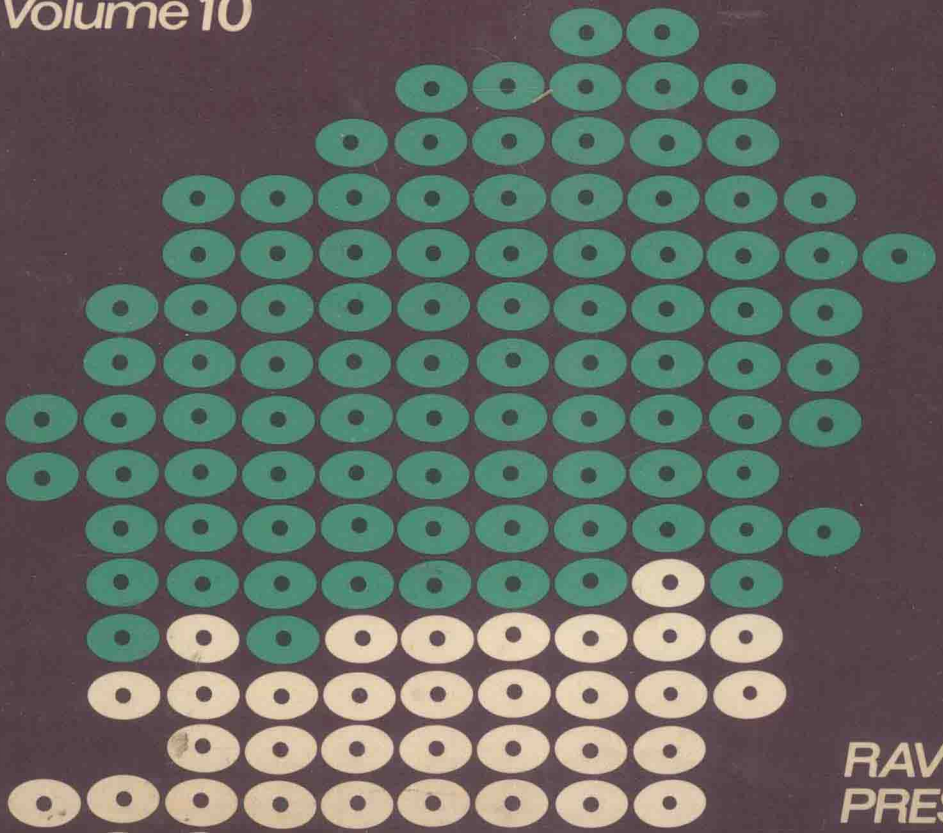
Infections in Cancer Patients

Editor
Jean Klastersky

EUROPEAN ORGANIZATION FOR RESEARCH ON TREATMENT OF CANCER (EORTC) MONOGRAPH SERIES

Volume 10



RAVEN PRESS

Infections in Cancer Patients

Monograph Series of the European Organization for Research on Treatment of Cancer Volume 10

Editor

Jean Klastersky, M.D.
Service de Médecine et Laboratoire d'Investigation Clinique H. J. Tagnon Institut Jules Bordet Centre des Tumeurs de l'Université Libre de Bruxelles Brussels, Belgium

Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

International Standard Book Number 0–89004–627–1
Library of Congress Catalog Number 80–5851

INFECTIONS IN CANCER PATIENTS

Monograph Series of the European Organization for Research on Treatment of Cancer
Volume 10

MONOGRAPH SERIES OF THE
EUROPEAN ORGANIZATION FOR RESEARCH
ON TREATMENT OF CANCER

The Mongraph Series of the EORTC deals with selected topics related to cancer treatment. Volumes are usually, but not necessarily, based on the proceedings of an EORTC symposium. The responsibility of the Editorial Advisory Board is to approve the subject of each monograph; the Board does not review individual manuscripts.

Preface

One of the most difficult problems that frequently faces the oncologist, infectious disease specialist, and all physicians who must manage patients with cancer is the broad range of viral, bacterial, and fungal infections to which these patients are frequently subject as the result of their immunosuppressed state and general lack of resistance to disease.

