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Evaluation of Sequential Thallium and Gallium Scans of the Chest in AIDS Patients

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With decreasing incidence of pneumocystis carinii pneumonia (PCP) in AIDS as a result of prophylactic regimens, there is a higher incidence of tuberculosis (TB), mycobacterium avii complex (MAC), kaposi sarcoma and malignant lymphoma. There is a need for differentiating these various pathological entities. The purpose of this study was for a retrospective evaluation of sequential thallium and gallium scans in AIDS patients for differentiating intrathoracic kaposi sarcoma from malignant lymphoma and opportunistic infections. **Methods:** A total of 181 patients had both studies completed between March 1992 and May 1994. The final diagnosis was verified only in 83 patients. Results were correlated with the CD4 counts, bronchoscopic and chest radiograph findings. **Results:** In patients with pulmonary kaposi sarcoma and no opportunistic infections (19 patients), a thallium-positive, gallium-negative pattern was detected in 17 patients with a sensitivity of 89%. In the presence of kaposi sarcoma plus opportunistic infections, this pattern was only detected in 7 of 19 patients (sensitivity dropped to 37%). In 45 patients with opportunistic infections and no kaposi sarcoma, only two false-positive findings were found in patients with cytomegalic virus pneumonia for a specificity of 96%. For the whole group of 83 patients, sensitivity was 63%; specificity 95%; positive predictive value 92%; accuracy 81%; and negative predictive value 75%. **Conclusion:** A thallium-positive, gallium-negative pattern in AIDS patients has a high specificity for the diagnosis of kaposi sarcoma, however, the sensitivity dropped from 89% to 37% in the presence of opportunistic infections.

Key Words: AIDS; kaposi sarcoma; opportunistic infections; gallium-67-citrate; thallium-201-chloride

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AIDS has reached epidemic proportions in the United States with more than 800,000 Americans thought to be infected with the causative agent of HIV (1). Early in the epidemic, PCP

occurred in 75% of patients with the syndrome (2). With the common use of primary and secondary prophylaxis against PCP, its incidence decreased and the life of AIDS patients is prolonged without stopping a decline in immune function. Accordingly, there has been a shift in the clinical manifestations of HIV infection from PCP to other illnesses that occur when immune function is depressed. Mycobacterium avii complex disease, wasting syndrome, cytomegalic virus disease and esophageal candidiasis occur more frequently in patients who received prophylaxis against PCP than in those who did not (3).

Kaposi sarcoma is the most common neoplasm observed in HIV-infected individuals, followed by non-Hodgkin's lymphoma (4,5). The frequency of pulmonary involvement of kaposi sarcoma varied between 21% to 44% (6-8). Non-Hodgkin's lymphoma was reported in homosexual men shortly after recognition of the AIDS epidemic (9). Subsequently, other studies confirmed the increased incidence of this tumor in patients at risk for AIDS (10-17) and is now recognized as the second most common HIV-associated malignancy (18). Although an association between kaposi sarcoma and the development of lymphoma had been reported before AIDS, patients with AIDS and kaposi sarcoma do not appear to be at greater risk of developing lymphoma than do patients with AIDS without kaposi sarcoma (11). Thoracic involvement does occur with non-Hodgkin's lymphoma, but it is usually not the major presenting feature of AIDS-associated lymphoma. The incidence of thoracic involvement by lymphoma varied from zero to 25% in most of the large series (13,19). In both kaposi sarcoma and malignant lymphoma, the behavior of the disease is more aggressive and patients die because of additional opportunistic infections.

Problems in AIDS patients occur for several reasons: (a) the existence of more than one disease at any given time, (b) the difficulty in early verification of the diagnosis, (c) nonspecificity of the clinical presentation of symptoms and (d) the abnormalities seen on morphological imaging modalities. In

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addition, laboratory testing is not highly sensitive or fast enough in many occasions.

