Systemic Blastomycosis in Childhood

Case Report and Review

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In a 21-month-old infant with systemic blastomycosis blood and bone marrow specimens were found reliable sources for culture, whereas sputum cultures were negative. A clinical cure followed hydroxystilbamidine therapy. Family members and neighbors tested for serum precipitins had no evidence of infection, past or present. The true prevalence of blastomycosis in the pediatric population of the United States is not known.

SYSTEMIC mycotic infections are not as rare, exotic or obscure today as perhaps they may have seemed in the past. Although the prevalence in children of some disseminated fungus infections such as candidiasis, nocardiosis, histoplasmosis and mucormycosis has apparently increased, such a trend has not been noted with North American blastomycosis.

Blastomycosis, a chronic mycotic disease caused by *Blastomyces dermatitidis,* may become manifest clinically either as a localized skin lesion, or as a more widely disseminated systemic disease with a predilection for the lungs, digestive system, and musculoskeletal and subcutaneous tissues.

Blastomycosis is found most frequently in adults between 20 and 50 years old; it is rarely encountered in children. It occurs in about three Whites to one Negro and is six times more common in males than females. Little is known of the natural habitat of *Blastomyces dermatitidis* or how man acquires the infection.

A 21-month-old Negro girl with systemic blastomycosis and a small epidemiologic survey form the subject of this paper.

Case Description

This 21-month-old Negro girl was admitted to Louisville Children's Hospital on October 10, 1966 with a mass in the right supraclavicular area which had been first noted the day before. Since she was 16 months old she had been treated for "bronchitis" by a private physician. After the last bout of coughing, which occurred one month prior to admission, the mother was told the child had "fluid in her right lung." Growth had slowed noticeably since age 15 months. Other than iron-deficiency anemia at 16 months of age, there had been no other illnesses.

The infant appeared chronically ill and in moderate cardiorespiratory distress. Temperature was 101° F., rectally; respiratory rate was 70 per minute; heart rate 160 per minute. A firm, rubbery, nontender mass (2 × 3 cm.) was palpated in the right supraclavicular area, fairly well-fixed to the underlying tissue. An inspiratory lag was noted in the right hemithorax with dullness to percussion and tubular breath sounds on auscultation. The remainder of physical examination was normal.

A chest roentgenogram revealed consolidation of the entire right lung with some atelectasis and pleural effusion on the same side (Fig. 1). The hemoglobin level was 9 Gm./100 ml. The white blood cell count was 16,000 per cu. mm. with neutrophils, 69%; lymphocytes, 26%; and monocytes, 5%. Sedimentation rate was 63 mm. in an hour. Gastric washings cultured for acid-fast bacilli were negative. Skin tests with PPD (intermediate and

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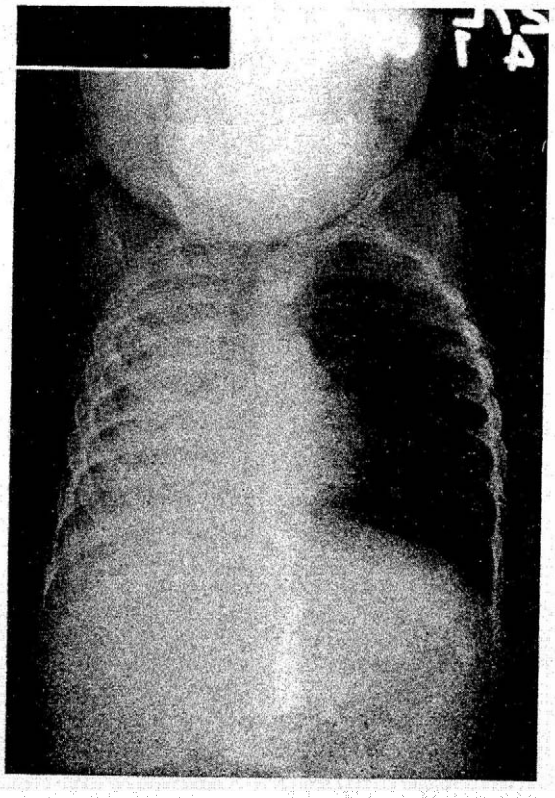

FIG. 1. Roentgenogram of the chest at the time of admission showing extensive consolidation with atelectasis and pleural effusion of the right lung.

