Lymphocytic Interstitial Pneumonitis: A Cause of Pulmonary Gallium-67 Uptake in a Child with Acquired Immunodeficiency Syndrome

Lionel S. Zuckier, Fukiat Ongseng, and C. Richard Goldfarb

Departments of Radiology and Nuclear Medicine, Albert Einstein College of Medicine, Bronx; and Beth Israel Medical Center, New York, New York

Lymphocytic interstitial pneumonitis (LIP) is currently recognized as a frequent pediatric manifestation of the acquired immunodeficiency syndrome (AIDS). We report the gallium scan findings in a 3-yr-old girl with this disorder and review its clinical, radiologic, and pathologic features. LIP must be a prime consideration in the differential diagnosis of diffuse pulmonary gallium uptake in pediatric AIDS patients. Further experience will afford greater perspective on the diagnostic role that nuclear medicine will ultimately play in this disease.

J Nucl Med 29:707–711, 1988

Gallium-67 citrate scanning has achieved widespread utility in the imaging of adult patients with the acquired immunodeficiency syndrome (AIDS) (*1–7*). We describe here the gallium scan findings in a 3-yr-old girl with lymphocytic interstitial pneumonitis (LIP), a frequent pediatric manifestation of AIDS (*8–14*). While the radiographic appearance of LIP has been previously reported (*14–16*), we believe this to be the first scintigraphic description of an increasingly recognized condition [Since submission of this report, two gallium scans in patients with this disorder have been described (*49*)].

CASE REPORT

A 3-yr-old Hispanic girl with a chronic seizure disorder and recurrent bilateral otitis media was admitted to the hospital in March of 1985 following several weeks of recurrent fever and cough. Family history was significant for parental intravenous drug abuse. A 10-day course of sulfamethoxazole/trimethoprim (Bactrim) had been recently completed as empiric treatment for suspected *Pneumocystis carinii* pneumonia (PCP). Additional medications included phenobarbital and phenytoin (Dilantin) for her seizure disorder, the latter having been recently discontinued.

Received July 14, 1987; revision accepted Jan. 20, 1988.

For reprints contact: C. Richard Goldfarb, MD, Beth Israel Medical Center, Div. of Nuclear Medicine, New York, NY 10003.

Physical examination disclosed hepatosplenomegaly, diffuse shotty lymphadenopathy, and scattered pulmonary crackles. Mild clubbing of the fingers was present. Arterial pO_2 measured 67 mmHg on room air. Chest radiograph (Fig. 1) demonstrated a widened mediastinum, prominent hila, and nodular densities scattered throughout both lungs. The child was found to be human immunodeficiency virus-antibody positive and helper/suppressor lymphocyte ratios were reversed. Epstein-Barr virus antibody titers were elevated. A gallium scan was requested during the hospitalization to assess the extent and activity of pulmonary disease. Whole-body scintiphotos obtained at 48 hr postinjection showed diffuse pulmonary uptake, equal in intensity to hepatic activity (Fig. 2). The patient was intermittently treated with short courses of antibiotics for pulmonary aspiration, fevers and otitis media. Two months after the gallium scan, open-lung biopsy was performed which revealed a nodular peribronchiolar lymphocytic infiltration without evidence of pneumocystis, fungi, acid-fast bacilli, or inclusion bodies. She has been maintained on an outpatient protocol of gamma-globulin and steroids (*13,17*) and is stable 2 yr after diagnosis.

DISCUSSION

In 1983, the acquired immunodeficiency syndrome was described in children born of high-risk families (*18, 19*). These and subsequent reports have elaborated on the unique pediatric manifestations of this disease (*8–14,20–22*). Among differences seen in the pediatric

