Journal of the Neurological Sciences 369 (2016) 377–389

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Inflammatory myopathies and lymphoma

Joerg-Patrick Stübgen

Department of Neurology, Weill Cornell Medical College/New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065-4885, USA

ARTICLE INFO

Article history:
Received 1 July 2016
Received in revised form 28 August 2016
Accepted 29 August 2016
Available online 31 August 2016

Keywords:
Dermatomyositis
Polymyositis
Lymphoma
Autoimmunity

ABSTRACT

The inflammatory myopathies comprise a group of immune-mediated muscle diseases. Lymphoma is a term for a variety of lymphatic system malignancies. Autoimmune diseases and lymphoproliferative malignancies share a complex bidirectional relationship. A causal relationship between inflammatory mypathies and lymphoma has not been established. The diagnosis/treatment of inflammatory myopathy usually precedes the detection/diagnosis of lymphoma. Immune system dysregulation presumably underlies the evolution of lymphoma in patients with inflammatory myopathies. Inflammatory activity with chronic B-cell activation and/or antigen stimulation is deemed the major risk factor for lymphoma in patients with autoimmunity. A "paraneoplastic" phenomenon or the effects of immunosuppressive therapy may be alternative immune-based mechanisms. In chronic lymphocytic leukemia immune system disturbance rarely results in non-hematological autoimmune disease, including inflammatory myopathies.

Contents

1. Introduction

The lymphomas are a group of lymphatic system malignancies. Many lymphoma classification systems exist; 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 lymphoid malignancies each distinguished by the specific characteristics of lymphocytes (85% B-cells, less commonly T-cells or NK-cells) [1]. The annual incidence of NHL in the USA from 2009 to 2013 was 19.5 per 100,000 persons per year (http://seer.cancer.gov). About 10% of lymphomas are of the Hodgkin type (HD) characterized by the presence of

E-mail address: pstuebge@med.cornell.edu.

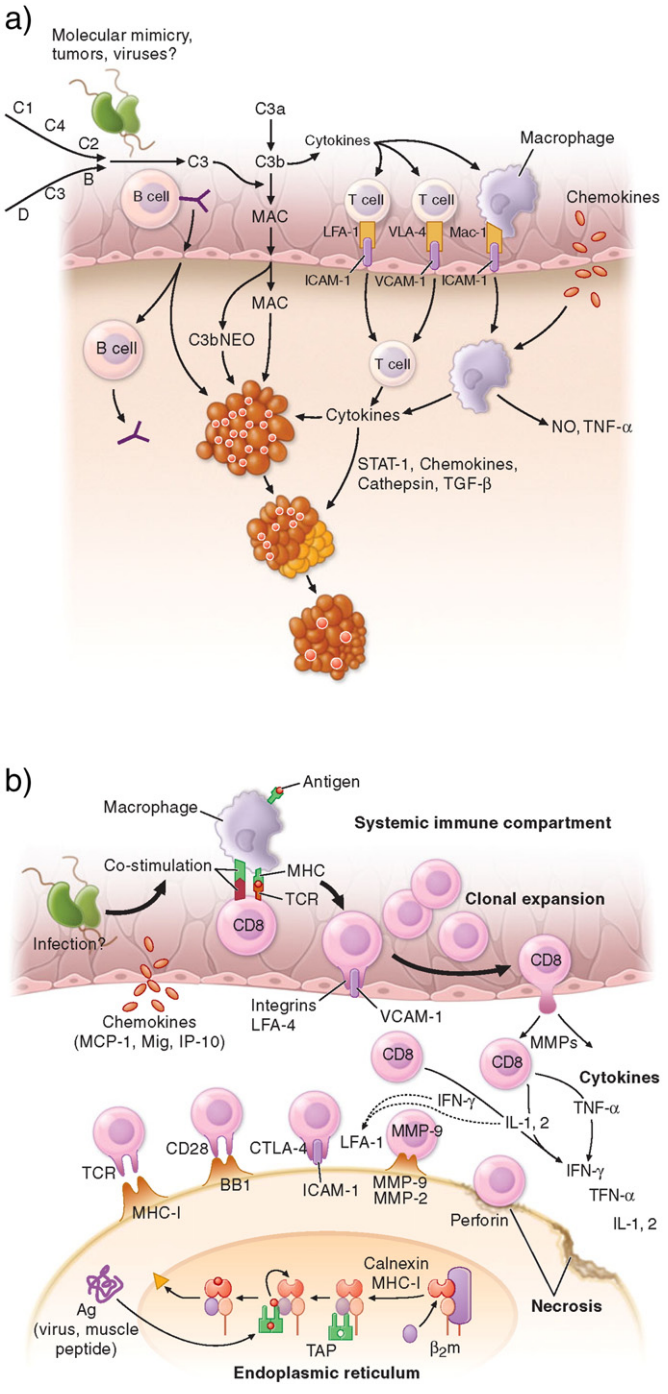
http://dx.doi.org/10.1016/j.jns.2016.08.060
0022-510X/

germinal center B-lymphocyte-derived Reed-Sternberg cells. The annual incidence of HD in the USA from 2009 to 2013 was 2.7 per 100,000 persons per year (http://seer.cancer.gov).

