

# Preface

In medicine and science, two inseparable sisters, a modern renaissance has occurred in which the pursuit of knowledge has provided the world with fascinating discoveries and answers to age-old questions. Perhaps one of the most shining and striking moments in this modern renaissance was the elucidation of the human genome. From this momentous project were produced tools and knowledge that could be put to use to solve other problems and answer other questions. We find, however, that in seeking out an answer, we instead discover that we have more questions than when we started out. Moreover, answers that are found in chemistry, physics, insect genetics, and so forth frequently provide researchers in seemingly unrelated fields with clues that may prove to be important in their own hunts. It is important, then, that as true renaissance scientists, we open ourselves to the knowledge that is transmitted (literally on a daily basis now) in the world of science and medicine.

The world of ophthalmology is certainly partaking in this renaissance with ever new advancements in the field. Ocular immunopathology is at the forefront of these new advancements. The immune system, involved in diverse processes from inflammation to cancer, has proven to play a central role in many diseases. Even when an organ system is seemingly tucked away from the immune system, as are the brain and intraocular structures, dysfunctions involving components of the immune system can nonetheless manifest themselves. Yet again we are left with more questions than answers in attempting to understand disease.

It is with a sense of excitement and hunger for new knowledge that we present this book, the first to be published on the subject, on primary intraocular lymphoma (PIOL). This is exciting because it is within recent memory when the first histopathological presentations of PIOL were presented in the literature. Moreover, as we acquired knowledge of the inner

workings of the immune system, we were able to modify our thoughts on the precise cell involved in this cancer. As genetics burgeoned into a powerful science, we were able to uncover ever more information on this rare tumor. Our appetite, however, is not abated. We are perhaps more hungry now for answers than in our first descriptions of this tumor in the literature of the 1940s and 1950s.

One might think of this book, then, as a menu. In the first four chapters we seek to stimulate the appetite with discussion of the definition of primary intraocular lymphoma, historical reviews and cases of PIOL, the classification systems that once existed and those in use today, and the epidemiology in PIOL. The next two chapters deal with the clinical presentation of the disease and ways that we image PIOL. As the disease often masquerades as a uveitis, it is important to recognize the salient features of this lymphoid malignancy, especially when it occurs in patients who fit the disease profile. We then turn our attention to the pathology and immunology involved in PIOL, in two respective chapters. It is perhaps here that we ought to pause during our feast of knowledge and reflect on just how much information we have acquired on PIOL in the past six decades. No longer are we dealing with the abstract reticulum cell sarcoma, but rather an immunologically and genetically distinct entity.

From the important main courses of clinical, pathological, and immunological presentations, we then turn to the important subject of diagnostic techniques and then to the unsettled business, but absolutely essential concepts, of therapy in PIOL. It has been noted by some gastronomic connoisseurs that a dinner ending without cheese is like a beautiful woman with only one eye. Something integral is missing. Similarly, our knowledge of the best therapeutic approaches to this tumor is not complete. Yet, while perfect treatment regimens for PIOL are missing, we have made important advancements in treating this tumor and we strive to make even further developments in this arena. The more effect we have on treating this tumor, the more we can affect the prognostics associated with the disease. Prognosis is dealt with in its own chapter and it is important to recognize here that PIOL is a malignant disease where we as ophthalmologists have the opportunity to extend or save our patients' lives. With manifestations limited to the eye (unless the brain is involved) patients will seek out, or be referred to, ophthalmologists. Therefore, it is of the utmost importance that ophthalmologists be able to identify

possible presentations of PIOL and in appropriate cases seek out diagnostic procedures. Furthermore, it is important to consider what testing should be performed when attempting to diagnose PIOL with limited tissue specimens. Ocular pathologists and cytologists will certainly play an important role in drawing out the diagnostic plan for a patient. Finally, the ophthalmologist must guide his or her patient into appropriate care and management that is coordinated with neurooncologists. Thus, a great responsibility is shouldered by the ophthalmologist for the very quality of life of patients with PIOL.

There are hypotheses for the origin of PIOL, which are discussed in another chapter and it is here that we are struck with the fact that we still have much to learn about the fundamental problems that allow for a lymphoma to occur in the eye. This chapter is followed by another describing animal models of the disease developed at the National Eye Institute, in order to begin to understand some of the fundamental mechanisms involved in PIOL.

We end our book with illustrative cases that presented at the National Eye Institute. Some of these cases are classical presentations of PIOL, while others proved to be more challenging, both diagnostically and therapeutically. These cases are useful in that they allow the reader to follow some of the typical diagnostic and therapeutic techniques that are commonly employed.

The topic of PIOL is certainly a full plate and not always easy to digest. We feel that we have presented the important concepts and future directions in this disease in a manner that will allow the reader to better understand this most interesting cancer. We also wish to inform the reader that this story is far from complete. We and others around the world continue to work on elucidating the factors and mediators involved in this cancer and ways that important components of the disease might be modulated for therapeutic benefit. We hope that this book will whet the appetite of our readers and produces in them a hunger similar to ours for understanding PIOL.

We wish to thank the National Eye Institute and the Howard Hughes Medical Institute Research Scholars Program for their support. We also thank our colleagues, the physicians who refer patients to the NEI and the staff who work on the PIOL cases at the NEI. We are deeply indebted to the more than 100 patients who have contributed to our

understanding of the disease, and to their families for their support during such a challenging time. Finally, we save our most profound thanks to our families and friends, whose love and encouragement helped us through the writing process of this book.

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