Life-Threatening Infection in an Older Man with Leukemia

Stenographic reports of weekly clinicopathologic conferences held in Barnes and Wohl Hospitals are published in each issue of the *Journal*. Members of the Departments of Internal Medicine, Radiology and Pathology of the Washington University School of Medicine participate jointly in these conferences. Kenneth M. Ludmerer, M.D., and John M. Kissane, M.D., are the editors of this feature.

A 69 year old white man with leukemia entered Barnes Hospital July 18, 1980. He died 22 days later.

Four weeks prior to admission, fatigue, malaise, mild dyspnea, anorexia and weight loss developed. He had no fever, rash, easy bruising or gingival bleeding. He consulted his physician, who found that his white blood cell count was markedly elevated.

The patient, a petroleum geologist, had traveled extensively, including trips to Africa and South America. Two years earlier, he had contracted a self-limited episode of mild diarrhea. At that time, an indirect fluorescent antibody test for schistosomiasis gave positive results, but there was no evidence of eosinophilia, hepatic or pulmonary involvement or parasites in the stool or urine. Cytoscopy, proctoscopy and biopsy of rectal and bladder mucosa revealed no abnormalities. The patient also had a previous history of malaria, hypertension and hyopthyroidism.

Physical examination on admission revealed a temperature of 37.4°C, a heart rate of 72 beats per minute and a blood pressure of 150/70 mm Hg. There was a large bruise on the right thigh but no other skin lesion. The liver could be palpated 3 cm and the spleen 2 cm below the costal margins. The remainder of the examination was unremarkable.

Admission laboratory studies included a hematocrit level of 36 percent, a white blood cell count of 39,100/mm^3 (88 unclassified blast forms, two polymorphonuclear leukocytes, seven mature lymphocytes, three young lymphocytes), a platelet count of 13,000/mm^3 and a reticulocyte count of 0.4 percent. The bone marrow could not be aspirated, but bone marrow biopsy confirmed the diagnosis of leukemia of indeterminable cell type. Sudan black B and alpha-naphthyl butyrate esterase stains gave negative results. The prothrombin time and partial thromboplastin time were normal. Except for a potassium level of 2.5 meq/liter, the serum electrolyte values were normal. The blood urea nitrogen was 18 mg/dl, creatinine 1.5 mg/dl, total bilirubin 0.7 mg/dl, uric acid 11.9 mg/dl, glucose 148 mg/dl, alkaline phosphatase 126 mIU/ml, glutamic-oxaloacetic transaminase 82 mIU/ml and lactate dehydrogenase (LDH) 1,800 mIU/ml. The chest x-ray and urinalysis were unremarkable.

On the second hospital day, the patient's temperature rose to 38.6°C. Results of physical examination were unchanged, and blood and urine cultures gave negative results. Two stool samples contained no evidence of parasites. Therapy was initiated with gentamicin, cefazolin, ticarcillin and trimethoprim/sulfamethoxazole, and the temperature returned to normal.

Between the third and 10th hospital days, the patient received a course of vincristine, prednisone, cytarabine, 6-thioguanine and doxorubicin. He also received allopurinol and transfusions of red blood cells and platelets. By the seventh hospital day, the white blood cell count had fallen to 750/mm^3.

On the fifteenth hospital day the patient became lethargic, and a temperature of 39.8°C developed. He complained of nausea, diarrhea and diffuse achiness. The fundi, skin, lungs and heart were normal. There was no abdominal or perirectal tenderness. The white blood cell count was less than 50/mm^3. Examination of the cerebrospinal fluid showed 5 mononuclear cells/mm^3, glucose of 109 mg/dl and protein of 26 mg/dl. Urinalysis revealed 2+ protein, 3 white blood cells/high-power field and no bacteria. The serum creatinine was 1.1 mg/dl, and the chest x-ray was normal. After blood, urine and cerebrospinal fluid culture samples were obtained, amphotericin B was added to the antibiotic regimen.

