

Nuclear Medicine applications in immunosuppressed patients, "AIDS"

Hussein M. ABDEL-DAYEM, M.D.

*Professor of Radiology, New York Medical College, Valhalla, New York
and Director Nuclear Medicine Service, Department of Radiology,
Saint Vincent's Hospital & Medical Center of New York, USA*

Introduction

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) is a serious and a major global health problem. It is induced by integration of the human immunodeficiency virus (HIV) into the cellular immune system. There are five groups who are predisposed to HIV infection: homosexuals, IV drug abuse, those receiving transfusion of blood or its products, prostitutes or children of any of the previous ones. The incidence in homosexuals is reaching a plateau while it is increasing in heterosexuals. The 1994 USA AIDS data shows that in the age group 25-44 it is the leading cause of death in men and the third leading cause of death in women. Between 1993 and 1994 there has been an increase of death: 30% in white women, 28% in black women (1 in 5 deaths), and 13% in black men (1 in 3 deaths). There is a total of 41,930 deaths from AIDS in 1994 (9% increase from 1993) with an increase of 9% and may be as high as 30% from 1993. There has been 63,000 newly diagnosed patients.

Early after infection the disease might present with flu like symptoms and generalized lymphadenopathy that stays for a few days. A latent period that varies from 2 > 10 years usually passes until the immune system in the body is weakened enough for the syndrome of AIDS becomes manifested. The virus attacks the T-cells in the body leading to continuous reduction of T-cells count until they become below 200/ml when opportunistic infections (O.I.) starts invading the different organs in the body.

Based on an invited educational lecture at the 6th Asia and Oceania Congress of Nuclear Medicine and Biology, and the 36th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine, Kyoto, October 1996.

For reprint contact: Hussein M. Abdel-Dayem, M.D., Chief, Nuclear Medicine Service, Department of Radiology, Saint Vincent's Hospital & Medical Center of NY, 153 West 11th Street, New York, NY 10011, USA.

AIDS patients are liable to the development of opportunistic infections, Kaposi Sarcoma or malignant lymphoma. Opportunistic infections can attack almost any organ in the body. The respiratory tract is the most commonly affected system followed by the gastrointestinal tract. Pneumocystis carinii pneumonia (PCP) used to be the most common organism affecting the lungs. Because of the use of prophylactic treatment, its incidence is decreasing while other opportunistic infections such as *Mycobacterium tuberculosis* (TB) and disseminated *Mycobacterium avii* complex (MAI) is increasing.

The increasing incidence of TB is a major health problem in big cities to both AIDS patients and health workers. The problem is more complicated by different factors: 1) the disease is more common in the poor population: blacks; IV drug abusers and poor socioeconomic living conditions; 2) TB infection in HIV positive patients can precede AIDS syndrome; 3) the presence drug resistant strains; 4) because of lack of immune reaction the disease behaves like primary TB and has problems in verifying the diagnosis. Patients are usually anergic. The usual tests for diagnosing TB infection as skin PPD testing is negative in the majority of patients. Sputum smear is positive only in 30 to <60% of the cases. Blood culture takes up to 6 weeks. Radiological findings in the chest x-ray are atypical. Lung apices are not usually the most common site for the diseases. Changes can simulate pneumonic infiltrate and hilar adenopathy is common. In our series, chest x-ray could be negative in up to 17% of the patients inspite of positive sputum smear and culture.

The diagnosis of disseminated *Mycobacterium avii* complex is usually established by lymph node biopsy, blood or bone marrow culture or biopsy from affected organs. Sputum smear and culture are not reliable for establishing the diagnosis. The presenting symptoms are usually fever, weight loss and diarrhea. It can affect almost any organ.

The organs most commonly affected are the lungs, liver, spleen, small and large bowels and the lymph nodes.

Pneumocystis carinii pneumonia is currently less common than TB or MAI because of the use of prophylactic therapy. Presenting symptoms are usually fever, shortness of breath, tachypnea. The diagnosis is usually established by sputum cytology. Early in the course of the disease, the chest x-ray could be negative. Treatment is usually started once the diagnosis is suspected.

