

chemicals as causes of bronchial reactions in the workplace.

## REFERENCES

1. Hagmar L, Bellander T, Eng M, Bergoo B, Simonsson BG. Piperazine-induced occupational asthma. *J Occup Med* 1982;24:193-7.
2. Malo JL, Bernstein IL. Other chemical substances causing occupational asthma. In: Bernstein IL, Malo JL, Yeung MC, Bernstein DI, eds. *Asthma in the workplace*. New York: Marcell Dekker Inc, 1993:481-502.
3. Bernstein IL. Allergic reactions: other addition products. In: Weiner M and Bernstein IL eds. *Adverse Reactions to Drug Formulation agents*. New York: Marcell Dekker Inc, 1989;291-3.
4. Zhang YG, Wright WJ, Tam WK, Nguyen-Dang TH, Salome CM, Woolcock AJ. Effect of inhaled preservatives on asthmatic subjects. II. Benzalkonium chloride. *Am Rev Respir Dis* 1990;141:1405-8.
5. Sly RM. Effect of inhaled preservatives on asthmatic subjects: II. Benzalkonium chloride. *Am Rev Respir Dis* 1990;142:1466-7.

# Fatal pulmonary nocardiosis in a patient with chronic mucocutaneous candidiasis

Joram S. Seggev, MD Las Vegas, Nev.

Chronic mucocutaneous candidiasis (CMC) consists of infection of the skin, nails, oral cavity, and esophagus, most commonly with *Candida albicans*, and is associated with various immunologic defects.<sup>1, 2</sup> Severe non-candidal infections, as a major complication of CMC, have not been well documented until recently.<sup>2, 3</sup> The present case is a report of a patient with unusual features, who eventually succumbed to overwhelming *Nocardia* infection 10 months after an apparent cure.

## CASE REPORT

A 20-year-old man, diagnosed with CMC at 22 months of age, was admitted to the University of Missouri-Columbia Health Sciences Center for treatment of *Nocardia* pneumonia. At the age of 5 years, he was reported to be euthyroid and to have partially responded to administration of transfer factor.<sup>4</sup> Hypothyroidism was diagnosed at age 12, requiring daily administration of thyroxine. One year later, administration of ketoconazole was started. Throughout child-

### Abbreviations used

ALP: Alkaline phosphatase  
CMC: Chronic mucocutaneous candidiasis  
IL-2: Interleukin 2

hood and adolescence, he experienced recurrent upper respiratory tract infections and pneumonia.

Physical examination at the time of admission was remarkable for cachexia, hypopigmented areas on the hands and arms, clubbing, dystrophic nail changes, and white patches on the tongue and throughout the oral cavity and pharynx. The chest was clear. Pertinent laboratory data included microcytic, hypochromic anemia, elevated alkaline phosphatase (ALP) and alkaline phosphatase  $\gamma$ -glutamyl transferase levels, normal parathyroid hormone and cortisol levels, and a negative ELISA result for human immunodeficiency virus. An esophagogram was interpreted as showing evidence of candidal esophagitis, and a chest roentgenogram revealed a non-homogeneous infiltrate in the left lower lobe. Treatment was started with sulfadiazine 3 gm/day, which led to elevation of ALP to greater than 3000 U/ml; thus, minocycline was substituted. One month later, increasing candidal lesions and bilateral maxillary sinusitis required inpatient therapy with amphotericin B and cefazolin. After discharge, minocycline and alternate-day ketoconazole administration (daily administration led to increases in ALP) were continued. Because the patient's sinusitis was uncontrolled, a Caldwell-Luc operation was required. Minocycline was discontinued after 1 year, when chest roentgenograms were normal. Ketoconazole eventually became ineffective in controlling his candidiasis, and treatment was changed to alternate-day admin-

From the Allergy and Clinical Immunology Section, Department of Internal Medicine, University of Nevada School of Medicine, Las Vegas.

Received for publication Jun. 24, 1993; accepted Sept. 23, 1993.

Reprint requests: Joram S. Seggev, MD, Chief, Allergy/Clinical Immunology Section, Department of Internal Medicine, University of Nevada School of Medicine, 2040 West Charleston Blvd., Suite 503, Las Vegas, NV 89102.

J ALLERGY CLIN IMMUNOL 1994;94:259-62.

Copyright © 1994 by Mosby-Year Book, Inc.