Two days later, the patient's fever still remained. In addition, a diffuse erythematous papular rash as well as white lesions on the palate had developed. The serum creatinine level had risen to 1.4 mg/dl; a urine culture grew less than 10,000 colonies/ml of yeast.

A procedure was performed.

CLINICAL DISCUSSION

Dr. Stuart Kornfeld: I would like to begin the discussion by considering the problem of classifying this patient's leukemia. The peripheral blood film clearly demonstrated that the predominant cell was a blast and that the patient had some type of acute leukemia. However, the morphologic features of the cells did not permit further classification of the leukemia in terms of acute lymphoblastic leukemia, acute myeloblastic or myelomonoblastic leukemia or acute monoblastic leukemia. Several cytochemical stains were used, all of which gave indeterminate results. Therefore, the patient was considered to have acute leukemia of an undetermined type. This problem with classification occurs often. What has been lacking in this area is the availability of precise reagents that can be used to identify the various types of blood cells. This situation is rapidly changing, and I believe that we are in the midst of a genuine revolution in the area of cell identification and classification. This revolution is occurring because of the development of a technique that allows the generation of large numbers of monoclonal antibodies that can be used as highly specific probes for identifying cells. I have asked Dr. Griffith to tell us about the use of monoclonal antibodies for typing cells and to review the current status of the application of this methodology to leukemia and lymphoma.

Dr. Rogers Griffith: I believe your observations are correct. The problem of classification applies to many malignancies, not just leukemias. In every tumor class, a certain percentage of neoplasms cannot be easily classified because of their primitive appearance. Traditional classifications, based on recognition of morphologic features that define a given cell lineage, have not proved totally satisfactory.

Several years ago, a number of investigators attempted to improve the traditional approach to the classification of acute leukemias by developing heteroantisera to leukemic cells. These antisera were generally obtained in the following way: rabbits would be immunized with leukemic cells, and the resultant antisera would be extensively absorbed against cells of other leukemic subtypes as well as against normal cells, tissue homogenates or established cell lines. The common acute lymphoblastic leukemia antigen, an antigen that defines a large percentage of cases of childhood acute lymphoblastic leukemia (ALL), was discovered using this approach. Heteroantisera-specific antigens associated with other leukemic subtypes and homologous cell lineages—including monocytes/myelocytes, thymocytes, and T and B lymphocytes—were also developed and used to identify and classify leukemic subtypes not readily recognized by the light microscope. One major disadvantage to this approach was that each particular antiserum was essentially unique to the laboratory in which it was developed and in some instances to the very rabbit from which it was produced.

With the advent of somatic cell hybridization, described by Kohler and Milstein in the early 1970s, it became possible to immortalize B lymphocytes that produce antibodies of a desired specificity. This exotic technology, initially limited to a few research laboratories, has now become very commonplace in many research and commercial laboratories. Although at first there was skepticism that a single species of antibody could replace a monospecific, heteroantiserum directed against a molecularly complex cell surface antigen, there was also great hope that this technology could provide unlimited sources of well-characterized, homogeneous reagents for cell surface analysis. What was once hope has apparently become reality. All the surface antigens demonstrated by heteroantisera have now been reportedly demonstrated by monoclonal antisera. Monoclonal antibodies have now been produced

that react with many antigens, among which are the common ALL antigen, the histocompatibility framework antigens (including HLA-DR) and antigens associated with T and B lymphocytes, myelocytes, monocytes, platelets, erythroid cells, and the purported SRBC receptor on T lymphocytes [1].

The system of antigens studied most intensively thus far has been that of the T lymphocyte. Dr. Stuart Schlossman has developed a panel of monoclonal antibodies that defines discrete stages of differentiation of thymocytes; these antibodies also identify two functional compartments of peripheral T cells that appear to be analogous to those of the murine Lyt-defined lymphocytes [2]. These investigators have also identified T-lymphocytic neoplasms that correspond to each stage of differentiation defined by these antibodies [2,3]. It seems probable that as other antigen systems are better defined, heterogeneity will be recognized in other morphologically homogeneous neoplasms.

