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The Future of Primary Intraocular Lymphoma (Retinal Lymphoma)

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Abstract

Basic science and clinical investigations in cancer research have contributed to our understanding of the genetic causes of various neoplasms and discovery of novel therapeutic interventions to fight malignancies such as lymphoma. During this exciting time, we have witnessed the advent of new technologies to further characterize primary intraocular lymphoma (PIOL), or retinal lymphoma, which is selected as the first "Disease of the Year" by *Ocular Immunology and Inflammation.* Different comprehensive aspects of PIOL, including epidemiology, clinical manifestations, diagnosis, pathophysiology, therapy, and animal models are discussed. The future of PIOL holds an opportunity to really understand the unique cytologic, histopathologic, physiological and immunologic features, as well as the genotypic traits (gene expression, interaction, polymorphism, epigenetics, etc.) and epidemiology. This information will empower us to truly make a difference in patients' managements with this devastating disease. While most of this technology already exists, much work still needs to be done to make translational therapy a reality for PIOL patients in the future.

Keywords

primary intraocular lymphoma; retinal lymphoma; genetics; imaging; therapy; mouse model; pathology

This era of rapidly advancing technology and abundant information allows for an exponentially expanding knowledge base that has the ability to significantly impact the practice of medicine. Basic science and clinical investigations in cancer biology and oncology and innovations in cancer genetics, immunology, virology, and cell and molecular biology are contributing to the understanding of the genetic causes of various malignancies and discovery of novel therapeutic interventions to fight malignancies including lymphoma. In this exciting time, we have seen new technologies further characterize primary intraocular lymphoma (PIOL) or retinal lymphoma.[1, 2] Intraocular lymphoma is chosen to be the first "Disease of the Year" and a series of articles has been published in *Ocular Immunology and Inflammation* in 2009.[3–7] We have a lot to learn about this intraocular malignant lymphoproliferation, but it is exciting to be in the midst of truly understanding this disease process. Significant progress has been made since the first descriptions of this intraocular "reticulum cell sarcoma" in the 1950s.[8]

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The immunologic and histologic features of most IOLs place them in the diffuse large B-cell (DLBCL) histologic subtype according to the WHO-REAL classification system.[9] Since these lymphomas occur outside lymph nodes and lymphoid structures, they are extranodal by definition. With the discovery of three pathogenetically and clinically distinct sub-categories within the DLBCL histologic subtype of NHLs by lymphochip complementary DNA microarray technology,[10, 11] one can classify PIOLs as belonging to the activated B-cell (ABC) and/or germinal center B-cell (GCB) subtypes.[7] As current technology evolves, we will be able to better analyze and characterize gene expression profiles of IOLs by their unique genetic signature. This will result in the stratification of patients with IOL based on the genetic signature of the cancer into prognostic categories with differing treatment options.[12]

Since the sequencing of the human genome, it is now possible to identify single nucleotide polymorphisms (SNPs) that are associated with disease. Genetic variance likely plays an important role in the evolution of some diseases and their responses to treatment. For example, malfunction of the tumor suppressor p53 pathway is an almost universal hallmark of human tumors.[13] SNPs in this pathway might have cancer-related phenotypic manifestations and biological consequences. Many SNPs have been associated with age-related macular degeneration (AMD), including the most recognized *complement factor H (CFH)* and age-related maculopathy susceptibility 2/high-temperature requirement A-1 (ARMS2/HtrA-1).[14–20] Responses and toxicity to methotrexate therapy are reportedly due to SNPs in the methotrexate pathway genes.[21, 22] Analyses of genes important in PIOL i.e. those associated with IL-10,[23–27] chemokines and their receptors,[28, 29] and drug sensitivity or resistance proteins[30, 31] may reveal that some patients are more susceptible than others to develop PIOL. IL-10 gene variation is reported to be associated with the clinical course of non-Hodgkin's lymphoma.[32] The IL-10 rs180089 (-3575 T>A) SNP is significantly associated with an increased risk for non-Hodgkin's lymphoma,[33, 34] and the IL-10 (-3575 A/A) genotype signifies a favorable prognosis.[35]