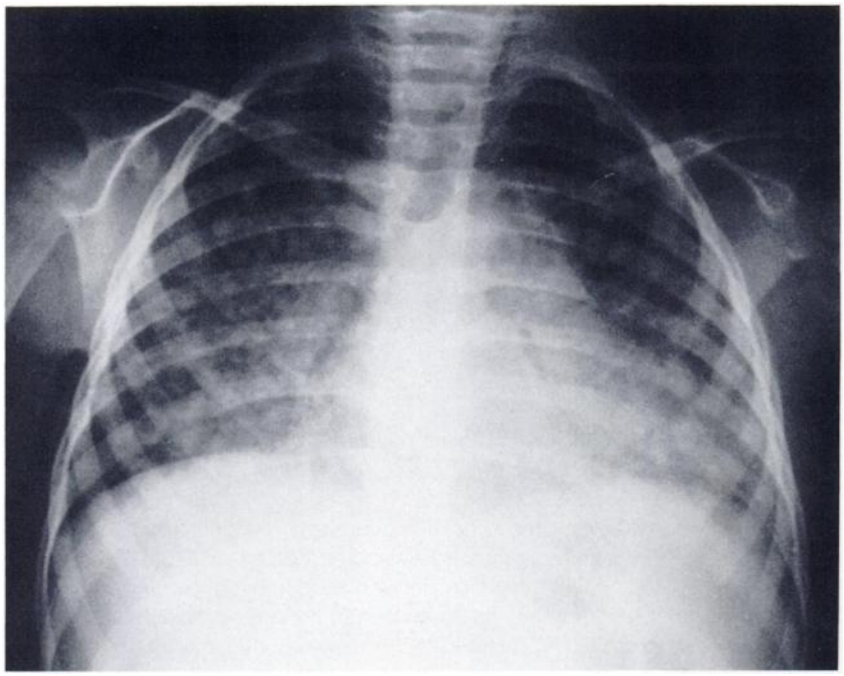

FIGURE 1
Postero-anterior radiograph of the chest demonstrates coarse interstitial nodules distributed throughout the lung parenchyma in a diffuse pattern. The mediastinum and hila appear full.

population are the relative rarity of Kaposi's sarcoma and the frequent presence of an interstitial lymphocytic pulmonary infiltrate, generally termed "lymphocytic interstitial pneumonitis." LIP is highly uncommon in adult patients with AIDS (*23–26*) although it has been described in isolated case-reports (*27–30*).

The etiology of the pulmonary changes in AIDS-related LIP is uncertain, but it has been postulated that one or more viruses may trigger hyperplasia of the bronchial-associated lymphoid tissue (*14,16,31,32*). Preliminary evidence links this disorder to infection by either Epstein-Barr virus (*13,14,31,33*) or human immunodeficiency virus (*28,32*).

Rubinstein and co-workers have enumerated several salient clinical features of LIP. The children present at a slightly older age than those with PCP. The onset of symptoms is more insidious than in PCP, and the clinical course is less fulminant. Salivary gland swelling, digital clubbing and extensive lymphadenopathy are prominent findings (*14*). Radiographic findings in AIDS-associated LIP resemble those seen in the present case, namely a diffuse coarse nodular interstitial infiltrate with progressive hilar and mediastinal lymphadenopathy (*14–15*). Interestingly, of 15 children with AIDS or AIDS-related complex studied, no patient manifested concurrent LIP and PCP though in one patient this association could not be conclusively ruled out due to delay in biopsy (*14*).

The classic form of LIP originally described by Carrington and Liebow in 1966 (*34*) is a rare idiopathic disorder that is seen primarily in middle-aged women and is frequently associated with systemic diseases, particularly Sjogren's syndrome and dysproteinemias. A diffuse lymphoid infiltrate is present in the interstitial compartment of the alveolar septa and along lymphatic pathways, in a predominately linear pattern. Hilar and mediastinal lymphadenopathy is typically absent (*10, 35–37*).

In the syndrome of AIDS-associated LIP, lung tissue contains large aggregates of lymphocytes and plasma cells around bronchiolar epithelium and in adjacent interalveolar septa (*9–14,20*). In many of these children, the infiltrate is more nodular than in the classic form of LIP, with the most prominent finding being peribronchiolar lymphoid aggregates (*10,14,20*). These differences have led some authors to term the AIDS-related condition 'pulmonary lymphoid hyperplasia' (PLH) as distinct from the classic syndrome of LIP (*10, 14*). Joshi and co-workers (*20*) currently refer to a "PLH/LIP complex" and others stress a spectrum of pathologic changes including LIP, desquamative interstitial pneumonitis, chronic interstitial pneumonitis, bronchus associated lymphoid tissue, and immunoblastic sarcoma, which they have labeled "lymphoid associated disorders" (*16*). We have chosen to employ the initial though less precise term "lymphocytic interstitial pneumonitis" to conform with the usage of the majority of authors. Further consensus is needed before a standardized nomenclature is achieved and the relationship between the various reported interstitial lymphocytic disorders can be elucidated.

