a 2-year slowly progressive sensorimotor neuropathy developed B-cell CLL [49]; in this case, HTLV-1 co-infection could have triggered malignant transformation of an antigen-committed B-cell clone [61], or HTLV-1-infected T-cells activated autologous B-cells in a contact-dependent manner [62]. (2) In some patients lymphoma diagnosis preceded onset of neuropathy: (a) in 1 report, relapsing–remitting cranial polyneuropathy occurred in a patient with established cutaneous lymphoma in remission and subsequent recurrence [45]; (b) recurrent, treated [58,59] or indolent, untreated [60] lymphoma preceded the onset of neuropathy symptoms at intervals of 2 years, 10 and 6 months in 3 patients, respectively. (3) In the remainder of patients, lymphoma was diagnosed during the initial presentation and evaluation of neuropathies of variable duration [8,50,53,55,56].

In this non-uniform group of patients, serum autoantibodies were detected against a spectrum of peripheral nerve antigens. Presumably, these antibodies played a pathogenic role in the development of neuropathies. There was no evidence to suggest that autoantibodies were

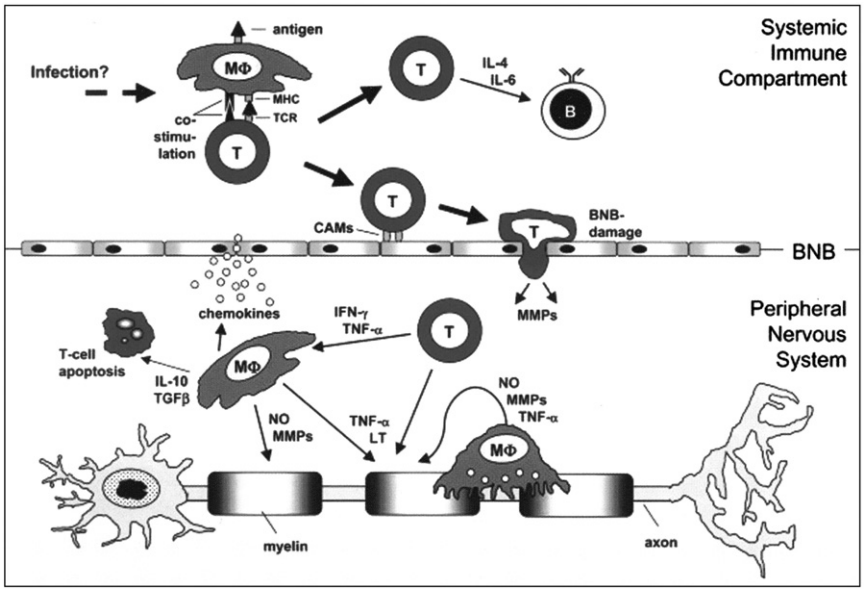

Fig. 1. Summary of the cellular immune response in inflammatory neuropathies: autoreactive T-cells recognize autoantigen presented by MHC class II on antigen presenting cells (with release of co-stimulatory signals) in systemic immune compartment. Activated T-cells cross the blood–nerve barrier into the peripheral nervous system. T-cells activate macrophages releasing mediators that promote demyelination and axonal loss. Termination of inflammation is promoted by macrophages that induce T-cell apoptosis and release of anti-inflammatory cytokines.
[32] [with permission Wiley and Sons]

produced in response to peripheral nerve damage of direct lymphoma spread; moreover, any fortuitous association was minimized by adequate search for other causes of polyneuropathy in these patients. In most, but not all [8,48], patients the clinical presentation of neuropathy conformed to the literature descriptions of the specific autoantibody-associated polyneuropathy subtypes.

Serum paraprotein (IgMκ or λ) was detected in all but 4 patients [49,54,60]; however, 3 patients showed tri-clonal bands, specifically IgMκ/λ and IgGκ [47]; IgMκ and bi-IgGκ [50] or tri-IgMκ [58]. Serum mixed cryoglobulins were detected in 3 cases, and possibly played a pathogenic role in neuropathy in 2 patients [8], but were deemed causally unrelated to neuropathy in 1 patient [48].

CSF analyses were reported on 12 patients: protein was elevated in 9 patients; cell count was elevated in 3 patients. By definition, any patient with malignant cells in CSF was not included in this review.

Peripheral nerve specimens were obtained by biopsy or autopsy from 7 patients: all showed a predominant decrease of large myelinated fibers; in some samples there was evidence also of active or chronic (i.e., sparse onion bulb formation) demyelination [47–49,51,53,54,57].

Nerve immunohistochemical analysis (IA) was performed on 5 patients. Direct study on a sural nerve biopsy revealed deposition of IgM along myelin sheaths of nerve fibers [49,51]. IA showed that serum from a patient exclusively labeled isolated rat sciatic nerve myelin sheath as if it had been labeled by anti-P0 antibody [52]. Thin layer

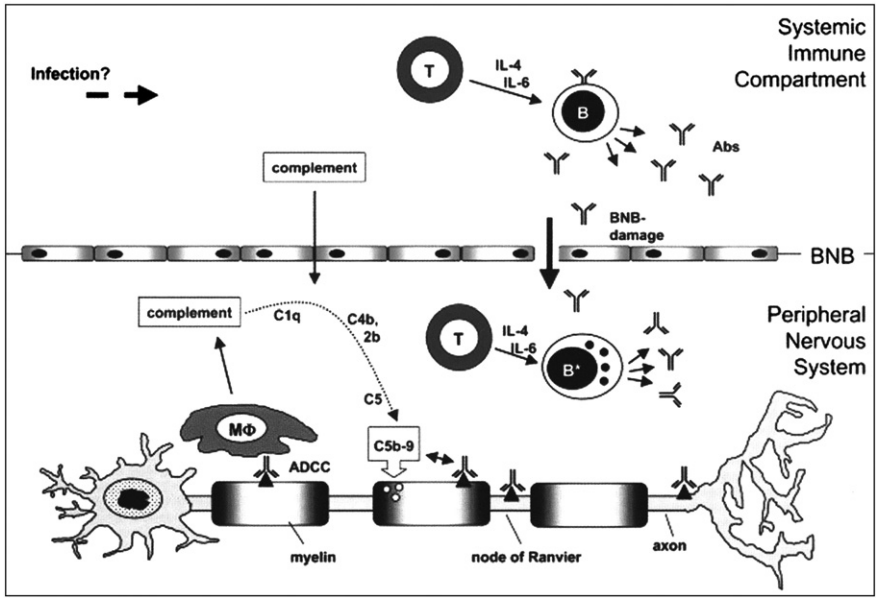

Fig. 2. Summary of humoral immune response in inflammatory neuropathies. Autoantibodies (cross blood–nerve barrier or produced locally by B-cells) contribute to demyelination and axonal injury by: (a) antibody-dependent cytotoxicity; (b) blocking functionally relevant epitopes for nerve conduction, and (c) activating the classic pathway of the complement system.
[32] [with permission Wiley and Sons]

Table 1
Lymphoma-associated autoantibody-mediated neuropathy.