The gastrointestinal tract is the second most commonly involved system in the body. Esophagitis, pancreatitis and colitis are frequently encountered. There is no adequate prophylaxis for the GI tract against opportunistic infections because of the multiplicity of organisms and poor antibiotics response. Candidiasis, cryptosporidiosis, MAI, TB and cytomegalic virus infections are common organisms that affects GI tract.

Kaposi's sarcoma (KS) in AIDS patient has a more aggressive course than in non-AIDS. It can affect the skin, bronchi, lung parenchyma, GI tract, liver spleen, and almost any organ of the body. The diagnosis is usually established by clinical examination by recognizing the pinkish lesions in the skin or by bronchoscopy. Biopsy of the skin lesions is sometimes undertaken to verify the diagnosis. Because the lesions are vascular and bleeds profusely, biopsy is usually not recommend from the bronchi or internal organs. Kaposi's sarcoma affecting the pulmonary parenchyma is difficult to diagnose on the chest x-ray.

Malignant lymphoma incidence is increasing in AIDS patients. Almost 20% of AIDS patients will develop the disease. The disease clinically is more aggressive characterized by lymphocytic depletion and extranodal involvement of the organs in the body especially the brain and heart. Involvement of the liver spleen and bowel in addition to multiple sites of nodal infiltration is usually seen in the abdomen. Bone marrow involvement is usually early in the course of the disease. In the brain, the disease usually starts in the basal ganglia and in the paraganglionic regions and is difficult to differentiate from toxoplasmosis. MRI is occasionally of help for this differentiation. An increased toxoplasmosis titre in the serum with a therapeutic test associated with good response clinically and on MRI images verifies the presence of toxoplasmosis. Toxoplasmosis and intracranial lymphoma could exist together in the same patient.

Diagnosis of opportunistic infections in general in AIDS patients has several problems:

- 1) The symptoms are vague, non-specific and almost common in the majority of the patients.
- 2) The chest x-ray as the most common diagnostic imag-

ing test, however, lacks sensitivity in the early stage of infection and specificity when the radiological changes are manifested.

- 3) More than one organisms and/or pathology could be involved and more than one organ could be affected in the same patient i.e. multiplicity of the problem.
- 4) The need to verify the diagnosis and organs involved in the shortest possible time in order to initiate appropriate treatment as soon as possible.
- 5) Lack of sensitivity of diagnostic tests as sputum smears, culture, stool culture and antibody skin testing.
- 6) Patients are usually debilitated and invasive diagnostic procedures as bronchoscopy, esophagoscopy and colonoscopy are usually neither tolerated nor accepted by the patient.

NUCLEAR MEDICINE PROCEDURES IN AIDS PATIENTS

In view of the previously mentioned short review of multiplicity of pathology, organisms and organs involved by opportunistic infections, there is need for accurate diagnosis in the shortest period and using the least invasive procedures. Nuclear Medicine procedures have the advantages of total body imaging of multiple organs and could be positive before radiological changes appear on the chest x-ray. Its disadvantages are the non-specificity of the findings. The approach of the Nuclear Medicine procedures at Saint Vincent's Hospital of NY is presented here.

Usually patients are presented with one or more of the following clinical problems:

- 1) Fever, cough, shortness of breath and weight loss.
- 2) GI tract symptoms of esophagitis, gastritis, enteritis or colitis with diarrhea, weight loss and abdominal pain.
- 3) Kaposi's sarcoma lesions of the skin, bronchi with fever and need for verification of the parenchymal KS involvement. The chest x-ray could be normal or abnormal.
- 4) Lymphadenopathy and there is need to differentiate TB and MAI from lymphoma.
- 5) Intracranial lesions seen on the MRI and there is need to differentiate toxoplasmosis from lymphoma.
- 6) Upper abdominal pain and need to exclude acute cholecystitis.