0091-6749/94 \$3.00 + 0 1/1/52649

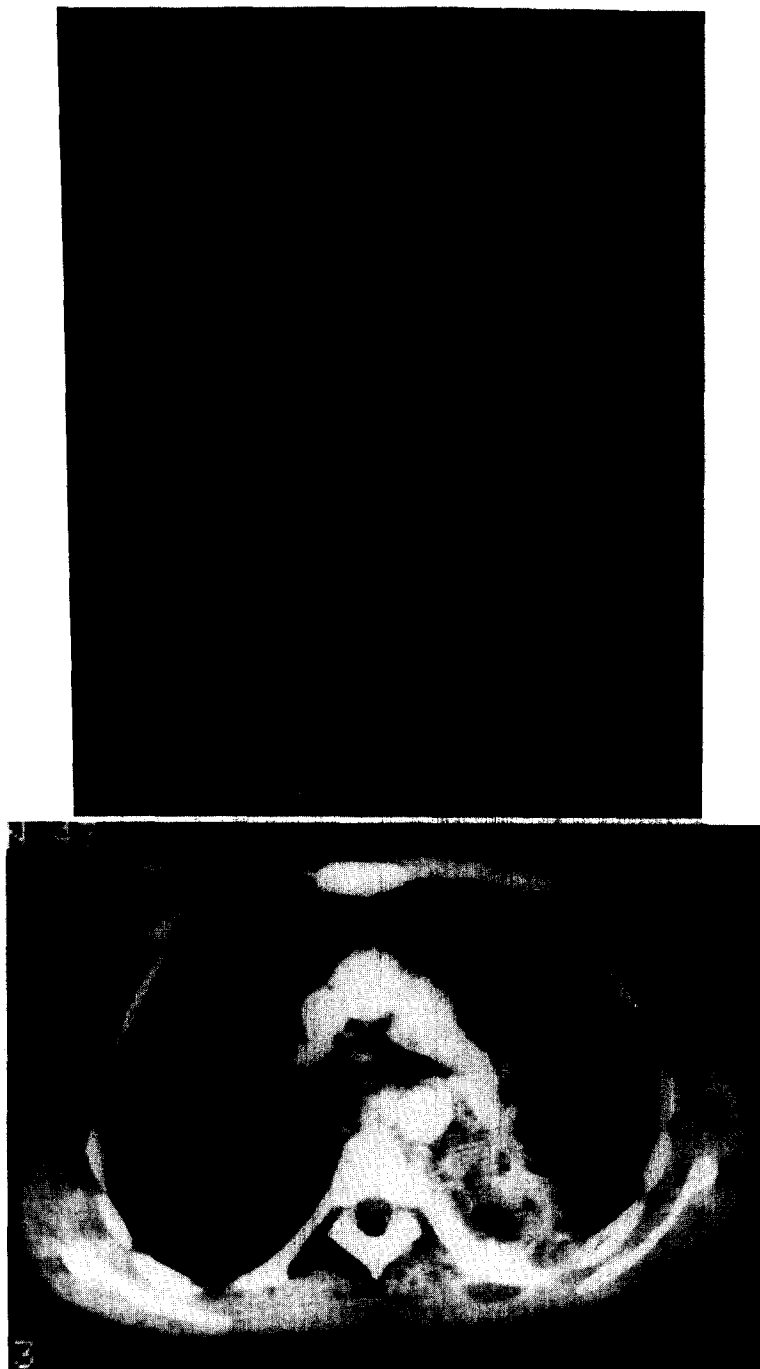


**FIG. 1.** **A,** Chest roentgenogram showing a nonhomogeneous infiltrate in the superior segment of the left lower lobe and destruction of the seventh rib posteriorly. **B,** Computed tomogram of the chest (mediastinal window) showing a nonhomogeneous infiltrate in the superior segment of the left upper lobe, extension into the mediastinum, involvement of the rib, and extension to the chest wall, with abscess formation.

istration of itraconazole, because he could not tolerate daily administration. Seventeen months after the initial admission, he was readmitted with a 1-month history of fever and left shoulder pain. Physical examination re-

vealed a  $5 \times 7$  cm fluctuant nodule above the left scapula, an extension through the chest wall of *Nocardia* infection from the superior segment of the left lower lobe (Fig. 1). During the next  $4\frac{1}{2}$  months, the infection

spread, in spite of intravenous administration of doxycycline, amikacin, and sulfa; two surgical drainage procedures; and nutritional support. The patient died before therapy with transfer factor could be initiated.

## IMMUNOLOGIC EVALUATION

### Humoral immunity

Immunoglobulins (including IgG subclasses), complement, and hemagglutinins and responses to tetanus toxoid, pneumococcal, and *Hemophilus influenzae* type B vaccines, were normal.

### Cellular immunity

Delayed-type hypersensitivity skin tests showed 5 mm induration in response to tetanus toxoid and negative responses to purified protein derivative of *Mycobacteria*, *Trichophyton* species, *Candida* species, histoplasmin, and mumps.

Normal numbers of lymphocytes and subsets were demonstrated by a fluorescein-activated cell sorter, as were normal numbers of CD11b/18 and CD58 receptors on neutrophils and lymphocytes and normal numbers of CD11c receptors on neutrophils. Thymidine incorporation during lymphocyte transformation to phytohemagglutinin, concanavalin A, and pokeweed mitogen was 50% of three controls. Interleukin-2 (IL-2) production was normal in response to pokeweed mitogen, but 25% of control in response to phytohemagglutinin and concanavalin A. Lymphocyte transformation in response to *Candida* species, tetanus, and purified protein derivative of *Mycobacteria* was normal. Mixed lymphocyte reaction to lymphocytes of two of three donors was normal, but no IL-2 was produced. Nitroblue tetrazolium reduction by neutrophils was 50% to 64% (4 determinations [control of 98%]). Normal oxidative metabolic burst was determined with a fluorescein-activated cell sorter, and results of chemotactic and bactericidal assays were normal.

