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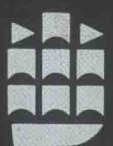
CT OF THE IMMUNOCOMPROMISED HOST

Edited by
Janet E. Kuhlman, M.D.



CHURCHILL LIVINGSTONE

CT of the Immunocompromised Host

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To my co-workers –
Bea, Nancy, Cindy, Vicki, Maryanna, and Maureen.
With intelligence, dedication, and good humor,
they manage the front lines and care for our patients.

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Preface

We live in an increasingly complex and daunting world. The problems of the immunocompromised host are no longer the domain of academicians in large teaching institutions; the specter of AIDS has spread these problems to every community hospital and private physician's office. Organ transplantation, once considered a novelty, is now routine at many institutions across the country. We no longer talk only of kidney transplantation, but also of heart, lung, liver, pancreas, and multi-organ transplantation. Newer, more effective drugs that suppress rejection also suppress the natural immune response. The medical assault on leukemia, lymphoma, and solid organ cancers involves increasingly potent chemotherapies, sophisticated radiation planning, bone marrow transplantation, and targeted radiolabeled antibodies. The aggressively treated cancer patient is equally likely to succumb to a complication of treatment as to die from the cancer itself.

Thus it seemed appropriate at this time to devote a volume in this series to the radiology of the immunocompromised host, emphasizing diagnostic considerations and problem solving techniques. We are pleased to include material from a group of individuals who are actively involved in evaluating immunocompromised patients: Judith E. Karp of the Adult Leukemia Program of The Johns Hopkins Oncology Center, David Yousem of the Neuroradiology Section of the Hospital of the University of Pennsylvania, Elliot K. Fishman of the Division of Computed Body Tomography, and Donna Magid of the Division of Orthopaedic and Skeletal Radiology of The Johns Hopkins Hospital.

Janet E. Kuhlman, M. D.

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1 Dilemmas in the Immunocompromised Host: A Clinical Overview

JUDITH E. KARP

In the homeostatic state, organ integrity is preserved by intact structural barriers and protected by a number of systemic surveillance mechanisms that can eradicate or sequester invasive microorganisms and infiltrative cells that might impair overall organ function. When structural barriers are interrupted or when humoral or cellular surveillance become inadequate to provide such protection, organ integrity is sacrificed and the host is at risk for organ invasion. It is this loss of protection and consequent loss of integrity for multiple organ systems that characterizes the *compromised host*.

TYPES OF COMPROMISED HOSTS

In terms of systemic defects, there are two types of compromised hosts: one is the immunocompromised patient with quantitative or qualitative defects in lymphoid function, as in acquired immunodeficiency syndrome (AIDS), lymphoproliferative malignancies including lymphoma or multiple myeloma, or immunosuppressive drugs; the other is the granulocytopenic patient with bone marrow failure resulting from primary hematopoietic malignancies such as acute leukemia and/or from myelodestructive cytotoxic chemotherapy. These compromised states, whether primary or drug-induced, translate into systemic defects with varying degrees of tissue infiltrates, mucosal disruption, and barrier breakdown; the net result is major organ dysfunction and a propensity for overwhelming infection.

In fact, infection with either common or unusual (*opportunistic*) organisms is the hallmark of the compromised host. The specific organisms causing infection and the clinical presentations of these infections depend to a large extent on the type of underlying defect (lymphoid or granulocytic) and whether the overall compromised condition is the result of only one factor (e.g., primary

disease) or a combination of factors (disease plus cytotoxic therapy). For example, while *Pneumocystis carinii* is a common pathogen in AIDS patients or those with lymphoid dysfunction owing to immunosuppressive therapies (steroids, cyclosporine) or diseases (lymphoma, graft versus host disease), it is unusual in patients with acute myelogenous leukemia (AML) who are deeply granulocytopenic but are not intrinsically immunocompromised. On the other hand, the patient with AML who is receiving cytotoxic chemotherapy that induces profound bone marrow aplasia and damages the gastrointestinal (GI) mucosa, where GI barriers may already be mechanically disrupted by leukemic infiltrates, is especially prone to overwhelming infection by aerobic gram-negative bacteria such as *Pseudomonas aeruginosa* from the damaged GI tract. Fungal and viral pathogens affect all of these compromised hosts; however, the specific organ involvement and extent of local or disseminated organ destruction ultimately relate to whether the underlying defect is finite (as in chemotherapy-induced granulocytopenia) or continuing without clear endpoint of resolution (severe graft versus host disease, AIDS).