Gallium and Thallium Scanning

Gallium scan is the most common Nuclear Medicine procedure used for AIDS patients. It has problems of:

- 1) Bowel excretion at 24 or 48 hr images which does not help to differentiate colitis from physiological excretion. Because of this we always image the patients for the abdomen in the anterior projection at 4 hours following the gallium injection. We do not expect to have physiologic bowel excretion so early. Increased

bowel activity of high intensity at this 4 hours which persists and becomes more intense in the delayed images is indicative of bowel involvement with either opportunistic infections or lymphomas.

- 2) Gallium is negative for KS while thallium is positive. It was suggested by Lee that lesions which are thallium positive and gallium negative are KS. Thallium positive and gallium positive are lymphoma. Thallium negative and gallium positive are acute infections. Our approach is to examine the patient and review the chart. If there is any question or the diagnosis of pulmonary KS or if there is a question of malignant lymphoma, TB or MAI, we recommend to do sequential thallium and gallium scans on the same day. The patient is imaged for the chest 20 minutes following the intravenous injection of 148 MBq thallium-201 chloride. Planar and SPECT images for the lungs are usually obtained. If there is positive thallium uptake in the lungs or the lymph nodes, the patients are reimaged at two to three hours later. If thallium uptake disappears in the delayed images, this is usually suggestive of pulmonary congestion (PCP if diffusely involving both lungs, TB or MAI if focal involving the mediastinal or supraclavicular lymph nodes). If thallium uptake persists in the delayed images then it is most likely indicative of KS or lymphoma. Certain types of TB might show persistent thallium uptake in the delayed images with slight decrease in the intensity. Gallium is usually injected when the thallium study is completed on the same day or next day and at 4 and 24 hours should be obtained. Planar total body anterior and posterior views and SPECT of the chest usually solves the problem in more than 95% of the cases at 24 hours. Occasionally in less than 5%, the patients have to be brought back at 48 hour images and repeat the chest planar and SPECT images because of high blood pool activity in the lungs. The thallium and gallium studies are always interpreted and reported together.

In summary, persistent thallium uptake in the delayed images suggest KS if there is no corresponding gallium uptake. Persistent thallium uptake in the delayed images with corresponding increased gallium uptake is suggestive of lymphoma. However, TB or MAI might be considered if there is a decrease in the thallium uptake in the delayed images. The presence of gallium uptake without corresponding thallium uptake is suggestive of acute infection, TB or MAI.

The sensitivity, of a Tl positive Ga negative lesion in the lungs depends on the presence or absence of associated O.I. The sensitivity is 89% which drops to 37% in the presence of O.I. The specificity of Tl positive, Ga negative pattern however is 96%. This pattern was seen in two patients with CMV involvement of the lung. The sensitiv-

ity for the whole group in our previous report is 63%, specificity 95% and PPV 92%, NPV 75% and accuracy 81%.

For the diagnosis of TB involvement chest x-ray was positive in 83% while the gallium scan was positive only in 66%. Causes of false negative gallium scans were antituberculosis treatment. Sixty-six percent of patients on antituberculosis treatment had negative gallium scans. Lymph nodes was recognized in all patients with proven diagnosis of TB. The sites of involvement were in this order: mediastinum, supraclavicular, axillary, retroperitoneal and inguinal. Lung parenchymal involvement was seen in addition to lymph nodes in 20% of the patients. Thallium positive lesions were seen only in 40% of tuberculous patients. In all the intensity of uptake decreased in the delayed images.

In disseminated *Mycobacterium avii* complex, the chest x-ray was positive in 41%, gallium scans in 84% and usually multiple sites are recognized. Lymph node involvement in 78% (hilar 37.5%, supraclavicular 78.1% (all on left side), paraaortic 31.2%, paratracheal 18.2%, mediastinal 6.2% and axillary 3.1%). Lung parenchyma in 18.7% and pleural in 9.3%. Increased uptake in the spleen is 16%, colitis 53.1% and enteritis 18.7%. Thallium scans were positive only 43.8%. There was a tendency of thallium uptake to decrease in delayed images in the majority of patients.