Reference	Age/sex	Target antigen	Neuropathy	Lymphoma subtype
[43,44]	65/M	SLPG	Polyradiculoneuropathy	DMBCL
[45]	70/F	MAG	Multiple cranial/axonal polyneuropathy	Cutaneous B-cell
[46]	74/F	MAG/SGPG	Demyelinating polyneuropathy	HG EBV + NHL-CNS
[8]	78/F	GM1/asialo-GM1	Predominant sensory polyneuropathy	LG NHL
	75/M	Sulfatide	Predominant sensory polyneuropathy	LG NHL
	78/F	IgMκ/λ/IgGκ	Predominant sensory polyneuropathy	LG NHL
[47]	79/M	MAG	Demyelinating poly-/cranial neuropathy	Centroblastic DLBCL
[48]	79/M	Sulfatide	Cervical motor neuropathy	B-cell NHL
[49]	65/M	Disialosyl ganglio +	CIDP-like	CLL (HTLV-1 +)
[50]	80/M	MAG	Predominant sensory polyneuropathy	Nodular sclerosing NHL
	62/M	MAG	Predominant sensory polyneuropathy	CLL IIB
[51]	53/M	MAG/SGPG	Demyelinating polyneuropathy	Nodal marginal zone NHL
[52]	33/F	P0 isoform	Cranial/sensory polyneuropathy	Malignant B-cell NHL
[53]	52/M	GM1/GD1b[a]	Multifocal motor neuropathy	DLBCL
[54]	63/M	Disialosyl ganglio + [b]	Predominant sensory polyneuropathy	DLBCL
[55]	76/F	GD1b[b]	Subacute demyelinating polyneuropathy	LG B-cell NHL
[56]	59/M	MAG	Chronic demyelinating polyneuropathy	LG B cell NHL
[57]	76/M	MAG	Demyelinating polyneuropathy	B-cell NHL
	68/M	MAG/SGPG	Demyelinating polyneuropathy	B-cell NHL
	79/F	MAG/SGPG	Demyelinating polyneuropathy	B-cell NHL
[58]	75/M	GM2	Acute inflammatory neuropathy	DLCBL
[59]	60/M	Disialosyl ganglio +	Predominant motor polyneuropathy	Mantle cell NHL
[60]	77/F	Asialo-GM1/GD1a	Predominant sensory polyneuropathy	Mantle cell NHL
	70/M	MAG/SGPG	Predominant sensory polyneuropathy	Marginal zone NHL

Reference	Rx Neuropathy	Rx lymphoma	Outcome/follow-up
[43,44]	Po CS/CPH	–	DMBCL diagnosis at autopsy (35 months)
[45]	Po CS	CHOP	Neuropathy/lymphoma remission (6 months)
[46]	Po CS/CHB/IVIG	Iv CS	Died of NHL-CNS (68 months)
[8]	Symptomatic only	–	Neuropathy stable (12 months)
	Po CS	–	Neuropathy stable (12 months)
	Po CS	CHB/IFNα_{2a}	Neuropathy stable (24 months)
[47]	Po CS/CPH	Not started	Died respiratory distress (11 months)
[48]	PPH pending	Po CS/CHB	Neuropathy worsened/died of PE (3 months)
[49]	Iv CS/CPH	–	Neuropathy improved (6 months)
[50]	–	ABVD/XRT	Improved neuropathy/NHL remission (3 months)
	–	CHB	Lost to follow-up
[51]	–	ChlVPP	Neuropathy improved/NHL remission (NR)
[52]	Iv CS	CHOP	Neuropathy improved (NR)
[53]	IVIG/PPH	CHOP	Died of multi-organ failure (<3 months)
[54]	PPH/po CS/IVIG	Not started	Died of DIC (84 months)
[55]	IVIG/po CS	Not started	Died of intestinal pseudo-obstruction (2 months)
[56]	–	R	Neuropathy/NHL improved (3 months)
[57]	NR	NR	NR
	NR	NR	NR
	NR	NR	NR
[58]	IVIG/PPH	NR	Neuropathy improved (2 months)
[59]	IVIG/Iv/po CS/PPH	B	Neuropathy improved/NHL stable (15 months)
[60]	IVIG	–	Neuropathy stable (7 months)
	IVIG	–	Neuropathy stable (8 months)

CLL = chronic lymphocytic leukemia; disialosyl ganglio + = GD1a/GD1b/GD2/GD3/GQ1b/GT1a and/or GT1b; DLBCL = diffuse large B-cell lymphoma; DMBCL = diffuse medium B-cell lymphoma; EBV = Epstein–Barr virus; GD = ganglioside disialic acid; GM = ganglioside monosialic acid; HG = high grade; HL = Hodgkin lymphoma; HTLV-1 = human T-lymphotropic virus-1; LG = low grade; MAG = myelin-associated glycoprotein; NHL = non-Hodgkin lymphoma; P0 = myelin protein zero; SGPG = sulfated glucoronyl paraglobloside; SLPG = sialosyl lactosaminyl paragloboside.
ABVD = Adriamycin/bleomycin/vinblastine/dacarbarbazine; B = bendamustine hydrochloride; CHB = chlorambucil; ChlVPP = chlorambucil/vincristine/procarbazine/prednisolone; CHOP = cyclophosphamide/hydroxydaunorubicin/Oncovin/prednisone; CS = corticosteroids; CPH = cyclophosphamide; IFN = interferon; iv-intravenous; po = oral; PPH = plasmapheresis; R = rituximab; XRT = radiation therapy.
[a] Galβ1–3GalNAc terminal disaccharide.
[b] NeuAc(α2-8)NeuAc(α2-3)Gal disialosyl epitope.

chromatography (TLC) immunostaining of patient neural tissue extract stained with patient serum IgMλ antibody, and bound preferentially to glycolipids GM1 and Gd1b [53]. However, in another patient with elevated serum anti-disialosyl IgM antibodies, immunoblotting against human and rat sciatic nerve was deemed not significant [54].