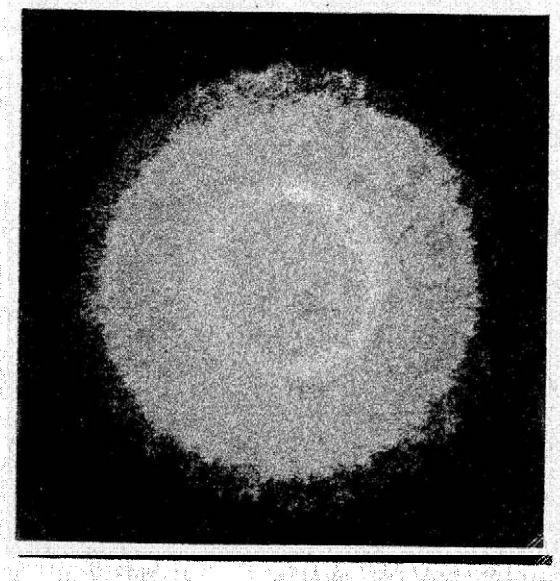

FIG. 2. Colony of *Blastomyces dermatitidis* isolated from blood. Photograph was taken 20 days after subculture on Sabouraud's dextrose agar.

first strength), histoplasmin and atypical mycobacteria (PPD-B and PPD-Y) were negative.

When the mass was incised two weeks later, a considerable amount of yellow purulent material appeared. This was cultured for pyogenic bacteria, acid-fast bacilli and fungi.

She became afebrile shortly after admission, but the fever (100° to 102.4° F.) recurred after incision and drainage of the mass. A week prior to incision, treatment with isoniazid, PAS and streptomycin was initiated. She was discharged 30 days after admission.

Her course was followed with serial chest roentgenograms; she remained relatively asymptomatic, but without improvement of the extensive right lung atelectasis.

When *Blastomyces dermatitidis* was isolated from the material drained from the mass (Fig. 2), the child was admitted to Louisville General Hospital for therapy and further study.

Complement-fixation tests proved to be positive to *Blastomyces dermatitidis* (yeast) 1:16 on two successive occasions. No cross reactions were evident with *Histoplasma capsulatum* complement-fixing antigens or precipitinogens. The serum, however, did show a positive precipitin reaction with the homologous antigen. Blood and bone marrow cultures yielded growth of *Blastomyces dermatitidis* on Mycosel and Sabouraud's dextrose agar at room temperature. Cultures of the urine and gastric washings did not yield any fungal growth. Blastomycin skin tests were repeatedly negative.

Treatment was begun with hydroxystilbamidine isothiocyanate, given intravenously in 100 ml. of 5 per cent dextrose in water. The initial dosage was 9 mg. per day. This was increased daily until 28 mg. per day were reached on the fourth day of treatment, and continued at that level for 17 days. A total of 531 mg. was administered over a three-week period.

On the tenth day of treatment, a blood culture for the fungus was still positive. Such cultures were negative thereafter. Her appetite improved and steady weight gain was observed. She was discharged asymptomatic three and one-half weeks later. The pulmonary abnormalities as demonstrated by roentgenogram persisted for five months after treatment. A planned bronchoscopy was refused by the parents and no further visits to the clinic were made. A home visit by the public health nurse one year after treatment found the infant thriving with no respiratory problems.

Family and Neighborhood Studies

The father was 32 years old and well. He worked as a chemical mixer. He had been treated for tuberculosis when he was 12 years old. The mother and nine siblings were in good health. The patient had been in contact

TABLE 1. *Summary of Patients with Childhood Blastomycosis Reported in Medical Literature*