Sequential thallium and gallium scans had been initially proposed by Lee et al. (20,21) to differentiate pulmonary kaposi sarcoma from opportunistic infections. They suggested that kaposi sarcoma lesions are thallium positive but gallium negative, opportunistic infections are thallium negative but gallium positive, while malignant lymphoma is thallium and gallium positive. We have used this approach for more than three years and previously presented our data in several abstract forms (22–25). The purpose of this article is to present the final review of sequential thallium and gallium scans in AIDS patients to differentiate kaposi sarcoma from opportunistic infections and malignant lymphoma.

MATERIALS AND METHODS

Between March 1992 and May 31, 1994, a total of 181 sequential thallium and gallium scans were obtained. Institutional approval and the patients' consent were obtained for this study. All patients were HIV-positive and all classified as having AIDS. In the majority, chest radiographs were either positive for pneumonic infiltrate, hilar enlargement or the patient had cutaneous kaposi and the scans were requested to rule out pulmonary kaposi. The charts of these patients were retrospectively reviewed and the findings were entered in a database for analysis. Only those cases with proven diagnosis were analyzed for this presentation. Proof of diagnosis was by biopsy, bronchoscopy for kaposi sarcoma or by blood culture, serological studies, sputum AFB or culture PCP. Eighty-three sequential thallium and gallium scans were evaluated in this article.

Thallium scans of for the chest were started 20 min after the intravenous injection of 148 MBq (4 mCi) of ^{201}Tl -chloride. Planar chest images were acquired 10 min for each of the anterior and posterior projections. SPECT images of the chest were acquired either on a single- or dual-head gamma camera according to the following parameters: 360° rotation, 64 projections for the single-head camera and 90 projections for the dual, 64 × 64 × 16 matrix and 40-sec acquisition time per projection. Data were presmoothed and processed with a Butterworth filter, cutoff frequency 0.3–0.4 and order 8. Only 15 patients had positive thallium studies in the early images; delayed images were obtained 2 hr later using the same parameters. All patients were subsequently injected with 296 MBq (8 mCi) ^{67}Ga -citrate. Either total-body images with the dual-head camera were acquired 24–48 hr later or static images for the anterior, posterior chest and abdomen for two million counts for each view. SPECT images of the chest were acquired according to the same parameters since the thallium studies and data were processed according to the same parameters.

The results were interpreted by at least three nuclear medicine physicians and differences were solved by consensus. All studies were interpreted twice without knowledge of the previous interpretation. In patients with positive thallium uptake in the early images and who underwent delayed imaging 2 hr later, early and delayed images were compared visually to determine whether thallium uptake in the lesion on the planar and SPECT images persisted or washed out during the 2 hr interval. No quantitation of thallium washout was made. Comparison was made visually between lesion uptake lesion and the adjacent background activity. The charts reviewed the chest radiograph results, CD4 counts, bronchoscopic findings and results of culture specimens.

The sensitivity and specificity, positive predictive values (PPV), negative predictive values (NPV) and accuracy for the thallium-positive, gallium-negative pattern were calculated as follows:

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} \times 100.$$

Sensitivity was calculated for the group of kaposi sarcoma alone, kaposi sarcoma with opportunistic infections and for the whole group.

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} \times 100.$$

Specificity was calculated separately from 45 patients included in the study who had no kaposi sarcoma and only opportunistic infections. In 14 of these 45 patients, opportunistic infections was outside the chest. Three of them had abdominal lymphoma without chest involvement. The positive and negative predictive values were calculated for the whole group.

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}} \times 100.$$

$$\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}} \times 100.$$

$$\text{Accuracy} = \frac{\text{TN} + \text{TP}}{\text{TN} + \text{TP} + \text{FP} + \text{FN}} \times 100.$$

in which TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative.