The gallium scan in our case shows diffuse pulmonary uptake, equal in intensity to liver activity [grade 4 (*38*)] and corresponding in distribution to the widespread radiologic changes. The patient had been recently tapered off phenytoin (Dilantin) for a chronic

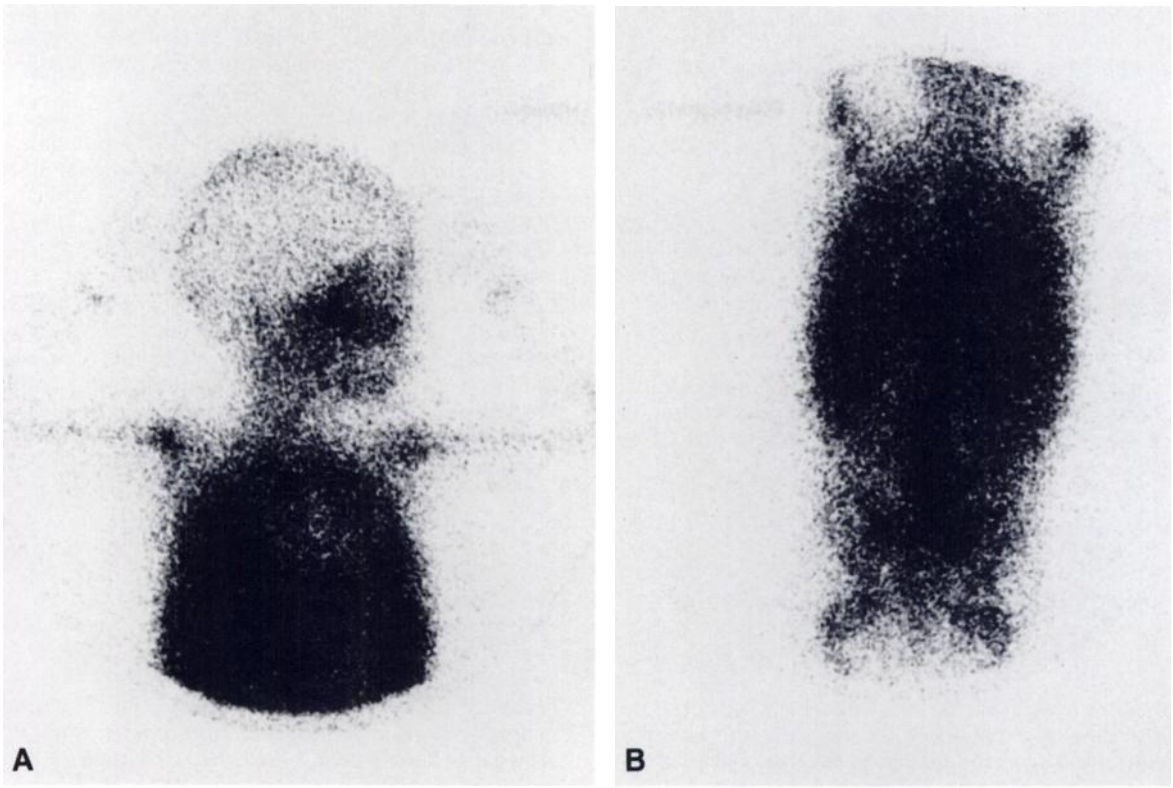

FIGURE 2
A, B: Anterior view of the thorax (A) demonstrates diffuse pulmonary uptake of gallium equal to hepatic intensity. A central defect is seen corresponding to the cardiac silhouette. Within the limited resolution of the scan, no increased activity is visualized in the parotid region or in peripheral lymph node groups included within the field of view. Posterior view (B) again demonstrates marked, diffuse pulmonary uptake of radiotracer. Prominence of the spleen corresponds to splenomegaly on physical examination.

seizure disorder. While this medication has been reported to alter the pulmonary biodistribution of gallium-67 in five of 16 patients described, the resultant pattern was nodal rather than diffuse (*39*).