This volume will be an invaluable reference for physicians dealing with cancer patients, as it provides a comprehensive and detailed guide to prevention and management. Chapters deal with predisposing factors to infection, mechanisms of acquisition and development of infections, laboratory diagnosis, and approaches to therapy for a range of types of infection that commonly occur.

Contributors

Donald Armstrong
Infectious Disease Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

John E. Bennett
Clinical Mycology Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205

R. Cappel
Department of Virology, Institut Pasteur, Rue du Remorqueur 28, 1040 Brussels, Belgium

James R. Commers
Infectious Disease Section, Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland 20205

Merril Gersten
Infectious Disease Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Michel P. Glauser
Division des Maladies Infectieuses, Département de Médecine, Centre Hospitalier Universitaire Vaudois, Lausaunne, Switzerland

Martin S. Hirsch
Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114

G. Höffken
Medical Department of Klinikum Steglitz, Freie Universität Berlin, D-1000 Berlin 45, Federal Republic of Germany

B. Kemmerich
Medical Department of Klinikum Steglitz, Freie Universität Berlin, D-1000 Berlin 45, Federal Republic of Germany

J. Klastersky
Service de Médecine et Laboratoire d'Investigation Clinique H. J. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, 1000 Brussels, Belgium

H. Lode
Medical Department of Klinikum Steglitz, Freie Universität Berlin, D-1000 Berlin 45, Federal Republic of Germany

F. Meunier-Carpentier
Service de Médecine et Laboratoire d'Investigation Clinique H. J. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, 1000 Brussels, Belgium

Philip A. Pizzo
Infectious Disease Section, Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland 20205

Stephen C. Schimpff
Baltimore Cancer Research Center, University of Maryland Hospital, Baltimore, Maryland 21201

Hans Stalder
Medizinische Klinik, Kantonsspital, 4410 Liestal, Switzerland

D. van der Waaij
Laboratory for Medical Microbiology, University of Groningen, The Netherlands

James C. Wade
Baltimore Cancer Research Center, University of Maryland Hospital, Baltimore, Maryland 21201

F. A. Waldvogel
Infectious Disease Division, Department of Medicine, University Hospital, 1211 Geneva 4, Switzerland

O. Zak
Research Department, Pharmaceuticals Division, Ciba-Geigy Limited, 4002 Basel, Switzerland

Stephen H. Zinner
Division of Infectious Diseases, Department of Medicine, Brown University, Roger Williams General Hospital, Providence, Rhode Island 02912

Contents

Infections in Cancer Patients, edited by
J. Klastersky. Raven Press, New York © 1982.

Predisposing Factors to Fungal and Viral Infections in Cancer Patients

F. A. Waldvogel

Infectious Disease Division, Department of Medicine, University Hospital, 1211 Geneva 4, Switzerland

Advances in chemotherapy of leukemias and solid tumors as well as the development of supportive care have undoubtedly lengthened the life expectancy for many patients with various types of malignancies and have thereby also increased their exposure time to and risk of various types of complications. Whereas transfusions of blood components have helped to alleviate many hematological problems, a variety of ill-defined secondary immune deficiencies and host factor modifications have favored the emergence of an increasingly diversified, potentially pathogenic, often purely commensal, microbiological flora.

Among the microorganisms sometimes merely isolated as colonizing agents from cancer patients, viruses and fungi play a nonnegligible role. Thus, in a large series including 354 autopsied patients, death was associated with fungal septicemia in 16%, with fungal pneumonia in 15%, and with viral infections in close to 4% of the cases (33). Overall morbidity data are evidently much harder to obtain, particularly in viral diseases where nonspecific symptoms, spontaneous cure, and various modes of presentation preclude an accurate evaluation of the attack rates. Nevertheless, viral diseases with well-defined and easily recognizable pathogenic effects and clinical manifestations such as varicella–zoster can be shown to have an impressive predilection for some cancer patient groups: thus, a recent review gives an incidence of 0.2% to 2% in the general population and of 0.46% and 3.5% in male patients with solid tumors and in female patients previously irradiated for mammary carcinoma, respectively, and of 11.4% and 15.4% for patients with lymphoma and Hodgkin's disease (19).