Based on the presumed autoimmune pathogenesis of neuropathy, the majority of patients was offered and responded to some form of immunomodulatory therapy. Any neuropathy clinical response was independent of time of discovery or any treatment of the underlying lymphoma. Less frequently, cytotoxic therapy was aimed at lymphoma, and proved either effective [50,56] or ineffective [48] treatment also for the neuropathy. Lymphoma was not treated when the nature of disease was presumed indolent, or when lymphoma was discovered only at autopsy [43,44]. Any reported deaths among patients during the varying length observation periods were ascribed to the lymphoma or associated systemic complications; no patient death was directly related to polyneuropathy.

An apparent pathogenic role of circulating antibody with affinity for peripheral nerve antigen(s) was demonstrated by immunofluorescent study on some reported lymphoma patients [49,51–54], or was otherwise presumed. Some evidence suggested that circulating anti-nerve monoclonal autoantibodies, usually immunoglobulin-M paraprotein, were actually produced by lymphoma B-cells. A single report provided evidence of production of monoclonal IgMλ anti-GM1/GD1b

autoantibody by tumor cells in a patient with diffuse large B-cell NHL [53]: (a) on immunofluorescent flow cytometry simultaneous expression of CD79b (part of a heterodimer transmembrane protein) and IgMλ on the surface of CD19-positive lymphoma cells indicated that most IgMλ antibodies were not adherent to the lymphoma cells; rather, they were present on the surface in a secretory form; and (b) levels of monoclonal antibody (with affinity for Galβ1-3GalNAc terminal disaccharide antigenic determinant) were significantly higher in the supernatant from a 2-d culture of lymphoma cells compared to normal lymphocytes.

In another report, the clonal origin of monocytoid B-cell lymphoma suggested that lymphoma cells synthesized IgMκ paraproteins, and were determined to be autoantibodies to MAG and SGPG [51]. The clinical improvement of neuropathy in response to chemotherapy also favored the production of these autoantibodies by neoplastic lymphoid proliferation.

In conclusion, in patients with established lymphoma an accurate neuropathy diagnosis should guide the appropriateness of serum autoantibody determination, with consequent treatment implications. Based on reviewed literature it is difficult to advise on the value of such antibody determination in patients with "atypical" neuropathy syndromes, or of the yield of a comprehensive lymphoma screen in patients with antibody-mediated polyneuropathies.

2.3. Inflammatory demyelinating polyneuropathies (IDP)

2.3.1. Guillain–Barré syndrome (GBS)

GBS occurs rarely in patients with lymphoma. The frequency of GBS may be slightly higher in HL compared to NHL [1,3], and probably relates to the persistent defect in cellular immunity with relatively intact humoral immune responses common to patients with HL [63]. A retrospective study assessed the neurological complications in 229 patients with the "reticuloses" (a group of disorders characterized by the usually malignant proliferation of any of the cells of the reticuloendothelial system) [64]: 4 patients were diagnosed with peripheral neuropathy (2 severe; 2 mild) without evidence of a primary demyelinating process on post-mortem examination (reported on 3 patients). Another retrospective study of the non-metastatic neurological syndromes "of obscure origin" in 774 patients with the "reticuloses", established 5 cases of peripheral neuropathy in patients with HL, lymphosarcoma and CLL: resolved GBS was reasonably diagnosed in 1 patient with HL in remission [65]. A combined prospective (in-patients) and retrospective (out-patients) study evaluated for peripheral nervous system and spinal cord involvement in 989 patients with lymphoma (563 NHL; 426 HL): GBS was diagnosed in only 1 patient with HL [66]. A smaller, prospective clinical and electrophysiological study of 30 patients with lymphoma established 1 patient each with acute/remitting and subacute/unremitting severe demyelinating polyneuropathies; the main histological abnormality was segmental demyelination/remyelination, but with negative immunofluorescence studies [67]. A series of 16 patients with peripheral neuropathy and lymphoma without monoclonal gammopathy included 3 patients with GBS (insufficient information to tabulate cases); other cases of neuropathy were not immune-mediated [4].

Conversely, lymphoma is also rarely detected in patients with GBS. In a retrospective study of 1100 patients with GBS reported in the literature since 1949, an associated/underlying malignancy was found in 33 patients; HL accounted for only 3 of these cases [68]. In a retrospective study of 38 patients with polyradiculoneuritis, an association with HL was determined in only 2 cases [69].

Case histories and series report on lymphoma-associated GBS (Table 2). Sufficient information existed on 35 patients (16 females; 19 males) for inclusion in this review; this included 3 children (<18 years) and 11 elderly (>65 years) patients. From these case reports it could not be established that there exists particular age or gender susceptibility to lymphoma-associated GBS, despite the observation that lymphoma occurs more common in older patients and in men (for NHL) (www.cancer.org). The type of lymphoma varied, and included 11 patients with HL, 7 patients with CLL, with various subtypes of NHL comprising the remainder. Thus, this collected case report information could not support published statements that HL (more than other types of lymphoma) is more commonly associated with immune-mediated polyneuropathies [1,3,87,102].

The time correlate between the diagnosis of GBS and discovery of lymphoma followed no consistent pattern: (1) In 11 patients, lymphoma was diagnosed during the initial hospitalization/evaluation for GBS (with delay up to 274 days) [5,71,79–81,83,92,94,99,100]. In 3 patients, probable lymphoma-associated symptoms had not been recognized before subsequent presentation/evaluation of GBS e.g., alcohol-induced bone pain for 2 years [79], pruritis for 9 months [80] or erythema nodosum-like skin lesions for 2 years [92]. In 1 patient a retrospective diagnosis of intravascular lymphoma was made on a skin biopsy only posthumously [92]. (2) In most patients, lymphoma was diagnosed before the development of GBS. Also this temporal correlation varied, so that the onset of GBS developed: (a) with lymphoma relapse [70, 77,78,88,89,101]; (b) during lymphoma maintenance therapy [74]; (c) at varying intervals (2 weeks and 3 months) after completion of chemotherapy for lymphoma deemed in remission [72,73,75,76,82]; (d) while undergoing (interval 6 days to 3 weeks) chemotherapy for lymphoma (cycles #1 to #6) [91,93,95,97,98]; (e) after induction chemotherapy for lymphoma (interval 11 to 16 days) [87,96], or (f) during the course (as long as 10 years) of indolent disease not under active treatment e.g., CLL [73,86,101].