Although 2 mo elapsed between the gallium scan and biopsy, it is unlikely that the positive scan findings were due to PCP or other infectious causes. At the time of gallium scan, the chest radiograph (figure 1) exhibited coarse nodular interstitial densities, typical of LIP and unlike the radiographic changes of PCP (*14,15*). These interstitial findings remained unchanged at the time of biopsy. Concurrence of LIP and PCP is highly uncommon. In a series of 15 children with AIDS or AIDS-related complex reported by Rubinstein and co-workers, none of the patients with LIP had evidence of coexisting opportunistic lung infections, such as PCP (*14*). Additional studies have confirmed this observation (*12,16,20*). Because our patient had recently completed an empirically prescribed 10-day course of Bactrim, the likelihood of active PCP infection at the time of gallium scan becomes even more remote.

The parotids are frequently enlarged in the syndrome of AIDS-associated LIP (*13,14,18,22*), though this finding was not clinically apparent in the current case. A single view of the face included in the present study does not demonstrate uptake in the parotid region. Increased activity is seen in the nasopharynx, possibly related to upper respiratory tract infection associated with the patient's recurrent otitis media.

The role of gallium scanning in AIDS-associated LIP needs to be evaluated. Reported radiologic findings are characteristic, if not pathognomic, in the proper clinical setting (*14,15*). Nevertheless, sensitivity of the chest x-ray in this disorder is currently unknown and gallium imaging may facilitate earlier detection of abnormality, as in PCP (*1–3,40–44*). Additionally, the course and management of LIP in pediatric AIDS patients is not well understood. Scintigraphy may provide a useful marker of disease activity, as it currently does in several other pulmonary conditions (*1–3,38,45–48*).

LIP is a common manifestation of AIDS in children which can produce a diffusely intense pulmonary uptake of gallium. In addition to infectious causes, LIP must be a prime consideration in the differential diagnosis of diffuse lung activity in pediatric AIDS patients. Further experience will afford greater perspective on the diagnostic role that gallium imaging will ultimately play in this new disease.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance and suggestions of Drs. R. Morecki and H. S. Goldman.