As I stated earlier, many laboratories interested in differentiation and neoplasms are producing monoclonal antibodies to cell surface structures. Most of the obvious specific antigens now have antibodies targeted directly against them. This progress has come relatively easily. The difficult task now is to sort out the specificities of new antibodies produced, to characterize the antigenic determinants to which they bind and to map the cellular distribution of these determinants. A case in point is one of the antibodies, T9, which initially was thought to be specific for an early stage of thymocyte differentiation. With further testing, it was found to be associated with many types of rapidly proliferating cells, and it is now thought to recognize a non-cell lineage-specific antigen, the transferrin receptor [1].

Monoclonal antibodies, produced in large quantities, can be tested for specificity by many laboratories and in many cell systems. They hold much promise for the future. Potentially, they might be able to characterize stem cell compartments and cell lineage differentiation pathways, to classify more accurately poorly differentiated neoplasms, and, in time, to achieve more specific therapies for malignancies.

Dr. Kornfeld: Thank you. After the diagnosis of acute leukemia was made, a course of chemotherapy consisting of vincristine, prednisone, cytosine arabinoside, 6-thioguanine and doxorubicin was started. This resulted in bone marrow aplasia, but the protocol ends before we know whether or not a complete remission was achieved. Dr. Herzig, could you tell us what the current results have been in the treatment of adult leukemia with this regimen and with similar regimens.

Dr. Geoffry Herzig: This patient was treated with a combination of five drugs, a regimen that has been used for adult acute nonlymphocytic leukemia by Peterson and co-workers [4] at the University of Minnesota with a complete response rate of 82 percent. In view of the difficulty in classifying this patient's leukemia, it should be noted that the regimen also contains agents that are effective against acute lymphoblastic leukemia. The most active single agents are prednisone and vincristine; in childhood acute lymphoblastic leukemia, the combination of the two produces a complete response in approximately 90 percent of cases. In adult lymphoblastic leukemia, vincristine and prednisone are less effective, producing only a 40 to 50 percent rate of complete responses. The addition of a third active drug (L-asparaginase, daunorubicin, doxorubicin or methotrexate) raises the rate of complete response to between 70 and 80 percent. For acute nonlymphocytic leukemia, the first drug found to have substantial activity was cytosine arabinoside, which produced complete responses in as many as 40 to 50 percent of cases. Shortly thereafter daunorubicin, probably the single most active agent in nonlymphocytic leukemia, was introduced. This agent regularly produces a complete response rate of 50 percent when used alone.

Currently, the combination of cytosine arabinoside plus an anthracycline (daunorubicin or doxorubicin) has become the standard therapy for acute nonlymphocytic leukemia, achieving complete responses approximately 70 percent of the time. The addition of other agents as in this case, particularly 6-thioguanine, has led to remission rates in the range of 80 to 85 percent in several small series, although large controlled studies have not yet been done to determine whether a third agent significantly improves the response. Although most adults with acute leukemia can now be expected to achieve a complete remission, the median duration of the remissions is still short, approximately one to two years for acute lymphoblastic leukemia and one to one and a half years for acute nonlymphocytic leukemia.

The most recent approach to the problem of retaining remission has been to give repeated courses of therapy after the initial induction of remission. With this approach, investigators at Roswell Park [5] have reported a small series of patients with a projected 80 percent relapse-free survival at two years. Thus progress is being made both in the proportion of patients that achieve complete remission and in the number that may ultimately be cured. Data from large series of patients treated five to 10 years ago indicate that 20 to 25 percent of complete responders remain continuously free of disease beyond five years [6]. Many of these long survivors may have achieved cure.