Recently, epigenetics, epigenomics, and macro-physiology have provided novel and exciting data on oncogenesis and tumor progression. Epigenetic alterations, which comprise mitotically and meiotically heritable changes in gene expression not caused by changes in the primary DNA sequence, are increasingly recognized for their roles in carcinogenesis.[36] Alterations of the epigenome have been identified in virtually all types of cancer and involve multiple genes and molecular pathways. Epigenetic gene interaction may represent the first step in tumorigenesis.[37] Recent studies from multiple laboratories indicate that many tumor suppressor genes and pathways are epigenetically suppressed in acute lymphocytic leukemia.[38] This information can potentially be used to predict response to therapy, detect at risk patients in morphological relapse, and target the incorporation of hypomethylating agents in acute lymphocytic leukemia. Epigenetic silencing of multiple genes is also documented in 25 cases of primary CNS lymphoma (PCNSL) as a potential biomarker of the disease.[39]

Infectious agents could be involved in lymphomagenesis. Some cases of PIOL have been reported to be associated with microorganisms including Epstein-Barr virus (EBV) or human herpes virus-8 (HHV-8),[40] and parasites (*Toxoplasma gondii*),[41] suggesting these infections could play a role in the emergence of the disease. The multiplicity of causing factors, especially for the ABC DLBCL subtype, led us presume that PIOL could potentially emerge from multifactorial events, including intraocular infections. A triggering factor or multiple factors may facilitate the development of the disease. However, the limited few number of PIOL patients makes this hypothesis difficult to prove with extended genotypic studies. If diagnostic methods advance, this approach should be feasible in the future.

Since PIOL is a potentially fatal malignancy, early and accurate diagnosis is critical for the initiation of appropriate therapy. Imaging of the eye and brain is often the first step in evaluating

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a diagnostic suspicion of the disease. A combination of fluorescein angiography, indocyanine green angiography, and optical coherence tomography may yield a positive predictive value of 88.9% with a negative predictive value of 85%.[42] Novel imaging techniques of the eye and brain may play a role in the future. We may begin to see the emergence of magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), novel positron emission tomography (PET) agents, and other technologies that will be able to detect even a few PIOL cells between the RPE and Bruch's membrane. Recently, normal T-cell and lymphoma populations are reported to be clearly distinguishable based on autofluorescence intensity spectra based on their emissions when excited with wavelengths including 351, 458, and 488 nm.[43] This difference can be detected by characterizing the autofluorescence signal from as few as 8 cells. The autofluorescent emissions can be detected from within the anterior chamber of a BALB/c mouse eye.[43] In addition to these imaging techniques, new molecular tools are emerging and should help in the near future to the detection of the presence of tumor cells and to evaluate the associated local immune response. Instead of ELISA, multiplex analysis of protein levels is a high sensitivity technique that allows the measurement of several (1 to 100) molecules simultaneously with a high range of detection, and needs only a small volume of biological sample (25-50μL). Detection of combinatory molecules at the protein level might rapidly replace the conventional methods based on the IL-10 measurement in the vitreous or the aqueous humor.

Currently, no treatment is standard of care for PIOL, but high-dose intravenous methotrexate has been proven to be an effective therapy.[44] Intrathecal and intravitreal methotrexate may become first-line routes of administration, and systemic methotrexate is considered depending on the tumor bulk or refractory nature of the disease.[45–48] Most cases of PIOL lead to CNS involvement, and this is considered when determining the route of chemotherapy administration. In 2008, the international PCNSL collaborative group analyzed 102 IOL patients from 16 centers and reported that patients additionally treated with local ocular therapy (79 with ocular radiotherapy, 22 with intravitreal methotrexate, and 1 with both) did not have a statistically significant decreased risk of failing in the eyes ($p = 0.7$), and overall survival was not impacted.[49] A very recently published article by the International Extranodal Lymphoma Study Group addresses the beneficial combination of high-dose cytarabine (2 g/m) and high-dose methotrexate (3.5 g/m), improving outcomes with acceptable toxicity compared to high-dose methotrexate alone in patients age 75 and younger who are newly diagnosed PCNSL.[50] The role of radiation therapy after methotrexate administration needs to be further defined.[51, 52] Additionally, the effective treatment of recurrent disease and the management of chemotherapy and radiation toxicities continue to be significant challenges.

