

HOSPITAL PHYSICIAN®

NEUROLOGY BOARD REVIEW MANUAL

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Cancer Neurology: Primary CNS Lymphoma, Paraneoplastic Syndromes, and Pituitary Adenoma

Editor:

Alireza Atri, MD, PhD

Instructor in Neurology, Harvard Medical School; Assistant in Neurology, Memory Disorders Unit, Massachusetts General Hospital, Boston, MA

Associate Editor:

Tracey A. Milligan, MD

Instructor in Neurology, Harvard Medical School; Associate Neurologist, Brigham and Women's and Faulkner Hospitals, Boston, MA

Contributors:

Andrew D. Norden, MD

Clinical Fellow in Neuro-oncology, Harvard Medical School, Departments of Neurology, Brigham and Women's and Massachusetts General Hospitals, Boston, MA

Santosh Kesari, MD, PhD

Instructor in Neurology, Harvard Medical School; Neuro-oncologist, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA

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Cover Illustration by Kathryn K. Johnson

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Cancer Neurology: Primary CNS Lymphoma, Paraneoplastic Syndromes, and Pituitary Adenoma

Andrew D. Norden, MD, and Santosh Kesari, MD, PhD

INTRODUCTION

This manual is the second of a 2-part review of neuro-oncology. The first part of the review addressed the evaluation and management of patients with primary malignant brain tumors and central nervous system (CNS) metastases.¹ In this part, 3 clinical cases are presented that evolve over the course of the discussion to encompass evaluation and management of primary CNS lymphoma (PCNSL), paraneoplastic syndromes, and pituitary adenomas. These topics frequently appear on board examinations and represent some of the more intriguing entities encountered in neuro-oncology.

PRIMARY CNS LYMPHOMA

EPIDEMIOLOGY AND PATHOGENESIS

Systemic non-Hodgkin's lymphoma (NHL) may secondarily involve the nervous system in 5% to 10% of patients.² PCNSL is an unusual extranodal NHL variant that exclusively involves the nervous system and eyes. Only rarely is there spread to the systemic compartment. PCNSL represents 3.1% of CNS tumors, with approximately 2000 new diagnoses per year in the United States.³

In 90% of cases, PCNSL is diagnosed histopathologically as diffuse, large B-cell lymphoma, which is also the most common subtype of systemic NHL (**Figure 1**). Other subtypes of PCNSL have been described, including very rare T-cell variants. The pathogenesis of PCNSL is perplexing, because lymphatic tissue is not found in the normal brain. Emerging data suggest that PCNSL may develop outside the nervous system and then traffic to the brain by poorly defined mechanisms. Although the cell of origin remains unknown, PCNSL cells frequently express markers associated with the germinal center stage of B-cell differentiation.

RISK FACTORS AND PROGNOSIS

Immunodeficiency is the strongest known risk factor for all subtypes of lymphoma, including PCNSL. The immunocompetent population is infrequently affected; most immunocompetent patients with PCNSL are older adults, and there is a slight male preponderance. Patients with HIV have at least a 1000 times greater risk of developing PCNSL compared with the general population.⁴ Other acquired and congenital immunodeficiency states are also risk factors. The Epstein-Barr virus (EBV) plays a critical role in the development of immunodeficiency-associated PCNSL, although a detailed mechanism remains to be established. There are no convincing data to suggest that EBV or any other infectious agent is involved in the pathogenesis of PCNSL in immunocompetent patients.

Although localized extranodal systemic NHL is compatible with long-term survival in 70% or more of patients, PCNSL is universally fatal.⁵ Factors that predict decreased survival among patients with PCNSL include age greater than 60 years, impaired performance status, elevated serum lactate dehydrogenase (LDH), increased cerebrospinal fluid (CSF) protein, and involvement of deep brain structures. Depending upon the number of adverse prognostic factors, 2-year survival rates vary between 24% and 85%.⁶ Expression of B-cell lymphoma-6 (BCL6), a transcriptional repressor involved in germinal center formation, may be an important marker of favorable prognosis in patients with PCNSL.⁷ The precise mechanism by which BCL6 contributes to the pathogenesis of NHL is unknown, but impaired BCL6 expression may prevent normal lymphocyte differentiation.⁸ BCL6 and other emerging molecular prognostic markers are the focus of current research efforts.

CLINICAL FEATURES

Case 1 Presentation

A healthy, 78-year-old woman is referred by her primary care physician to a neurologist for further evaluation. The patient has experienced 2 to 3 months