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Review article

Lymphoma-associated dysimmune polyneuropathies

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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

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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