Considerable effort has gone to identifying factors present at diagnosis that can predict the response to treatment. Age above 55 to 60 years stood out particularly noticeably as a harbinger of poor response in most older series, but as therapy has improved, age has become less important as a prognostic factor. Indeed,

several recent series using anthracycline-cytosine arabinoside combinations failed to show any clear age-related differences in response rate. The poor response formerly observed in older patients resulted primarily from complications that occurred during the period of marrow aplasia, as happened in the patient today. Paradoxically, the more intensive chemotherapeutic regimens of today may actually reduce the over-all duration of pancytopenia by producing a remission after a single course of therapy. In addition, we have developed better techniques for managing the complications of infection and hemorrhage. For these reasons, older patients with acute nonlymphocytic leukemia can now be treated with the same regimens used for younger patients, provided their general health is otherwise satisfactory. Patients with other serious underlying diseases are still at great risk from chemotherapy and might not receive aggressive treatment. Other factors associated with a poor response to therapy are an antecedent myelodysplastic ("preleukemic") phase and prior chemotherapy or radiation therapy for other malignancies.

Clearly, as we approach the 80 or 85 percent rate of achieving complete remission, the urgency of predicting response to therapy beforehand becomes much less. What now becomes more important is discovering factors that can predict the duration of remission. Such knowledge would enable patients at low risk of relapse to be spared the hazards of intensive therapy during remission, while patients in whom relapse can be expected shortly might be good candidates for investigational approaches, such as allogenic bone marrow transplantation. A recent report from the M. D. Anderson Hospital suggests that factors related to remission duration can be identified [7].

Dr. Kornfeld: Now I would like to consider the infectious complications that apparently occurred in this patient. On the second hospital day, a fever developed. The findings on physical examination were unchanged, and cultures of the blood and urine showed no growth. The patient began receiving antibiotics, and the fever promptly disappeared. I think it is reasonable to assume that the patient had a bacterial infection that could not be localized but that responded to antibiotics. Such infections are very common in patients with acute leukemia, even when the culture results are negative. Subsequently, the chemotherapy was started, and the patient became very leukopenic. On the 15th hospital day, the temperature became very elevated, and the patient complained of nausea, diarrhea and diffuse muscle aching. The physical examination was unremarkable at that time, but two days later a diffuse erythematous papular rash appeared. In addition, white palatal lesions were noted. Dr. Varki, would you discuss the kinds of infectious agents that should be considered under these circumstances and tell us which of these you think is most likely to be present in this case.

Dr. Ajit Varki: I will first review the causes of infection in the general category of immunocompromised hosts, and then consider the situation in this particular patient. A recent series from the Memorial-Sloan Kettering Institute [8] reported 148 clinical isolates from blood in patients with leukemias, lymphomas and multiple myeloma. Gram-negative enteric organisms, especially Escherichia coli, Pseudomonas and Klebsiella species, were far and away the most common offenders, followed by *Staphylococcus aureus*. Polymicrobial sepsis also occurred frequently. However, it was noted that as the duration of hospitalization lengthened, the percentage of fungal infections increased strikingly [8]. As Dr. Kornfeld pointed out, this patient had already had one episode of fever. This fever responded promptly to empiric antibiotic therapy, suggesting a bacterial infection, despite the negative culture results. The second episode of fever occurred after two weeks of hospitalization in the face of continued antibiotic therapy. This situation strongly suggests a fungal superinfection. Parenthetically, I should point out one of the other significant conclusions of the study that I just mentioned. During a period of prospective follow-up, it was found that one of the major factors that helped to reduce mortality was consultation with a specialist in infectious diseases [8]. I think this serves to underline how complex such situations are as well as the need for optimal evaluation and management.

To return to the patient, before pursuing the question of fungal infections further, let us mention some other less likely possibilities. We will do this keeping in mind the caveat that although uncommon manifestations of common diseases occur more often than common manifestations of uncommon diseases, exceptions to the rule always exist in clinical medicine. The patient was a big-game hunter who had been exposed to schistosomiasis in Africa. Schistosomiasis is estimated to affect about 200,000,000 people, or one in 20 of the world's population. Although there are 400,000 cases in the continental United States, the lack of the appropriate snail vector precludes transmission in this country [9]. The acute manifestations of schistosomiasis include a dermatitis called "swimmers' itch," which occurs at the point of cercarial penetration, and "Katayama disease," in which fever and lymphadenopathy are caused by the sudden entry of a large worm burden. However, the late manifestations of schistosomiasis—the only ones of concern in this patient—are the consequence of a granulomatous fibrosis that occurs in the portal, mesenteric or vesical venous plexuses [9]. It is very unlikely, therefore, that the cause of the patient's acute symptoms is schistosomiasis. Although the patient gave a distant history of malaria, the con-