This review includes also: (a) chronic lymphocytic leukemia (CLL), because it is considered the same disease as small lymphocytic lymphoma (SLL), a NHL subtype, but with abnormal cells in the blood (www.lymphomas.org.uk), and (b) lymphoproliferative disorders (LPD) defined as malignant diseases of the lymphoid and reticuloendothelial systems that usually occur on a background of compromised immune systems *e.g.*, patients with organ transplants and/or immunosuppressive therapy [2].

The inflammatory myopathies (IM) comprise a heterogeneous group of immune-mediated, inflammatory muscle diseases. Recognized entities include dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (sIBM), and necrotizing autoimmune myositis (NAM) [3,4]. The autoimmune pathogenesis of IM is incompletely understood, but provides a rationale for offering patients an immunomodulatory or immunosuppressive therapy. DM is a complement-mediated microangiopathy that results in the destruction of capillaries, hypoperfusion and inflammatory cell stress within the perifascicular regions. In PM and sIBM, cytotoxic CD8-positive T-cells clonally expand *in situ* and invade muscle fibers that express major histocompatibility antigen type 1 (Fig. 1a and b). In sIBM, there are additional degenerative features characterized by vacuolization and an accumulation of stressor and amyloid-related misfolded proteins. NAM, is an increasingly recognized subacute myopathy triggered by statins, viral infections, cancer or autoimmunity with macrophages as the final effector cells causing fibers injury. There likely exists a combination of genetic and environmental factors *e.g.*, viruses [5] and vaccines [6] that determine susceptibility to IM [7]. A more complete discussion of disease mechanisms and pathology appears in recent, updated reviews [1,8–11]. An estimate of the annual worldwide incidence of IM ranges from 1.16 to 19 per million of the adult population [12].

This manuscript aims to provide insight into any association between IM and lymphoma, and to assess the profile of these conditions when they occur in the same patient. A systematic search was conducted of the relevant publications using databases such as MEDLINE [PubMed], EMBASE and DynaMed, and included case reports and series, retrospective studies, and reviews. Publications were retrieved, analyzed and scrutinized; article bibliographies were cross-referenced to ensure a most comprehensive review. Search terms included “inflammatory myopathy”, “myositis” “polymyositis”, “dermatomyositis”, “inclusion body myositis”, “immune-mediated”, “autoimmune”, and “lymphoma” “Hodgkin disease”, “non-Hodgkin's lymphoma”, “chronic lymphatic/lymphocytic leukemia”, and “lymphoproliferative disorder”.



2. Autoimmune diseases and lymphoma

Several systemic and non-systemic autoimmune diseases increase patient risk to develop lymphoma, particularly NHL [13–16]. The pathogenesis of both autoimmunity and lymphoma includes B- and T-cell activation. Immunological disturbance with high inflammatory activity, chronic inflammation and/or antigen stimulation, rather than effects of immune suppression therapy, predispose patients with active autoimmune diseases to develop lymphoma [17]; any role of shared genetic susceptibility or loss of control of latent infection (*e.g.*, Epstein Barr virus) is less well established. A number of study formats addressed the risk to develop lymphoma in patients with various autoimmune diseases. However, DM/PM was mostly not included in such studies partly due relative infrequency of IM.

Fig. 1. a. In DM, autoantibodies (Y) against endothelial cells activate complement with formation of C3. Activated C3 forms C3b, C3bNEO, and membrane attack complexes (MAC) that deposit on endothelial cells of endomysial capillaries. Destruction of capillaries leads to ischemia or microinfarctions mostly in fascicle periphery with perifascicular atrophy. B cells, CD4+ T-cells, and macrophages traffic from circulation to muscle. Cytokines released by the mononuclear cells induce endothelial expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM). Integrins *e.g.*, late activation antigen (VLA)-4 and leukocyte function-associated antigen (LFA)-1, bind VCAM and ICAM and promote T-cell and macrophage infiltration of muscle through the endothelial cell wall. 1b. In PM/sIBM, antigen-specific CD8+ T-cells expand in the periphery, cross the endothelial barrier, and bind to muscle fibers *via* T-cell receptor (TCR) molecules that recognize aberrantly expressed MHC-I. Engagement of co-stimulatory molecules (BB1 and ICOSL) with their ligands (CD28, CTLA-4, and ICOS) along with ICAM-1/LFA-1 stabilizes this CD8+ T-cell-muscle fiber interaction. Metalloproteinase (MMP) facilitates the migration of T-cells and binding with the muscle fiber surface. Muscle fiber death by necrosis occurs *via* perforin granules released by the autoaggressive T-cells. A direct myocytotoxic effect is also exerted by the cytokines interferon (IFN)-γ, interleukin (IL)-1, or tumor necrosis factor (TNF)-α. MHC class I molecules consist of a heavy chain and a light chain [ß2-microglobulin (ß2m)] in complex with an antigenic peptide that is transported into the endoplasmic reticulum by TAP proteins.