Hepatobiliary Scintigraphy in AIDS Patients

Review of our data show that AIDS patients with T-cells > 200 behave like non-AIDS patients and majority of acute cholecystitis is calculous in nature. However, patients with T-cells < 200 has different pathology and poor prognosis. More than half of the patients (52%) has a calculous cholecystitis. The most common organisms are cryptococcal infections, CMV and lymphomatous involvement of the gallbladder. The mortality in these patients was 25% with surgical cholecystectomy versus < 0.5% in non-AIDS patients.

Differentiation of intracranial toxoplasmosis from malignant lymphoma

Gallium is not sensitive for toxoplasmosis for this intracranial lesions. Both Thallium or Tc-99m SestaMIBI in our experience has correlated very well. Previous reports compared thallium with F18-FDG glucose imaging. We prefer Tl over Tc-99m sestaMIBI because of the proximity of the lesions to the basal ganglia. Normal Tc-99m sestaMIBI uptake in the choroid plexus overshadows uptake in the lesion. Lesions with Tl uptake ratio of > 1.6 is usually considered suggestive of malignant lymphoma. There are two limitations for the accuracy of the Tl ratio: 1) Necrotic lesions on MRI could be the cause of false negative since there is limitation to diagnose micro-

scopic disease.

2) Treated toxoplasmosis could cause false positive.

Cardiac Lymphoma

Gallium-67 total body scan is superior to all other imaging modalities in delineating the extent of the disease.