The clinical presentation of GBS associated with lymphoma has been regarded no different from the presentation of sporadic/post-infectious GBS [103]. In cases reported herein, cranial nerve involvement was documented in 20 patients. Respiratory muscle involvement was reported in 11 patients; 8 of these 11 patients required ventilation assistance. CSF analysis was performed on 31 patients; findings were compatible with GBS, and by definition showed no evidence of lymphomatous spread or infectious disease. Electrodiagnostic studies were performed on 25 patients and were consistent with acquired, mostly acquired IDP; predominant axonal injury was recorded in 3 of these patients [93,96,100]. Pathological study of peripheral nerves confirmed acquired IDP (with/without secondary axonal injury) at autopsy in 4 patients [70, 72,75,76,88] and on biopsy in 5 patients [75,76,81,84,93]. Such study is important because lymphomatous nerve/root infiltration may mimic GBS [5,104,105] i.e., there exists a risk of GBS misdiagnosis.

The treatment protocols for GBS varied. In earlier reports, patients were offered only supportive care or treatment with oral corticosteroids; treatment of more recent cases reflects modern "standard" care of GBS with intravenous corticosteroids, IVIG and/or plasmapheresis. Additional immune therapy was offered to patients who developed GBS after completing or while undergoing chemotherapy for lymphoma. Immunomodulatory treatment for GBS was not offered when: (a) onset of GBS coincided with relapsed [78] or newly diagnosed [5] lymphoma i.e., treatment was directed primarily at lymphoma, and (b) GBS improved spontaneously before chemotherapy commenced for newly diagnosed lymphoma [80]. In a case with recurrent Burkitt's lymphoma, no specific treatment for GBS was offered (no explanation given) so that the patient died of rapidly progressive bulbar weakness and respiratory failure [88].

Therapy for the various types of lymphoma was offered according to preferred chosen protocol. However, patients were not treated specifically for lymphoma when: (a) the patient refused therapy [71]; (b) the nature of disease was indolent [73], and (c) the diagnosis was made at autopsy [92].

The prognosis of GBS was mostly favorable, so that most patients improved or recovered. A total of 8 patients died in the acute phase of illness: (a) 5 patients died of cardio-/respiratory failure within 3 to 12 days after onset of GBS; (b) 1 patient died after approximately 17 days of sepsis/organ failure [92]; (c) 1 patient died after 3 weeks

Table 2
Case reports of Guillain–Barré syndrome associated with lymphoma.

Reference	Sex/age	Classification	Rx neuropathy	Rx lymphoma	Outcome/follow-up
[70]	30/F	HL	Supportive	NH/XRT	Died (12 days)
[71]	30/M	Lymphoblastic NHL	Po CS	–	≈Recovered (1 month)
[72]	30/M	HL IIIB	Supportive	XRT/NH	Died (5 days)
[73]	60/M	CLL	Po CS	CAB	Improved (NR)
	59/F	CLL	Po CS	–	Recovered (1 year)
[74]	35/M	Lymphosarcoma	Iv CS	CPH	Improved (NR)
[75,76]	19/M	HL IVB	Po CS	VCR/VBL	≈Recovered (8 months)
	27/M	HL IIIB	Iv/po CS	NR	Improved (18 months)
	52/M	HL IVB	Supportive	VCR	Died/NR
[77]	23/M	HL III	Po CS	CBPP	Recovered (10 weeks)
[78]	46/M	HL II	–	cobalt XRT/CTX	≈Recovered (3 months)
[79]	48/F	HL IIIB	Po CS	PCZ/NH/VBL	≈Recovered (15 months)
[80]	31/M	HL IV	–	MOPP	Recovered (NR)
[81]	66/M	MCHL III	PPH/iv/po CS	CTX	Impaired (10 months)
[82]	77/F	CLL IIIB	IVIG	CAB	Improved (3 weeks)
[83]	$2^1/_2$/M	T-cell lymphoblastic NHL IV	IVIG	Modified LSA_2L_2	Died (6 weeks)
[5]	67/M	Lymphocytic lymphoma	–	CPH/VND/po CS	≈Recovered (2 years)
[84]	54/F	CLL	NR	CHOP/MOPP	NR
[85]	73/F	CLL	Po CS	CAB	Improved (16 weeks)
[86]	84/F	CLL	PPH	CAB/po CS	≈Recovered (23 days)
[87]	21/F	Precursor T-cell NHL IV	IVIG/PPH	Standard BFM	Improved (3 months)
[88]	59/F	Sporadic BL IVB	–	CEVEP/CHOP	Died (12 days)
[89]	42/F	Angioimmunoblastic NHL IIIB	PPH	CHOP	Recovered (4 months)
[90]	14/M	HL IIA	Iv CS	OEPA	Recovered
[91]	74/M	Precursor B-cell BLL I	Iv CS	CHOP	Died (3 days)
[92]	78/F	IVBCL	IVIG	–	Died (≈17 days)
[93]	36/F	BLL IV	IVIG/PPH	CHOP/R	Slightly better (3 months)
[94]	59/M	fNHL II	NR	NR	NR
[95]	67/M	DLCBL III	Iv CS	CHOP	Worsened (>2 months)
[96]	8//M	NHL IIIB	IVIG	BFM-90 protocol	Recovered (8 weeks)
[97]	70/F	T/NK-cell NHL IEA	NR	CHOP	Worsened (hospice)
[98]	14/F	T-cell lymphoblastic NHL III	IVIG	THP-COP/IT MTX	Resolved (4 weeks)
[99]	74/F	NHL IV	IVIG	CHOP-R/IT CY	Slightly better (died)
[100]	21/F	ATLL	IVIG	CTX	Died (3 weeks)
[101]	79/M	CLL	IVIG/PPH/alemtuzumab	B + R	Recovered (1 year)

ATLL = adult T-cell lymphoma/leukemia; B = bendamustine; BFM = Berlin–Frankfurt–Munster regimen; BL/L = Burkitt's/like lymphoma; BLM = bleomycin; CAB = chlorambucil; CBPP = CCNU/bleomycin/procarbazine/prednisone; CCNU = lomustine; CEVEP = cyclophosphamide/epirubicin/vinblastine/etoposide/prednisone; CHOP = cyclophosphamide/hydroxydaunorubicin/oncovin/prednisone; CPH = cyclophosphamide; CS = corticosteroids; CTX = chemotherapy (unspecified); CY-cytarabine; IT = intra-thecal; iv = intravenous; IVBCL = intravascular B-cell lymphoma; LSA_2L_2 = cyclophosphamide/vincristine/methotrexate/daunomycin/prednisone/cytarabine/thioguanine/asparaginase/hydroxyurea/carmustine; MOPP = mustargen/oncovin/procarbazine/prednisone; NH = nitrogen mustard; NR = not reported; OEPA = oncovin/etoposide/prednisone/adriamycin; PCZ = procarbazine; po = oral; PPH = plasmapheresis; R = rituximab; THP-COP = pirarubicin-cyclophosphamide/oncovin/prednisone; VBL = vinblastine; VCR = vincristine; VND = vindesine; XRT = radiation therapy.

due to complications of lymphoma treatment [100], and (d) a child died after 6 weeks of neutropenic septicemia [83]. Later deaths during the observation periods were due to lymphoma e.g., septic shock 2 months after chemotherapy was suspended [99] i.e., unrelated to GBS.