RESULTS

Eighty-three patients (79 men and 4 women age 23–53 yr) were included in this study. Twenty-one patients were between 20–30 yr; 39 between 31–40 yr and 19 between 41–50 yr. In other words, 95% of the patients studied were between 20 and 50 yr. The relationship of the CD4 counts and the presence of kaposi sarcoma and opportunistic infections showed that 50.5% of patients with kaposi sarcoma and opportunistic infections had CD4 counts of < 50, 22.5% had CD4 counts between 50–100 and only 4 patients (4.5%) had CD4 counts between 100–200, one of these two had kaposi sarcoma, one had pulmonary TB and 2 with bacterial pneumonia. The CD4 counts were not available in 19 patients (22.5%). There is a relationship between the incidence of kaposi sarcoma, opportunistic infections and low CD4 counts whereby the incidence is higher with lower CD4 counts. The results of the thallium and gallium scans are presented in Table 1. The fourteen patients who had sequential thallium and gallium studies did not have pulmonary kaposi sarcoma or chest infection. Three had abdominal lymphoma and all had AIDS-related colitis. None of these 14 patients had a pattern of thallium-positive/gallium-negative scan in the chest. Only one patient had faint gallium and thallium uptake in both hilar regions, which was thought to be due to blood-pool activity. Table 2 shows a breakdown of the 19 patients who had kaposi sarcoma and opportunistic infections. The final diagnosis for the presence of opportunistic infections was established by sputum smears, sputum culture, bronchial aspirate, blood culture or by lymph node biopsy. The sensitivity of a thallium-positive, gallium-negative pattern in pulmonary kaposi sarcoma alone is 89% (17 of 19 patients) and drops to 37% if there is opportunistic infections associated with kaposi sarcoma (7 of 19 patients). The specificity of this thallium positive, gallium negative pattern in this series is 96%, since this pattern was recognized in two patients with CMV infections out of 45 patients with opportunistic infections alone and no kaposi sarcoma. One of these two patients was the subject of our previous report (26). For the whole group, the sensitivity is

TABLE 1

Results of the Sequential Thallium and Gallium Chest Scans in 83 AIDS Patients with Kaposi Sarcoma and Opportunistic Infections

Diagnosis	No.	Pattern type			
		Tl+ Ga-	Tl- Ga-	Tl- Ga+	Tl+ Ga+
KS alone	19	17	1	-	1
KS + OI	19	7	1	1	10
BP	9	-	4	4	1
MTB	7	-	1	2	4
MAI	4	-	-	2	2
PCP	7	-	1*	-	6
CMV	3	2	1	-	-
Candida	1	-	-	-	1
Nonpulmonary†	14	-	13	-	1‡
Total	83	26	22	9	26

*Low grade PCP.

†They had no chest infection. Opportunistic infection was located in the gastrointestinal tract and presented as AIDS-related colitis. Three of them were abdominal lymphoma.

‡Most likely bilateral hilar uptake most likely due to increased blood-pool activity.

KS = kaposi sarcoma; BP = bacterial pneumonia; MTB = mycobacterium tuberculosis; MAI = mycobacterium avii intracellulare; PCP = pneumocystis carinii pneumonia; CMV = cytomegalic virus pneumonia.

63%, specificity 95%, positive predictive value 92%, negative predictive value 75% and accuracy of 81%. The results of the chest radiograph findings are presented in Table 3. The chest radiograph was available in 81 patients and had abnormal findings in 64 (77%) and was negative in 17 (20.5%). Bronchoscopic findings are presented in Table 4. Bronchial kaposi sarcoma was confirmed in all patients who had bronchoscopy: in 18 out of 19 patients who had kaposi sarcoma alone and in all 19 patients who had kaposi sarcoma plus opportunistic infections.

In all cases of kaposi sarcoma, delayed thallium uptake remained on the lung without change in intensity. In patients who had thallium uptake in the early images due to opportunistic infections, a significant tracer washout on the delayed images. There was a 100% agreement on the interpretation of

TABLE 2

Results of Sequential Thallium and Gallium Chest Scans in 19 Patients with Kaposi Sarcoma and Opportunistic Infection

Diagnosis	No.	Pattern type			
		Tl+ Ga-	Tl- Ga-	Tl- Ga+	Tl+ Ga+
KS + MTB	3	2	1	0	0
KS + PCP	4	1	0	0	3
KS + PCP + MAI	1	0	0	0	1
KS + MAI	4	1	0	1	2
KS + PCP + BP	1	0	0	0	1
KS + aspergillus + SS	1	1	0	0	0
KS + coccidiomycosis	1	1	0	0	0
KS + MTB + coccidiomycosis	1	1	0	0	0
KS + cryptococcosis	1	0	0	0	1
KS + CMV	1	0	0	0	1
KS + BP	1	0	0	0	1
Total	19	7	1	1	10

SS = staph sepsis. See Table 1 for other definitions.