TABLE I Disseminated Candidiasis in Hematologic Malignancies

	Wingard et al. [10] (14 cases)	Kressel et al. [11] (5 cases)	Jarowski et al. [12] (2 cases)
Fever	14	5	2
Generalized rash	8	5	2
Myalgias	3	5	2
Gastrointestinal symptoms	8	?	1
Positive culture/histologic results			
Blood	13/14	4/5	1/2
Urine	12/14	4/5	1/2
Skin	3/4	0/2	1/2
Muscle	N.D.	N.D.	2/2
Days to positive blood/urine cultures	?	9–14	7

N.D. = not done.

tinuous nonremittent nature of the fever, the lack of chills and sweats, and the negative blood smears make this diagnosis very unlikely as well. Viral infections such as cytomegalovirus are also unlikely in view of the normal liver function results and the clear chest x-ray.

The major fungal infections to be considered include candidiasis, aspergillosis, mucormycosis [8] and, in this part of the country, histoplasmosis. The latter three very frequently involve the lungs. The recent literature suggests that the triad of fever, rash and myalgias (which this patient had) is a relatively common manifestation of disseminated candidiasis in hematologic malignancies [10–12]. (Table I). Blood and urine cultures often give positive results, but they invariably do so only after an interval of more than a week. For this reason, skin and muscle biopsy specimens (for direct visualization of the organism) have been used in an attempt to obtain a more rapid diagnosis. Although the numbers of patients studied are small, the available information suggests that this approach may often be successful (Table I). I should emphasize, however, that this form of infection with Candida is very distinct from the more common syndrome of disseminated candidiasis, consisting of endocarditis and its embolic consequences. This latter form occurs in a different subset of patients, persons who are not usually immunocompromised, such as patients with prosthetic cardiac valves or who are receiving hyperalimentation [13].

Finally, it is possible to proceed further with the analysis and predict the subspecies of Candida that was responsible for the illness in this patient. In a large series consisting of all types of patients with candidiasis, the most common blood isolate was Candida albicans [13]. However, the majority of these patients were not immunocompromised and had the syndrome of Candida endocarditis. In contrast, another study examined colonization and infection with Candida species in 89 consecutive patients undergoing treatment for hematologic malignancies [10]. When prospectively studied, 85 of these patients were found to be colonized with Candida prior to treatment—60 with C. albicans and 25 with C. tropicalis. However, more than 80 percent of the cases of disseminated systemic candidiasis, which occurred in 17 of these patients, were caused by C. tropicalis. The reasons for this striking association, which is borne out in other series [11,12], are not clear.

Dr. Kornfeld: Thank you. Dr. Medoff, do you agree that the most likely diagnosis in this patient is disseminated fungal infection, with the organism probably being Candida?

Dr. Gerald Medoff: Yes, I agree with the analysis presented by Dr. Varki.

Dr. Kornfeld: Dr. Medoff, what is the best method for making the diagnosis of disseminated candidiasis?

Dr. Medoff: The best way to make a diagnosis of candidiasis is to isolate the organism from body fluid or tissue. Unfortunately, in the case of candidiasis, the blood culture frequently gives negative results. I think the most recent data from our bacteriology laboratory is that about 70 to 80 percent of patients with documented disseminated Candida infections will have positive blood cultures. As a comparison, for aspergillosis infections, the level of positive blood cultures is less than 10 percent.

Dr. Kornfeld: According to the patient's chart, a Candida complement fixation titer of less than 1:8 was obtained. Are the serologic findings useful in cases like this?