## DISCUSSION

In two series of 101 patients with CMC, 9 had hypothyroidism, 27 had hypoadrenalism, and 15 had hypoparathyroidism. Endocrine dysfunction usually occurred at an earlier age than in our patient.<sup>1-3</sup> Treatment with ketoconazole failed in our patient, although there was no evidence of dermatophyte infection, and the patient was not taking antacids or H<sub>2</sub> blockers,<sup>1-2</sup> suggesting development of resistance of *Candida* organisms to the drug. Interestingly, ketoconazole, itraconazole, and sulfa caused predictable increases in

ALP and  $\gamma$ -glutamyl transferase levels without an increase in transaminases.<sup>5</sup>

Immunologic evaluation revealed that humoral immunity was normal. Although nitroblue tetrazolium reduction by neutrophils was persistently low (reference 4 and this report), other neutrophil functions, including killing of staphylococci, were normal, suggesting that there was no major functional defect. Delayed-type hypersensitivity skin reactions and lymphocyte transformation by mitogens were reduced, and IL-2 production was defective. These results are compatible with those of previously reported studies.<sup>1-3</sup> Because cellular immunity, including lymphocyte-mediated activation of macrophages, is required for effective killing of *Nocardia* organisms,<sup>6</sup> the defect in IL-2 production in our patient may have contributed to his poor outcome.

CMC is considered a "cutaneous" immunodeficiency. However, adequate control of cutaneous lesions required candidacidal medication and immunomodulation.<sup>1, 2</sup> Sinopulmonary infections occurred in 25 of 101 patients with CMC, and systemic bacterial and fungal infections occurred in 27 of 101.<sup>1, 3</sup> Interestingly, only two of 43 children with CMC had *Nocardia* pneumonia, and both survived.<sup>3</sup> The relentless course of our patient's *Nocardia* infection, after an apparent cure, is unusual, especially because the mortality rate does not usually exceed 20%.<sup>6</sup> *Nocardia* infection is more likely to occur in immunodeficient patients, whose response to therapy is inadequate.<sup>6</sup> The severity of noncandidal infections in CMC is still an underestimated feature of the syndrome, and the high incidence of systemic infections requires us to regard patients with CMC as having a cellular immune defect, which has not been fully characterized. Therefore patients with CMC need to be evaluated and treated as immunodeficient patients; physicians should search for unusual severity of infections with common pathogens and opportunistic infections; infections should be treated for longer than usual, and indefinite treatment of hard-to-eradicate infections should be considered. Immunomodulation may be required as well.

I thank Charles W. Caldwell, MD, for the flow cytometry studies; Alan M. Luger, MD, for lymphocyte transformation and mixed lymphocyte reaction; Michael L. Misfeldt, PhD, for IL-2 production studies; Timothy A. Springer, PhD, for providing antibodies to neutrophil adhesion receptors; and Charles H. Kirkpatrick, MD, for the evaluation for transfer factor therapy, and Jack Lazerson, MD, for review of the manuscript.

## REFERENCES

1. Kirkpatrick CH, Sohnle PG. Chronic mucocutaneous candidiasis. In: Safai B, Good RA, eds. Immunodermatology. New York: Plenum Press, 1981:495-514.
2. Kirkpatrick CH. Chronic mucocutaneous candidiasis. In: Bodey GP, ed. Candidiasis. 2nd ed. New York: Raven Press, 1992:167-84.
3. Herrod HG. Chronic mucocutaneous candidiasis in childhood and complications of non-Candida infection: a report of the Pediatric Immunodeficiency Collaborative Study Group. J Pediatr 1990;116:377-382.
4. Feigin RD, Shackelford PG, Eisen S, Spitler LE, Pickering LK, Anderson DC. Treatment of mucocutaneous candidiasis with transfer factor. Pediatrics 1974;53:63-70.
5. Ketoconazole. In: American Medical Association, Department of Drugs. AMA drug evaluations. 6th ed., Chicago: American Medical Association, 1986:1559-61.
6. Lerner PI. *Nocardia* species. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill-Livingstone, 1990: 1926-31.

**Bound volumes available to subscribers**

Bound volumes of THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY are available to subscribers (only) for the 1994 issues from the Publisher, at a cost of \$66.00 for domestic, \$88.62 for Canadian, and \$84.00 for international subscribers for Vol. 93 (January-June) and Vol. 94 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone 1 (800) 453-4351 or (314) 453-4351.

**Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.**