Reference	Age	Race	Sex	Chief Complaint	Duration of Symptoms Prior to Admission	Major Organs or Systems Involved	Method of Diagnosis	Treatment	Outcome
D'Aunoy and Beven, 1931[12]	14 yr.	N	F			Skin, lungs, liver, bones	Autopsy		Died
Rosenthal, 1935[11]	6 mo.			Epidermal abscess	3 wk.	Skin and subcutaneous tissue	Abscess culture	KI; X-ray	Recovered after six months
Martin and Smith, 1939[2]	16 yr.	N	M	Ulcer on chest wall	1 yr.	Skin, subcutaneous tissue, lungs, bone, heart, lymph nodes, liver	Sputum culture, C.F. test	KI; Feradin	Died 2 yr. after onset
	12 yr.	N	M	Sores on back and leg	3 yr.	Skin, subcutaneous tissue, lungs, lymph nodes	Biopsy	KI	Temporary improvement; died 1 yr. after therapy
Schwartz and Baum, 1951[9]	8 yr.	N	F	Bone pain					
Smith, Harris, Conant and Smith, 1955[6]	7 mo.	N	F	Pneumonia	2 mo.	Lungs	Abscess culture	None	Recovered
	3 yr.	W	M	Fever, red throat, anorexia	2 mo.	Lungs	Sputum culture	None	Died
	1 yr.	W	F	Fever, grunting, respiration, coryza	12 days	Lungs	Sputum culture, C.F. test	2-Hydroxy-stilbamidine	Recovered
	6 yr.	W	F	Fever, cough, coryza	2½ wk.	Lungs	Sputum culture, C.F. test	2-Hydroxy-stilbamidine	Recovered
	16 yr.	N	M	Fever, cough and chest pain	3–4 wk.	Lungs	Sputum culture	Stilbamidine	Recovered
	16 yr.	W	F	Fever, chest pain	2 wk.	Lungs	Sputum, gastric washings	2-Hydroxy-stilbamidine	Recovered
	9 yr.	W	M	Fever, chest pain	1 wk.	Lungs	Sputum, gastric washings	2-Hydroxy-stilbamidine	Recovered
Cherniss and Waisbren, 1955[5]	15 yr.	W	M	Painful leg	6 mo.	Subcutaneous tissue, skin, bone	Biopsy	KI, NaI, x-ray, sulfadiazine, I & D immune serum	Death 14 mo. after onset
	16 yr.	I	F	Painful swellings of neck	7 mo.	Lung, lymph nodes, subcutaneous tissue	Smear of exudate	KI, incision and drainage	Unknown
Chick, Sutliff *et al.*, 1956[3]	6–10 yr.	2 cases							
Abernathy, 1959[4]	2 yr.	N	M			Skin, hilar nodes	Culture	KI, X-ray	Many recurrences, 7 yr. follow-up
	7 yr.	N	M			Skin, lungs, bone	C.F. test, culture	Stilbamidine and I & D	5 mo. improved
	14 yr.	N	F			Skin, lungs, bone, hilar nodes, psoas		Antibiotics	Died
	16 yr.	W	F			Lungs		None	Died (had L.E.)
Palmer and McFadden, 1968[13]	9 yr.	N	F	Fatigue, malaise, cough, shortness of breath	1 mo.	Lungs, spleen, hilar nodes, kidney	Sputum smear, cultures at autopsy	Amphotericin B	Died

with an aunt and uncle with pulmonary tuberculosis; sputum cultures from the uncle were positive for *Mycobacterium tuberculosis.*

The family had lived in the west end of Louisville for the past three years on the ground floor of an old brick house. The patient had never lived elsewhere.

Twenty-seven individuals including family members in the immediate vicinity were interviewed, with special inquiries concerning any pulmonary symptoms. The only ones found with a history of significant pulmonary illness were the patient's father, aunt and uncle. In the survey were four adults, 33 to 45 years old, and 23 children, three to 16 years old. Most of the children had lived in the same neighborhood for their lifetimes. Two adults had resided in the area for three years, one for eight years, and one for 20 years. Serologic studies from these 27 individuals, utilizing the microimmunodiffusion technic for precipitins to blastomycin and histoplasmin were all negative. Blastomycin skin tests of both parents were negative.

A total of 12 cases of blastomycosis, all adults, were admitted to Louisville General Hospital in the past 20 years, six in 1947–1956 and six in 1957–1967 (excluding this patient). Seven of these patients were residents of Louisville, and three of these were admitted in the last six years. None lived in the immediate vicinity of the infant.

Comments

In contrast to the many reports which describe adult cases,[1-7] a review of the American literature reveals only 21 instances of childhood blastomycosis, in the age range five months to 16 years (Table I). Despite the relatively high frequency of the disease in Kentucky,[1] no affected children had been reported until the present case.

A population survey in North Carolina following an epidemic showed a number of asymptomatic individuals with positive blastomycin and negative histoplasmin skin tests which suggests both subclinical illnesses and manifest infections with spontaneous remissions.[6] Assuming equal immunologic competence, it is unlikely that children would recover more often or develop subclinical infections more frequently than adults.

The entry of the fungus in this child was probably through inhalation into the lungs of infective conidia, followed by hematogenous dissemination. This is in keeping with Schwartz and Baum's concept[9] that the initial infection in blastomycosis is via the lungs. The primary manifestations in this child, as often occurs in affected children, were nonspecific pulmonary symptoms. It was not until a cutaneous lesion appeared four months after onset of illness, and the causative fungus recovered from it, that the true nature of the pulmonary lesion was determined.

A cutaneous lesion as the primary sign of infection has not been as commonly observed among children, in contrast to its frequency as the initial manifestation in adults. A lack of awareness that the disease occurs in children, as illustrated in this case, probably explains the disparity in reported incidence between the two age groups. A higher index of suspicion and better recognition of the disease is required to ascertain the true incidence in childhood.

In addition to the skin lesion in this patient, the blood and bone marrow were successful sources for culture. With patients who have pulmonary lesions solely, reliance on sputum cultures alone may allow the diagnosis to be missed, as in this case whose sputum and gastric-washing cultures were repeatedly negative.

Despite the positive cultures, precipitin and complement-fixation tests, repeated blastomycin skin tests on this child remained negative. Smith *et al.*[6] have indicated that the combination of a negative blastomycin skin test with a positive complement-fixation test was a poor prognostic sign, but this observation was not borne out in this case.

