Management of Rare Adult Tumours

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Springer

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ISBN-13 : 978-2-287-92245-9 Springer Paris Berlin Heidelberg New York

Maquette de couverture : Jean-François Montmarché

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Preface

P.H. Levine

The importance of Studying Rare Malignancies

Rare cancers play an important role in the epidemiology of cancer in view of the clues they give us to cancer etiology in general. The most obvious example is the study of cancer clusters, which provide excellent opportunities to identify etiologic agents. The study of cancer clusters has many problems and is usually unproductive [8] usually because reported clusters involve large numbers of common tumors with long latent periods, but the most dramatic successes involve rare malignancies. In such cases, alert clinicians play an important role as exemplified by Gottlieb in 1981 [3] who noticed the unusual new occurrence of Kaposi's sarcoma in gay San Francisco males which eventually led to the identification of Acquired Autoimmune Deficiency Syndrome (AIDS) as a potential public health problem and subsequent identification of Human Immunodeficiency Virus (HIV) as the etiologic agent. A non-infectious danger was recognized in Boston with the appearance of a rare cancer in young women, vaginal cancer, which was eventually traced to the administration of a hormone, diethylstilbestrol (DES) to the mothers to maintain a pregnancy [5]. DES proved to be unsuccessful in maintaining pregnancies but more important, the danger of this hormone being given to pregnant women was quickly identified.

Another important consideration in cancer epidemiology is the study of a rare tumor in one country that is not rare in other countries. The etiology or an etiologic component may or may not be known but it is important to understand the cofactors that increase or decrease the incidence of a specific malignancy after exposure to the suspected agent. Such studies these days involve the integration of laboratory studies into the development of epidemiologic protocols, and it now seems to be the exception rather than the rule that a large epidemiologic study does not include the collection of biospecimens for multiple laboratory investigations. Our experience in this area began with Burkitt's lymphoma (BL), a malignancy first described by Denis Burkitt in Sub-Saharan Africa geographically limited by climate and altitude to areas of holoendemic malaria. Because BL was unknown in England, where Burkitt had practiced as an experienced surgeon, he was fascinated by this rare tumor which led to extensive international collaborative studies involving clinicians, epidemiologists and laboratory investigators culminating in the discovery of the Epstein-Barr virus (EBV) [1, 4]. One of the epidemiologists-statisticians focusing on BL was Malcolm Pike who, noting the occasional clusters of the disease, proposed a "Factor X", an etiologic agent in addition to EBV and malaria, which could contribute to the etiology. He suggested that a comparison of the endemic African disease be compared with non-endemic cases where malaria was not a factor and thus the American Burkitt's Lymphoma Registry was initiated [6].

More than 143 cases of BL in the US were reported in eight years [7] and biospecimens, particularly paraffin blocks, revealed that at least two distinct forms of BL could be identified [2], the prototypical EBV-associate BL, the most common form in sub-Saharan Africa but rare in the US, and the non-EBV-associated form, the more common form in the U.S. with distinct chromosomal and clinical differences from African BL.

The identification of patients with rare tumors is now greatly facilitated by the internet, which is now being used to investigate a number of rare tumors, as demonstrated by the many interesting chapters in this book. The Rare Cancer Network (RCN) has been using the WEB to connect clinicians to improve the management of rare cancers, as described in these chapters. This is an important beginning, since much more needs to be done to understand the pathobiology and control of a variety of rare malignancies. As advances occur in the laboratory, more sophisticated studies are now feasible, such as the use of oral rinses to collect DNA for sophisticated analysis. The findings resulting in the study of rare tumors can be expected to have major implications for cancer etiology in general.

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Foreword

R.C. Miller

This work addresses the problem of rare tumour management. By definition, these are uncommon malignancies whose diagnosis and treatment are made more complicated by a relative absence of information in the medical literature. A uniform definition of a "rare tumour" does not currently exist. In some instances, terminology even for individual disease entities remains indeterminate because of their infrequent occurrence. The National Institute of Health's Office of Rare Disease Research defines a "rare disease" as one effecting less than 200,000 individuals in the United States [2]. In contrast, the European Commission has more broadly defined rare diseases as those diseases which "are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them" or those that affect less than 5 per 10,000 persons. Although individually the incidence of any given rare disease is low, it is estimated that 6% to 8% of the population of the European Union has a disease classified as "rare" when all entities meeting this definition are considered in aggregate [3]. The unusual neoplastic processes presented in Management of Rare Tumours of the Adult range from the very rare, where the cases reported in the medical literature consist only of a few dozens of patients, such as Erdheim-Chester disease and primary spinal epidural lymphoma, to more common entities that clinicians may occasionally encounter, but where a low incidence has left their best management incompletely defined, such as thymoma and ductal carcinoma *in-situ* in very young women. The European Commission has identified rare diseases as a subject where cooperative action within the international community may be of benefit. On November 11th, 2008, the European Commission published proposed recommendations for European action in the field of rare diseases, calling for global action in concert given the rarity of these conditions and the often complex requirements of their diagnosis and management. *Management of Rare Tumours of the Adult* is a timely addition towards that effort.

In an era where evidence based medicine (EBM) has become the focus of clinical research and medical practice, the treatment of rare diseases presents a unique challenge. EBM practice is founded on a hierarchy of evidence, with the greatest value being assigned to evidence derived from sources with robust statistical power, such as meta-analyses and randomized clinical trials. By definition, the study of rare tumours is problematic from the EBM perspective given that their infrequent occurrence prevents their study through prospective means. Despite the challenges of dealing with patient populations too small for testing research questions through randomized controlled trials, these problems are not insurmountable [1-4]. The internet has proved to be important in increasing communication and awareness of rare diseases, as well as providing a powerful tool for fostering cooperative investi-

gations. International collaborations through such organizations as The Rare Cancer Network (www.rarecancer.net) permit a pooling of data and an increase in statistical power in the study of malignant entities in which no single institution can produce sufficient cases for definitive analysis.

Management of Rare Tumours of the Adult is meant to provide a concise summary of the state of the art of rare tumor management for clinicians and medical scientists interested in uncommon malignancies. Arranged on the basis of anatomic site of the primary tumours, the authors address the classification, diagnosis, and therapy of 61 rare tumours. The focus of their work is on providing a summary of the medical literature to date that can assist the clinician in decision making during the diagnosis and treatment of such tumours. The authors have been chosen because of their expertise in this difficult field of investigation. Their efforts are greatly appreciated and it is hoped that this book will serve as a valuable resource for those caring for adult patients with rare malignancies.

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