An interesting feature of infections in cancer patients is their lack of specific etiologic agents as exemplified by the following observations. Traditional infectious diseases in otherwise healthy, normal subjects are partially predictable as to their etiology: for instance, bacterial meningitis in childhood is usually due to one of three encapsulated bacteria, *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Hemophilus influenzae*. Pneumonia in the adolescent is frequently due to *Mycoplasma pneumoniae*. In striking contrast to this, patients with malignancies do not develop infections due to any particular or even specific agent but show an increased susceptibility to organisms characterized among others by their ubiquitous presence

in nature. In other words, there is to my knowledge no single agent responsible for severe infection in cancer or immunosuppressed patients that cannot be occasionally cultured from asymptomatic, immunocompetent hosts, as well; that is, there is no single agent characterized by its close association with cancer patients only. Thus, even Papova viruses, which have been associated with degenerative disease of the central nervous system apparently only in immunosuppressed patients, seem to have a worldwide distribution (1). This observation leads to the conclusion that almost all of the predisposing factors to viral and fungal infections in cancer patients have to be found in the host himself or his immediate surroundings and not in some unusual behavior of particular strains that preferentially colonize cancer patients.

Before reviewing the predisposing factors conducive to fungal or viral infections in cancer patients, it seems appropriate to make two other comments. First, description and analysis of the predisposing factors leading to these diseases presuppose that the "nonpredisposing factors," i.e., the normal defense mechanisms against these same organisms, are well known. For this reason, this chapter will concentrate on the normal defense mechanisms, leaving it up to the reader to evaluate the consequences of the specific host defense deficiencies. Second, an enumeration of the various host defense mechanisms active against each specific pathogenic organism seems to be as inappropriate as would be a general review of the immune mechanisms in normal or cancer patients. I shall, therefore, take an intermediate stand, first reviewing some general aspects of the host responses to fungi and viruses and then discussing particular disease entities that are of major importance to the clinician involved in the care of cancer patients.

GENERAL COMMENTS

As briefly mentioned before, the fungi, yeasts, and viruses causing disease in cancer patients have ubiquitous locations and frequently colonize normal subjects. This observation is particularly striking when one considers the main microorganism involved in this type of infections, i.e., *Candida*. This yeast can be found, when looked for meticulously, in 50% of mouth washes, and in 90% of the feces of normal adults (20,21). In a recent study on recurrent vaginal candidiasis, half of the examined subjects carried *Candida albicans* in their stool, including all those complaining of recurrent vaginitis (36). Another human reservoir of *Candida* to be considered is the tracheobronchial tree which is frequently colonized by this yeast, particularly in patients with chronic bronchitis (27). Frequent upper airway contamination with *Aspergillus* (16%) has also been documented in normal subjects (4), and gastrointestinal contamination through ingestion of various commercial food products (including spaghettis and noodles!) is suspected. An exception to this rule is probably provided by *Cryptococcus neoformans*, a rather unusual inhabitant of normal bronchial secretions (4) which probably colonizes the respiratory tree after specific exposures to bird excreta. As to the known virus burden of a normal adult population of an industrialized country, it is considerable and might represent only the tip of an iceberg: most adults are immunized to at least four adenoviruses,

to the various herpesviruses [Herpes simplex (HSV) I and II, EB virus (EBV), cytomegalovirus (CMV), and varicella–zoster virus (VZV)]. The same holds true for a variety of orthomyxoviruses and paramyxoviruses (including mumps, measles, respiratory syncytial virus, etc.). A lower incidence of individuals infected during lifetime has been given for the picornaviruses and the various hepatitis viruses (15).

Epidemiological data obtained on cancer patients and reviewed by Levine et al. (33) demonstrate that among the specific viruses that have been reported to cause frequent disease in compromised hosts are the DNA viruses HSV I and II, CMV, EBV, VSV, vaccinia, papovaviruses, and, among the RNA viruses, the measles virus. Recent data also suggest that adenoviruses might be more frequently isolated during symptomatic disease in these patients (57). It is of great interest to realize that most of these viruses are characterized either by latency and possible recurrences (e.g., the herpesvirus group) or by occasional persistent infection (e.g., papova group and measles). Latency has also recently been observed in an animal experimental model infected with adenovirus (41).