TABLE 3

Chest Radiographic Findings in Kaposi Sarcoma and Opportunistic Infections

Diagnosis	No.	CXR		
		Positive	Negative	Not available
KS	19	17	2	-
KS + OI	19	19	-	-
B.Pn.	9	8	1	0
MTB	7	6	1	-
MAI	4	2	2	0
PCP	7	7	-	-
Candida	1	1	-	-
CMV	3	2	1	-
Nonpulmonary	14	2	10	2
Total	83	64 (77%)	17 (20.5%)	2 (2.5%)

See Table 1 for abbreviations.

the scans between all three nuclear medicine physicians and there was no disagreement between the two readings.

Examples from kaposi sarcoma and kaposi sarcoma with opportunistic infections are presented in Figures 1 and 2. Figure 1 shows kaposi sarcoma of the lung alone without opportunistic infections. The study shows a thallium-positive and gallium-negative lesion in the lungs. Thallium uptake persisted in both early and delayed images. Figure 2 depicts kaposi sarcoma with opportunistic infections showing a presence of a thallium-positive, gallium-negative lesion in the right base suggestive of kaposi sarcoma and thallium-negative, gallium-positive left hilar uptake secondary to TB involvement.

DISCUSSION

After the recognition of AIDS in the early 1980s, ⁶⁷Ga-citrate has been widely used for the early diagnosis of PCP and other opportunistic infections (27,28). With widespread use of prophylactic treatment for PCP, other opportunistic infections such as pulmonary TB, mycobacterium avium-intracellulare (MAI), cryptococcus and viral pneumonia are more frequently diagnosed than PCP (29). In addition, the incidence of kaposi sarcoma or malignant lymphoma with intrathoracic involve-

TABLE 4

Bronchoscopic Findings in Kaposi Sarcoma and Opportunistic Infections

Diagnosis	No.	Bronchoscopy		
		Positive	Negative	Not available
KS	19	18	-	1
KS + OI	19	19	-	-
B.Pn.	9	-	2	7
MTB	7	-	-	7
MAI	4	-	2	2
PCP	7	-	4	3
Candida	1	-	1	-
CMV	3	-	1	2
Nonpulmonary	14	-	1	13
Total	83	37	11	35

*Bronchoscopic findings were positive for underlying lesions of the OI but not for bronchial KS.

See Table 1 for definitions.