The value of hydroxystilbamidine as therapy could not be definitely ascertained. Though she markedly improved following therapy and remained clinically well four months post-therapy, her roentgenographic findings of atelectasis changed little. Unfortunately, no further clinical examinations or roentgenograms could be done afterwards. However, a home visit one year later found the child

clinically well with no respiratory problems since her last examination.

Negative results of the serologic survey of 27 immediate contacts support the nontransmissible nature of the disease, as previously observed by other investigators.[8, 9] The sample population surveyed was too small to give any indication of the true childhood incidence of the disease. The survey was helpful for minimizing the role of environmental conditions in the spread of blastomycosis, since those living in the local area had no evidence of even subclinical infection.

Acknowledgment

The identity of *Blastomyces dermatitidis* was confirmed by Dr. Lucille K. George and the complement-fixation tests were done by Dr. Leo Kaufman at the National Communicable Disease Center, Atlanta, Georgia. Precipitin tests were performed on sera from contacts by Coy D. Smith, University of Kentucky College of Medicine.

References

1. Furcolow, M. L., Balows, A., Menges, R. W., Pickar, D., McClellan, J. T. and Saliba, A.: An important medical problem in central U. S. JAMA 198: 529, 1966.
2. Martin, D. S. and Smith, D. T.: Blastomycosis. Amer. Rev. Tuberculosis 39: 488, 1939.
3. Chick, E. W., Sutliff, W. D., Rakick, J. H. and Furcolow, M. L.: Epidemiological aspects of cases of blastomycosis admitted to Memphis, Tennessee, hospitals during the period of 1922–1954; a review of 86 cases. Amer. J. Med. Sci. 231: 253, 1956.
4. Abernathy, P. S.: Clinical manifestations of pulmonary blastomycosis. Ann. Intern. Med. 51: 707, 1959.
5. Cherniss, E. I. and Waisbren, B. A.: North American blastomycosis; a clinical study of 40 cases. *Ibid.* 44: 105, 1956.
6. Smith, J. G., Jr., Harris, J. S., Conant, N. F. and Smith, D. T.: An epidemic of North American blastomycosis. JAMA 158: 641, 1955.
7. Walkup, H. E.: Blastomycosis. W. Virginia Med. J. 56: 187, 1960.
8. Schwarz, J. and Baum, G. L.: Results of skin tests in contacts of blastomycosis patients. J. Invest. Dermat. 18: 3, 1952.
9. —— and ——: Blastomycosis. Amer. J. Clin. Path. 21: 999, 1951.
10. Conant, N. F. *et al.:* Manual of Clinical Mycology, 2nd ed. Philadelphia, W. B. Saunders Company, 1954, pp. 45–74.
11. Rosenthal, J. J.: Blastomycosis in an infant six months old. J. Lab. Clin. Med. 20: 1164, 1935.
12. D'Aunoy, R. and Beven, J. L.: Blastomycosis. *Ibid.* 16: 124, 1930.
13. Palmer, P. and McFadden, S. W.: Blastomycosis; report of an unusual case. New Eng. J. Med. 279: 979, 1968.

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Heredity and Disease. IAN H. PORTER. New York, McGraw-Hill Book Co., 1968. 407 pp. 116 illus. $12.00.

A smoothly readable textbook, for medical students and the graduate study-minded physician. Plenty of clear definitions!

Physical Diagnosis: The History and Examination of the Patient. 3rd ed. JOHN A. PRIOR and JACK S. SILBERSTEIN, eds. St. Louis, C. V. Mosby Co., 1969. 486 pp. 454 illus. $10.50.

A 17-chapter glossy-papered clearly written and beautifully illustrated book, directed to "the physician of tomorrow," the medical student. With one exception, the numerous contributors are on the faculty of Ohio State College of Medicine, Columbus, Ohio. The informative chapter on the "Pediatric Examination" is by Bruce D. Graham, Chairman of that Department.

Proceedings of the International Conference on Leukemia–Lymphoma. C. J. D. ZARAFONETIS, ed. Philadelphia, Lea & Febiger, 1968, 56 contributors. 519 pp. $15.00.

An International Conference on Leukemia–Lymphoma was held at Ann Arbor, Michigan, in October 1967, as part of the celebration of the University of Michigan Sesquicenteunial. This volume is a transcript of all the presentations and pertinent discussions, the participants being leading workers from all over the world. Hardly a question may come up during the next few years in connection with basic science knowledge as related to clinical phenomena which has not already been discussed informatively in these pages.

Recent Advances in Pediatric Clinical Pathology. C. C. MABRY, I. E. ROECKEL, R. E. GEVEDON, and J. A. KOEPKE. New York, Grune & Stratton, 1968. 247 pp. $14.50.

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