Most PIOLs are B-cell lymphomas that express CD20 on their cell surface.[1] CD20 is an optimal target because it is neither shed nor internalized and is not found unbound in circulation.[53] Rituximab, a humanized monoclonal antibody directed against CD20 antigen, has recently been used for PIOL with promising results.[54, 55] In limited case reports with PIOL patients treated with rituximab, results were mixed but encouraging. Generally, rituximab is well tolerated as monotherapy and can be combined safely with chemotherapy for systemic diffuse large B-cell lymphoma. The cure rate in DLBCL with adjunctive rituximab therapy is increased by at least 20%.[56] This warrants further studies of the usage of rituximab in PIOL with longer follow-up. The future of this therapeutic strategy has already been announced with the arrival of new generations of humanized monoclonal antibodies (mAb) modified in their Fc part, such as a low fucose content. Apoptosis and complement activities for these engineered mAb are similar to conventional mAb but they display a highly improved Fcgamma receptor IIIA/CD16 binding inducing a higher antibody-dependent cellular cytotoxicity activity.[57] Thus, efficacy will be more pronounced at low doses and even if target cells express few CD20 molecules.

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Soussain's group has demonstrated the use of intensive chemotherapy followed by autologous hematopoietic stem cell rescue as another potential alterative in 22 patients with relapsing and refractory PCNSL and/or PIOL.[58] Recently, these authors reported that, with a median follow-up of 36 months on 27 refractory and recurrent patients who completed intensive chemotherapy and stem-cell transplantation, the 2-year overall survival was 69% compared to 45% in the whole lymphoma population, and the 2-year progression-free survival probability was 58% compared to 43% in the whole lymphoma population.[59] They concluded that intensive chemotherapy followed by autologous hematopoietic stem cell rescue is effective for refractory and recurrent PCNSL/PIOL. A randomized phase II clinical trail that is sponsored by the International Extranodal Lymphoma Study Group will hopefully provide useful information on the best conditioning regimen, the role of concomitant intrathecal chemotherapy, the neurotoxicity risk of further WBRT after transplant, the best time for response assessment and late effects both on neurological performance and extraneural organs remain to be characterized.[60]

The precise genetic profile will need to be identified for each PIOL patient to determine potential response to therapies. Some PIOLs may be less susceptible to mainstay treatments by virtue of drug resistance proteins. Hence, understanding PIOL genetics will allow us to approach the gold standard of individualized cancer treatment and offer a maximal increase in survival using our current therapies. Genetic signatures of PIOLs will also identify cancer pathways that can be targeted in this population.

Animal models of PIOL have offered tools to identify important factors involved in the development of PIOL and identification and testing of novel therapies for PIOL.[61–66] In these models, mice are inoculated systemically or locally with T- or B- cell lymphomas. The models provide us to study PIOL kinetics, metastases, and immune response, and investigate new diagnostic and prognostic markers. Moreover, these murine models help us to identify new biomarkers for therapeutic follow up, such as tumor relative molecules or molecular effectors of an effective immune response. Several innovative therapeutic agents have been evaluated in murine models of PIOL, including immunotoxin HA22[63] and intravitreal and intrathecal rituximab.[65] In addition to these direct anti-tumor therapeutic strategies, molecular and cellular characterization of tumor microenvironment is essential. Indeed, since the microenvironment plays a crucial role in the development of tumors, it has been shown that immune infiltrates, including several T-cell populations, increase proportionally to the tumor burden.[63] These immune infiltrates seem to contain anti-tumor effectors. However, these powerful cells are partially inhibited by the immunosuppressive microenvironment and by the tumor itself. Understanding of the molecular mechanisms involved in this suppression will open new potential therapeutic perspectives. The animal models are crucial in order to test the emerging novel therapeutic strategies involving a combination of several battlefronts, such as a global (chemotherapy and/or radiotherapy) or a specific anti-tumor strike (e.g., anti-HA22, anti-CD20 mAb), a contra-suppressive modulation targeting cellular (e.g., regulatory T-cells) and/or molecular factors (e.g., IL-10, TGFβ), and an immunostimulation of adaptive immune responses to generate specific memory T-cells tracking disseminating tumor cells even in ‘undetectable’ micro-metastatic lesions.

The future holds an opportunity to truly understand the unique cytologic, histopathologic, physiological and immunologic features, as well as the genotypic traits and epidemiology of PIOL, which will empower us to truthfully make a difference in the way we treat patients with this devastating disease. Hopefully in the near future, when we need to inform a patient that he or she has PIOL, we can say that we know why the disease has occurred in this patient and how to effectively treat him or her with ‘individual medication’. We will be able to obtain genetic data including SNPs and the epigenome of each person, predict the potential risk of developing PIOL, make early diagnoses, anticipate disease outcomes, and select the most

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efficacious therapies. Keeping the potential benefit to PIOL patients in mind, we must relentlessly amplify our efforts to reach this end. While most of this technology exists, much work still needs to be done to make translational therapy a reality for PIOL patients in the near future.

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