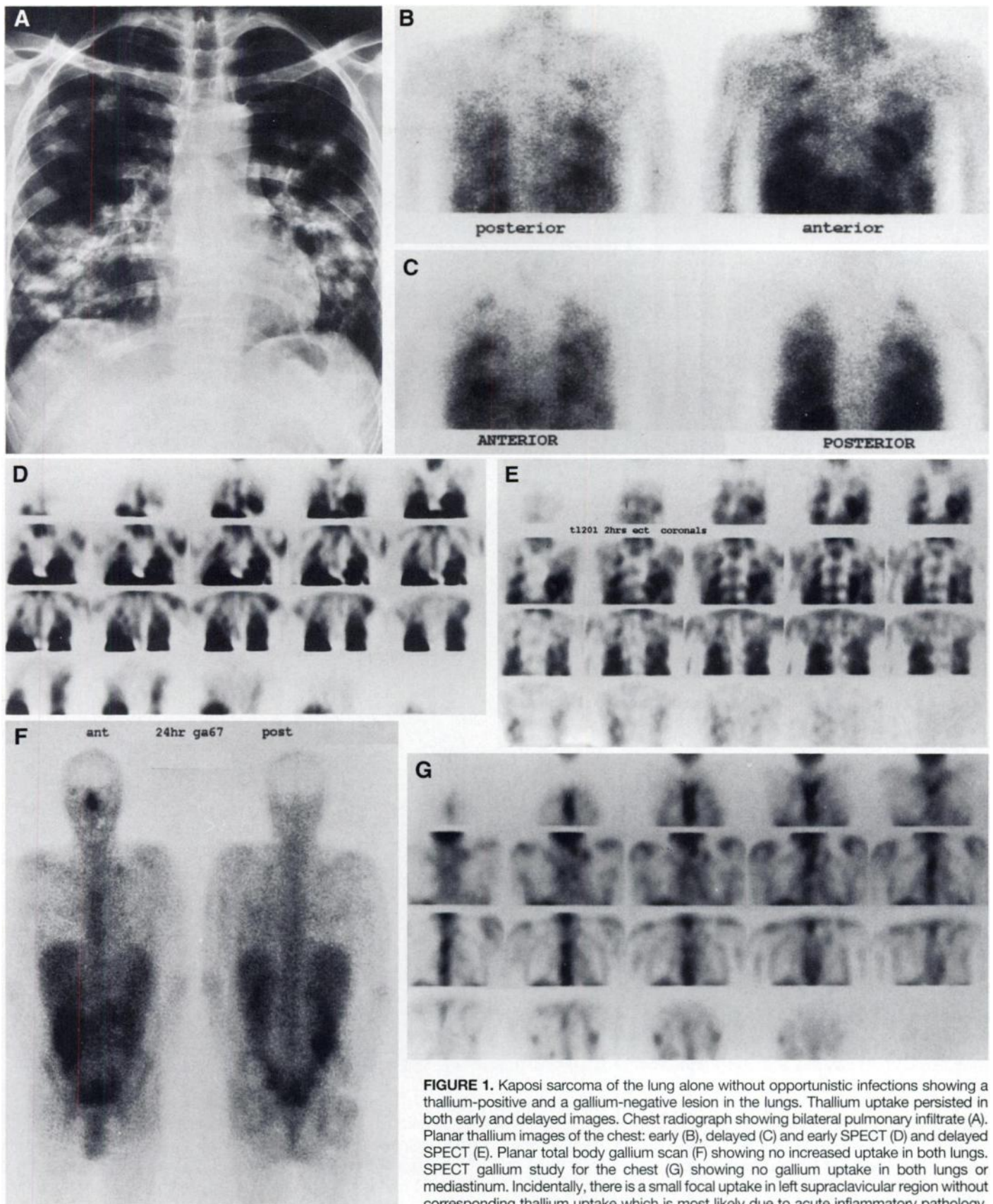


FIGURE 1. Kaposi sarcoma of the lung alone without opportunistic infections showing a thallium-positive and a gallium-negative lesion in the lungs. Thallium uptake persisted in both early and delayed images. Chest radiograph showing bilateral pulmonary infiltrate (A). Planar thallium images of the chest: early (B), delayed (C) and early SPECT (D) and delayed SPECT (E). Planar total body gallium scan (F) showing no increased uptake in both lungs. SPECT gallium study for the chest (G) showing no gallium uptake in both lungs or mediastinum. Incidentally, there is a small focal uptake in left supraclavicular region without corresponding thallium uptake which is most likely due to acute inflammatory pathology.

ment of the lungs is more reported in the 1990s than in the 1980s (29).