2.3.2. Miller Fisher syndrome (MFS)

Four cases of lymphoma-associated somewhat "atypical" MFS were retrieved from the literature (Table 3). The temporal association between a diagnosis of MFS and lymphoma varied: (a) onset of MFS coincided with the 2nd relapse of lymphoma [106]; (b) MFS coincided with the discovery of lymphoma in a renal transplant recipient on anti-rejection therapy [107]; (c) MFS developed in a patient with CLL during chemotherapy [108], and (d) a detailed evaluation during recurrence of MFS detected lymphoma [109]. An elevated serum anti-GQ1b antibody titer is deemed useful supportive evidence for (? post-infectious) MFS [110,111], but was recorded in only 1 of 4 lymphoma patients [106]. CSF analysis on 3 patients showed only elevated protein concentration [106,107,109]; however, "atypical", non-neoplastic lymphocytes were detected on repeat CSF evaluation in the patient with recurrent MFS [109]. Electrodiagnostic studies were variably interpreted as: (a) axonal sensory polyneuropathy [106]; (b) diffuse, predominantly axonal sensorimotor polyneuropathy [107,108], or (c) sensorimotor demyelinating polyradiculoneuropathy [109].

Immunomodulating therapy was offered to all patients. Three patients showed neurological response to treatment [106,108,109]; 1 treatment-unresponsive patient showed neurological improvement to systemic chemotherapy for lymphoma [107]. The patient with recurrent MFS and CSF atypical pleocytosis showed neurological improvement to a combined systemic/intrathecal chemotherapy regimen [109]; neurological response to systemic chemotherapy was interpreted as evidence

Table 3
Lymphoma-associated Miller Fisher syndrome.

Reference	Age/sex	lymphoma	Rx neuropathy	RX lymphoma	Outcome
[106]	27/M	Mixed cellularity HL IVB	IVIG	ESHAP	Recovered (3 months)
[107]	42/M	Burkitt's lymphoma	IVIG	CTX	Recovered (2 years)
[108]	47/M	B-cell CLL Rai IV	PPH	CHB/R	≈Recovered (≈16 months)
[109]	61/M	DLBCL	IVIG/IT MTX	R-CHOP	Improved/died of PE

CHB = chlorambucil; CTX = chemotherapy (not specified); DLBCL = diffuse large B-cell lymphoma; ESHAP = etoposide/methylprednisolone/ara-C/platinum; IT MTX = intrathecal methotrexate; PE = pulmonary embolus; PPH = plasmapheresis; R-CHOP = rituximab with cyclophosphamide/hydroxydaunorubicin/oncovin/prednisone; R = rituximab.

of a "paraneoplastic" pathogenesis (herein defined as the production of a specific antibody against an antigen of malignant cells that cross-reacts with an antigen of normal neurological tissue).

2.3.3. Chronic/subacute inflammatory demyelinating polyneuropathy (CIDP/SIDP)

Lymphoma-associated CIDP has a potential for misdiagnosis. A study assessed the clinical, electrophysiological and histopathological features of 32 patients with treatment-unrelated neuropathy associated with NHL [6]. Eleven patients fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society electrodiagnostic criteria of "definite" CIDP. However, neuropathology established 5 patients with neurolymphomatosis, 1 patient with sensory ganglionopathy, and 3 patients with primary axonal degeneration and secondary demyelination (clinically manifesting as multiple mononeuropathy). Moreover, some patients (including cases of neurolymphomatosis) at least initially responded to immune modulation therapy. Therefore, peripheral nerve pathological study is recommended to guide appropriate treatment, because neurolymphomatosis may mimic CIDP in patients with lymphoma.

Case histories and short series report on lymphoma-associated SIDP (evolution 4–8 weeks) in 8 patients and CIDP (evolution >8 weeks) in 15 patients (Table 4). Most patients were diagnosed with various types of NHL at various stages of disease, and also did not support (see GBS) literature statements that immune disorders of the nervous system more commonly affect patients with HL compared to NHL [3,102]. The significance of an apparent male preponderance is unclear, and may reflect the observation that most types of NHL occur more common in men [129]. A wide age-spectrum of lymphoma-associated SIDP/CIDP included 5 elderly (>65 years) patients, but no children.

The temporal correlation between onset of CIDP/SIDP and the diagnosis/treatment of lymphoma varied: (a) onset of CIDP followed a diagnosis of recurrent/untreated lymphoma by periods as long as 132 months [6,115,122,125]; (b) CIDP/SIDP preceded diagnosis of new lymphoma by 3 to 15 months [6,116–118,126,127]; (c) onset of SIDP/CIDP coincided with diagnosis of new lymphoma [116,121,123]; (d) onset of SIDP/CIDP coincided with clinical or subsequent autopsy evidence of lymphoma recurrence [112,114,118,120]; (e) relapse of CIDP/SIDP (also interpreted as recurrent GBS [119]) coincided with diagnosis of new lymphoma [113,117,124,128], and (f) in hindsight, erythematous skin papules (probably related to T-cell lymphoma) preceded initial diagnosis of CIDP by 6 months [124].

The clinical presentation of CIDP associated with lymphoma has been regarded no different from the presentation of sporadic CIDP [103]. Cranial nerve involvement was reported in 9 patients with lymphoma. One patient required mechanical ventilation for respiratory failure [127]. CSF analysis commonly showed albuminocytologic dissociation compatible with acquired IDP; by definition no patient showed evidence of lymphomatous meningitis.

Electrodiagnostic study findings on 18 patients were compatible with acquired IDP; predominant axonal findings were reported in 5 of these patients [116,118,119,125]. In earlier case reports, such studies had not yet become a routine part of patient evaluation.