REFERENCES

1. Tuazon CU, Delaney MD, Simon GL, et al. Utility of gallium-67 scintigraphy and bronchial washings in the diagnosis and treatment of pneumocystis carinii pneumonia in patients with the acquired immune deficiency syndrome. *Am Rev Respir Dis* 1985; 132:1087–1092.
2. Folmer SCC, Danner SA, Bakker AJ, et al. Gallium-67 lung scintigraphy in patients with acquired immune deficiency syndrome (AIDS). *Eur J Respir Dis* 1986; 68:313–318.
3. Barron TF, Birnbaum NS, Shane LB, et al. Pneumocystis carinii pneumonia studied by gallium-67 scanning. *Radiology* 1985; 154:791–793.
4. Bach MC, Bagwell SP, Masur H. Utility of gallium imaging in the diagnosis of mycobacterium avium-intracellulare infection in patients with the acquired immunodeficiency syndrome. *Clin Nucl Med* 1986; 11:175–177.
5. Malhotra CM, Erickson AD, Feinsilver SH, et al. Ga-67 studies in a patient with acquired immunodeficiency syndrome and disseminated mycobacterial infection. *Clin Nucl Med* 1985; 10:96–98.
6. Woolfenden JM, Carrasquillo JA, Larson SM, et al. Acquired immunodeficiency syndrome: Ga-67 citrate imaging. *Radiology* 1987; 162:383–387.
7. Hung GL, Chen DCP, Siegel ME, et al. The utilization of gallium scintigraphy in AIDS-related lymphomas. *J Nucl Med* 1987; 28:694.
8. CDC. Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR* 1987; 36:225–235.
9. Joshi VV, Oleske JM, Minnerfor AB, et al. Pathology of suspected acquired immune deficiency syndrome in children: a study of eight cases. *Pediatr Pathol* 1984; 2:71–87.
10. Kradin RL, Mark EJ. Benign lymphoid disorders of the lung, with a theory regarding their development. *Human Pathol* 1983; 14:857–867.
11. Pahwa S, Fikrig S, Kaplan M, et al. Expressions of HTLV-III infection in a pediatric population. In: Gupta S, ed. *AIDS-associated syndromes.* New York: Plenum Press, 1985.
12. Joshi VV, Oleske JM, Minnerfor AB, et al. Pathologic pulmonary findings in children with the acquired immunodeficiency syndrome. A study of ten cases. *Human Pathol* 1985; 16:241–246.
13. Bernstein LJ, Rubinstein A. Acquired immunodeficiency syndrome in infants and children. *Prog Allergy* 1986; 37:194–206.
14. Rubinstein A, Morecki R, Silverman B, et al. Pulmonary disease in children with acquired immune deficiency syndrome and AIDS-related complex. *J Pediatr* 1986; 108:498–503.
15. Goldman HS, Ziprkowski MN, Charytan M, et al. Lymphocytic interstitial pneumonitis in children with AIDS: a perfect radiographic-pathologic correlation. *Am J Roentgenol* 1985; 145:868.
16. Zimmerman BL, Haller JO, Price AP, et al. Children with AIDS—is pathologic diagnosis possible based on chest radiographs? *Pediatr Radiol* 1987; 17:303–307.
17. Charytan M, Krieger BZ, Wiznia A, et al. Treatment of AIDS associated lymphoid interstitial pneumonitis with intravenous gammaglobulin and prednisone. *Pediatr Res* 1985; 19:401A.
18. Rubinstein A, Sicklick M, Gupta A, et al. Acquired immunodeficiency with reversed T_4/T_8 ratios in infants born to promiscuous and drug-addicted mothers. *JAMA* 1983; 249:2350–2356.
19. Oleske J, Minnefor A, Cooper R, et al. Immune deficiency syndrome in children. *JAMA* 1983; 249:2345–2349.
20. Joshi VV, Oleske JM. Pulmonary lesions in children with the acquired immunodeficiency syndrome: a reappraisal based on data in additional cases and follow-up study of previously reported cases. *Human Pathol* 1986; 17:641–642.
21. Scott GB, Buck BE, Letterman JG, et al. Acquired immunodeficiency syndrome in infants. *N Engl J Med* 1984; 310:76–81.
22. Rogers ME. AIDS in children: a review of the clinical, epidemiologic and public health aspects. *Pediatr Infect Dis* 1985; 4:230–236.
23. Marchevsky A, Rosen MJ, Chrystal G, et al. Pulmonary complications of the acquired immunodeficiency syndrome: a clinicopathologic study of 70 cases. *Human Pathol* 1985; 16:659–670.
24. Murray JF, Felton CP, Garay SM, et al. Pulmonary complications of the acquired immunodeficiency syndrome. *N Engl J Med* 1984; 310:1682–1688.
25. Stover DE, White DA, Romano PA, et al. Spectrum of pulmonary diseases associated with the acquired immune deficiency syndrome. *Am J Med* 1985; 78:429–437.
26. Suster B, Akerman M, Orenstein M, et al. Pulmonary manifestations of AIDS: Review of 106 episodes. *Radiology* 1986; 161:87–93.
27. Saldana SJ, Mones J, Buck BE. Lymphoid interstitial pneumonia in Haitian residents of Florida [Abstract]. *Chest* 1983; 84:347.
28. Ziza J, Brun-Vezinet F, Venet A, et al. Lymphadenopathy-associated virus isolated from bronchoalveolar lavage fluid in AIDS-related complex with lymphoid interstitial pneumonitis. *N Engl J Med* 1985; 313:183.
29. Solal-Celigny P, Couderc LJ, Herman D, et al. Lymphoid interstitial pneumonitis in acquired immunodeficiency syndrome-related complex. *Am Rev Respir Dis* 1985; 131:956–960.
30. Grieco MH, Chinoy-Acharya P. Lymphocytic interstitial pneumonia associated with the acquired immune deficiency syndrome. *Am Rev Respir Dis* 1985; 131:952–955.
31. Fackler JC, Nagel JE, Adler WH, et al. Epstein-Barr virus infection in a child with acquired immunodeficiency syndrome. *Am J Dis Child* 1985; 139:1000–1004.
32. Chayt KJ, Harper ME, Marselle LM, et al. Detection of HTLV-III RNA in lungs of patients with AIDS and pulmonary involvement. *JAMA* 1986; 256:2356–2359.
33. Andiman WA, Eastman R, Martin K, et al. Opportunistic lymphoproliferations associated with Epstein-Barr viral DNA in infants and children with AIDS. *Lancet* 1985; 2:1390–1393.
34. Carrington CB, Liebow AA. Lymphocytic interstitial pneumonia. *Am J Pathol* 1966; 48:36a.
35. Halprin GM, Ramirez-R J, Pratt PC. Lymphoid interstitial pneumonia. *Chest* 1972; 62:418–423.
36. Strimlan CV, Rosenow III EC, Weiland LH, et al.