The biological significance of this general characteristic of the viruses responsible for infections in cancer patients is unknown. As seen previously, and in spite of a few exceptions such as hyperalimentation-induced *Candida* sepsis, nosocomial upper respiratory tract infections, and CMV infections after transfusions or transplantation, it can be stated that there is growing evidence for prolonged carriage and endogenous activation, rather than horizontal spreading, of potentially pathogenic fungi or viruses in cancer patients. This observation can be carried somewhat further: since everyone, either with or without cancer, has apparently similar chances to be exposed to the great variety of pathogenic ubiquitous fungi and viruses known to the microbiologist, the increased propensity to infectious diseases found in cancer patients is probably a consequence of their inability to contain the infectious agent within its initial site of colonization rather than a problem of increased exposure.

This second conclusion is based on several clinical and epidemiological observations. All patients with disseminated candidiasis studied by Eras et al. (14) had extensive gastrointestinal candidiasis proven at autopsy, suggesting this location as a portal of entry. Cytotoxic immunosuppressive therapy of patients with severe rheumatological disorders has led to a striking increase in CMV excretion in previously seropositive patients (12), pointing towards endogenous activation of the virus as the initiating mechanism. Clinically evident CMV infection with various organ involvements could not be reduced in 83 children with acute lymphoblastic leukemia nursed under standard contagious isolation procedures (6), again arguing in favor of dissemination from an endogenous focus within the patient as the initiating event. If, as mentioned above, the incidence of VZV infections is increased in some cancer patient groups, dissemination of local zoster lesions is almost a hallmark of malignancies such as Hodgkin's disease and lymphomas: in three recent studies addressing this question, dissemination could be shown to occur in 16% (19), 30% (46), and 39% (53) of the patients, respectively (46). Needless to say, this general statement also has its few restrictions: thus, reasoning by analogy with other fungal infections in which the tracheobronchial tree is probably the primary

site of colonization (e.g., *Aspergillus* species), there should be a large number of healthy subjects carrying *Nocardia asteroides* in their bronchial secretions. Thus far, however, evidence for such a large reservoir of subclinical colonization, as defined for other fungi and viruses, seems to be lacking (39).

If overt viral and fungal diseases in cancer patients are most often a consequence of early colonization (usually after or sometimes even before the development of the malignancy) followed by rapid growth and dissemination as a result of tumor- or chemotherapy-induced immunosuppression, we have to concentrate our efforts on a better understanding of the physiological factors responsible for early elimination of the pathogenic agent and for the containment of the infectious disease process. It is beyond the scope of the present chapter to describe the complexities and intricacies of the human immune system or to describe and evaluate the many experimental models developed over the last few years.

It is, nevertheless, important to emphasize that besides the well-known immune responses of a normal subject, each organ has its characteristic nonspecific or specific individual defense mechanisms which it shares only partially with other organs: thus, the lung has its own expression of an immune response due to its unique structure and location. We do not yet know, for instance, whether or when pulmonary macrophages function to protect immunocompetent tissue from interaction with inhaled antigens by ingesting the latter, or when they process the antigens to enhance the immune response (29). In experimental disseminated candidiasis, the kidney and the heart are the most affected organs, whereas the others tend to eliminate the organisms with time (25). Thus, future research will have to evaluate these various organ-specific, probably nonimmunological defense mechanisms, which are probably of great importance in containing infection within certain sanctuaries.

FUNGAL INFECTIONS

It has been generally accepted that T-cell-mediated immunity is an important host defense mechanism against infections caused by the opportunistic yeasts, fungi, and fungal-like bacteria *(Aspergillus, Candida, Cryptococcus, Nocardia)*, as we shall discuss (56). In addition to these and other host factors described below, recent data have revealed the fascinating observation that morphologic changes of the fungi themselves probably influence the way they are handled in the host. Thus, Diamond et al. (7) have beautifully shown that the large, filamentous forms of *Candida pseudohyphae*, as well as *Aspergillus* and *Rhizopus hyphae* were recognized and damaged directly, without phagocytosis, by neutrophils in the absence of serum, as opposed to encapsulated *Cryptococcus neoformans* and *Candida* yeast forms (7,8).