Peripheral nerve specimens were obtained by biopsy or at autopsy from 11 patients: findings were consistent with an inflammatory demyelinating process with variable loss of myelinated fibers; however, in 2 patients the pathology was interpreted as a predominantly axonal variant of acquired IDP [118,119].

Treatment protocols for CIDP varied. Immunomodulatory treatment was offered when: (a) a new diagnosis or recurrence of CIDP/SIDP preceded the diagnosis of lymphoma; (b) treatment of CIDP preceded treatment of relapsed lymphoma; (c) treatment of CIDP followed completed treatment of lymphoma (i.e., in remission), or (d) onset of CIDP coincided with unrecognized lymphoma recurrence. Eight patients were not offered immunotherapy for neuropathy: a decision was made to aim chemotherapy at the malignancy when a diagnosis of new lymphoma [116,118,119,123] or recurrent lymphoma [6,118] temporally coincided with the onset or relapse of CIDP/SIDP. In a case with immunotherapy-unresponsive CIDP, the neuropathy clinically responded to chemotherapy directed at lymphoma [125].

Treatment programs of lymphoma varied, so that appropriate or preferred protocols were chosen according to the biology and staging

Table 4
Lymphoma-associated subacute/chronic inflammatory (demyelinating) polyneuropathy.

Reference	Age/sex	Lymphoma	Rx neuropathy	Rx lymphoma	Outcome/follow-up
[112]	64/M	Reticulum cell NHL	Po CS	–	Died (6 months)
[113]	64/M	Giant follicular NHL	Po CS	NR	Improved (4 months)
[114]	70/M	Lymphosarcoma	–/intra-thecal MTX	CAB/Thd	Recurred/died (9 years)
[115]	75/M	CLL	NR	NR	NR
[116]	48/F*	HL II	–	PCV	Improved (9 months)
	31/M*	HL III	–	MOPP/CCNU-VPP	Improved (40 months)
[117]	51/M	Diffuse histiocytic NHL	Po CS/AZA	CHOP	Recurred/died (35 months)
	58/M	CLL	Po CS	CAB/po CS	≈Recovered (20 months)
[118]	55/F*	Nodular sclerosing HL IVB	–	CTX	≈Recovered (>5 months)
	40/F*	Nodular sclerosing HL IIA	–	Resection/XRT/CTX	≈Recovered (20 months)
[119]	60/M*	NHL IE	–	Modified CVP	Recovered (40 months)
[120]	42/M	DLCBL III	PPH	Resection/CN(O)P	Recovered (18 months)
[121]	39/–	HL IIIB	–	MOPP ABV hybrid	Recovered (6 months)
[122]	27/M	HL IIA	Iv CS	MOPP/ABVD	Recovered (6 months)
[123]	73/F	EBV-associated NHL IIIB	–	CHEP-R	Improved (2 months)
[124]	58/M	"Unspecified" T-cell NHL	Po CS	–	Recurred/died (31 months)
[125]	58/M	Mycosis fungoides IB	Po CS/IVIG	MTX	Improved (6 months)
[126]	29/F*	NK/T-cell lymphoma IE	Po CS	CODOX-M//IVAC	Recovered (>1 year)
[127]	60/M	Cutaneous T-cell NHL	IVIG/po CS	Topical CS	Improved (10 months)
[6]	65/M*	AITL	–	MST-16/VP-16/CS/L-PAM	Improved/died (80 months)
	61/M	Lymphoplasmacytic lymphoma	IVIG	R/CPH/po CS	Improved (46 months)
	61/M*	Cutaneous T-cell NHL	Iv CS	INFγ/PUV/rINN	Improved/died (132 months)
[128]	74/M	Nodular sclerosing HL	Po CS/IVIG	ABVD	Improved (NR)

* = SIDP; ABV(D) = adriamycin/bleomycin/vinblastine/(±)dacarbazine; AITL = angioimmunoblastic T-cell lymphoma; AZA = azathiprine; CAB = chlorambucil; CCNU-VPP = CCNU/vincristine/procarbazine/prednisone; CHOP = cyclophosphamide/hydroxydaunorubicin/oncovin/prednisone; CHEP–R = cyclophosphamide/hydroxydaunorubicin/etoposide/prednisone–rituximab; CS = corticosteroids; CODOX-M//IVAC = cyclophosphamide/oncovin/doxorubicin-methotrexate//ifosphamide//VP-16/ara-C; CN(O)P = cyclophosphamide/mitoxantrone/(±oncovin)/prednisone; CPH = cyclophosphamide; CTX = high dose cytotoxic chemotherapy; DLCBL = diffuse large B-cell lymphoma; IFN = interferon; iv = intravenous; L-PAM = melphelan; modified CVP = cyclophosphamide/vincristine/prednisone; MOPP = mechlorethamine/oncovin/procarbazine/prednisone; MST16 = perazolin; MTX = methotrexate; NR = not reported; PCV = procarbazine/CCNU/vincristine; PPH = plasmapheresis; po = oral; PUVA = ultraviolet light therapy; rINN = vorinostat; R = rituximab; Thd = thalidomide; VCR = vincristine; VP16 = etoposide.

of the malignancy. Lymphoma was not treated when the patient refused treatment [124] or when the diagnosis of lymphoma was subsequently made only at autopsy [112].

Prognosis of CIDP/SIDP was favorable during the reported observation periods; benefit was observed both in patients treated with immunotherapy for neuropathy and in patients treated with chemotherapy directed at lymphoma. Patients died of ventilatory failure [112], broncho-/pneumonia complicating lymphoma treatment [114,117], cardiac arrest without known cause [124], or was not specified [6].

The immunopathogenesis of acquired IDP in patients with lymphoma has not been much studied. A report showed variable depression of indices of cell-mediated immunity, transient abnormality in B:T cell ratios, and abnormal serum immunoglobulin levels [75,76]. It was postulated that selective/unique depression of cell-mediated immunity in NHL allowed the development of a humoral and/or cellular immune reaction to peripheral nerve antigens; the rare association between GBS and lymphoma was attributed to the role of host genetic control on the development of antigen-reactive cells in the pathogenesis of disease. Support for this autoimmune hypothesis came from an electron microscopic study that showed activated (i.e., immune competent) lymphocytes penetrating Schwann cells [78].

The rarity of an association between CLL and GBS was explained by the almost invariable hypogammaglobulinemia in patients while the cell-mediated immune system remains largely intact [82]. In a report, the distinction between neoplastic and autoimmune/paraneoplastic processes was somewhat blurred in a patient with IDP associated with T-cell type CLL because tumor cells appeared the likely effectors of active demyelination [4]. In addition, the local release of immunoglobulins [130] and pro-inflammatory cytokines [131] by infiltrating CLL B-cells may contribute to the mechanism of a demyelinating component of the inflammatory response.