Detection of Infection

The key to successful eradication or suppression of active infection in the host with impaired defenses is early detection and prompt intervention with specific organism-directed antibiotics. Unfortunately, such infections, for a number of reasons, evade attempts at early detection and present a diagnostic challenge. The absence or impairment of a localizing inflammatory response, particularly in the granulocytopenic host, often mutes localizing tissue-specific physical signs, making clinical findings characteristically nonspecific early in the course of infection.

Invasive procedures to establish definitively the diagnosis of deep tissue involvement are often contraindicated in patients with deep marrow aplasia, and the significance of positive microbiologic cultures obtained noninvasively from respiratory, GI, or urinary tract with respect to colonization versus definitive infection is controversial, particularly with respect to fungal pathogens. Furthermore, invasive procedures may have a low yield in the face of deep granulocytopenia, where the absence of a localizing infiltrate that would otherwise highlight an infected area can result in erroneous sampling of unaffected tissue. Moreover, there is a lack of rapid non-invasive diagnostic tests that can specifically identify causative pathogens; this is especially the case with fungal and viral infections. Tests aimed at early detection of specific fungal (*Candida* or *Aspergillus*) or viral (cytomegalovirus) antigens or antibodies have yielded inconsistent results in these compromised hosts. Additionally, both fungal and viral pathogens may be fastidious, and they may not be detected or identified for a substantial time after diagnostic specimens are obtained for culture.

In the granulocytopenic host, the dilemma is most clearly demonstrated for

diagnosis and treatment of fungal infections, in part because of the difficulties in rapid identification of the infectious culprit and in part because of the need for aggressive intervention with the moderately toxic antifungal agent amphotericin-B. Early detection leading to prompt therapeutic intervention in this host population is critical to survival; while granulocyte recovery is the major factor in ultimate control of active fungal disease, aggressive antifungal antibiotic therapy achieves fungal stasis and disease containment until host defenses return. It is in this setting that the role of non-invasive CT has been clearly demonstrated, particularly for invasive pulmonary aspergillosis (IPA), where early presumptive diagnosis and rapid institution of aggressive antifungal therapy has led to enhanced survival.

At our institution, the ability to recognize or confirm the clinical suspicion of IPA in its initial stages, when clinical clues may be subtle and before extensive lung destruction ensues, has led to early implementation of high dose amphotericin-B. Despite profound (less than $100/mm^3$) and prolonged (at least 30 days) granulocytopenia, this approach has resulted in at least 80 percent survival from an infection occurring in a clinical milieu that has previously defied attempts at antemortem documentation and curative therapy. In this clinical setting, CT provides a noninvasive method for establishing or substantiating the early diagnosis of IPA, often at a time when radiographic chest film findings are nonspecific, fungal cultures remain negative, and biopsy procedures are prohibited by thrombocytopenia. The lesions seen on CT evolve characteristically from initial infection with early invasion of small vessels and focal tissue infarction, to cavitation when granulocytes return and begin the healing process by migrating into infected sites, to fibrosis when both infectious and inflammatory activities have resolved. Thus, CT assessment of IPA and other fungal pneumonias has become important at all stages of the disease process, including the monitoring for potential reactivation during repeat cycles of intensive chemotherapy. Based on our initial studies, we now routinely employ serial lung CT as part of our assessment of the acute leukemia patient throughout marrow aplasia and use the findings to help guide specific antifungal therapy during the period of major risk. CT has made a significant impact on both the diagnosis and the antibiotic management of fungal pneumonia and has contributed to the increasing survival from this complication of profound chemotherapy-induced bone marrow suppression.

CT has also made an impact on rapid, noninvasive diagnosis and subsequent management in the detection of foci of occult malignancy. CT's high resolution is particularly useful to document the presence and magnitude of metastatic involvement in areas where small foci of disease might easily be missed by more conventional radiographic techniques, as in the retroperitoneum. The ability to define such lesions may either abrogate the need for surgical intervention or may provide the surgeon with anatomic localization that improves the diagnostic yield. Further, with the ability to positively detect or definitively exclude the presence of residual malignant disease, the need for antitumor therapy can be determined and the response to that therapy can be monitored

noninvasively. The ease of obtaining rapid CT documentation may therefore facilitate therapeutic decision-making in a fashion similar to CT's role in the management of infections in the compromised host.