Dr. Medoff: Serologic study has been touted as useful in making a diagnosis of candidiasis, particularly when serial blood specimens are available. However, I have not found the results particularly useful, and the litera-

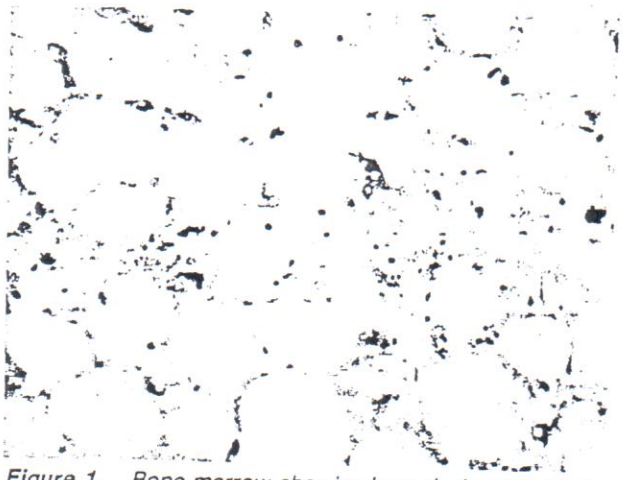

Figure 1. Bone marrow showing hypoplasia and fatty replacement (H & E; original magnification X 400, reduced by 15 percent).

Figure 2. Silver-stained lung demonstrates the free yeasts and pseudohyphae with chlamydospores of C. tropicalis (original magnification X 400, reduced by 15 percent).

ture suggests they have a less than desirable level of sensitivity and specificity [14]. More recently, several investigators have been trying to identify fungal antigens circulating in blood or body fluids that are specific for such infections using high-pressure liquid chromatography or radioimmunoassays [15,16]. It is really too early to evaluate these new techniques at the present time.

Dr. Kornfeld: It has been reported that biopsy of skin or muscle is very useful for making the diagnosis of disseminated candidiasis. Has that been the experience here at Barnes Hospital?

Dr. Medoff: I think so. If there is a lesion from which a biopsy specimen can easily be obtained, biopsy should be performed.

Dr. Kornfeld: When the patient had his second episode of fever, the physicians taking care of him suspected that he might have a disseminated fungal infection, and therefore he began receiving amphotericin B even though an etiologic agent had not been identified. Dr. Medoff, should one start antifungal therapy in the granulocytopenic, immunosuppressed patient in whom you suspect a fungal infection when the definitive diagnosis is lacking?

Dr. Medoff: I believe that it is frequently necessary to treat these patients empirically with a variety of antibiotics, including amphotericin B.

Dr. Kornfeld: In the past few years, several new drugs have become available for treating fungal infections, and new ways of using these agents have been developed. Dr. Medoff, could you tell us about these new agents and give us your opinion concerning the optimal way to treat disseminated candidiasis.

Dr. Medoff: I believe that the treatment of choice for most systemic fungal infections is still amphotericin B. In this particular patient, the differentiation between C. albicans and C. tropicalis is more than just of academic interest. There have been several reports of isolates of Candida resistant to amphotericin B, and most of these have been of the non-albicans species [17]. Since these have been sensitive to miconazole, it should be used in this clinical situation. Depending on the experience in your own institution, miconazole may be the first-line agent in the type of patient under discussion today. Experience with the oral imidazole has been too limited to recommend it for use at the present time, and I do not believe 5-fluorocytosine should be used alone. It is most effective when used in combination with amphotericin B [18].

Dr. Kornfeld: We now come to the final diagnosis. I believe the patient had acute leukemia that was complicated by the development of an opportunistic infection, which was most likely disseminated candidiasis. I think that the procedure performed was a biopsy of either the skin or the muscle. Since the triad of fever, rash and muscle tenderness occurs most commonly with disseminated candidiasis due to *C. tropicalis*, I suspect that this organism was found in the biopsy specimen.

PATHOLOGIC DISCUSSION

Dr. Richard Lynch: The skin biopsy specimen did show Candida, and a blood culture grew C. tropicalis. At autopsy, the bone marrow was markedly hypoplastic and also showed a tremendous depletion of the lymphoid tissues (**Figure 1**). Both these findings reflected the anti-leukemic therapy.