In conclusion, the uncommon occurrence of acquired IDP in patients with lymphoma requires complete evaluation (including CSF analysis and nerve biopsy) to rule out lymphomatous polyneuropathy; results have management implications. The rare association between acquired IDP and lymphoma suggests that the yield is bound to be low of a "routine" search for neoplasm, and should be guided by other more specific clinical suspicions.

2.4. Multifocal motor neuropathy with conduction block (MMNCB)

There exist 2 case reports of lymphoma-associated, anti-ganglioside antibody-negative MMNCB; a case with anti-GM1-associated MMNCB was included in the discussion on autoantibody-associated polyneuropathies earlier [53]. A 67-year-old man was diagnosed with MMNCB and prurigo nodularis. MMNCB responded slightly to pulse IVIG and moderately to intravenous methylprednisolone. Diffuse large B-cell NHL was detected 19 months later. Treatment with CHOP and consolidation radiotherapy resulted in a "dramatic" improvement also of MMNCB, so that no further immune treatment was required. Based on sequence of events, the authors proposed that the undetected/preclinical lymphoma caused "paraneoplastic" skin and nerve disease via an undefined common autoimmune pathogenic mechanism [132].

A 47-year-old woman with recurrent DLBCL isolated to the CNS developed MMNCB. Neuraxis MRI showed parenchymal mass lesions and leptomeningeal enhancement. CSF analysis confirmed recurrent lymphoma. Despite imaging and CSF response to combined systemic and intra-thecal chemotherapy, the patient developed progressive limb weakness. Electrodiagnostic study fulfilled the criteria for MMNCB. Pulse and maintenance IVIG achieved neurological improvement over a 22-month follow-up period; cycles of chemotherapy resulted in lymphoma remission [133]. In this patient, more than a single cause of weakness existed, so that a precise electrophysiological study diagnosis was important to determine the appropriate management decisions.

In conclusion, based on the strong association between well-defined MMNCB and positive serum anti-GM1 antibodies at least some suspicion should arise of a possible lymphoproliferative disease in antibody-negative patients.

2.5. Diverse retrospective studies

In a report of 62 patients with various types of lymphoma, sural nerve biopsy was performed on 5 of 22 patients with clinical and/or electrophysiological evidence of generalized peripheral neuropathy [2]. Teased fiber preparation showed segmental demyelination/remyelination (2 patients), mixed segmental demyelination/axonal degeneration (2 patients), or predominant axonal degeneration (1 patient), without evidence of cellular infiltration. The authors speculated about an unidentified lymphoma-associated toxic/metabolic disorder affecting Schwann cells and/or nerve cells; to the reviewer an immune-mediated mechanism seems more likely.

In a series of 13 patients with NHL and neuropathy, an immune-mediated pathogenesis included 1 case of GBS (see Table 2) [5]; Waldenström's macroglobulinemia (usually not included under NHL) was associated with CIDP (1 patient) and "dysglobulinemic" polyneuropathy i.e., serum ± endoneurial deposits of monoclonal IgMκ with antimyelin activity (3 patients).

In a subset of 26 patients with lymphoma and neuropathy (unrelated to drugs or IgM-antimyelin antibodies), 13 patients were diagnosed with demyelinating polyneuropathy [102]. Onset of neuropathy was acute (<4 weeks) or subacute (4–8 weeks) in 10 patients, and progressive (>8 weeks) in 3 patients. Neuropathy preceded lymphoma diagnosis in 9 patients (mean = 13 months); lymphoma diagnosis preceded onset of neuropathy in 4 patients (mean = 48 months). HL was exclusively associated with demyelinating polyneuropathy, but not vice versa. Immunotherapy (IVIG/PPH) combined with chemotherapy offered the best neurological prognosis. Neurological and hematological improvement was observed in 69% and 46% of patients, respectively. With the application of appropriate investigations, the identification of the etiopathogenesis of neuropathy in patients with lymphoma was deemed important to limit diagnostic delay and error, define therapeutic options, and improve the neurological prognosis.

3. Autoimmunity and non-Hodgkin lymphoma

There exists a complex bi-directional inter-relationship between lymphoproliferative malignancies and autoimmunity. The development of lymphatic malignancy during the course of autoimmune and chronic inflammatory conditions is well established; conversely, biological and/or clinical evidence of autoimmunity can be detected at any stage of the lymphoma disease course [134,135]. An accurate assessment of the prevalence of autoimmunity in patients with lymphoma has not been ascertained due to lack of systematic study [135]. Autoimmunity is observed in all lymphoma subtypes; however, it appears that biological and/or clinical autoimmunity is more common in patients with indolent B-cell NHL subtypes (e.g., marginal zone or follicular lymphoma, and CLL) compared to more aggressive types of lymphoma [136]. In T-cell NHL subtypes immune manifestations are frequent and polymorphous [137]. Biological autoimmunity is detected more frequently than clinically manifest autoimmune disease [134]; there exists a significant increase in the incidence of serum autoantibodies (e.g., anti-RNP, anti-Sm and ANA) among patients with lymphoma compared to controls [138].

Hypotheses exist regarding the biological mechanisms of autoimmunity in lymphoma. More-or-less consistent immune system dysfunction has been established in patients with the relatively well-defined lymphoma subtypes, i.e., HL (Table 5) and CLL (Table 6), but not in patients with NHL (an umbrella term for a large number of distinct lymphoma subtypes divided according to a spectrum of growth pattern aggressiveness and involved lymphocyte types). The development of

Table 5
Immune dysfunction in Hodgkin's disease.
[63]

1. Normal antigen-induced antibody production
2. Neutrophil function
   a. Decreased chemotaxis
   b. Decreased metabolic activity
3. Delayed hypersensitivity skin tests
   a. Recall antigens: anergic
   b. Neoantigens: anergic
4. Decreased E-rosette formation
5. Decreased mitogen-induced T-cell proliferation
6. Mixed lymphocyte-induced proliferation
   a. Decreased autologous
   b. Minimally decreased allogenic
7. Enhanced sensitivity to suppressor monocytes
8. Enhanced sensitivity to suppressor T-cells
9. Minimally decreased CD4:CD8 ratio

autoimmunity in NHL patients has been proposed to entail any of the following mechanisms.