SUGGESTED READINGS

1. Padhani A, Kuklman JE. Pulmonary manifestations of AIDS. *Applied Radiology* 22: 13-19, 1993.
2. Wachter H, Fuchs D, Hausen A, et al. Who will get AIDS? *Lancet* 2: 1216-1217, 1986.
3. Woolfenden JM, Carrasquillo JA, Larson SM, et al. Acquired immunodeficiency syndrome: Ga-67 citrate imaging. *Radiology* 162: 383-387, 1987.
4. Kramer EL, Sanger JJ, Garay SM, et al. Gallium-67 scans of the chest in patients with acquired immunodeficiency syndrome. *J Nucl Med* 28: 1107-1114, 1987.
5. Abdel-Dayem HM, Scott A, Macapinlac H, Elgazzar A, Larson SM. Role of thallium-201 and Tc-99m sestaMIBI in tumor imaging. In *Nuclear Medicine in Clinical Diagnosis and Treatment, Volumes I and II*. Murray IPC, Ell PJ (eds.), Churchill Livingstone, 1994.
6. Lee UW, Rosen MP, Baum A, et al. AIDS related Kaposi's sarcoma: Finding in thallium-201 scintigraphy. *Am J Roentgenol* 151: 1233-1235, 1988.
7. Lee UW, Fuller JD, O'Brien MJ, Parker DR, Cooley TP, Liberwan HA. Preliminary Kaposi's sarcoma in patients with AIDS; Scintigraphic diagnosis with sequential thallium and gallium scanning. *Radiology* 180: 409-412, 1991.
8. Abdel-Dayem HM, DiFabrizio L, Aras T, et al. Prospective evaluation of sequential Tl-201 and Ga-67 scans in AIDS patients. *J Nucl Med* 34: 172P, 1993. (abstract)
9. Abdel-Dayem HM, DiFabrizio L, Aras T, et al. Accuracy of sequential Tl-201 and Ga-67 scans in the diagnosis of pulmonary Kaposi's sarcoma in AIDS patients. *Eur J Nucl Med* 20: 837, 1993. (abstract)
10. Abdel-Dayem HM, DiFabrizio L, Kowalsky W, et al. Diffuse thallium uptake in the lungs in PCP. *Clin Nucl Med* 19 (4): 287-291, 1994.
11. Murray JF, Felton CP, Garay SM, et al. Pulmonary complications of acquired immunodeficiency syndrome: Defective chemotaxis. *J Clin Invest* 74: 2121-2128, 1984.
12. Bitran J, Beckerman C, Weinstein C, et al. Patterns of Gallium-67 scintigraphy in patients with acquired immunodeficiency syndrome and AIDS related complex. *J Nucl Med* 28: 1103-1106, 1987.
13. Palestro GS, Swyer AL, Aim CR, et al. Relative efficiency of In-111-leukocytes and Ga-67 imaging in AIDS patients. *J Nucl Med* 32: 1003, 1991.
14. Tow TWY, Rosen MJ, Teirstein AS. Normal chest roentgenogram as a prognostic factor in pneumocystic carinii pneumonia in patients with acquired immunodeficiency syndrome. *Am Rev Respir Dis* 129: 54, 1984. (abstract)
15. Barron JP, Birnbaum NS, Sharel B, et al. Pneumocystic carinii pneumonia studied by Ga-67 scanning. *Radiology* 154: 791-793, 1985.
16. Kramer EL, Sanger JH, Garay SM, et al. Diagnostic implications of Ga-67 chest scan patterns in human immunodeficiency virus-seropositive patients. *Radiology* 170: 671-679, 1989.
17. DeLorenzo JL, Maguire GP, Worsler GP, et al. Persistence of pneumocystic carinii pneumonia in the acquired immunodeficiency syndrome: Evaluation of therapy by follow-up transbronchial lung biopsy. *Chest* 88: 79-83, 1985.
18. Ganz WI, Serafini DM. The diagnostic role of Ga-67 in the acquired immunodeficiency syndrome. *J Nucl Med* 30: 1935-1945, 1989.
19. Macher AM, Reichart CM, Strauss SE, et al. Death in the AIDS patient: Role of cytomegalovirus. *N Eng J Med* 309: 1454, 1983.
20. Pitchnik A, Burr J, Fertel D, et al. Tuberculosis in HIV infected patients: Epidemiology, infectivity, clinical features, response to treatment, prognostic factors and long term outcome. International Congress for Infectious Disease, Montreal, Canada 1990, July 15-19: 152. (abstract)
21. Pitchnik AE, Fertel D. Mycobacterial disease in patients with HIV infection. Wormser GP (ed.), in *AIDS and Other Manifestations of HIV Patients*. Raven Press, New York, pp. 277-313.
22. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Eng J Med* 320: 545-550, 1989.
23. Kuhlman JE, Knowls M, Fishman EK, et al. Diseases of the chest in AIDS: CT diagnosis. *Radiographics* 9: 827-867, 1989.
24. Rieder HL, Cauthen GM, Bloch AB, et al. Tuberculosis and acquired immunodeficiency syndrome. Florida. *Arch Intern Med* 149: 1268-1273, 1989.
25. Theuer CP, Chaisson RE, Schecter GF, et al. Human immunodeficiency virus in tuberculosis patients in San Francisco. *Am Rev Respir Dis* 137: 121, 1988. (abstract)
26. Bloch AB, Snider DE Jr. Reported AIDS patients with extrapulmonary tuberculosis in the United States. 6th International Conference on AIDS, San Francisco, June 1990, p 437. (abstract)
27. Pitchnik AE. The treatment and prevention of mycobacterial disease in patients with HIV infection. *AIDS* 2: s177-182, 1988.
28. CDC. Tuberculosis and human immunodeficiency virus infection: Recommendations of the advisory committee for the elimination of tuberculosis ACET. *MMWR* 38: 236-238, 243-250, 1989.
29. Smith PD, Quinn TC, Strober W. Gastrointestinal infections in AIDS. Janoff EN, Masur H (ed.), *NIH Conference Annals of Intern Med* 116: 63-77, 1992.
30. Janoff EN, Smith PD. Perspectives on gastrointestinal infections in AIDS. *Gastroenterol Clin North Am* 17: 451-463, 1988.
31. Dworkin B, Wormser GP, Rosenthal WS, Braunstein M, Weiss L, et al. Gastrointestinal manifestations of the acquired immunodeficiency syndrome: A review of 22 cases. *Am J Gastroenterol* 80: 774-778, 1985.
32. Malebranche R, Arnoux E, Guerin JM, Pierre GD, Laroche AC, Pean-Guichard C, et al. Acquired immunodeficiency syndrome with severe gastrointestinal manifestations in Haiti. *Lancet* 2: 873-878, 1983.
33. Colenuders R, Francis H, Mann JM, Bila KM, Izaley L,