The need for differentiating the various types of opportunistic infections or malignant involvement of the lungs with kaposi sarcoma or lymphoma is required for subscription of appropri-

ate treatment. Since Lee et al. (20,21) reported the affinity of kaposi sarcoma for thallium uptake without corresponding positive gallium uptake, investigators have sought to discover whether sequential thallium and gallium scans will help to differentiate opportunistic infections from kaposi sarcoma or

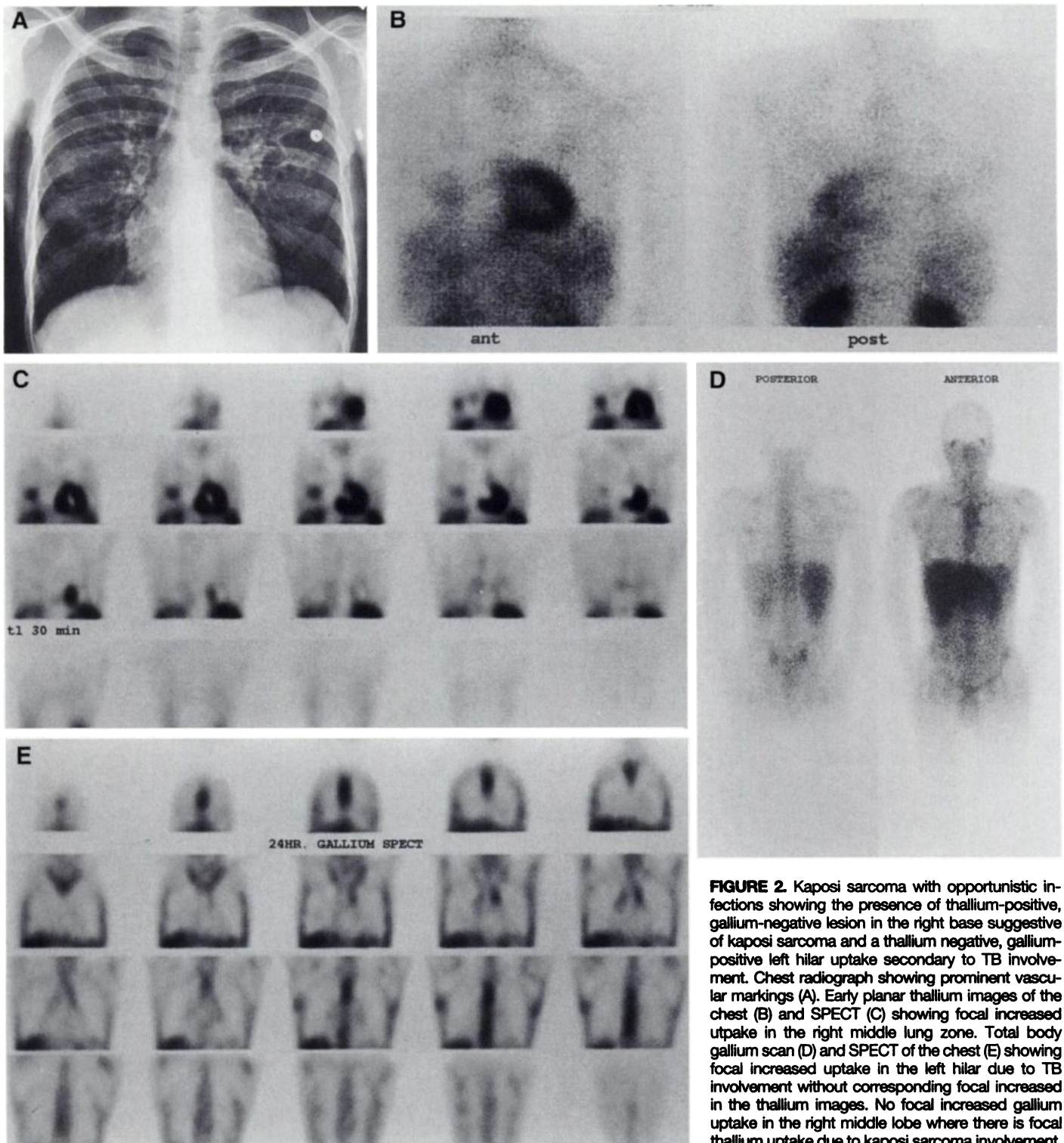


FIGURE 2. Kaposi sarcoma with opportunistic infections showing the presence of thallium-positive, gallium-negative lesion in the right base suggestive of kaposi sarcoma and a thallium negative, gallium-positive left hilar uptake secondary to TB involvement. Chest radiograph showing prominent vascular markings (A). Early planar thallium images of the chest (B) and SPECT (C) showing focal increased uptake in the right middle lung zone. Total body gallium scan (D) and SPECT of the chest (E) showing focal increased uptake in the left hilar due to TB involvement without corresponding focal increased in the thallium images. No focal increased gallium uptake in the right middle lobe where there is focal thallium uptake due to kaposi sarcoma involvement.