'his patient's infection with C. tropicalis was dis-ɔninated, with prominent involvement of the lungs, ıyocardium, bowel, kidneys, liver, brain, skin and ɔleen. These organisms grew from most tissues in an xtremely luxurious fashion. Both lungs showed total onsolidation with the agranulocytic type of pneumonia 'pical of opportunistic infections in patients with severe one marrow suppression and leukopenia (**Figure 2**).

Although not the immediate focus of this case, the ungs also had areas of old granulomatous inflammation, ome of which contained identifiable schistosomes.

In summary, this patient had severe marrow and lymphoid depletion that led to systemic infection with C. tropicalis and visceral hemorrhage.

Final pathologic diagnosis: Severe hypoplasia of the bone marrow and lymphoid tissues; disseminated C. tropicalis with bilateral pneumonia, enteritis and myocardial abscesses, and colonization of the kidney, spleen, brain, skin, liver and pancreas; diffuse hemorrhagic gastritis and cystitis; subcapsular splenic infarct, recent; and pulmonary schistosomiasis, old.

REFERENCES

1. Knopp W, ed: Proceedings of the leukemia marker conference. New York: Academic Press, 1981.
2. Reinberg EL, Kung PC, Goldstein G, Levey R, Schlossman S: Discrete stages of human intrathymic differentiation: analysis of normal thymocytes and leukemic lymphoblasts of T-cell lineage. Proc Natl Acad Sci USA 1980; 77: 1588–1592.
3. Kung PC, Berger CL, Goldstein G, LoGerfo P, Edelson RL: Cutaneous T-cell lymphoma: characterization by monoclonal antibodies. Blood 1981; 57: 261–266.
4. Peterson B, Bloomfield C, Bosl G, Gibbs G, Malloy M: Intensive five-drug combination chemotherapy for adult acute non-lymphocyte leukemia. Cancer 1980; 46: 663–668.

   Preisler H, Browman G, Henderson E, Hryniuk W, Freeman A: Treatment of acute myelocytic leukemia: effects of early intensive consolidation (abstr). Proc Am Soc Clin Oncol 1980; 21: 443.
6. Bloomfield C: Treatment of adult acute non-lymphocytic leukemia. Ann Intern Med 1980; 93: 133–135.
7. Keating MJ, Smith TL, Gehan EA, et al.: Factors related to length of complete remission in adult acute leukemia. Cancer 1980; 45: 2017–2029.
8. Singer C, Kaplan MH, Armstrong D: Bacteremia and fungemia complicating neoplastic disease. Am J Med 1977; 62: 731.
9. Mahmoud AA: Schistosomiasis. N Engl J Med 1977; 297: 1329.
10. Wingard JR, Merz WG, Saral R: Candida tropicalis—a major pathogen in immunocompromised patients. Ann Intern Med 1979; 91: 539.
11. Kressel B, Szewczyk C, Tuazon CU: Early clinical recognition of disseminated candidiasis by muscle and skin biopsy. Arch Intern Med 1978; 138: 429.
12. Jarowski CI, Fialk MA, Murray H, et al.: Fever, rash, and muscle tenderness—a distinctive clinical presentation of disseminated candidiasis. Arch Intern Med 1978; 138: 544.
13. Klein JJ, Watanakunakorn C: Hospital-acquired fungemia. Its natural course and clinical significance. Am J Med 1979; 67: 51.
14. Guinan ME, Portos MR, Hill HR: The candida precipitin test in an immunosuppressed population. Cancer 1979; 43: 299–302.
15. Miller G, Witwer M, Braude A, Davis C: Rapid identification of Candida albicans septicemia in man by gas-liquid chromatography. J Clin Invest 1974; 54: 1235–1240.
16. Weiner MH, Coats-Stephen M: Immunodiagnosis of systemic aspergillosis. J Lab Clin Med 1979; 93: 111–119.
17. Pappagianis D, Collins MS, Hector R, Remington J: Development of resistance to amphotericin B in Candida lusitaniae infecting a human. Antimicrob Agents Chemother 1979; 16: 123–126.
18. Medoff G, Kobayashi G: Strategies in the treatment of systemic fungal infections. N Engl J Med 1980; 302: 145–155.

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