Candida albicans

Killing of the yeast forms by polymorphonuclear neutrophils or eosinophils as well as by monocytes has been repeatedly documented in different test systems (30,32). The clinical correlates of these discoveries are the observations of increased *Candida* infections in severely neutropenic patients and in patients with chronic

granulomatous disease or with myeloperoxydase deficiency. Antibody and complement without effector cells are not fungicidal. The role of the cellular immune system in controlling *Candida* infection is less well defined. On the one hand, BCG- or *C. parvum*-stimulated mouse peritoneal macrophages prolonged survival of the animals after intravenous challenge with *Candida*, but on the other hand, transfer of immune lymphocytes to infected mice did not afford appropriate protection (40,49).

It is to be remembered that macrophage protection can probably be used as an effector mechanism in some infections without cell-to-cell cooperation with T lymphocytes. It is quite conceivable that many contradictory results recently published on the killing of *Candida* in various experimental models might be a reflection of a multifactorial defense system against *Candida*, the many factors of which having been poorly controlled in the test systems. Thus, besides the morphology of the yeast already alluded to, other factors modulate the survival of *Candida*: heat-labile and heat-stable candidicidal factors have been described in human serum. The poor growth-promoting capacity of serum can be made similar to that of Sabouraud's medium by lowering its pH to 6.3 or by adding excess iron ions, the former mechanism probably influencing the latter one (13). Other factors promoting disseminated candidiasis are more controversial: it has been repeatedly proposed, and confirmed experimentally, that chronic administration of steroids increases the risk of dissemination. Antibiotic therapy in several animal models favors *Candida* dissemination. Antibiotic therapy also strikingly increases the prevalence of *Candida* in the gastrointestinal tract, thus providing an increased inoculum for later dissemination in an immunocompromised host (16). Tetracycline has particularly been used in animal models to favor dissemination of an organ infection by *Candida* (47).

Cryptococcus neoformans

The situation is even more complex regarding this yeast which exists in nonencapsulated form in soil but becomes readily encapsulated when inhaled into the lung. The close association of cryptococcal infections and Hodgkin's disease has led to the conclusion that cellular immunity might be the crucial determinant controlling invasion. There is, however, still ample room for other speculations, and poor monocyte and macrophage function, as repeatedly demonstrated in Hodgkin's disease, could also explain this striking association observed by clinicians. Phagocytic cells of all sorts, particularly monocytes, can clearly ingest and kill *Cryptococcus neoformans*, but ingestion depends on proper opsonization and on the size of the capsule (9,10). Rabbit, guinea pig, and human granule-rich fractions from phagocytes have been shown to contain a cidal activity against *Cryptococcus neoformans* and *Candida parapsilosis* (31). Finally, in analogy with results described previously regarding *Candida albicans*, rabbit peripheral phagocytic cells can form tight rings around cryptococci possessing large capsules and can penetrate them by forming pseudopodia.

These morphological observations suggest the possibility of extracellular killing as an additional means of handling cryptococcal invasion (28). Intense oxidative activity and release of several hydrolases into the ring-like structure established by the phagocytes attested to the intense metabolic activity of these cells (28). The presently suggested sequence of events for cryptococcal infections implies that this unencapsulated yeast becomes encapsulated after inhalation into lung tissue, where it can be ingested, but not killed, by pulmonary alveolar macrophages. It is then the responsibility of circulating phagocytic cells to kill cryptococci, provided that they can rely on appropriate functional intracellular cidal mechanisms (54). Extracellular killing will also limit the infection, provided again that the phagocytic cells have intact metabolic activities.