other malignant lesions in AIDS patients. We have been using this approach for more than 3 yr (22–26). This article contains a retrospective evaluation of studies done for almost 2 yr. We realized that there are several problems:

1. AIDS patients can have more than one pathology at any given time (i.e., more than one opportunistic infections in addition to the presence of kaposi sarcoma or malignant lymphoma of the lungs).
2. There is difficulty in confirming the diagnosis in AIDS patients because of the low sensitivity of laboratory tests, sputum cytology and the time needed for sputum culture in certain infections such as pulmonary TB.

3. Invasive procedures, bronchoscopic lavage and biopsy are sometimes needed, which are exhausting to these patients.
4. Chest radiograph findings, which is the most common morphological imaging modality used, may be nonspecific and is not sensitive in the early phases of infections as in the case of PCP.

The difficulties in confirming diagnosis in AIDS patients is reflected in our study. Only 83 of 181 total sequential thallium and gallium studies performed had confirmed final diagnoses. In the absence of opportunistic infections, sequential thallium and gallium scans are helpful in identifying the involvement of the lung parenchyma with kaposi sarcoma. The thallium-

positive, gallium-negative pattern was specific for kaposi sarcoma and was seen in 17 of 19 patients with a sensitivity of 89%. The specificity of the test is 96%. In the presence of kaposi sarcoma with opportunistic infections, however, the pattern of a thallium-positive, gallium-negative scan has a sensitivity of only 37%. The reasons for this low sensitivity are the presence of other opportunistic infections that are thallium-positive and the poor sensitivity of gallium in some of these infections. According to our data in patients with no kaposi sarcoma, the gallium scans were positive only in five of nine patients with bacterial pneumonia and six of seven with mycobacterium TB.

A smaller group of patients with opportunistic infections and positive thallium uptake group underwent 2-hr delayed thallium imaging. The intensity of thallium uptake decreased between the early and delayed images. This clearance of thallium has been previously reported by us and others and was found to be helpful in differentiating malignant lesions where the intensity of thallium uptake will stay the same or will show minimal washout, whereas in inflammatory lesions it either clears completely or shows significant washout (30–32). The mechanism of thallium uptake in both malignant and inflammatory lesions is different. In malignant lesions, it is active uptake related to blood flow, number of viable cells, ATPase, sodium pump activity and energy consumption. Whereas in inflammatory lesions, it is due to passive diffusion to the extravascular space which occurs early after the intravenous injection and diffuses back to the intravascular component by the time of delayed imaging due to the lower concentration and clearance of thallium from the intravascular component (32).

Kaposi sarcoma involvement of the intrathoracic structures could involve the trachea, bronchi, mediastinal nodes or lung parenchyma. Tracheal kaposi sarcoma is usually recognized by bronchoscopy, whereas mediastinal nodal involvement or parenchymal involvement with kaposi sarcoma is suspected on radiographic appearance. The findings on plain chest radiograph or x-ray CT are usually nonspecific and are not highly sensitive. A thallium-positive, gallium-negative pattern at these locations is highly specific for the diagnosis of kaposi sarcoma and increases the sensitivity for the recognition of parenchymal pulmonary kaposi sarcoma involvement.

CONCLUSION

In AIDS patients, sequential thallium and gallium scans are helpful in differentiating the nature of lesions in the lungs. The pattern of a thallium-positive, gallium-negative appearance of the lesion on the scan is highly specific for kaposi sarcoma. The sensitivity of the test is high in the absence of opportunistic infections, however, it is quite low in the presence of opportunistic infections.

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