SUMMARY

The ability to detect organ disruption by infiltrative pathology, be it infectious or neoplastic, translates into the ability to institute appropriate therapeutic maneuvers. The potential for rapid diagnosis is especially important in the compromised host, where endogenous defenses are so impaired that the host can be overwhelmed by invasive pathogens unless therapy is implemented quickly and aggressively. CT provides a rapid, easily obtainable, noninvasive modality with high resolution and enhanced sensitivity over conventional radiography.

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2 Opportunistic Fungal Infection: The Neutropenic Patient with Leukemia, Lymphoma, or Bone Marrow Transplantation

JANET E. KUHLMAN

Patients with acute leukemia, lymphoma, or bone marrow transplantation undergoing prolonged periods of absolute granulocytopenia are at high risk for developing opportunistic lung infections, particularly invasive fungal disease.[1, 2] Prognosis in this setting is poor and mortality rates are high, ranging from 65 to 70 percent in some series.[1–3] Early recognition of opportunistic chest infection is imperative in these patients and may improve survival.[1, 4] Early detection and diagnosis, however, is often difficult.[5] Sputum cultures are frequently negative early in the course of infection. Initial chest film findings are often subtle or nonspecific. Invasive biopsy procedures, which might provide a definitive diagnosis, are often prohibited by the patient's compromised respiratory status or deficient coagulation parameters. Although broad spectrum antibiotics have dramatically decreased the morbidity and mortality from bacterial infection in these patients, empiric treatment of invasive fungal disease with antifungal drugs is not without complications; amphotericin B carries the substantial risk of nephrotoxicity. Thus, substantiating evidence supporting a clinical suspicion of invasive fungal infection is highly desired before embarking upon a course of empiric high-dose antifungal therapy.

In this clinical setting, CT has become an important noninvasive tool for evaluating the aplastic or otherwise immunosuppressed patient at risk for opportunistic fungal disease.[6–9] Early detection of invasive fungal disease and improved survival can be achieved through the use of early CT examination and prompt institution of high-dose antifungal therapy.[9] CT surveillance in these patients[7–9]

1. Contributes to early identification and diagnosis of invasive fungal infections
2. Further characterizes nonspecific pulmonary infiltrates demonstrated on conventional radiographs
3. Effectively monitors disease activity, documenting progression or resolution in response to therapy
4. Quickly detects reactivation of fungal disease during subsequent cycles of chemotherapy or exposure to immunosuppressive drugs

TECHNIQUE

All patients with acute leukemia, lymphoma, or bone marrow transplantation at risk for opportunistic lung infection are examined using a modified high-resolution CT protocol consisting of 2- or 4-mm thick scan slices obtained at 1-cm intervals from the lung apex to the diaphragm. CT examinations are performed on a Somatom DR3 or DRH (4 sec, 310 mAs, 125 kVp) or a PLUS scanner (1 sec, 260 mAs, 137 kVp) (Siemens, Iselin, NJ). A special high-resolution algorithm that enhances edge detection is routinely employed to detect subtle, early parenchymal or interstitial disease and to better characterize morphology. When invasive fungal disease is a consideration, additional scans are obtained through the liver and spleen, a common site for dissemination. Complete evaluation includes assessment of each scan at both lung window (window width 1450, window center −540) and mediastinal window (window width 421, window center 21) settings. Oral and intravenous contrast are not routinely used unless mediastinal involvement is suspected.

CT examination of the chest can be performed in as little as 10 minutes and requires no special patient preparation or positioning. Because many immunocompromised and febrile patients are acutely short of breath or on respiratory ventilators, one-second and subsecond CT scanning times available on state-of-the-art scanners allow for high quality lung examination without breath holding or significant degradation from respiratory motion.

CT DETECTION AND DIAGNOSIS OF INVASIVE FUNGAL DISEASE

Disseminated candidiasis and invasive pulmonary aspergillosis are the two most common opportunistic fungal infections to affect the profoundly neutropenic host with acute leukemia, lymphoma, or bone marrow transplantation. The CT features of invasive pulmonary aspergillosis are characteristic and easily recognized; they can provide a strong presumptive diagnosis of invasive fungal disease early in the course of infection.[6–9]

Early CT signs of invasive pulmonary aspergillosis include the presence of one or more inflammatory nodules and the CT halo sign (Figs. 2-1 and 2-2).[6–8] The CT halo sign consists of a pulmonary nodule surrounded by a peripheral zone or halo of intermediate CT attenuation (Figs. 2-3 and 2-4).[6–8] Nodules demonstrating the CT halo sign appear early in the course of infection, during