Lymphocytic interstitial pneumonitis. Review of 13 cases. *Ann Intern Med* 1978; 88:616–621.
37. Liebow AA, Carrington CB. Diffuse pulmonary lymphoreticular infiltrations associated with dysproteinemia. *Med Clin North Amer* 1973; 57:809–843.
38. Line BR, Hunninghake GW, Keogh BA, et al. Gallium-67 scanning to stage the alveolitis of sarcoidosis: correlation with clinical studies, pulmonary function studies, and bronchoalveolar lavage. *Am Rev Respir Dis* 1981; 123:440–446.
39. Lentle BC, Starreveld E, Catz Z, et al. Abnormal biodistribution of radiogallium in persons treated with phenytoin. *J Can Assoc Radiol* 1983; 34:114–115.
40. MacMahon H, Bekerman C. The diagnostic significance of gallium lung uptake in patients with normal chest radiographs. *Radiology* 1976; 127:189–193.
41. Turbiner EH, Yeh SDJ, Rosen PP, et al. Abnormal gallium scintigraphy in pneumocystis carinii pneumonia with a normal chest radiograph. *Radiology* 1978; 127:437–438.
42. Moses SC, Baker SR, Seldin MF. Diffuse pulmonary gallium accumulation with a normal chest radiogram in a homosexual man with pneumocystis carinii pneumonia. A case report. *Clin Nucl Med* 1983; 8:608–609.
43. Bekerman C, Bitran J, Weinstein R, et al. Diagnostic significance of Ga-67 scintigraphic patterns in patients with acquired immunodeficiency syndrome (AIDS) and the AIDS related complex (ARC). *J Nucl Med* 1987; 28:648.
44. Coleman DL, Hattner RS, Luce JM, et al. Correlation between gallium lung scans and fiberoptic bronchoscopy in patients with suspected pneumocystis carinii pneumonia and the acquired immune deficiency syndrome. *Am Rev Respir Dis* 1984; 130:1166–1169.
45. Siemsen JK, Grebe SF, Sargent EN, et al. Gallium-67 scintigraphy of pulmonary diseases as a complement to radiography. *Radiology* 1976; 118:371–375.
46. Niden AH, Mishkin FS, Khurana MML. ^{67}Gallium citrate lung scans in interstitial lung disease. *Chest* 1976; 69:266–268.
47. Johnson DG, Johnson SM, Harris CC, et al. Ga-67 uptake in the lung in sarcoidosis. *Radiology* 1984; 150:551–555.
48. Siemsen JK, Grebe SF, Waxman AD. The use of gallium-67 in pulmonary disorders. *Semin Nucl Med* 1978; 8:235–249.
49. Schiff RG, Kabat L, Kamani N. Gallium scanning in lymphoid interstitial pneumonitis of children with AIDS. *J Nucl Med* 1987; 28:1915–1919.