- Kimputu L, et al. Persistent diarrhea, strongly associated with HIV infection in Kinshasa, Zaire. *Am J Gastroenterol* 82: 859–864, 1987.
34. Smith PD, Janoff EN. Infectious diarrhea in human immunodeficiency virus infection. *Gastroenterol Clin North Am* 17: 587–598, 1988.
 35. Gillin JS, Shike M, Alcock N, Urmacher C, Krown S, Kurtz RC, et al. Malabsorption and mucosal abnormalities of the small intestine in the acquired immunodeficiency syndrome. *Ann Intern Med* 101: 421–428, 1984.
 36. Levy RM, Bredesen DE, Rosenblum ML. Neurological complications of the acquired immunodeficiency syndrome (AIDS): Experience of UCSF and review of the literature. *J Neurol* 62: 775–798, 1985.
 37. Post JD, Tate LG, Quencer RM, et al. CT, MRI and pathology in HIV encephalitis and meningitis. *Am J Roentgenol* 151: 373–380, 1988.
 38. Macapinlac HA, Scott AM, Yeh SDJ, et al. The role of Tl-201 SPECT and F-18 FDG PET in the diagnosis of CNS lymphoma vs toxoplasmosis in patients with AIDS. *Eur J Nucl Med* 20: 835, 1993. (abstract)
 39. Ganz WI, Feun L, Panzer D, et al. Application of SPECT thallium scintigraphy in imaging of primary and metastatic brain tumors. *Radiology* 169: 392, 1988. (abstract)
 40. Masdeu JC, Yudd A, Van Heertum RL, et al. Single-photon emission computed tomography in human immunodeficiency virus encephalopathy: A preliminary report. *J Nucl Med* 32: 1471–1475, 1991.
 41. Kostakoglu L, Roistacher N, Kalaigan H, Larson S, Abdel-Dayem HM. Simultaneous gallium-67 citrate and technetium-99m sestaMIBI SPECT in a case of myocardial lymphoma: Comparison with echocardiography before and after chemotherapy. *Eur J Nucl Med* 1013–1016, 1994.
 42. Abdel-Dayem HM, DiFabrizio L, Bag R, Aras T, Turoglu HT, Kempf JS, et al. Evaluation of sequential thallium and gallium scans in AIDS patients. *J Nucl Med* 37 (10): 1662–1667, 1996.
 43. Abdel-Dayem HM, Omar WS, Aziz M, LaBombardi V, DiFabrizio L, Kempf JS, et al. Disseminated *Mycobacterium avium* complex: Review of gallium and thallium scans and autopsy findings. *Clin Nucl Med* 21 (7): 547–556, 1996.
 44. Naddaf SY, Mina B, Aziz MS, DiFabrizio L, Kempf JS, Abdel-Dayem HM. Sites of tuberculous (T.B.) involvement in AIDS patients (pts): Correlation with gallium (Ga) scans. Presented at the 81st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November 26–December 1, 1995, *Radiology*, Nov. 1995, 197 (P): 421. (supplement)
 45. Kempf JS, Abdel-Dayem HM. Detection of 2.1 cm hepatocellular carcinoma in an 11 year old male by thallium-201 chloride. Case presentation and correlative imaging findings. *Clin Nucl Med* 20 (7): 601–604, 1995.
 46. Cacciarelli AG, Abdel-Dayem HM, Aziz MS, Zuretti A, Kempf JS, Gillooley J. The incidence of acute cholecystitis (ACC) in AIDS patients. Presented at the 81st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, November 26–December 1, 1995. *Radiology*, Nov. 1995, 197 (P): 385. (supplement)