Firstly, autoantibodies produced by a malignant transformation of the normal repertoire of autoreactive B-cells [139], share characteristics of natural autoantibodies (NAA). NAA represent a proportion of circulating normal immunoglobulins, and production does not require antigenic stimulation of secretory CD5 + B-cells. NAA are directed against well-conserved public isotopes i.e., low affinity to bind a wide range of self and non-self antigens [140]. Molecular analysis of V-genes in lymphoma favors a malignant transformation of autoreactive B-cells provoked by continuous challenge by self-antigens (e.g., CDR3 sequence and adjacent regions of immunoglobulin genes from B-cell lymphoma display homology with autoantibody-associated lymphocyte clones) [141]. Also, the asymmetric pattern of usage of the V_H4-21 gene (encodes for heavy chain variable region of immunoglobulins with autoantibody activity) by different B-cell tumor types seems to correlate with the frequency of associated autoimmune manifestations [142]. CD5-B-cells retain capacity to produce autoantibodies despite the frequent loss of CD5 antigen expression during lymphomagenesis [143].

Secondly, non-lymphoma cells may be the source of autoantibody production in patients with lymphoma. The detection of serum autoantibodies directed against various, yet distinct, antigens implies that a single tumoral clone cannot secrete these immunoglobulins. Thus, autoantibody production results from a lymphoma-induced generalized, more-or-less disordered immune regulation. Such a mechanism appears likely in angioimmunoblastic T-cell lymphoma and Hodgkin disease (Reed–Sternberg cells are incapable of antibody production) [63,135]. The role of T_{reg} cells in lymphoma-associated autoimmunity has not been established. T_{reg} cells suppress autoreactive T-cells as well as the immune response to malignancy. T_{reg} cells are over-represented in biopsy samples of B-cell NHL, and B-cells may help to recruit T_{reg} cells into lymphoma tissue [144]. Thus, a T_{reg} population that regulates the immune response to lymphoma cells is conceivably involved in the development of autoimmunity. Thirdly, an alteration of the Fas/Fas-ligand pathway can lead to autoimmunity. Fas receptor (CD95) is a cell-surface receptor involved in programmed cell-death (i.e., apoptosis) signaling. Acquired somatic mutations of Fas receptor can occur during normal germinal center proliferation, and are prevalent in NHL (e.g., MALT) with autoimmune manifestations [145]. Moreover, clues to lymphomagenesis were obtained from evidence that Fas-mediated apoptosis can be inhibited by exposure to surface-binding IgM antibody that engages anti-Fas antigen for which the malignant clone has affinity e.g., in Burkitt's lymphoma [146].

Lastly, a process of viral antigen-specific stimulation can lead to B-cell activation and clonal expansion that promote both lymphomagenesis and autoimmunity [147,148]. For instance, HCV-associated lymphomas are often indolent [149] with frequent and varied autoimmune manifestations. The expression of a limited repertoire of immunoglobulin VH- and VL-genes by HCV-associated lymphoma B-cells due to viral E2 antigenic stimulation can lead to the development of autoimmunity [150,151]. Moreover, viral antigen can promote production of certain cytokines that are involved in B-cell terminal differentiation via autocrine or paracrine mechanisms e.g., IL-6 can facilitate differentiation of lymphoma cells into antibody-producing cells and, thereby, autoimmunity [152,153].

Table 6
Immune dysfunction in chronic lymphocytic leukemia.
[157]

1. B-cells
   a. Hypogammaglobulinemia
   b. Production of inhibitory cytokines IL-6, IL-10, TNF, TGFβ
   c. Poor response to vaccination
2. T-cells
   a. Quantitative: increased number
   b. Qualitative
      i. Skewed repertoire, inversion CD4:CD8 ratio
      ii. Th2 polarization
      iii. Abnormal CD30 response
      iv. Reversible acquired CD40L deficiency
      v. Gene expression abnormalities (cytoskeleton/granules)
3. NK-cells
   a. Lack of granules
   b. Reduced killing activity
4. Neutrophils
   a. Reduced phagocytic and bactericidal function
   b. Abnormal migration and chemotaxis
5. Monocytes/macrophages
   a. Reduced cytotoxicity
6. Complement
   a. Reduction in levels and defects in activation and binding

4. Autoimmunity and chronic lymphocytic leukemia

CLL is characterized by the progressive accumulation of monoclonal lymphocytes with a distinctive immunophenotype (CD5 +, CD19 +, $CD20^{dim}$, CD23 +, $SmIg^{dim}$) in peripheral blood, bone marrow, and lymphoid tissues [154]. Non-hematologic autoimmunity occurs in 1 to 2% of patients with CLL, and tends to affect patients in early-stage disease due to underlying alterations in immune function [155–158]. Both cellular and humoral immunity are impaired with qualitative and quantitative defects in B-cells, T-cells, NK-cells, neutrophils and the monocyte/macrophage linage [159]; hypogammaglobulinemia is common, and affects all 3 classes (predominantly IgG3 and IgG4) (Table 6).

Healthy human CD5 + B-cells generally do not secrete antibodies [160], but in CLL such B-cells have the potential to produce autoreactive antibodies in vivo in sufficient quantity to cause clinical disease. However, in CLL autoantibodies are commonly polyclonal and differ in specificity and isotype from the immunoglobulins secreted directly by lymphomatous cells; presumably residual non-malignant B-cells produce these autoantibodies [157]. T_{reg}-cells are ineffective in CLL, and may result in activation of the autoreactive T-cells. While the capacity of CLL cells to function as antigen-presenting cells is suppressed, autoimmunity may include aberrant antigen processing by the malignant B-cells with presentation of cryptic peptides that are seen as foreign by T_H-cells i.e., lack of immune tolerance [161,162]. Against this background dysimmune neuropathies may occur in patients with CLL, but the precise mechanisms linking neoplastic disease and the immune components of nerve injury have not been studied [163], and may vary between patients.

5. Summary

The mechanism of immune attack against the peripheral nervous system in patients with lymphoma has not been properly studied, and

probably varies among patients. An all-encompassing hypothesis on the immune pathogenesis is improbable because of the incompletely understood complexity of immune dysregulation in patients with the many different types of lymphoma combined with the incompletely understood immune mechanisms against either known or undetermined antigens involved in the acquired immune-mediated polyneuropathies. In the mean time, an accurate clinical diagnosis of polyneuropathies and proper categorization of lymphoma are important to ensure appropriate management strategies when these conditions occur in the same patient.

Conflict of interest

No financial support was received for the preparation of this manuscript. The author reports no conflict of interest.

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