Aspergillus fumigatus

This fungus, as well as the less frequent varieties *A. flavus* and *A. glaucus*, cause dramatic invasive, often lethal infections in severely immunosuppressed hosts. The risk of invasive disease seems to be highest in leukemic patients (35). Pulmonary involvement is almost always present, from which dissemination to other organs has been described in particularly severe cases (35). The cellular mechanisms by which the human immune system eliminates these organisms are poorly understood. Many pathogenic and infection-promoting factors have been suggested on a clinical or epidemiological basis in view of our lack of understanding of the defense mechanisms; these include immunosuppressive drugs, cytotoxic chemotherapy, antibacterial treatment, recent bacterial infections, mechanical ventilation, intrapulmonary hemorrhage, etc. In view of these complexities, cellular *in vitro* systems will, it is hoped, shed some light in the near future on the interplay between this fungus and host defense mechanisms.

Nocardia asteroides

Similar comments have to be made regarding this bacterium, which produces fungus-like disease, most often in the lungs and in the central nervous system (39). Clinical data do not help us toward a better understanding of the pathogenic factors leading to this disease as illustrated in a recent review in which half of the patients had, in fact, no detectable underlying disease (39). Pathological descriptions of purulent exudates surrounding the infectious focus suggest a role for polymorphonuclear leukocytes for containment of the disease, whereas limited animal data rather favor an important role of cell-mediated immunity.

VIRAL INFECTIONS

Considering the complexity of the mechanisms involved in viral pathogenesis and clinical expression of the diseases, one has to assume that a great variety of these biological reactions will be modified in cancer patients, modulating, in turn, the clinical picture, the incidence and the severity of these infectious diseases. It

can thus be assumed that the deep cellular changes induced by malignancies or by anticancer or immunosuppressive therapy will influence the kinetics of association/dissociation of potentially pathogenic viruses with their host cells as well as their intimate intracellular interrelations.

In addition to the usual and well-known mechanisms of host defense against viral infections which imply various interplays between humoral and cellular immunity, two important antiviral mechanisms should be recalled to the clinician. First of all, as recently reemphasized, viruses can be inactivated by an antibody- and/or complement-dependent neutralization reaction, as are bacteria, without involvement of effector leukocytes. Specific antiviral antibodies can, after binding, directly inactivate viral infectivity by interfering with adherence of the virion to a susceptible cell, by interfering with penetration or uncoating, by degrading antibody-coated viral particles in lysosomes, by agglutinating the virus particles, thereby decreasing the number of infectious units, or by triggering the complement cascade (5). Recent studies have also suggested that complement itself, without the help of specific antibodies, can neutralize viruses, admittedly with less efficiency.

Antibody–complement-mediated virus neutralization does not necessarily lead to the lysis of the virion but can inactivate viral infectivity by other means as previously described. Viruses that can be neutralized without lysis by this mechanism include, among others, HSV and lymphotytic choriomeningitis virus. Immune virolysis, i.e., lysis of enveloped viruses with antibody and complement, has been shown to occur for myxoviruses and paramyxoviruses (5). Thus, hematogenous or lymphogenic spread of virions will encounter on its way very effective cell-free defense mechanisms that might prevent new associations of the viral particles with various target organs. Second, it should be remembered that although it is customary to consider the polymorphonuclear neutrophil as an effector cell primarily involved in antibacterial as well as anti-yeast defense, recent evidence points towards a nonnegligible role of this cell in modulating viral infections: thus, neutrophils have been shown to phagocytize opsonized viral particles, to act as effector cells in antibody-dependent cell cytotoxicity, to prevent, in conjunction with specific antibodies, viral dissemination in cell monolayers, and to release subcellular mediators of viral infections, possibly distinct from type I and type II interferons (44).

Herpes Simplex

It is presently generally accepted that after primary infection, latent HSV virions reside in nerve ganglia which serve as reservoirs. Experimentally, various stimuli including pneumococcal disease can reactivate dormant viruses (52). Possible defense mechanisms against reactivation or dissemination include interferon production, various macrophage functions, antibodies, and lymphocyte subtype activities, to name but a few.

Unfortunately, these various parameters are often difficult to test independently. Interferons are undoubtedly produced and liberated during infection and recurrence, but their role in controlling HSV disease is still not proven. Although tissue culture